SECTION 2 | THE THYROID GLAND

CHAPTER 3

Hypothyroidism

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ANATOMY AND PHYSIOLOGY OF THE THYROID GLAND

The thyroid gland was first described in detail by Vesalius in the sixteenth century. Thomas Wharton (1614-1673) named the gland from the Greek word *thyreos,* or shield, based on its physical appearance. One of the first described thyroid disorders was an association between iodine deficiency and enlargement of the thyroid (goiter), which was initially suspected in the 1500s to be a possible cause of cretinism. This description also represents the

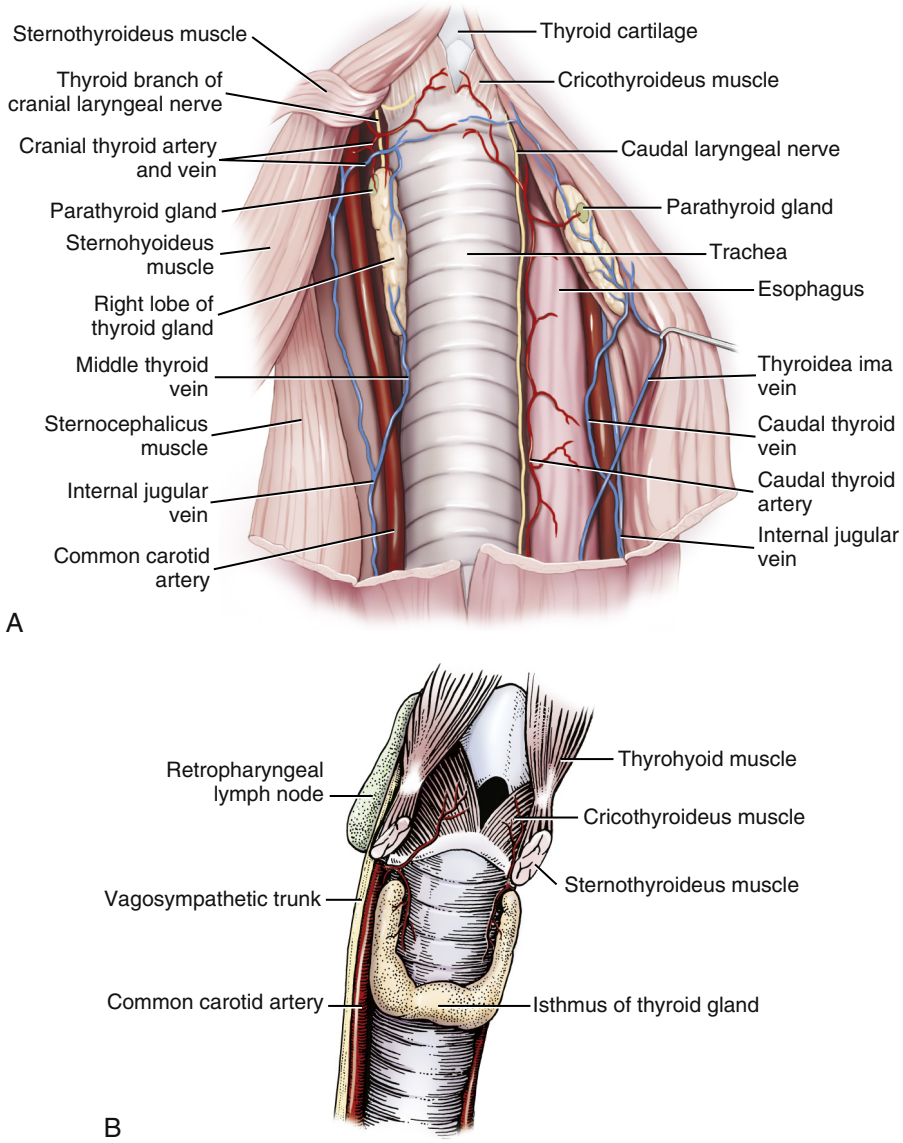

FIGURE 3-1 **A** and **B,** Thyroid anatomy of the dog and cat. (From Hullinger RL: The endocrine system. In Evans HE, de Lahunta A, editors: *Miller's anatomy of the dog,* ed 4, St Louis, 2013, Elsevier.)

first mention of thyroid gland enlargement. Endemic cretinism in the region around Salzburg, Austria, was described by the Swiss-German physician Paracelsus (1493-1541).

The thyroid gland develops in the embryo in close association with the gastrointestinal tract, which explains why both the gastric and salivary glands concentrate iodide in their secretions. In dogs and cats the thyroid gland is comprised of two lobes in the mid-cervical region that lie to either side of the trachea. The lobes are elongated dark red structures adjacent to the right and left lateral surfaces of the proximal trachea (Fig. 3-1) and are not normally palpable. The thyroid gland has an extensive vascular supply primarily from the cranial and caudal thyroid arteries. The functional unit of the thyroid gland is the follicle, a sphere of cells with a lumen containing a clear proteinaceous colloid (Fig. 3-2). The colloid contains primarily thyroglobulin (Tg), a large glycoprotein dimer that serves as a reservoir for thyroid hormone. Parafollicular cells (C cells) lie in the interstitium between the follicles and synthesize and secrete calcitonin.

Thyroid Hormone Synthesis

Thyroxine (T_4) and 3,5,3′-triiodothyronine (T_3) are iodine–containing amino acids. Thyroid hormone synthesis requires iodine and is dependent upon ingestion of adequate iodide from the diet. Iodide is actively transported from the extracellular fluid into the thyroid follicular cell by the sodium-iodine symporter (NIS), where it is rapidly oxidized by thyroid peroxidase (TPO) into a reactive intermediate (Fig. 3-3). At the apical membrane, iodine is incorporated into the tyrosine residues of Tg (Salvatore et al, 2011). TPO also catalyzes the coupling of the non-biologically active iodinated tyrosine residues (monoiodotyrosine [MIT], and diiodotyrosine [DIT]) to form the biologically active iodothyronines—T_4 and T_3 (Fig. 3-4). These iodination reactions are referred to as *organification* and occur within Tg rather than on the free amino acids.

Tg is stored extracellularly in the follicular lumen. As a prerequisite for thyroid hormone secretion into the blood, Tg must first reenter the thyroid cell and undergo proteolysis. Pseudopods from the apical cell surface extend into the colloid in the follicular lumen, and large colloid droplets enter the cytoplasm by endocytosis (Salvatore et al, 2011). Each colloid droplet is enclosed in a membrane derived from the apical cell border. Electron-dense lysosomes then fuse with the colloid droplets to produce phagolysosomes. These phagolysosomes migrate toward the basal aspect of the cell, while lysosomal proteases hydrolyze Tg. T_4 and, to a much lesser degree, T_3 liberated from Tg by the proteolytic process pass from the phagolysosome into the

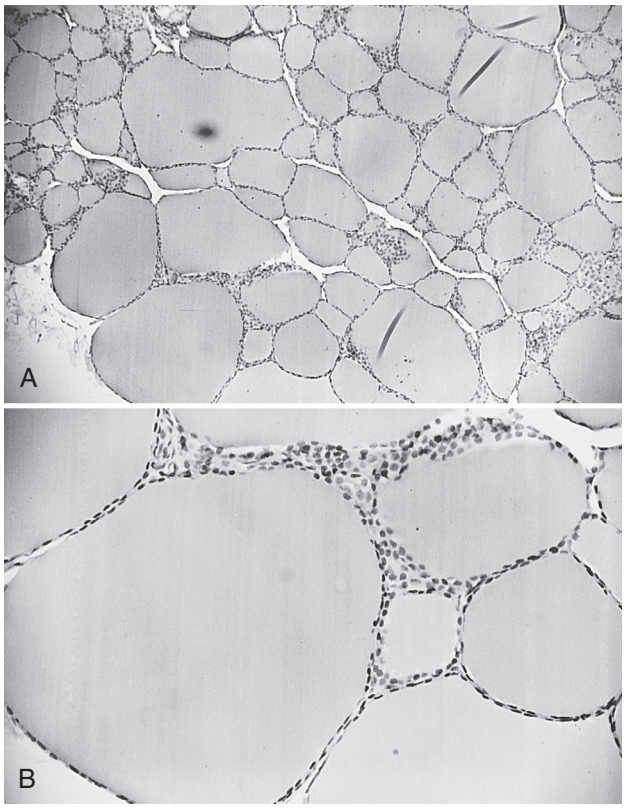

FIGURE 3-2 **A** and **B,** Histologic section of a thyroid gland from a healthy dog, illustrating variable-sized follicles, each lined by follicular epithelial cells with a lumen containing colloid. The follicle is surrounded by a basement membrane which separates the follicular cells from a capillary bed. The wall of the follicle is a single layer of follicular epithelial cells, which are cuboidal when quiescent and columnar when active. (**A,** H&E ×40; **B,** H&E ×160.)

blood by diffusion. Most of the liberated iodotyrosines (MIT, DIT) are de-iodinated, releasing iodide, which can be reused for Tg iodination or diffuse out into the circulation. A small quantity of intact Tg also enters the circulation. This leakage is increased when the thyroid cells are damaged, such as in lymphocytic thyroiditis.

Regulation of Thyroid Function

Thyroid hormone synthesis and secretion are regulated by extrathyroidal (thyrotropin) and intrathyroidal (autoregulatory) mechanisms. Thyroid-stimulating hormone (also known as thyrotropin; TSH) increases both synthesis and secretion of T_4 and T_3 and is the major modulator of thyroid hormone concentration (Fig. 3-5). TSH secretion by the pituitary is modulated by thyroid hormone in a negative feedback regulatory mechanism. At the pituitary, it is primarily T_3, produced locally by the monodeiodination of T_4 that inhibits TSH secretion (Salvatore et al, 2011). TSH secretion from the pituitary gland is modulated by thyrotropin-releasing hormone (TRH) from the hypothalamus (see Fig. 3-4). Hypothalamic production and release of TRH are controlled by poorly understood neural pathways from higher brain centers.

Autoregulatory intrathyroidal mechanisms also regulate iodide uptake and thyroid hormone synthesis. Examples of autoregulatory mechanisms include the Wolff-Chaikoff block (decrease in Tg iodination and thyroid hormone synthesis with increasing iodide intake), intrathyroidal alterations in thyroid sensitivity to TSH stimulation, and increased ratio of T_3 to T_4 secretion by the thyroid gland during periods of iodide insufficiency.

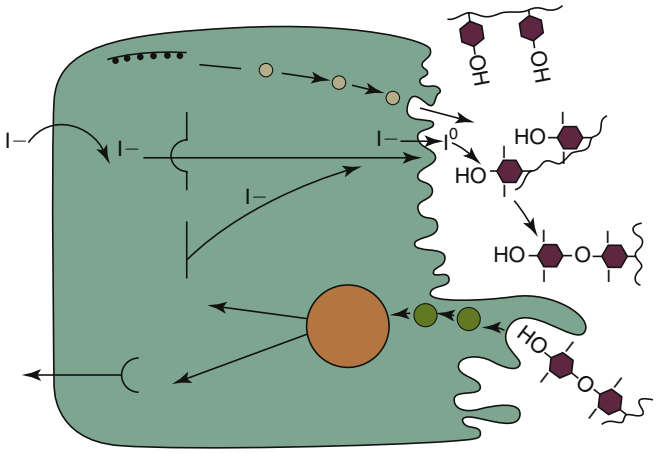

FIGURE 3-3 Thyroid hormone synthesis. Thyroglobulin (Tg) is synthesized within thyroid follicular cells and secreted into the colloid. Iodide is oxidized and bound to tyrosine residues on the Tg molecule by thyroid peroxidase (TPO). Iodinated tyrosine residues (monoiodotyrosine [MIT] and diiodotyrosine [DIT]) within the Tg molecule then undergo oxidative condensation to form the iodothyronines (T_3 and T_4), which remain bound to Tg until secreted. Tg is ingested by endocytosis from the colloid; the peptide bonds between the iodinated residues and the Tg are hydrolyzed; and MIT, DIT, T_4, and T_3 are released into the cytoplasm. MIT and DIT are de-iodinated and the iodine is recycled, whereas T_4 and T_3 are released into the bloodstream. (Modified from Mountcastle VB: *Medical physiology,* ed 14, vol 2, St Louis, 1980, Mosby.)

Thyroid Hormones in Plasma

T_4 is the major secretory product of the normal thyroid gland. Thyroid hormones in plasma are highly protein bound with T_4 more highly bound than T_3. Less than 1% of T_4 and T_3 circulate in the unbound "free" state. In the dog, the thyroid binding proteins are thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), albumin, and certain plasma lipoproteins. TBG is the major binding protein in the dog but is absent in the cat. The lower concentration of TBG and differences in structure between species may explain the low serum T_4 levels and rapid T_4 metabolism seen in dogs compared to humans. Only free or unbound thyroid hormones enter cells to produce a biologic effect or regulate pituitary TSH secretion. Protein-bound thyroid hormones serve as a large reservoir that is slowly drawn upon as the free hormone dissociates from the binding proteins and enters the cells.

Thyroid hormone entry into cells is mediated by transporter proteins. T_3 enters cells more rapidly, has a more rapid onset of action, and is three to five times more potent than T_4. Thyroid hormones bind to receptors in the nuclei; the hormone receptor complex then binds to DNA and influences the expression of many genes coding for regulatory enzymes. Thyroid hormone is also believed to have some non-genomic effects mediated by receptors in the plasma membrane and the cytoplasm (Yen and Brent, 2013).

Physiologic Functions of Thyroid Hormones

Thyroid hormones regulate many metabolic processes, influencing the concentration and activity of numerous enzymes; the metabolism of substrates, vitamins, and minerals; the secretion and degradation rates of virtually all other hormones; and the response of their target tissues to those hormones. Thyroid hormones are critically important in fetal development, particularly of the neural and skeletal systems. Thyroid hormones stimulate calorigenesis,

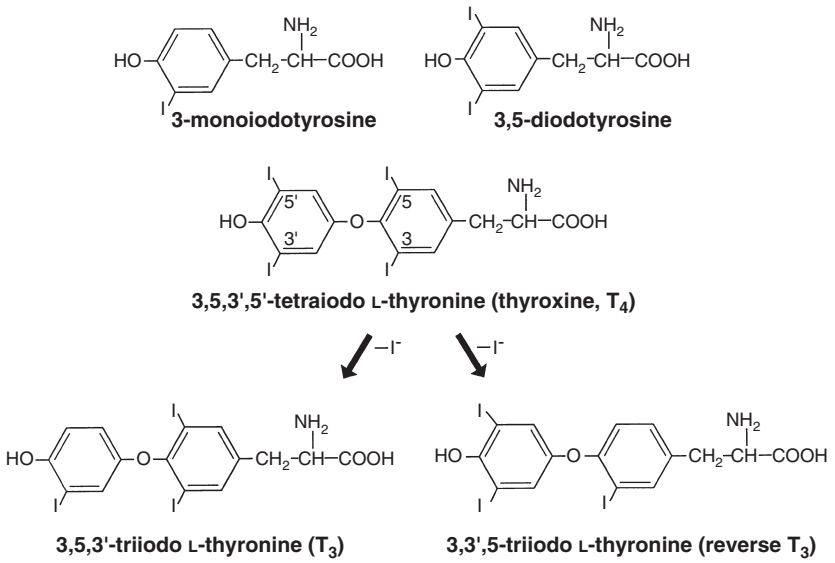

FIGURE 3-4 Structure of the thyroid hormones and their precursors.

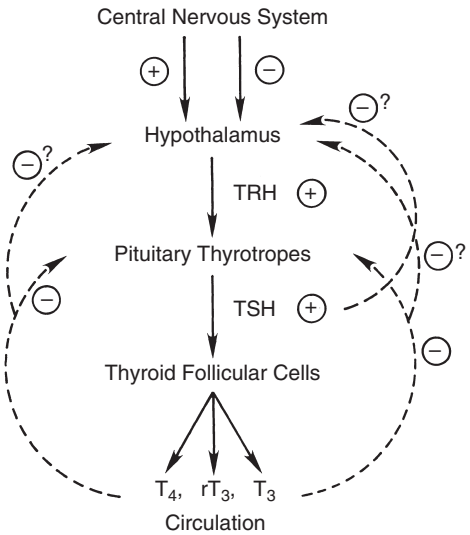

FIGURE 3-5 Regulation of thyroid hormone concentration by the hypothalamic-pituitary-thyroid axis. Thyroid hormone concentrations are controlled by the hypothalamic-pituitary-thyroid axis, which operates as a negative feedback loop. Thyrotropin *(TSH)* causes synthesis and release of thyroxine *(T_4)* and lesser amounts of 3,5,3′-triiodothyronine *(T_3)* from the thyroid gland. Intracellular T_3, derived from de-iodination of T_4 within the pituitary gland, causes decreased TSH synthesis and secretion and is the main determinant of TSH concentration. Thyrotropin-releasing hormone *(TRH),* secreted by the hypothalamus, modulates TSH release from the pituitary gland. Increased thyroid hormone concentrations are also believed to decrease TRH synthesis and secretion. Hormones that inhibit TSH secretion include dopamine, somatostatin, serotonin, and glucocorticoids. TRH, prostaglandins, and alpha-adrenergic agonists increase TSH secretion. *rT_3,* Reverse 3,3′,5′-triiodothyronine; +, stimulation; –, inhibition.

protein and enzyme synthesis, and virtually all aspects of carbohydrate and lipid metabolism, including synthesis, mobilization, and degradation (Yen and Brent, 2013). Furthermore, thyroid hormones have marked chronotropic and inotropic effects on the heart; increase the number and affinity of beta-adrenergic receptors; enhance the response to catecholamines; are necessary for normal hypoxic and hypercapnic drive to the respiratory centers; stimulate erythropoiesis; and stimulate bone turnover, increasing both formation and resorption of bone (Greenspan, 2001). In essence, no tissue or organ system escapes the adverse effects of thyroid hormone excess or insufficiency.

Thyroid Hormone Metabolism

The major pathway of T_4 metabolism is the progressive deiodination of the molecule. The initial deiodination of T_4 may occur in the outer ring, producing T_3, or in the inner ring, producing reverse T_3 (rT_3; see Fig. 3-4). Because conversion of T_4 to T_3 increases biologic activity, whereas conversion of T_4 to rT_3 has the opposite effect, the conversion of T_4 to T_3 or rT_3 by outer or inner ring iodothyronine deiodinase is a pivotal regulatory step in determining thyroid hormone biologic activity. Three unique deiodinases (D1, D2, and D3) with different tissue distributions, and different affinity for inner or outer ring deiodination, play a major regulatory role in thyroid hormone homeostasis by influencing the concentration of intracellular T_3. The integration of plasma T_3 and local deiodinase produced T_3 together with local inactivation of thyroid hormone, ultimately determines nuclear T_3 concentration and the thyroid status of the cell (Bianco and Kim, 2013). In dogs approximately 40% to 60% of T_3 is believed to be derived from outer ring monodeiodination of T_4 in peripheral tissues. Conjugation of thyroid hormone to soluble glucuronides and sulfates with subsequent excretion in the bile and urine represents another major metabolic pathway for thyroid hormone.

CANINE HYPOTHYROIDISM

CLASSIFICATION

Canine hypothyroidism may occur due to thyroid gland destruction, decreased stimulation by TSH from the pituitary gland, or failure in any of the steps of thyroid hormone synthesis. Hypothyroidism is the most common thyroid disorder in dogs and may be acquired or congenital. Hypothyroidism is classified as primary if it is due to an abnormality at the level of the thyroid gland, secondary if it is due to decreased TSH secretion, and tertiary if it is due to TRH deficiency. Primary hypothyroidism is the most

BOX 3-1 Potential Causes of Hypothyroidism in the Dog

Primary Hypothyroidism
Lymphocytic thyroiditis*
Idiopathic atrophy*
Neoplastic destruction*
Iodine deficiency*
Goitrogen ingestion
Iatrogenic*
  Surgical removal*
  Anti-thyroid medications/potentiated sulfonamides*
  Radioactive iodine treatment*

Congenital*
Thyroid gland dysgenesis*
Dyshormonogenesis*
Defective thyroid hormone transporters/receptors
Iodine deficiency
Maternal antibodies
Maternal medications

Secondary Hypothyroidism
Pituitary malformation*
Pituitary cyst
  Pituitary hypoplasia
Pituitary destruction*
  Neoplasia
Defective TSH molecule
Defective TSH-follicular cell receptor interaction
Iatrogenic*
  Drug therapy, most notably glucocorticoids
  Radiation therapy
  Hypophysectomy

Tertiary Hypothyroidism
Congenital hypothalamic malformation
Acquired destruction of hypothalamus
  Neoplasia*
  Hemorrhage
  Abscess
  Granuloma
  Inflammation
Deficient/defective TRH molecule
Defective TRH-thyrotroph receptor interaction

TRH, Thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone (also known as thyrotropin).
* Established etiology in the dog

common cause of hypothyroidism in dogs. Secondary hypothyroidism due to impaired secretion of TSH is rare in dogs, and tertiary hypothyroidism is presumed to be extremely rare.

ETIOLOGY

Primary Hypothyroidism

Acquired primary hypothyroidism is the most common cause of naturally occurring thyroid failure in the adult dog, accounting for more than 95% of cases. Two histologic forms of primary hypothyroidism are recognized in dogs; lymphocytic thyroiditis and idiopathic atrophy (Box 3-1). It is likely that some cases of idiopathic atrophy are the end result of severe lymphocytic thyroiditis. Other much more rare causes of primary hypothyroidism include iodine deficiency, goitrogen ingestion, congenital hypothyroidism, thyroid gland destruction by neoplasia, drug therapy, surgical thyroidectomy, and treatment with radioactive iodine.

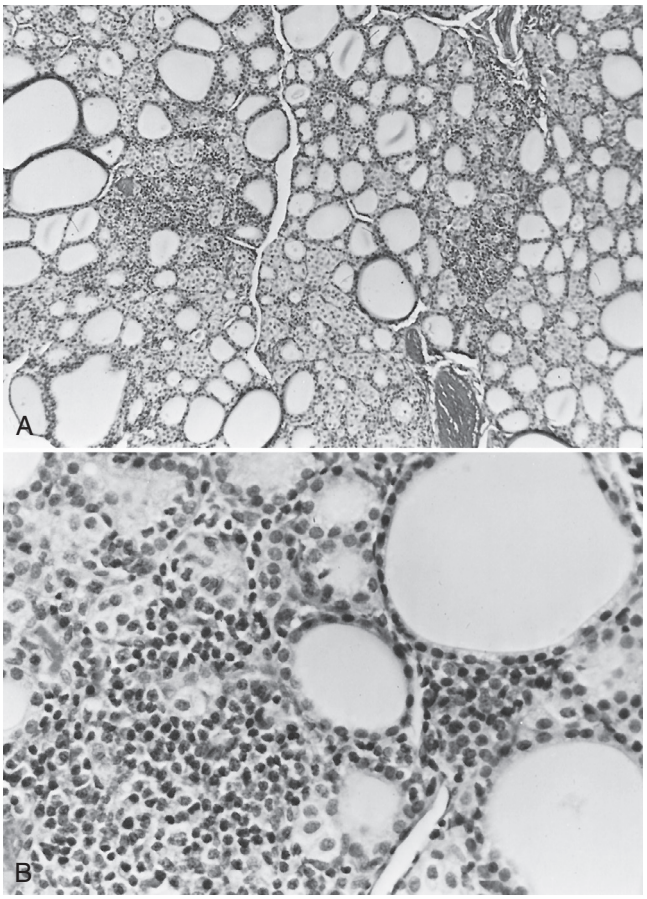

FIGURE 3-6 A and **B,** Histologic section of a thyroid gland from a dog with lymphocytic thyroiditis and hypothyroidism. Note the mononuclear cell infiltration, disruption of the normal architecture, and loss of colloid-containing follicles. (**A,** H&E ×63; **B,** H&E ×250.)

Lymphocytic Thyroiditis

Lymphocytic thyroiditis is characterized histologically by diffuse infiltration of lymphocytes, plasma cells, and macrophages into the thyroid gland, resulting in progressive destruction of follicles and secondary fibrosis (Gosselin et al, 1981b; Fig. 3-6). Destruction of the thyroid gland is progressive, and clinical signs do not become evident until at least 80% of the gland has been destroyed. Studies suggest that the onset of clinical signs and development of decreased serum thyroid hormone and increased serum TSH concentrations occurs over a prolonged time period of 1 to 3 years, suggesting a slowly progressive destructive process (Nachreiner et al, 2002; Graham et al, 2007). Graham, et al. (2007) have proposed four stages in the development of lymphocytic thyroiditis in dogs. The first stage (subclinical thyroiditis) is characterized by focal lymphocytic thyroid gland infiltration and positive Tg and thyroid hormone autoantibody tests. In stage 2 (antibody positive subclinical hypothyroidism) loss of greater than 60% to 70% of thyroid mass results in a compensatory increase in TSH, which stimulates the thyroid gland to maintain normal T_4 concentrations. In stage 3 (antibody positive overt hypothyroidism) most functional thyroid tissue is destroyed, and decreased serum thyroid hormone concentrations and increased TSH concentration are present (Table 3-1). Stage 4 (noninflammatory atrophic

TABLE 3-1 **PROPOSED FUNCTIONAL STAGES OF LYMPHOCYTIC THYROIDITIS IN DOGS**

STAGE OF THYROIDITIS	CLINICAL SIGNS OF HYPOTHYROIDISM	SERUM THYROXINE AND FREE THYROXINE	SERUM THYROTROPIN	ANTI-THYROGLOBULIN ANTIBODY
I: Subclinical thyroiditis	Not present	Normal	Normal	Positive
II: Subclinical hypothyroidism	Not present	Normal	Increased	Positive
III: Overt hypothyroidism	Present	Decreased	Increased	Positive
IV: Noninflammatory atrophic hypothyroidism	Present	Decreased	Increased	Negative

Adapted from Graham PA, et al.: Lymphocytic thyroiditis, *Vet Clin North Am Small Anim Pract* 37(4):617, 2007.

hypothyroidism) is characterized by replacement of thyroid tissue by fibrous and adipose tissue and disappearance of inflammatory cells and circulating antibodies. What proportion of cases of antibody negative idiopathic thyroid atrophy is actually due to stage 4 thyroiditis has not been determined. Analysis of age distributions of dogs with laboratory test results (i.e., Tg antibody, T_4, and TSH) consistent with the different stages or classifications of lymphocytic thyroiditis suggests that the age of peak prevalence progresses by 1 to 2 years through each of the classifications (Graham et al, 2001; Fig. 3-8). Studies also suggest that there are breed-specific differences in the progression rate and likelihood of progression of thyroiditis.

Lymphocytic thyroiditis is an immune-mediated disorder, and both humoral and cell mediated immunity play a role in pathogenesis. The major thyroid antigens that initiate an immune response in the thyroid gland are Tg and TPO. Tg is the main antigen in colloid, and anti-thyroglobulin antibodies (ATAs) are a sensitive indicator of canine thyroiditis (Gosselin et al, 1980; Nachreiner et al, 1998). TPO is a membrane bound glycosylated hemoprotein that catalyzes the biosynthesis of thyroid hormones. Despite being the most prevalent anti-thyroid antibody in humans with Hashimoto thyroiditis, anti-TPO antibodies are found in only 17% of dogs with thyroiditis (Skopek et al, 2006). Evidence for humoral mechanisms in the pathogenesis of canine thyroiditis is the presence of circulating autoantibodies to thyroid antigens; identification by electron microscopy of thickened basement membranes containing electron-dense deposits that are believed to be antigen-antibody complexes in thyroid follicles; and the induction of lesions similar to lymphocytic thyroiditis in dogs following the intrathyroidal injection of Tg antibodies (Gosselin et al, 1980; 1981a; 1981b; 1981c; Gaschen et al, 1993). Antibody binding to the follicular cell, colloid, or Tg antigens is believed to activate the complement cascade, antibody-dependent cell-mediated cytotoxicity, or both, causing follicular cell destruction. In humans anti-TPO antibodies but not ATAs have been demonstrated to fix complement. The cell-mediated immune system may also play an important, and possibly primary, role in the development and perpetuation of lymphocytic thyroiditis. Canine peripheral blood mononuclear cells in hypothyroid dogs that are positive for ATAs show proliferation in response to canine Tg. There was a positive correlation between the number of CD4+ cells and the concentration of Tg in the cultures, suggesting that a loss of self-tolerance of CD4 + cells is important in the pathogenesis of canine thyroiditis (Tani et al, 2005).

The initiating factors involved in the development of lymphocytic thyroiditis are poorly understood. Genetics undoubtedly plays a major role, especially given the increased incidence of this disorder in certain breeds. Lymphocytic thyroiditis is an inherited disorder in colony-raised Beagles, with a polygenic mode of inheritance, and was identified as an autosomal-recessive trait in a family of Borzoi dogs (Conaway et al, 1985a). An increased prevalence of circulating thyroid hormone autoantibodies has also been found in certain breeds, and the progression rate is different for different breeds (Nachreiner et al, 2002; Graham et al, 2007; Ferm et al, 2009; Table 3-2). A strong association between thyroiditis and certain major histocompatibility complex DLA class II haplotypes has been demonstrated in Doberman Pinchers, English Setters, Rhodesian Ridgebacks, and Giant Schnauzers (Kennedy et al, 2006a; 2006b; Wilbe et al, 2010). Environmental risk factors for canine thyroiditis have not been well defined. Infection-induced damage to the thyroid gland, causing release of antigens into the circulation and their subsequent exposure to the host's immune system, or antigenic mimicry of thyroid antigens by viral or bacterial agents could initiate the immune-mediated inflammatory process. The proportion of euthyroid dogs with evidence of thyroiditis is highest in the summer and lowest in the winter months (Graham et al, 2007). The significance of this finding is unclear, but it could indicate a relationship between infection and thyroiditis. Vaccine administration has also been hypothesized to be a contributing factor for development of lymphocytic thyroiditis. A significant increase in ATAs was documented in Beagles after repeated vaccination beginning at 8 weeks of age (Scott-Moncrieff et al, 2002; 2006); however further research did not document an increased prevalence of thyroiditis in the vaccinated beagles at necropsy after 5½ years of follow-up.

Lymphocytic Thyroiditis and Polyglandular Autoimmune Syndromes

Because autoimmune mechanisms play an important role in the pathogenesis of lymphocytic thyroiditis, it is not surprising that lymphocytic thyroiditis may sometimes occur together with other immune-mediated endocrine deficiency syndromes. Combinations of immune-mediated endocrine deficiency disorders such as hypothyroidism and diabetes mellitus, and hypothyroidism and hypoadrenocorticism have been documented in dogs (Hargis et al, 1981; Haines and Penhale, 1985; Bowen et al, 1986; Ford et al, 1993; Kooistra et al, 1995; Greco, 2000; Blois et al, 2011). These combined disorders are rare, occurring in less than 2% of dogs with immune-mediated endocrinopathies (Blois et al, 2011). In a retrospective study of 225 dogs with hypoadrenocorticism, 4% of the dogs also had hypothyroidism, 0.5% had concurrent diabetes mellitus, and one dog had concurrent hypothyroidism, diabetes mellitus, and hyperparathyroidism (Peterson et al, 1996). In a retrospective study of multiple endocrine disease in 35 dogs, the most common combination of immune-mediated endocrine disorders were hypothyroidism and diabetes mellitus in 10 dogs and hypothyroidism and hypoadrenocorticism in 8 dogs (Blois et al, 2011). Concurrent thyroiditis and orchitis have been documented in a colony of related Beagles and both disorders are highly heritable (Fritz et al, 1976). In humans, two polyglandular

TABLE 3-2 NINETEEN BREEDS WITH THE HIGHEST AND TWENTY BREEDS WITH THE LOWEST PREVALENCE OF THYROGLOBULIN ANTIBODY IN 140,821 SERUM SAMPLES SUBMITTED FOR INVESTIGATION OF THYROID DISEASE*

NAME	TOTAL SERA	THYROGLOBULIN AUTOANTIBODY–POSITIVE	PREVALENCE
English Setter	585	184	31%
Old English Sheepdog	368	86	23%
Boxer	2642	496	19%
Giant Schnauzer	263	49	19%
American Pit Bull Terrier	345	64	19%
Beagle	2452	449	18%
Dalmatian	1372	246	18%
German Wirehaired Pointer	112	20	18%
Maltese Dog	594	105	18%
Rhodesian Ridgeback	626	107	17%
Siberian Husky	1129	164	15%
American Staffordshire Terrier	151	24	16%
Cocker Spaniel	8576	1305	15%
Chesapeake Bay Retriever	509	74	15%
Tibetan Terrier	106	15	14%
Shetland Sheepdog	5765	813	14%
Golden Retriever	17782	2397	13%
Borzoi	266	35	13%
Brittany Spaniel	556	71	13%
Dachshund	3612	115	3%
Basset Hound	699	22	3%
Cairn Terrier	590	18	3%
Schnauzer (unspecified)	1257	38	3%
Wirehaired Fox Terrier	170	5	3%
Cavalier King Charles Spaniel	274	8	3%
Welsh Corgi (undetermined)	457	13	3%
Yorkshire Terrier	1178	33	3%
Norwegian Elkhound	263	7	3%
Belgian Tervuren	235	6	3%
Chihuahua	611	15	2%
Greyhound	1409	32	2%
Pekingese	407	9	2%
Boston Terrier	500	11	2%
Pomeranian	1301	26	2%
Irish Wolfhound	210	4	2%
Whippet	114	2	2%
Soft-coated Wheaten Terrier	214	3	1%
Bichon Frise	657	8	1%
Miniature Schnauzer	828	10	1%

From Graham PA, et al.: Etiopathologic findings of canine hypothyroidism, *Vet Clin North Am Small Anim Pract* 37(4):617-631, 2007; with permission.
*Overall thyroglobulin autoantibody prevalence in this study was 10%.

autoimmune syndromes, type I and type II, have been described. In polyglandular autoimmune syndrome type II (Schmidt syndrome), which is the most common of the immunoendocrinopathy syndromes in humans, there is primary adrenal insufficiency in combination with autoimmune thyroiditis, insulin-dependent diabetes mellitus, or both; whereas in type I the components are more variable (Eisenbarth et al, 2004).

Polyglandular autoimmune syndromes should be suspected when multiple endocrine gland failure is identified in a dog. Hypoadrenocorticism, hypothyroidism, and diabetes mellitus are the most common disorders involved, and the time between diagnosis of the first and second disorder ranges from 0 to 53 months (median 4 months). Diagnosis and treatment are directed at each disorder as it becomes recognized, because it is not possible to reliably predict or prevent any of these disorders. It is important to recognize that the clinician must consider the effects that one endocrine disorder may have on the tests used to diagnose another disorder (e.g., untreated diabetes mellitus suppresses circulating thyroid hormone concentrations) and the effects that treating one endocrine disorder may have on the treatment of concurrent endocrine disorders (e.g., initiation of thyroid supplementation may dramatically improve insulin sensitivity in a diabetic animal; thyroid supplementation may precipitate an Addisonian crisis in hypoadrenocorticism). Immunosuppressive drug therapy is not indicated in these syndromes and may actually create problems (e.g., insulin resistance or thyroid suppression with high-dose glucocorticoid therapy).

Idiopathic Atrophy

Idiopathic atrophy of the thyroid gland is characterized microscopically by progressive reduction in the size of the thyroid follicles, and replacement of the degenerating follicles with adipose tissue (Fig. 3-7). An inflammatory infiltrate is absent, even in areas in which small follicles or follicular remnants are present (Gosselin et al, 1981b) and tests for lymphocytic thyroiditis are negative. The parathyroid glands are not affected, and variable numbers of parafollicular cells remain.

Idiopathic thyroid atrophy may be either a primary degenerative disorder (Gosselin et al, 1981b), or an end stage of lymphocytic thyroiditis. Evaluation of the morphologic changes involved in lymphocytic thyroiditis in a colony of related Borzoi dogs revealed initial degenerative thyroidal parenchymal changes, which progressed to progressively worsening inflammation, subsequent fibrosis, and thyroid gland destruction, that was histologically similar to idiopathic follicular atrophy (Conaway et al, 1985b). However, residual inflammation was still evident. Idiopathic atrophy can be distinguished from the atrophy associated with decreased TSH secretion (i.e., secondary hypothyroidism), because in secondary degeneration, the follicles are lined by low cuboidal epithelial cells with no indication of degeneration.

In one study, the mean age at the time of diagnosis of hypothyroidism was older in dogs with suspected idiopathic atrophy when compared with dogs diagnosed with lymphocytic thyroiditis; a finding that supports the theory that idiopathic atrophy may be an end stage of lymphocytic thyroiditis (Graham et al, 2001). Results for serum Tg and thyroid hormone autoantibody tests also progress from positive to negative with time in dogs with lymphocytic thyroiditis, suggesting that the inciting antigens for lymphocytic thyroiditis disappear with time. Although idiopathic atrophy may represent an end-stage form of autoimmune lymphocytic thyroiditis, the inability to demonstrate an inflammatory cell infiltrate, even when follicles are still present, suggests that there may be more than one etiology for thyroid atrophy in the dog. Unlike for

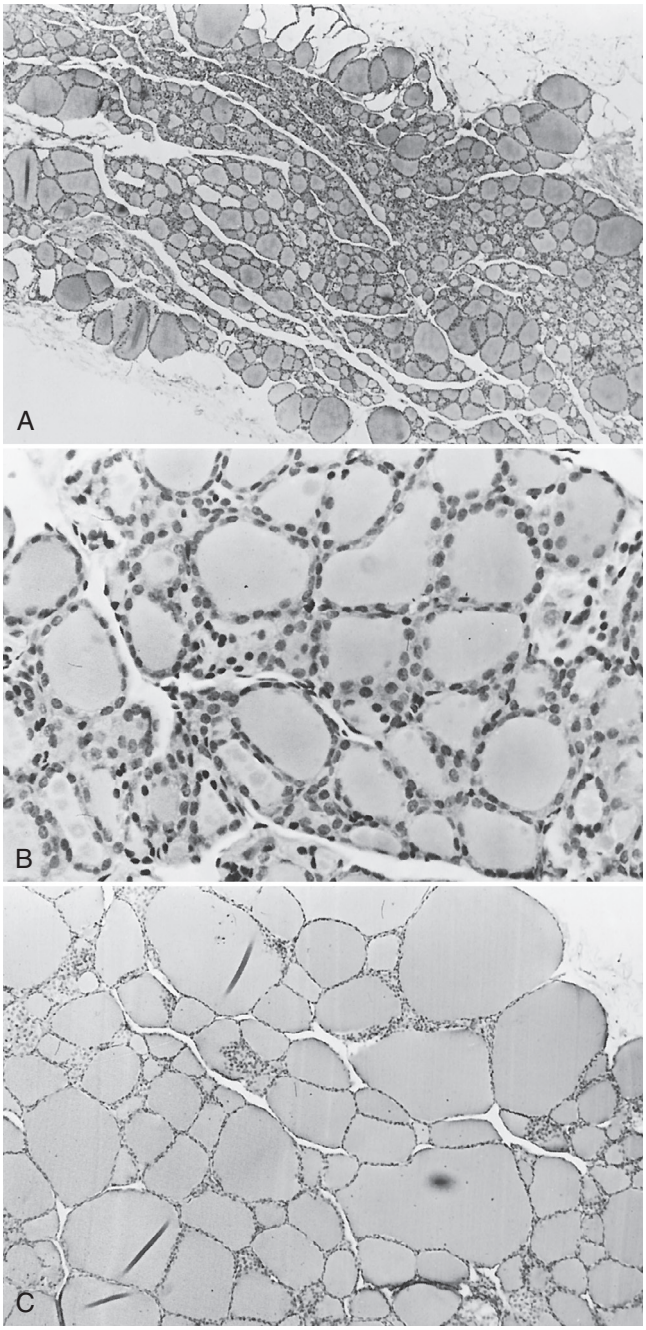

FIGURE 3-7 **A** and **B,** Histologic section of a thyroid gland from a dog with idiopathic atrophy of the thyroid gland and hypothyroidism. Note the small size of the gland (compare with **C**), decrease in follicular size and colloid content, and lack of a cellular infiltration. (**A,** H&E ×40; **B,** H&E ×250.) **C,** Histologic section of a normal thyroid gland at the same magnification as **A.** Note the increased size of the gland, the follicles, and the colloid content compared with the gland in **A.** (**C,** H&E ×40.)

lymphocytic thyroiditis, there are no blood tests currently available that establish the diagnosis of idiopathic atrophy. Hence the diagnosis is one of exclusion; that is, if the tests for lymphocytic thyroiditis are negative, a diagnosis of idiopathic atrophy is made.

Neoplastic Destruction

Clinical signs of hypothyroidism may develop following destruction of more than 80% of the normal thyroid gland by an infiltrative tumor. Tumors may arise from the thyroid gland or may metastasize to or invade the thyroid gland from adjacent tissues. Because most thyroid tumors are unilateral and do not destroy more than 80% of thyroid tissue, hypothyroidism due to thyroid gland destruction is only identified in approximately 10% of thyroid tumors. 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 in dogs with thyroid neoplasia (Benjamin et al, 1996). For more information on canine thyroid tumors, see Chapter 5.

Iodine Deficiency/Excess

The iodine requirement in the adult Beagle is estimated to be 140 μg/day. In one study, decreased concentrations of serum T_4 and serum T_3 did not occur until iodine intake was restricted to 20 to 50 μg/day, and even when thyroid hormone concentrations decreased, clinical signs of hypothyroidism did not develop (Belshaw et al, 1975). Free T_4 (fT_4) concentrations, determined by equilibrium dialysis, remained in the reference range regardless of the amount of dietary iodine restriction. Two histologic changes were observed in the thyroids of dogs with iodine deficiency. In one group, thyroid follicles were small and contained minimal amounts of colloid. Follicular cell hyperplasia was present, and increased uptake and rapid release of radioiodine occurred. In the second group, thyroid follicles were larger and contained more colloid. Increased uptake but slower release of radioiodine occurred. TSH-secreting cells of the pituitary were enlarged and sparsely granulated, suggesting increased activity and secretion of TSH. Iodine deficiency is a rare cause of hypothyroidism in dogs because commercial pet foods usually contain adequate amounts of iodine; however interest in bone and raw food diets has increased in recent years, and such diets may be deficient in iodine (Dillitzer et al, 2011). Clinical hypothyroidism due to iodine deficiency has been reported in working dogs fed all meat diets (Nuttall, 1986).

Excessive iodine intake inhibits iodide uptake and organification and thyroid hormone secretion by thyroid follicular cells, resulting in a small but significant compensatory increase in circulating TSH concentrations (Wolff-Chaikoff effect) (Roti and Vagenakis, 2013). Ingestion of diets containing an excessive amount of iodine caused impairment of thyroid function and hypothyroidism in puppies fed a high iodine diet for 45 days (Castillo et al, 2001). In humans, high iodine diets can result in transient or subclinical hypothyroidism (Roti and Vagenakis, 2013).

Miscellaneous Causes

Acquired primary hypothyroidism may rarely result from ingestion of goitrogens, administration of anti-thyroid medications (e.g., propylthiouracil and methimazole), and chronic use of high doses of potentiated sulfonamides. A palpable goiter may develop in dogs treated chronically with potentiated sulfonamides (Seelig et al, 2008; Taeymans and O'Marra, 2009). Surgical removal of the thyroid gland for treatment of thyroid neoplasia may also result in hypothyroidism, but because accessory thyroid tissue may be found from the base of the tongue to the base of the heart in dogs, hypothyroidism does not always occur after surgery. In a report of 15 dogs undergoing bilateral thyroidectomy for treatment of thyroid tumors, approximately 50% of dogs required long-term thyroid hormone supplementation (Tuohy et al, 2012). Use of high dose radioactive iodine (iodine-131 [^{131}I]) for treatment of thyroid neoplasia also results in hypothyroidism (Turrel et al, 2006). Other rare causes of primary hypothyroidism include leishmaniasis and congenital hypothyroidism (see Congenital Hypothyroidism).

Summary

Although there are several potential causes of canine hypothyroidism (see Box 3-1), lymphocytic thyroiditis and idiopathic atrophy account for most of the clinical cases of primary hypothyroidism diagnosed in dogs. Both cause progressive loss of thyroid function as a result of either immune-mediated destruction (lymphocytic thyroiditis) or degeneration (idiopathic atrophy) of the thyroid. The result is a deficiency in thyroid hormone synthesis and secretion and development of clinical signs of hypothyroidism.

Secondary Hypothyroidism

Secondary hypothyroidism results from failure of pituitary thyrotrophs to develop due to pituitary malformation or acquired dysfunction of the pituitary thyrotrophs causing impaired secretion of TSH. Deficiency of TSH leads to decreased thyroid hormone synthesis and secretion and thyroid gland hypoplasia. Histologically, the thyroid gland has small hypoplastic follicles that lack or contain only scant colloid and apical resorption follicles (Gal et al, 2012).

Potential causes of secondary hypothyroidism include congenital malformations of the pituitary gland, pituitary destruction, and pituitary suppression. In the dog, secondary hypothyroidism caused by naturally acquired defects in pituitary thyrotroph function or destruction of pituitary thyrotrophs (e.g., pituitary neoplasia) is uncommon. In contrast, suppression of pituitary thyrotroph function by hormones or drugs (e.g., glucocorticoids, spontaneous hyperadrenocorticism) is quite common. Serum TSH concentrations should be decreased or undetectable with secondary hypothyroidism. Unfortunately, current assays used to measure endogenous TSH in dogs are insensitive and unable to differentiate between decreased and normal concentrations (see Baseline Serum Thyrotropin Concentration), making confirmation of secondary hypothyroidism difficult; although one would expect the serum TSH concentration to be undetectable in a dog with secondary hypothyroidism, such a finding does not confirm the diagnosis.

Pituitary Malformation

Congenital abnormalities involving the pituitary gland have been recognized in many breeds but are reported most commonly in German Shepherd dogs. In German Shepherd dogs, pituitary dwarfism is caused by a simple autosomal recessive mutation of the LHX3 gene, which leads to combined pituitary hormone deficiency. Combined pituitary hormone deficiency is characterized by deficiency of growth hormone (GH), TSH, prolactin, and gonadotrophins. Because the various cell types of the adenohypophysis arise from the progenitor cells in a distinct order with corticotrophs differentiating first, secretion of adrenocorticotrophic hormone (ACTH) is unaffected. Pituitary cysts may be detected at a young age and gradually increase in size with time (Eigenmann, 1981; Hamann et al, 1999; Kooistra et al, 2000a). Because of the involvement of other anterior pituitary hormones—most notably GH, congenital defects affecting the anterior pituitary usually result in the development of proportionate dwarfism (see Chapter 2).

Pituitary Destruction

Although uncommon, pituitary tumors may cause secondary hypothyroidism, following destruction of thyrotrophs by an expanding, space-occupying mass. Other endocrinopathies, such as hypocortisolism (secondary adrenal insufficiency), diabetes insipidus, and reproductive dysfunction, may occur when pituitary dysfunction is due to neoplasia. The most common pituitary tumor affecting thyroid gland function in the dog is a functional corticotrophic tumor causing pituitary-dependent hyperadrenocorticism. In this case, secondary hypothyroidism may result from suppression of thyrotroph function and suppressed TSH secretion, rather than from destruction of thyrotrophs by the tumor.

Pituitary Thyrotroph Suppression

The most common cause of secondary hypothyroidism is believed to be suppression of TSH secretion due to concurrent illness, drugs, hormones, or malnutrition (see Factors Affecting Thyroid Gland Function Tests). Although endogenous and exogenous glucocorticoids are believed to suppress pituitary TSH secretion, in a study of 47 dogs with pituitary dependent hyperadrenocorticism, basal and TRH stimulated TSH concentrations did not differ from those of control dogs (Meij et al, 1997).

Miscellaneous Causes

In humans, secondary hypothyroidism may also develop following production of a defective TSH molecule or impaired interaction between TSH and the TSH receptor on follicular epithelial cells. These causes have not yet been reported in the dog. Secondary hypothyroidism can also result from radiation therapy or hypophysectomy for ACTH-secreting pituitary tumors (Lantz et al, 1988; Meij et al, 1998).

Tertiary Hypothyroidism

Tertiary hypothyroidism is defined as a deficiency in the secretion of TRH by peptidergic neurons in the supraoptic and paraventricular nuclei of the hypothalamus. Lack of TRH secretion causes deficiency of TSH secretion and follicular atrophy of the thyroid gland. In humans, impaired secretion of TRH by the hypothalamus may result from a congenital defect, acquired destruction secondary to a mass lesion or hemorrhage, a defective TRH molecule, or defective TRH-thyrotroph receptor interaction (Sunthornthepvarakul, 1994; Persani, 2013). Neurologic signs and additional pituitary dysfunction may be present, depending on the cause. Diagnosis of tertiary hypothyroidism is based on measurement of a low TSH concentration that increases after administration of TRH. Tertiary hypothyroidism is assumed to be rare in dogs. Unfortunately the poor sensitivity of the current canine TSH assay would make confirmation of this diagnosis difficult. Tertiary hypothyroidism was suspected in a 9-year-old Labrador Retriever with a highly infiltrative pituitary adenoma that invaded the hypothalamus (Shiel et al, 2007b).

Congenital Hypothyroidism

Congenital hypothyroidism is rare in dogs. Unfortunately, congenital hypothyroidism frequently results in early puppy death, and the cause of death is rarely documented. A defect anywhere in the hypothalamic-pituitary-thyroid axis or of the thyroid hormone receptor can result in congenital hypothyroidism (see Box 3-1). Congenital hypothyroidism with goiter (CHG) develops if the hypothalamic-pituitary-thyroid gland axis is intact; TSH binds appropriately with its receptor, but there is an intra-thyroidal defect in thyroid hormone synthesis (dyshormonogenesis). Increased serum TSH concentrations result in development of thyroid hyperplasia and a goiter. If the hypothalamic-pituitary-thyroid gland axis is not intact (e.g., as occurs with pituitary TSH deficiency), a goiter will not develop.

Documented causes of congenital primary hypothyroidism in the dog include dietary iodine deficiency, dyshormonogenesis (i.e., iodine organification defect), and thyroid dysgenesis (Chastain et al, 1983; Greco et al, 1985). CHG caused by a nonsense mutation in the TPO gene has been recognized in Toy Fox Terriers and Rat Terriers

(Fyfe et al, 2003; Pettigrew et al, 2007). In a study of Rat Terrier puppies with congenital goiter and a mutation in the TPO gene, central nervous system (CNS) hypomyelination was demonstrated in affected puppies (Pettigrew et al, 2007). The hypomyelination was regionally distributed and most severe in the corpus callosum. Myelin reduction was paralleled by axon reduction, suggesting that hypomyelination was due to reduced axonal formation. Different mutations of the TPO gene cause CHG in Tenterfield Terriers and Spanish Water dogs. (Dodgson et al, 2012; Fyfe 2013). Both defects are autosomal-recessive traits.

Secondary hypothyroidism resulting from an apparent deficiency of TSH was reported in a family of Giant Schnauzers (Greco et al, 1991) and a Boxer dog (Mooney and Anderson, 1993). Pedigree analysis suggested an autosomal recessive mode of inheritance in the family of Giant Schnauzers. Pituitary dwarfs with combined anterior pituitary hormone deficiencies usually lack TSH in addition to GH and prolactin (Hamann et al, 1999; Kooistra et al, 2000a; see Chapter 2). Lack of TSH may contribute to abnormal body maturation and growth in pituitary dwarfs.

CLINICAL FEATURES OF HYPOTHYROIDISM IN THE ADULT DOG

Signalment

Reports regarding breed incidence and genetics of canine hypothyroidism should always be examined critically, because confirming a definitive diagnosis of hypothyroidism is challenging, and breed popularity and geographic variation in breed distribution may influence the perception of which breeds are predisposed to the disease. Hypothyroidism is typically a disease of middle-aged to older dogs. Golden Retrievers and Doberman Pinschers are the breeds most commonly reported to be at increased risk for hypothyroidism, although many breeds are represented in published studies (Table 3-3). Based upon measurement of serum Tg and thyroid hormone autoantibodies, many breeds have been reported to have an increased incidence of lymphocytic thyroiditis (see Table 3-2), and this is likely due to a genetic predisposition to thyroiditis (Nachreiner et al, 2002; Kennedy et al, 2006a; 2006b). Thyroiditis is usually documented at an earlier age (2 to 4 years) than development of clinical signs (4 to 6 years), which fits with the hypothesis that thyroiditis may progress to complete thyroid failure over time. Of 143,800 serum samples from dogs with thyroid disease, the age distribution profile peaked at 2 years for dogs with subclinical thyroiditis, 4 years for dogs with anti-Tg positive hypothyroidism, and 5 to 8 years for dogs with anti-Tg negative hypothyroidism (Graham et al, 2007; Fig. 3-8). Age of onset of symptomatic hypothyroidism may vary between breeds, presumably as a result of the underlying etiology and rate of progression of thyroid pathology. The majority of studies do not suggest a consistent association of hypothyroidism with sex or neuter status.

TABLE 3-3 **BREED DISTRIBUTION OF 154 DOGS WITH PRIMARY HYPOTHYROIDISM***

BREED	NUMBER (%) OF DOGS
Golden Retriever	26 (17%)
Doberman Pinscher	21 (14%)
Labrador Retriever	7 (5%)
Mixed breed	24 (16%)
Other breeds	76 (49%)

*Based on four published and one unpublished study (Peterson et al, 1997; Scott-Moncrieff et al, 1998; Ramsey et al, 1997; Panciera, 1994).

Clinical Signs

A deficiency in circulating thyroid hormone affects the metabolic function of almost all organ systems. Destruction of the thyroid gland is typically slowly progressive, and the onset of clinical signs may be gradual and initially subtle. Clinical signs are quite variable and may differ among breeds. For example, different breeds have markedly different hair cycles and follicular morphology, which may influence the clinical and histologic features of the disease (Credille et al, 2001). Because of the slow progression of the disease, owners may fail to recognize the clinical signs until they become severe. Only after the dog returns to normal following initiation of thyroid hormone supplementation does the owner recognize that the problem existed for much longer than initially believed.

In the adult dog, the most consistent clinical signs of hypothyroidism are those due to decreased cellular metabolism and dermatologic manifestations (Box 3-2 and Table 3-4). Additional clinical signs may affect the cardiovascular system, neuromuscular system, gastrointestinal system, and reproductive system.

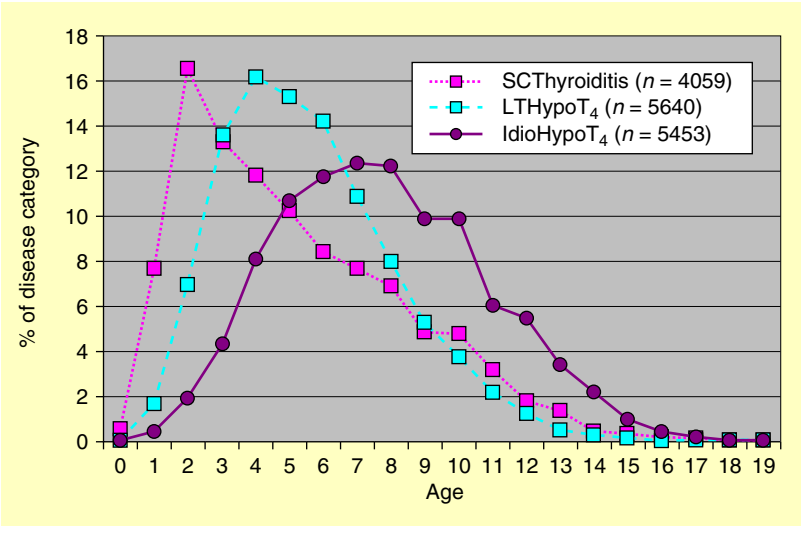

FIGURE 3-8 Age distribution profiles for different categories of thyroid disease and dysfunction based on findings in 143,800 samples submitted for the investigation of thyroid disease in which an age was provided. IdioHypoT_4, thyroglobulin autoantibody–negative hypothyroidism; LTHypoT_4, thyroglobulin autoantibody–positive hypothyroidism; SC Thyroiditis, subclinical thyroglobulin autoantibody–positive thyroiditis. (From Graham PA, et al.: Etiopathologic findings of canine hypothyroidism, *Vet Clin North Am Small Anim Pract* 37[4]: 620, 2007.)

General Metabolic Signs

Most adult dogs with acquired hypothyroidism have clinical signs that result from a generalized decrease in metabolic rate. Energy expenditure, as measured by indirect calorimetry, is approximately 15% lower in hypothyroid dogs, compared with healthy dogs, and energy expenditure returns to normal after initiating levothyroxine (L-thyroxine; L-T_4) sodium treatment (Greco et al, 1998). Clinical signs due to the decreased metabolic rate include mental dullness, lethargy, exercise intolerance or unwillingness to exercise, cold intolerance, and a propensity to gain weight without a corresponding increase in appetite or food intake. Obesity occurs in approximately 40% of hypothyroid dogs, but it is important to remember that the most common cause of obesity is overnutrition rather than hypothyroidism.

Metabolic signs are usually gradual in onset and initially very subtle but become more obvious with longer duration of hypothyroidism. Sometimes these clinical signs are missed on the history and physical examination and not recognized until the dog shows improvement in activity within 7 to 10 days of initiating thyroid hormone supplementation.

BOX 3-2 Clinical Manifestations of Hypothyroidism in the Adult Dog

Metabolic
Lethargy*
Mental dullness
Inactivity*
Weight gain*
Cold intolerance

Dermatologic
Endocrine alopecia*
- Symmetric or asymmetrical
- Areas of friction and pressure
- "Rat tail"

Dry, brittle hair coat
Hyperpigmentation
Seborrhea
Pyoderma
Otitis externa
Myxedema

Reproductive
Prolonged parturition
Periparturient mortality
Low birth weight puppies
Female infertility
Inappropriate galactorrhea or gynecomastia

Neuromuscular
Polyneuropathy/myopathy
Vestibular signs (central or peripheral)
Facial/trigeminal nerve paralysis
Seizures
Disorientation/circling
Myxedema coma
Laryngeal paralysis (?)

Ocular
Corneal lipid deposits

Cardiovascular
Bradycardia
Cardiac arrhythmias

Gastrointestinal
Esophageal hypomotility (?)
Diarrhea
Constipation

Hematologic
Anemia*
Hyperlipidemia*

*Common.
?indicates that a causal relationship is not proven.

TABLE 3-4 INCIDENCE OF CLINICAL SIGNS IN 162 ADULT DOGS WITH HYPOTHYROIDISM

CLINICAL SIGN	PERCENT OF DOGS
Dermatologic	88
Obesity	49
Lethargy	48
Weakness	12
Neurologic	
Facial nerve paralysis	4
Peripheral vestibular	3
Polyneuropathy	2
Reproductive	< 2
Cardiovascular (bradycardia)	10

Adapted from Panciera DL: Conditions associated with canine hypothyroidism, *Vet Clin North Am* 31:935, 2001.

Dermatologic Signs

Alterations in the skin and hair coat occur in 60% to 80% of hypothyroid dogs and are the most commonly observed abnormalities in dogs with hypothyroidism. Dermatologic changes can be quite varied and dependent on the breed of dog and severity and chronicity of the disease. The classic cutaneous sign of hypothyroidism is bilaterally symmetric, nonpruritic truncal alopecia.

Thyroid hormone is necessary to initiate and maintain the anagen, or growing, phase of the hair cycle (Credille et al, 2001). With thyroid hormone deficiency, hair follicles prematurely enter the telogen phase of the hair cycle. Excessive shedding with lack of hair regrowth leads to alopecia. Decreased concentrations of cutaneous fatty acids and prostaglandin E_2 in canine hypothyroidism may lead to sebaceous gland atrophy, hyperkeratosis, scale formation, seborrhea sicca, and a dry and lusterless hair coat (Campbell and Davis, 1990). The hair coat may appear faded in color, and subtle changes in hair coat quality may initially be appreciated by the owner but not the veterinarian. In the early stages of hypothyroidism, hair loss is often asymmetric and develops over areas of excessive wear or pressure, such as the caudal thighs, ventral thorax, tail base, and tail (i.e., development of a "rat tail;" Fig. 3-9). As hypothyroidism becomes more severe or chronic, alopecia becomes more symmetric and truncal, eventually developing into the classic cutaneous finding of bilaterally symmetric, nonpruritic truncal alopecia that tends to spare the head and distal extremities (Fig. 3-10). Although nonpruritic endocrine alopecia is not pathognomonic for hypothyroidism, when it is present in a dog with other signs of decreased metabolic rate and no polyuria or polydipsia, hypothyroidism is the most likely diagnosis.

There are breed variations in the dermatologic effects of hypothyroidism presumably because of differences in the hair cycle and follicular morphology. In some breeds, failure to shed leads to hypertrichosis, and in other breeds primary hairs are lost giving the hair coat a "wooly" appearance. In some dogs there is a loss of the undercoat, and the remaining primary hairs give the coat a coarse appearance. In some breeds the hair shafts within telogen follicles may be retained for long periods (months to years) without falling out. In a study evaluating the effect of induced hypothyroidism on the skin of Beagle dogs, none of the untreated hypothyroid dogs had a discernible alopecia after 10 months of observation despite the hypothyroid dogs having one-third fewer hair shafts than healthy Beagles (Credille et al, 2001). The most common finding was a failure of the hypothyroid dogs to regrow their hair after clipping. Retaining telogen hairs maintains the pelage, which explains why truncal alopecia does not usually develop in hypothyroid Beagle dogs.

Hyperpigmentation is common in hypothyroidism, especially in regions of alopecia and areas of wear, such as the axilla and inguinal regions (Fig. 3-11). In severe cases of hypothyroidism, the

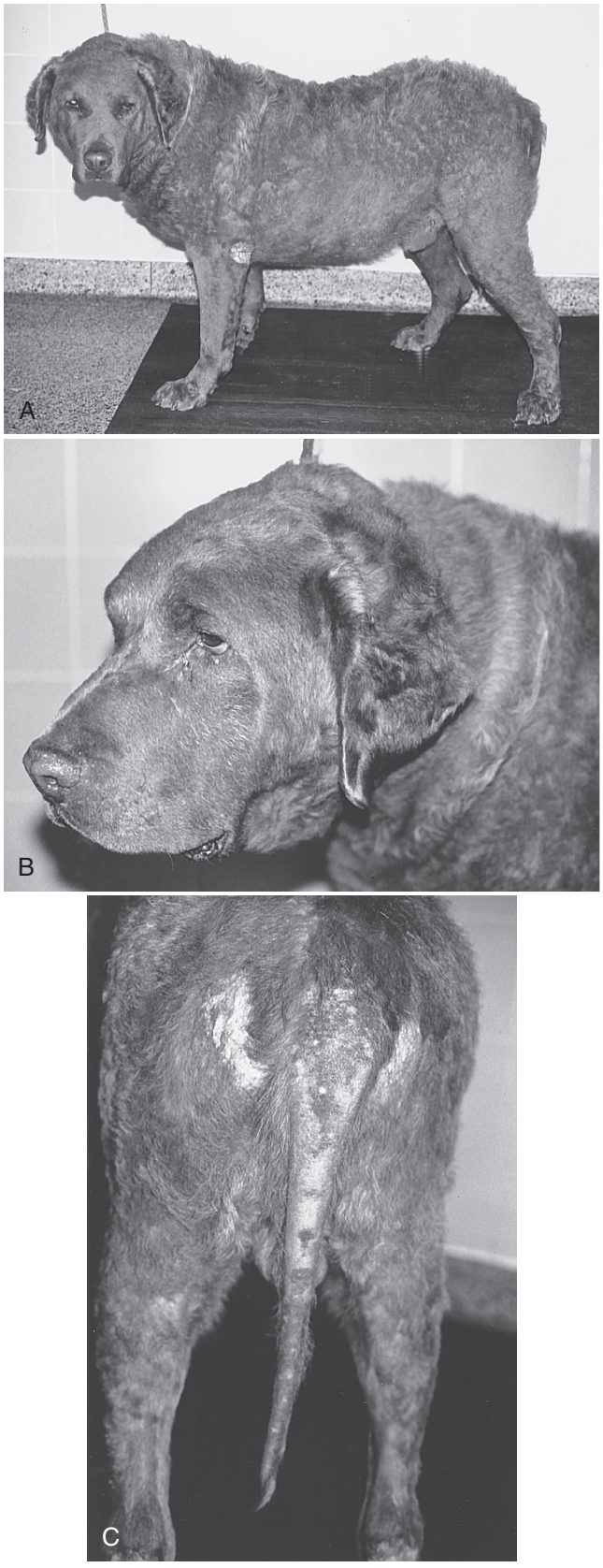

FIGURE 3-9 An 8-year-old male Chesapeake Bay Retriever with hypothyroidism. Note the poor hair coat, lethargic appearance, myxedema of the face with drooping of the eyelids **(A** and **B),** and "rat tail" **(C).**

hygroscopic glycosaminoglycan, hyaluronic acid may accumulate in the dermis, bind water, and result in increased thickness and non-pitting edema of the skin, referred to as *myxedema,* or *cutaneous mucinosis* (Doliger et al, 1995). Myxedema predominantly affects the forehead, eyelids, and lips, and it contributes to the development of the classic "tragic facial expression" described in hypothyroid dogs (see Fig. 3-9). A rare complication of myxedema is cutaneous mucinous vesiculation (Miller and Buerger, 1990).

Thyroid hormone is believed to play a role in the normal immune response. Depletion of thyroid hormone suppresses humoral immune reactions, impairs T cell function, and reduces the number of circulating lymphocytes. Dogs with hypothyroidism may develop superficial bacterial infections (folliculitis, superficial spreading pyoderma, impetigo) characterized by papules, pustules, epidermal collarettes, and/or focal areas of alopecia. Bacterial infections are usually caused by *Staphylococcus spp.* and are variably pruritic. Hypothyroidism may also predispose to adult onset demodicosis and chronic otitis externa (Duclos et al, 1994).

The skin changes associated with hypothyroidism are generally nonpruritic; however secondary infection, seborrhea, or concurrent pruritic diseases (e.g., atopy or flea bite hypersensitivity) may cause pruritus. The presence of pruritic skin disease therefore does not rule out underlying hypothyroidism.

Neurologic Signs

Both the peripheral nervous system and CNS may be affected by hypothyroidism (Indrieri et al, 1987; Bichsel et al, 1988; Jaggy et al, 1994). Diffuse peripheral neuropathy characterized by exercise intolerance, weakness, ataxia, quadriparesis or paralysis, deficits of conscious proprioception, and decreased spinal reflexes has been reported to occur in dogs with hypothyroidism. Single or multifocal cranial nerve dysfunction with predisposition for the facial, vestibulocochlear, and trigeminal nerves has also been reported. Neurologic dysfunction may be multifocal, acute or chronic, and static or progressive. Other physical examination findings consistent with hypothyroidism may be absent. Hypothyroid dogs with vestibular deficits may have abnormal brainstem auditory evoked responses and electromyographic abnormalities identified in the appendicular muscles. Proposed mechanisms include nerve entrapment from accumulation of mucinous deposits, demyelination due to disrupted Schwann cell metabolism, vascular nerve damage due to alterations in the blood-nerve barrier, and disturbances in axonal cell transport. Although there are numerous reports of the association between hypothyroidism and peripheral nerve dysfunction, the cause and effect relationship has been questioned, because in an experimental model of canine hypothyroidism, it was not possible to reproduce a peripheral neuropathy (Rossmeisl, 2010). It has been proposed that other factors such as immune dysregulation may play a role in the pathogenesis of the peripheral neurologic abnormalities. Because immune-mediated thyroiditis is present in as many as 50% of hypothyroid dogs, it is conceivable that immune-mediated mechanisms contribute to the pathogenesis of the neuromuscular changes observed in hypothyroid dogs. Clinical signs of peripheral neuropathy resolve with L-T_4 sodium supplementation; however this finding must be interpreted carefully because peripheral vestibular disease, facial nerve paralysis, and polyradiculoneuritis of unknown etiology may also improve or resolve over time.

A subclinical myopathy has been well-documented in hypothyroid dogs and also occurs in experimental models of canine hypothyroidism (Delauche, 1998; Rossmeisl et al, 2009). Hypothyroid myopathy is accompanied by increased plasma creatine kinase, aspartate aminotransferase, and lactate dehydrogenase activities.

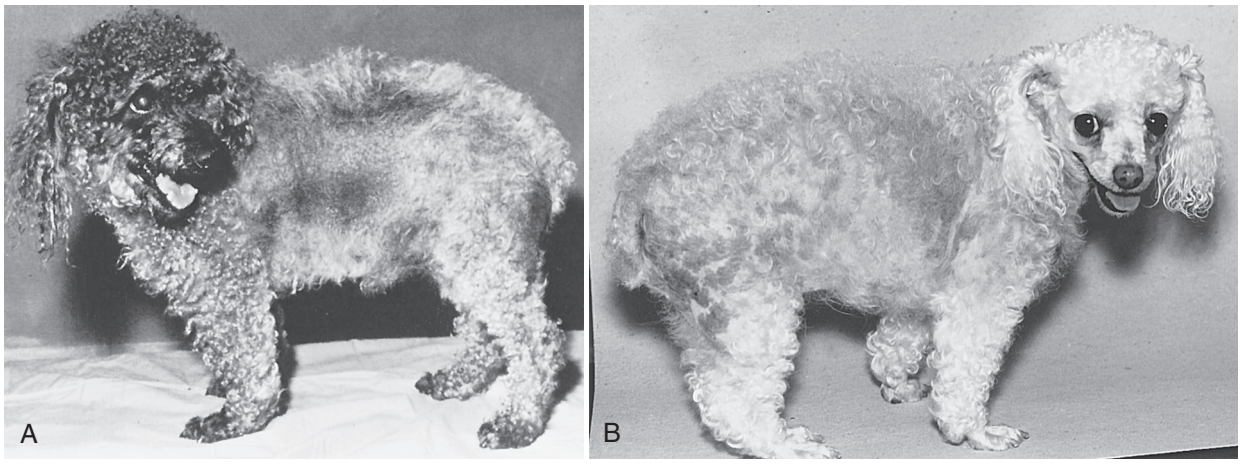

FIGURE 3-10 A 5-year-old male Miniature Poodle **(A)** and a 6-year-old spayed Miniature Poodle **(B)** with hypothyroidism and endocrine alopecia. Note the truncal alopecia and hyperpigmentation, which have spared the head and extremities, in both dogs.

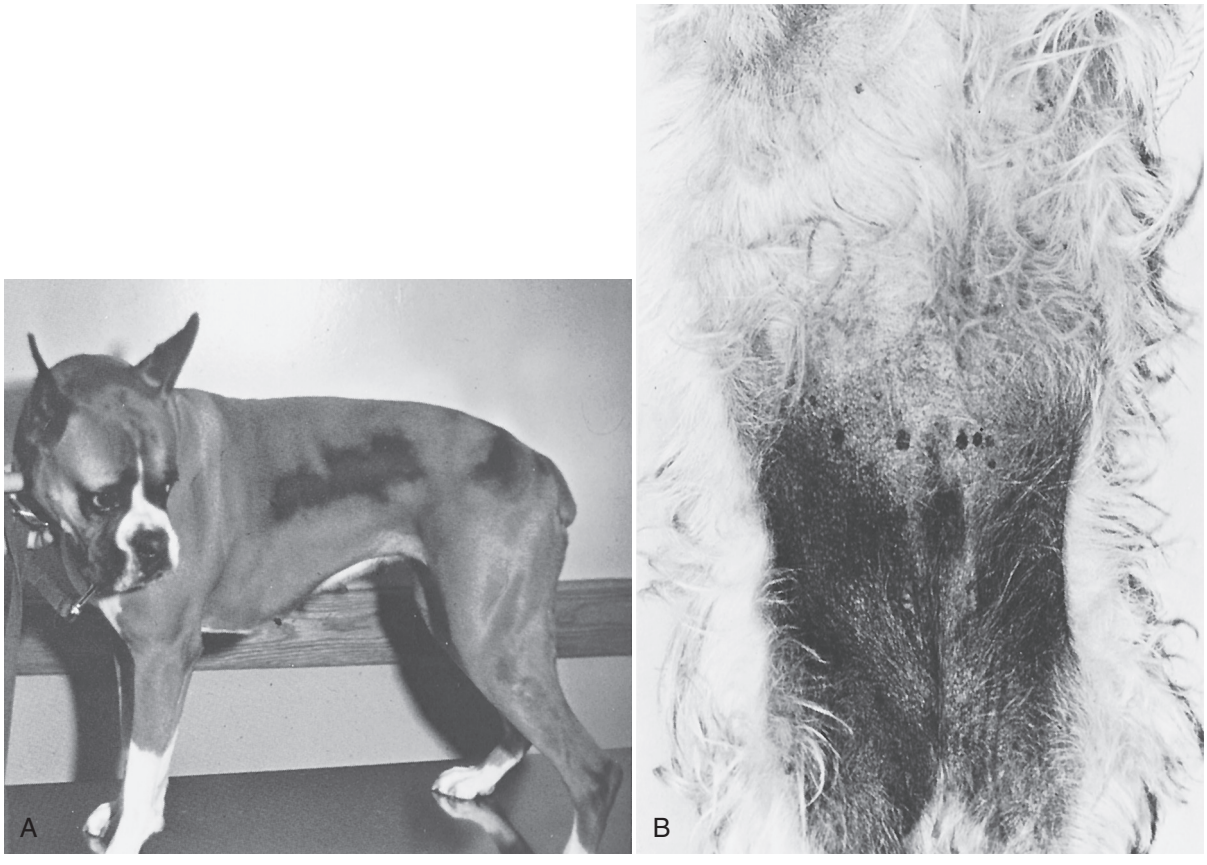

FIGURE 3-11 **A,** Truncal hyperpigmentation in a 4-year-old female spayed Boxer with hypothyroidism. **B,** Severe hyperpigmentation involving the inguinal region in a 6-year-old spayed mixed-breed dog with hypothyroidism.

Histopathologic abnormalities include nemaline rod inclusions, predominance of type I myofibers, decrease in mean type II fiber area, subsarcolemmal accumulations of abnormal mitochondria, and myofiber degeneration (Delauche, 1998; Rossmeisl et al, 2009). Substantial depletion of skeletal muscle free carnitine has also been documented in affected dogs. Although an obvious clinical myopathy is not recognized associated with these changes, the abnormalities may contribute to nonspecific clinical signs, such as lethargy and exercise intolerance in canine hypothyroidism.

Central vestibular dysfunction has also been reported in association with hypothyroidism. In 10 dogs with central vestibular dysfunction associated with hypothyroidism, lesions consistent with an infarct were identified in three dogs, but cranial imaging studies were normal in the other five dogs that were imaged (Higgins et al, 2006). Albuminocytologic dissociation was identified in five of six cerebrospinal fluid (CSF) analyses and most dogs had hypercholesterolemia or hypertriglyceridemia. Clinical signs completely resolved after 4 weeks of supplementation with L-thyroxine, apart

from residual head tilt in one dog. Cerebral dysfunction manifested by seizures, disorientation, and circling may also rarely occur in canine hypothyroidism, although there is little evidence to suggest that hypothyroidism is a common cause of seizure disorders in dogs. In a series of 113 dogs with seizure disorders, 38% of dogs with idiopathic epilepsy had thyroid hormone profiles consistent with nonthyroidal illness, but fewer than 3% of dogs were definitively diagnosed with hypothyroidism (von Klopmann et al, 2006). In a retrospective study of 96 dogs with metabolic and toxic causes of seizures, hypothyroidism was the suspected cause in only three dogs (Brauer et al, 2011). An incorrect diagnosis of hypothyroidism may be made in dogs already being treated for idiopathic epilepsy because anticonvulsant therapy may influence thyroid hormone testing (see Anticonvulsants). The reason for CNS dysfunction in canine hypothyroidism is poorly understood and is likely multifactorial. Atherosclerosis, hyperlipidemia, vascular encephalopathy, and functional metabolic derangements of neuronal or glial cell populations due to hypothyroidism may all play a role. Dogs with atherosclerosis, which is likely due to hypercholesterolemia, are over 50 times more likely to have hypothyroidism than dogs without atherosclerosis (Hess et al, 2003). Severe hyperlipidemia has been reported to cause neurologic dysfunction in hypothyroid dogs, and it has been proposed that Labrador Retrievers may be predisposed to this manifestation of hypothyroidism (Vitale et al, 2007). Dogs with experimentally induced hypothyroidism have disruption of the blood brain barrier as evidenced by albuminocytologic dissociation and increased CSF concentrations of plasma vascular endothelial growth factor (VEGF) (Pancotto et al, 2010). Two of nine dogs with induced hypothyroidism in this study developed CNS signs and evidence of cerebrovascular disease during the 18-month study. Myxedema coma or a pituitary tumor causing secondary hypothyroidism may also rarely cause CNS signs.

Other Neurologic Disorders

Laryngeal paralysis and megaesophagus may both occur in association with hypothyroidism; however, a causal relationship has not been established, and treatment of hypothyroidism does not consistently result in improvement of clinical signs of either disorder (MacPhail and Monnet, 2001; Gaynor et al, 1997). Myasthenia gravis has been identified in dogs with hypothyroidism (Dewey et al, 1995) and is a well-recognized cause of acquired megaesophagus in the dog. Concurrent hypothyroidism may exacerbate clinical signs of myasthenia gravis, such as muscle weakness and megaesophagus. In human beings, there is a link between autoimmune thyroiditis and acquired myasthenia gravis, and myasthenia gravis is a recognized component of polyglandular autoimmune syndrome type II. Presumably a common abnormality in immune function allows development of autoimmune attack on both the thyroid gland and acetylcholine receptors. Myasthenia gravis was documented in only 1 of 162 dogs with hypothyroidism reviewed by Panciera (2001), implying that hypothyroidism is rarely associated with myasthenia gravis. A causal relation between hypothyroidism and myasthenia gravis remains to be established.

Myxedema Coma

Myxedema coma is an extremely rare syndrome of severe hypothyroidism characterized by profound weakness, hypothermia, bradycardia, and a diminished level of consciousness, which can rapidly progress to stupor and then coma (Chastain et al, 1982; Kelly and Hill, 1984; Henik and Dixon, 2000; Atkinson and Aubert, 2004). Clinical signs in addition to the more typical clinical signs of hypothyroidism, include mental dullness, depression, unresponsiveness, and weakness. Physical findings include profound weakness; hypothermia; non-pitting edema of the skin, face, and jowls (myxedema); bradycardia; hypotension; and hypoventilation. Myxedema results from the accumulation of acid and neutral mucopolysaccharides and hyaluronic acid in the dermis, which bind water and result in increased thickness of the skin. Laboratory findings may include hypoxemia, hypercarbia, hyponatremia, and hypoglycemia in addition to the typical findings of hyperlipidemia, hypercholesterolemia, and nonregenerative anemia. Serum thyroid hormone concentrations are usually extremely low or undetectable; serum TSH concentration is variable but typically increased. There is commonly a precipitating event, such as hypothermia or infection. Mortality is high, likely because of late recognition and concurrent illness.

Alterations in Behavior

A relationship between thyroid function and behavioral changes is well established in humans. Neurologic and psychiatric symptoms (e.g., slowing of thought and speech, memory loss, poor concentration, anxiety, depression, and psychosis) may occur in hypothyroid adults (Schuff et al, 2013). These changes are proposed to result from alterations in expression of neurotransmitters, neuromodulators, and growth factors associated with thyroid dysfunction. The influence of thyroid dysfunction on serotonergic receptors has received particular attention because of the role of serotonin in depressive illness. It has been postulated that canine hypothyroidism may lead to aberrant behavior, including aggression, submissiveness, shyness, fearfulness, excitability, passivity, irritability, moodiness, and unstable temperament (Dodds, 1995). To date, most reports on alterations in behavior and hypothyroidism have been anecdotal and based on apparent improvement in behavior following initiation of thyroid hormone treatment. Proposed mechanisms for hypothyroidism associated aggression include a lowered threshold for aggression due to lethargy and irritability and disturbances in serotonergic or noradrenergic pathways. Two small prospective studies in dogs failed to demonstrate an association between hypothyroidism and behavioral problems, such as aggression (Carter et al, 2009; Radosta et al, 2012); however further larger prospective studies would be required to prove the absence of such a relationship. The benefits, if any, of using thyroid hormone to treat behavioral disorders remain to be clarified.

Reproductive Signs

Historically, hypothyroidism was believed to cause lack of libido, testicular atrophy, and oligospermia or azoospermia in male dogs. However, work by C. Johnson, et al. (1999) in Beagles failed to document any deleterious effect of experimentally induced hypothyroidism on any aspect of male reproductive function. Although other classic clinical signs and clinicopathologic abnormalities of hypothyroidism developed in the hypothyroid dogs studied, libido, testicular size, and the total sperm count per ejaculate remained normal. These findings suggest that hypothyroidism is an uncommon cause of reproductive dysfunction in male dogs; however, the duration of the study (2 years) may have been too short to allow reproductive abnormalities to develop, or the induced model used in the study may not have been representative of naturally occurring hypothyroidism, which commonly is due to lymphocytic thyroiditis. It is possible that lymphocytic thyroiditis and lymphocytic orchitis are comorbid conditions, which could account for the clinical observation of reproductive dysfunction in male hypothyroid dogs. Hypothyroidism appears to be an uncommon cause of infertility in male dogs. However, it should be considered when other causes for infertility cannot be identified, especially if decreased libido is part of the clinical picture.

Although thyroid hormone is believed to be necessary for normal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, an association between hypothyroidism and infertility in the female dog has been poorly documented in the veterinary literature. Two prospective studies failed to identify an association between poor reproductive performance and hypothyroidism in pure bred dogs (Beale et al, 1992b; Segalini et al, 2009). In a prospective study of female dogs with experimentally induced hypothyroidism, short-term hypothyroidism (median 19 weeks) was associated with prolonged parturition and reduced periparturient puppy survival (Panciera et al, 2007). In the same study, dogs with more chronic hypothyroidism (56 weeks) had higher periparturient mortality and lower puppy birth weights than control dogs. Fertility was decreased in the hypothyroid dogs compared to control dogs, but the difference was not statistically significant, likely due to the small numbers of dogs in each group (Panciera et al, 2012). Hypothyroidism has also been implicated in causing prolonged interestrus intervals and failure to cycle in the female dog. However this was not documented in the studies by Panciera, et al (2007, 2012). Additional reproductive abnormalities that have been reported in the veterinary literature include weak or silent estrus cycles, prolonged estrual bleeding, and inappropriate galactorrhea and gynecomastia. The latter is believed to develop following a thyroid hormone deficiency–induced increase in TRH secretion, which in turn stimulates prolactin secretion (Chastain and Schmidt, 1980; Cortese et al, 1997). Increased prolactin concentrations were documented in dogs with experimentally induced hypothyroidism 39 weeks after induction of hypothyroidism, but this was not associated with abnormalities in progesterone concentrations or ovulation (Kolster et al, 2010). Evaluation of thyroid gland function is recommended as part of the evaluation of female dogs for infertility, fetal resorption, or periparturient mortality, although it appears that hypothyroidism is an uncommon cause of reproductive failure.

Cardiovascular Signs

Clinical signs related to dysfunction of the cardiovascular system are uncommon in canine hypothyroidism. Abnormalities identified on physical examination may include bradycardia and a weak apex beat. Atrial fibrillation has been suggested to be associated with hypothyroidism in dogs (Gerritsen et al, 1996), but this appears to be rare based on findings in other studies (Panciera, 2001). More commonly, functional abnormalities are identified on electrocardiography or echocardiography in dogs exhibiting the more common clinical signs of hypothyroidism. Electrocardiographic abnormalities include sinus bradycardia, decreased amplitude of the P and R waves, inversion of the T waves, and first-degree and second-degree atrioventricular block (Panciera, 1994; 2001). Echocardiographic abnormalities include increased left ventricular end systolic diameter, prolonged preejection period, and decreases in left ventricular posterior wall thickness during systole, percentage change in left ventricular posterior wall from diastole to systole, interventricular wall thickness during systole and diastole, aortic diameter, velocity of circumferential fiber shortening, and fractional shortening (Panciera, 1994; 2001). Many of the hemodynamic effects of hypothyroidism appear to be attributable to direct effects of hypothyroidism on the myocardium, which include decreased cardiac muscle myosin adenosine triphosphatase (ATPase) activity, decreased sarcoplasmic reticulum calcium-ATPase activity, decreased calcium channel activity, decreased sodium-potassium ATPase activity, and reduced β-adrenergic receptors in the myocardium (Bilezikian and Loeb, 1983; Haber and Loeb, 1988; Hawthorn et al, 1988; Dowell et al, 1994). Alterations in the circulatory system may also contribute to the decrease in cardiac output present in hypothyroidism, including increased systemic vascular resistance, decreased vascular volume, and atherosclerosis (Klein, 1990; Hess et al, 2003). It is not known which of these alterations contribute to the myocardial abnormalities identified in dogs with hypothyroidism. Fortunately, the decrease in cardiac contractility in dogs with hypothyroidism is usually mild and asymptomatic, but it may become relevant during a surgical procedure requiring prolonged anesthesia and aggressive fluid therapy. Cardiac abnormalities are usually reversible with thyroid hormone supplementation although it may take months of supplementation to restore normal cardiovascular function (Panciera, 1994).

It is important to emphasize that although hypothyroidism can induce echocardiographic changes, thyroid hormone deficiency alone rarely causes heart failure. In most cases heart failure associated with primary hypothyroidism is considered to represent an exacerbation of intrinsic cardiac disease by the superimposed hemodynamic effects of thyroid hormone deficiency. Both cardiomyopathy and hypothyroidism are common problems in Doberman Pinschers, and Calvert, et al. speculated on a possible cause-and-effect relationship between these two disorders in 1982. However, subsequent studies failed to identify any relationship between hypothyroidism and cardiomyopathy in Doberman Pinschers (Lumsden et al, 1993; Calvert et al, 1998). Although low baseline serum thyroid hormone concentrations occur in dogs with idiopathic dilated cardiomyopathy and heart failure, the thyroid gland in most of these dogs is responsive to TSH, suggesting that the low thyroid hormone concentrations are due to nonthyroidal illness rather than hypothyroidism. One case report documented dramatic long-term improvement in cardiac function after treatment with T_4 in two Great Danes with concurrent dilated cardiomyopathy and hypothyroidism (Phillips, 2003). Pericardial disease has also been associated with canine hypothyroidism. Aortic thromboembolism and a cholesterol-based pericardial effusion that resolved after L-T_4 sodium supplementation were reported in a 9-year-old mixed-breed dog with hypothyroidism (MacGregor, 2004).

Ocular Signs

Ocular signs are rare in hypothyroid dogs and most commonly are secondary to hyperlipidemia. Corneal lipid deposits (i.e., arcus lipoides corneae) have been described in a group of hypothyroid Alsatians with concomitant hyperlipidemia (Crispin, 1978). Corneal ulceration, uveitis, lipid effusion into the aqueous humor, secondary glaucoma, lipemia retinalis, retinal detachment, keratoconjunctivitis sicca (KCS), and Horner's syndrome have been reported in hypothyroid dogs, but the evidence for a causal association is weak (Kern and Riis, 1980; Gosselin et al, 1981b; Peruccio, 1982; Kern et al, 1989). Dogs with experimentally induced hypothyroidism did not develop ocular signs over a 6-month period (Miller, 1994). In another study decreased tear production was documented in hypothyroid dogs compared to control dogs, but only 2 of 12 dogs evaluated had clinical signs of keratoconjunctivitis sicca (Williams et al, 2007).

Gastrointestinal Signs

Clinical signs related to the gastrointestinal system have been described but are not common in hypothyroid dogs. Constipation may occur, presumably as a result of alterations in electrical control activity and smooth muscle contractile responses in the gastrointestinal tract. Diarrhea has also been reported with hypothyroidism, although a cause-and-effect relationship has not been established, and some of these dogs may have had nonthyroidal illness rather than hypothyroidism.

Generalized megaesophagus has been identified in some dogs with hypothyroidism, and some investigators have theorized that megaesophagus is caused by hypothyroidism, presumably as a

result of hypothyroid-induced neuropathy or myopathy (Jaggy et al, 1994). Unfortunately, no published reports document a cause-and-effect relationship between hypothyroidism and megaesophagus, and one recent retrospective study failed to identify an association between hypothyroidism and acquired megaesophagus in dogs (Gaynor et al, 1997). As with cardiomyopathy, a low baseline thyroid hormone concentration in a dog with generalized megaesophagus more often represents nonthyroidal illness rather than hypothyroidism. The thyroid gland in most of these dogs is responsive to TSH, megaesophagus persists despite thyroid hormone supplementation, and treatment has minimal to no effect on clinical signs (Panciera, 1994; Jaggy et al, 1994).

Coagulopathy

In humans, hypothyroidism may cause several abnormalities in the coagulation system, including a reduction in concentration of factors VIII and IX, a reduction in factor VIII–related antigen (von Willebrand factor), reduced platelet adhesiveness, and increased capillary fragility (Hymes et al, 1981; Rogers et al, 1982; Dalton et al, 1987). These abnormalities account for the easy bruising observed in some humans with hypothyroidism. Numerous studies have evaluated the association between canine hypothyroidism and the concentration of factor VIII–related antigen both in euthyroid and hypothyroid dogs and found no evidence of an association (Avgeris et al, 1990; Heseltine, 2005; Panciera and Johnson, 1994; 1996). Evaluation of the coagulation cascade or factor VIII–related antigen is not recommended in dogs with untreated hypothyroidism unless concurrent bleeding problems are present. Thyroid hormone supplementation in euthyroid dogs with von Willebrand disease is not recommended.

CLINICAL FEATURES OF CONGENITAL HYPOTHYROIDISM

Normal physical and mental development depends on the presence of normal plasma thyroid hormone concentrations. Thyroid hormone is critical for normal neurologic development and bone growth. Thyroid hormone acts synergistically with GH and insulin-like growth factor-1 (IGF-1) to promote chondrogenesis. Retardation of growth and impaired mental development are the hallmarks of congenital hypothyroidism (cretinism) (Box 3-3). Clinical signs of hypothyroidism are not usually present at birth but develop postnatally. Abnormalities usually become obvious to owners between 2 and 12 weeks of age. Puppies with congenital hypothyroidism are typically of normal weight at birth, but fail to thrive and gain weight in the weeks after birth. They develop disproportionate dwarfism with a large, broad head, short thick neck, enlarged or protruding tongue, wide/square trunk, and short limbs (Fig. 3-12). This is in contrast to the proportionate dwarfism caused by GH deficiency (see Chapter 2). Delayed epiphyseal development and retarded epiphyseal growth with reduced long bone growth cause the disproportionate dwarfism of congenital hypothyroidism (Saunders and Jezyk, 1991).

Affected puppies are mentally dull and lethargic, may be unable to eat without assistance, and lack the typical playfulness seen in normal puppies. They often have stenotic ear canals and delayed opening of the eyelids. The soft, fluffy "puppy hair coat" persists, and diffuse truncal thinning of the hair with lack of guard hairs develops, which may progress to complete alopecia often with seborrhea. Additional clinical signs may include inappetence, constipation, delayed dental eruption, and goiter (Fig. 3-13). The presence of goiter is variable and dependent on the underlying etiology (see Congenital Hypothyroidism).

BOX 3-3 Clinical Signs Associated with Congenital Hypothyroidism

- Dwarfism
- Short, broad skull
- Shortened mandible
- Enlarged cranium
- Shortened limbs
- Kyphosis
- Mental dullness
- Constipation
- Inappetence
- Gait abnormalities
- Delayed dental eruption
- Alopecia
- "Puppy" hair coat
- Dry hair
- Thick skin
- Lethargy
- Dyspnea
- Goiter

Abnormalities detected on neuromuscular examination may include mental dullness, weakness, hyporeflexia, joint laxity, spasticity, ataxia, hypermetria, and muscle tremors. Differential diagnoses for failure to grow include endocrine (e.g., pituitary dwarfism) and non-endocrine causes. See Chapter 2 for more information on pituitary dwarfism.

CLINICAL FEATURES OF SECONDARY HYPOTHYROIDISM

The array of clinical signs is similar for primary and secondary hypothyroidism in the adult dog; however, other clinical signs may dominate depending on the underlying cause. If acquired secondary hypothyroidism is caused by a pituitary tumor, the clinical signs will depend on the hormonal activity of the tumor and the degree of compression/destruction of surrounding structures. Clinical signs of hypoadrenocorticism or hyperadrenocorticism, diabetes insipidus, or hypothalamic/thalamic dysfunction (i.e., lethargy, stupor, anorexia, adipsia, loss of temperature regulation) may predominate. Subtle changes associated with hypothyroidism, GH deficiency, or reproductive dysfunction are less likely to be observed by an owner.

CLINICOPATHOLOGIC ABNORMALITIES OF HYPOTHYROIDISM

There are a number of laboratory abnormalities associated with hypothyroidism. Although most of the changes are nonspecific and observed in many other disorders, their presence adds support for a diagnosis of hypothyroidism in an animal with appropriate clinical signs.

Complete Blood Count

A normocytic, normochromic, nonregenerative anemia (packed cell volume [PCV], 28% to 36%) is identified in approximately 30% of dogs (Panciera, 2001). The cause is unknown but is believed to be due to decreased erythrocyte production. Decreased erythropoietin, decreased erythroid progenitor response to erythropoietin, and lack of a direct effect of thyroid hormone on early hemopoietic pluripotent stem cells may all contribute to the anemia. Erythrocyte

FIGURE 3-12 **A** and **B,** Eight-month-old female Giant Schnauzer littermates. The dog on the left is normal, whereas the smaller dog on the right has congenital hypothyroidism (cretinism). Note the small stature, disproportionate body size, large broad head, wide square trunk, and short limbs in the hypothyroid dog. **C** and **D,** A 3-year-old male Doberman Pinscher with congenital hypothyroidism. Note the small stature, juvenile appearance, and retention of a soft, fluffy puppy hair coat. **E,** Same dog as in **C** and **D,** shown next to his female littermate.

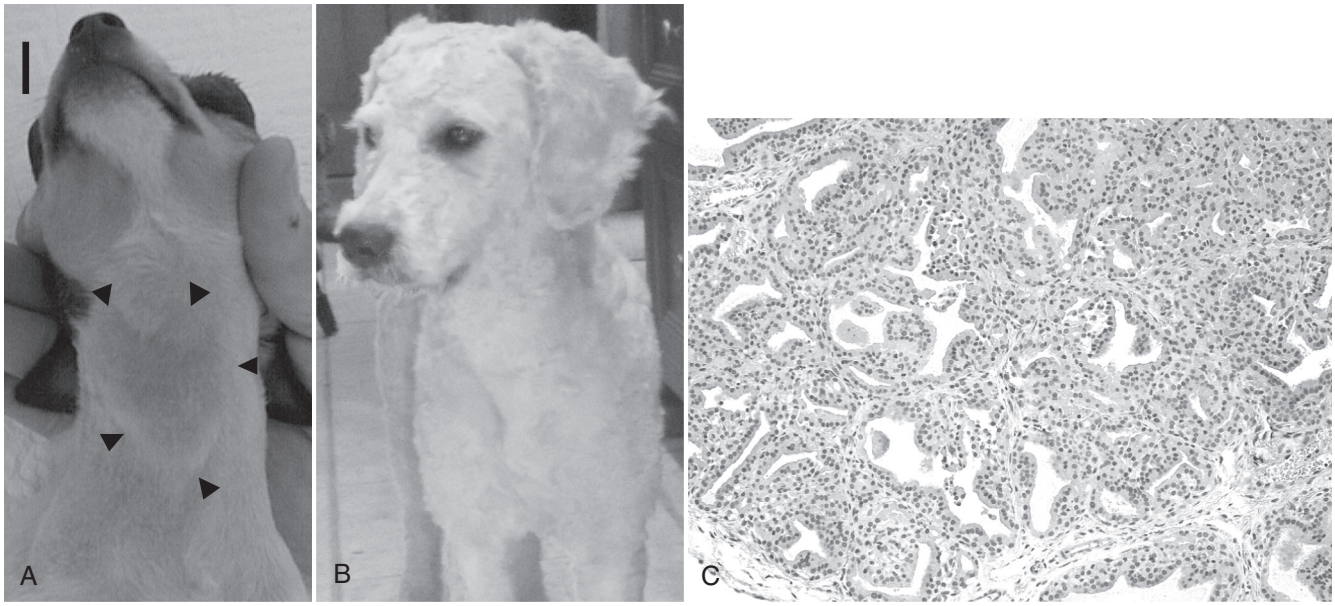

FIGURE 3-13 **A,** External appearance of a goiter in a 5-week-old Toy Fox Terrier puppy with congenital hypothyroidism. (Reprinted with permission from Fyfe JC, et al.: Congenital hypothyroidism with goiter in toy fox terriers, *J Vet Intern Med* 17:50, 2003.) **B,** A 16-month-old Spanish Water dog with congenital hypothyroidism and goiter. The dog was started on supplementation at 4- week-old and avoided all growth and morphologic abnormalities except the huge goiter. Histopathologic appearance of goiter from the Spanish Water dog shown above at 17-months-old. The gland measured 4.5 x 2.5 x 2 cm. There are typical dyshormonogenic features including diffuse follicular epithelial cell hyperplasia, with colloid spaces largely filled with cuboidal to columnar epithelial cells piled up as blunt papillae (Courtesy of Dr. John C. Fyfe, Associate Professor Microbiology and Molecular Genetics, Michigan State University.)

survival time is not affected by hypothyroidism. Evaluation of red blood cell morphology may reveal increased concentrations of leptocytes (target cells). These cells are believed to develop from increased erythrocyte membrane cholesterol loading, a direct result of the concomitant hypercholesterolemia associated with thyroid deficiency. Platelet counts are normal to increased, and platelet size is normal to decreased in dogs with hypothyroidism (Sullivan et al, 1993).

Serum Biochemistry Panel

The classic abnormality seen on a screening biochemistry panel is fasting hypercholesterolemia, which is present in approximately 75% of hypothyroid dogs. Fasting hypertriglyceridemia is also very common. Thyroid hormones stimulate virtually all aspects of lipid metabolism, including synthesis, mobilization, and degradation. Both the synthesis and degradation of lipids are depressed in hypothyroidism, with degradation affected more than synthesis. The net effect is an accumulation of plasma lipids in hypothyroidism and the potential for development of atherosclerosis (Hess et al, 2003).

Lipoprotein electrophoretic evaluation of plasma from 26 hypothyroid dogs revealed three general groups of findings: (1) normal plasma lipid concentrations and lipoprotein electrophoresis; (2) hypercholesterolemia with increased intensity of the alpha$_2$-lipoprotein band; and (3) hypercholesterolemia and hypertriglyceridemia with prominent pre-beta, beta, and alpha$_2$-lipoprotein bands (Rogers et al, 1975). Hyperlipidemia and altered lipoprotein electrophoretic patterns normalized following supplementation with thyroid hormone. A more recent study used a combined ultracentrifugation and precipitation technique to quantify plasma lipoprotein concentrations in 10 dogs with hypothyroidism (Barrie et al, 1993). The plasma concentrations of cholesterol, very–low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were significantly higher, compared with healthy dogs. Thyroid hormone deficiency-induced decrease in hepatic LDL receptor activity and reduced activities of lipoprotein lipase and hepatic lipase were proposed as the underlying mechanisms responsible for the lipoprotein cholesterol abnormalities identified in hypothyroid dogs (Valdermarsson et al, 1983). Fasting hypercholesterolemia and hypertriglyceridemia can be associated with several other disorders (Box 3-4) and thus are not pathognomonic for hypothyroidism. However, their presence in a dog with appropriate clinical signs is strong supportive evidence for hypothyroidism.

BOX 3-4 Causes of Hyperlipidemia in the Dog and Cat

- Postprandial hyperlipidemia
- Secondary hyperlipidemia
  - Hypothyroidism
  - Hyperadrenocorticism
  - Diabetes mellitus
  - Pancreatitis
  - Cholestasis
  - Hepatic insufficiency
  - Nephrotic syndrome
  - Protein-losing enteropathy
- Primary hyperlipidemia
  - Idiopathic hyperlipoproteinemia (Miniature Schnauzer)
  - Idiopathic hyperchylomicronemia (cat)
  - Lipoprotein lipase deficiency (cat)
  - Idiopathic hypercholesterolemia
- Drug-induced hyperlipidemia
  - Glucocorticoids
  - Megestrol acetate (cat)

Mild hypercalcemia has been reported in some dogs with congenital hypothyroidism and has also been reported in an adult dog with hypothyroidism (Lobetti, 2011). Hypercalcemia has been documented in hypothyroid children secondary to increased intestinal absorption and decreased urinary excretion of calcium. Hyponatremia occurs in dogs with myxedema coma (Atkinson and Aubert, 2004; Henik and Dixon, 2000).

Hypothyroid dogs may have a mild to moderate increase in serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP) activities. These increases are believed to be associated with hypothyroid myopathy. In a study of nine dogs with experimentally induced hypothyroidism, a subclinical myopathy associated with increases in creatine kinase, AST, and lactate dehydrogenase was documented within 6 months of induction of hypothyroidism (Rossmeisl et al, 2009).

Urinalysis

Results of urinalysis are usually normal in dogs with hypothyroidism. In dogs with lymphocytic thyroiditis, concurrent immune-complex glomerulonephritis may result in proteinuria (Mansfield and Mooney, 2006). Although an increased risk of glomerulonephritis would be expected in dogs with thyroiditis, there are few reports of dogs with both conditions in the published literature.

Other Hormone Concentrations

Hypothyroidism can affect the secretion of nonthyroidal hormones from other endocrine glands—most notably the pituitary gland. In dogs, chronic hypothyroidism induces hypersecretion of GH possibly due to transdifferentiation of somatotrophic pituitary cells to thyrosomatotropes (Diaz-Espiñeira 2008a; 2008b; 2009). Thyroid hormone deficiency–induced increase in TRH secretion can stimulate prolactin secretion, resulting in hyperprolactinemia and, in intact female dogs, inappropriate lactation (Chastain and Schmidt, 1980; Cortese et al, 1997, Diaz-Espiñeira, 2009).

DERMATOHISTOPATHOLOGIC FINDINGS IN HYPOTHYROIDISM

Histopathology of skin biopsies is sometimes recommended as part of the diagnostic evaluation for hypothyroidism. Unfortunately histopathology findings in the various disorders associated with noninflammatory alopecia are often nonspecific and do not discriminate between Alopecia X, hyperadrenocorticism, hyperestrogenism, recurrent flank alopecia, and hypothyroidism. Histopathologic findings common to all these disorders include increased kenogen (hairless) follicles, decreased anagen and catagen follicles, excessive trichilemmal keratinization, follicular atrophy, or follicular dystrophy. The only feature that distinguished hypothyroid biopsies from those of other noninflammatory causes of alopecia was a significantly thicker epidermis and dermis and fewer atrophic follicles (Müntener et al, 2012).

RADIOGRAPHY, ULTRASONOGRAPHY, AND NUCLEAR IMAGING

Conventional Radiography

Conventional radiography is not a routine procedure for evaluation of acquired canine hypothyroidism. Cervical radiography is ineffective in determining the status of the thyroid gland except when thyroid neoplasia is suspected (see Chapter 5). In congenital hypothyroidism, radiographic abnormalities include delayed epiphyseal ossification (Fig. 3-14); epiphyseal dysgenesis (i.e., irregularly formed, fragmented, or stippled epiphyseal centers), most common in the humeral, femoral, and proximal tibial condyles; short broad skulls; shortened vertebral bodies; and delayed maturation (Greco et al, 1991; Saunders and Jezyk, 1991; Mooney and Anderson, 1993). Ventral borders of vertebral bodies may be scalloped, suggesting lack of normal longitudinal growth (see Fig. 3-14). Overall length of the diaphyses of long bones is reduced, and carpal and tarsal bones appear to have retarded ossification. Valgus deformities are common. Accelerated epiphyseal ossification occurs during thyroid hormone supplementation, but degenerative joint changes with consequent osteoarthritis may develop despite thyroid hormone supplementation (Saunders and Jezyk, 1991).

Ultrasonography

The thyroid gland can be identified and its size, shape, and echogenicity determined using real-time ultrasonography in dogs. Ultrasonography is commonly employed for evaluation of suspected thyroid neoplasms, especially for guidance in performing needle biopsy (see Chapter 5). Ultrasound may also be helpful in differentiating between hypothyroidism and the euthyroid sick syndrome. The normal thyroid gland is homogenous and well delineated with a hyperechoic capsule. The parenchyma is hyperechoic to the surrounding muscles, and the size is correlated with the size (body surface area) of the dog (Brömel, 2006). The thyroid lobe in healthy dogs is fusiform in shape with a triangular to oval shape on the transverse view (Fig. 3-15). Differences in thyroid lobe size and echogenicity between hypothyroid and euthyroid dogs have been documented and are helpful in assessment of thyroid function (Brömel et al, 2005; Reese et al, 2005; Taeymans et al, 2007a; 2007b). In dogs with hypothyroidism, the thyroid lobes tend to be round or oval in shape on the transverse plane, are hypoechoic compared to surrounding musculature, and have a smaller volume and cross-sectional area relative to body size. One study reported a diagnostic specificity of 96% for diagnosis of hypothyroidism using relative thyroid volume and relative cross sectional area (Reese et al, 2005). Sensitivity was 98% for diagnosis of hypothyroidism when combining evaluation of relative thyroid volume and echogenicity relative to the echogenicity of the sternothyroid muscle (Reese et al, 2005). Changes in the thyroid gland progress with time, and in early hypothyroidism the thyroid lobes may appear relatively normal on ultrasound examination. It is also important to recognize that there is relatively high interobserver variability for thyroid gland measurements, and sequential studies should ideally be performed by the same operator.

Nuclear Imaging

Thyroid scintigraphy is useful for evaluating the size, shape, and location of thyroid tissue (see Chapters 4 and 5). Either technetium-99m pertechnetate ($^{99m}TcO_4$) or iodine-123 (^{123}I) can be used for scintigraphy in dogs. ^{99m}-TcO_4 is concentrated but not organified by the thyroid gland and is the most commonly used isotope used for thyroid scintigraphy in veterinary medicine because of its low cost, short half-life, and safety (no beta emissions). On scintigraphy, normal canine thyroid lobes appear as two uniformly dense, symmetric ovals in the mid-cervical area (Fig. 3-16), although asymmetrical uptake has been reported in some euthyroid dogs, particularly Greyhounds (Pinilla et al, 2009). The thyroid lobes are slightly smaller than the parotid salivary glands, which also concentrate $^{99m}TcO_4$. A 1:1 thyroid-to-salivary ratio is considered normal in the dog, although there is some variability depending upon the time of the scan in relation to radioisotope administration (Adams 1997, Taeymans et al, 2007a). Percentage thyroidal uptake of radioisotope

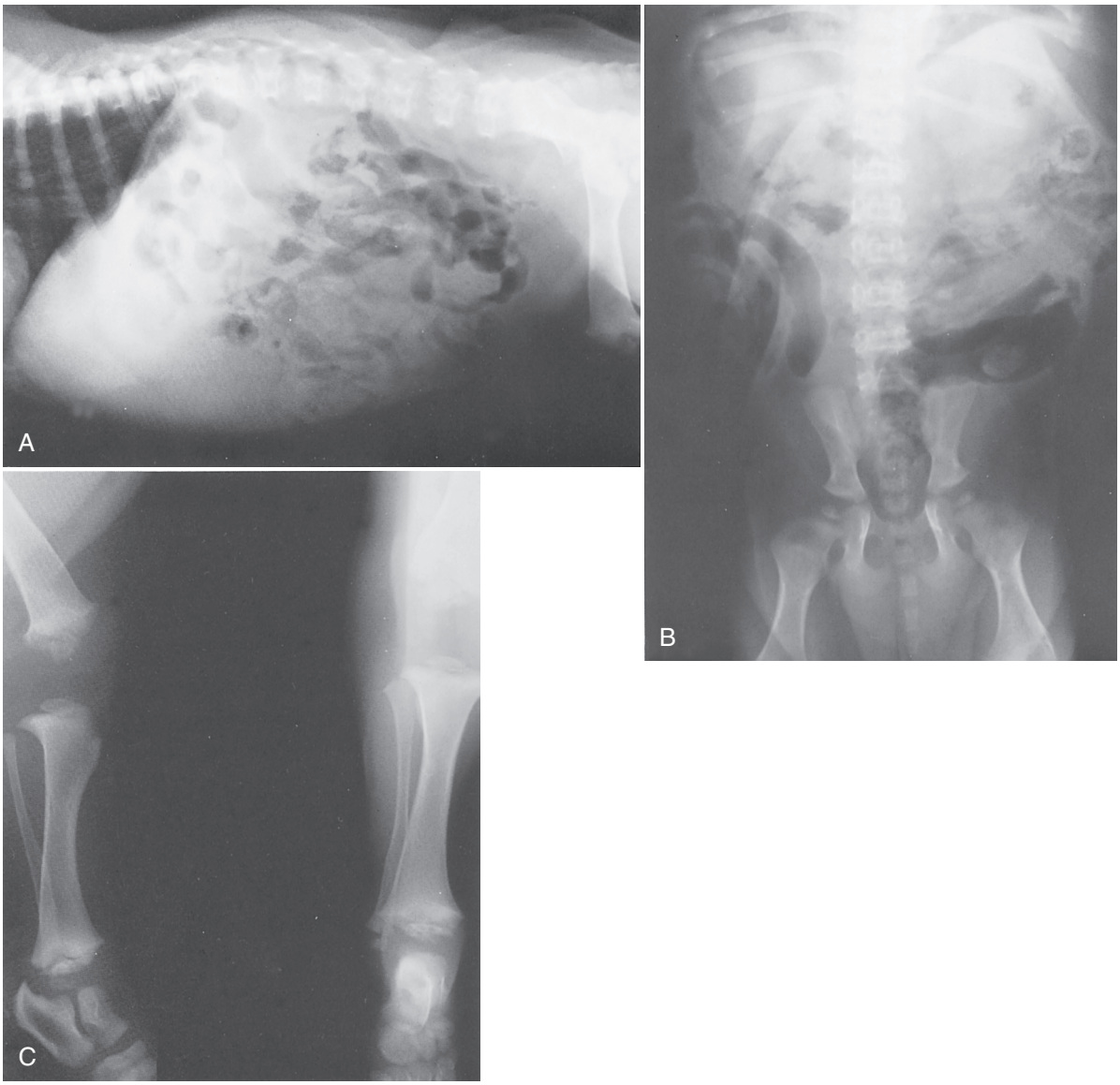

FIGURE 3-14 **A** and **B,** Lateral and ventrodorsal radiographs of the spine of a dog with congenital hypothyroidism. Note the shortened vertebral bodies with scalloped ventral borders and only partially calcified vertebral endplates. **C,** Lateral and anteroposterior radiograph of the tibia and fibula of a dog with congenital hypothyroidism, illustrating epiphyseal dysplasia and poor calcification of the bones.

can also be calculated with euthyroid dogs having a percentage uptake of approximately 1% of the administered dose. Scintigraphy is regarded as one of the gold standard methods for differentiating between hypothyroid and euthyroid dogs. Adult dogs with primary hypothyroidism typically have low or non-detectable accumulation of radioisotope by the thyroid gland, and the thyroid gland may also appear smaller than normal (see Fig. 3-16). Similar results are found in puppies with congenital hypothyroidism caused by thyroid dysgenesis and dogs with secondary hypothyroidism (Greco et al, 1991; Kintzer and Peterson, 1991). In contrast, puppies with congenital hypothyroidism caused by iodination defects have normal to enlarged thyroid lobes and normal to increased $^{99m}TcO_4$ uptake. Dogs with nonthyroidal illness should also have normal isotope uptake. In a study of 14 dogs with histologically confirmed hypothyroidism and 13 dogs with nonthyroidal illness, the percentage uptake of technetium at 60 minutes in the hypothyroid dogs ranged from 0.03% to 0.26% of the injected dose, whereas in the dogs with nonthyroidal illness uptake ranged from 0.39% to 1.86% with no overlap between the groups (Diaz-Espiñeira et al, 2007; Fig. 3-17). In another study, however, some dogs had uptake in the equivocal range of 0.3% to 0.33% (Shiel et al, 2012). Thyroiditis may cause false positive results on scintigraphy (normal or increased uptake in a hypothyroid dog) and increased iodine intake may cause a false positive (low uptake in a euthyroid dog). Glucocorticoid administration may also cause suppression of thyroidal radioisotope uptake into the equivocal range (Shiel et al, 2012). Isotope uptake is typically normal or increased in dogs with hypothyroidism induced by potentiated sulfonamides (Hall et al, 1993; Gookin et al, 1999).

BLOOD TESTS OF THYROID GLAND FUNCTION

Function of the thyroid gland is typically initially assessed by measuring baseline serum thyroid hormone concentrations. Evaluating the responsiveness of the thyroid gland to provocative stimulation

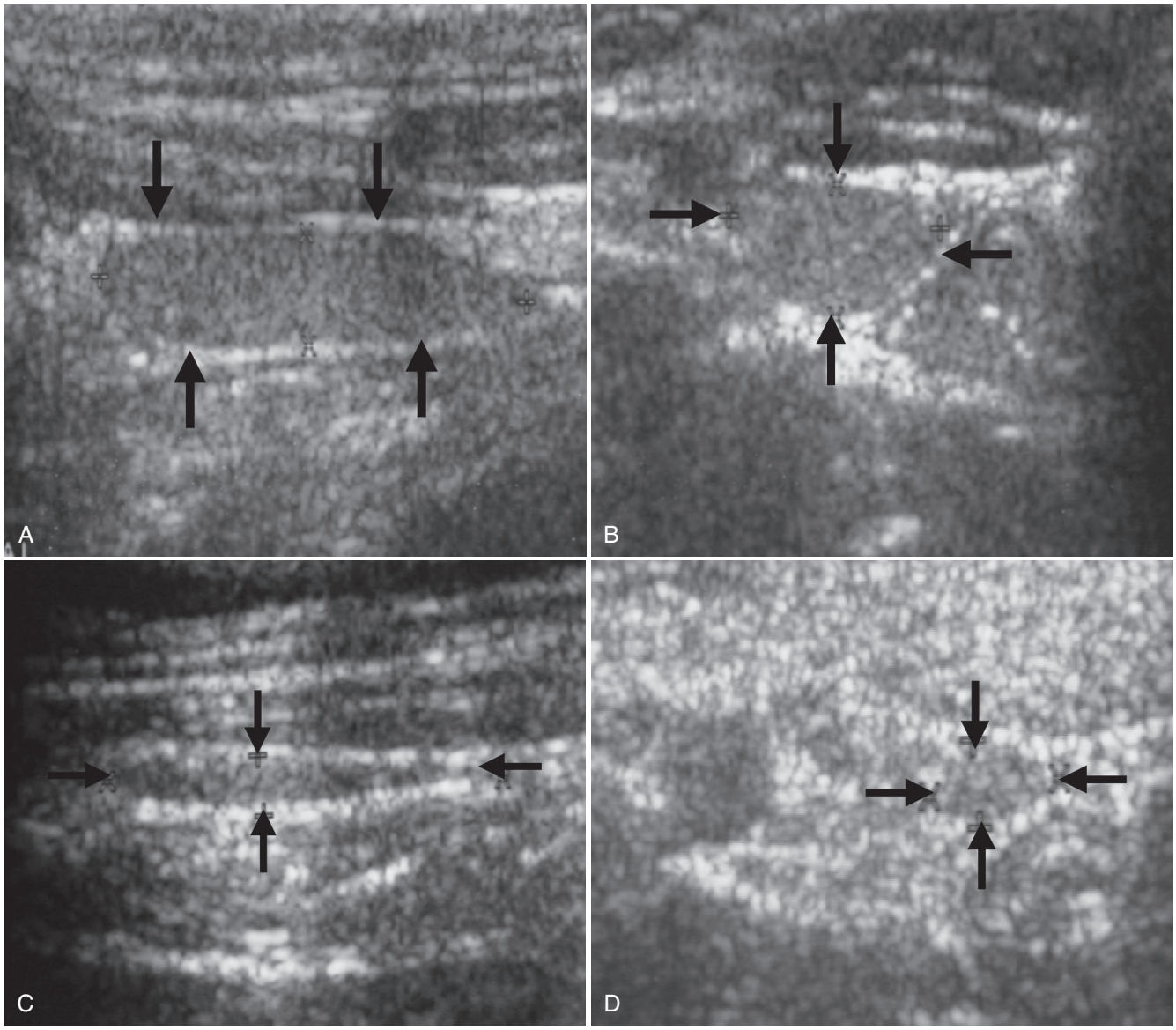

FIGURE 3-15 Longitudinal and transverse ultrasound images of the left thyroid lobe in a healthy Golden Retriever dog **(A** and **B)** and a Golden Retriever dog with hypothyroidism **(C** and **D).** Note the smaller size of the thyroid lobe in the dog with hypothyroidism compared with the healthy dog. The maximum length, width, and height of the thyroid lobe measured 24.8 mm, 7.9 mm, and 4.6 mm in the healthy dog and 20.2 mm, 4.1 mm, and 2.8 mm in the hypothyroid dog.

(e.g., TSH stimulation test) is considered to be the gold standard for definitive diagnosis of thyroid dysfunction, but this is rarely performed in clinical practice because of the expense of recombinant TSH. Baseline tests to assess thyroid gland function include measurement of T_4, fT_4, 3,5,3′-T_3, free T_3 (fT_3), 3,3′,5′-triiodothyronine (rT_3), and endogenous TSH concentration. T_4 accounts for the majority of the thyroid hormone secreted by the thyroid gland, with only small quantities of T_3 and minor amounts of rT_3 released. Once secreted into the circulation, more than 99% of T_4 is bound to plasma proteins. The unbound, or free, T_4 is biologically active, exerts negative feedback inhibition on pituitary TSH secretion (see Fig. 3-5), and is capable of entering cells throughout the body (Fig. 3-18). Protein-bound T_4 acts as a reservoir and buffer to maintain a steady concentration of free hormone in the plasma, despite rapid alterations in the delivery of thyroid hormone to tissues. Serum T_4 concentrations represent the sum of the protein-bound and free levels circulating in the blood, whereas fT_4 concentration is a measure of the free hormone only.

Within the cell, fT_4 is de-iodinated to form either T_3 or rT_3, depending on the metabolic demands of the tissues at that particular time (see Fig. 3-18). T_3 is preferentially produced during normal metabolic states, whereas rT_3, which is biologically inactive, is produced during periods of illness, starvation, or excessive endogenous catabolism. Intracellular T_3 binds to nuclear receptors and exerts its physiologic effects by activation of target genes. T_3 is believed to be the primary hormone that induces physiologic effects, because of its greater biologic activity and volume of distribution compared with T_4, the preferential de-iodination of T_4 to T_3 within the cell, and the presence of specific intracellular receptors for T_3 (Yen and Brent, 2013).

All serum T_4, both protein-bound and free, comes from the thyroid gland. Therefore tests that measure the serum total and

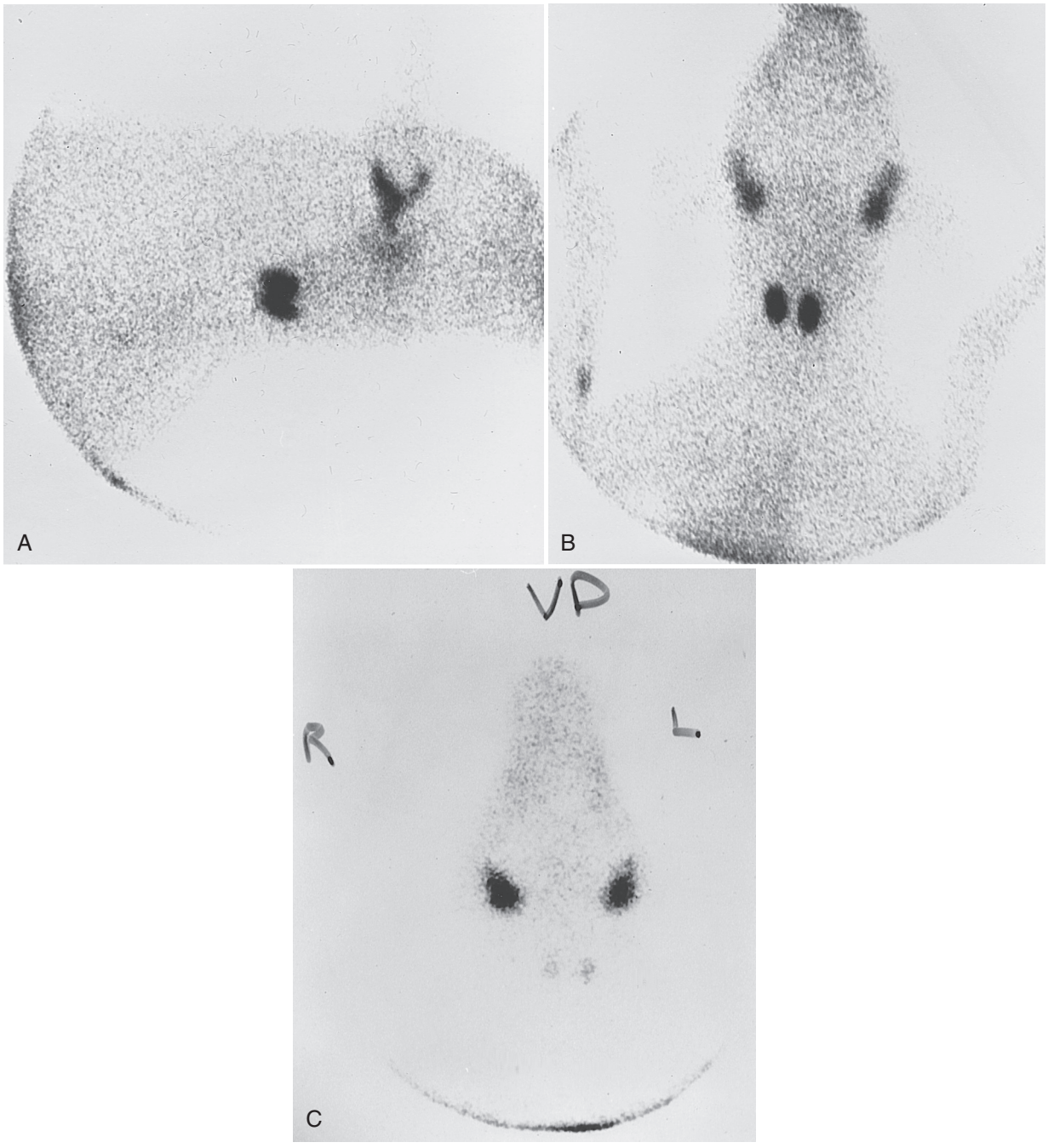

FIGURE 3-16 **A** and **B,** Lateral and ventrodorsal views of a sodium pertechnetate nuclear scan performed in a normal dog. The normal thyroid lobes appear as two uniformly dense symmetric spots in the cervical region. The parotid salivary glands are also visible. **C,** Ventrodorsal view of a sodium pertechnetate nuclear scan performed in a dog with primary hypothyroidism. Uptake of sodium pertechnetate is normal by the parotid salivary glands, which are readily visible, but is markedly reduced by the thyroid lobes, which are barely visible.

fT_4 concentrations, in conjunction with the serum TSH concentration, are currently recommended for the assessment of thyroid gland function in dogs suspected of having hypothyroidism. In contrast, most T_3 and rT_3 is formed through the deiodination of T_4 in extrathyroidal sites—most notably the liver, kidney, and muscle. Serum T_3 concentration is a poor gauge of thyroid gland function because of its predominant intracellular location and the minimal amount of T_3 secreted by the thyroid gland compared with T_4. Thus measurement of serum T_3, fT_3, or rT_3 concentration is not routinely recommended for the assessment of thyroid gland function in dogs.

Baseline Serum Total Thyroxine Concentration

Assay Technique

Baseline serum total T_4 concentration is the sum of both protein-bound and free hormone circulating in the blood. In the last few years, new methods for measurement of total T_4 have been

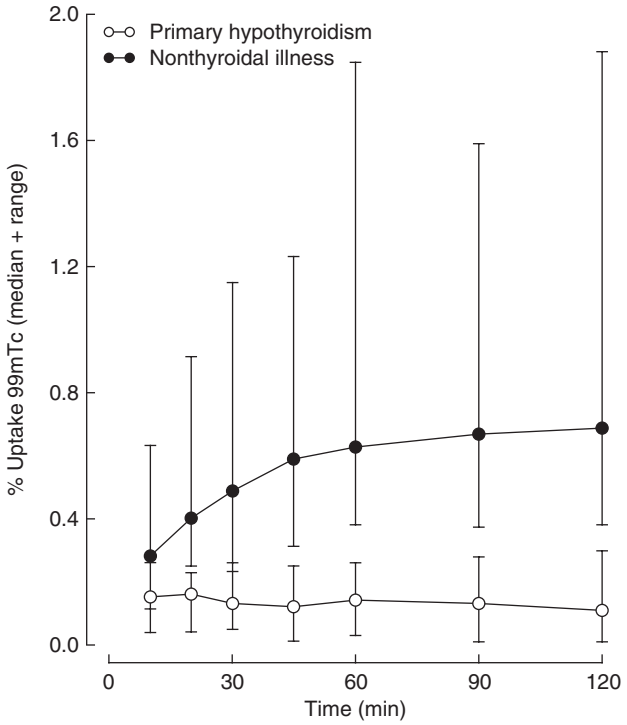

FIGURE 3-17 Median values and ranges for thyroidal uptake of $^{99m}TcO4^-$ measured as percent uptake of injected dose, in 14 dogs with primary hypothyroidism and 13 dogs with nonthyroidal illness. (From Diaz-Espiñeira, Assessment of thyroid function in dogs with low plasma thyroxine concentration, *J Vet Intern Med* 21[1]:25-32, 2007.)

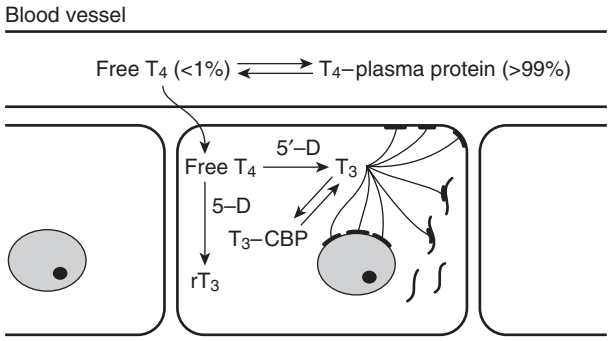

FIGURE 3-18 Schematic of intracellular metabolism of free T_4 (fT_4) to either triiodothyronine *(T_3)* or reverse T_3 *(rT_3)* by 5′- or 5-monodeiodinase, respectively. Intracellular T_3 formed from monodeiodination of fT_4 can interact with T_3 receptors on the cell membrane, mitochondria, or nucleus of the cell and stimulate the physiologic actions of thyroid hormone or bind to cytoplasmic binding proteins *(CBP)*. The latter forms an intracellular storage pool for T_3.

developed and are increasingly replacing the use of radioimmunoassays (RIAs), which have been considered the gold standard for measurement of serum T_4 concentration.

The reference range for serum T_4 concentration varies between laboratories because of differences in laboratory technique and the specific commercial kit utilized. There is excellent cross-reactivity for thyroid hormone between species. Most assays for measurement of serum thyroid hormones are manufactured for use in humans, although there are now some canine-specific commercial assays. Baseline serum T_4 concentrations are lower in healthy dogs than in humans (1.0 to 3.5 versus 4.0 to 10.0 µg/dL, respectively) because of weaker protein binding in dogs, hence the RIA technique must be sensitive enough to detect T_4 concentrations less than 1.0 µg/dL to accurately differentiate hypothyroidism from euthyroidism in dogs. For most laboratories, the serum T_4 concentration in healthy dogs ranges between 1.0 and 3.5 µg/dL. The lower limit of the normal range varies between laboratories, depending on whether the laboratory wants greater specificity or sensitivity for the test (see Interpretation of Results later).

Chemiluminescent Immunoassays

Many reference laboratories now use chemiluminescent immunoassays for measurement of total T_4 in dogs, and studies suggest that these assays provide similar and consistent results compared to RIA (Kemppainen and Birchfield, 2006). In chemiluminescent assay systems, unlabeled hormone in the patient sample competes for antibody sites with a known amount of thyroid hormone labeled with an enzyme, such as alkaline phosphatase. The amount of the labelled hormone binding to the antibody in the tube is detected by addition of a chemiluminescent substrate rather than a radioactive label. Sample and reagents are automatically pipetted into the test unit, which is then incubated. Unbound material is removed by washing, and a chemiluminescent substrate is added to the test unit. Light emission is read with a sensitive photon counter. These assays have the advantage of speed, automation, and are much safer for laboratory personnel because radioactive isotopes are not utilized. Appropriate reference ranges provided by laboratories should be used to interpret the results.

Point-of-care enzyme-linked immunosorbent assays (ELISAs) for measuring serum T_4 in dogs and cats are also available for in clinic use. The advantage of an in-house test is that it is economical, quick, easy to perform, and it allows the clinician to make recommendations the same day the animal is evaluated. Evaluations of an in-house ELISA (Snap T_4 test kit and VetTest Snap Reader; IDEXX Laboratories Inc., Westbrooke, ME) for quantitative measurement of serum T_4 concentration in dogs and cats have been conflicting. In one study, substantial discrepancies between the in-house ELISA and RIA results for T_4 concentrations were detected (Lurye et al, 2002). In dogs, the in-house ELISA both overestimated and underestimated the serum T_4 concentration compared with a RIA assay. Interpretation of the ELISA results from 62% of 50 samples would have led to inappropriate clinical decisions. In cats, the in-house ELISA consistently overestimated the serum T_4 concentration obtained with RIA, and interpretation of the ELISA results from 50% of 50 samples would have led to inappropriate clinical decisions. In contrast, another study found good correlation between the in-house ELISA and both RIA and chemiluminescent assays for measurement of serum T_4 in feline and canine blood samples; in general total T_4 concentrations measured by RIA were lower than for the other two methods, emphasizing that laboratory-specific reference ranges should always be utilized (Kemppainen, 2006). Because a quality control system is an important part of maintaining assay consistency, accuracy of any point-of-care ELISA should always be documented in an ongoing quality control program by comparing ELISA and RIA results from the same blood samples.

Stability and Factors Interfering with Measurement

T_4 is a relatively stable hormone that is resistant to degradation by contact with cells in blood, long-term storage following centrifugation, hemolysis, or repeated thawing and freezing (Reimers et al, 1991). In addition, serum may be stored in plastic tubes for 8 days at room temperature and for 5 days at 37° C without affecting the concentration of T_4 (Behrend et al, 1998). This is also true for heparinized plasma and ethylenediaminetetraacetic acid

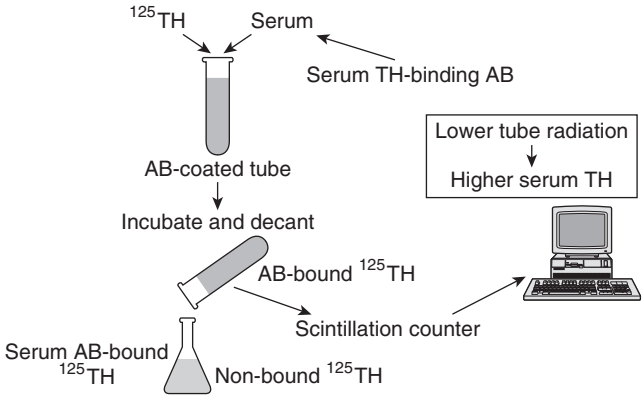

FIGURE 3-19 Schematic illustration of how anti-thyroid hormone antibodies may cause spuriously increased thyroid hormone values for a radioimmunoassay (RIA) using a single-step, antibody-coated tube separation system. Patient serum and radiolabeled thyroid hormone (which comes with the assay) are added to a test tube coated with anti-thyroid hormone antibody. Thyroid hormone in serum competes with radiolabeled thyroid hormone for antibody-binding sites in the tube. After incubation, the liquid in the tube is decanted, the radioactivity of the tube is measured in a scintillation counter, and the serum thyroid hormone concentration is determined based on the tube radioactivity. An inverse relationship exists between tube radioactivity and serum thyroid hormone concentration. If anti-thyroid hormone binding antibodies are present in the patient's serum, these antibodies compete with the antibodies attached to the tube for serum thyroid hormone and radiolabeled thyroid hormone. Because serum thyroid hormone antibodies are not attached to the tube, they are decanted along with any radiolabeled thyroid hormone that has bound to them. This causes a falsely low radioactivity of the tube and a corresponding spuriously high serum thyroid hormone value. *AB,* Antibody; *TH,* thyroid hormone.

(EDTA) plasma samples; however, storage of serum or plasma at 37° C in glass can cause a significant increase in serum T_4 concentration, compared with storage at –20° C (Behrend et al, 1998). Because of potential for environmental extremes during shipping, whenever possible, blood samples should be centrifuged, serum should be decanted into plastic tubes, frozen, and sent to the laboratory on cold packs.

Many physiologic and pharmacologic factors influence the pituitary-thyroid axis and interfere with the accuracy of baseline serum T_4 concentration for differentiating hypothyroidism from euthyroidism (see Factors Affecting Thyroid Gland Function Tests). However, the only factor that directly interferes with the ability of an assay to measure T_4 is the presence of anti-T_4 antibodies in the serum sample. Anti-thyroid hormone antibodies occur in dogs with lymphocytic thyroiditis and are present in approximately 2% of dogs with clinical signs of hypothyroidism and 15% of hypothyroid dogs (Nachreiner et al, 2002; Graham et al, 2007). Anti-T_4 antibodies may cause spuriously increased or decreased serum T_4 values (Thacker et al, 1992). The effect of anti-thyroid hormone antibodies on the serum T_4 value depends on the type of assay being used by the laboratory, but in most currently utilized commercial assays, anti-T_4 antibodies cause a spurious increase in the measured T_4 concentration (Fig. 3-19). Although antibody interference can potentially lead to a falsely increased T_4 concentration, the probability of antibody interference resulting in a falsely normal T_4 concentration appears to be quite low (Piechotta et al, 2010). Hyperlipidemia and hemolysis do not affect measurement of T_4 in serum by RIA (Lee et al, 1991; Reimers et al, 1991); for other assay methods, the individual laboratory should be contacted for information about assay interference by hyperlipidemia and hemolysis.

Interpretation of Results

Measurement of the serum T_4 concentration can be used as the initial screening test for hypothyroidism or used in a thyroid panel, which typically includes T_4, fT_4, TSH, and an antibody test for lymphocytic thyroiditis (Fig. 3-20). Theoretically, the interpretation of baseline serum T_4 concentration should be straightforward; that is, dogs with hypothyroidism should have low values compared with healthy dogs. Unfortunately, the range of serum T_4 concentration overlaps between hypothyroid dogs and healthy dogs, and this overlap becomes more evident in euthyroid dogs with nonthyroidal illness (Fig. 3-21). In one study, the range of serum T_4 concentration in 62 healthy dogs was 1.0 to 3.3 µg/dL, and in 51 hypothyroid dogs it was from undetectable to 1.5 µg/dL (Nelson et al, 1991). The amount of residual thyroid gland function at the time the sample is obtained, the suppressive effects of extraneous factors especially concurrent nonthyroidal illness on serum thyroid hormone concentrations, and the presence of circulating anti-thyroid hormone antibodies all affect the sensitivity and specificity of serum T_4 concentration in diagnosing hypothyroidism.

These overlap between euthyroidism and hypothyroidism creates a dilemma when a laboratory tries to establish its normal range for serum T_4 concentration. If the laboratory keeps the lower limit of the normal serum T_4 range high (e.g., 1.5 µg/dL), sensitivity of the test is sacrificed for specificity. That is, the number of hypothyroid dogs misdiagnosed as euthyroid is minimized, but the number of euthyroid dogs misdiagnosed as hypothyroid is increased, leading to inappropriate thyroid replacement treatment of euthyroid dogs. Alternatively, by decreasing the lower limit of the normal serum T_4 range (e.g., 0.8 µg/dL), specificity is sacrificed for sensitivity. The number of euthyroid dogs misdiagnosed as hypothyroid is minimized, but the number of hypothyroid dogs misdiagnosed as euthyroid increases.

The reference range for serum T_4 concentration also varies between breeds. The reference range is usually established based on the mean ± two standard deviations calculated from results of serum T_4 measured in a large population of dogs without regard for breed. The reference range for serum T_4 and fT_4 measured by modified equilibrium dialysis (MED) is now recognized to be lower in some breeds—most notably Sighthounds (Gaughan and Bruyette, 2001; Shiel et al, 2007a; Table 3-5). These findings suggest that breed-specific reference range values for thyroid hormone tests should be established and used when evaluating thyroid gland function. Until such information is established, interpretation of thyroid hormone test results in such breeds will continue to be challenging.

The use of an arbitrary serum T_4 value to separate euthyroidism from hypothyroidism is not recommended. Rather, the serum T_4 result should be evaluated in the context of the history, physical examination findings, and other clinicopathologic data (Tables 3-6 and 3-7; see Fig. 3-20). All of this information yields an index of suspicion for euthyroidism or hypothyroidism. For the clinician, it is difficult to judge the influence of extraneous factors, especially concurrent illness, on the serum T_4 concentration. Although nonthyroidal illness can suppress the baseline serum T_4 concentration to less than 0.5 µg/dL in a euthyroid dog, hypothyroid dogs rarely have serum T_4 concentrations greater than 1.5 µg/dL, so the baseline serum T_4 concentration is best used to rule out hypothyroidism. The higher the T_4 concentration, the more likely the dog is euthyroid. The one exception is the hypothyroid

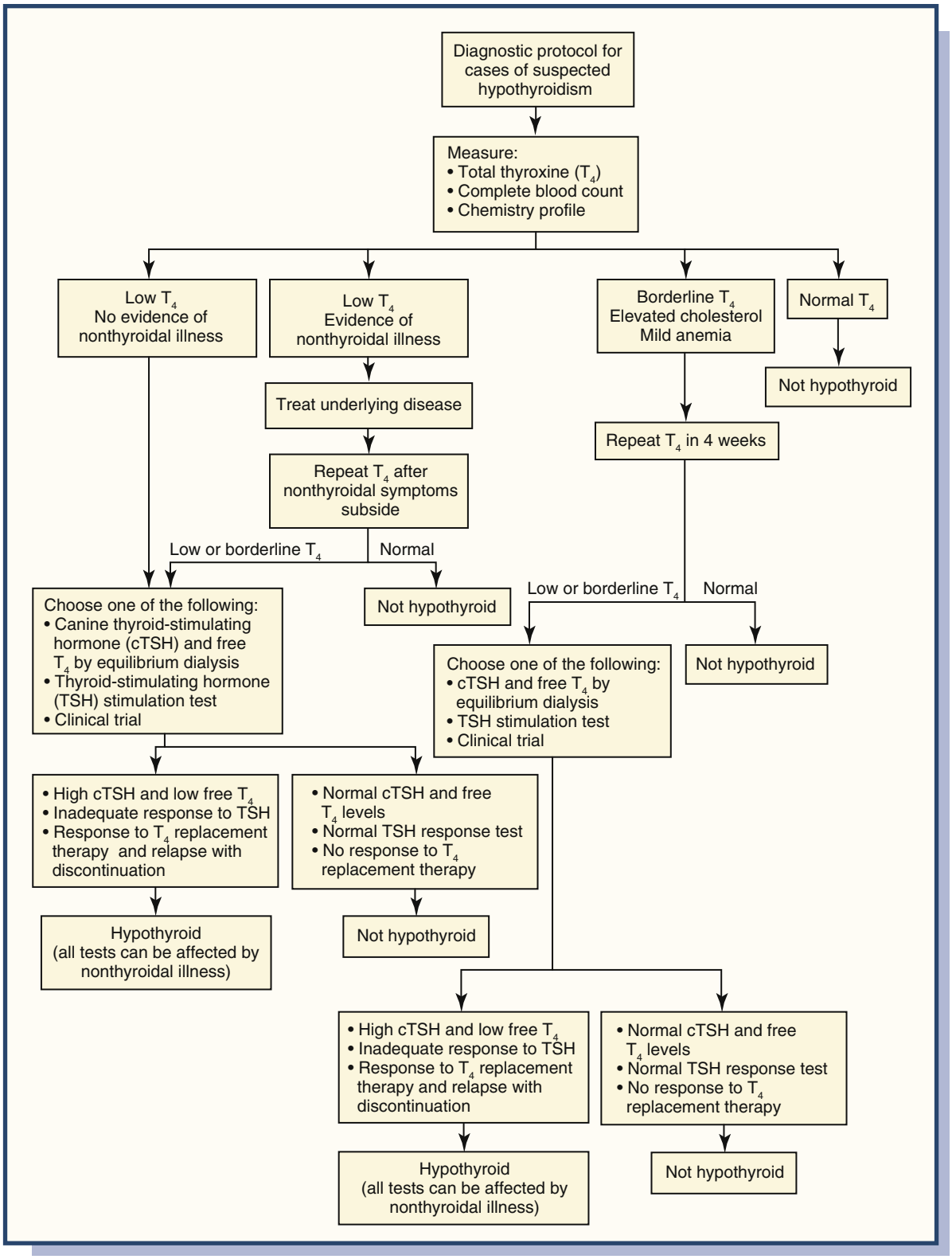

FIGURE 3-20 Algorithm for diagnosis of canine hypothyroidism. (From EttingerSJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 7, St Louis, 2010, Elsevier, p. 1756.)

dog with circulating anti-thyroid hormone antibodies (see Fig. 3-19). Conversely, the lower the T_4 value, the more likely the dog has hypothyroidism, assuming the history, physical examination findings, and clinicopathologic data are also consistent with the disease and severe systemic illness is not present. If the clinician's index of suspicion is not high for hypothyroidism but the serum T_4 concentration is low, other factors such as nonthyroidal illness should be strongly considered.

Interpretation: Concurrent Thyroid Hormone Supplementation

Occasionally, a clinician wants to determine whether a dog receiving thyroid supplementation is, in fact, hypothyroid. The

exogenous administration of thyroid hormone, either T_4 or T_3, will suppress pituitary TSH secretion and cause pituitary thyrotroph atrophy, and subsequently thyroid gland atrophy in a healthy euthyroid dog (Panciera et al, 1990). Immediately after withdrawal of exogenous supplementation, serum T_4, and fT_4, may be decreased or undetectable; the severity of the decrease is dependent on the severity of thyroid gland atrophy induced by the thyroid hormone supplement. Basal serum T_4 and response to TRH and TSH results may be suggestive of hypothyroidism, in a previously euthyroid dog, if the testing is performed within a month of discontinuing treatment (Panciera, 2002). Thyroid hormone supplementation must be discontinued, and the pituitary-thyroid axis must be allowed to recover function before meaningful results of baseline serum T_4, fT_4, and TSH concentrations can be obtained. The time interval between the discontinuation of thyroid hormone supplementation and the acquisition of meaningful results regarding thyroid gland function depends on the duration of treatment, the dosage and frequency of administration of the thyroid hormone supplement, and individual variability. As a general rule, thyroid hormone supplements should be discontinued a minimum of 4 weeks and preferably 6 to 8 weeks before critically assessing thyroid gland function.

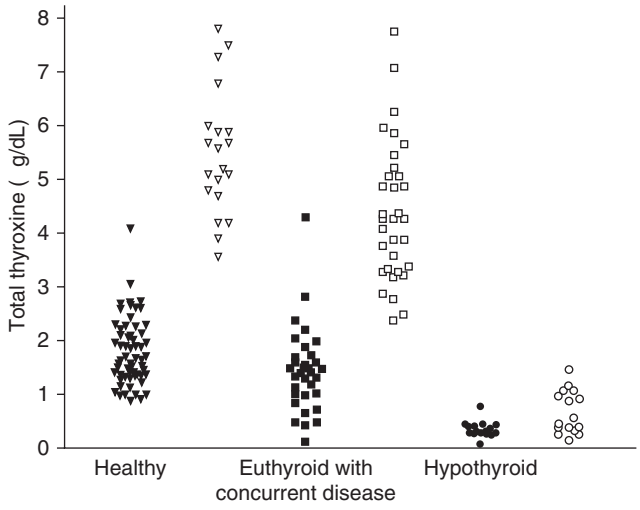

FIGURE 3-21 Serum total T_4 concentrations in healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease before and after administration of thyroid-stimulating hormone (TSH). (From Scott-Moncrieff J, Nelson RW: Change in serum thyroid-stimulating hormone concentration in response to administration of thyrotropin-releasing hormone to healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease, *J Am Vet Med Assoc* 213[10]:1435-1438, 1998.)

Baseline Serum Total Triiodothyronine Concentration

Assay Technique

Serum total T_3 concentrations are the sum of the protein-bound and free levels circulating in the blood. Almost all commercial laboratories currently use either RIA or chemiluminescent techniques for measuring T_3 concentrations in the blood. Most human RIAs for T_3 are suitable for use in the dog, because blood concentrations are similar for both species. Using the RIA technique, an approximate normal range for blood T_3 concentrations is 0.8 to 2.1 nmol/L—although the exact range varies from laboratory to laboratory because of differences in assays used and laboratory technique.

Stability and Factors Interfering with Measurement

Stability of serum T_3 and factors interfering with its measurement are as described for serum T_4. In dogs with suspected hypothyroidism, the incidence of anti-T_3 antibodies is greater than that of anti-T_4 antibodies (6% of dogs with suspected hypothyroidism) (Nachreiner et al, 2002).

Interpretation of Results

Measurement of baseline serum T_3 concentration is of minimal value in differentiating euthyroidism from hypothyroidism in the dog (Fig. 3-22). Essentially no difference exists in the mean or range of serum T_3 concentration between groups of healthy dogs, dogs with hypothyroidism, and euthyroid dogs with concurrent illness (Nelson et al, 1991; Miller et al, 1992). The majority of circulating T_3 is produced from deiodination of T_4 at extra thyroidal sites, and thyroidal secretion of T_3 and peripheral tissue 5′-deiodination of T_4 to T_3 may increase with mild thyroid gland dysfunction (Utiger, 1980; Lum et al, 1984). In addition, the high proportion of anti-T_3 antibodies in hypothyroid dogs contributes to the poor diagnostic performance of T_3. When anti-T_3 positive dogs were excluded, the diagnostic performance of T_3 was similar to that of T_4 (Graham et al, 2007). Although serum T_3 is included as part of the canine thyroid panel run by some commercial diagnostic laboratories, it has limited diagnostic value. Measurement of T_3 may be justified in Greyhounds who tend to have low concentrations of T_4 and fT_4 but T_3 concentrations within the laboratory reference range (Shiel et al, 2007a; Pinilla et al, 2009; see Table 3-5).

TABLE 3-5 **CANINE BREEDS WITH UNIQUE THYROID HORMONE REFERENCE RANGES**

BREED	TOTAL THYROXINE (↓ OR N)	FREE THYROXINE (↓ OR N)	TOTAL TRIIODOTHYRONINE (↓ OR N)	THYROTROPIN (↑ OR N)	THYROXINE RESPONSE TO TSH
Greyhound	↓	↓	Usually N	N	Decreased
Whippet	↓	N	—	N	
Saluki	↓	↓	↓	N or ↑	
Sloughi	↓	↓ or ↑ (ED)	—	↑	Normal to slightly decreased
Basenji	↓	—	—	N	—
Irish Wolfhound	↓	—	—	—	
Conditioned Alaskan sled dogs	↓	↓	↓	Variable	

Baseline Serum Free Thyroxine Concentration

Although the gold standard technique for measurement of fT_4 is equilibrium dialysis, this technique is expensive and time consuming and is only performed in research laboratories. In commercial laboratories, canine serum fT_4 is measured by one of three methods: modified equilibrium dialysis (MED), analog 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. Analog methods measure fT_4 directly by RIA or chemiluminescence, but the reagents are optimized for human serum and depend upon the dominance of hormone binding by TBG (Ferguson, 2007). MED techniques are regarded as the most accurate commercially-available technique for determining serum fT_4 concentrations in dogs. In one study, the accuracy of one MED technique for fT_4 was 95% (Fig. 3-23) (Peterson et al, 1997). In

TABLE 3-6 **INTERPRETATION OF BASAL THYROID HORMONE AND THYROTROPIN CONCENTRATIONS***

	NORMAL THYROXINE/FREE THYROXINE	DECREASED OR BORDERLINE NORMAL THYROXINE/FREE THYROXINE
Normal TSH	Normal dog	Hypothyroid, normal variation, or concurrent illness
	Consider further thyroid testing only if strong clinical suspicion of hypothyroidism	Consider further diagnostic evaluation of thyroid function (e.g., thyroid autoantibodies, provocative testing) or therapeutic trial
Increased TSH	Early subclinical hypothyroidism or recovery from concurrent illness	Hypothyroid
	Consider reevaluation of thyroid function in 1 to 3 months; if strong clinical suspicion for hypothyroidism, evaluate for thyroiditis by measuring ATAs	Lifelong therapy with L-T_4 sodium is indicated; use therapeutic monitoring to adjust dose

ATA, Anti-thyroglobulin antibody; *L-T_4,* levothyroxine, or L-thyroxine; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone, or thyrotropin.
*T_4, free T_4, TSH.

TABLE 3-7 **INTERPRETATION OF BASELINE SERUM THYROXINE AND FREE THYROXINE CONCENTRATION IN DOGS WITH SUSPECTED HYPOTHYROIDISM**

SERUM THYROXINE CONCENTRATION (μg/dL)	SERUM FREE THYROXINE CONCENTRATION (ng/dL)	PROBABILITY OF HYPOTHYROIDISM
> 2.0 μg/dL	> 2.0 ng/dL	Very unlikely
1.5 to 2.0 μg/dL	1.5 to 2.0 ng/dL	Unlikely
1.0 to 1.5 μg/dL	0.8 to 1.5 ng/dL	Unknown
0.5 to 1.0 μg/dL	0.5 to 0.8 ng/dL	Possible
< 0.5 μg/dL	< 0.5 ng/dL	Very likely*

*Assuming that a severe systemic illness is not present.

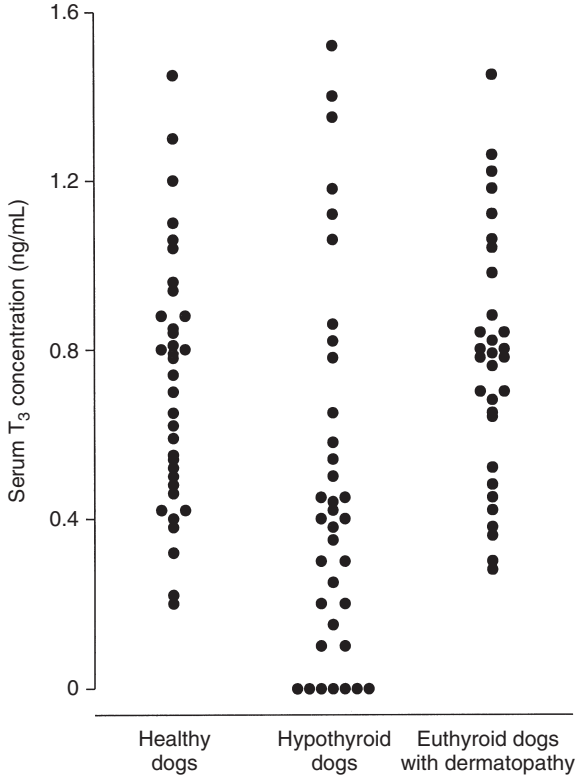

FIGURE 3-22 Baseline serum T_3 concentrations in 35 healthy dogs, 35 dogs with hypothyroidism, and 30 euthyroid dogs with concurrent dermatopathy. Note the overlap in serum T_3 results between the three groups of dogs.

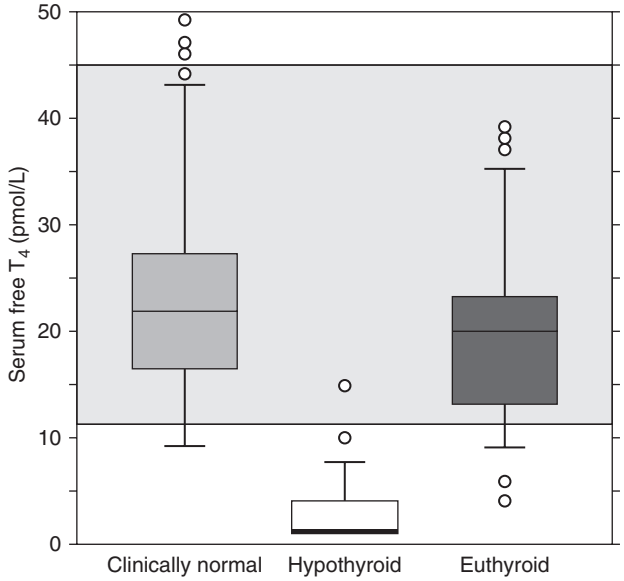

FIGURE 3-23 Box plots of serum free T_4 (fT_4) concentrations in 150 clinically normal dogs, 54 hypothyroid dogs, and 54 euthyroid dogs with nonthyroidal disease. The box represents the interquartile range (i.e., 25th to 75th percentile range, or the middle half of the data). The horizontal bar in the box represents the median value. For each box plot, the *T bars* represent the main body of data. Outlying data points are represented by *open circles*. The *shaded area* indicates the reference range for the serum free T_4 concentration. (From Peterson et al.: Measurement of serum total thyroxine, triiodothyronine, free thyroxine, and thyrotropin concentrations for diagnosis of hypothyroidism in dogs, *J Am Vet Med Assoc* 211[11]:1398, 1997.)

TABLE 3-8 **SENSITIVITY, SPECIFICITY AND ACCURACY OF FOUR FREE THYROXINE ASSAYS IN DOGS***

ASSAY	SENSITIVITY (%)	SPECIFICITY (%)	ACCURACY (%)
Analog free T_4	80	97	89
MED IVD	92	90	91
MED AN	71	100	86
Two-step	96	90	93

T_4, Thyroxine.
*The dog population included 56 dogs with clinical signs of hypothyroidism (31 euthyroid, 25 hypothyroid). Assays included the IMMULITE 2000 Veterinary Free T_4 *(Analog free T_4)* (Siemens Health Care Diagnostics), Direct Free T_4 by Equilibrium Dialysis *(MED IVD)* (IVD technologies), free T_4 by equilibrium dialysis *(MED AN)* (Antech Diagnostics), and GammaCoat Free T_4 *(Two-step)* radioimmunoassay (RIA) (Diasorin Inc).

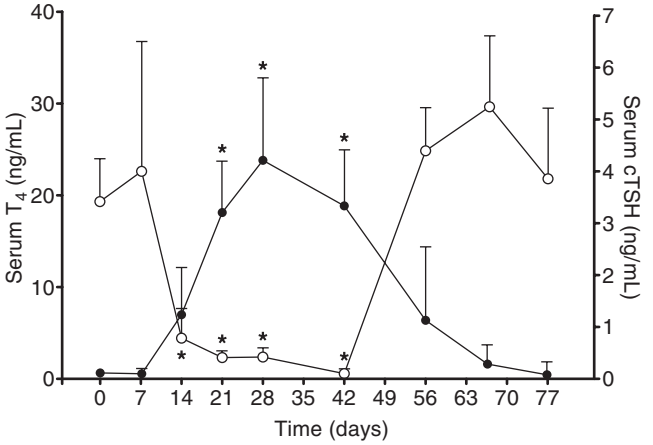

FIGURE 3-24 Mean serum thyroxine (T_4; ◦) and canine thyroid-stimulating hormone (cTSH; •) concentrations after experimental induction of hypothyroidism (day 0) and treatment with levothyroxine (L-T_4 sodium; beginning on day 42). Bars represent SD. *Significantly ($P < 0.05$) different from day 0 values. (From Williams DA, et al.: Validation of an immunoassay for canine thyroid-stimulating hormone and changes in serum concentration following induction of hypothyroidism in dogs, *J Am Vet Med Assoc* 209[10]:1730, 1996.)

more recent studies, reported accuracy of different MED assays has ranged from 86% to 93%, compared with an accuracy of 75% to 85% for serum T_4 (Nelson et al, 1991; Scott-Moncrieff et al, 1994; 2011; Peterson et al, 1997). It is important to use a fT_4 assay that has been demonstrated to have adequate diagnostic performance in dogs, because some human analog assays for fT_4 have accuracy that is no better than measurement of total T_4 in dogs (Schachter, 2004), whereas others compare favorably to the MED methods (Table 3-8) (Scott-Moncrieff et al, 2011). Serum for measurement of fT_4 can be stored in plastic tubes and shipped without cooling if assayed within 5 days (Behrend et al, 1998); however, because of the potential for extremes of temperature during transportation, it is recommended that serum samples are frozen and shipped to the laboratory on ice packs. In general, serum fT_4 concentrations greater than 1.5 ng/dL are consistent with euthyroidism, and values less than 0.8 ng/dL (especially those less than 0.5 ng/dL) are suggestive of hypothyroidism, assuming that the history, physical examination, and clinicopathologic abnormalities are also consistent with the disorder and severe systemic illness is not present (see Table 3-7). Circulating anti-thyroid hormone antibodies do not affect the fT_4 results determined by the MED technique but may still influence fT_4 measured by analog methods. Serum fT_4 is less affected by the suppressive effects of nonthyroidal illness than is the serum T_4, although severe illness can cause fT_4 concentrations to decrease below 0.5 ng/dL; see Concurrent Illness (Nonthyroidal Illness Syndrome). The reference range for serum fT_4 concentration is also lower in some breeds, such as the Greyhound (see Table 3-5) (Shiel et al, 2007a).

Baseline Serum Free Triiodothyronine Concentration

Serum fT_3 is derived from intracellular 5′-deiodination of fT_4 in peripheral tissues and, to a lesser extent, in the thyroid gland. The theoretical principle behind measuring serum fT_3 is similar to that for fT_4. RIAs designed for measurement of serum fT_3 in humans have been used in the dog. A critical assessment of the sensitivity and specificity of these RIAs has not been reported in dogs, nor has the diagnostic usefulness of measuring serum fT_3 for evaluating thyroid gland function been demonstrated.

Baseline Serum Reverse Triiodothyronine Concentration

rT_3 is a relatively inactive product of T_4 5′-deiodination (see Fig. 3-4). The vast majority of rT_3 is produced intracellularly from T_4; very little is secreted by the thyroid gland. Serum rT_3 concentration can be measured by specific RIAs that do not cross-react with T_4 or T_3. The clinical benefit of measuring rT_3 has not yet been demonstrated in dogs, and the assay has limited availability.

Baseline Serum Thyrotropin Concentration

TSH is a highly glycosylated molecule with an alpha and beta subunit. The alpha subunit is identical to that of the alpha subunit of the related glycoprotein hormones LH, FSH, and chorionic gonadotrophin, whereas the beta subunit is unique to TSH and confers the biologic properties of TSH. Assays for measurement of human TSH cannot be used to measure canine TSH. The first assay for canine TSH was validated in 1996 (Williams et al, 1996), and since that time there have been other commercial assays developed. Studies in dogs with ^{131}I-induced hypothyroidism have shown good assay performance with a 35-fold increase in the mean serum TSH concentration after induction of hypothyroidism and return of the mean serum TSH concentration to baseline after treatment with L-T_4 sodium (Fig. 3-24) (Williams et al, 1996). The assay used most commonly is the chemiluminescent TSH assay (Immulite Canine TSH), which has been demonstrated to have the highest precision compared to immunoradiometric and enzyme immunometric methods (Marca et al, 2001). Unfortunately all current commercial assays for canine TSH have poor sensitivity for diagnosis of spontaneous hypothyroidism. Twenty percent to 40% of dogs with hypothyroidism have TSH concentrations within the reference range, giving a test sensitivity of only 63% to 82% (Fig. 3-25). Although TSH as a stand-alone test also has poor specificity because of overlap in results between hypothyroid dogs and euthyroid dogs with concurrent illness (see Fig. 3-25), clinical studies have shown that a high serum TSH concentration has high specificity (90% or higher) for diagnosis of hypothyroidism in dogs when the baseline serum T_4 or fT_4 concentration is concurrently low (Dixon et al, 1996; Ramsey et al, 1997; Peterson et al, 1997; Scott-Moncrieff et al, 1998).

The reason for the low sensitivity of TSH concentration for diagnosis of canine hypothyroidism has been the subject of investigation, because TSH is a highly sensitive diagnostic test in humans.

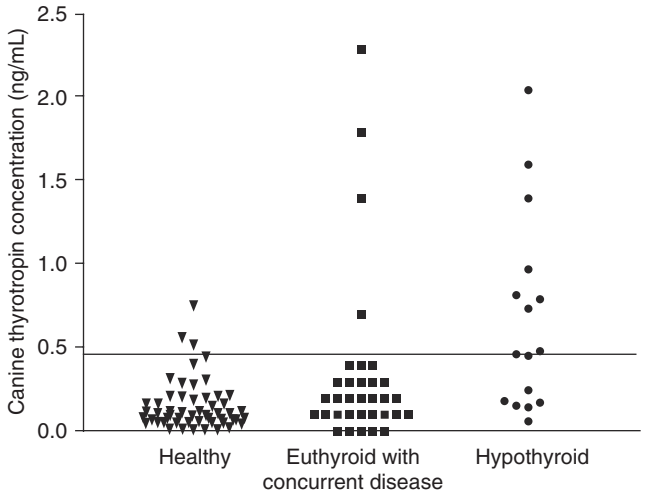

FIGURE 3-25 Canine thyroid-stimulating hormone (thyrotropin [TSH]) concentrations in healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease. (From Scott-Moncrieff JC, et al.: Comparison of serum concentrations of thyroid-stimulating hormone in healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease, *J Am Vet Med Assoc* 212[3]:389, 1998.)

Studies in dogs with ^{131}I-induced hypothyroidism demonstrated that over several months' time there was a loss of the TSH response to the low T_4 concentration, hypersecretion of GH, hyposecretion of prolactin, and pituitary enlargement (Fig. 3-26). The enlarged pituitary glands were characterized by thyrotroph hyperplasia, presence of large pale staining vacuolated "thyroid deficiency" cells similar to those observed in hypothyroid rats and humans, and double staining cells indicative of transdifferentiation of somatotrophs into thyrotrophs. The presence of mitoses in the thyrotrophs suggested that the division of pre-existing thyrotrophs or less differentiated stem cells contributed to the "thyroid deficiency" cells. It was hypothesized by the study authors that persistent stimulation of thyrotrophs via negative feedback led to TRH-receptor desensitization and gradual loss of TSH secretion (Diaz-Espiñeira, 2008b). Similar changes were demonstrated in dogs with spontaneous chronic hypothyroidism, and this is likely the reason for the poor sensitivity of the TSH assay in naturally occurring hypothyroidism (Diaz-Espiñeira, 2009). Other possible reasons that hypothyroid dogs might have serum TSH concentrations within the reference range include pulsatile TSH secretion, resulting in ultradian fluctuations (Fig. 3-27), secondary hypothyroidism, suppression of pituitary TSH secretion by concurrent disease or drug administration, and inability of the current TSH assay to detect all isoforms of circulating TSH (Kooistra et al, 2000b). Sample collection time does not appear to predictably influence serum TSH test results (Bruner et al, 1998; see Fig. 3-27). The lower limit of the reference range in dogs is currently below the sensitivity of the TSH assay, so it is not possible to differentiate low from normal serum TSH concentrations, which impairs the ability to identify secondary hypothyroidism, suppression of pituitary TSH secretion by concurrent drugs and diseases, and excess administration of L-T_4 sodium during treatment of hypothyroidism.

Because of the limitations discussed earlier, the serum TSH concentration should always be interpreted in conjunction with the serum T_4 or fT_4 concentration measured in the same blood sample and should never be used as the sole test for assessing thyroid gland function. A low serum T_4 or fT_4 concentration and a high TSH concentration in a blood sample obtained from a dog with appropriate history and physical examination findings supports the diagnosis of primary hypothyroidism, whereas a finding of normal serum T_4, fT_4, and TSH concentrations rules out hypothyroidism. Any other combination of serum T_4, fT_4, and TSH results is difficult to interpret (see Table 3-6).

Thyrotropin Stimulation Test

The TSH stimulation test evaluates the thyroid gland's responsiveness to exogenous TSH administration and is a test of thyroid gland reserve. The TSH stimulation test is indicated in dogs with low basal thyroid hormone concentrations to differentiate hypothyroidism from nonthyroidal illness syndrome (NTIS). The biologic activity of the TSH molecule is not species-specific so human recombinant TSH can be used for the test; however, this product is extremely expensive and is only available in a vial containing 1.1 mg of lyophilized recombinant TSH synthesized in a genetically modified Chinese hamster ovary cell line. TSH (Thyrogen; Genzyme Corporation, Cambridge, ME) is reconstituted in 1.2 mL of sterile water for injection (final solution 0.9 mg/mL). This is sufficient TSH for 7 to 15 stimulation tests depending upon the dose used. Recombinant TSH can be reconstituted and stored at 4° C for 4 weeks or frozen at −20° C for up to 12 weeks (De Roover et al, 2006; Daminet et al, 2007).

The protocol for the TSH stimulation test requires collection of a serum sample for measurement of T_4, followed by administration of 75 to 150 μg of TSH intravenous (IV). An additional blood sample for measurement of total T_4 is collected 6 hours later (Boretti et al, 2006a; 2006b; De Roover et al, 2006). The higher dose of TSH is recommended in dogs with concurrent disease and those receiving medication (e.g., glucocorticoids) that might suppress thyroid function (Boretti et al, 2009). Hypothyroidism is confirmed by a pre and post total T_4 concentration below the reference range for basal total T_4 concentration (< 1.5 μg/dL). Euthyroidism is confirmed by a post total T_4 concentration > 2.5 μg/dL and at least 1.5 times the basal T_4 concentration (see Fig. 3-21). Serum fT_4 concentrations increase in a manner similar to serum total T_4, do not provide additional diagnostic information, and therefore are not routinely measured in the TSH stimulation test. Although the TSH stimulation is more accurate for assessment of thyroid function than measurement of basal thyroid hormone concentrations, false positive results can occur. In a study of 30 dogs in which the diagnosis of thyroid status was confirmed histopathologically, some euthyroid dogs failed to respond to bovine TSH administration, and nuclear imaging had higher discriminatory power for diagnosis of true thyroid status than TSH stimulation testing (Diaz-Espiñeira et al, 2007). Stimulation results that fall in the intermediate range may also lead to interpretation difficulties especially in dogs with nonthyroidal illness. Interpretation of the results of the TSH stimulation test should take into consideration the clinical signs and severity of concurrent systemic disease, results of other thyroid testing (total T_4, fT_4, TSH, ATA concentration), and results of nuclear scintigraphy if available.

Thyrotropin-Releasing Hormone Stimulation Test

Indications

The TRH stimulation test evaluates the pituitary gland's responsiveness to TRH and the thyroid gland's responsiveness to TSH secreted in response to TRH administration. In humans, the TRH stimulation test is used to differentiate secondary and tertiary hypothyroidism. TRH response tests are not routinely performed for evaluation of humans with suspected primary hypothyroidism; however, there is a greater and more prolonged increase in TSH

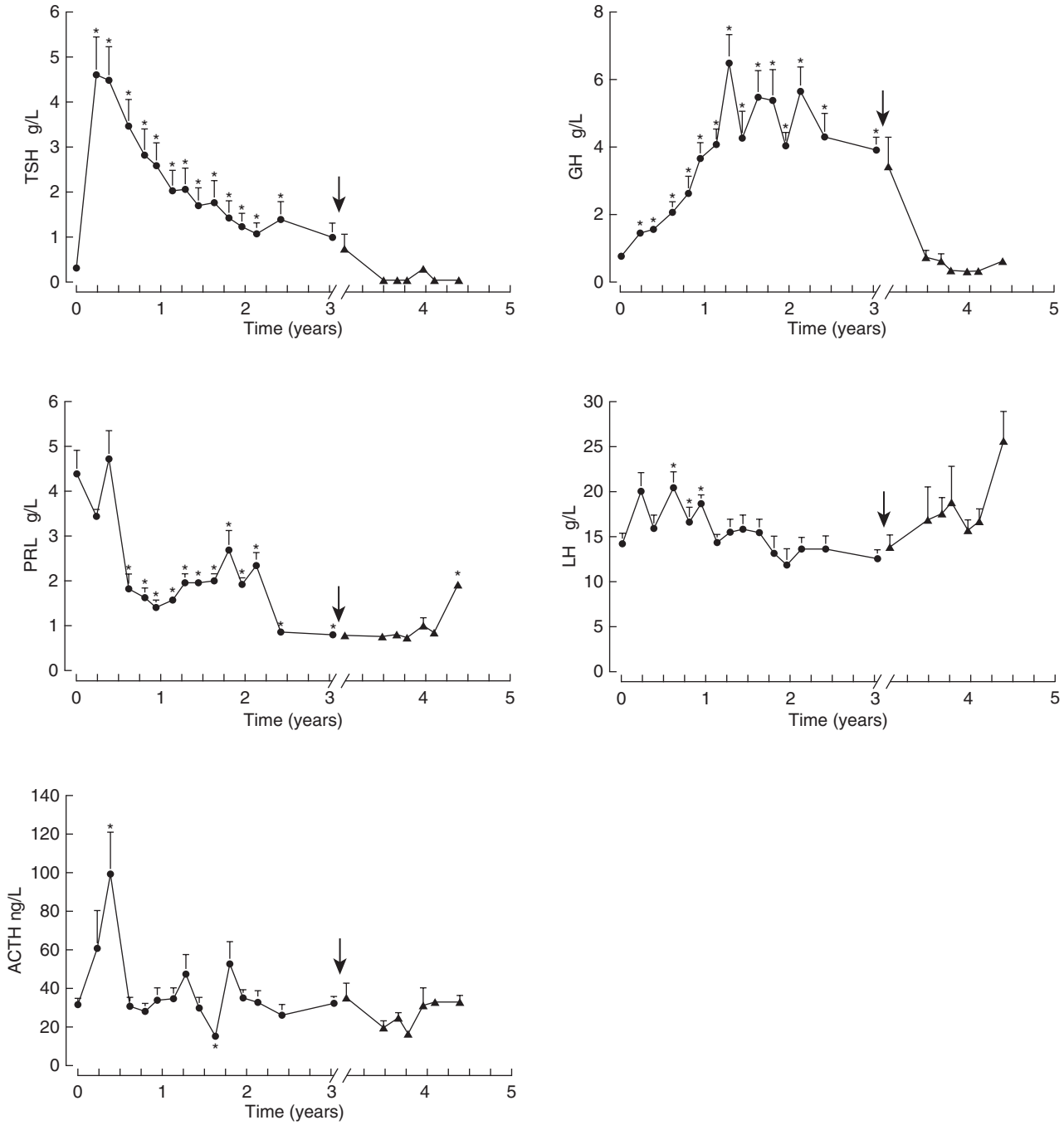

FIGURE 3-26 Mean basal plasma concentrations of thyrotropin *(TSH),* growth hormone *(GH),* prolactin *(PRL),* luteinizing hormone *(LH),* and adrenocorticotropic hormone *(ACTH)* measured at monthly intervals in seven Beagle dogs with hypothyroidism induced at time 0. Three of these dogs were followed up for another 1½ years while on levothyroxine (L-thyroxine; L-T_4) sodium supplementation *(arrow).* (From Diaz-Espiñeira MM, et al.: Functional and morphological changes in the adenohypophysis of dogs with induced primary hypothyroidism: loss of TSH hypersecretion, hypersomatotropism, hypoprolactinemia, and pituitary enlargement with transdifferentiation, *Domest Anim Endocrinol* 35[1]:98-111, 2008.)

concentration after TRH administration in humans with primary hypothyroidism than in healthy humans. In contrast, dogs with primary hypothyroidism have a lower change in TSH concentration after TRH administration than do healthy dogs (Scott-Moncrieff et al, 1998). This finding has been attributed to TRH receptor desensitization due to persistent stimulation of the pituitary thyrotrophs by the negative feedback loop (Diaz-Espiñeira, 2008b). In dogs, the TRH stimulation test has been used to differentiate between hypothyroidism and the NTIS in dogs with low basal thyroid hormone concentrations; however the test can be difficult to interpret because of the relatively small increase in serum T_4 concentration after TRH administration, and the test has little advantage for diagnosis of hypothyroidism over measurement of baseline TSH and total or free T_4 concentration. The primary current use of the TRH stimulation test is to assess anterior pituitary function as part of a combined pituitary function test.

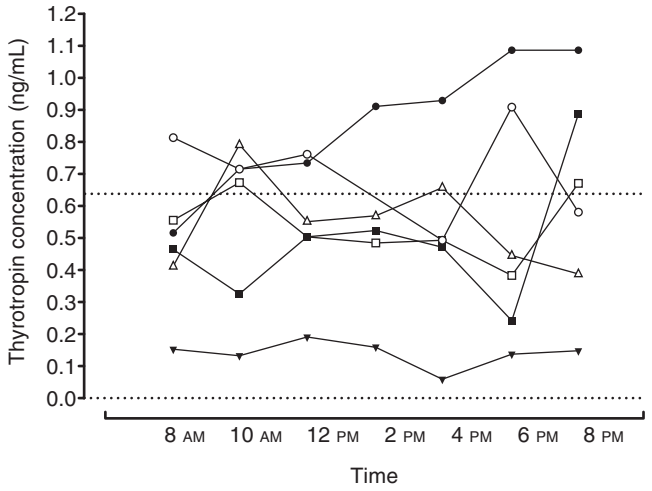

FIGURE 3-27 Serum thyrotropin (TSH) concentrations measured at 2-hour intervals from 8 AM to 8 PM in six dogs with naturally developing hypothyroidism. Reference range is between the *horizontal dotted lines*. Each symbol represents values obtained for one hypothyroid dog. (From Bruner JM, et al.: Effect of time of sample collection on serum thyroid-stimulating hormone concentrations in euthyroid and hypothyroid dogs, *J Am Vet Med Assoc* 212[10]:1572, 1998.)

Protocol

TRH is administered at a dose of 10 µg/kg or 200 µg/dog IV; blood for serum total T4 determination is obtained before and 4 hours after TRH administration, and blood for serum TSH determination is obtained before and 30 minutes after TRH administration (Scott-Moncrieff and Nelson, 1998). Measurement of serum TSH concentration after TRH administration is used to assess pituitary responsiveness to TRH, whereas measurement of serum T_4 concentration is used to assess the thyroid gland's responsiveness to the TRH-induced increase in pituitary TSH secretion. Serum fT_4 concentrations increase in a manner similar to serum T_4, do not provide additional diagnostic information, and therefore are not routinely measured.

Interpretation

The increase in serum total T_4 concentration is less dramatic with TRH than with TSH (Frank, 1996). Euthyroid dogs should have a post-TRH serum T_4 concentration greater than 1.5 to 2.0 µg/dL (Scott-Moncrieff et al, 1998). In contrast, dogs with primary hypothyroidism have a post-TRH serum T_4 concentration below the normal baseline serum T_4 range (i.e., < 1.5 µg/dL) (Fig. 3-28), but there is substantial overlap between the groups, and some euthyroid dogs fail to have any increase in T_4 after TRH administration. Because of these findings, there is currently little indication for the use of the TRH stimulation test in the evaluation of dogs with suspected hypothyroidism. TRH is not currently commercially available in the United States.

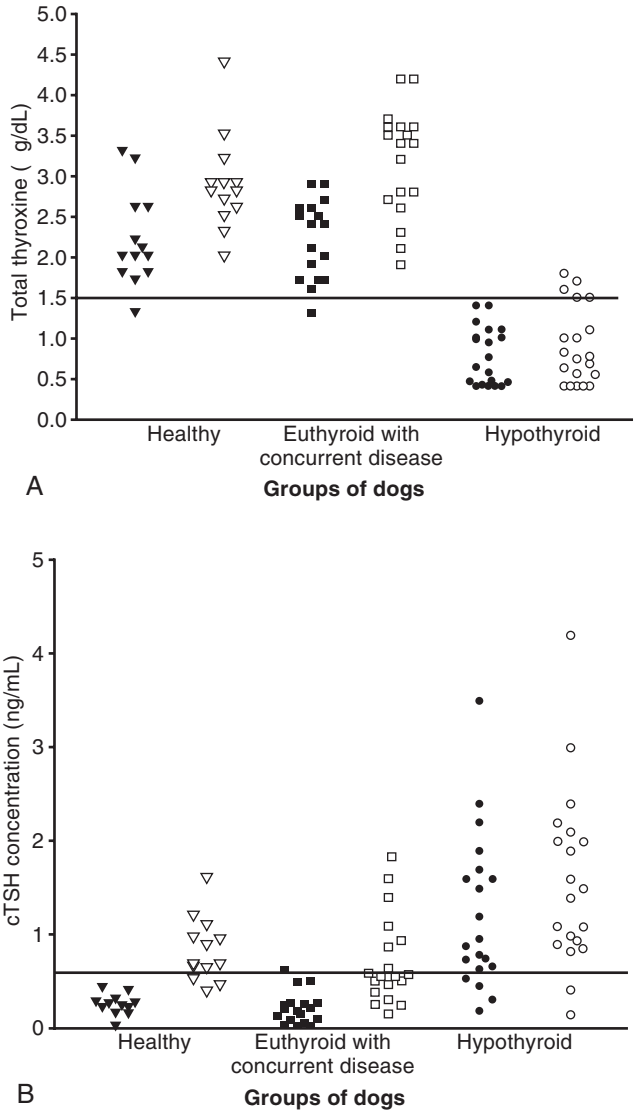

FIGURE 3-28 Thyroxine (T_4) concentration **(A)** and thyrotropin (TSH) concentration **(B)** before *(solid symbol)* and 30 minutes (for TSH) and 4 hours (for T_4) after *(open symbols)* administration of TRH to healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent diseases. The *horizontal line* represents the upper limit of the reference range for T_4 **(A)** and TSH **(B)**. (From Scott-Moncrieff JC, Nelson RW: Change in serum thyroid-stimulating hormone concentration in response to administration of thyrotropin-releasing hormone to healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease, *J Am Vet Med Assoc* 213[10]:1435, 1998.)

TESTS FOR LYMPHOCYTIC THYROIDITIS

During the inflammatory phase of lymphocytic thyroiditis, antibodies are released into the circulation. In dogs, the predominant antibody that arises is directed against Tg. Tg is a large complex protein molecule with several epitopes and antibodies formed against it are heterogenous. The thyroid hormones T_3 and T_4 are haptens and do not elicit an antibody response unless attached to a larger protein molecule (Gaschen et al, 1993). When an epitope contains a hormonogenic site, antibodies that cross-react with either T_3 or T_4 may develop. These antibodies are a subset of total ATAs and therefore dogs with thyroid hormone autoantibodies also have autoantibodies against Tg, whereas the converse is not true (Graham et al, 2007). Thus the Tg autoantibody test is a more sensitive test for lymphocytic thyroiditis than is measurement of anti-T_3 and anti-T_4 antibodies. Anti-TPO antibodies are the most common antibodies detected in human thyroiditis, but they are only detected in 17% of dogs with thyroiditis and are not detected in dogs that lack ATAs (Skopek et al, 2006). Assays for anti-TPO antibodies, therefore, have little clinical utility and are not currently commercially available.

Serum Thyroglobulin Autoantibodies

Circulating Tg autoantibodies are detected in approximately 50% of hypothyroid dogs (Nachreiner et al, 1998; Graham et al, 2007).

A commercially available ELISA (Oxford Biomedical Research Inc., Oxford, MI) for detection of Tg autoantibodies has been shown to be sensitive and specific for identification of Tg autoantibodies (Nachreiner et al, 1998). This ELISA is currently the most common Tg autoantibody assay used by commercial laboratories and results are expressed as a percentage of a standardized positive control. Nonspecific binding ELISA plates that do not contain Tg are included to reduce the effect of nonspecific immunoglobulin G (IgG). Some of the initial concern about borderline positive results after vaccination may have been related to nonspecific antibody binding.

Presence of serum Tg autoantibodies implies the presence of thyroiditis within the thyroid gland but provides no information on the severity or progressive nature of the inflammatory response or the function of the thyroid gland. Detection of Tg autoantibodies should not be used as the sole criteria to establish the diagnosis of hypothyroidism but can increase the index of suspicion for hypothyroidism in dogs with consistent clinical findings and equivocal basal thyroid hormone concentrations. Dogs with confirmed hypothyroidism can have negative Tg autoantibody concentrations, and euthyroid dogs can be positive for Tg autoantibodies. The value of serum Tg autoantibodies as a marker for eventual development of hypothyroidism remains to be clarified. A 1 year longitudinal study of 171 dogs with positive Tg autoantibody and normal serum fT_4 and TSH test results, found that approximately 20% of dogs developed decreased fT_4 and/or increased TSH concentrations consistent with hypothyroidism during the 1 year of follow-up. Fifteen percent of dogs reverted to negative Tg autoantibody status with no change in fT_4 and TSH concentrations, and 65% remained Tg autoantibody positive or had an inconclusive result with no change in fT_4 and TSH test results (Graham et al, 2001).

The prevalence of Tg autoantibodies varies with the breed (Table 3-2). Measurement of Tg autoantibodies has been advocated for

TABLE 3-9 ODDS OF HAVING SERUM THYROID HORMONE AUTOANTIBODIES (THAA) AMONG BREEDS WITH AN INCREASED RISK OF THAA COMPARED WITH DOGS OF ALL OTHER BREEDS

		Percentage with Autoantibodies					
BREED	NUMBER OF DOGS	TRIIODOTHYRONINE AUTOANTIBODIES	THYROXINE AUTOANTIBODIES	BOTH	TOTAL	ODDS RATIO	*P* VALUE
Pointer	118	11.86	0.85	6.78	19.49	3.61	0.001
English Setter	1,246	13.88	1.2	3.53	18.61	3.44	0.001
English Pointer	99	14.14	2.02	2.02	18.18	3.31	0.001
Skye Terrier	53	13.21	1.89	1.89	16.99	3.04	0.001
German Wirehaired Pointer	324	11.42	1.54	2.47	15.43	2.72	0.001
Old English Sheepdog	1,031	10.96	0.87	3.20	15.03	2.65	0.001
Boxer	5,239	9.14	0.88	3.47	13.49	2.37	0.001
Maltese	962	9.56	0.94	2.60	13.10	2.25	0.001
Kuvasz	180	10.56	2.22	0.00	12.78	2.18	0.001
Petit Basset Griffon Vendeen	63	6.35	3.17	3.17	12.69	2.16	0.036
American Staffordshire Terrier	246	8.54	1.22	1.22	10.98	1.84	0.003
Beagle	3,988	7.70	0.80	2.16	10.66	1.79	0.001
American Pit Bull Terrier	676	9.02	0.44	1.18	10.64	1.78	0.001
Dalmatian	2,332	6.82	1.07	2.53	10.42	1.74	0.001
Giant Schnauzer	406	8.37	0.74	1.23	10.34	1.72	0.001
Rhodesian Ridgeback	1,025	8.39	0.39	1.56	10.34	1.72	0.001
Golden Retriever	36,016	7.19	0.77	2.37	10.33	1.90	0.001
Shetland Sheepdog	11,423	7.84	0.61	1.51	9.96	1.69	0.001
Chesapeake Bay Retriever	1,005	7.26	0.70	1.49	9.45	1.56	0.001
Siberian Husky	1,153	6.94	0.69	1.21	8.84	1.45	0.001
Brittany	1,257	6.76	0.72	1.19	8.67	1.42	0.001
Borzoi	527	7.21	0.19	1.14	8.54	1.39	0.034
Australian Shepherd	1,328	5.72	0.60	1.58	7.90	1.28	0.016
Doberman Pinscher	11,084	6.21	0.64	0.77	7.62	1.24	0.001
Malamute	1.449	6.21	0.48	0.90	7.59	1.22	0.042
Cocker Spaniel	18,976	5.83	0.63	0.76	7.22	1.17	0.001
Mixed	42,647	4.92	0.66	0.99	6.57	1.05	0.012
Total all breeds	**287,948**	**4.64**	**0.63**	**1.03**	**6.30**	**NA**	**NA**

From Nachreiner RF, et al.: Prevalence of serum thyroid hormone autoantibodies in dogs with clinical signs of hypothyroidism, *J Am Vet Med Assoc* 220:468, 2002.
NA, Not applicable.

screening breeding stock with the aim of ultimately eliminating heritable forms of thyroiditis. The Orthopedic Foundation for Animals (OFA) maintains a thyroid registry and issues a breed database number to all dogs found to have normal thyroid function at 12 months of age (based on measurement of fT_4, TSH, and Tg autoantibodies by an OFA-approved laboratory). Each dog also must be examined by a veterinarian. Because hypothyroidism usually develops after 1 year of age, it is recommended that reexamination and retesting occur at 2, 3, 4, 6, and 8 years of age.

Serum Thyroid Hormone Autoantibodies

Thyroid hormone autoantibodies are also considered an indicator of lymphocytic thyroiditis and may be a better predictor of the potential for development of hypothyroidism in dogs. In a recent study, thyroid hormone autoantibodies were detected in 6.3% of 287,948 serum samples from dogs with clinical signs consistent with hypothyroidism (Nachreiner et al, 2002; Table 3-9). T_3 autoantibodies alone were detected in 4.64%, T_4 autoantibodies alone were detected in 0.63%, and both T_3 and T_4 autoantibodies were detected in 1.03% of the serum samples. An inverse correlation existed between prevalence of thyroid hormone autoantibodies and age of the dogs; females had a significantly higher chance of being positive for thyroid hormone autoantibodies than did males, and neutered males and females had a significantly higher prevalence of thyroid hormone autoantibodies than did sexually intact dogs. Breeds at increased risk for having thyroid hormone autoantibodies were also identified (Table 3-9).

Measurement of serum T_4 and T_3 autoantibodies is offered by some commercial endocrine laboratories as part of an extensive thyroid panel. Testing for serum T_3 and T_4 autoantibodies is indicated in dogs with unexpected or unusual serum T_3 or T_4 test results. T_3 and T_4 autoantibodies may interfere with the RIAs used to measure serum T_3 or T_4 concentrations, causing unexpected and often confusing test results (Graham et al, 2007; see Fig. 3-19). The type of interference depends on the separation system employed in the RIA. Falsely low results are obtained if nonspecific separation methods are used (e.g., ammonium sulfate, activated charcoal); falsely increased values are obtained if single-step separation systems utilizing antibody-coated tubes are used. For most commercially available T_4 assays, T_4 autoantibodies will falsely increase the measured T_4 concentration. The false increase may be enough to raise a hypothyroid dog's result into the reference or hyperthyroid range. The same false increase occurs with non-dialysis (direct) RIAs used for measuring serum fT_4 concentrations (Kemppainen et al, 1996). False elevations in serum fT_4 concentration do not occur if fT_4 is measured using an assay that includes a dialysis step (MED assays), because autoantibodies cannot pass through the dialysis membrane and interfere with the assay. Thus evaluation of serum fT_4 concentration measured by MED should be performed in lieu of measurement of serum T_4 in dogs suspected of having T_4 autoantibodies. Fortunately spurious T_4 values resulting from clinically relevant concentrations of T_4 autoantibody are uncommon (Nachreiner et al, 2002; Piechotta et al, 2010).

Positive serum thyroid hormone autoantibody test results imply pathology in the thyroid gland but provide no information on the severity or progressive nature of the inflammatory response or the extent of thyroid gland involvement, nor are these tests an indicator of thyroid gland function. T_3 and T_4 autoantibodies should not be used as the sole criteria for establishing the diagnosis of hypothyroidism. Dogs with confirmed hypothyroidism can be negative and euthyroid dogs can be positive for thyroid hormone autoantibodies. Identification of T_3 or T_4 autoantibodies support hypothyroidism caused by lymphocytic thyroiditis if the dog has clinical signs, physical findings, and thyroid hormone test results consistent with the disorder.

FACTORS AFFECTING THYROID GLAND FUNCTION TESTS

Correct interpretation of tests of thyroid gland function is one of the primary diagnostic challenges in canine clinical endocrinology. There are many factors that influence baseline thyroid hormone and endogenous TSH concentrations, including age, breed, body size, diurnal or random fluctuations, athletic training, gender, reproductive status, concurrent illness, and drug therapy. Because many of these factors decrease baseline thyroid hormone concentrations and some can concomitantly increase endogenous TSH in euthyroid dogs, misdiagnosis of hypothyroidism may occur if the clinician accepts the results out of context. In our experience, the most common factors that result in lower baseline thyroid hormone concentrations in euthyroid dogs are concurrent illness (i.e., NTIS), use of drugs (especially glucocorticoids), and random fluctuations in thyroid hormone concentrations. In any given dog, other factors may also influence baseline thyroid hormone concentrations. It is important to recognize the potential influence of these factors when interpreting thyroid hormone test results.

Age

In dogs there is a progressive decline in T_4 concentration with age; serum T_4 concentration is highest in puppies, and the T_4 concentration progressively declines during adulthood. In a study of 27 female Beagles of different ages, mean serum T_4 concentrations in old dogs were 40% lower than those of young adult dogs (Gonzalez and Quadri, 1988). In a larger study of serum collected from 1074 healthy dogs of differing ages, the mean total T_4 concentration was 21% lower in in dogs older than 6 years of age compared to young adult dogs; similar trends with age were not identified for serum T_3 concentration (Reimers et al, 1990; Fig. 3-29). In a longitudinal study of 48 Labrador Retrievers studied for 12 years, the mean total T_4 decreased by 29% from the age of 6 to 12 years of age (Lawler et al, 2007). Similar trends occur for fT_4 and serum total T_3 concentrations, although this was not true in a study of healthy Salukis (Reimers et al, 1990; Lawler et al, 2007; Shiel et al, 2010). Older dogs have a higher mean TSH concentration than younger dogs (Bhatti et al, 2006) and middle-aged and older dogs also have a blunted T_4 response to TSH compared to young animals (Gonzalez and Quadri, 1988). Changes in other parameters of thyroid function have been less studied, but increases in anti-T_4 antibody in older dogs have been reported (Lawler et al, 2007). Although older dogs as a group have lower total T_4 concentrations than younger animals, the mean and median total T_4 concentration still falls within the lower end of most reference ranges (Table 3-10). None of the studies cited earlier reported a range for total T_4 in healthy geriatric dogs; it is likely that for many geriatric dogs a total T_4 below the reference range is a normal age related change. Reasons for the decline in thyroid hormone concentrations with age in dogs are not fully understood; proposed reasons include effect of concurrent illness, change in responsiveness of the thyroid gland to TSH, subclinical thyroid pathology (fibrosis, atrophy, degenerative changes), and decreased biologic activity of TSH with age.

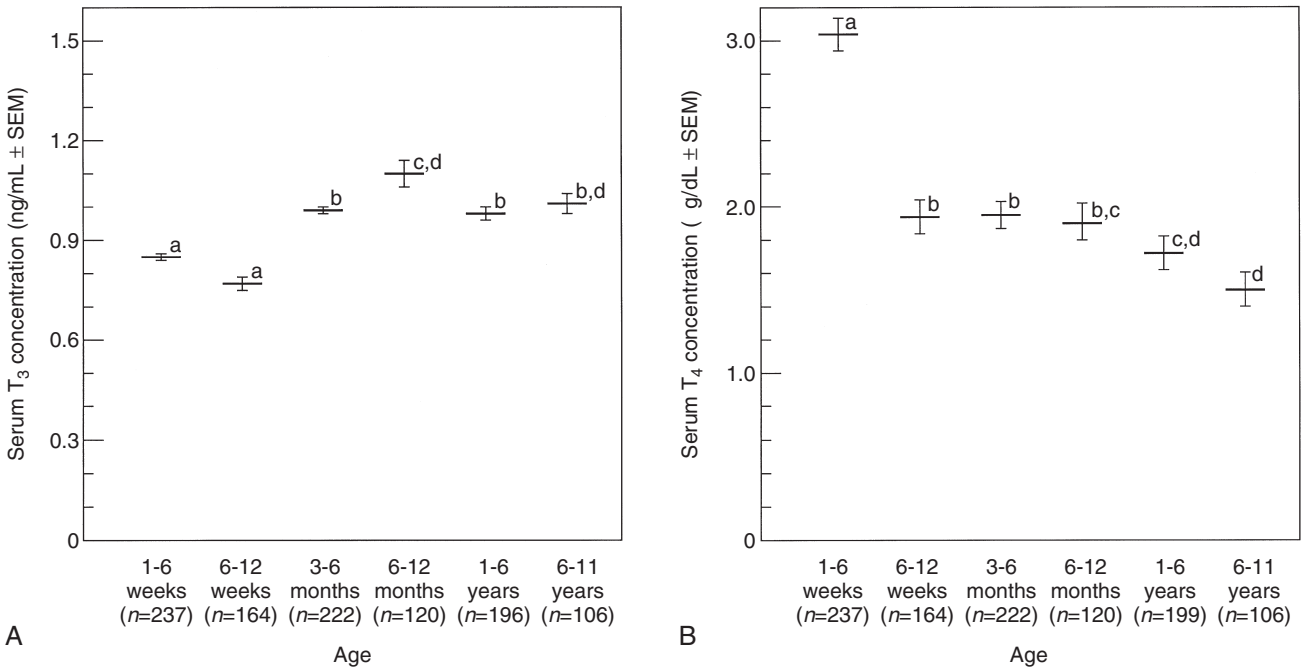

FIGURE 3-29 Mean (± SEM) serum triiodothyronine (T_3) **(A)** and thyroxine (T_4) **(B)** concentrations in nursing puppies (1 to 6 weeks), weanling puppies (6 to 12 weeks), juvenile dogs (3 to 6 months), young adults (6 to 12 months), middle-aged adults (1 to 6 years), and old dogs (6 to 11 years). Means having different superscripts are significantly ($P < 0.05$) different. (Adapted from Reimers TJ, et al.: Effects of age, sex, and body size on serum concentrations of thyroid and adrenocortical hormones in dogs, *Am J Vet Res* 51[3]:454, 1990.)

TABLE 3-10 **MEAN AND MEDIAN SERUM TOTAL THYROXINE CONCENTRATION OF SAMPLES SUBMITTED TO A REFERENCE LABORATORY FOR DOGS OF DIFFERENT AGES***

AGE, y	MEAN THYROXINE, μg/dL	MEDIAN THYROXINE, μg/dL	NUMBER OF PATIENTS
0 to 2	1.94	1.9	1043
3 to 5	1.91	1.8	2773
6 to 8	1.83	1.6	6975
9 to 11	1.75	1.5	5064
12 to 14	1.67	1.4	4016
> 14	1.46	1.2	736
All ages	1.78	1.5	20,607
Total T_4 reference range	1.0-4.0		

Data was provided by IDEXX Laboratories, Inc., Westbrook, ME.
Modified from Scott-Moncrieff CJ: Thyroid disorders in the geriatric veterinary patient, *Vet Clin North Am Small Anim Pract* 42(4):709, 2012.
*Patients with an age listed as 0 were excluded.

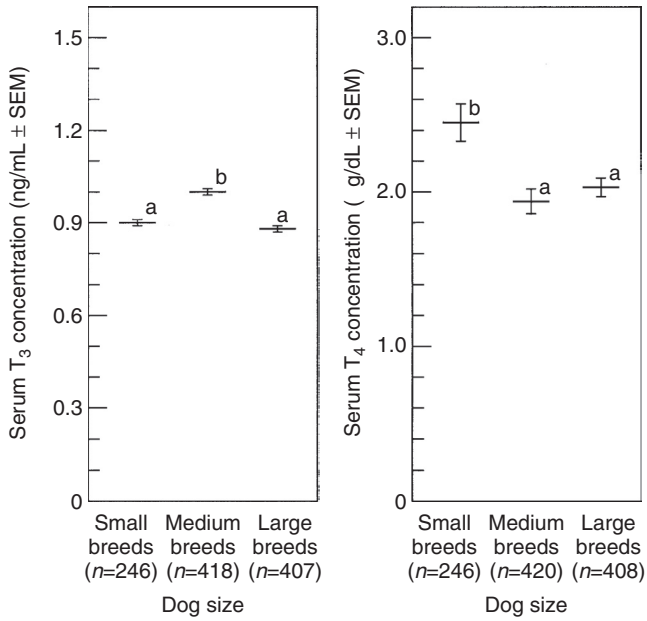

FIGURE 3-30 Mean (± SEM) serum triiodothyronine (T_3) and thyroxine (T_4) concentration in small breed dogs (mean body weight, 7.1 kg), medium breed dogs (mean body weight, 23.3 kg), and large breed dogs (mean body weight, 30.6 kg). Means having different superscripts are significantly ($P < 0.05$) different. (Adapted from Reimers TJ, et al.: Effects of age, sex, and body size on serum concentrations of thyroid and adrenocortical hormones in dogs, *Am J Vet Res* 51[3]:454, 1990.)

Body Size

Comparison of normal thyroid hormone values between groups of dogs based on body size has identified differences in mean serum T_4 and T_3 concentrations (Reimers et al, 1990; Fig. 3-30). Dogs were divided into three groups based on body size. Small dogs had a mean middle-aged body weight of 7.1 kg and included Poodles, Beagles, and Miniature Schnauzers; medium-sized dogs had a mean middle-aged body weight of 23.3 kg and included English Pointers, English Setters, and Siberian Huskies; large dogs had a mean middle-aged body weight of 30.6 kg and included Black

TABLE 3-11 **THYROID FUNCTION TEST RESULTS IN HEALTHY AKITAS, GOLDEN RETRIEVERS, BEAGLES, AND MINIATURE AND TOY POODLES***

VARIABLE	AKITA (N = 12)	GOLDEN RETRIEVER (36)	BEAGLE (12)	TOY AND MINIATURE POODLES (12)	REFERENCE RANGE
Serum T_4 (μg/dL)	2.4 ± 0.9	2.0 ± 0.5	1.9 ± 0.6	1.9 ± 0.5	1.0-3.6
Serum fT_4 (ng/dL)	1.1 ± 0.3	1.1 ± 0.4	1.3 ± 0.5	1.3 ± 0.5	0.8-3.5
Serum cTSH (ng/mL)	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0-0.6
Thyroglobulin autoantibody positive sera	None	None	None	None	NA

From Brömel C, et al.: Comparn of ultrasonographic characteristics of the thyroid gland in healthy small-, medium-, and large-breed dogs, *Am J Vet Res* 67(1):72, 2006.
*Data for serum hormone concentrations are presented as mean ± SD.

and Tan Coonhounds, Labrador Retrievers, Doberman Pinschers, and German Shepherd dogs. Mean serum T_4 concentration was greater in small than in medium-sized and large dogs. However, mean serum T_3 concentration was greater in medium-sized than in small and large dogs. In a smaller more recent study, there was no difference in total T_4, fT_4, or TSH concentrations between groups of healthy Akitas, Golden Retrievers, Beagles, or Toy/Miniature Poodles (Brömel et al, 2006; Table 3-11).

Breed

Most laboratories report reference ranges based on measurement of thyroid hormone concentrations in large groups of dogs of various breeds and ages; however there are significant differences between breeds in regard to thyroid hormone concentration, particularly for Sighthounds. In a study of 46 young healthy Greyhounds, 91% of the dogs had total T_4 concentration below the non-breed specific reference range, and 16% had total T_4 concentrations that were either at or below the limit of detection of the assay (Shiel et al, 2007a). Free T_4 was lower than the non-breed specific reference range in 21% of dogs and at or below the limit of detection in 13% of dogs. In the same study, T_3 concentrations were all within the non-breed specific reference range. Differences in reference ranges have also been reported for Whippets, Salukis, Sloughis, Basenjis, Borzois, Scottish Deerhounds, Irish Wolfhounds, and conditioned Alaskan sled dogs (van Geffen, 2006; Panacova, 2008; Seavers, 2008; see Table 3-5). The reason for the difference in thyroid hormone concentrations between Greyhounds and other breeds has not yet been elucidated, but studies suggest that it is not due to changes in concentration or function of thyroid binding globulin (Shiel et al, 2011). These findings suggest that breed-specific reference ranges for thyroid hormone tests need to be established and used when evaluating thyroid gland function especially in Sighthounds. For breeds in which total T_4 and fT_4 concentrations are close to the limit of detection in many healthy dogs, diagnosis of hypothyroidism should rely on history, physical examination, results of the complete blood count (CBC) and serum biochemistry panel and multiple tests of thyroid gland function. Measurement of total T_3 may be more useful in Greyhounds than in other breeds, because it is the only measurement that typically falls within the non-breed specific reference range, and because there is a low prevalence of thyroiditis in this breed (Nachreiner et al, 2002).

Athletic Training

Most studies on the effect of athletic training on thyroid function have focused on Alaskan sled dogs and Greyhounds. After sprint racing, total T_4 but not fT_4 concentration decreased after adjustment for hemoconcentration (Hill et al, 2001). Concentrations of T_4, T_3, and fT_4 are below the non-breed specific reference range in conditioned Alaskan sled dogs, and these concentrations decrease further during prolonged endurance racing (Panciera et al, 2003; Lee et al, 2004; Evason et al, 2004). The reported effect of conditioning and racing on serum TSH is variable. Reasons for the change in thyroid hormone concentrations after endurance exercise are poorly defined but likely include nutritional changes, effect of ambient temperature, or an appropriate physiologic response to increased metabolic rate associated with racing.

Gender and Reproductive Stage of the Female

When the specific stage of the female reproductive cycle is not considered and dogs are merely classified as male or female, gender has no apparent effect on serum thyroid hormone concentrations (Reimers et al, 1990). The mean (± SE) serum T_4 and T_3 concentrations in approximately 550 female versus 515 male dogs were 2.11 ± 0.04 versus 2.08 ± 0.04 μg/dL and 0.94 ± 0.01 versus 0.92 ± 0.01 ng/mL, respectively.

Testosterone decreases thyroid-binding protein and can decrease serum T_4 while having little effect on serum fT_4 concentrations (Wenzel, 1981). The effect of testosterone on thyroid hormone test results in dogs is unclear. In one study, serum T_4 concentration increased significantly after male Greyhound dogs were castrated and when not in training (Hill et al, 2001). There was no effect of castration on serum fT_4 or TSH concentrations. However, in another study, serum T_4, fT_4, and TSH concentrations were not different between testosterone-treated and untreated female Greyhound dogs, suggesting that exogenous testosterone administration may not affect thyroid hormone test results (Gaughan and Bruyette, 2001).

In the female dog, progesterone (but not estrogen) affects serum T_4 and T_3 concentrations. In one study, serum T_4 and T_3 concentrations were greater in diestrus females, than in females in anestrus, proestrus, lactating females, or male dogs (Reimers et al, 1984). Medroxyprogesterone treatment of five euthyroid bitches once a month for 11 months did not change basal plasma TSH concentration or TRH stimulated TSH concentration (Beijerink et al, 2007). In another study, dogs with hyperestrogenism did not have changes in baseline serum T_4 or T_3 concentrations, although the T_4 response to TSH administration was mildly depressed (Gosselin et al, 1980). It has been postulated that progesterone (elevated during diestrus with or without pregnancy) may enhance the binding affinity of plasma proteins for thyroid hormones, resulting in an increase in serum concentrations of total T_4 and T_3 (Wenzel, 1981).

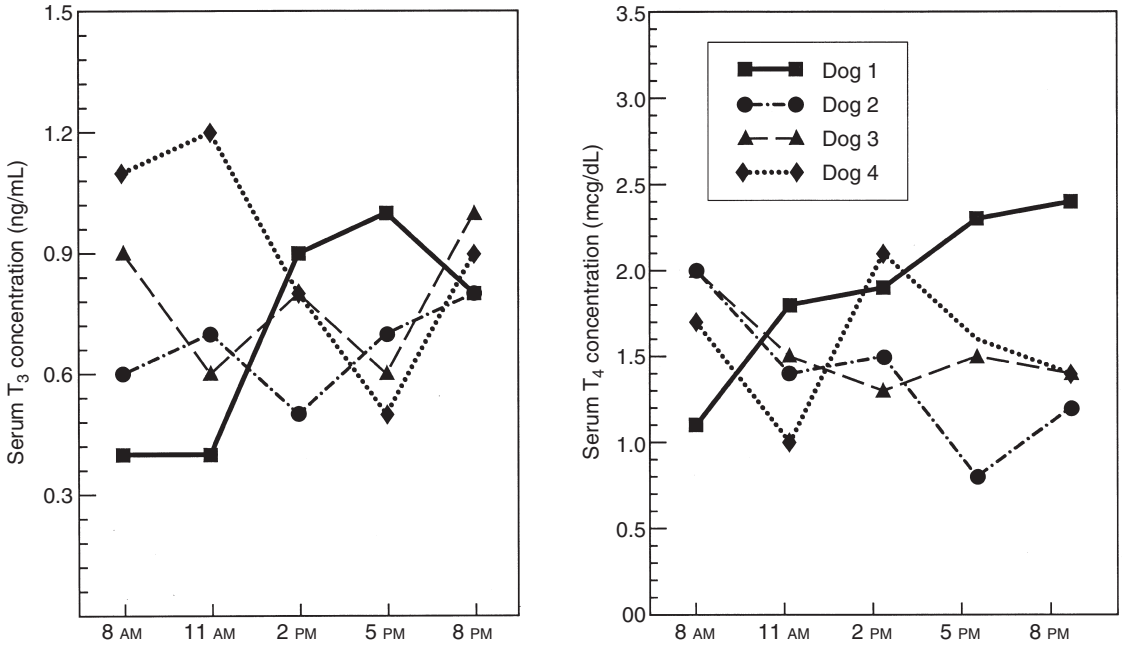

FIGURE 3-31 Sequential baseline serum triiodothyronine (T_3) and thyroxine (T_4) concentrations from blood samples obtained at 8 AM, 11 AM, 2 PM, 5 PM, and 8 PM in four healthy dogs. Note the random fluctuation in serum T_3 and T_4 concentrations throughout the day and the occasional low value, which could result in a misdiagnosis of hypothyroidism.

Diurnal Rhythm

In a study of 11 healthy mixed breed dogs in which blood samples were collected every 3 hours between 8 AM and 8 PM, total T_4 concentration was higher between 11 AM and 8 PM compared to 8 AM (Hoh et al, 2006). For fT_4 the concentrations at 11 AM and 2 PM were higher than those at 8 AM. This suggests the possibility of a diurnal rhythm with a peak in serum thyroid hormone concentration at mid-day in the dog. Further studies are needed to confirm this finding. A diurnal rhythm in TSH secretion was not identified in healthy euthyroid dogs (Bruner et al, 1998; see Fig. 3-27).

Random Fluctuations

Random or pulsatile fluctuations in baseline serum T_4, and T_3, occur in healthy dogs, euthyroid dogs with concurrent illness, and hypothyroid dogs (Fig. 3-31; Kemppainen and Sartin, 1984; Miller et al, 1992). Although there was little fluctuation in TSH concentration during the day in euthyroid dogs, sporadic and pulsatile fluctuations in TSH concentrations during the day were documented in hypothyroid dogs (Bruner et al, 1998; Kooistra et al, 2000a; see Fig. 3-27).

Concurrent Illness (Nonthyroidal Illness Syndrome)

The nonthyroidal illness syndrome (NTIS; euthyroid sick syndrome) refers to suppression of serum thyroid hormone concentrations that occur in euthyroid patients due to concurrent illness. Causes of NTIS include almost any systemic illness, surgery, and trauma, as well as inadequate caloric intake. Disorders such as dermatologic diseases and osteoarthritis are unlikely to cause NTIS (Paradis et al, 2003). Although drugs may also affect thyroid function, thyroid suppression induced by drugs is not generally included within the definition of NTIS. Mechanisms that are believed to contribute to NTIS include decreased TSH secretion, decreased synthesis of T_4, decreased concentration or binding affinity of circulating binding proteins, presence of serum protein binding inhibitors, inhibition of the de-iodination of T_4 to T_3, or any combination of these factors (Wiesinga and Van den Berghe, 2013). Decreased serum thyroid hormone concentrations are believed to be a physiologic adaptation that decreases cellular metabolism during illness. Generally, the magnitude of the change in serum thyroid hormone concentrations is not related to the specific disorder but rather reflects the severity of the illness, with more severe systemic illness resulting in more severe suppression of serum thyroid hormone concentrations (Kaptein, 1988; Kantrowitz et al, 2001; Mooney et al, 2008; Fig. 3-32). In a study of dogs with idiopathic epilepsy, there was a significant correlation between seizure frequency and thyroid hormone concentrations; the longer the interval between seizures the higher the thyroid hormone concentration (von Klopmann et al, 2006). There was no correlation with the time span between the most recent seizure episode and blood collection, suggesting that it was the severity of illness rather than the seizure itself that suppresses thyroid hormone concentrations. Disorders that are frequently associated with NTIS in dogs include neoplasia, renal disease, hepatic disease, cardiac failure, neurologic disease, inflammatory disorders, and diabetic ketoacidosis. It may be difficult or impossible to establish a diagnosis of concurrent hypothyroidism in dogs with NTIS, especially when relying on results of a single test of thyroid gland function. Normal test results are indicative of euthyroidism, but abnormal test results do not confirm a diagnosis of hypothyroidism because dogs with NTIS often have serum T_4 concentrations that are indistinguishable from true hypothyroidism.

In humans the pattern of thyroid hormone suppression is quite predictable, and T_3 is more commonly suppressed than total T_4 or fT_4 (low T_3 syndrome). In dogs, however, most studies have

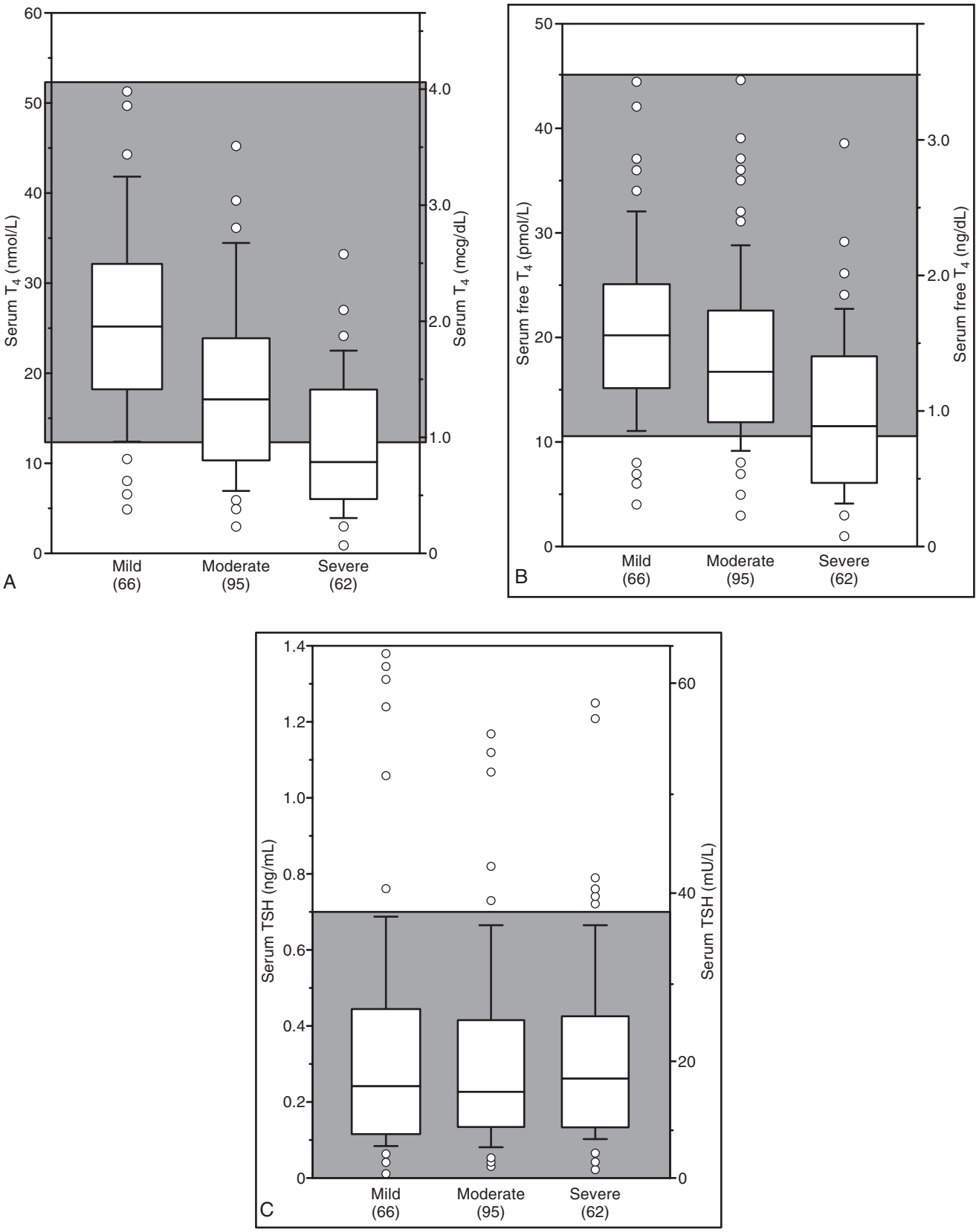

FIGURE 3-32 Box plots of serum concentrations of total thyroxine (T_4) **(A),** free T_4 (fT_4) **(B),** and thyrotropin (TSH) **(C)** in 223 dogs with nonthyroidal disease stratified according to severity of disease. For each box plot, T-bars represent the main body of data, which in most instances is equal to the range. Each box represents interquartile range (25th to 75th percentile). The *horizontal bar* in each box is the median. *Open circles* represent outlying data points. *Numbers in parentheses* indicate the numbers of dogs in each group. Reference range is indicated by the *shaded area.* (From Kantrowitz LB, et al.: Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in dogs with nonthyroidal disease, *J Am Vet Med Assoc* 219[6]:765, 2001.)

reported that the most common finding in systemically ill dogs is a decreased total T_4. Alterations in serum concentrations of T_3, fT_4, and TSH are more variable and may depend in part on the pathophysiologic mechanisms involved in the illness. Although serum fT_4 concentrations are decreased to a lesser extent than total T_4 concentrations (Peterson et al, 1997; Kantrowitz et al, 2001), in the presence of severe systemic illness, fT_4 concentrations can also be markedly decreased. Results of TSH and TRH stimulation testing can also be suppressed and suggestive of true hypothyroidism. Serum TSH concentrations are usually normal but may be increased in a small percentage of patients especially during recovery from NTIS. In one study of 223 dogs with NTIS, approximately 31% of dogs had low total T_4 concentrations and 22% had low fT_4, whereas only 8% had high serum TSH concentrations (Kantrowitz et al, 2001). In a more recent study of 196 dogs with NTIS, total T_3, total T_4, and fT_4 were decreased in 76%, 35%, and 5% of dogs respectively, whereas canine TSH was increased in only 3% of dogs (Mooney et al, 2008). In this study, decreased total T_3 concentrations were relatively common, and total T_3 was significantly lower in dogs that were euthanized compared to those that survived. The high percentage of dogs in this study with a low total T_3 is more similar to what is typically reported in humans with NTIS. Multiple studies in dogs, cats, and humans with NTIS have confirmed that the severity of suppression of serum thyroid hormone concentrations can be used as a prognostic indicator. Lower serum thyroid hormone concentrations are associated with a higher mortality rate (Peterson and Gamble, 1990; Elliott et al, 1995: Mooney et al, 2008; Schoeman et al, 2007). In a study of 63 critically ill puppies with parvoviral enteritis, serum T_4 and fT_4 were significantly lower in non-survivors than survivors (Schoeman et al, 2007). Similar findings have been documented in dogs with other severe systemic illness.

The existence of NTIS makes it very difficult to confirm a diagnosis of concurrent hypothyroidism in systemically ill dogs. If possible, evaluation of thyroid function should be postponed until resolution of the underlying illness. In some circumstances, however, treatment of concurrent hypothyroidism could improve outcome if hypothyroidism is contributing to the pathogenesis of the disorder. Examples of clinical situations in which this might occur are dogs with laryngeal paralysis and megaesophagus in which hypothyroidism may contribute to decreased neurologic function. In this situation multiple thyroid parameters should be evaluated in the context of history, physical examination findings, and other laboratory data. The simultaneous occurrence of low T_4, fT_4, and high TSH concentration is uncommon in NTIS, occurring in only 1.8% of 223 dogs with nonthyroidal illness in one study and in none of 66 dogs in another study (Kantrowitz et al, 2001; Torres, 2003). Therefore if this combination of findings is identified in a dog with supportive clinical findings, a diagnosis of true hypothyroidism is more likely. A TSH stimulation test, thyroid scintigraphy, or a therapeutic trial may all be appropriate options in such a scenario.

Treatment of NTIS should be directed at resolution of the concurrent illness. Serum thyroid hormone concentrations return to normal once the concurrent illness is corrected. Because NTIS is believed to be a physiologic protective mechanism, it is not recommended to treat affected patients with thyroid supplementation, and there are no studies that document a benefit of such treatment. In a study of euthyroid dogs with congestive heart failure, supplementation with thyroid hormone did not improve survival (Tidholm et al, 2003). Although many dogs with euthyroid sick syndrome are inadvertently treated with L-T_4 sodium without obvious deleterious consequences, it is not recommended—especially if the concurrent illness is severe and there is nothing in the history, physical examination, or blood work to support a diagnosis of concurrent hypothyroidism.

Dermatologic Disorders

Hypothyroidism is frequently included in the differential diagnosis of many dermatologic disorders in the dog. Studies suggest that common dermatologic disorders (e.g., pyoderma, flea hypersensitivity, allergic dermatitis) do not typically cause serum thyroid hormone concentrations to decrease into the hypothyroid range in euthyroid dogs (Slade et al, 1984; Nelson et al, 1991; Beale et al, 1992a; Daminet et al, 2000). Borderline serum T_4 and fT_4 concentrations however may occur in individual euthyroid dogs with skin disease.

Diabetes Mellitus

Thyroid hormones play an important role in glucose homeostasis. and hypothyroidism and diabetes mellitus can occur together (Hess et al, 2003; Dixon et al, 1999). Concurrent hypothyroidism in diabetic dogs may cause insulin resistance (Ford et al, 1993), although in most hypothyroid dogs increased secretion of insulin results in maintenance of normal blood glucose concentration. Increased concentrations of IGF-1 and GH have been documented in hypothyroid dogs and likely contribute to insulin resistance (Diaz-Espiñeira, 2009; Hofer-Inteeworn, 2012). Hypothyroid dogs have increased fructosamine concentrations due to decreased metabolic rate and resultant decreased protein turnover, which may complicate the assessment of glycemic control in hypothyroid diabetic dogs (Reusch, 2002). Recognition of hypothyroidism may be difficult in dogs with poorly controlled diabetes mellitus, because clinical signs (e.g., lethargy and weakness) and abnormalities in clinical pathologic values (e.g., lipemia and hypercholesterolemia) may be present in both disorders. Reliance on baseline serum thyroid hormone concentrations can be misleading because of NTIS. Evaluation of baseline thyroid hormone and TSH concentrations in the diabetic dog should not be undertaken until after treatment for diabetes mellitus has improved the initial systemic signs of illness. Interpretation of test results should take into consideration the degree of success achieved in controlling hyperglycemia and the impact that poorly controlled diabetes mellitus may have on serum T_4, fT_4, and TSH concentrations. If hypothyroidism is diagnosed and treated in a diabetic patient, the blood glucose should be carefully monitored when thyroid supplementation is initiated because establishment of euthyroidism results in increased insulin sensitivity and a decreased need for insulin.

Hyperadrenocorticism

Endogenously produced and exogenously administered glucocorticoids frequently lower baseline serum T_4, T_3, and fT_4 concentrations in the dog (Peterson et al, 1984; Nelson et al, 1991; Ferguson and Peterson, 1992). Most studies suggest that 40% to 50% of dogs with spontaneous hyperadrenocorticism have decreased total T_4 and T_3 concentrations, whereas fT_4 is usually maintained within the reference range (Peterson et al, 1984; Ferguson and Peterson, 1992). There are several proposed mechanisms for the alterations in serum thyroid hormone concentrations in dogs with hyperadrenocorticism (Box 3-5), including inhibition of TSH secretion, reduced serum protein binding of T_4, reduced T_3 production and degradation, and possibly inhibition of peripheral 5′-deiodination of T_4 (Kemppainen et al, 1983; Ferguson and Peterson, 1992). Although glucocorticoids are believed to suppress pituitary TSH secretion, in a study of 47

BOX 3-5 Proposed Alterations in Thyroid Hormone Physiology Caused by Glucocorticoids

Decreased 5′-monodeiodination enzyme activity
Decreased binding affinity of plasma proteins for T_4, T_3
Decreased cellular binding of T_4, T_3
Increased metabolic clearance rate of T_4
Decreased metabolic clearance rate of T_3, rT_3
Inhibition of TSH secretion (secondary hypothyroidism)
Inhibition of TRH secretion

T_3, Triiodothyronine; *T_4*, thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone (also known as thyrotropin).

dogs with pituitary dependent hyperadrenocorticism, basal and TRH stimulated TSH concentrations did not differ from those of control dogs (Meij et al, 1997).

In some cases it can be difficult to clinically differentiate hyperadrenocorticism from hypothyroidism in dogs with endocrine alopecia, although usually the history (e.g., polydipsia, polyuria, polyphagia in hyperadrenocorticism but not hypothyroidism), the presence of additional physical abnormalities, and the presence of abnormalities on a CBC, urinalysis, and serum biochemical panel (e.g., increased alkaline phosphatase activity) are helpful. If hyperadrenocorticism is considered possible, a screening test, such as the urine cortisol/creatinine ratio or low dose dexamethasone suppression test, should be considered in addition to tests of thyroid gland function to avoid a misdiagnosis of hypothyroidism in a dog with hyperadrenocorticism. If a dog with hyperadrenocorticism is inadvertently treated with L-T_4 sodium, a poor response to treatment or development of additional clinical manifestations of hyperadrenocorticism (e.g., polyuria and polydipsia) will eventually lead the clinician back toward the diagnosis of hyperadrenocorticism.

Environmental and Body Temperature

Seasonal influence on thyroid hormone concentrations was evaluated in healthy outdoor dogs in Hokkaido, Japan (Oohashi et al, 2001). Serum T_4 concentration decreased in January and increased in August and September, fT_4 concentration increased in January and November, and there was no significant seasonal variation in serum TSH concentration. It is not known whether a similar seasonal variation occurs in dogs housed indoors or whether temperature variation, photoperiod, or region of the world may impact the results. Acute cold exposure may increase serum concentrations of TSH and thyroid hormones in the rat and possibly in humans, and acute exposure to heat may decrease serum TSH, T_4, and T_3 and increase serum rT_3 concentrations (Wartofsky and Burman, 1982). Hypothermia and hyperpyrexia may also alter serum T_4, T_3, rT_3, and TSH. It is not known, however, whether these alterations are a result of temperature fluctuations or other factors associated with NTIS.

Obesity, Fasting, and Cachexia

An increase in serum T_3 and T_4 concentrations has been reported in obese euthyroid dogs (Gosselin et al, 1980; Daminet et al, 2003a). It is believed that increased serum thyroid hormone levels are the result of increased caloric intake rather than obesity itself. The changes reported are small and unlikely to influence clinical interpretation of thyroid hormone concentrations.

TABLE 3-12 MECHANISMS BY WHICH DRUGS INFLUENCE THYROID FUNCTION IN HUMANS

MECHANISM	EXAMPLE
Decrease TSH secretion	Glucocorticoids
Change thyroid hormone secretion	Amiodarone
Decrease gastrointestinal absorption	Sucralfate
Alter serum binding	Phenylbutazone
Change hepatic metabolism	Phenobarbital
Inhibit TPO	Sulfonamides

TPO, Thyroid peroxidase; *TSH*, thyroid-stimulating hormone (also known as thyrotropin).

In humans, fasting causes a significant rapid decrease in serum concentrations of T_3 and an increase in serum rT_3 without affecting serum T_4 or TSH concentrations (Wartofsky and Burman, 1982). Re-feeding with either a mixed-nutrient or carbohydrate-rich diet causes the fasting-induced changes to reverse quickly. Impaired conversion of T_4 to T_3 from inhibition of peripheral 5′-deiodinase has been proposed to account for these abnormalities (Borst et al, 1983), although studies in rats have also shown decreased thyroidal secretion of T_4. Fasting for up to 36 hours did not affect baseline serum T_4 or T_3 concentrations in euthyroid Beagles (Reimers et al, 1986). However, fasting in excess of 48 hours did decrease T_3 concentrations in dogs (de Bruijne et al, 1981). In Labrador Retrievers subjected to life-time caloric restriction, only T_3 concentrations were consistently lower in dogs subjected to dietary restriction (Lawler et al, 2007). Serum T_4 and T_3 but not fT_4 concentrations were significantly lower in dogs with chronic weight loss causing cachexia, compared with dogs that had not undergone weight loss (Vail et al, 1994). The decrease in serum T_4 and T_3 concentration was proportional to the degree of weight loss associated with their disease. The decline in serum T_4 and T_3 was believed to be related to the severity of the illness or an abnormal nutritional state.

Drugs

Our knowledge of the effect, if any, of various drugs and hormones on serum thyroid hormone and TSH concentrations in dogs is gradually expanding as investigators continue to examine the interplay between medications and thyroid hormone test results (Tables 3-12 and 3-13). Undoubtedly, many more as yet unrecognized drugs also affect serum thyroid hormone and TSH concentrations in dogs. Until proved otherwise, any drug should be suspected of influencing thyroid hormone test results, especially if the drug has been shown to alter serum thyroid hormone concentrations in humans (see Table 3-13; Box 3-6).

Glucocorticoids

Glucocorticoids are the most commonly used drugs that influence serum thyroid hormone concentrations. The effect of exogenously administered glucocorticoids on serum thyroid hormone concentrations is similar to that seen with naturally occurring hyperadrenocorticism (see Chapter 10). Serum T_4, fT_4, and T_3 concentrations are decreased, often into the hypothyroid range. Proposed mechanisms for this decrease include decreased binding of T_4 to carrier proteins, alterations in clearance and metabolism of thyroid hormones, decreased conversion of T_4 to T_3 at peripheral sites, and suppressed pituitary TSH secretion (Woltz et al,

TABLE 3-13 **DRUGS THAT HAVE BEEN DEMONSTRATED TO INFLUENCE THYROID FUNCTION IN DOGS**

DRUG	TOTAL THYROXINE (↓ OR N)	FREE THYROXINE (↓ OR N)	THYROTROPIN (↑ OR N)	CLINICAL SIGNS OF HYPOTHYROIDISM? (Y/N)	NOTES
Glucocorticoids	↓	(↓ or N)	N	N	Effect dose and duration dependent
Phenobarbital	↓	↓	Slight ↑	N	TSH not increased outside reference range
Trimethoprim/sulfonamides	↓	↓	↑	Y	Effect dose and duration dependent
Nonsteroidal anti-inflammatory drugs					Effect varies depending on specific drug used
Aspirin	↓	N or ↓	N	N	
Deracoxib	N	N	N	N	
Ketoprofen	N	N	N	N	
Meloxicam	N	N	N	N	
Carprofen	N	N	N	N	
Etodolac	N or ↓	N	N or ↑	N	
Clomipramine	↓	↓	N	N	

TSH, Thyroid-stimulating hormone (also known as thyrotropin).

1984; Kaptein et al, 1992; Moore et al, 1993). Because serum TSH concentrations are not increased in dogs with hyperadrenocorticism, measurement of TSH can be helpful in distinguishing hyperadrenocorticism and hypothyroidism. An increased TSH concentration is consistent with hypothyroidism rather than hyperadrenocorticism, although it is important to recognize that the two disorders can occur together. The magnitude and duration of suppression of serum thyroid hormone concentrations depend on the type of glucocorticoid, dosage, route of administration, and duration of glucocorticoid administration. The higher the dosage, the longer the administration, and the more potent the glucocorticoid administered, the more severe the suppression of serum thyroid hormone concentrations. Topical glucocorticoids can have a similar effect as parenterally-administered glucocorticoids (Gottschalk, 2011). Administration of exogenous glucocorticoids does not typically result in clinical signs of hypothyroidism, although clinical signs of iatrogenic hyperadrenocorticism may mimic clinical signs of hypothyroidism particularly in regard to dermatologic signs. Because of the overlap in clinical signs between iatrogenic hyperadrenocorticism and hypothyroidism and the effects of glucocorticoids on laboratory evaluation of the thyroid axis, in some situations it can be difficult or impossible to determine whether glucocorticoid induced hypothyroidism is contributing to a dog's clinical signs and on rare occasions a therapeutic trial may be appropriate.

Because of the common use of glucocorticoid therapy in the management of various medical and dermatologic disorders, a thorough history regarding prior glucocorticoid therapy is extremely important before evaluating thyroid gland function, because failure to identify prior glucocorticoid administration can result in a misdiagnosis of hypothyroidism. If glucocorticoids have been administered in the recent past, measurement of baseline serum thyroid hormone concentrations should be delayed or interpreted carefully. Normal serum T_4, fT_4, and TSH concentrations in these dogs confirm normal thyroid function, whereas low serum T_4 and fT_4 concentrations in conjunction with high TSH concentrations suggest hypothyroidism if clinical signs and physical examination findings are consistent with the disease. Any other combination of test results is difficult to interpret, and the ideal approach is to discontinue glucocorticoid treatment and reassess serum thyroid hormone and TSH concentrations 4 to 8 weeks later. In hypothyroid dogs already being treated with thyroid hormone supplementation, prednisone at a dose of 1.0 mg/kg for 7 days decreased total T_4 but not fT_4 or TSH. Every other day treatment at the same dose did not alter any thyroid parameter over a 28-day period (O'Neill and Reynolds, 2011).

Anticonvulsants

In dogs, phenobarbital treatment at therapeutic dosages decreases serum T_4 and fT_4 concentrations into the range consistent with hypothyroidism (Gaskill et al, 1999; Kantrowitz et al, 1999; Gieger et al, 2000; Muller et al, 2000). Although the mechanism remains unproven in dogs, increased metabolism and excretion of T_4 secondary to hepatic microsomal enzyme induction is believed to be the primary cause, although other mechanisms such as displacement of T_4 from plasma protein binding sites may also play a role. A delayed increase in serum TSH concentration occurs as serum T_4 and fT_4 concentrations decline, although TSH concentrations do not usually exceed the upper limit of the reference range (Muller et al, 2000). Increased serum TSH concentrations quickly return to the reference range following discontinuation of phenobarbital treatment, whereas serum T_4 and fT_4 concentrations may take up to 4 weeks to return to pretreatment values (Gieger et al, 2000). Although in most cases clinical signs of hypothyroidism do not develop in phenobarbital-treated dogs, rarely we have seen dogs with clinical signs suggestive of hypothyroidism in dogs treated chronically with phenobarbital.

Bromide, a halide similar to iodide, could potentially affect the thyroid axis by interfering with iodide uptake or iodide organification by the thyroid gland. Potassium bromide treatment did not have a significant effect on serum T_4, fT_4, T_3, and TSH concentrations in five healthy dogs or in eight dogs with a seizure disorder (Kantrowitz et al, 1999; Paull et al, 2003).

BOX 3-6 Some Drugs and Diagnostic Agents that can Alter Basal Serum Thyroid Hormone Concentrations in Humans and Possibly Dogs

Decrease T_4 and/or T_3
Amiodarone (T_3)
Androgens
Cholecystographic agents
Diazepam
Dopamine
Flunixin
Furosemide
Glucocorticoids
Heparin
Imidazole
Iodide
Methimazole
Mitotane
Nitroprusside
Penicillin
Phenobarbital
Phenothiazines
Phenylbutazone
Phenytoin
Primidone
Propranolol
Propylthiouracil
Radiopaque dyes (ipodate) (T_3)
Salicylates
Sulfonamides (sulfamethoxazole)
Sulfonylureas

Increase T_4 and/or T_3
Amiodarone (T_4)
Estrogens
5-Fluorouracil
Halothane
Insulin
Narcotic analgesics
Radiopaque dyes (e.g., ipodate) (T_4)
Thiazides

T_3, triiodothyronine; *T_4*, thyroxine.

Sulfonamide Antibiotics

Sulfonamides interfere with thyroid hormone synthesis by means of dosage- and duration-dependent inhibition of TPO activity (Doerge and Decker, 1994). TPO is responsible for oxidation of iodide, iodination of tyrosine residues on Tg, and coupling of tyrosine residues prior to thyroid hormone secretion. Decreases in serum T_4, fT_4, and T_3 and an increase in TSH concentrations have been documented in dogs treated with potentiated sulfonamides (e.g., trimethoprim-sulfamethoxazole, trimethoprim-sulfadiazine; Hall et al, 1993; Torres et al, 1996; Gookin et al, 1999). Serum T_4 concentrations can decrease into the hypothyroid range within 1 to 2 weeks, and serum TSH concentrations can increase above the reference range within 2 to 3 weeks after initiating sulfonamide therapy at doses of 15 mg/kg every 12 hours or higher (Hall et al, 1993; Williamson et al, 2002; Frank et al, 2005). Clinical signs of hypothyroidism may develop with sulfonamide administration and chronic treatment may result in a palpable goiter due to persistent TSH stimulation (Torres et al, 1996; Seelig et al, 2008). Thyroid gland function tests return to normal within 1 to 12 weeks after cessation of the antibiotic depending upon the dose and chronicity of treatment (Hall et al, 1993; Williamson et al, 2002; Frank et al, 2005). Administration of sulfadiazine in combination with trimethoprim during the last 4 weeks of pregnancy in female dogs did not affect the thyroid gland in the neonates (Post et al, 1993).

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease serum T_4, fT_4, T_3, and TSH concentrations in humans and other species (Bishnoi et al, 1994). Proposed mechanisms include displacement of thyroid hormone binding to plasma proteins, decreased thyroid hormone de-iodination and inhibition of binding of thyroid hormone to receptors in the plasma membrane, cytoplasm, and nucleus. The effect of NSAIDs on thyroid function tests varies depending on the drug. In dogs, administration of aspirin causes a decrease in total T_4 and fT_4 concentration but no change in TSH concentration. Etodolac, deracoxib, ketoprofen, meloxicam, and carprofen do not result in significant alterations in thyroid hormone concentrations in dogs (Ferguson, 1999; Panciera and Johnston, 2002; Daminet, 2003b; Ness, 2003; Sauve, 2003; Panciera, 2006; see Table 3-13).

Tricyclic Antidepressants

Clomipramine is a tricyclic antidepressant commonly used in dogs with behavioral problems. Clomipramine inhibits thyroid hormone synthesis by altering thyroid follicular cell uptake of iodide and inhibition of TPO. Clomipramine at a dose of 3 mg/kg every 12 hours decreased total T_4 and fT_4 in dogs after 28 days of treatment but did not change TSH concentrations during the 112 days of the study (Gulickers and Panciera, 2003). Because hypothyroidism has been implicated in causing behavioral changes in dogs, it is important that thyroid function is not evaluated while dogs are being treated with clomipramine.

THYROID BIOPSY

The gold standard method for identifying pathology of the thyroid gland is histologic evaluation of a thyroid biopsy specimen. Severe lymphocytic thyroiditis or thyroid atrophy are readily identified histologically (see Figs. 3-6 and 3-7), and in the dog with appropriate clinical signs and diagnostic test results, these findings confirm the diagnosis of primary hypothyroidism (Diaz-Espiñeira et al, 2007). Unfortunately, histologic evaluation of a thyroid biopsy does not always clarify the status of thyroid gland function, especially when clinical signs or diagnostic test results are vague and changes in thyroid pathology are less severe. Thyroiditis can be present in the thyroid gland without causing overt clinical thyroid failure and does not always progress to cause clinical hypothyroidism. Approximately 80% of both thyroid lobes must be destroyed before clinical thyroid gland failure is evident. Variants of normal can be also difficult to differentiate from secondary hypothyroidism, primary atrophy, and follicular cell hyperplasia, especially when the last two conditions are in the early stages of development. The influence of concurrent illness on thyroid gland morphology may also affect biopsy results. Biopsies of the thyroid gland must be obtained surgically and are rarely performed because of the invasiveness of the procedure, cost to the client, and lack of guarantee that diagnostically useful information will be obtained. The only clinical indication for thyroid biopsy in dogs is identification of an enlarged thyroid gland when thyroid neoplasia is suspected.

ESTABLISHING THE DIAGNOSIS

Recommendations regarding the approach to the diagnosis of hypothyroidism are shown in Fig. 3-20. The presence of appropriate clinical signs is imperative, especially when relying on baseline thyroid hormone concentrations for a diagnosis. Identification of a mild nonregenerative anemia on the CBC and especially an increased serum cholesterol concentration on a serum biochemistry panel adds further support for hypothyroidism. Baseline serum T_4 concentration is often used as the initial screening test for thyroid gland function, in part because it is widely available at low cost and can be measured in-house. It is important to remember that serum T_4 concentrations can be suppressed by a variety of factors, most notably NTIS. Thus measurement of the serum T_4 concentration should be used to confirm a euthyroid state. A normal serum T_4 concentration establishes euthyroidism in the vast majority of dogs. The exceptions are a very small number of hypothyroid dogs with lymphocytic thyroiditis and serum T_4 autoantibodies that interfere with the RIA used to measure T_4 (see Fig. 3-19). A low serum T_4 concentration (i.e., less than 0.5 µg/dL) in conjunction with hypercholesterolemia and clinical signs strongly suggestive of the disease, supports the diagnosis of hypothyroidism, especially if systemic illness is not present.

Although measurement of serum T_4 concentration can be used as an initial screening test, measuring a combination of thyroid gland tests is preferred to confirm the diagnosis. Many diagnostic laboratories offer a variety of thyroid panels that incorporate two or more of the following: serum T_4, fT_4 by RIA or MED, T_3, fT_3, rT_3, TSH, and antibody tests for lymphocytic thyroiditis. A normal serum T_4, fT_4, and TSH concentration rules out hypothyroidism. Low serum T_4 and fT_4 and increased serum TSH concentrations in a dog with appropriate clinical signs and clinicopathologic abnormalities strongly support the diagnosis of hypothyroidism, especially if systemic illness is not present and drugs known to affect thyroid test results have not been recently administered. Concurrent presence of Tg autoantibodies suggests lymphocytic thyroiditis as the underlying etiology.

Unfortunately, discordant test results are common. In this situation, reliance on presence of clinical signs, clinicopathologic abnormalities, and clinician index of suspicion become the most important parameters in deciding whether to treat the dog with L-T_4 sodium (see Table 3-6). Serum fT_4 concentration measured by MED is the single most accurate test of thyroid gland function. The combination of a high TSH concentration and a low fT_4 or total T_4 has high specificity for a diagnosis of hypothyroidism. Positive anti-thyroid antibodies alone do not equate with a diagnosis of hypothyroidism but increase the likelihood of the disease in the presence of borderline or discordant thyroid hormone concentrations. Ultimately when discordant test results occur, the clinician must decide whether to initiate trial therapy with L-T_4 sodium or to repeat the testing in 3 to 6 months. In general the most important factor influencing this decision is the severity of clinical signs consistent with hypothyroidism.

Trial therapy should be considered only when thyroid hormone supplementation does not pose a risk to the patient. Response to trial therapy with L-T_4 sodium is nonspecific. Because of the general increase in the metabolic rate that can result from pharmacologic doses of thyroid hormone, thyroid hormone supplementation can temporarily improve clinical signs in a dog without thyroid dysfunction. The effect on the quality of the hair coat is most notable. Thyroid hormone supplementation stimulates telogen hair follicles to become anagen follicles and improves the hair coat, presumably even in euthyroid dogs (Gunaratnam, 1986; Credille et al, 2001). For this reason, a dog that has a positive response to therapy either has hypothyroidism or has "thyroid-responsive disease." Therefore, if a positive response to trial therapy is observed, thyroid supplementation should be discontinued once clinical signs have resolved. If clinical signs recur, hypothyroidism is confirmed, and the supplement should be reinitiated. If clinical signs do not recur, a "thyroid-responsive disorder" or a beneficial response to concurrent therapy (e.g., antibiotics, flea control) should be suspected.

Diagnosis in a Previously Treated Dog

Occasionally, a clinician wants to determine whether a dog receiving thyroid hormone supplementation is, in fact, hypothyroid. The exogenous administration of thyroid hormone, either T_4 or T_3, to a healthy euthyroid dog, suppresses pituitary TSH secretion and causes pituitary thyrotroph atrophy and, subsequently, thyroid gland atrophy. Once the supplement is withdrawn, serum T_4, and T_3 concentrations may be suggestive of hypothyroidism, even in a previously euthyroid dog, if testing is performed within a month of discontinuing treatment (Panciera et al, 1989). Thyroid hormone supplementation must be discontinued and the pituitary-thyroid axis allowed to regain function before meaningful baseline serum T_4 concentrations can be obtained. The time between the discontinuation of thyroid hormone supplementation and the acquisition of meaningful results regarding thyroid gland function depends on the duration of treatment, the dose and frequency of administration of the thyroid hormone supplement, and individual variability. As a general rule, thyroid hormone supplements should be discontinued for a minimum of 4 weeks, but preferably 6 to 8 weeks, before thyroid gland function is critically assessed.

Diagnosis in Puppies

An approach similar to the one described earlier is used to diagnose congenital hypothyroidism. In general, the clinical signs are more obvious in dogs with congenital hypothyroidism; and if the hypothalamic-pituitary-thyroid gland axis is intact, a goiter will be present (see Fig. 3-13). Serum TSH concentrations in dogs with congenital hypothyroidism are also dependent on the etiology of hypothyroidism. Serum TSH concentrations will be increased in dogs with primary dysfunction of the thyroid gland (e.g., iodine organification defect) and an intact hypothalamic-pituitary-thyroid gland axis. However, serum TSH concentrations will not be increased in dogs with congenital hypothyroidism in which pituitary or hypothalamic dysfunction is the cause of the hypothyroidism.

TREATMENT

The initial treatment of choice, regardless of the underlying cause of hypothyroidism, is synthetic L-T_4 sodium (Fig. 3-33; Box 3-7). The same treatment protocol is used for both a therapeutic trial and definitive therapy. Treatment with L-T_4 sodium preserves normal regulation of T_4 to T_3 de-iodination, which allows physiologic regulation of individual tissue T_3 concentrations and decreases the risk of iatrogenic hyperthyroidism. The plasma half-life of L-T_4 sodium in dogs ranges from 9 to 14 hours and depends, in part, on the dosage and frequency of administration, with higher dosages and more frequent administration associated with a shorter half-life of L-T_4 sodium (Nachreiner et al, 1993; Le Traon, 2007). In one study, the mean (± SD) serum half-life of L-T_4 sodium was 9.0 ± 5.9 and 14.6 ± 6.3 hours when L-T_4 sodium was administered at 22 µg/kg once a day or divided twice a day, respectively (Nachreiner et al, 1993). At this dosage, mean time to peak serum T_4 concentration was 3.8

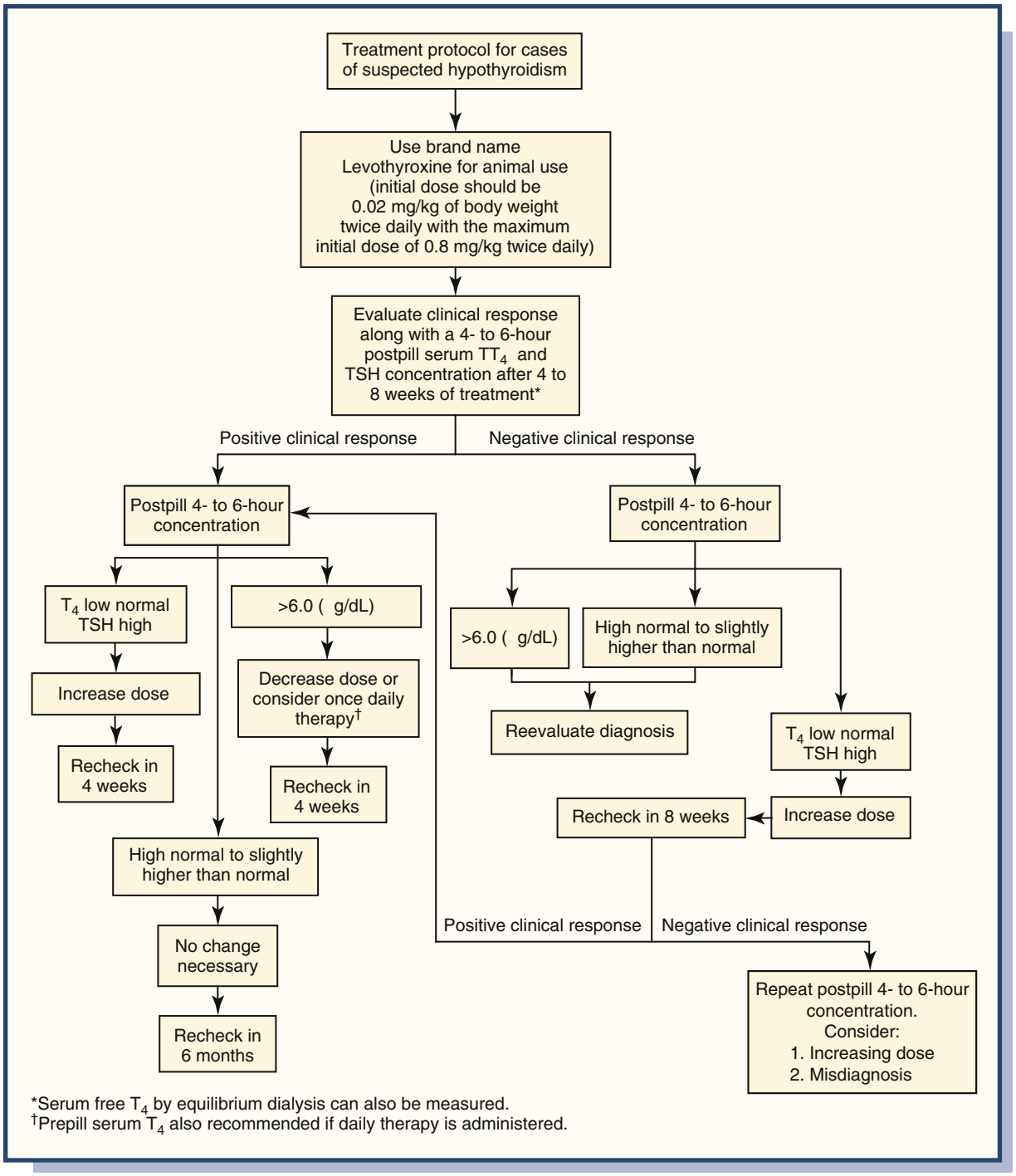

FIGURE 3-33 Algorithm for treatment of canine hypothyroidism. *TSH,* thyroid-stimulating hormone, also known as thyrotropin; *TT_4,* total thyroxine. (Modified from Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 7, St Louis, 2010, Elsevier, p. 1760.)

± 2.0 hours after L-T_4 sodium administration. Maximal and minimal serum T_4 concentrations were higher and lower, respectively with once daily L-T_4 sodium administration, than with twice-daily administration. As a result, serum T_4 concentrations were above the physiologic range for a number of hours with single L-T_4 sodium administration, whereas concentrations closer to physiologic ranges were achieved by use of divided doses. The ideal dose and frequency of L-T_4 sodium supplementation varies among dogs because of variability in T_4 absorption and serum half-life between individual dogs. A dose of 0.02 mg/kg every 24 hours normalizes TSH concentration in most dogs; higher doses (0.04 mg/kg every 12 hours) are required to consistently normalize T_3 concentration, but there is no evidence that normalization of T_3 is necessary for a good clinical response. The recommended initial dose for otherwise healthy hypothyroid dogs is 0.02 mg/kg by mouth every 12 hours (0.1 mg/10 lb; maximum starting dose, 0.8 mg). This dosage is similar to the average calculated oral replacement dosage (0.018 mg/kg) determined in a study evaluating replacement T_4 requirements in thyroidectomized dogs (Ferguson and Hoenig, 1997). The dose for treatment of hypothyroid dogs is 10 times higher than the dose used in hypothyroid humans because of poorer gastrointestinal absorption and a shorter serum half-life of T_4 in dogs compared to humans. Some

BOX 3-7 Recommendations for the Initial Treatment and Monitoring of Hypothyroidism in Dogs

Initial Treatment

Use a name brand synthetic L-T_4 sodium product approved for animal use.

The initial dosage per administration should be 0.02 mg/kg of body weight (0.1 mg/10 pounds) with a maximum initial dose of 0.8 mg.

The initial frequency of administration is every 12 hours.

Initial Monitoring

Response to treatment should be critically evaluated 6 to 8 weeks after initiating treatment.

Serum T_4 or fT_4 (measured by equilibrium dialysis) and TSH concentration should be measured 4 to 6 hours after administration of thyroid hormone.

- Serum T_4 or fT_4 concentration should be in the normal range or increased.
- Serum TSH concentration should be in the normal range.

Measuring serum T_4 or fT_4 (measured by equilibrium dialysis) concentration immediately prior to thyroid hormone administration (i.e., trough level) is optional but is recommended if thyroid hormone is being given once a day.

- Serum T_4 or fT_4 concentration should be in the normal range at this time.

Adapted from consensus recommendations reached at an international symposium on canine hypothyroidism held in August 1996 (*Canine Practice,* vol 77, 1997).
fT_4, Free thyroxine; *L-T_4*, levothyroxine (also known as L-thyroxine), *T_4*, thyroxine; *TSH,* thyroid-stimulating hormone (also known as thyrotropin).

investigators believe that the dose of L-T_4 sodium may correlate better with body surface area than with body weight (Chastain, 1982). The recommended dosage of L-T_4 sodium based on body surface area is 0.5 mg/m^2, however the authors prefer to dose L-T_4 sodium based on body weight rather than body surface area. Most studies have shown that the majority of dogs have a good clinical response to treatment with once daily L-T_4 sodium; however dose adjustments are required in 20% to 50% of dogs started on once a day therapy (Le Traon et al, 2009; Dixon et al, 2002). Twice daily administration of T_4 is recommended initially to improve the likelihood of a positive response to treatment, which is especially important when performing a therapeutic trial. If clinical signs resolve and T_4 concentrations are within the therapeutic range, the frequency of T_4 administration can be decreased to once daily. The final L-T_4 sodium dose should be adjusted based on the measured serum T_4 concentration and TSH concentration (see Fig. 3-33). In humans the TSH concentration is used to titrate the dose, but this is problematic in dogs because of the lower sensitivity of the TSH assay.

Most L-T_4 sodium products are formulated as a tablet ranging in strength from 0.1 to 0.8 mg; chewable L-T_4 sodium formulations and an L-T_4 sodium solution (Leventa Merck Animal Health) solution are also available. There are differences in potency and bioavailability between different brands and formulations of L-T_4 sodium supplements. Unfortunately, even in human patients, not all available products have been directly compared for bioequivalence, and even when products have been documented to be bioequivalent, the biologic response can vary between products in individual patients. The methods used to establish bioequivalence in humans also have some limitations. One concern is that the methods rely on administration of a supra-physiologic dose of L-T_4 sodium to euthyroid volunteers. The outcome measures are area under the curve, maximum concentration, and time to maximum concentration, rather than measurement of TSH concentration and adjustment for endogenous T_4 secretion is not required (Di Girolamo et al, 2008). The Food and Drug Administration (FDA) allows variability in potency of 80% to 125%, which for a drug such as L-T_4 sodium with a relatively narrow therapeutic window could have clinical consequences. In dogs the relative bioavailability of a liquid L-T_4 sodium solution was demonstrated to be 50% higher than that of a tablet formulation in euthyroid dogs; however, the dose required for establishment of euthyroidism in hypothyroid dogs (0.02 mg/kg every 24 hours) was similar to that required for an oral tablet formulation (Soloxine, Daniels Pharmaceuticals) (Le Traon et al, 2007; 2009; Dixon et al, 2002). Because of the limitations of bioequivalence studies, it is recommended that clinicians use one formulation of L-T_4 sodium consistently; and if a change in formulation needs to be made, therapeutic monitoring should be used to confirm that the dose of the new product is appropriate. Many other factors, including concurrent drug administration, nutritional supplements, food type, timing of meals, concurrent illness, and physiologic conditions such as age and obesity influence L-T_4 sodium absorption from the gastrointestinal tract. For example in people, consumption of a meal at the time of L-T_4 sodium administration decreases absorption. Administration of L-T_4 sodium with food has been shown to decrease bioavailability of liquid L-T_4 sodium formulations in dogs (Le Traon et al, 2007). If possible, it is recommended to avoid giving L-T_4 sodium supplements at the time of a meal. When therapeutic monitoring is performed, it is important not to change any of the aforementioned variables. For example, if the medication is given at the time of a meal, the same protocol should be followed on the day of testing.

Response to Levothyroxine Sodium Therapy

Thyroid hormone supplementation should be continued for a minimum of 6 to 8 weeks before critically evaluating the effectiveness of treatment. With appropriate therapy, all of the clinical signs and clinicopathologic abnormalities associated with hypothyroidism should resolve (Fig. 3-34). An increase in mental alertness and activity usually occurs within the first week of treatment (Table 3-14); this is an important early indicator that the diagnosis of hypothyroidism was correct. Although some hair regrowth may be observed during the first month in dogs with endocrine alopecia, it may take several months for complete regrowth and a marked reduction in hyperpigmentation of the skin to occur. Initially, the hair coat may appear to worsen as hairs in the telogen stage of the hair cycle are shed (Credille et al, 2001). If obesity is caused by hypothyroidism, it should also begin to improve within 2 months after initiating L-T_4 sodium therapy along with adjustments in diet and exercise (Fig. 3-35). Improvement in myocardial function is usually evident within 1 to 2 months, but it may be delayed for as long as 12 months. Neurologic deficits improve rapidly after treatment, but complete resolution may take 2 to 3 months (Jaggy et al, 1994).

Therapeutic Monitoring

Therapeutic monitoring includes evaluation of the clinical response to thyroid hormone supplementation and measurement of serum T_4 and TSH concentrations before or after L-T_4 sodium administration, or both. Therapeutic monitoring allows treatment to be individualized to the patient based on clinical response, thyroid hormone concentrations, and presence or absence of concurrent illness. Serum T_4 and TSH should be measured 6 to 8 weeks after initiating therapy, whenever signs of thyrotoxicosis develop, or when there is a poor response to therapy. T_4 concentration and TSH should also be measured 2 to 4 weeks after any adjustment in L-T_4 sodium therapy.

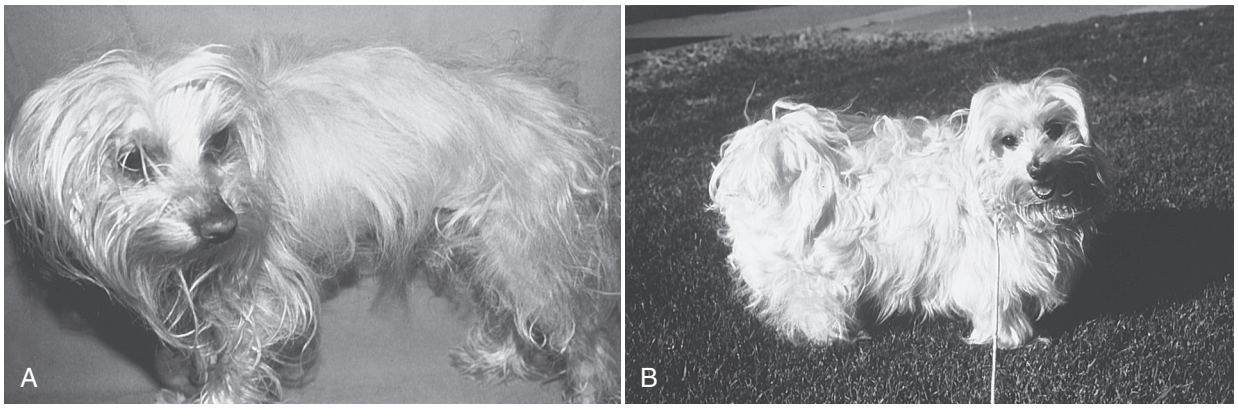

FIGURE 3-34 **A,** A 7-year-old male Maltese with hypothyroidism and diabetes mellitus. **B,** Same dog as in **A** after 3 months of levothyroxine (L-T_4) sodium treatment. Note the marked improvement in appearance and hair coat.

TABLE 3-14 **ANTICIPATED TIME OF CLINICAL RESPONSE TO SODIUM LEVOTHYROXINE TREATMENT IN DOGS WITH HYPOTHYROIDISM**

AREA OF IMPROVEMENT	TIME TO IMPROVEMENT
Mentation and activity	2 to 7 days
Lipemia and clinical pathology	2 to 4 weeks
Dermatologic abnormalities	2 to 4 months
Neurologic abnormalities	1 to 3 months
Cardiac abnormalities	1 to 2 months
Reproductive abnormalities	3 to 10 months

Serum T_4 and TSH concentrations are typically evaluated 4 to 6 hours after the administration of L-T_4 sodium in dogs receiving the medication twice daily and just before and 4 to 6 hours after administration in dogs receiving it once a day (Nachreiner and Refsal, 1992). This information allows the clinician to evaluate the dose, frequency of administration, and adequacy of intestinal absorption of L-T_4 sodium. Measurement of serum fT_4 by the MED technique can be done in lieu of T_4 but is more expensive and usually does not have benefit except in dogs with serum T_4 autoantibodies. Although the presence of thyroid hormone autoantibodies does not interfere with the physiologic actions of thyroid hormone supplements, they will interfere with measurement of total T_4 concentration (see Fig. 3-19). Results of serum fT_4 measured by assays that use a dialysis step (e.g., MED technique) are not affected by thyroid hormone autoantibodies. Measurement of serum TSH is only useful in dogs in which the TSH concentration was above the reference range at the time of diagnosis.

Post dosing serum T_4 and TSH results and recommendations for changes in therapy are given in Fig. 3-33. If the dose of the thyroid hormone supplement and the dosing schedule are appropriate, the serum T_4 concentration should be in the upper half of or a little above the reference baseline range (i.e., 3.0 to 6.0 μg/dL) when measured 4 to 6 hours after thyroid hormone administration, and the serum TSH concentration should be in the reference range (i.e., less than 0.6 ng/mL) in all blood samples evaluated. If the clinical signs do not resolve and the post-pill T_4 is below or within the lower half of the reference range (< 2.0 μg/dL), the dose of L-T_4 sodium should be increased. If the clinical signs have resolved but the post-pill concentration is in lower half of the reference range, a serum TSH should be measured. If this is within the reference range indicating good biological response to supplementation, the dose does not need to be adjusted. Post dosing serum T_4 concentrations measured at times other than 4 to 6 hours after L-T_4 sodium administration should be interpreted with the realization that serum T_4 may not be at peak concentrations. Ideally, all post-pill serum T_4 concentrations should be greater than 1.5 μg/dL, regardless of the time interval between L-T_4 sodium administration and post-pill blood sampling. The post-dosing serum T_4 concentration may also be affected by the pharmaceutical preparation administered, concurrent drugs such as glucocorticoids, and possibly diet. Post-dosing serum T_4 concentrations are frequently above the reference range. The finding of an increased post-dosing serum T_4 concentration is not an absolute indication to reduce the dose of L-T_4 sodium, especially if there are no clinical signs of thyrotoxicosis. However, we recommend a reduction in the dose whenever serum T_4 concentrations exceed 6.0 μg/dL. Dogs are relatively resistant to development of iatrogenic hyperthyroidism because of the short half-life of T_4 in this species; however, the risk of long-term over-supplementation of thyroid hormone in dogs has not been investigated. Current assays for TSH are not sensitive enough to distinguish a normal from a low TSH concentration and thus cannot distinguish between those dogs that are adequately supplemented and those that are over-supplemented. If the clinical response is poor to thyroid hormone supplementation, post dosing serum T_4 concentrations are within or above the reference range, and serum TSH concentrations are less than 0.6 ng/mL, other causes of the clinical signs of concern should be investigated. Although trial therapy with liothyronine sodium may be attempted, it is usually ineffective in producing a beneficial response in a dog that has failed to respond to L-T_4 sodium and whose serum T_4 concentrations are in the normal range during treatment.

Treatment of Dogs with Concurrent Nonthyroidal Illness

Cardiomyopathy

Because euthyroid dogs with cardiac disease may have decreased thyroid hormone concentrations, accurate diagnosis of hypothyroidism may be challenging. It is important to be confident of the diagnosis in such dogs to avoid inappropriate treatment. In hypothyroid dogs with cardiac disorders, thyroid hormone supplementation increases myocardial oxygen demand, increases heart rate, and may reduce ventricular filling time. Decompensation of the

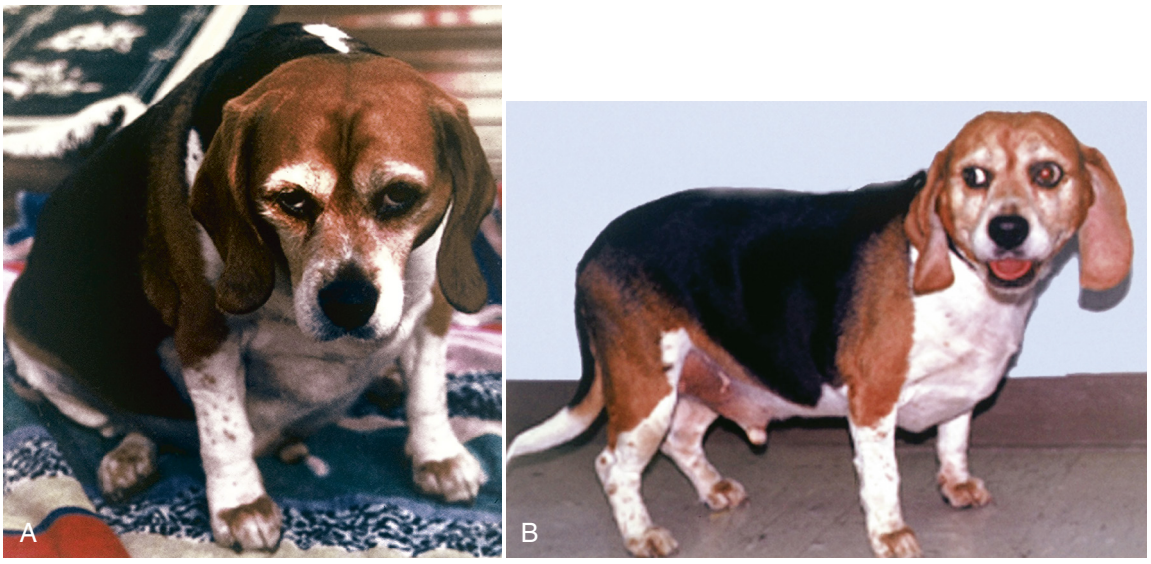

FIGURE 3-35 A, An 8-year-old male castrated Beagle with hypothyroidism. The primary owner complaints were obesity, lethargy, and weakness. The dog weighed 31 kg. **B,** Same dog as in **A** after 6 months of levothyroxine (L-T_4) sodium treatment and adjustments in caloric intake and type of diet to promote weight loss. The owner reported marked improvement in the dog's alertness and activity, and its body weight had decreased to 19 kg.

cardiac disease can therefore occur with initiation of thyroid hormone supplementation. Because of these concerns the initial dose of thyroid hormone replacement in dogs with cardiac diseases such as cardiomyopathy should be 25% to 50% of the usual starting dose. The dose may then be increased incrementally based on the results of therapeutic monitoring and reevaluation of cardiac function.

Hypoadrenocorticism

In dogs with concurrent hypoadrenocorticism and hypothyroidism, replacement of mineralocorticoid and glucocorticoid deficiency should be initiated before treatment with L-T_4 sodium, because the increased basal metabolic rate resulting from thyroid hormone supplementation may exacerbate electrolyte disturbances and cause decompensation of hypoadrenocorticism.

Diabetes Mellitus

In dogs with concurrent hypothyroidism and diabetes mellitus, hypothyroidism can cause insulin resistance that resolves with treatment of hypothyroidism (Ford et al, 1993). When hypothyroidism is diagnosed and treated in a diabetic patient, the blood glucose should be carefully monitored for hypoglycemia during the 1 to 2 weeks after initiation of thyroid supplementation. Once euthyroidism is reestablished, increased insulin sensitivity and a decreased need for insulin may lead to hypoglycemia.

Other Concurrent Illness

The appropriate therapeutic range for hypothyroid dogs with concurrent nonthyroidal illness, for geriatric dogs, and for dogs being treated with drugs, such as phenobarbital and glucocorticoids, that influence serum total T_4, is unknown. The target serum total T_4 concentration should be lower in dogs with concurrent illness and those being treated with drugs known to lower thyroid hormone concentrations. In such cases, the decision whether to adjust the dose of thyroid supplementation should be based primarily on response to therapy. If a positive response to therapy occurs but the post-pill T_4 concentration is low, no further dosage increase should be recommended.

BOX 3-8 Potential Reasons for Poor Clinical Response to Treatment with Levothyroxine Sodium (Synthetic Thyroxine)

- Owner compliance problems
- Use of inactivated or outdated product
- Use of some generic levothyroxine (L-T_4) sodium preparations
- Inappropriate L-T_4 sodium dose
- Inappropriate frequency of administration
- Use of thyroid extracts or combination thyroxine/triiodothyronine products
- Poor bioavailability (e.g., poor gastrointestinal absorption)
- Inadequate time for clinical response to occur
- Incorrect diagnosis of hypothyroidism
- Concurrent disease causing clinical signs (e.g., allergic dermatitis)

Treatment Failure

There are several possible reasons for a poor response to T_4 supplementation (Box 3-8). An inappropriate diagnosis of hypothyroidism is the most common cause. Hyperadrenocorticism can be mistaken for hypothyroidism especially if other clinical signs, such as polyuria and polydipsia, characteristic of hyperadrenocorticism are not present. This confusion results because of the suppressive effects of cortisol on serum thyroid hormone concentrations. Other causes of skin disorders (e.g., atopy and flea allergic dermatitis) may also be confused with hypothyroidism. Failure to recognize the impact of concurrent illness on thyroid hormone test results is another common cause for misdiagnosing hypothyroidism. When a dog shows a poor response to L-T_4 sodium therapy, the history, physical examination findings, and diagnostic test results that prompted the initiation of L-T_4 sodium therapy should be critically reevaluated and a thorough evaluation for concurrent disease undertaken. In addition, problems with the treatment regimen should be investigated, including poor owner compliance in administering the hormone, the use of outdated preparations, an inappropriate

dose or frequency of administration of L-T_4 sodium, the use of some generic L-T_4 sodium products, the use of thyroid extracts or combination thyroxine/triiodthyronine products, or poor intestinal absorption of L-T_4 sodium due to concurrent gastrointestinal disorders or administration of thyroid supplements with food. If poor gastrointestinal absorption is suspected, T_3 may be substituted for T_4.

Treatment with Liothyronine Sodium (Synthetic Triiodothyronine)

Liothyronine sodium is not the initial thyroid hormone supplement of choice for the treatment of hypothyroidism. Liothyronine sodium supplementation results in normal serum T_3 but low to non-detectable serum T_4 concentrations. In contrast, L-T_4 sodium therapy results in normal serum concentrations of both T_3 and T_4 because L-T_4 sodium is converted to T_3. Treatment with L-T_4 sodium preserves normal regulation of T_4 to T_3 conversion, which allows physiologic regulation of tissue T_3 concentrations and decreases the risk of iatrogenic hyperthyroidism (Siegmund et al, 2004).

Liothyronine therapy is indicated when L-T_4 sodium therapy has failed to achieve a response in a dog with confirmed hypothyroidism, when gastrointestinal malabsorption is the suspected cause for failure to respond to the L-T_4 supplement. Impaired absorption of L-T_4 sodium should be suspected when baseline serum T_4 concentrations are low, serum TSH is high, and no increase in serum T_4 concentration occurs following oral L-T_4 sodium administration. Thyroid hormone autoantibodies that interfere with the RIA technique should also be considered in this scenario. Gastrointestinal absorption of ingested T_3 approaches 100%, whereas absorption of L-T_4 sodium is only 10% to 50% of the administered dose. This more complete absorption of T_3 reflects less binding affinity of intestinal contents for T_3, especially plasma proteins secreted in the bowel lumen.

Historically, liothyronine sodium has been used for treatment of hypothyroidism in dogs with normal serum T_4 but low serum T_3 concentration. These dogs were often suspected of having a defect in the conversion of T_4 to T_3. It is now recognized that most of these dogs are either normal, have NTIS, or have T_3 autoantibodies that cause a false lowering of the serum T_3 concentration. T_4 to T_3 conversion abnormalities have not been documented in any species, including dogs. Conceptually, conversion defects are most likely to be congenital, and thus, affected puppies should either die shortly after birth or develop cretinism. If the decision is made to treat the dog with normal serum T_4 and low serum T_3 concentration, L-T_4 sodium should be used initially.

The initial dosage of liothyronine is 4 to 6 μg/kg body weight every 8 hours. As with L-T_4 sodium, the plasma half-life and time of peak plasma concentration after administration of liothyronine are variable among dogs. In most dogs, the plasma half-life of liothyronine is approximately 5 to 6 hours, with peak plasma concentrations occurring 2 to 5 hours after administration. Once clinical improvement is observed, the frequency of administration may be reduced to twice a day. If clinical signs recur, three daily doses should be reinstituted.

Blood for therapeutic monitoring should be obtained just before and 2 to 4 hours after administration of liothyronine sodium. Evaluation of serum T_3 is mandatory with this supplement because the risk of thyrotoxicosis is much higher. Serum T_4 concentrations are low to non-detectable with adequate T_3 supplementation because of the negative feedback suppression of TSH and the inability of T_3 to be converted to T_4. Guidelines for adjustments in T_3 therapy are similar to those for T_4 supplements. Serum T_3 concentrations before and following T_3 administration should be within the normal range in a dog receiving an adequate dosage of a T_3 supplement.

Combination Thyroxine/Triiodothyronine Products

Synthetic preparations are available that contain both L-T_4 sodium and liothyronine (Liotrix, Thyrolar). The T_4-to-T_3 ratio is generally 4 to 1 and the unphysiologic proportion of T_3 can make it difficult to maintain euthyroidism (Siegmund et al, 2004). Whether there are benefits to using such products for treatment of hypothyroid human patients is controversial. Although most controlled studies have not provided evidence that treatment with combination products improves patient outcome (Siegmund et al, 2004), anecdotally some patients report improved quality of life when treated with combination products. Combination T_4/T_3 products are not recommended in dogs for the following reasons: (1) the rate of metabolism and thus the frequency of administration differ between L-T_4 sodium and liothyronine; (2) L-T_4 sodium therapy provides adequate serum concentrations of both T_4 and T_3; and (3) the use of synthetic combinations may result in serum concentrations of T_3 that could cause thyrotoxicosis. In addition, synthetic combination products tend to be more expensive than either synthetic L-T_4 sodium or liothyronine alone.

Thyroid Extracts

Animal-origin preparations are desiccated thyroid that is derived from cleaned, dried, and powdered thyroid glands of slaughterhouse origin. The porcine product is the most commonly available (Armour Thyroid). The United States Pharmacopeia requires thyroid extracts to contain approximately 38 μg of T_4 and 9 μg of T_3 for each 60 to 65 mg tablet giving a T_4-to-T_3 ratio of approximately 4:1, which is similar to combination products. Potential problems with such products include the potential for allergy or sensitivity, batch to batch variability, variable shelf life, and the difficulties outlined earlier in maintaining euthyroidism with the unphysiologic ratio of T_4 to T_3. For these reasons crude animal-origin thyroid preparations are not recommended for the treatment of hypothyroidism in dogs.

Treatment of Myxedema Coma

Early recognition and aggressive therapy are critical to survival of myxedema coma. Consequently, the diagnosis should be made clinically, and therapy should be initiated without waiting for results of serum thyroid hormone concentrations if this disorder is suspected. Treatment consists of thyroid hormone administration and correction of the associated physiologic disturbances, such as hypothermia, hypovolemia, electrolyte disturbances, and hypoventilation. Because concurrent nonthyroidal disorders commonly precipitate myxedema coma, diagnosis and treatment of these disorders is critical. Because of the sluggish circulation and severe hypometabolism of profound hypothyroidism, absorption of therapeutic agents from the gut or from subcutaneous or intramuscular sites is unpredictable, and if possible, thyroid hormone should be administered intravenously. The recommended initial dosage for injectable L-T_4 sodium is 4 to 5 μg/kg every 12 hours (Pullen and Hess, 2006). A 50% to 75% reduction in the dosage should be considered if there is pre-existing cardiac disease or failure (Henik and Dixon, 2000). Oral administration of L-T_4 sodium can also be administered every 12 hours to provide sustained delivery of T_4. Appropriate supportive care should also be initiated, including IV sodium-containing fluids with dextrose

supplementation; slow, passive rewarming with blankets; and assisted ventilation, if needed. Clinical improvement is usually seen within 24 hours, although death due to concurrent illness is common. Once the dog has stabilized, oral thyroid hormone treatment can be started.

Thyrotoxicosis

It is unusual for thyrotoxicosis to develop as a result of excessive administration of L-T_4 sodium in the dog, because of the short half-life of L-T_4 sodium in the dog as well as physiologic adaptations that impair gastrointestinal tract absorption and enhance clearance of thyroid hormone by the liver and kidneys (Nachreiner and Refsal, 1992). Nevertheless, thyrotoxicosis may develop in dogs receiving excessive amounts of L-T_4 sodium (especially in dogs receiving L-T_4 sodium twice daily) and in dogs with impaired metabolism of L-T_4 sodium (e.g., concurrent renal or hepatic insufficiency).

Clinical signs of thyrotoxicosis include panting, nervousness, anxiety, tachycardia, aggressive behavior, polyuria, polydipsia, polyphagia, and weight loss. Sinus tachycardia, atrial flutter, and syncope have been reported in dogs with iatrogenic hyperthyroidism and concurrent cardiac disease (Fine et al, 2010). Documentation of mild to marked increased serum thyroid hormone concentrations supports the diagnosis; however, these concentrations can occasionally be within the upper end of the reference normal range in a dog with signs of thyrotoxicosis, and conversely some dogs with increased thyroid hormone concentrations have no clinical signs of thyrotoxicosis. A cardiac evaluation should be performed in dogs with arrhythmias due to suspected thyrotoxicosis. Adjustments in the dose or frequency of administration of thyroid hormone medication are indicated if clinical signs of thyrotoxicosis develop in a dog receiving thyroid hormone supplements. Supplementation may have to be discontinued for a few days in such animals if the clinical signs are severe. Signs of thyrotoxicosis should resolve within 1 to 3 days if they are due to the thyroid medication and the adjustment in treatment has been appropriate, although the presence of underlying heart disease may lead to persistence of cardiac arrhythmias. It is recommended that therapeutic monitoring should be repeated 2 to 4 weeks after the dose of L-T_4 sodium has been decreased. It is also important to review the criteria used for diagnosis in order to determine whether T_4 supplementation was appropriate in the first place.

PROGNOSIS

The prognosis for dogs with hypothyroidism depends on the underlying cause. The life expectancy of an adult dog with primary hypothyroidism that is receiving appropriate therapy should be normal. All the clinical manifestations should resolve in response to thyroid hormone supplementation. Prognosis in myxedema coma is dependent on early recognition and treatment. The prognosis for puppies with hypothyroidism (i.e., cretinism) is guarded and depends on the severity of skeletal and joint abnormalities at the time treatment is initiated. Although many of the clinical signs resolve with therapy, musculoskeletal problems, especially degenerative osteoarthritis, may develop as a result of abnormal bone and joint development (Greco et al, 1991; Saunders and Jezyk, 1991). Degenerative osteoarthritis is more prevalent in joints with adjacent epiphyseal dysgenesis. Epiphyseal dysgenesis may result in increased susceptibility to trauma, articular cartilage damage, osteochondrosis-type lesions, and degenerative joint changes. Contributing to these changes are the biomechanical abnormalities caused by radial bowing with subsequent humeroradial joint widening and humeroulnar joint subluxation, which is seen in some dogs with congenital hypothyroidism. In puppies with CHG due to TPO deficiency, the goiter persists and TSH concentrations remain high despite normalization of total T_4 concentrations with twice daily L-T_4 sodium at appropriate doses (Fyfe, 2003; Pettigrew et al, 2007). Whether further adjustment of thyroid hormone supplementation by therapeutic monitoring would result in resolution of the goiter is unknown.

The prognosis for dogs with secondary hypothyroidism caused by malformation or destruction of the pituitary gland is guarded to poor. The life expectancy is shortened in dogs with congenital malformation of the pituitary gland (i.e., pituitary dwarfism), primarily because of the multiple problems that develop in early life (see Chapter 2). Acquired secondary hypothyroidism is usually caused by destruction of the pituitary by a space-occupying mass, which has the potential to expand into the brainstem.

FELINE HYPOTHYROIDISM

Naturally acquired hypothyroidism is a rare clinical entity in the cat, and most clinical descriptions of feline hypothyroidism in the veterinary literature have been case reports of either primary congenital or adult onset hypothyroidism (Arnold et al, 1984; Sjollema et al, 1991; Jones et al, 1992, Rand et al, 1993; Mellanby et al, 2005; Traas et al, 2008; Blois et al, 2010; Quante et al, 2010). In contrast, iatrogenic hypothyroidism following any of the three common treatments for hyperthyroidism is well recognized (Nykamp et al, 2005; Williams et al, 2010).

Low serum T_4 concentrations in cats are frequently documented by veterinarians because of inclusion of serum T_4 concentration in the typical "feline geriatric panel" offered by many commercial laboratories. Unfortunately, the blood sample is usually submitted for evaluation of another problem (e.g., systemic illness) and the low T_4 concentration is almost always the result of the suppressive effects of nonthyroidal illness on serum T_4 concentration (i.e., NTIS) and not hypothyroidism.

ETIOLOGY

Iatrogenic Hypothyroidism

Iatrogenically induced hypothyroidism is usually the result of treatment of hyperthyroidism and is far more common than naturally acquired hypothyroidism in cats. Iatrogenic hypothyroidism can result from bilateral thyroidectomy, radioactive iodine treatment, or treatment with anti-thyroid drugs. Depending on the treatment used for hyperthyroidism, plasma thyroid hormone concentrations can decline to subnormal concentrations within hours (surgery), days (anti-thyroid drugs), or weeks to months (radioactive iodine) after treatment. In a study of 165 cats treated with radioactive iodine, 30% developed hypothyroidism defined by a total T_4 concentration less than the lower reference limit 3 months after treatment (Nykamp et al, 2005). Cats that had evidence of bilateral thyroid disease were more likely to become hypothyroid than those with unilateral dysfunction. In another study of 80 non-azotemic hyperthyroid cats treated with anti-thyroid drugs, 35% became hypothyroid (as defined by a total T_4 concentration below the reference range and a serum TSH concentration above the reference range) 6 months after initiating treatment (Williams et al, 2010). Hypothyroid cats were more

likely to become azotemic after treatment than euthyroid cats, and cats that were both hypothyroid and azotemic had shorter survival times than those that were azotemic but not hypothyroid. Azotemia was presumed to be due to a decrease in glomerular filtration rate in cats with underlying chronic kidney disease and concurrent hypothyroidism. Prolonged iatrogenic hypothyroidism should therefore be avoided especially in cats with known concurrent chronic kidney disease. In cats with iatrogenic hypothyroidism, the clinical signs are usually mild with decreased activity and weight gain typically observed. These clinical signs are usually not worrying to the owner of a previously hyperthyroid cat; however, because of the risk of progressive azotemia, thyroid hormone supplementation should be instituted in hypothyroid azotemic cats, in cats with clinical signs of hypothyroidism, and in cats with hypothyroidism that persists 3 to 6 months beyond definitive treatment with radioactive iodine or thyroidectomy. In cats treated with oral anti-thyroid drugs that become hypothyroid, a decreased drug dose should be implemented.

Adult-Onset Hypothyroidism

Naturally acquired adult-onset primary hypothyroidism is rarely documented in the cat. Two well documented cases have been published. One cat had lymphocytic thyroiditis, whereas in another cat the thyroid gland could not be identified at necropsy (Rand et al, 1993; Blois et al, 2010). Secondary hypothyroidism due to head trauma was reported in an 18-month-old cat with stunted growth and a history of head trauma at 8 weeks of age (Mellanby et al, 2005). The diagnosis was made by documentation of low total T_4 and TSH and no increase in T_4 or TSH after administration of TRH. A magnetic resonance imaging (MRI) scan of the brain revealed an almost empty sella turcica and a very small pituitary gland.

Congenital Hypothyroidism

Congenital primary hypothyroidism causing disproportionate dwarfism is recognized more frequently than adult-onset hypothyroidism in the cat. Reported causes of congenital hypothyroidism include thyroid dyshormonogenesis (Sjollema et al, 1991; Jones et al, 1992), thyroid dysmorphogenesis (Traas et al, 2008), and TSH resistance. Goiter is expected in congenital hypothyroidism due to dyshormonogenesis. An inherited defect in iodine organification was documented in a family of Abyssinian cats with congenital hypothyroidism and goiter (Jones et al, 1992); an autosomal recessive mode of inheritance was suspected. CHG due to TPO deficiency was reported in a family of Domestic Short-Hair cats and was also thought to be inherited as an autosomal recessive trait (Mazrier et al, 2003). A colony of cats with hypothyroidism and thyroiditis with severe signs of hypothyroidism developing 40 to 60 days after birth has also been reported (Schumm-Draeger et al, 1996). The severity of thyroiditis was decreased by early treatment with thyroid hormone. TSH resistance was proposed to be the cause of inherited primary hypothyroidism in a colony of Japanese cats (Tanase et al, 1991). The cats in this colony of hypothyroid cats did not develop a goiter, and the defect was inherited as an autosomal recessive trait. Although rare, iodine deficiency has been reported to cause hypothyroidism in kittens fed a strict all-meat diet.

BOX 3-9 Clinical Manifestations of Feline Hypothyroidism

Adult-Onset Hypothyroidism
- Lethargy
- Inappetence
- Obesity
- Dermatologic
  - Seborrhea sicca
  - Dry, lusterless hair coat
  - Easily epilated hair
  - Poor regrowth of hair
  - Endocrine alopecia
  - Alopecia of pinnae
  - Thickened skin
  - Myxedema of the face
- Bradycardia
- Mild hypothermia

Congenital Hypothyroidism
- Disproportionate dwarfism
  - Failure to grow
  - Large head
  - Short, broad neck
  - Short limbs
- Lethargy
- Mental dullness
- Constipation
- Hypothermia
- Bradycardia
- Retention of kitten hair coat
- Retention of deciduous teeth

CLINICAL SIGNS

Adult-Onset Hypothyroidism

The clinical signs that have been associated with feline hypothyroidism are listed in Box 3-9. Of these, the most commonly seen are lethargy, inappetence, dermatologic abnormalities, and obesity (Fig. 3-36). Lethargy and inappetence may become severe. Dermatologic signs are quite variable and often develop secondary to a decrease in grooming behavior by the cat. Affected cats develop a dull, dry, unkempt hair coat with matting and seborrhea. Easily epilated and poor regrowth of hair may lead to alopecia affecting the pinnae, pressure points, and the dorsal and lateral tail base region (Peterson, 1989; Rand et al, 1993; Blois et al, 2010). Asymmetric or bilaterally symmetric alopecia involving the lateral neck, thorax, and abdomen may also develop. Myxedema of the face, causing a "puffy" appearance, was reported in one cat with naturally acquired adult-onset hypothyroidism (Rand et al, 1993). Bradycardia and mild hypothermia may be additional findings on physical examination.

Congenital Hypothyroidism

The clinical signs of congenital hypothyroidism are similar to those in dogs. Affected kittens typically appear normal at birth, but a decrease in growth rate usually becomes evident by 6 to 8 weeks of age. Disproportionate dwarfism develops over the ensuing months with affected kittens developing large heads, short broad necks, and short limbs. Additional findings include lethargy, mental dullness, constipation, hypothermia, bradycardia, and prolonged retention of deciduous teeth (Arnold et al, 1984; Peterson, 1989; Sjollema et al, 1991; Jones et al, 1992; Traas et al, 2008; Fig. 3-37). The hair coat consists mainly of the undercoat with primary guard hair scattered thinly throughout. Radiographic abnormalities are similar to those described for the dog. Two littermate kittens with hypothyroidism had a concurrent

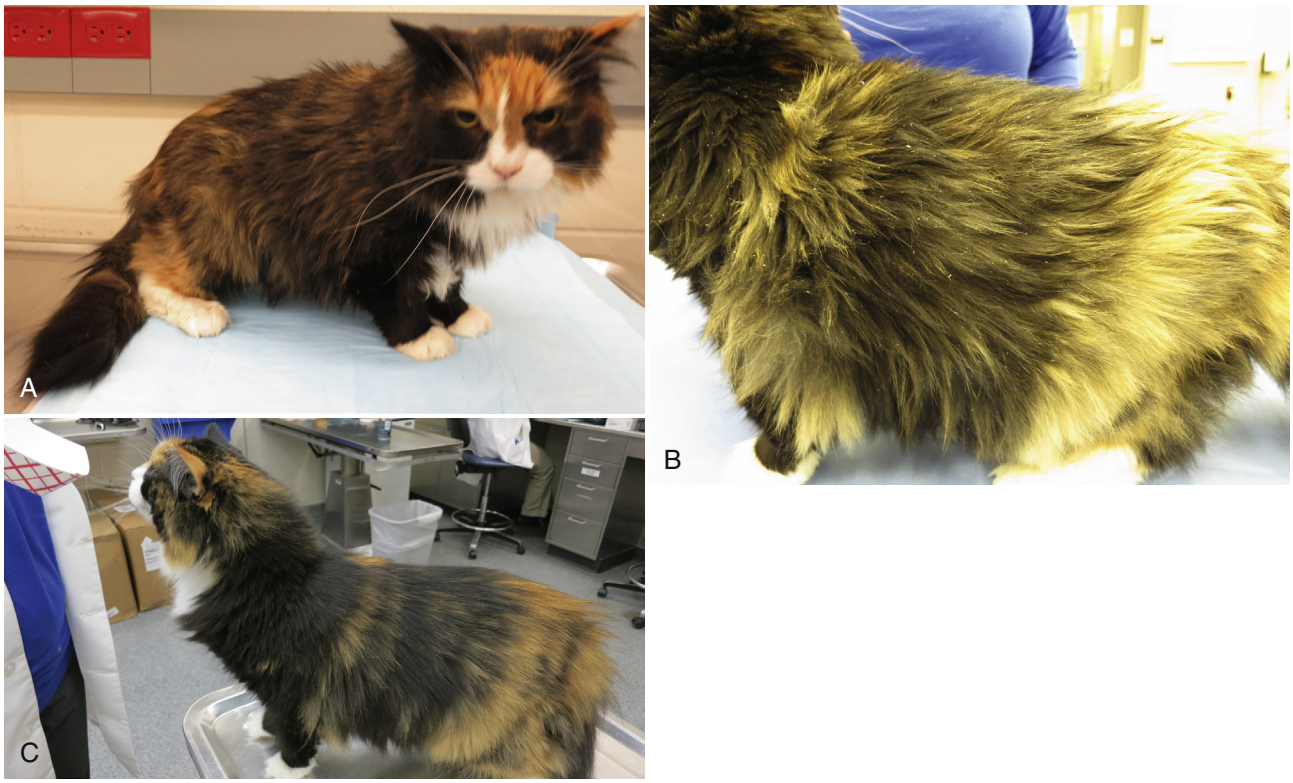

FIGURE 3-36 **A,** A 12-year-old spayed female cat with spontaneous adult onset hypothyroidism. The cat presented for evaluation of obesity, lethargy, and a dull dry hair coat. **B,** Close up of the hair coat showing dry dull coat with dry flaky skin. **C,** Same cat after 3 months of thyroid supplementation. Clinical signs had all resolved.

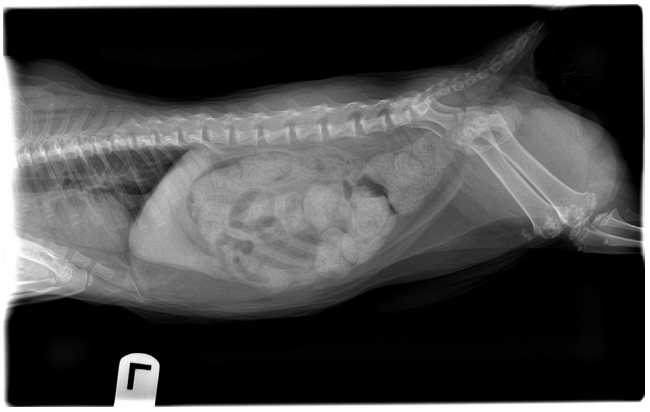

FIGURE 3-37 Lateral abdominal radiograph of a young cat with constipation due to hypothyroidism.

seizure disorder but whether the seizures were related to hypothyroidism was unclear (Traas et al, 2008).

TESTS OF THYROID GLAND FUNCTION

Hormone measurements that have been used for documentation of feline hypothyroidism include total T_4, fT_4, total T_3, and TSH concentration. For a detailed discussion of thyroid hormone assays in cats see Chapter 4.

Baseline Serum Thyroxine Concentration

Measurement of baseline serum T_4 concentration is the best initial screening test for hypothyroidism in a cat with appropriate clinical signs. Cats with hypothyroidism typically have baseline serum T_4 concentrations below the lower limit of the reference range, and sometimes T_4 is undetectable. A total T_4 within the reference range is useful to exclude a diagnosis of hypothyroidism, but because nonthyroidal illness and administration of drugs (e.g., glucocorticoids) can lower serum T_4 concentration into the hypothyroid range (Fig. 3-38), a low serum T_4 concentration does not, by itself, confirm hypothyroidism. As in the dog, the total T_4 should be interpreted in the context of the clinical signs and presence or absence of other concurrent illness and concurrent drug therapy. If the history and physical findings are consistent with the disease, the lower the T_4 value, the more likely it is that the cat truly has hypothyroidism. If the clinician's index of suspicion is not high for hypothyroidism but the serum T_4 concentration is low, then other factors such as nonthyroidal illness are much more likely.

Baseline Serum Triiodothyronine Concentration

Measurement of baseline serum T_3 concentration is not routinely performed in cats, and reported total T_3 concentrations have been variable in those cases of feline hypothyroidism in which it has been measured. Presumably, the problems encountered with serum T_3 measurements in differentiating euthyroidism from hypothyroidism in the dog also exist in the cat. Ideally, baseline serum T_3 concentration should be less than the lower limit of normal for the laboratory used in the cat with

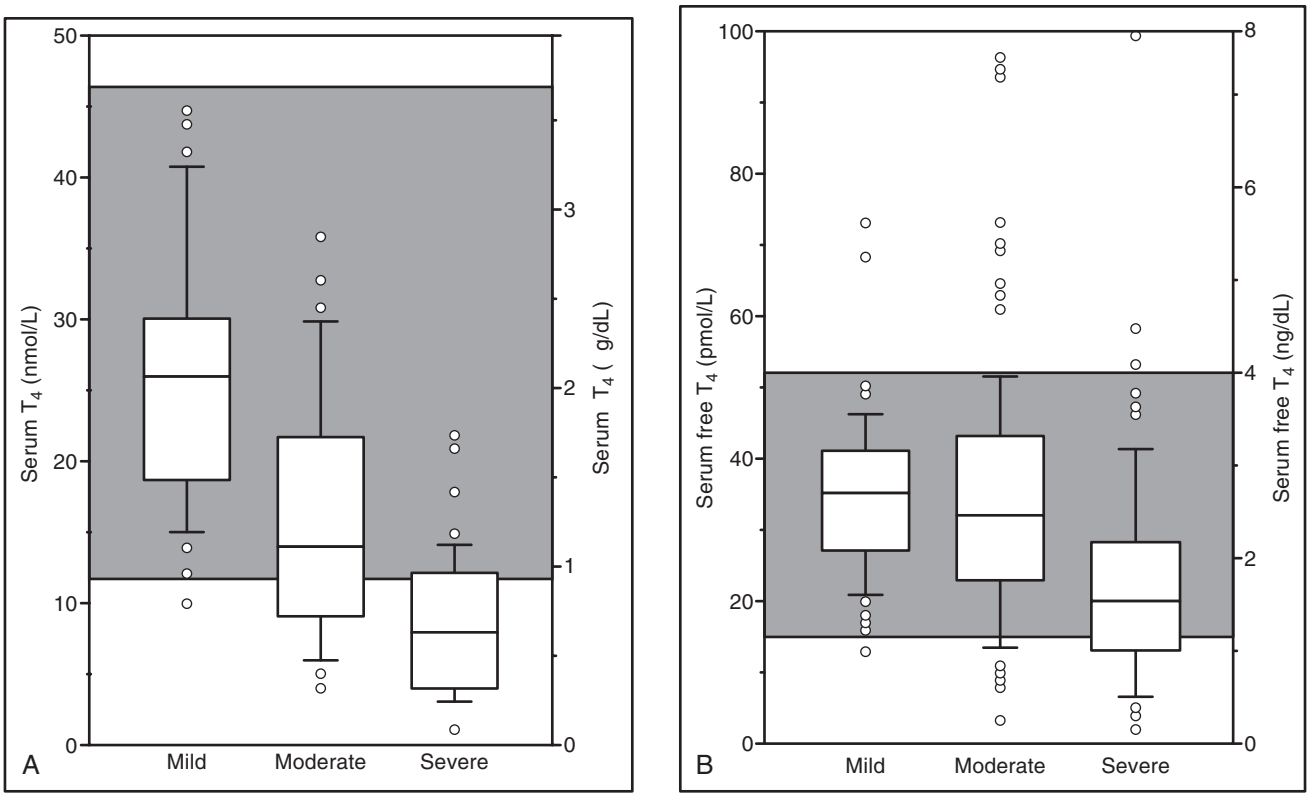

FIGURE 3-38 Box plots of serum total thyroxine (T_4) **(A)** and free T_4 (fT_4) **(B)** concentrations in 221 cats with nonthyroidal disease stratified according to severity of disease. Of the 221 cats, 65 had mild disease, 83 had moderate disease, and 73 had severe disease. For each box plot, T-bars represent the main body of data, which in most instances is equal to the range. Each box represents the interquartile range (25th to 75th percentile). The *horizontal bar* in each box is the median. *Open circles* represent outlying data points. The *shaded area* indicates the reference range. (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, 2001.)

hypothyroidism. However, a normal serum T_3 concentration in a cat with appropriate history, physical examination findings, and low serum T_4 concentration does not rule out hypothyroidism. Similarly, a low serum T_3 concentration in a cat with normal serum T_4 concentration is not consistent with hypothyroidism, especially if the remainder of the clinical picture does not support the diagnosis.

Baseline Serum Free Thyroxine Concentration

Cats with hypothyroidism should have baseline serum fT_4 concentrations below the lower limit of normal for the laboratory used. As with serum T_4, a low serum fT_4 concentration does not, by itself, confirm hypothyroidism. Nonthyroidal factors, most notably concurrent illness and administration of drugs (e.g., glucocorticoids), can falsely lower the serum fT_4 concentration into the hypothyroid range (see Fig. 3-38). Serum fT_4 is believed to be less influenced by factors such as nonthyroidal illness and administration of drugs than serum T_4, but serum fT_4 concentrations have been reported to increase rather than decrease in some euthyroid cats with nonthyroidal illness (Mooney et al, 1996a; Peterson et al, 2001). The comparative sensitivity and specificity of serum fT_4 versus serum T_4 for evaluation of thyroid gland function in cats with suspected hypothyroidism is unknown.

Baseline Serum Thyroid-Stimulating Hormone Concentration

A canine TSH assay (Immulite canine TSH assay, Diagnostic Products Corporation). 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 concurrent decrease in total T_4 is highly specific for a diagnosis of hypothyroidism. Increased TSH has been documented in cats with congenital hypothyroidism, spontaneous adult unset hypothyroidism, and iatrogenic hypothyroidism.

Tests for Lymphocytic Thyroiditis

Tests for the presence of circulating Tg and microsomal antibodies were reported to be positive in a colony of cats with early onset thyroiditis; however commercial assays for these antibodies are not currently available in the cat (Schumm-Draeger et al, 1996).

Factors Affecting Baseline Thyroid Hormone Concentrations

Many of the nonthyroidal factors known to influence serum thyroid hormone concentrations in dogs have yet to be evaluated in cats. The effects of age, gender, and breed on serum T_4 and T_3 concentrations in cats are controversial. In one study, serum T_4 and, to a lesser extent, serum T_3 concentrations in both genders tended to decrease until approximately 5 years of age and then increase again; females (intact and neutered) had significantly higher

serum T_4 but not T_3 concentrations than males (intact or neutered); and serum T_3 but not T_4 concentration was significantly higher in pedigree cats than in Domestic Short- and Long-Haired cats (Thoday et al, 1984). Serum thyroid hormone concentrations remained within the reference range in these cats regardless of any influence of age, gender, or breed on blood thyroid hormone levels. In another study, Zerbe, et al. (1998) identified values for serum T_4 and fT_4 concentrations within reference range for adult cats in kittens from birth to 12 weeks of age, whereas serum T_3 concentrations were low until kittens were 5 weeks of age. Other investigators have not identified an effect of age, gender, and/or breed on serum thyroid hormone concentrations. A diurnal variation in blood thyroid hormone concentrations apparently does not occur in the cat (Hoenig and Ferguson, 1983), so the time of day that the blood is sampled should not affect the results.

Nonthyroidal illness causing NTIS has been documented in the cat (Peterson and Gamble, 1990; Mooney et al, 1996a; Peterson et al, 2001; see Fig. 3-38). As with the dog, serum T_4 and T_3 concentrations are more likely to be decreased with nonthyroidal illness than serum fT_4 concentrations, and there is a direct correlation between the severity of illness and the magnitude of the decrease in serum thyroid hormone concentrations (see Fig. 3-38). The more severe the nonthyroidal illness, the more likely serum thyroid hormone concentrations will decrease into the hypothyroid range. Serum T_4 values less than 0.5 µg/dL and fT_4 values less than 0.5 ng/dL may occur with severe systemic illness in a euthyroid cat. It is interesting to note that some euthyroid cats with nonthyroidal disease will have decreased serum T_4 concentrations but increased serum fT_4 concentrations when an equilibrium dialysis technique is used to measure fT_4. Increased serum fT_4 concentrations were found in 12% of 98 euthyroid cats with nonthyroidal illness in one study (Mooney et al, 1996a) and 6.3% of 221 euthyroid cats with nonthyroidal illness in another study (Peterson et al, 2001). Nonthyroidal illnesses in these cats included diabetes mellitus, gastrointestinal tract disease, hepatic disease, renal insufficiency, and neoplasia. The reason for increased serum fT_4 concentrations in some cats with nonthyroidal illness is not known but may be related to decreased protein binding of circulating T_4 and/or impaired clearance of T_4 from the circulation.

The effects of drugs on serum thyroid hormone concentrations have not been extensively evaluated in the cat. Two classes of drugs that can decrease serum thyroid hormone concentrations into the hypothyroid range are glucocorticoids and anti-thyroid hormone drugs (i.e., methimazole, propylthiouracil). Undoubtedly, many more drugs also affect serum thyroid hormone concentrations in cats. Until proven otherwise, any drug should be suspected of affecting thyroid hormone test results, especially if the drug has been shown to alter serum thyroid hormone concentrations in humans and dogs (see Table 3-13 and Box 3-6) and the history and clinical signs of the patient do not support a diagnosis of hypothyroidism.

Thyroid-Stimulating Hormone Stimulation Test

The indications, protocol, and interpretation of the TSH stimulation test are similar for the cat and dog except that a lower dose of recombinant human thyrotropin (rhTSH) (25 micrograms IV) is used in the cat (Stegeman et al, 2003; van Hoek et al, 2010). In euthyroid cats, there is a two- to threefold increase in total T_4 6 to 8 hours after TSH administration. Although responses of healthy euthyroid cats to TSH have been studied, there are few studies reporting changes in total T_4 after TSH administration in cats with nonthyroidal illness or hypothyroidism. In one small study, the percent increase after TSH administration in healthy cats ranged from 111% to 300%, and in cats with nonthyroidal illness total T_4 increased by 146% to 414% (van Hoek et al, 2010). Cats with iatrogenic hypothyroidism after radioactive iodine treatment had a percent increase in total T_4 of 11% or less. These results suggest that the TSH stimulation test is useful for diagnosis of hypothyroidism in cats; however, the TSH stimulation test is rarely used clinically because of the expense of rhTSH.

Thyrotropin-Releasing Hormone Stimulation Test

The TRH stimulation test has been recommended for diagnosis of hyperthyroidism in cats (see Chapter 4) but is currently rarely used for this purpose and it has not been evaluated for diagnosis of hypothyroidism in cats. Theoretically in a cat with a functionally intact pituitary-thyroid axis, the serum T_4 concentration should increase 1 to 2 µg/dL or greater than 50% above baseline serum T_4 concentration, after administration of TRH. Failure of serum T_4 concentration to increase after TRH administration suggests dysfunction of either the pituitary or the thyroid gland or suppression of the pituitary-thyroid axis by nonthyroidal factors. If results of a previous TSH stimulation test were normal, an abnormal TRH stimulation test implies pituitary dysfunction.

ESTABLISHING THE DIAGNOSIS

The diagnosis of hypothyroidism in the cat should be based on a combination of history, clinical signs, physical examination findings, low serum thyroid hormone concentrations and increased serum TSH concentration. A minimum data base of CBC, serum chemistry profile, and urinalysis should be performed to identify changes supportive of hypothyroidism and assess for the presence of nonthyroidal illness. The most consistent findings in hypothyroid cats include hypercholesterolemia; normocytic, normochromic non-regenerative anemia; and an increase in creatine kinase. A low serum T_4 concentration in conjunction with an increased TSH concentration supports the diagnosis of primary hypothyroidism. Hypothyroidism is much more likely in a cat that has undergone thyroidectomy or radioactive iodine treatment or a kitten with disproportionate dwarfism; spontaneous adult onset hypothyroidism is so rare that nonthyroidal illness should be carefully considered prior to making a diagnosis of hypothyroidism. Further diagnostic testing that should be considered to confirm the diagnosis and localize the location of the defect includes scintigraphy and a TSH stimulation test. Response to trial therapy with L-T_4 sodium also supports the diagnosis.

Because naturally acquired primary hypothyroidism is rare and a low serum T_4 concentration in an adult cat is almost always caused by nonthyroidal illness, it is important to avoid making a diagnosis of hypothyroidism based solely on serum T_4 concentration in an adult cat that has not been previously treated for hyperthyroidism (see Chapter 4). A serum fT_4 concentration and TSH concentration should be measured prior to confirming the diagnosis. It is important to remember that response to trial therapy with L-T_4 sodium is nonspecific and does not, by itself, prove the diagnosis.

TREATMENT AND PROGNOSIS

For cats with iatrogenic hypothyroidism due to thyroidectomy or radioactive iodine treatment, transient hypothyroidism is expected after treatment, but cats should become euthyroid after 2 to 3 months. Treatment with L-T_4 sodium is indicated if clinical signs of hypothyroidism are present, if the cat is azotemic, or if hypothyroidism does not resolve by 3 to 6 months after treatment.

Treatment of hypothyroidism is similar for the cat and dog. L-T_4 sodium is the recommended thyroid hormone supplement. The initial dosage for cats is 0.05 to 0.1 mg once daily. A minimum of 6 to 8 weeks should elapse before critically assessing the cat's clinical response to treatment. Subsequent reevaluations should include history, physical examination, and measurement of serum thyroid hormone concentrations and serum TSH (see Therapeutic Monitoring). The goal of therapy is to resolve the clinical signs of hypothyroidism while avoiding signs of hyperthyroidism. This can usually be accomplished by maintaining serum T_4 concentration between 1.0 and 3.0 μg/dL. The dosage and frequency of L-T_4 sodium administration may need modification to achieve these goals. If serum thyroid hormone concentrations are normal after 6 to 8 weeks of treatment but there is no clinical response, the clinician should reassess the diagnosis.

The prognosis for feline hypothyroidism depends on the underlying cause and the age of the cat at the time clinical signs develop. With appropriate therapy, the clinical manifestations should resolve following thyroid hormone supplementation and the life expectancy of an adult cat with primary hypothyroidism should be normal. The prognosis for kittens with congenital hypothyroidism is guarded and depends on the severity of skeletal changes at the time treatment is initiated and neurologic status. Although many of the clinical signs resolve with therapy, musculoskeletal and neurologic problems may persist.

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