

## ANIMAL MODELS OF DISEASE

# Feline hyperthyroidism: an animal model for toxic nodular goiter

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## Abstract

Since first discovered just 35 years ago, the incidence of spontaneous feline hyperthyroidism has increased dramatically to the extent that it is now one of the most common disorders seen in middle-aged to senior domestic cats. Hyperthyroid cat goiters contain single or multiple autonomously (i.e. TSH-independent) functioning and growing thyroid nodules. Thus, hyperthyroidism in cats is clinically and histologically similar to toxic nodular goiter in humans. The disease in cats is mechanistically different from Graves' disease, because neither the hyperfunction nor growth of these nodules depends on extrathyroidal circulating stimulators. The basic lesion appears to be an excessive intrinsic growth capacity of some thyroid cells, but iodine deficiency, other nutritional goitrogens, or environmental disruptors may play a role in the disease pathogenesis. Clinical features of feline toxic nodular goiter include one or more palpable thyroid nodules, together with signs of hyperthyroidism (e.g. weight loss despite an increased appetite). Diagnosis of feline hyperthyroidism is confirmed by finding the increased serum concentrations of thyroxine and triiodothyronine, undetectable serum TSH concentrations, or increased thyroid uptake of radioiodine. Thyroid scintigraphy demonstrates a heterogeneous pattern of increased radionuclide uptake, most commonly into both thyroid lobes. Treatment options for toxic nodular goiter in cats are similar to that used in humans and include surgical thyroidectomy, radioiodine, and antithyroid drugs. Most authorities agree that ablative therapy with radioiodine is the treatment of choice for most cats with toxic nodular goiter, because the animals are older, and the disease will never go into remission.

## Key Words

- ▶ hyperthyroidism
- ▶ thyrotoxicosis
- ▶ thyroid
- ▶ cat
- ▶ Plummer's disease

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## Introduction

Spontaneous hyperthyroidism is an extremely common endocrine disorder of middle- to old-aged cats (Mooney & Peterson 2012, Peterson 2013a). Since first being reported in the USA in the late 1970s (Peterson *et al.* 1979), there has been a dramatic increase in the prevalence of hyperthyroidism in cats, and it has emerged worldwide

as one of the most common diseases affecting mature and senior cats (Peterson 2012).

The domestic cat is the only nonhuman species in which spontaneous thyrotoxicosis develops frequently enough to allow a system investigation into its pathogenesis. Because feline hyperthyroidism most often results

from benign adenomatous nodules of the thyroid gland, it is both clinically and pathologically similar to toxic nodular goiter or Plummer's disease in humans (Hoenig *et al.* 1982, Carpenter *et al.* 1987, Gerber *et al.* 1994, Paschke 2013). Similar to human toxic nodular goiter, this feline disease is a progressive disease, with cats transitioning from a subclinical stage to overt hyperthyroidism as the autonomous thyroid nodules increase in size (Wakeling *et al.* 2007, 2011, Broome & Peterson 2014, Peterson & Broome 2014a). As such, this disease offers a unique animal model for the study of toxic nodular goiter, as well as other disorders associated with benign neogenesis of endocrine tissue ranging from simple hyperplasia and adenomatous hyperplasia to true adenoma (Gerber *et al.* 1994, Derwahl & Studer 2002).

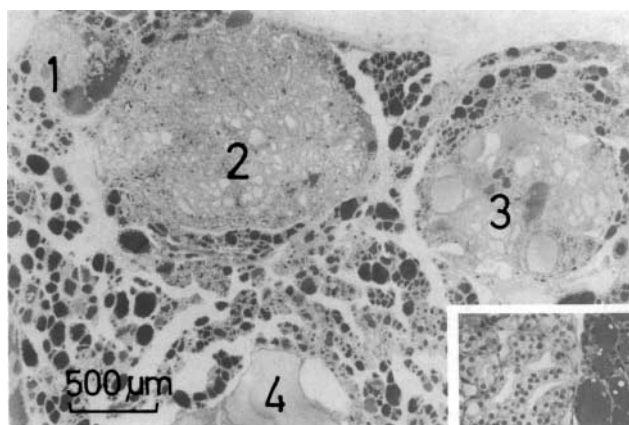
This review examines the etiopathology of spontaneous toxic nodular goiter in cats in the context of the corresponding human disease. In addition, the epidemiology, clinical features, laboratory diagnosis, scintigraphic features, and treatment for this feline thyroid disease have been reviewed, again comparing the disease with toxic nodular goiter of man.

## Studies characterizing feline hyperthyroidism as a toxic nodular goiter

### Pathology of feline toxic nodular goiter

Pathologically, hyperthyroidism in cats is most similar to the human toxic nodular goiter (i.e. Plummer's disease; Gerber *et al.* 1994, Khan & Nose 2010). Histopathological examination of tissues reveal that the thyroid glands of cats with hyperthyroidism contain single or multiple hyperplastic or adenomatous nodules ranging in size from <1 mm to 3 cm diameter (Hoenig *et al.* 1982, Carpenter *et al.* 1987, Peter *et al.* 1987; Fig. 1). The sizes of the cells, as well as the volume of the nuclei, are invariably much larger within the nodules than in the surrounding, normal paranodular tissue. These cells characteristically show little nuclear atypia or mitotic activity.

The follicles comprising the hyperplastic or adenomatous nodules are lined by a columnar to cuboidal epithelium and contain only faintly periodic acid Schiff (PAS)-stained colloid (Figs 1 and 2). As PAS avidly stains thyroglobulin in the colloid, the faint staining observed in these feline toxic nodules is due to decreased storage of thyroglobulin resulting from the hypersecretory state (Carpenter *et al.* 1987). Follicular size varies considerably between different nodules; from an almost solid growth pattern in some nodules to a macrofollicular architecture

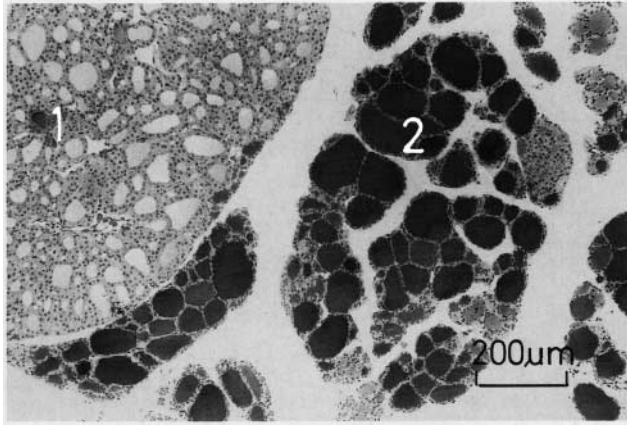


**Figure 1**

Histologic section across a nodular goiter of a hyperthyroid cat stained with periodic acid-Schiff (PAS). This stain was used to highlight glycoprotein content (thyroglobulin) within the colloid as well as follicular structure. Four nodules (1, 2, 3 and 4) consisting of follicles lined by cuboidal epithelial cells with large nuclei (see inset) and filled with pale, barely stained colloid are shown. Some areas within the nodules are almost solid structures with only tiny follicular lumina. Other nodules may contain some large follicles separated by densely cellular parenchyma (3). Occasionally, even a giant follicle may form within the nodules (4). Adapted, with permission, from Peter HJ, Gerber H, Studer H, Becker DV & Peterson ME 1987 Autonomy of growth and of iodine metabolism in hyperthyroid feline goiters transplanted onto nude mice. *Journal of Clinical Investigation* 80 491–498 (Copyright American Society for Clinical Investigation).

in others. The feline extranodular tissue is generally built up by colloid-rich follicles, which are lined by a flat epithelium (Fig. 2). The histologic appearance of this paranodular tissue resembles that of thyroid glands obtained from animals treated with levothyroxine (L-T<sub>4</sub>) and reflects the fact that circulating thyroid-stimulating hormone (TSH) is suppressed in these cats as a result of their chronic hyperthyroid state (Gerber *et al.* 1985, Capen 2001, Peterson 2013b).

The pathologic changes in the thyroid glands of cats with toxic nodular goiter are almost always benign (Hoenig *et al.* 1982, Carpenter *et al.* 1987, Peter *et al.* 1987, Wakeling *et al.* 2007). Approximately, 2% of hyperthyroid cats develop thyroid carcinoma, which can be classified as either follicular, papillary or mixed (Turrel *et al.* 1988, Hibbert *et al.* 2009). However, the prevalence of malignancy developing within a feline goiter appears to increase progressively over time, especially if the toxic goiter is not definitively treated with thyroidectomy or radioiodine (Peterson 2012, Broome & Peterson 2014, Peterson & Broome 2014a). A similar prevalence of thyroid cancer is also reported in humans with toxic nodular goiter (Sokal 1954, Gandolfi *et al.* 2004, Cerci *et al.* 2007, Khan & Nose 2010). In both man and cats, the thyroid



**Figure 2**

Histologic section of a hyperthyroid cat goiter obtained at surgery stained with periodic acid-Schiff (PAS). Note areas of hyperplastic nodular tissue with follicles lined by cuboidal or columnar epithelial cells (1) and areas of paranodular tissue with follicles filled with strongly PAS-positive colloid and lined by flat or cuboidal epithelial cells (2). Reproduced, with permission, from Peter HJ, Gerber H, Studer H, Peterson ME, Becker DV & Groscurth P 1991 Autonomous growth and function of cultured thyroid follicles from cats with spontaneous hyperthyroidism. *Thyroid* 1 331–338 (Copyright Mary Ann Liebert Inc).

cancer associated with long-standing toxic nodular goiter tends to have low metastasis potential.

#### Autoradiography studies of feline toxic nodular goiter

Autoradiographs obtained from the goiter tissue of hyperthyroid cats injected with  $^{125}\text{I}$  before surgery show that their hyperplastic or adenomatous nodules take up and incorporate radioiodine intensely (Peter *et al.* 1987; Fig. 3). Very little  $^{125}\text{I}$  is taken up by the paranodular tissue, which reflects the fact that the circulating TSH concentration is suppressed in these cats as a result of their chronic hyperthyroid state (Peterson 2013b). Within the nodules, radioiodine incorporation may not be increased in all individual follicles but varies from nil to very intense. This resembles the marked interfollicular heterogeneity of iodine metabolism reported in the thyroid of patients with multinodular goiter (Miller & Kawas 1966, Peter *et al.* 1985, Studer *et al.* 1989).

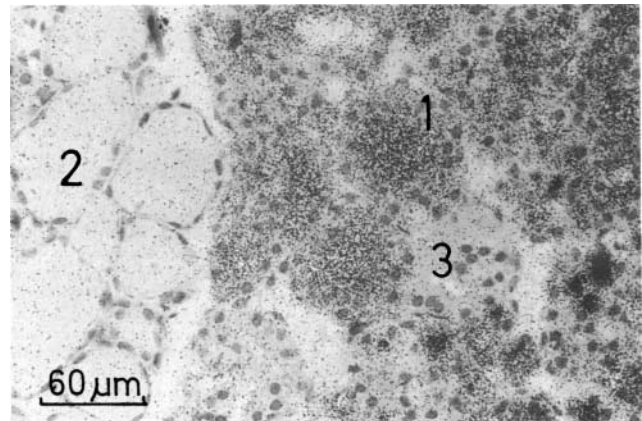
Marked heterogeneity of radioiodine incorporation is also seen in the thyroid tissue of normal cats (Peter *et al.* 1987). When evaluated <4 h after  $^{125}\text{I}$  administration, that is, before the newly iodinated thyroglobulin molecules could move away from the colloid-thyrocyte border and mix with the rest of the colloid (Gerber *et al.* 1985), clear-cut differences in the amount of radioiodine metabolism can be observed, even among the cells of individual follicles (Peter

*et al.* 1987). In this aspect, the feline thyroid gland does not differ from other species, including man (Studer *et al.* 1989).

#### Xenotransplantation studies with feline toxic nodular goiter

The autonomy of feline toxic goiter tissue has been studied by transplanting thyroid tumor tissue collected from the hyperthyroid cats at surgery into athymic nude mice (Gerber *et al.* 1996). In these studies, we evaluated the proliferation and iodine incorporation of transplanted normal cat thyroid tissue, as well as feline toxic goiter tissue, by injecting the mice with either  $^{125}\text{I}$  or  $^{131}\text{I}$  and tritium-thymidine respectively (see below). The mice were treated with either  $\text{L-T}_4$  to suppress circulating TSH or methimazole to raise TSH concentrations as needed (Peter *et al.* 1985, 1987).

When toxic nodular goiter tissue from normal or hyperthyroid cats was transplanted into dysthymic nude mice, the feline thyroid tissue continued to grow in its original nodular histologic pattern within the new host (Peter *et al.* 1987). These transplantation studies of feline hyperthyroid tissue into nude mice are similar to the results reported after transplantation of adenomatous thyroid tissue from human patients with toxic nodular goiter into nude mice (Peter *et al.* 1985).

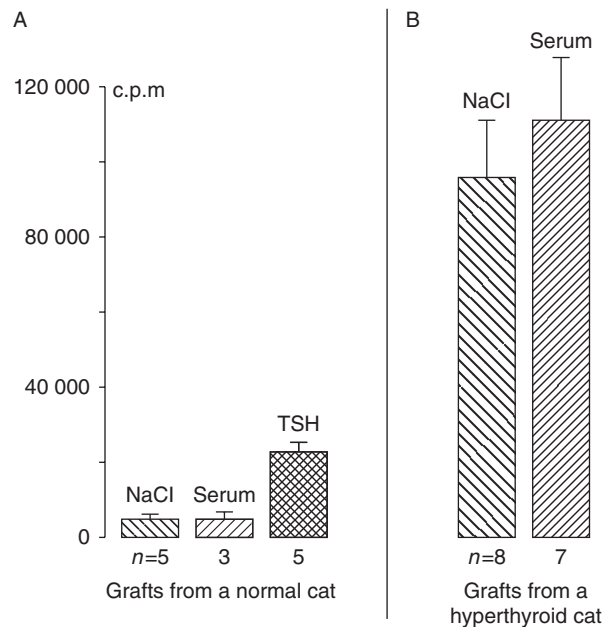


**Figure 3**

Autoradiograph of hyperthyroid cat goiter labeled with 20  $\mu\text{Ci}$  of  $^{125}\text{I}$  for 4 h before surgery, with nodular tissue then counter-stained with nuclear fast red stain. Note intense iodine organification within a hyperplastic nodule (1) and very little iodine uptake within the adjacent paranodular tissue (2). In some hyperplastic nodules, there was considerable heterogeneity of radioiodine organification among individual follicles, even within the same nodule (3). Exposure time 65 days. Reproduced, with permission, from Peter HJ, Gerber H, Studer H, Becker DV & Peterson ME 1987 Autonomy of growth and of iodine metabolism in hyperthyroid feline goiters transplanted onto nude mice. *Journal of Clinical Investigation* 80 491–498 (Copyright American Society for Clinical Investigation).

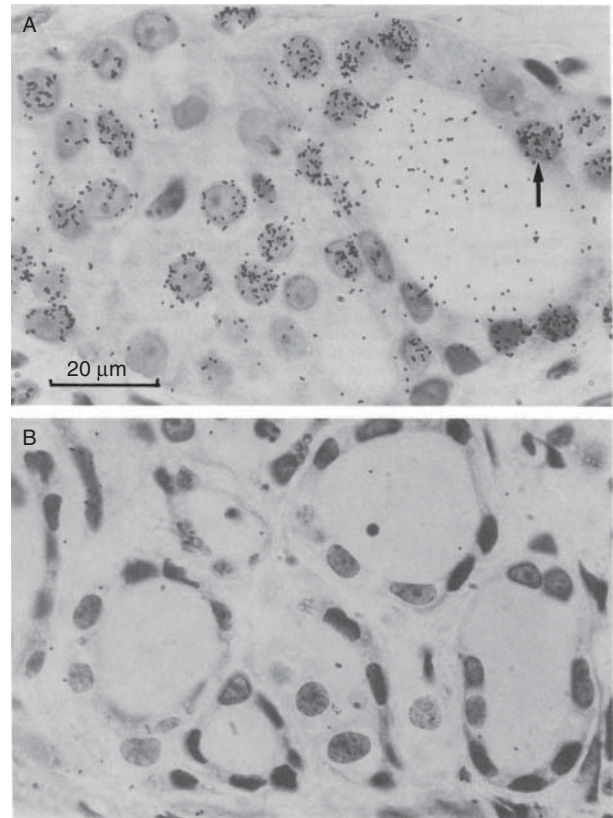
**Iodine metabolism, as evaluated by incorporation of radioiodine** To study the function and iodine metabolism of cat thyroid tissue, we investigated the radioiodine uptake into the transplanted feline normal and toxic goiter tissue, which had been growing in the  $T_4$ -treated host mice. In the normal cat thyroid tissue,  $^{131}\text{I}$  uptake was low in the absence of TSH and did not increase after administration of hyperthyroid cat serum, but the  $^{131}\text{I}$  uptake of the normal tissue did increase two- to fourfold after administration of bovine TSH (Peter *et al.* 1987). In contrast to the normal transplanted thyroid tissue, the uptake and organification of radioiodine was very intense in the transplanted feline goiter tissue (Fig. 4). As with the normal thyroid tissue, however, administration of serum from the hyperthyroid donor cat failed to increase the iodine uptake (Peter *et al.* 1987; Fig. 4).

Overall, these findings indicate that, regardless of the initiating cause of the cats' hyperthyroidism, the xenotransplanted toxic goiter tissue continues to function in



**Figure 4**

Radioiodine uptake into xenotransplanted normal (A) and toxic goiter tissue (B) growing in  $T_4$ -treated host mice labeled with  $20\ \mu\text{Ci}$  of  $^{131}\text{I}$  for 3 h before being killed.  $^{131}\text{I}$  uptake of mean ( $\pm$ s.e.m.) counts per minute (c.p.m.) into normal tissues (saline control, NaCl,  $n=5$ ) is low in the absence of TSH and is not enhanced by administration of hyperthyroid cat serum (serum,  $n=3$ ), but  $^{131}\text{I}$  uptake is readily stimulated by TSH (TSH,  $n=5$ ) (A). Toxic goiter tissue shows unabated high autonomous iodine uptake (NaCl,  $n=8$ ) that is not significantly altered by administration of serum from the hyperthyroid donor cat (serum,  $n=7$ ) (B). Reproduced, with permission, from Peter HJ, Gerber H, Studer H, Becker DV & Peterson ME 1987 Autonomy of growth and of iodine metabolism in hyperthyroid feline goiters transplanted onto nude mice. *Journal of Clinical Investigation* **80** 491–498 (Copyright American Society for Clinical Investigation).



**Figure 5**

Histological sections of a xenograft of a toxic goiter of a geriatric cat grown in a  $T_4$ -treated host mice labeled with  $[^3\text{H}]$ thymidine 3 months before being killed, then counter-stained with nuclear fast red. Autoradiograph A, taken from a hyperplastic area and exposed 3 months after radioiodine labeling, shows that despite the absence of TSH, a considerable fraction of the follicular cells has incorporated the thymidine label into their nuclei (arrow). The grains within the follicular lumina result from residual  $^{131}\text{I}$  activity. No incorporation of  $[^3\text{H}]$ thymidine into follicular cell nuclei is found in autoradiograph B showing a paranodular area, exposed under identical conditions (72 days). Reproduced, with permission, from Peter HJ, Gerber H, Studer H, Becker DV & Peterson ME 1987 Autonomy of growth and of iodine metabolism in hyperthyroid feline goiters transplanted onto nude mice. *Journal of Clinical Investigation* **80** 491–498 (Copyright American Society for Clinical Investigation).

the host mouse and is independent from circulating stimulatory factors (e.g. thyroid-stimulating immunoglobulins (TSIs)).

#### **Proliferation, as evaluated by incorporation of tritium-thymidine**

In this study, we used autoradiography to assess follicular cell proliferation in the transplanted feline toxic goiter tissue (Peter *et al.* 1987). Despite the fact that TSH was suppressed in the  $T_4$ -treated nude mice, a considerable fraction of the autonomously proliferating feline follicular cells incorporated the thymidine label into their nuclei. In contrast, no incorporation of the

<sup>3</sup>H-thymidine label was found within the suppressed paranodular thyroid tissue (Fig. 5).

These findings indicate that the xenotransplanted toxic goiter tissue continues to grow in the host mouse and, thus, is independent from circulating stimulatory factors. Again, these are similar to the results reported after transplantation of thyroid tissue from human patients with toxic nodular goiter (Peter *et al.* 1985).

### Studies using primary cultures of follicles and thyrocytes from toxic adenomatous cat thyroids

Consistent with these xenotransplantation studies, adenomatous thyroid cells from hyperthyroid cats cultured in TSH-free media also continue to grow and function autonomously (Peter *et al.* 1991). In those studies, primary cultures of enzymatically dissociated follicles from 15 hyperthyroid cat goiters and from three normal cat thyroid glands were embedded in collagen gels to preserve their 3D structure. Growth and function in chemically defined media were assessed by autoradiography after double labeling with <sup>3</sup>H-thymidine and <sup>131</sup>I-Na. Iodine organification in the follicles from normal glands was TSH-dependent, but intense radioiodine organification occurred in the follicles from hyperfunctioning goiters even in the absence of TSH (Fig. 6). Similarly, twice as many follicular cells of hyperfunctioning thyroid tissue, maintained without TSH in the medium, were labeled after exposure to <sup>3</sup>H-thymidine than in follicles from normal glands (Peter *et al.* 1991; Fig. 7).

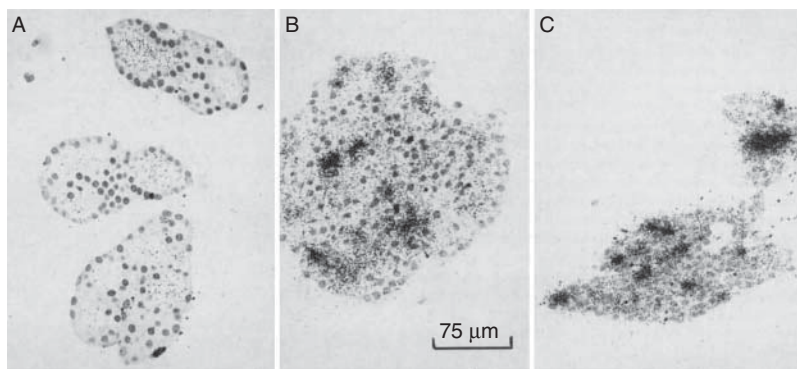
The results of these feline cell culture studies are in line with the xenotransplantation studies and suggest that

intrinsic alterations of thyroid cell function lead to the autonomy of follicular growth and function that characterizes hyperthyroidism in the domestic cat. Again, extrathyroidal-stimulating factors are not involved in the pathogenesis of feline nodular goiter.

In other studies, isolated thyroid follicular cells from normal and hyperthyroid cats were enzymatically digested and grown in a monolayer cell culture to evaluate both thyroglobulin production and DNA synthesis (Gerber *et al.* 1994, Ward *et al.* 2005a). TSH stimulated mitogenesis and thyroglobulin expression in both normal and hyperthyroid cells, but a higher concentration of TSH was needed to maximally stimulate both activities in the hyperthyroid cells (Ward *et al.* 2005a). Other studies of monolayer hyperthyroid cell culture, however, found no effect of TSH on <sup>3</sup>H-thymidine uptake in hyperthyroid cells (Gerber *et al.* 1991), illustrating that cells from different feline goiters may show a high degree of heterogeneity in culture. Overall, these data reinforce the idea that feline toxic nodular goiter cells have a high level of basal, unstimulated activity with dysregulated growth and hormone synthesis, as would be expected in autonomous cells (Gerber *et al.* 1994, Ward *et al.* 2005a).

### Mutations of the TSH receptor and G-protein alpha subunit G $\alpha_s$ (GNAS)

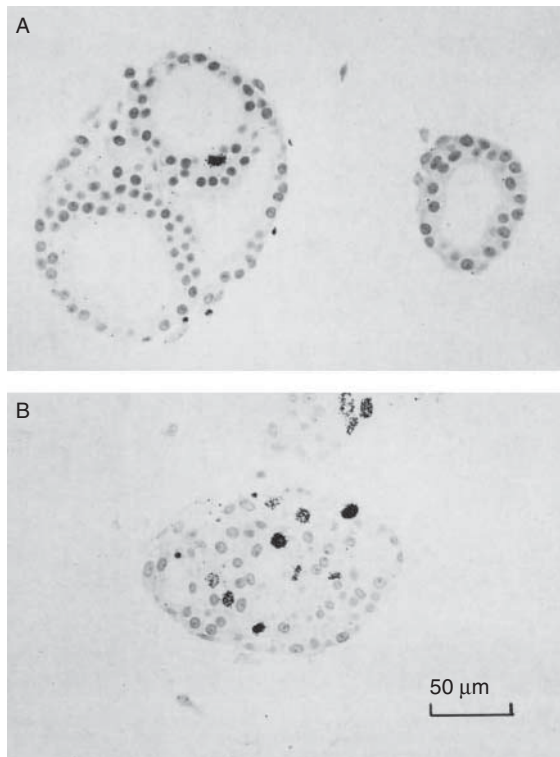
Mutations in the thyrotropin receptor gene, leading to constitutive activation of the TSH receptor (TSHR), are common in human patients with both toxic nodular goiter and toxic adenoma. Less commonly, constitutively activating mutations in the adenylate cyclase stimulation



**Figure 6**

Autoradiograph showing radioiodine organification in follicles embedded in collagen gel, counter-stained with nuclear fast red. In normal follicles cultured without TSH, the density of silver grains within the lumina is low (A), whereas intense <sup>131</sup>I organification occurs in the presence of TSH (B). In contrast, follicles from hyperthyroid goiter tissue intensely accumulate the iodine label despite the absence of TSH (C). All cultures were labeled

under identical conditions, and slides were exposed for 5 days. Reproduced, with permission, from Peter HJ, Gerber H, Studer H, Peterson ME, Becker DV & Groscurth P 1991 Autonomous growth and function of cultured thyroid follicles from cats with spontaneous hyperthyroidism. *Thyroid* 1 331–338 (Copyright Mary Ann Liebert Inc).



**Figure 7**

Autoradiograph of a histological section counter-stained with nuclear fast red showing follicular cell proliferation in follicles from normal and hyperfunctioning thyroid tissue cultured in the absence of TSH. In normal follicles (A), only an occasional cell has incorporated the thymidine label. In contrast, some clusters of follicles contain up to 12%  $^3\text{H}$ -thymidine-labeled cells in cultures from hyperthyroid goiters (B). Reproduced, with permission, from Peter HJ, Gerber H, Studer H, Peterson ME, Becker DV & Groscurth P 1991 Autonomous growth and function of cultured thyroid follicles from cats with spontaneous hyperthyroidism. *Thyroid* 1 331–338 (Copyright Mary Ann Liebert Inc).

protein  $G\alpha_s$  subunit (GNAS) are found (Krohn & Paschke 2002, Krohn *et al.* 2005, Liu *et al.* 2010). As a consequence of these mutations, chronic activation of the adenylate-cyclase–cAMP cascade takes place, leading to enhanced iodine uptake by the thyroid, increased thyroid hormone synthesis and release, and clinical hyperthyroidism (Kopp 2001, Krohn *et al.* 2005).

In hyperthyroid cats, early studies carried out in small numbers of cats failed to identify any *TSHR* mutations (Pearce *et al.* 1997, Peeters *et al.* 2002). However, a later detailed study of 134 nodules from 50 hyperthyroid cats found ten missense mutations, of which five have previously been associated with human hyperthyroidism (Watson *et al.* 2005). The most common *TSHR* mutation detected in cats is Met452–Thr (a substitution of methionine by threonine), which is analogous to the human mutation Met453–Thr observed in sporadic human

nodular goiter (Parma *et al.* 1997, Nishihara *et al.* 2009). In addition, *GNAS* mutations have also been documented in four of ten hyperthyroid cats examined (Peeters *et al.* 2002). None of these identified mutations are present in thyroid tissue of normal cats.

Not all nodules taken from an individual cat or thyroid lobe showed the same mutations, with different mutations appearing in different adenomas and hyperplastic nodules (Watson *et al.* 2005). A similar scenario has been found in human hyperthyroidism (Fuhrer *et al.* 1996, Duprez *et al.* 1997, Holzapfel *et al.* 1997, Tonacchera *et al.* 1998). Similar to human patients, the finding of mutations in the *TSHR* gene or the *GNAS* gene in hyperthyroid cats suggests that such mutations play a role in the pathogenesis of feline toxic nodular goiter in some, but not all, cases.

#### Abnormalities in thyroid growth and signaling in feline toxic nodular goiter

In the normal thyroid cell, growth and function are controlled by the interaction of TSH with its G-protein-coupled receptor on the surface of the thyroid cell (Dumont *et al.* 1992, Kleinau *et al.* 2013). Heterotrimeric G proteins of the  $G\alpha_s$  and  $G\alpha_i$  subgroups regulate adenylyl cyclase activity, which in turn controls the formation of cAMP (Wettschureck & Offermanns 2005). The  $G_s$  proteins are stimulatory to adenylyl cyclase, while the  $G_i$  proteins are inhibitory. Adenylyl cyclase activity and cAMP formation result from cumulative expression and activity of both the  $G_s$  and  $G_i$  proteins.

Abnormalities of any element of the *TSHR*–G protein–cAMP regulatory pathway can result in the uncontrolled cellular proliferation and excess hormone secretion seen in hyperthyroid disease (Kopp 2001, Krohn *et al.* 2005). As noted earlier, mutations in the *TSHR* gene and the alpha subunit of the  $G_s$  protein have been documented in both human and feline toxic nodular goiter. These findings suggest that these gene mutations play a role in the disease; however, the finding of such a gene mutation does not always equate to a functional defect leading to hyperthyroidism (Derwahl *et al.* 1996, Fuhrer *et al.* 1996, Watson *et al.* 2005).

For instance, increased expression of alpha subunits of both  $G_s$  and  $G_i$  has been demonstrated in human adenomatous thyroid tissue (Siperstein *et al.* 1991, Delemer *et al.* 1992), and one subset of  $G\alpha_i$  proteins,  $G\alpha_{i1}$ , has been shown to be selectively expressed in some thyroid nodules (Selzer *et al.* 1993). Still, marked variation in G-protein coupling and signal transduction has been reported, as supported by the variable  $G\alpha_s$  or  $G\alpha_i$  protein

expression in hyperfunctioning thyroid nodules (Selzer *et al.* 1993, Derwahl *et al.* 1996, Holzapfel *et al.* 2002). The relationship between  $G_s$  expression, the cAMP cascade, and the subsequent mitogenic response to this signaling pathway (eventually leading to thyroid nodular hyperplasia or adenoma) is complex. Therefore, correlating the expression of one protein with the overall activity of the cAMP cascade can be misleading (Uytterspot *et al.* 1995, Holzapfel *et al.* 2002).

In cats with toxic nodular goiter, two reports have also demonstrated that tissue from five hyperthyroid cats had a reduced quantity of  $G\alpha_i$  proteins (in particular,  $G\alpha_{i2}$ ), but no difference was detected in the amounts of  $G\alpha_s$  between hyperthyroid and control cats (Hammer *et al.* 2000, Ward *et al.* 2005b). These results suggest that decreased amounts of  $G\alpha_i$  may remove the negative inhibition of adenylyl cyclase and result in increased cAMP formation, which could contribute to the nodular growth in some hyperthyroid cats (Hammer *et al.* 2000, Ward *et al.* 2005b, 2010). In both of these studies, only five hyperthyroid cats were used, and unfortunately, we do not know whether any of the cats had activating mutations of either the *TSHR* or *GNAS*.

### Thyroid autoimmunity and circulating thyroid stimulators in feline toxic nodular goiter

Initial theories regarding the pathogenesis of feline hyperthyroidism revolved around it being similar to Graves' disease, an autoimmune disorder in which circulating stimulatory autoantibodies activate the TSHR leading to thyroid hyperplasia and unregulated thyroid hormone production and secretion (Schott *et al.* 2005, Menconi *et al.* 2014). As these TSIs stimulate growth of all thyrocytes, diffuse hyperplasia of the both thyroid lobes is a characteristic feature of Graves' disease.

In support of an autoimmune pathogenesis, early studies carried out in hyperthyroid cats suggested that circulating thyroid autoantibodies (i.e. thyroid microsomal and antinuclear) were not uncommon, being present in one-third of cats examined (Kennedy & Thoday 1988). However, subsequent studies by these same investigators failed to identify any evidence for circulating levels of TSIs (specific autoantibody characteristic of Graves' disease) in hyperthyroid cats, a finding confirmed by others (Peterson *et al.* 1987, Kennedy & Thoday 1989). These studies used a bioassay method (the Fischer rat thyroid cell line, FTRL5), in which cAMP production is used to indicate serum antibody action. No significant difference was detected in intracellular cAMP concentrations in FTRL5

cells incubated with the IgG extracted from normal vs hyperthyroid cat serum (Peterson *et al.* 1987, Kennedy & Thoday 1989). In the most recent and definitive study, the feline TSHR was cloned, and activation by whole and purified IgG fractions of hyperthyroid cat sera was investigated in a sensitive expression system (Nguyen *et al.* 2002). Serum and IgG fractions of serum from the 16 hyperthyroid cats did not stimulate cAMP production in human embryonic kidney cells (TSA-201) transfected with feline TSHRs, whereas serum and IgG fractions from patients with Graves' hyperthyroidism did stimulate cAMP production (Nguyen *et al.* 2002). Overall, these results indicate that feline hyperthyroidism does not result from high circulating concentration of TSIs and, in that respect, is not analogous to Graves' disease.

Although cats with toxic nodular goiter do not have circulating TSIs, high titers of serum thyroid growth-stimulating immunoglobulins (TGIs) have been measured in hyperthyroid cats (Brown *et al.* 1992). These autoantibodies, which act to promote thyroid growth but not to stimulate thyroid hormone secretion, also have been reported in human patients with toxic nodular goiter, as well as in patients with Graves' disease, Hashimoto's thyroiditis, and euthyroid goiter (Brown 1995). Despite the presence of these autoantibodies, their clinical significance in human patients remains unclear. Similarly, in cats, there is no correlation between thyroid function and TGI activity *in vitro*, and their role in the pathogenesis of hyperthyroidism remains unclear. Some have questioned whether circulating TGIs even exist (Zakarija & McKenzie 1990) and, in any case, TGIs have largely been forgotten over the last two decades. Our xenotransplantation and thyroid culture studies (see above) clearly show that *in vivo* growth and hyperfunction of cat toxic goiters no longer depends on circulating extra-thyroidal stimulators (Peter *et al.* 1987), and the basic lesion associated with feline nodular goiter appears to be an excessive intrinsic growth potential of some thyroid cell subsets, similar to that observed in human toxic nodular goiter (Peter *et al.* 1985, Studer *et al.* 1989). Of course, a very weak stimulator of thyroid growth (such as circulating TGIs) that enhances the initial transformation of a normal thyroid gland into a nodular goiter certainly remains a possibility.

Overall, all of these studies provide evidence against the presence of circulating thyroid-stimulating factors as a mechanism underlying the pathogenesis of feline toxic goiter. In contrast, these studies support a model involving an intrinsic autonomy of thyroid follicular cell growth and function similar to that seen in human toxic nodular goiter (Peter *et al.* 1985, Studer *et al.* 1989).

## Epidemiology of feline toxic nodular goiter: a common worldwide disorder of older domestic cats

Feline thyroid nodular disease and hyperthyroidism appears to be a relatively new disorder of cats, first described in 1979 (Peterson *et al.* 1979). Before that time, goiter had been found at necropsy in a few cats, and nodules were observed histopathologically, but these abnormalities were relatively rare and were not associated with the clinical signs related with hyperthyroidism (Lucke 1964, Leav *et al.* 1976).

Over the last 35 years, the prevalence of thyroidal pathologic abnormalities and the associated state of hyperthyroidism have steadily increased. It is now accepted as the most common endocrine disorder in cats and the most important cause of morbidity in middle-aged cats in the USA, Canada, UK, Europe, Australia, New Zealand, and Japan (Mooney & Peterson 2012, Peterson 2012).

The prevalence of feline hyperthyroidism (toxic nodular goiter) in my clinics has been reported to reach 10% of all cats older than 10 years (Peterson M E, 2014, unpublished observations), which is equivalent to a human age of over 60 years (Vogt *et al.* 2010), and the prevalence appears to increase ever further with advancing age. Similar prevalence rates have been reported in other parts of the world over the last decade, ranging from 7.4% in London (Wakeling *et al.* 2011) to 8.9% in Japan (Miyamoto *et al.* 2002), 11.4% in Germany (Sassnau 2006), and 20.1% in the most recent study in Warsaw (Gójska-Zygner *et al.* 2014). In contrast to these high feline prevalence rates, the prevalence of toxic nodular goiter in older human patients is much less, ranging between 0.4 and 2.0% (Vanderpump 2011), although a higher prevalence rate is seen in iodine-deficient areas (Aghini-Lombardi *et al.* 1999).

To put these prevalence rates into perspective, ~25% of domestic cats living in the USA and Canada are older than 10 years of age (Perrin 2009, American Veterinary Medical Association 2012). The estimated population of cats in the USA and Canada is 80 million, which calculates out to be about 20 million geriatric cats. If 10% of these are hyperthyroid, that means that we have 2 million cats in the USA and Canada alone suffering from overt toxic nodular goiter. Again, this is an extremely common disease in older cats.

As in human patients, thyroid nodules, nontoxic goiter, and subclinical hyperthyroidism are also very common in elderly cats. In three studies in which senior euthyroid cats were screened for thyroid nodules, 38%

(Chaitman *et al.* 1999), 59% (Norsworthy *et al.* 2002a), and 76% (Boretti *et al.* 2009) of these cats had a palpable goiter. When these euthyroid nodules were examined histopathologically, 65–85% were confirmed as nodular hyperplasia or adenoma (Norsworthy *et al.* 2002b, Ferguson & Freeman 2006). Similarly, in a postmortem study carried out in geriatric German cats (aged 13–16 years old, which is equivalent to 68–80 human years), 76% had nodular goiter on histopathologic examination (Reese *et al.* 2002); again, this rate is much higher than that of overt hyperthyroidism (11.4%) confirmed at the same institution (Sassnau 2006). Therefore, it has been demonstrated that histopathological thyroid changes consistent with nontoxic or toxic nodular goiter develop very frequently in older euthyroid cats.

Some euthyroid cats with palpable goiter will develop overt hyperthyroidism months to years later, as a result of continued growth of the thyroid nodule(s) (Ferguson & Freeman 2006, Wakeling *et al.* 2007, 2011). As in human patients with toxic nodular goiter, cats likely undergo a phase of subclinical hyperthyroidism – defined as a subnormal serum TSH concentration in a patient with normal T<sub>4</sub> and triiodothyronine (T<sub>3</sub>) concentrations (Cooper & Biondi 2012) – before becoming clinically hyperthyroid. In a recent prospective study of euthyroid geriatric cats, the annual incidence for development of hyperthyroidism was 7.4%; cats that became hyperthyroid were much more likely to have both goiter and an undetectable serum TSH concentration at time of initial evaluation (Wakeling *et al.* 2011). Similarly, euthyroid human patients with subclinical hyperthyroidism associated with nodular goiter develop overt thyrotoxicosis at a similar rate of around 5–10% per year (Hamburger 1980, Bartalena *et al.* 1991).

### Why has feline nodular goiter reached such epidemic proportions?

There is much speculation regarding the cause of hyperthyroidism in cats and why it reached the epidemic proportions seen today. This has been variously attributed to an increase in feline longevity, increased willingness of owners to seek treatment for their cats, improved diagnosis by practicing veterinarians, or a true increase in disease prevalence. It seems likely that all are true to some extent. Epidemiological studies have found associations of hyperthyroidism with increasing age, a protective effect in certain pure breeds (notably the Siamese and Burmese), and associations with certain lifestyle factors, most notably living indoors, consumption of canned cat food (especially fish flavors), and the use of cat litter



(Scarlett 1988, Kass *et al.* 1999, Edinboro *et al.* 2004, Olczak *et al.* 2005, Wakeling *et al.* 2009).

Theories abound as to why canned food should increase the risk of developing hyperthyroidism. It could just be a marker for cats that are most likely to enjoy a protected indoor existence and, therefore, are most likely to live to an advanced age (when hyperthyroidism develops). However, this is unlikely to be the sole explanation. Historically, chronic dietary iodine deficiency has long been considered to be the major underlying risk factor for the development of toxic nodular goiter in human patients (Laurberg *et al.* 1991, Van de Ven *et al.* 2013). Interestingly, low-grade iodine deficiency has also been implicated to be one of the inciting causes for this condition in hyperthyroid cats (Edinboro *et al.* 2010, 2013). Therefore, iodine deficiency may play a role in development of feline nodular goiter, but, as in human patients with toxic nodular goiter, it is unlikely to be the only cause (Derwahl & Studer 2000, 2001).

Other dietary factors that have been implicated in the pathogenesis of the feline toxic nodular goiter include dietary flavonoids, which are found in high concentrations in many cat foods (Court & Freeman 2002, Bell *et al.* 2006). Flavonoids can act to inhibit thyroid peroxidase and have known goitrogenic properties (Divi & Doerge 1996, Köhrle 2000, Doerge & Sheehan 2002). In addition, flavonoids may have additional actions on the thyroid gland of cats, because the flavonoid quercetin was reported to induce autonomous mitogenesis and thyroglobulin synthesis in cultured feline hyperthyroid cells (Ward *et al.* 2010).

Chronic exposure to thyroid-disrupting compounds in the diet, drinking water, or environment may also play a role in the pathogenesis of feline thyroid nodules and hyperthyroidism, as postulated to occur in human thyroid disease (Diamanti-Kandarakis *et al.* 2009, Jugan *et al.* 2010, Zoeller 2010). For example, the polyphenolic compound bisphenol A, which is used as a plasticizer in can linings, has been detected in canned cat food and may act as a thyroid disruptor (Edinboro *et al.* 2004, Schecter *et al.* 2010). In a similar vein, recent studies both in the USA and Sweden have reported high levels of polybrominated diphenyl ethers (PBDEs) in cats, a fire-retardant with known thyroid-disrupting properties (Dye *et al.* 2007, Guo *et al.* 2012, Mensching *et al.* 2012, Norrgran *et al.* 2012). As PBDEs migrate out of the flame-protected materials (e.g. plastics, textiles, furniture, or electronics), these chemicals end up in house dust as the natural sink (Suzuki *et al.* 2008). Therefore, in addition to dietary sources of PBDEs, domestic cats living indoors and lying on the floor

will normally collect dust in their fur and ingest these dust-enriched chemicals through grooming (Guo *et al.* 2012, Johnson *et al.* 2013). In the study of PBDEs and other endocrine-disrupting compounds, human beings and domestic cats share the same environments and tend to be chronically exposed to same chemical disruptors; however, because of their shorter life spans, companion animals may serve as good sentinels for human disease.

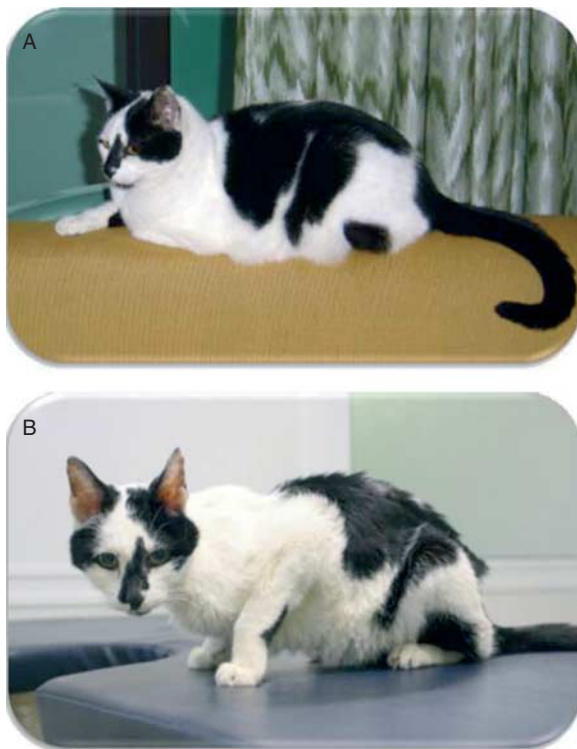
### Clinical features of toxic nodular goiter in cats

In human patients, the two major risk factors for toxic nodular goiter include being older (over 60 years of age) and female (Siegel & Lee 1998). As in human patients with toxic nodular goiter, hyperthyroidism occurs almost exclusively in the older to geriatric cat. Over 95% of cats will be older than 10 years at time of diagnosis (Mooney & Peterson 2012, Peterson 2013a), which is equivalent to the human age at which risk of developing toxic nodular goiter increases (Vanderpump 2011, Paschke 2013). There is no breed predilection; although the disease does occur in pure breed cats, most cats with hyperthyroidism are of mixed-breeding (i.e. mongrel cats). Female cats also develop hyperthyroidism more commonly than males (1.25:1; Peterson *et al.* 1988, Peterson & Becker 1995, Peterson & Broome 2014b), although the female sex predilection is not as marked as in human patients with toxic nodular goiter ( $\geq 4:1$ ; Vanderpump 2011, Paschke 2013).

In most cats with toxic nodular goiter, the recognition of hyperthyroidism is not difficult, and the clinical features closely parallel those of human hyperthyroid disease (Dabon-Almirante & Surks 1998, Burch 2013). The classic clinical signs include weight loss together with a good to increased appetite (Mooney & Peterson 2012, Peterson 2013a). Cats with severe hyperthyroidism will develop increased activity, nervousness, or restlessness, but milder cases do not generally show such symptoms. As in older human patients, some cats will develop an apathetic form of the disease, in which the appetite is reduced and lethargy, rather than hyperexcitability or nervousness, is noted (Mooney & Peterson 2012, Peterson 2013a). Cardiac signs, including sinus tachycardia and cardiac murmur, are also very common in hyperthyroid cats, as these are in human patients with thyrotoxicosis (Klein & Danzi 2007, Dahl *et al.* 2008). Occasionally vomiting, especially after overeating, is relatively common; other gastrointestinal signs, such as hyperdefecation or diarrhea, may also be reported. In some cats, dermatologic changes may develop as a result of an unkempt hair or

greasy hair coat will develop. If the disease is allowed to progress untreated, muscle wasting, fatigability, emaciation and cachexia will ultimately result, although this can take months to years (Fig. 8).

On physical examination, most cats have sinus tachycardia and show evidence of weight loss or loss of muscle mass. In addition, the finding of goiter is common (Boretti *et al.* 2009, Peterson 2013b). Cats have two separate thyroid lobes that normally lie on either side of the trachea, midway down the neck. Unlike that of man, the two feline thyroid lobes are separate and not connected via an isthmus (Dyce *et al.* 1987, Waters 1993). Goiter may be palpable in one or both lobes, and the thyroid nodules usually range in size from a pea to a grape, although much larger thyroid masses can be found. In cats with early or subclinical hyperthyroidism, the clinical signs are very mild or nonexistent other than the presence of one or two small thyroid nodule(s) (Norsworthy *et al.* 2002a, Ferguson & Freeman 2006, Boretti *et al.* 2009).



**Figure 8**  
A female, domestic shorthaired cat at 9 years of age before hyperthyroidism (A) and again at 13 years of age after diagnosis of hyperthyroidism (B). At time of diagnosis, the owner reported gradual but progressive weight loss despite an increasing appetite for at least a year. Notice the marked weight loss and muscle wasting due to the untreated, long-standing toxic nodular goiter.

## Diagnostic evaluation of cats with toxic nodular goiter

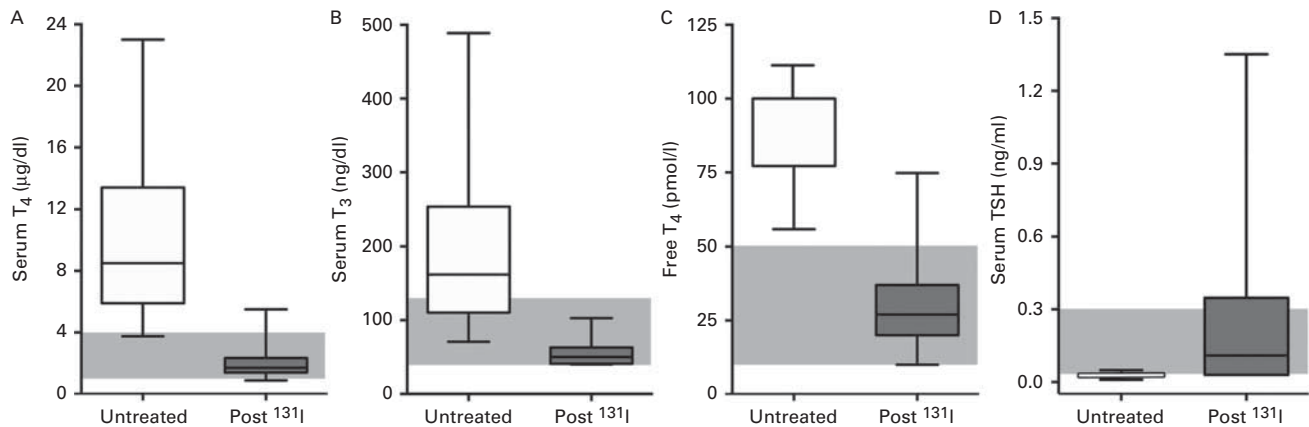
As in human patients, confirming the diagnosis of hyperthyroidism in cats requires use of one or more thyroid function tests to demonstrate increased circulating  $T_4$  and  $T_3$  concentrations, suppressed pituitary TSH secretion, or increased thyroidal radioisotope uptake. Thyroid imaging is also helpful to confirm the diagnosis, to determine the presence of ectopic or substernal extension of the nodular goiter, and to estimate the size of the goiter (Luster *et al.* 2010).

### Thyroidal radioisotope uptake

Hyperthyroid cats usually exhibit increased thyroidal uptake of both radioactive iodine ( $^{123}\text{I}$  or  $^{131}\text{I}$ ) and technetium-99m as pertechnetate ( $^{99\text{m}}\text{TcO}_4^-$ ; Peterson *et al.* 1983, Sjollem *et al.* 1989, Mooney *et al.* 1992, Nap *et al.* 1994). Calculation of an increased value for thyroid-to-salivary ratio also provide a sensitive means of diagnosing hyperthyroidism in cats (Peterson & Broome 2014b), as has been reported in man (Sostre & Parikh 1979, Anjos *et al.* 2006, Kandeel *et al.* 2009).

### Serum thyroid hormone and TSH concentrations

In cats, as in man, the finding of high serum  $T_4$  and  $T_3$  concentrations is the biochemical hallmark of hyperthyroidism and is extremely specific for the diagnosis (Fig. 9A, B and C). In older cats presenting with classical clinical features of hyperthyroidism (e.g. weight loss despite a good appetite and palpable goiter), confirming the diagnosis is straightforward, as over 90% of hyperthyroid cats will have a serum total  $T_4$  concentration that is clearly high (Mooney *et al.* 1992, Peterson *et al.* 2001, Peterson 2013b,c). As measurement of total  $T_4$  is cheap and readily available, this has become the screening test of choice for cats with suspected hyperthyroidism. However, cats with subclinical hyperthyroidism have normal serum  $T_4$  and  $T_3$  values (Wakeling *et al.* 2007, 2011), and up to half of cats with early or mild hyperthyroidism have serum  $T_4$  within the reference interval limits (Peterson 2001, Peterson *et al.* 2001). In these cats, thyroid imaging or  $T_3$  suppression testing can be performed to aid in early diagnosis (Peterson *et al.* 1990, Peterson 2001, Peterson & Broome 2014b). However, serum total  $T_4$  and  $T_3$  concentrations will eventually increase into the thyrotoxic range upon retesting a few weeks to months later as the goiter size continues to increase.



**Figure 9**

Serum concentrations of (A)  $T_4$  ( $\mu\text{g/dl}$ ), (B)  $T_3$  ( $\text{ng/dl}$ ), (C) free  $T_4$  ( $\text{pmol/l}$ ), and (D) TSH ( $\text{ng/ml}$ ) in 500 cats with toxic nodular goiter, before and after treatment with radioiodine. In each graph, the box represents the interquartile range (i.e. 25th–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 5th–95th percentile. The shaded areas indicate the reference interval for each hormone. (A and B) Before treatment, notice that hyperthyroid cats have clearly high levels of both total  $T_4$  and  $T_3$ , but some cats with mild hyperthyroidism may have values that remain within the reference interval. Also note that the reference intervals for total  $T_4$  and  $T_3$  in cats are  $\sim 50\%$  lower than the reference intervals in man (Kaptein *et al.* 1994, Davey 1997); the reason for this difference is that cats lack thyroxine-binding globulin (TBG), a major

binding protein for both  $T_4$  and  $T_3$  in man (Larsson *et al.* 1985, Kaptein *et al.* 1994). Three months after treatment with radioiodine (post  $^{131}\text{I}$ ), the high values have fallen into the reference interval. (C) Like total  $T_4$ , serum free  $T_4$  concentration is high in almost all hyperthyroid cats and normalizes after treatment. As free  $T_4$  methods measure the fraction of  $T_4$  not bound by TBG or other serum proteins, this is considered a more accurate way to assess thyroid function in both cats and man (Davey 1997, Peterson *et al.* 2001, Thienpont *et al.* 2013). (D) Before treatment, serum TSH concentrations in the hyperthyroidism cat are low, at or below the level of quantification. After treatment the suppressed TSH values increase. Some of the  $^{131}\text{I}$ -treated cats develop mild to subclinical iatrogenic hypothyroidism, as evidenced by the high post-treatment TSH concentrations.

In human patients, measurement of the circulating TSH concentration using a very sensitive third-generation assay is generally used as a first-line test for the assessment of thyroid function. The finding of a low to undetectable serum TSH value is consistent with a diagnosis of hyperthyroidism (Dabon-Almirante & Surks 1998, Bahn *et al.* 2011). Although both  $\alpha$ - and  $\beta$ -subunits of feline TSH have been cloned and sequenced (Rayalam *et al.* 2006a,b), a species-specific feline assay based on recognition of the  $\beta$ -subunit or heterodimer is not yet available. Most human TSH assays will not detect feline TSH, but canine TSH assays are commercially available and have been validated to measure feline TSH (Ferguson *et al.* 2007, Wakeling *et al.* 2007, 2011). That a canine assay might detect feline TSH is perhaps not surprising, as feline TSH has a higher homology with canine TSH (96%  $\alpha$ -subunit and 94%  $\beta$ -subunit) than with human TSH (68%  $\alpha$ -subunit and 88%  $\beta$ -subunit) (Rayalam *et al.* 2006b).

Untreated hyperthyroid cats have serum TSH concentrations at or below the detection limit, as might be expected (Fig. 9D). Unfortunately, the current commercial canine TSH assay (a first-generation assay) does not have the necessary test sensitivity to clearly distinguish normal feline TSH concentrations from low or undetectable TSH

concentrations. In support of that, about half of older euthyroid cats we have evaluated have serum TSH values that were at or below the level of quantification. Clearly, a better TSH assay is needed to help in the diagnosis of cats with mild hyperthyroidism, specifically one that has adequate sensitivity and specificity for feline TSH to reliably distinguish a normal value in a euthyroid cat from a low value in a cat with toxic nodular goiter.

### Thyroid imaging

As in human patients, it is difficult to estimate thyroid size or morphology in cats by neck palpation alone. Several imaging methods are available for thyroid imaging, including scintigraphy (with radioiodine or technetium; Daniel & Neelis 2014, Peterson & Broome 2014b), ultrasonography (Wisner 1994, Barberet *et al.* 2010), computed tomography scans (Drost *et al.* 2004, 2006), or magnetic resonance imaging (Hofmeister *et al.* 2001, Barthez *et al.* 2006).

**Thyroid scintigraphy** In cats, scintigraphy provides valuable information regarding both thyroid anatomy and physiology and plays an integral role in the diagnosis,

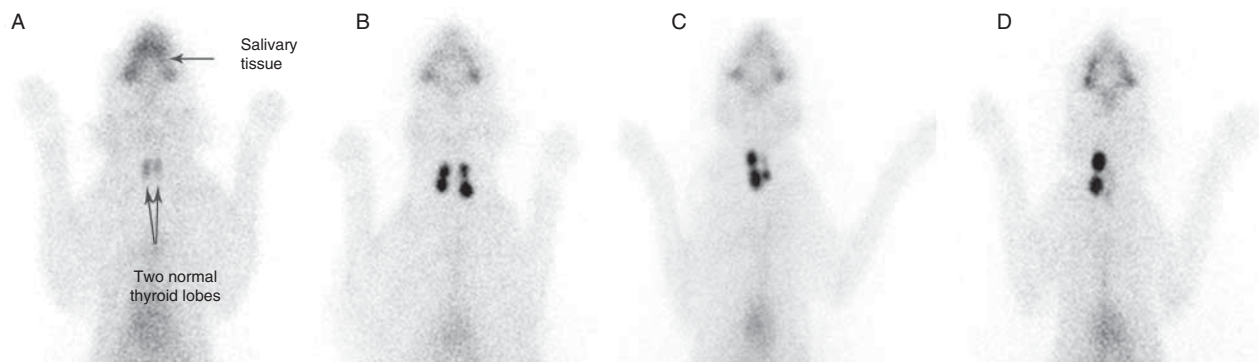
staging, and management of feline toxic nodular goiter. For hyperthyroid cats, scintigraphy is generally considered to be the thyroid imaging technique of choice for detecting and delineating all hyperfunctioning, adenomatous thyroid tissue. Advantages of nuclear scintigraphy include its ability to differentiate bilateral vs unilateral thyroid disease, assess thyroid size and activity, and identify ectopic or metastatic thyroid tissue (Daniel & Neelis 2014, Peterson & Broome 2014b).

In both humans and cats, the radionuclides most commonly used for thyroid scintigraphy are isotopes of radioactive iodine ( $^{123}\text{I}$  or  $^{131}\text{I}$ ) and sodium pertechnetate ( $^{99\text{m}}\text{TcO}_4^-$ ) (Peterson & Becker 1984, Daniel & Brawnier 2006, Wahl 2013, Peterson & Broome 2014b). Radioactive iodine, such as stable iodine, is trapped and concentrated within thyroid follicular cells by the sodium/iodine symporter (i.e. the iodine pump; Portulano *et al.* 2014). Once within the cell, iodine is oxidized to iodide as it passes through the thyroid follicular cell to the lumen of the thyroid follicle. Iodide is subsequently incorporated into tyrosine groups of thyroglobulin via organification; coupling of these iodotyrosyl groups forms  $\text{T}_4$  and  $\text{T}_3$ , which are stored within the follicular colloid until secreted (Kopp 2013). Pertechnetate, such as iodine, is trapped and concentrated within thyroid follicular cells. Uptake of pertechnetate, however, reflects only the trapping mechanism of the thyroid gland; unlike stable and radioactive iodine, pertechnetate is neither organically bound to thyroglobulin nor stored in the thyroid gland.

Because of these differences, the thyroid gland will initially take up pertechnetate just like radioiodine, but the peak uptake occurs sooner with pertechnetate (20 min vs 8 h), allowing an earlier imaging time after injection of radionuclide (Peterson & Becker 1984, Daniel & Brawnier 2006, Wahl 2013). This feature has made  $^{99\text{m}}\text{TcO}_4^-$  the reference standard radionuclide for thyroid scintigraphy in veterinary medicine (Daniel & Brawnier 2006, Daniel & Neelis 2014, Peterson & Broome 2014b).

In normal cats, the thyroid gland appears on thyroid scans as two well-defined, focal (ovoid) areas of radionuclide accumulation in the cranial to middle cervical region. The two separate thyroid lobes are symmetrical in size and shape and are located side-by-side (Fig. 10A; Daniel & Brawnier 2006, Daniel & Neelis 2014, Peterson & Broome 2014b). As noted earlier, no connecting isthmus is found in the feline thyroid gland (Dyce *et al.* 1987, Waters 1993). The normal thyroid and salivary glands take up a similar amount of pertechnetate, resulting in a 1:1 brightness ratio. In addition to visual inspection, the percentage thyroidal uptake of the radioactive tracer and/or the thyroid:salivary ratio can be calculated; both provide an extremely sensitive means of diagnosing hyperthyroidism (Daniel & Neelis 2014, Peterson & Broome 2014b).

As in human patients with toxic nodular goiter, the scintigraphic image in cats generally shows a heterogeneous pattern of increased radionuclide uptake, most commonly into both thyroid lobes (Peterson & Broome



**Figure 10**

Thyroid scintigraphy in a normal cat (A) and three cats with toxic nodular goiter (B, C and D), performed 1 h after intravenous administration of 110 MBq of sodium pertechnetate ( $^{99\text{m}}\text{TcO}_4^-$ ). (A) Image of the neck region of a cat with normal thyroid function. In normal cats, the thyroid gland appears on thyroid scans as two well-defined, focal (ovoid) areas of radionuclide accumulation in the cranial to middle cervical region. The two thyroid lobes are symmetric in size and shape and are located side-by-side; no isthmus is seen. Radioactivity in the normal thyroid closely approximates activity in the salivary glands, with an expected uptake ratio of 1:1.

(B, C and D) Image of the neck region of three cats with toxic nodular goiter. In cats B and C, both thyroid lobes contain adenomatous nodules with a heterogeneous pattern of  $^{99\text{m}}\text{TcO}_4^-$  uptake. In cat D, the left thyroid lobe contains two large nodules, whereas the radionuclide uptake by the normal right thyroid lobe is decreased and cannot easily be visualized. For all three hyperthyroid cats, the uptake of the radionuclide by the hyperactive nodular goiter is higher than that by the salivary tissue. Both the calculated percent uptake of  $^{99\text{m}}\text{TcO}_4^-$  and the thyroid:salivary ratio were high, diagnostic for hyperthyroidism in all three cats.

2014b; Fig. 10B, C and D). In cats with advanced nodular goiter and extensive autonomy, diffuse enlargement is seen, making it difficult to identify the adenomatous nodules on scintiscan. Similar findings are reported in human patients with advanced toxic nodular goiter (Meller *et al.* 2000, Meier & Kaplan 2001, Sarkar 2006, Ianni *et al.* 2013).

### Treatment options for cats with toxic nodular goiter

Treatment of toxic nodular goiter in cats is similar to that used in human patients with hyperthyroidism (Freitas 2000, Rios *et al.* 2005, Barbaro *et al.* 2007, Porterfield *et al.* 2008, Szumowski *et al.* 2012, Paschke 2013), although it is easier for humans to take daily antithyroid tablets than it is for most owners to give daily medications to their cat. Broadly speaking, there are three options: medical management with methimazole or carbimazole, surgical thyroidectomy, or treatment with radioactive iodine. Less commonly used therapies include percutaneous ethanol or thermal ablation of the cat's thyroid nodules (Goldstein *et al.* 2001, Wells *et al.* 2001, Mallery *et al.* 2003) or nutritional management with the chronic feeding of an iodine-deficient prescription diet (van der Kooij *et al.* 2013, Fritsch *et al.* 2014). Each of these treatments has advantages and disadvantages (Mooney & Peterson 2012, Daminet *et al.* 2014), which in many ways resemble those influencing treatment decisions in human patients with toxic nodular goiter.

As in the human disease, cats with toxic nodular goiter do not ever undergo spontaneous remission. Therefore, definitive therapy with radioiodine or thyroidectomy is usually recommended, especially if the cat is fairly young and healthy. However, in geriatric cats or in cats with concurrent nonthyroidal illness (chronic kidney disease is very common in older cats; Syme 2007), long-term antithyroid drug (methimazole) administration is frequently employed (Peterson *et al.* 1988, Mooney & Peterson 2012, Peterson 2013a, Daminet *et al.* 2014). In addition, pretreatment with methimazole to restore euthyroidism prior surgery is a common practice for cats (Peterson *et al.* 1988, Mooney & Peterson 2012). Hyperthyroid cats at increased risk for complications, including those with cardiovascular disease or severe hyperthyroidism, are sometimes treated with methimazole or  $\beta$ -adrenergic antagonists before definitive treatment with radioiodine. Such recommendations are similar to management guidelines established for human patients with toxic nodular goiter (Bahn *et al.* 2011).

Surgical thyroidectomy is associated with a high risk of recurrence if only a subtotal thyroidectomy is performed, because the disease is generally multinodular and involves both thyroid lobes (Welches *et al.* 1989, Swalec & Birchard 1990). In addition, cats with large goiters may have thyroid tissue that descends through the thoracic inlet into the chest; in these cats with substernal disease, surgical removal may be difficult. Finally, about 4% of hyperthyroid cats have adenomatous tissue in ectopic sites (lingual or substernal sites are most common), which would likely be missed at surgery (Peterson & Broome 2014b). Because of the short-half life of  $T_4$  and  $T_3$  in cats (Kaptein *et al.* 1994), euthyroidism after successful thyroidectomy can usually be achieved within 24–48 h after surgery. As in human patients, iatrogenic hypothyroidism and hypoparathyroidism are potential complications of total thyroidectomy in cats (Welches *et al.* 1989, Birchard 2006, Naan *et al.* 2006, Mooney & Peterson 2012).

Most authorities agree that radioiodine is the treatment of choice for most cats with toxic nodular goiter, as is commonly recommended in human patients. However, the relatively high cost and the long isolation period for cats after treatment (hospitalization times range from 3 days to 4 weeks dependent on the local radiation safety rules) are major disadvantages. The success rate of  $^{131}\text{I}$  therapy in cats is very high, over 95% in most studies (Peterson & Becker 1995, Peterson & Broome 2014c). Again, because of the short half-life of  $T_4$  and  $T_3$  in cats (Kaptein *et al.* 1994), euthyroidism is generally restored by 1–3 months after treatment. The prevalence of hypothyroidism in these cats ranges from 10% up to 75%, depending on the dose administered (Williams *et al.* 2010, Peterson 2014).

### Conclusions and future perspectives

Naturally occurring hyperthyroidism is a very common endocrinopathy in the cat, with close parallels to toxic nodular goiter in humans. Diagnosis and treatment of this condition are relatively straightforward and can be similarly successful in veterinary practice. What is not known is why the condition develops, or why its prevalence has continued to increase over the last 35 years to reach the near epidemic proportions seen today. Various nutritional and environmental risk factors have been suggested to contribute to the disease pathogenesis, and it may be that the cat is acting as a 'sentinel', alerting us to the potential danger to humans from exposure to environmental pollutants. Because of its impact on feline

health and similarity with human disease, further study into the nutritional, cellular, and molecular mechanisms of feline toxic nodular goiter is important to our understanding of this disease and other hyperfunctioning endocrine diseases in both animals and man.

#### Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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