Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2018; 6(6): 418-423

Received: 11-09-2018
Accepted: 12-10-2018

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Feline hyperthyroidism: An overview

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Abstract
The overall prevalence varies geographically from 2.4% to 11.4%, with more specifically a prevalence of 8.7% to 11.4% in older cats. Only about 5% of hyperthyroid cats are younger than ten years at the time of diagnosis [10]. In 99% of cases, the cause is benign nodular adenoma (s). These nodules autonomously secrete the thyroid hormones T_4 (thyroxine) and T_3 (triiodothyronine) in excess, resulting in multisystemic disease [12]. Thyroid hormones normally regulate many of the body's metabolic processes. High thyroid hormone concentrations also interact with and stimulate the central nervous system, which commonly leads to increased activity or restlessness. There are several diagnostic modalities available where scintigraphy stands out as the most important modality for diagnosis of hyperthyroidism. Some specific thyroid function tests like Total T_4 concentration, Free T_4 concentration and T_3 suppression test also help in the diagnosis of hyperthyroidism in cats and routinely used test for this purpose. The numbers of possible management options have expanded in recent years that include oral anti-thyroid medication, Iodine-restricted food, radioiodine, surgical thyroidectomy and transdermal anti-thyroid medication [1].

Keywords: Antithyroid, hyperthyroidism, appetite, scintigraphy

1. Introduction
Hyperthyroidism refers to the overproduction of thyroid hormones from abnormally functioning thyroid tissue and is the most common endocrine disorder in middle to older aged feline patients. It was first described in the late seventies and early eighties [4, 13]. The prevalence of hyperthyroidism in cats has much increased. Awareness of the disease, environmental factors and better veterinary care most likely play an important role in this aspect. The overall prevalence varies geographically from 2.4% to 11.4%, with more specifically a prevalence of 8.7% to 11.4% in older cats. Only about 5% of hyperthyroid cats are younger than ten years at the time of diagnosis [6, 10].

2. Thyroid gland anatomy
The thyroid glands are two small elongated structures, located caudal to the larynx and lateral to the trachea on each side. The size of a single lobe in cats is approximately 2 cm in length and 0.3 cm in width. The size of the gland can vary depending on factors such as the dietary iodine content.
The presence of accessory, also called ectopic thyroid tissue, is not uncommon. This can occur in any location from the larynx along the trachea, at the level of the thoracic inlet or along the thoracic part of the descending aorta until the level of the diaphragm.

2.1 Synthesis and secretion of thyroid hormones
The process starts at the level of the intestinal tract where iodine is trapped and converted to iodide that is transported by the blood. At the level of the thyroid, the iodide ion (I^-) is extracted from the blood stream by the sodium iodide (Na^+I^-) symporters (NIS) of the thyroid follicular cells. The iodide ion is then oxidized to iodine (I_2) by the peroxidase enzyme and tyrosine is incorporated in thyroglobine, a glycoprotein produced by the thyroid follicular cells. The tyrosyl residues will then be attached to iodine to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). These can be coupled with the help of the thyroperoxidase enzyme to form biologically active iodothyronines: tetraiodothyronine or thyroxine (T_4) and triiodothyronine (T_3). These molecules are stored outside the peripheral follicular cells, within the colloid, which forms the center of a thyroid follicle and where a large reserve can be stored. When these molecules return to the follicular cell lumen and fuse with lysosomes, T_4 and T_3 are cleaved from the thyroglobin and can be secreted into the blood stream.

In the peripheral tissues, mainly the liver and kidneys, a large amount of T_4 is deiodinated to T_3, the more potent hormone [3, 5]. Thyrotropin-releasing hormone (TRH), produced by the hypothalamus and thyroid stimulating hormone (TSH) produced by the adenohypophysis and released into the bloodstream in response to TRH, are the two controlling factors of thyroid hormone secretion. They interact together in a negative feedback system controlling serum hormone concentrations (hypothalamus-hypophysis-thyroid-axis). When the thyroid hormone concentration in the blood stream decreases, the hypothalamus is triggered to release TRH into the portal system of the adenohypophysis. TSH will then be secreted and stimulate the thyroid glands to increase the expression of the NIS and increase the production and release of hormones. The reverse is also true, when the thyroid hormone concentration in the blood increases, the synthesis and release will be decreased [3, 5].

3. Functions of thyroid

Thyroid hormones are responsible for the basal metabolic regulation. They work at all levels of the metabolism and are known to work generally catabolic. They cause an increased intestinal absorption of glucose and increased glycolysis and gluconeogenesis; an increase in the protein synthesis and lipid metabolism. At the same time, they will activate lipoprotein lipase and create an increase sensitivity of the adipose tissue to lipolysis, regulated by other hormones. They also increase the conversion of cholesterol into bile acids and other substances. All these processes increase the oxygen consumption and heat production of tissues and as a consequence the body temperature will increase. Other effects that can be observed are an increase in heart rate, contraction force, cardiac output and finally blood flow; and an increase in neural transmission and cerebration. Thyroid hormones are also responsible for the development of the nervous system in young animals and normal growth and development in cooperation with growth hormone.

4. Etiology/risk factors

In 99% of cases, the cause is benign nodular adenoma(s). These nodules autonomously secrete the thyroid hormones T_4 (thyroxine) and T_3 (triiodothyronine) in excess, resulting in multisystemic disease. The excessive secretion has negative feedback to the pituitary, suppressing thyroid-stimulating hormone (TSH) secretion. Normal thyroid tissue atrophies because of lack of TSH from the pituitary gland and ceases secretion of T_4 and T_3. In the other rare 1% of cases, the cause is a mild to moderately malignant thyroid adenocarcinoma [12]
A number of published studies have also identified several common factors, including increased risk with age, decreased risk in Siamese and Himalayan cats and increased risk in cats that consume canned cat food, especially pop-top canned food [11]. It must be noted that all of these above factors are mere epidemiological associations and cannot demonstrate cause and effect.

5. Environmental chemicals

Exposure to environmental chemicals (e.g. pesticides, herbicides) is known to induce thyroid abnormalities in other species [2]. Chemicals applied directly to the cat or the cat's environment have been associated with increased risk of hyperthyroidism in some epidemiological studies [8]. Regular exposure of cats to topical flea control products was also shown to be associated with increased risk of developing the disease.

6. Other goitrogenic compounds

Many other goitrogenic compounds can contribute to the development of adenomatous lesions in exposed cats. These may be of particular importance, because most are metabolised by glucuronidation, a metabolic pathway that is particularly slow in the cat [7]. Most commercial cat foods contain relatively high levels of goitrogenic compounds (e.g. phthalates), and cats can also be exposed to many goitrogens (e.g. resourcenel, polyphenols, polychlorinated biphenols, polybrominated diphenyl ethers and isoflavones) in the environment [9].

7. Pathogenesis

The feline thyroid gland normally contains a subpopulation of follicular cells that have a high growth potential. In the thyroid gland eventually destined to develop adenomatous changes, this subpopulation of thyrocytes starts to replicate in an autonomous fashion. Once these rapidly dividing cells are present in sufficient numbers, they continue to grow in the absence of extrathyroidal stimulation (eg.TSH). Therefore, these thyroid adenomatous/ hyperplastic cells show autonomy of thyroid growth as well as the ability to function and secrete thyroid hormone autonomously. Once overt hyperthyroidism develops, the adenomatous hyperplastic thyroid tissue or nodules found in these cat's function and secrete thyroid hormone in an autonomous fashion. In other words, these are true thyroid neoplasms, which exhibit growth and function similar to other hyper functional endocrine tumors.

8. Clinical signs

Thyroid hormones normally regulate many of the body's metabolic processes. As circulating levels of thyroid hormones rise higher and higher in cats with hyperthyroidism, a progressive increase in their metabolic rate develops: this leads to a multitude of changes throughout the entire body, including loss of weight and muscle wasting. High thyroid hormone concentrations also interact with and stimulate the central nervous system, which commonly leads to increased activity or restlessness.

8.1 Weight loss

Weight loss despite a normal to increased appetite is the classic and most common sign of hyperthyroidism in cats. The weight loss associated is generally progressive and is usually first noticed by the owner as a loss of muscle mass around the cat's back (spine). With time, severe muscle wasting, emaciation and death from starvation can occur if the cat's hyperthyroidism is left untreated.

8.2 Increased appetite

The weight loss characteristic of cats with hyperthyroidism is typically associated with an increase in the appetite. This increase in appetite can be dramatic, with some cats doubling the amount of food eaten and frequently begging for food. Hyperthyroid cats eat more in an attempt to compensate for their higher than normal metabolic rate by increasing the number of calories ingested. Unfortunately, most cats cannot fully compensate and continue to lose weight even if they have a good to increased appetite. A few hyperthyroid cats will even develop a reduced appetite that is improved after treatment of their hyperthyroidism. Most of these cats with a poor appetite have a rare form of hyperthyroidism called "apathetic hyperthyroidism,"

8.3 Hyperactive, increased energy or nervous behavior

Hyperactivity, exhibited particularly as nervousness or restlessness, is relatively common in cats with hyperthyroidism. In extreme hyperthyroidism, muscle tremor or twitching may be apparent and affected cats are often described as having an anxious or frantic facial expression.

Some of these behavior signs especially restlessness or aggression are often more noticeable to the examining veterinarian than to the cat owners themselves. Many hyperthyroid cats have an impaired tolerance for stress and do not wish to be held or restrained. Some will even develop a "panic attack" as a result of an impaired tolerance for examination or restraint during blood sampling. These cats may also develop panting, overt respiratory distress, weakness and even collapse during these episodes.

8.4 Increased thirst and urination

About half of cats with hyperthyroidism will show signs of increased thirst (polydipsia) and urination (polyuria). Veterinarians often refer to polyuria and polydipsia simply as "PU/PD". There are a number of possible reasons for the increase in thirst and urination seen in hyperthyroid cats. The most common explanation for the PU/PD is mild, concurrent kidney disease.

8.5 Vomiting or regurgitation

Gastrointestinal signs including intermittent vomiting or regurgitation are fairly common in cats with hyperthyroidism. Vomiting may result from a direct action of thyroid hormones on an area of the brain called the chemoreceptor trigger zone. In other cats, the vomiting can result from gastric stasis (e.g., delay emptying of the stomach).

Vomiting appears to be more common in cats from multi-cat households and usually occurs shortly after feeding. Therefore, vomiting and regurgitation in most hyperthyroid cats may simply be related to rapid overeating.

8.6 Night yowling & nervous signs

The behavioral sign most obvious to owners is night yowling (a long loud mournful cry). This yowling most often occurs in the middle of the night for no apparent reason and generally causes the owner to awaken. Aimless pacing and easily interrupted sleep patterns may also occur in some hyperthyroid cats.

All of these behavior signs appear to reflect a state of confusion, anxiety, or restless associated with the increased central nervous stimulation caused by the hyperthyroidism.

8.7 Diarrhea

Soft stools and diarrhea can occur in about a third of cats with hyperthyroidism. Other cats develop large voluminous stools with frequent defecation. It is likely that accelerated gastrointestinal transit contributes to the increased frequency of defecation, soft stools and diarrhea. Some of these cats also develop malabsorption, in which they do not normally absorb the food from the intestinal tract.

8.8 Respiratory distress

Respiratory abnormalities, including a rapid respiratory rate, panting, or difficulty in breathing at rest, are also common. Respiratory signs tend to occur most frequently during periods of stress. However, some affected cats will be noticeably intolerant of heat and seek out cooler places to sit and some (especially advanced cases) may pant or breathe more rapidly in warm or hot environments. In the absence of heart failure, weakness of the respiratory muscles due to chronic hyperthyroidism is the most probable reasons for these signs. However, central nervous or psychogenic effects also play a major role in development of these respiratory signs, especially in states of stress.

8.9 Skin, hair coat, and nail changes

Skin and hair coat changes often develop in hyperthyroid cats. The hair coat, especially in long-haired breeds, is often unkempt, dull and may even be matted. Some hyperthyroid cats can groom obsessively resulting in alopecia (baldness) or a miliary dermatitis (crusty rash, often with intense itching). This is sometimes associated with an underlying skin allergy, but the skin problem is magnified by the cat's apparent obsessive and compulsive behavior associated with increased licking and grooming. Excessive nail growth may also occur, especially in cats with chronic and advanced hyperthyroidism. These nails appear thickened and may be more fragile than normal.

8.10 Apathetic hyperthyroidism

A small percentage (less than 5%) of hyperthyroid cats shows atypical signs where hyperexcitability or restlessness is replaced by depression, apathy, or weakness. Although weight loss is present in these cats, it is accompanied by poor appetite, instead of increased appetite. These disparate signs heighten the importance of clinicians having a high index of suspicion for such a common disease.

9. Diagnosis

The diagnostic work-up of hyperthyroidism is often based on a strong clinical suspicion. However, the disease may sometimes be accidentally recognized on annual health screenings. The diagnosis starts with an anamnesis and clinical examination and is completed with a blood test and often the use of medical imaging, where scintigraphy stands out as the most important modality.

9.1 Complete blood count (CBC)

Hyperthyroidism does not usually cause significant changes in the blood cell profile, with the exception of a mild increase in red blood cell numbers. Therefore, the presence of significant alterations in any of these blood parameters may alert us to the existence of other disease conditions.

9.2 Serum biochemistry profile

The major change, found in approximately 75% of hyperthyroid cats, is related to mild increases in the liver related enzymes; alkaline phosphatase (AP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Excess thyroid hormone may have a direct 'toxic' effect on the liver or the increase may be related to increased blood flow through the liver resulting from the hyperthyroid state.

Many hyperthyroid cats have increases in the kidney related parameters, blood urea nitrogen (BUN) and creatinine. Increases in BUN and creatinine may be seen with kidney disease, or with dehydration or decreased blood flow to the kidneys. It can be difficult to determine whether increases in BUN and creatinine are related to primary kidney disease or related to the effects of the thyroid hormones on the kidneys. Similarly, it is impossible to accurately predict if these parameters will increase or decrease with treatment of hyperthyroidism.

9.3 Urinalysis

The majority of cases of hyperthyroidism can be diagnosed with a single blood test that measures the total thyroxine (T_4) concentration. Because hyperthyroidism in cats is due to the excess production of thyroid hormones (primarily T_4), the blood T_4 concentration is usually markedly elevated in cats with the disease.

9.4 Specific thyroid function tests

9.4.1 Total T_4 concentration

Although T_3 is the biologically active form of thyroid hormone, T_4 is the primary hormone secreted from the thyroid gland and found in the circulation and is later metabolized to T_3 in peripheral tissues. Although total T_4 concentrations vary considerably throughout the day in cats with hyperthyroidism, more than 90% of hyperthyroid cats will be confirmed via random serum total T_4 testing In contrast, over 25% of hyperthyroid cats will have a serum total T_3 within the reference interval. Thus, circulating serum total T_4 is superior to serum total T_3 in identifying cats with hyperthyroidism and is the initial screening test of choice.

Radioimmunoassay is the gold standard method for measurement of serum total T_4, but methodologic limitations associated with radioimmunoassay have prompted validation of other assay methods, including a homogeneous enzyme immunoassay and chemiluminescent enzyme immunoassay. The availability of these methods varies with the laboratory used. In addition, a commercial semiquantitative enzyme-linked immunosorbent assay (ELISA) T_4 kit is available for in-house use. The ELISA method has the advantage of providing rapid results to the practitioner and is accurate when compared with the radioimmunoassay method.

Reference value =0.8 to 4.7µg/dl

Interpretation

More than 90% of hyperthyroid cats will be confirmed via random serum total T_4 testing.

9.4.2 Free T_4 concentration

Serum free T_4, the unbound fraction of T_4 hormone, represents less than 1% of total circulating thyroid hormone. Free T_4 is the only T_4 fraction that can diffuse across cell membranes and serves as a "prohormone" for T_3, Serum free T_4 is a more sensitive test for hyperthyroidism than the serum total T_4. More than 95% of hyperthyroid cats with a total T_4 concentration within the reference interval will have an elevated free T_4 concentration.

It is generally accepted that cats with a total T_4 value in the upper third of the reference interval, an elevated free T_4 concentration and compatible clinical signs, are likely hyperthyroid. Because free T_4 is the only fraction able to diffuse across cell membranes, it is also the fraction that causes thyrotoxicosis. The free T_4 level is also affected by nonthyroid factors. Up to 12% of euthyroid cats may have an elevated free T_4 concentration due to nonthyroid illness, making measurement of free T_4 less specific for diagnosis of hyperthyroidism than total T_4. For this reason, free T_4 should not be used as the sole diagnostic test for hyperthyroidism. If total T_4 and free T_4 concentrations are found within the reference interval on several separate occasions, but clinical suspicion of hyperthyroidism remains high, additional testing, with, eg, a T_3 suppression test, thyrotropin-releasing hormone (TRH) stimulation test, TSH response test, or thyroid scintigraphy should be considered.

Reference value = 0.7 to 3.9 µg/dl.

9.4.3. T_3 suppression test

The T_3 suppression test evaluates the integrity of the physiological feedback loop via which thyroid hormone regulates pituitary gland function. In normal cats, thyroid hormone exerts negative feedback on the hypothalamus and anterior pituitary, and leads to decreased secretion of TRH and TSH, respectively, until inhibition is released by a fall in circulating thyroid hormone concentrations. The T_3 suppression test works according to the principle that administration of exogenous T_3 to a cat with normal thyroid function suppresses pituitary TSH secretion and leads to a decrease in endogenous T_4 secretion. Cats with primary hyperthyroidism, however, secrete thyroid hormones independent of pituitary control. In contrast with normal cats, TSH secretion is chronically suppressed during primary hyperthyroidism, and exogenous T_3 administration has little to no effect on endogenous serum T_4 concentrations. The T_3 suppression test is helpful in distinguishing mildly hyperthyroid cats from euthyroid cats; however, it requires multiple days of treatment for suppression to occur and owner compliance is critical.

Reference value=0.7 to 9.4 nmol/L

9.5 Thyroid scintigraphy

If the results of thyroid hormone tests are equivocal but clinical suspicion remains high, thyroid scintigraphy should be considered to confirm hyperthyroidism. In addition to confirming hyperthyroidism, thyroid scintigraphy can also provide information that aids in treatment decisions and is the best way to detect metastasis of malignant thyroid tumors. Multiple radionuclides have been utilized for imaging the thyroid glands. The use of radioactive iodine (^{131}I or ^{123}I) has been described; however, radioactive technetium-99m (pertechnetate; $^{99m}TcO_4$) is the radionuclide most commonly used. $^{99m}TcO_4$ is trapped and concentrated within thyroid follicular cells because the molecular configuration of $^{99m}TcO_4$ mimics the size and charge of iodide. After intravenous injection of $^{99m}TcO_4$, concentration of the radionuclide within the thyroid tissue occurs over 20–120 minutes and all functioning thyroid tissue can be detected using a gamma camera. The normal thyroid glands are elongated ovals of similar size and location bilaterally. Thyroid activity is assessed by comparing the ratio of $^{99m}TcO_4$ uptake by the thyroid gland with uptake by the zygomatic molar salivary gland using a region of interest drawn around the salivary tissue and thyroid tissue. The thyroid to salivary gland uptake ratio is approximately 1:1 in normal cats and more than 1:1 in hyperthyroidism. The increase in thyroid to salivary ratio is directly proportional to thyroid gland function.

10. Treatment

10.1 Initial management

Once a diagnosis of hyperthyroidism has been made, physician have a number of important roles, including explaining the diagnosis and educating a cares about the condition. The number of possible management options has expanded in recent years and includes:

- Oral anti-thyroid medication

- Iodine-restricted food
- Radioiodine
- Surgical thyroidectomy
- Transdermal anti-thyroid medication (not veterinary licensed)

All the treatment options have potential advantages and disadvantages and the most appropriate long-term treatment choice often depends on factors including the individual patient circumstances, home background, presence/severity of concurrent disease and financial limitations.In addition to management of their hyperthyroidism, patients may also require specific treatment for complications associated with this, such as congestive heart failure, urinary tract infections and systemic hypertension.All treatments have the potential to unmask or worsen pre-existing renal disease. This is due to the reduction in renal blood flow and glomerular filtration rate that occurs with successful treatment of hyperthyroidism.

10.2 Oral anti-thyroid medication

The two UK veterinary licensed thioureylenes are carbimazole (Vidalta, MSD) and methimazole (Felimazole, Dechra Veterinary Products; Thiafeline, Animalcare) have a rapid mechanism of action and typically result in euthyroidism within a few weeks of starting treatment.

Carbimazole is rapidly metabolised to the active drug, methimazole, following administration. Methimazole blocks synthesis of both of the thyroid hormones (T_4 and T_3) within the thyroid gland. Continuous treatment is required since this is a reversible therapy – levels of thyroid hormones rapidly return to pre-treatment levels if dosage is stopped. Long-term treatment with thioureylenes is very popular and generally successful and well tolerated.

As with all drugs, the thioureylenes can cause side effects in some cats, although these are not common. Side effects usually occur within the first three months of treatment. Mild, typically transient side effects are seen in up to 20 per cent of cats and include reduced appetite, nausea and vomiting. Severe side effects are seen in fewer than five per cent of treated cats and include persistent gastrointestinal signs, pruritic dermatitis affecting the head and neck, hepatopathies and haematological complications, such as thrombocytopaenia and leucopaenia.

10.3 Iodine-restricted food

A restricted-iodine diet (Hill's Prescription diet y/d Feline; Hill's Pet Nutrition) containing 0.2 ppm (mg/kg) iodine on a dry matter basis is currently available for the management of Feline hyperthyroidism.

10.4 Radioiodine

Treatment with radioactive I^{131} (radioiodine), a form of radiotherapy, results in irradiation and destruction of functioning thyroid cells. It is often regarded as the "gold standard" treatment for hyperthyroidism as it is so safe and effective.

The treatment is given either by oral capsule or by injection and naturally targets the thyroid tissue. The radioactivity is able to destroy the abnormal thyroid tissue, shrinking the goitre and reducing the amount of thyroid hormones produced.

The dose of radioactivity required is very low and is therefore not damaging to other tissues of the body, such as the parathyroid glands and other structures that could be damaged by surgery. Hyperthyroid cats receiving anti-thyroid treatments, such as methimazole or an iodine-restricted food, usually need to stop this treatment one week to four weeks before the radioiodine is given.

10.5 Surgical thyroidectomy

Surgical thyroidectomy is a potentially curative treatment that has disadvantages of requiring general anaesthesia (which may be contraindicated in some patients) and is suitable only for those cases with easily accessible hyper-functional thyroid tissue.

In routine cases, side effects of thyroidectomy, such as damage to the parathyroid glands resulting in hypocalcaemia, are possible.

10.6 Transdermal anti-thyroid medication

Transdermal preparations are designed to deliver therapeutic drug concentrations into the systemic circulation following application to the skin. Several publications have reported success in management of hyperthyroidism using transdermal methimazole [1]

Fewer gastrointestinal side effects are reported when using the transdermal route. Cats treated by this route generally need a similar or slightly higher dose than that required with oral dosing. It may take longer to achieve euthyrodism compared to oral anti-thyroid medication, although most treated cats are euthyroid by about four weeks.

Carers should be advised to wear gloves or a finger cot when handling the medication. The site of previous administration should be gently cleaned to remove any residual product before applying another dose.

If using the inner pinna, alternate which ear is used for each dose of medication. The medication can be applied to the gloved finger or directly to the inner pinna before gently rubbing in/spreading over this area. Carers should wash their hands after applying the medication.

11. Conclusion

Hyperthyroidism is the most common endocrine disorder in middle to older aged feline patients. The overall prevalence varies geographically from 2.4% to 11.4%, with more specifically a prevalence of 8.7 to 11.4% in older cats. In 99% of cases, the cause of hyperthyrodism is benign nodular adenoma(s). These nodules autonomously secrete the thyroid hormones (i.e T_4 and T_3) in excess, resulting in multi systemic disease. Weight loss despite a normal to increased appetite is the classic and most common sign of hyperthyroidism in cats.

There are several diagnostic modalities are available where scintigraphy stands out as the most important modality for diagnosis of hyperthyroidism. Some specific thyroid function tests like Total T_4 concentration, Free T_4 concentration and T_3 suppression test are also helps in the diagnosis of hyperthyroidism in cats and routinely used test for this purpose. The number of possible management options has expanded in recent years that include Oral anti-thyroid medication, Iodine-restricted food, Radioiodine, Surgical thyroidectomy and Transdermal anti-thyroid medication.

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