Paparella: Volume III: Head and Neck

Section 2: Disorders of the Head and Neck

Part 6: The Thyroid Gland

Chapter 39: Benign Diseases of the Thyroid Gland

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Histology

Microscopically, the thyroid gland is composed of spherical clusters of cells called follicles. The follicles are invested in a network of capillaries and are filled with colloid. Colloid is a proteinaceous substance that constitutes the majority of the thyroid mass and contains stored thyroid hormone. The diameter of the follicles averages 200 microns.

Blood vessels, lymphatics, fibrous tissue, and parafollicular cells surround the follicles. This network composes the interstitium. The parafollicular cells, or C-cells, also are located in the interstitium and secrete the hormone calcitonin. Calcitonin is responsible for lowering the serum calcium levels.

Physiology

The thyroid gland has a primary role that includes the concentration of iodine followed by the synthesis and storage of thyroid hormones and their subsequent release into the circulation.

Iodine intake averages 100 to 150 microg/day, of which approximately 60 to 70 per cent is excreted in the urine, 10 per cent is excreted via the gut, and the remainder is trapped by the thyroid gland. More than 95 per cent of the iodine that is trapped by the thyroid gland is stored there, and the remaining 5 per cent is carried in thyroid hormones in the circulation and nonthyroidal tissues.

Iodide transport into the follicular cell occurs at the basement membrane. The iodide transport mechanism may be blocked by compounds including perchlorate, thiocyanate, and pertechnetate. In addition, the transport mechanism may be saturated by iodine and substances that contain iodine, such as kelp, amiodarone, and iodinated contrast media. Following trapping by the thyroid cell, iodide is oxidized to iodine in the presence of peroxidase in the cell membrane.

Iodine is attached to the amino acid tyrosine to form monoiodinated tyrosine (MIT) and diiodinated tyrosine (DIT). Two molecules, either MIT or DIT, couple together as two DIT molecules to form thyroxine (T4) or one MIT and one DIT to form triiodothyronine (T3), as well as other metabolically inactive molecules. All of these tyrosine-containing compounds, including T3, T4, reverse T3, MIT, and DIT, are intermittently bound to a large, complex intrathyroidal protein called thyroglobulin and are stored in the center of thyroid follicles as colloid.

Normal thyroid function is dependent on hypothalamic stimulation of the anterior pituitary gland via thyrotropin-releasing hormone (TRH). Thyrotropin (thyroid-stimulating hormone; TSH) is then released from the anterior pituitary gland and, in turn, stimulates the thyroid gland directly to promote thyroid hormone synthesis as well as release.

TRH is found in the hypothalamus. The highest concentration occurs in the median eminence and arcuate nuclei, with somewhat lesser amounts being found in the peri- and paraventricular nuclei. TRH traverses the hypothalamoportal system to stimulate the production of cyclic adenosine monophosphate (cAMP) in the anterior pituitary gland. Following the production of cAMP, TSH and prolactin are released. The release from the pituitary gland of TSH normally is inhibited by elevated thyroid hormone levels. The hypothalamus does not appear to be affected by elevations in thyroid hormone levels or by the other entities that may also inhibit TSH release from the anterior pituitary gland, including somatostatin, dopamine, and glucocorticoids.

TSH is a polypeptide with two polypeptide chains known as the alpha- and beta-subunits. All hypophyseal glycoproteins share the alpha-subunit's structure and composition; hence, it is the individuality of the beta-subunit that provides the specific activities of TSH. TSH has a short biologic half-life in the circulation of approximately 60 minutes. TSH stimulates iodine uptake by the thyroid gland, as well as the synthesis and secretion of thyroid hormone. It appears that the action of TRH on the pituitary gland is primarily to increase the release of TSH. The thyroid hormones subsequently produced signal the anterior pituitary gland to produce and release less TSH. This overrides the positive influence produced by TRH. This is diagrammatically represented.

The apical surface of the thyroidal epithelial cells may be though of as microvilli, which ultimately extend into the follicular lumen. Colloid droplets are consumed by the microvilli via endocytosis, in which fusion occurs with molecules known as dense bodies. The dense bodies are identical to cellular lysosomes and release proteolytic enzymes that promote thyroid hormone release from the thyroglobulin. If nonhormonal iodinated tyrosines are released (ie, MIT or DIT), the enzyme tyrosine dehalogenase allows the iodine to be released for intrathyroidal recycling. The schematic representation of thyroidal iodine metabolism and hormonogenesis is demonstrated.

Once released from thyroglobulin, the thyroid hormones enter the circulation in which they are largely bound to the protein molecules T_4-binding globulin (80 to 90 per cent), T_4-binding prealbumin (5 to 15 per cent), and albumin (5 per cent). Only a very small percentage (0.05 per cent) of T_4 is not bound to these aforementioned binding proteins, and this is the fraction of hormone responsible for the metabolic actions. T_3 is also highly bound, with only approximately 0.5 per cent in the free form. T_3 is the most metabolically active form of thyroid hormone and demonstrates a greater affinity for intracellular receptors (nuclear and mitochondrial) in the peripheral tissues (to the thyroid gland) than does T_4.

Approximately 20 to 30 per cent of circulating T_3 is released directly from the thyroid gland, with the remainder being produced in the peripheral tissues via monodeiodination of T_4. As a consequence of higher noncellular protein binding, T_4 has a longer half-life in the circulation of 7 to 10 days, when compared with T_3, which has a rather short half-life of approximately 24 hours.

Once thyroid hormones have been released into the systemic circulation, they move intracellularly. Both anabolic and catabolic responses are noted following thyroid hormone stimulation. Characteristic end-organ responses include the induction of protein synthesis at both translational and transcriptional levels, as well as enzyme induction and increased sensitivity of cellular responses to other compounds (ie, catecholamines).

Benign Diseases of the Thyroid Gland

Benign diseases of the thyroid gland are quite common. Females are afflicted about five times more frequently than are males. About 1 per cent of females will manifest hypo- or hyperthyroidism, whereas another 3 to 4 per cent may have detectable nodules on physical examination.

Hyperthyroidism

The differential diagnosis of hyperthyroidism can be divided into six categories. Thyrotoxicosis caused by excessive production of thyroid hormone by the thyroid gland may be due to diffuse toxic goiter, uninodular goiter, multinodular goiters, or rarely to excessive TSH production. Thyrotoxicosis may also occur as a result of the release of stored thyroid hormone from the thyroid gland secondary to inflammation of that organ or secondary to the ingestion of thyroid hormone intentionally (eg, thyroid hormone preparations) or unintentionally (eg, foods that accidentally include thyroid tissue such as contaminated ground meat or sausage).

The clinical features of hyperthyroidism with their relative frequency are depicted in Table 1. Not all individuals with hyperthyroidism present with all symptoms. Some may have only a monosymptomatic presentation otherwise known as masked hyperthyroidism. In addition, the serendipitous discovery of an abnormal laboratory value in a grossly asymptomatic patient (biochemical thyrotoxicosis) may occur.

Patients who are known to have psychiatric disorders or chemical dependencies may present in fashions clinically commensurate with hyperthyroidism. As a result, it should be noted that not all those who present with clinical evidence of hypermetabolic states are truly hyperthyroid.

In essence, then, the diagnosis of thyrotoxicosis revolves around both a clinical and a biochemical complex.

Graves' Disease

Graves' disease most commonly presents in the third or fourth decade of life, is rare in the prepubescent pediatric population (less than 10 years of age), and appears to be increasing in frequency in older age groups. This disease has a marked predilection for females in the ratio of approximately 7:1 compared with males. It is an autoimmune disease caused by the production of any of a variety of abnormal immunoglobulins that fix on the TSH receptor of the thyroid epithelial cells, thus stimulating autonomous hypertrophy and function. In addition to a toxic diffuse goiter, an autoimmune infiltrative ophthalmopathy or thyroid dermopathy, or both, may be present. These latter findings occur approximately 55

per cent and 5 per cent of the time, respectively, Graves' ophthalmopathy is an autoimmune disease that may include both a spastic and a mechanical component. The stare, eyelid lag, and eyelid retraction that occur with thyrotoxicosis constitute the spastic component. The mechanical component of the ophthalmopathy includes chemosis, conjunctival irritation, periorbital edema, corneal ulceration, optic neuritis, atrophy, and ophthalmoplegia and may be found in non-thyrotoxic autoimmune states such as Hashimoto's thyroiditis as well as in Graves' disease. The physiologic consequences of the thyroid hormone's action in hyperthyroidism is depicted in Table 2.

Table 1. Incidence of Symptoms and Signs Observed in 247 Patients with Thyrotoxicosis

Symptom	**%**	**Symptom**	**%**
Nervousness	99	Increased appetite	65
Increased sweating	91	Eye complaints	54
Hypersensitivity to heat	89	Swelling of legs	35
Palpitation	89	Hyperdefecation	33
Fatigue	88	(without diarrhea)	
Weight loss	85	Diarrhea	23
Tachycardia	82	Anorexia	9
Dyspnea	75	Constipation	4
Weakness	70	Weight gain	2
Sign	**%**	**Sign**	**%**
Tachycardia	100	Eye signs	71
Goiter	100	Atrial fibrillation	10
Skin changes	97	Splenomegaly	10
Tremor	97	Gynecomastia	10
Bruit over thyroid	77	Liver palms	8.

Table 2. Basic Physiologic Effects of Thyroid Hormone and Their Relationship with Syndromes of Thyroid Dysfunction

System
Thyroid Hormone Effects
Usual Symptoms
Hyperthyroidism
Hypothyroidism

Metabolic
Increased calorigenesis and O_2 consumption
Heat intolerance
Cold intolerance
Increased heat dissipation
Flushed skin
Dry and pale skin
Increased protein catabolism
Increased perspiration
Decreased perspiration

Increased glucose absorption and production (gluconeogenesis)
Increased appetite and food ingestion
Decreased appetite and food ingestion
Increased glucose use
Muscle wasting and weakness
Weight loss
Generalized weakness
Weight gain

Cardiovascular
Increased adrenergic activity and sensitivity
Palpitations
Increased heart rate
Fast heart rate (tachycardia)
Slow heart rate (bradycardia)
Increased myocardial contractility
Increased blood pressure, mainly systolic
Low blood pressure
Increased cardiac output
Bouncy, hyperdynamic arterial pulses
Shortness of breath
Heart failure
Heart enlargement

Central nervous
Increased adrenergic activity and sensitivity
Restlessness, hypermotility
Apathy
Nervousness
Mental sluggishness
Emotional lability
Depressed reflexes
Fatigue
Mental retardation
Exaggerated reflexes
Depressed reflexes

Gastrointestinal (GI)
Increased motility
Hyperdefecation
Constipation.

The thyroidal iodide clearance rate invariably will be increased and usually will be reflected in an increased radioactive iodine uptake. In addition, the thyrotoxic gland will secrete increased amounts of thyroid hormone, usually elevating the serum concentrations of both T_3 and T_4. In some cases, the T_3 value will be elevated and the T_4 value will not, resulting in so-called T_3 toxicosis (about 5 per cent of cases). Generally the diagnosis may be established by elevated levels of serum T_4, although it may be necessary to supplement the

test with a free T_4 or free T_4 index using a T_3 resin uptake to exclude excess T_4-binding globulin producing elevated total T_4 levels.

The T_3 suppression radioiodine uptake test is useful to confirm the presence of autonomy of the thyroid gland. The TRH stimulation test suggests the presence of thyrotoxicosis when a blunted TSH response is present.

Treatment

There are three approaches to therapy of thyrotoxic Graves' disease. Pharmacologic (so-called nonablative therapy includes use of the thionamides, beta-adrenergic blockade, and nonradioactive iodine). Surgical intervention or radioactive iodine, or both, (so-called ablative therapies) may also be used.

Drug Therapy of Thyrotoxicosis

Thionamides. The antithyroid effects of thionamides were described in 1943. The mechanism of action of this category of agents revolves around their inhibition of coupling of iodotyrosines to form T_3 and T_4 and a less pronounced effect on iodide oxidation. Unique to propylthiouracil (PTU) but not to carbimazole and methimazole is its ability to inhibit the peripheral, extrathyroidal conversion of T_4 to T_3 and its possible immunosuppressive activity, which may contribute to the induction of remission in patients with Graves' disease.

The two most commonly used antithyroid preparations in the USA are PTU and methimazole. These medications cannot be expected fully to result in biochemical euthyroidism until after 6 to 8 weeks of therapy. This reflects the fact that patients with thyrotoxicosis usually have increased stores of thyroid hormone both in the follicles and in the circulation, which must be exhausted.

Although single daily dosing may result in clinical and biochemical euthyroidism in some patients, most physicians use a three times daily dosage schedule. Gwinup showed that oral doses of 150 mg of PTU every 8 hours produced euthyroidism in 25 of 26 patients. The results were much more discouraging with single daily doses: only 6 of 23 patients receiving 450 mg of PTU in a single dose became euthyroid after 8 weeks of therapy. The generally accepted starting dose of PTU is between 300 and 600 mg daily with a maximum daily dose of around 1200 mg. Methimazole doses are about one-tenth those of PTU.

The success of antithyroid dosage regimens may be evaluated with the use of the perchlorate discharge test. The percentage of discharge may be used to determine whether an individual may be controlled initially with single daily dosing. Additionally, patients currently controlled with multidosing regimens may be converted to a single daily dosing if a greater than 70 per cent discharge of iodine occurs. This reflects the fact that thionamides induce an organification defect (Table 3).

Table 3. use of the Perchlorate Discharge Test to Determine Antithyroid Drug Dose Schedules in Thyrotoxic States

Patient already controlled on medications every 8 hours.
Switch usual total daily dose to a single dose for 7 days.
12 hours after the last dose, perform a perchlorate discharge test.
Patient to be started on once a day regime.
Give anticipated required total dose daily for 7 days.
12 hours after the last dose, perform a perchlorate discharge test.

Results:	**% Discharge**	**Dosage Schedule**
	≥ 70	Once a day
	18-69	Every 12 hours
	≤ 17	Every 8 hours

Adjust total daily dosage to the schedule.

Complications of treatment vary from minor drug toxicity in 3 to 8 per cent of patients to more severe complications such as erythema multiforme, drug fever, and drug-induced hepatitis in approximately 4 per cent of patients. The most dreaded complication if agranulocytosis, which occurs with a frequency of approximately 0.3 per cent. Children may be more subject to the untoward effects of the thionamides than are adults.

The clinical setting most appropriate for the use of thionamide agents is in patients who have small goiters (less than two times the normal size of the gland), have mild hyperthyroidism, and are in the pediatric and adolescent age groups. For patients who cannot follow safety precautions for I-131 therapy or for pregnant females, thionamide drug therapy also seems the most appropriate choice. Following involution of the gland to normal size and the onset of euthyroidism or after 1 year of continued therapy (whichever occurs first), reevaluation should be undertaken.

Antithyroid drug therapy for the treatment of thyrotoxicosis has demonstrated disappointing results. In the Cooperative Thyrotoxicosis Follow-Up Study, 1238 patients were treated with antithyroid drug therapy for more than 1 year. Of them, 57 per cent were shown to have continued or recurrent thyrotoxicity, 6 per cent were hypothyroid, and 37 per cent were euthyroid at a mean follow-up for all individuals of 8.2 years. More recent reports indicate that even under optimal circumstances, only 49 to 59 per cent of patients treated with antithyroid drugs will be euthyroid in remission at 4 years of follow-up. Hypothyroidism in this same patient population was noted in an additional 16 to 17 per cent.

The 1-hour radioiodine uptake test has been used to predict remission in patients treated with antithyroid medication (Table 4). TSH levels should be undetectable during the testing. If the uptake value is less than 4 per cent, remission is likely, reflecting the fact that initial iodine trapping has decreased to normal rates presumably because of less immunoglobulin stimulator activity.

Table 4. Use of the 1-hour Radioiodine Uptake Test to Predict Remission in Patients Receiving Antithyroid Drugs

The patient should continue taking thionamide drugs as regularly prescribed.

If the endogenous serum TSH concentration is detectable in a reliable assay, exogenous T_3 (Cytomel) should be given in full replacement doses for 1 week.

A 1-hour radioiodine uptake is performed:

Uptake Value	Remission
< 4%	Likely*
> 10%	Unlikely**
4-10%	Indeterminate

* Especially if goiter has resolved.
** Especially if goiter is unchanged in size.

Sympathetic Blockade. The clinical features of hyperthyroidism that are directly attributed to the sympathetic nervous system may be abolished or diminished with the addition of sympatholytic agents. These features include tachycardia, hyperreflexia, hyperhydrosis, tremor, anxiety, and muscle fatigue. It should be noted that propanolol, a beta-blocker, also inhibits the peripheral conversion of T_4 to T_3. The usual starting dose of this beta-blocker is 40 mg by mouth three to four times daily. Oral doses of up to 320 mg of propranolol daily may be used. Contraindications include a history of asthma and severe congestive heart failure, as this drug may induce bronchospasm and exacerbate heart failure secondary to its inherent negative inotropic properties.

Iodine. Use of nonradioactive iodine in patients with hyperthyroidism is generally limited to preparation of patients for thyroidectomy and to the treatment of thyroid storm. The administration of iodine in thyrotoxicosis produces an inhibition of organic binding and release of thyroid hormone as well as involution of the gland. In both toxic diffuse and toxic multinodular goiter, the vascularity of the gland may be decreased by as much as 50 per cent by using supersaturated potassium iodide solutions. The beneficial effects of iodine in the toxic thyroid gland are transient and generally last only a few weeks. Thereafter, the patients may actually become worse.

Surgical Therapy of Graves' Disease

Although surgical intervention for hyperthyroidism attributed to Graves' disease has decreased in the last 50 years, there are certain indications for surgery that warrants its continued consideration. Individuals who do not desire or who are not candidates for long-term therapy with antithyroid drugs or radioactive iodine are surgical candidates. In addition, patients with concomitant hyperparathyroidism or coexisting nonfunctional nodules with equivocal or positive cytologic results for malignancy may be considered candidates for surgery.

Preparation of the patient must include the administration of pharmacologic agents to produce biochemical euthyroidism. This is generally undertaken with one of the thionamides for 6 to 8 weeks followed by the addition of nonradioactive iodine for a period of 10 to 14 days to decrease the vascularity of the gland.

The operation performed usually is a bilateral subtotal thyroidectomy. Following subtotal thyroidectomy, approximately 7 to 8 gm of nodule-free tissue is generally left behind if a concomitantly occurring cancer (about 4 of 1000 cases) is not present. Both recurrence rates and complication rates are directly related to the amount of tissue left behind.

Surgery alone was used in 5221 patients in the Cooperative Thyrotoxicosis Follow-Up Study. At a mean follow-up of 12.5 years, 14 per cent of the patients demonstrated recurrent hyperthyroidism, 25 per cent were hypothyroid, and 61 per remained euthyroid. The incidence of postsurgical hypothyroidism is greatest within the first 12 months after surgery and is about 50 per cent in some series. Much smaller numbers of individuals later become hypothyroid, about 1 per cent/year thereafter. This delayed hypothyroidism may reflect the natural course of Graves' disease.

In the hands of experienced surgeons, complication rates of both permanent hypoparathyroidism and recurrent laryngeal nerve damage are infrequent (0.5 to 1.0 per cent). It should be noted that there is a tenfold increase in complications when reoperation is performed for thyrotoxicosis.

Radioactive Iodine Treatment of Graves' Disease

Radioactive iodine therapy for various forms of hyperthyroidism has been used for approximately 40 years. Radioactive iodine has largely replaced surgery as the treatment of choice for hyperthyroidism secondary to Graves' disease.

Before choosing to treat individuals with radioactive iodine, it is appropriate that all pregnant women be excluded, since the I-131 would cross the placenta and damage or destroy the fetal thyroid gland. A reliable standardized negative pregnancy test result must be obtained prior to treatment of any female of childbearing age. Additionally, the patient should sign a statement attesting to the date of her last menstrual period and to her opinion that she is not pregnant. Subsequent pregnancy should be avoided by reliable contraception for a minimum of 3 months or until the patient is biochemically euthyroid, whichever occurs last.

Therapy with radioactive iodine may be preceded by symptomatic treatment of hyperthyroidism. Potential radioprotection conferred to the thyroid cell by previous thionamide administration may result in a diminished response to radioiodine, so we prefer not have the patient pretreated with those drugs. If used, thionamides should be discontinued at least 3 to 5 days prior to radioactive iodine administration.

Following a single administration of I-131, generally, 80 to 90 per cent of cases are cured, with 10 to 20 per cent requiring two administrations, and less than 5 per cent requiring more than two administrations. The proper amount of I-131 to be administered depends on a multitude of variables, including the desired end point of therapy, the mass of the thyroid gland, the uptake and half-life of the I-131 in the thyroid gland, and the desired radiation dose

to the gland. In general, higher radiation doses produce more rapid control of hyperthyroidism and a higher incidence of early hypothyroidism. The mass of the thyroid gland is difficult to assess clinically, and both scintigraphic and ultrasound methods may assist in volume-mass measurements. The half-life of radioiodine is variable, with values between 2 and 8 days.

The complications of radioactive iodine are generally considered to be either short- or long-term. Acute side effects of radioactive iodine are unusual. Radiation thyroiditis may occur with doses greater than 18.000 to 20.000 rad, although less than 5 per cent of patients will have capsular swelling and necrosis with a tender thyroid gland indicative of radiation thyroiditis. The symptoms usually are controlled with adrenal corticosteroids.

About 10 to 15 per cent of patients may experience only transient hypothyroidism following I-131 administration. More commonly, hypothyroidism persists more than 2 months and is permanent. Data from several different studies suggest that there is a direct dose-response relationship for I-131 therapy in Graves' disease. Dose of 16.000 rad are associated with the highest rate of both cure of hyperthyroidism and onset of hypothyroidism (Table 5).

Table 5. Examples of the Relationship Between Radiation Dose, Persistent Hyperthyroidism, and Hypothyroidism in I-131 Therapy for Graves' Disease

Number	228	35	229
Approximate Mean Thyroidal Dose (rad)	5.000	10.000	16.000
Approximate % Hyperthyroidism at 1 year	15	6	0
Approximate % Hypothyroidism at 1 year	10	40	90*

* All subjects were treated until hyperthyroidism had resolved. Some subjects (~10%) were apparently not permanently hypothyroid.

Long-term complications of I-131 therapy for Graves' disease have been screened for and addressed in several studies. Thyroid cancer has been found to co-exist with Graves' disease in about 4 of 1000 surgically treated patients, yet it has been described in only 17 patients out of hundreds of thousands of subjects receiving I-131. Doses to the blood and bone marrow are low (Table 6). In spite of the fact that I-131 may induced lymphocyte chromosomal changes, there has not been any evident increase in leukemia in patients treated with I-131 for thyrotoxicosis. The potential for genetic damage to ova of childbearing women has been addressed by Robertson and Gorman. The radiation doses to the ovaries from an average I-131 treatment are similar to those obtained with a radiographic excretory urogram and barium enema or with a hysterosalpingogram. The probability of having a child with a harmful trait resulting from I-131 therapy is less than 0.4 per cent of the spontaneous rate.

Table 6. Radiation Doses to Blood and Marrow from I-131 Therapy of Thyrotoxicosis

Reason for I-131 Therapy: Hyperthyroidism
Mean Radiation Doses (rad) to Red Marrow and to Blood per mCi I-131 Administered Red Marrow 0.59 Blood (0.84)

It appears evident that the I-131 treatment of Graves' disease is safe and effective. When prompt resolution of symptoms is desired, thyroidal doses of approximately 16.000 ± rad appear satisfactory.

Toxic Multinodular Goiter

Toxic multinodular goiter is generally seen in older individuals (more than 50 years of age) who have an antecedent history of nontoxic goiter. They usually present without infiltrative ophthalmopathy or dermopathy. Tachyarrhythmias, such as atrial fibrillation complicated by heart failure, may dominate the clinical presentation, and muscle weakness with wasting is common.

The laboratory diagnosis in these patients may be subtle. Minor elevations of the radioactive iodine uptake may be seen in nontoxic multinodular goiters, and thyrotoxicosis may be present with a normal radioactive iodine uptake. Furthermore, normal T_4 levels may be seen with thyrotoxicosis. Elevated T_3 levels and low TSH levels may be the only biochemical indication of thyrotoxicosis. One also may use the blunted response of TSH to TRH stimulation as an indicator of thyrotoxicosis in the equivocal biochemical setting.

The treatment of toxic multinodular goiter is generally ablative (ie, surgery or radioiodine). Spontaneous remission rarely occurs, and response to I-131 is far less predictable than with Graves' disease. In the individuals who become biochemically and clinically hypothyroid following I-131 therapy, the goiter often will not resolve. It appears that surgery following failed control is advisable in patients with toxic multinodular goiter, especially those with compressive symptoms.

Solitary Toxic Adenoma

The least prevalent form of hyperthyroidism in the USA is toxic solitary adenoma, although as many as 30 per cent of hyperthyroid patients in some locations in Europe may have solitary toxic nodules. It is generally believed that solitary toxic nodules are true benign neoplasms of the thyroid gland. Rarely more than one adenoma of this type may be present simultaneously in the same thyroid gland.

As a rule, toxic adenoma affects younger patients (20 to 40 years of age) than does toxic multinodular goiter. Thyrotoxicosis is generally not manifested clinically until the nodule has exceeded 2.5 to 3.0 cm in diameter. Spontaneous resolution of the hyperthyroidism may occur if central necrosis occurs in the nodule. In this case, the scintigraphic appearance may be one of a non-radionuclide-concentrating "cold" nodule.

The clinical signs of hyperthyroidism may be subtle when compared with those associated with Graves' disease. Cardiovascular symptoms predominate. Infiltrative ophthalmopathy and dermopathy are lacking.

The treatment of toxic solitary adenomas generally is either surgery or radioactive iodine. Pharmacologic restoration to normal metabolic status is necessary prior to surgical intervention.

The amount of I-131 to use is controversial. Doses as low as 10 mCi have been used routinely with a very low incidence of hypothyroidism. However, there are others who recommend much higher doses of I-131 to achieve more rapid ablation. In such cases, rates of hypothyroidism of up to 21 per cent over an 8-year period of follow-up may occur. Even with higher doses, hyperthyroidism may recur up to 11 per cent of the time. Thus, it appears that in those individuals who will tolerate surgical intervention, excision of the adenoma is the treatment of choice. Since cancer in such nodules is rare, a subtotal lobectomy is often all that is required.

Thyroiditis

Several recent reviews of thyroiditis offer excellent perspectives on the subject of thyroiditis. Essentially there are three main categories of spontaneous thyroiditis: acute, subacute, and chronic. Acute radiation thyroiditis has been discussed earlier.

Acute Thyroiditis

Acute infectious thyroiditis is an extremely rare form of thyroiditis. The cause is generally bacteria (68 per cent), with fungal and parasitic involvement being less common. No age preference appears to be evident. Men are affected slightly more often, and 60 per cent of patients have pre-existing thyroid disease.

Symptoms include anterior neck pain, thyroid tenderness, fever, and dysphagia in greater than 90 per cent of patients. Laboratory findings include a leukocytosis in greater than 70 per cent of the presentations, normal thyroid function studies, and positive culture results from appropriate needle aspiration procedures. *Staphylococcus aureus, Streptococcus pyogenes,* and *Streptococcus pneumoniae* represent the most common bacterial agents.

Treatment revolves around appropriate uses of antimicrobial and surgical intervention.

Subacute Granulomatous Thyroiditis

Subacute granulomatous thyroiditis is a spontaneously remitting inflammatory disorder of the thyroid gland. Many synonyms have been used, including de Quervain's disease, giant cell thyroiditis, and struma granulomatosa, to name a few.

This disease entity is common in the northern USA, Canada, the UK, Japan, and Israel. It is generally a disease of the second through fifth decades of life, affecting women more than men in a ratio of at least 3:1. The cause of this subtype of thyroiditis is obscure. Some patients have proven antecedent viral illness (33 per cent). The most common viruses are thought to be influenza, coxsackievirus, adenoviruses, measles, and the Epstein-Barr virus.

As a rule, symptoms include fever, chills, a painful thyroid gland, and constitutional symptoms, including thyrotoxicosis. Up to 16 per cent of patients have a history of pre-existing goiter. The thyroid gland may demonstrate palpable tenderness (77 per cent) and firmness (90 per cent).

The course of the disease is variable but usually lasts 2 to 5 months. Approximately 20 per cent of patients will have recurrences. Hyperthyroidism caused by the release of stored hormone may become manifest initially in approximately 54 per cent of patients, followed by transient hypothyroidism secondary to depletion of stored colloid. The initial laboratory findings invariably include elevation of the erythrocyte sedimentation rate (ESR), depression of the 24-hour thyroidal radioiodine uptake, and elevation of serum thyroglobulin levels. The pattern of thyroid function tests will vary over time. The initial hyperthyroid phase is noted with an elevated T_4 level, a low radioactive iodine uptake, and depressed TSH. This is followed by a fall in the serum T_4 level, with an increasing radioactive iodine uptake and TSH, and finally a return to a biochemically euthyroid status.

The treatment of this disorder revolves around avoidance of overreaction on the part of the physician, patient reassurance, and the implementation of symptomatic care, usually with propranolol and anti-inflammatory agents. Those more severely affected patients may require corticosteroids for several months. Anti-inflammatory therapy should not be stopped until the radioiodine uptake has returned to normal. Surgical excision usually is not indicated. Occasionally the hypothyroidism is permanent, in which case thyroid hormone replacement is required.

Subacute Lymphocytic Thyroiditis

The lymphocytic type of subacute thyroiditis accounts for approximately 30 to 50 per cent of all cases of thyroiditis. It may account for as much as 23 per cent of all cases of hyperthyroidism in North America. Ninety per cent of such cases from outside Japan are from the Great Lakes region in the USA, and fully 10 per cent of all cases of this variety are found in postpartum women (see below). The remainder are thought to be spontaneous.

Clinical manifestations are similar to those of subacute granulomatous thyroiditis, with 33 per cent demonstrating persistent goiter and 10 per cent demonstrating recurrent thyrotoxicosis. The thyroid gland may be painless and nontender in 50 per cent of patients with the subacute lymphocytic variety. Laboratory characteristics include a normal ESR and triphasic thyroid function tests similar to those in subacute granulomatous thyroiditis.

The treatment of this type of subacute thyroiditis includes pharmacologic control of hyperthyroidism. Corticosteroids are reserved for refractory cases.

Postpartum Lymphocytic Thyroiditis

In addition to spontaneously occurring lymphocytic thyroiditis, a postpartum variety has also been identified. It has been reported as a clinically evident complication in about 5.5 to 6.5 per cent of pregnancies. Additionally, recurrences are highly likely after subsequent pregnancies. The presence of serum antimicrosomal antibodies usually is closely correlated with the biochemical expression of hypothyroidism. However, a study of 460 postpartum women in Sweden revealed a 9.6 per cent incidence of elevated microsomal antibodies, but most of these women had no clinical manifestations.

The presence of antimicrosomal antibodies in the first trimester of pregnancy has been associated with the HLA-DR4 antigen, consistent with an autoimmune disease.

There also appears to be a form of subacute thyroiditis other than the lymphocytic subtype associated with pregnancy and the postpartum state. The cause of this phenomenon remains unclear. Associations with viral infections or ill-defined immunologic changes have been proposed.

Chronic Riedel's Thyroiditis

Invasive fibrous thyroiditis was first described by Riedel in 1896. It is an exceedingly rare type of thyroiditis, with the age at presentation noted to be from the second to sixth decade of life. Female cases generally exceeded male cases in a ratio of 3:1. The thyroid gland is usually very firm and nontender. Bilobar involvement is generally noted, with fibrosis extending to the parathyroidal structures in some cases. The laboratory findings include variable ESR values, normal thyroid function tests, and inconsistent low levels of autoantibody elevations.

The clinical association of this form of thyroiditis with extracervical fibrosis has been established and includes sclerosing cholangitis, retroperitoneal fibrosis, and mediastinal fibrosis. The prognosis of this disease entity is directly dependent on the presence and extent of these complicating factors.

This particular category of chronic thyroiditis is rare, and strong consideration should be given to the presence of thyroid carcinoma in this clinical setting. Therefore, an excisional biopsy may be required to establish the diagnosis. Thyroidectomy generally should be avoided because of complications secondary to disruption of normal surgical landmarks and altered tissue planes resulting from the fibrosis. Corticosteroids may be used in an attempt to decrease the size of the goiter and palliate symptoms.

Chronic Lymphocytic Thyroiditis

As early as 1912, a fibrotic, lymphocyte-infiltrated thyroid gland was described by Hashimoto. This disease entity has come to be known as chronic lymphocytic thyroiditis or Hashimoto's thyroiditis and is classically manifested by diffuse enlargement of the thyroid gland in young to middle-aged women, often with hypothyroidism. The prevalence of this type of thyroiditis appears to be increasing and has been reported to be present in as many as 2 per cent of autopsied women.

The association of chronic lymphocytic thyroiditis with autoantibodies has been established and includes reactions with thyroglobulin, thyroid microsomes, and various colloidal proteins. There may also be components of cell-mediated immunity. Strong genetic predispositions have been described with the HLA-B8 and HLA-DR5 antigens. It is clearly an autoimmune thyroid disease.

The presentation of chronic lymphocytic thyroiditis generally occurs in individuals from 30 to 50 years of age, with a prevalence in women 15 to 20 times that found in men. The clinical presentation usually includes an insidious enlargement of the thyroid gland with mild neck pain manifesting in occasional patients. As a rule, no pain is associated and dyspnea or dysphagia are quite rare. In as many as 20 per cent of patients, the signs and symptoms of hypothyroidism may be present at initial examination. Associations have been

reported with vitiligo, pernicious anemia, hypoadrenalism, hypoparathyroidism, diabetes, and hypogonadism.

Palpatory features include a diffusely enlarged thyroid gland that is firm, irregular, and symmetric. If a patient presents with hypothyroidism with a concomitant goiter, chronic lymphocytic thyroiditis should be given strong diagnostic consideration. Overt signs of thyrotoxicosis or infiltrative ophthalmopathy, or both, are uncommon but do occur.

Typically the total T_4 and free T_4 index are normal early in the disease, although exceptions do exist, with both hypo- and hyperthyroidism apparent. The ESR may be elevated but is not consistently so. Radioactive iodine uptake values are variable, tending to be high early in the disease and low later on. Antibodies to thyroglobulin or microsomal antigens are usually present in the serum. Titers of greater than 1:2500 are consistent with chronic lymphocytic thyroiditis.

Treatment of this disorder depends on the clinical presentation of the patient. Thyrotoxic subjects are usually controlled medically or, less commonly, with I-131. Thyroid hormone replacement in nontoxic patients may produce a significant decrease in gland size, especially in younger patients prior to the onset of fibrosis. If the TSH levels are elevated, T_4 replacement is warranted.

Diffuse and Multinodular Nontoxic Goiter

When thyroid enlargement is not associated with an inflammatory process or neoplasm, and clinical and biochemical euthyroidism is present, the patient has a non-toxic goiter. Agreement exists regarding the fact that this disease entity occurs secondary to a compensatory response to decreased efficiency of thyroid hormone production, although controversy exists over the role of TSH. Although rare in the USA, dietary iodine deficiency is a common cause worldwide.

Females appear to be affected preferentially over males in the ratio of about 8:1. The condition more commonly expresses itself during adolescence or pregnancy, and spontaneous regression may occur. The initial diffuse goiter may persist or evolve into multinodular goiters. If this occurs, functional thyroid gland autonomy may occur with a flat or subnormal response to TRH. Further, thyrotoxicosis may occur spontaneously or secondary to iodine exposure (the so-called jodbasedow phenomenon). Therefore, avoiding medications that contain iodine as well as appropriate monitoring of such patients who receive iodinated contrast media is warranted.

The clinical expression generally revolves around pressure sensations in the neck as well as dysphagia, stridor, or occasional choking. If hemorrhage occurs, the gland may enlarge acutely and become painful. Venous engorgement secondary to narrowing of the thoracic inlet may be apparent and may be accentuated with raising the patient's arms (known as Pemberton's sign).

As a rule, the serum T_3 and T_4 levels are normal, with defective iodination suggested by increased T_3:T_4 ratios. Serum thyroglobulin concentrations are increased in many of these patients.

The treatment of nontoxic goiter may be thought of as an attempt to alleviate the stimulus to thyroid hyperplasia. Meticulous withdrawal of goitrogens may suffice. Supplying exogenous thyroid hormone to decrease the TSH stimulation of the thyroid gland may be helpful. Generally, patients with diffuse goiter are relatively young and will accordingly tolerate suppressive therapy without a high degree of untoward effects. Suppressive therapy is initiated in young people with about 75 microg of levothyroxine/100 pounds of body weight. In older people, a more gradual approach is warranted. Low doses of levothyroxine of 25 to 50 microg/day are initiated with gradual incremental increases. Surgical intervention may be necessary secondary to obstructive symptoms.

Hypothyroidism

The prevalence of hypothyroidism is thought to be approximately 1 per cent in females and 0.1 per cent in males. The frequency of the disease increases with aging.

The causes of hypothyroidism are variable (Table 7). The most common cause of hypothyroidism in the USA is autoimmune thyroiditis, of which chronic lymphocytic thyroiditis is most commonly encountered. Additionally, previously hyperthyroid patients treated with radioiodine, surgery, or pharmacologic manipulation are often hypothyroid. Less commonly in the USA, iodine deficiency or environmental goitrogens may cause hypothyroidism. Excessive iodine in the diet (eg, seaweed) or pharmacologic agents (eg, saturated solution of potassium iodide, iodinated glycerol, amiodarone, x-ray contrast media) may precipitate hypothyroidism or hyperthyroidism, especially in patients with a history of antecedent thyroid disease.

Table 7. Causes of Hypothyroidism

- Primary thyroid dysfunction
  - Parenchymal damage
    - Thyroiditis
      - Chronic lymphocytic (Hashimoto's) thyroiditis
      - Subacute thyroiditis
    - Therapeutic ablation
      - After I-131 therapy
      - After surgery
    - Thyroid dysgenesis
      - Aplasia
      - Dysplasia
    - Thyroid infiltration
      - Tumors
    - Abnormal hormonogenesis
      - Iodine deficiency
      - Iodine excess
      - Thyroid-blocking drugs
      - Congenital and acquired defects of hormone synthesis and thyroglobulin metabolism defects
- Pituitary hypothyroidism (TSH deficiency)
- Hypothalamic hypothyroidism (TRH deficiency)
- Reduced peripheral response to thyroid hormone.

Agenesis or maldevelopment of the thyroid gland congenital defects in hormone secretion, and end-organ resistance to thyroid hormone are less common causes of hypothyroidism. Hypothyroidism in adults often develops secondary to earlier neck irradiation for lymphoma. Antithyroid medications such as PTU and methimazole may produce hypothyroidism in previously hyperthyroid patients, as may other pharmacologic agents, such as lithium carbonate.

Infiltrating diseases of the thyroid gland that uncommonly cause hypothyroidism include granulomatous disease, amyloidosis, and invasive fibrous thyroiditis. Replacement of normally functioning tissue by neoplastic processes (ie, metastatic or primary) rarely results in hypothyroidism in the patient who has not undergone surgery or irradiation. Hypothalamic (tertiary) and pituitary (secondary) diseases may cause thyroid failure. These causes collectively account for less than 1 per cent of all cases of hypothyroidism.

Other systemic diseases may be associated with the development of hypothyroidism. Pseudohypoparathyroidism, scleroderma, hemochromatosis, celiac disease, the polyglandular failure syndrome, and both Down's and Klinefelter's syndromes have been demonstrated to have an association with hypothyroidism.

Hypothyroidism usually is lifelong, and the patient is obligated to continual follow-up with appropriate treatment. Drug-induced hypothyroidism may be reversible, as may hypothyroidism secondary to subacute thyroiditis. As a rule following nodulectomy, subtotal thyroidectomy, or discontinuation of thyroid replacement therapy, hypothyroidism is temporary until the gland or remnants become functional.

The clinical presentation of hypothyroidism typically includes fatigue, xerosis, muscle cramps, depression, difficulty concentrating, constipation, fluid retention, cold intolerance, and delayed reflexes. With the advent of widespread thyroid function testing, other causes may be discovered only on a biochemical basis, with few if any of the clinical signs and symptoms appearing.

Confirmation of the diagnosis of hypothyroidism depends on biochemical documentation of the process, especially in newborns and the elderly, in whom the clinical presentation may be subtle. The presence of an elevated serum TSH concentration is the most specific indicator of primary hypothyroidism, but it should be combined with serum T_4 levels to help exclude secondary or tertiary hypothyroidism with normal or low TSH levels. TSH values may vary, and if a patient has clinical suggestions of hypothyroidism and borderline TSH levels, a TRH stimulation test should be performed (Table 8).

One approach to the treatment of primary hypothyroidism involves the use of oral T_4 and routine serial TSH determinations. The TSH should be rechecked 4 to 6 weeks after initiating oral levothyroxine therapy. If the TSH level remains elevated, the dose should be increased in weekly increments of 25 to 50 microg/day. This process should be followed at 1-month intervals until the TSH level falls into the normal range. Required doses to accomplish this will range from 50 to 300 microg/day with an average of about 75 microg of T_4/100 pounds of body weight. To lower the TSH to normal versus subnormal ranges remains controversial and is a matter of preference.

Table 8. Laboratory Findings in Hypothyroidism

Type	Primary	Secondary	Tertiary	Peripheral unresponsiveness
T_4	Low	Low	Low	Up
T_3	Low, N	Low	Low	Up
T_3RU	Low, N	Low	Low	N
FT_4I	Low	Low	Low	Up or N
TSH	Up	Low, N	Low, N	Up or N
TRH Stimulation*	Up	Low	N	N or Up.

* Assessed by response of serum TSH to TRH administration.

Patients with ischemic heart disease may require purposeful undertreatment to avoid exacerbation of angina. In this specific patient population, treatment should be cautious and should begin with small doses (about 25 microg/day) of T_4. Incremental change should be based not only on the clinical thyroid status and TSH levels but also on serial cardiologic evaluations.

The Evaluation of the Thyroid Nodule

The primary objective of investigation of the thyroid nodule is to differentiate between malignant and benign processes. Certainly, a history of head and neck irradiation should raise the suspicion of malignant involvement. Familial associations are noted in about 80 per cent of medullary carcinomas. The age of the patient also is important, since 30 to 50 per cent of nodules in children are malignant.

Following adequate accumulation of both historic and physical data, the next step in the diagnostic workup of the patient should include thyroid scintigraphic imaging. Maxon and colleagues have shown that palpatory diagnosis of solitary nodules may be incorrect in approximately 33 per cent of cases. In addition, needle aspiration studies of functional (radioiodine-concentrating) nodules may be misleading. Therefore, basing decisions on needle biopsy results alone without thyroid imaging may alter appropriate treatment incorrectly.

Thyroid scintiscanning is commonly accomplished with one of three radiopharmaceutical agents. Two of the radiopharmaceutical agents are isotopes of iodine (I-131 and I-123); the basis of the uptake includes both trapping and organification of the radionuclide. The imaging properties as well as radiation dosimetry to the patient have made I-123 the most appropriate choice. However, I-123 is a cyclotron-produced radionuclide, has limited availability, and is more expensive. As a result, Tc-99m is the imaging agent often used. The advantages of technetium include low cost, ready availability, short half-life, and optimal imaging characteristics. The main drawback is the fact that it is only trapped by the thyroid gland and not converted to an organic substance. Significant disparity between technetium and radioiodine images may occur in 2 to 3 per cent of patients. I-123 images should be obtained to confirm the functional status of nodules that are not "cold" on T-99m images.

The prevalence of autonomous, functioning nodules in patients with nodular thyroid glands varies from 6 to 25 per cent. Only about 2/1000 malignant nodules demonstrate increased uptake of I-123. If the nodule in a euthyroid patient is "hot", it may represent an autonomous nodule or a hypertrophic nodule. Autonomous nodules are independent of TSH stimulation, whereas nonautonomous hypertrophic nodules are dependent on TSH stimulation. Autonomous nodules are not responsive to hormone therapy, whereas nonautonomous hypertrophic nodules may be suppressed with T_4. The autonomous nodule may remain unchanged in the thyroid gland in approximately one third of cases. An additional one third of cases will spontaneously involute, with the remaining one third of such nodules eventually becoming toxic. The use of a T_3 suppression radioiodine uptake and scan differentiates nonautonomous from autonomous nodules.

Seventy-five per cent of patients with solitary nonfunctional (or "cold") thyroid nodules on scans will have benign disease seen histopathologically, and these nodules often may be treated with T_4 suppression. If the gland is multinodular without a history of head and neck irradiation, the incidence of malignancy is less than 5 per cent. When cold nodules are noted, needle biopsy may be required for further nodule evaluation.

Of the types of needle biopsy available, it appears that thin or fine needle aspiration of the thyroid gland is the most simple technique and may be performed on nodules of any size provided that the nodule is palpable with the patient in the recumbent position. Large needle biopsies are more likely to be successful with nodules at least 1.5 cm in diameter, and cutting needle biopsies limited to nodules larger than approximately 2.5 cm in diameter.

The limitation of needle biopsy do exist and include the presence of degenerative and reactive changes. Blood present with the biopsy may dilute the actual tissue specimen. Differentiation of benign and malignant processes is difficult with follicular lesions, since not infrequently the number of cells processed is small and the major histologic criteria for malignancy (capsular-vascular invasion) cannot be accomplished by aspiration alone. For these reasons, the overall diagnostic accuracy of fine needle aspiration cytologic procedures is about 90 per cent.

Radiation-Induced Thyroid Disease

Following both iatrogenic and accidental radiation doses to the head and neck, a variety of disorders are seen to occur with increased frequency. It is generally accepted that with low-dose irradiation (10 to 1500 rad) to the thyroid gland, the predominant effect will be the development of benign and malignant neoplasms. However, when larger doses are involved (greater than 2000 rad), thyroiditis and thyroid function disorders predominate. This most likely reflects the fact that with lower doses, follicular cell sterilization does not occur, and the chance of metaplasia and dysplasia of the damaged cell remains. With higher doses, more cells are sterilized and functional changes predominate. In the USA, the composite risk of thyroid cancer following external radiation therapy in childhood is about 2.5 excess cancers/millions persons/rad/year at risk. Human carcinogenesis has not been documented with I-131.

It appears that thyroid neoplasms derived from external irradiation are at least as aggressive in presentation and clinical course as are the thyroid neoplasms that occur without

a history of irradiation. The mortality rates for the two differently derived cancers are essentially the same.

The induction period for the development of thyroid malignancy appears to be at least 5 years after radiation exposure. The duration of risk has been reported to be variable. It may be up to 40 years after exposure, although it has been suggested that beyond 25 years the risk is less.

Age may play a role in the risk of malignant sequelae after radiation. Exposure to patients younger than 20 years of age connotes increased risk, and females appear to be more susceptible than males.

There are no reports of increased risks of thyroid malignancy following I-131 treatment for thyroid diseases. When considering nontherapeutic doses (less than 200 rad), there is no evidence for the production of thyroid carcinogenesis in humans, and there is inconsistent evidence for carcinogenesis in animals.

Thyroiditis may follow radiation exposure. Acute thyroiditis within 2 weeks of exposure to I-131 therapy may occur. Inflammation and necrosis of part or all of the thyroid gland are characteristic features. However, no reports following external radiation or accidental radiation exposure have appeared in the literature.

Benign thyroid nodules have longer induction times of at least 10 years after radiation exposure. The risk is predominant in females, with a ratio of 2 to 3:1.

Hypothyroidism following high-dose external neck irradiation for lymphoma (greater than 2000 rad) has been demonstrated to occur at a significantly increased rate. Also, patients who have received therapeutic I-131 doses to the thyroid gland in excess of 2500 rad demonstrate increased development of hypothyroidism.

Glossary

C-cells - Calcitonin-secreting cells of the thyroid gland.

DIT - Diiodotyrosine.

Follicular cells - Thyroid hormone-producing cells arranged in spheric vesicle-like units.

FT_4I - The free thyroxine index. This is a derivation that is indicative of the patient's free circulating T_4. It may be calculated by ($T_3U/100$) x T_4.

Goiter - Enlargement of the thyroid gland.

Goiter, multinodular - Enlarged thyroid gland containing numerous superficial and deep indurations.

Graves' disease - Immune disorder caused by antibodies binding to TSH receptors resulting in an unregulated increase in thyroid hormone production and release.

Hashimoto's thyroiditis - Inflammatory process of the thyroid gland caused by a derangement of the immune system, which may or may not lead to abnormal thyroid function.

Hyperthyroidism - Metabolic and clinical state caused by an increase in circulating active thyroid hormone.

Hypothyroidism - Metabolic and clinical state caused by decreased levels of circulating active thyroid hormone or increased tissue resistance.

Hypothyroidism, primary - Decreased thyroid function caused by disease of the thyroid gland.

Hypothyroidism, secondary - Decreased thyroid function caused by disease of the pituitary gland.

Hypothyroidism, tertiary - Decreased thyroid function caused by disease of the hypothalamus.

Iodine trapping - The ability of the thyroid gland to sequester the iodine against a concentration gradient.

MIT - Monoiodotyrosine.

Monodeiodination - Loss or removal of a single iodine atom.

Myxedema - Advanced hypothyroid state characterized clinically by distinctive external appearance: pallor, skin edema (swelling) of face and hands, apathy, and so on.

Parafollicular cells - Calcitonin-secreting C-cell located between follicles.

Perchlorate discharge test - A test used to differentiate iodine organification defects from defects in iodine trapping by the thyroid gland.

Resin uptake test - Measurement of the number of available binding sites on plasma thyroid transporting proteins.

rT_3 - So-called reverse triiodotyrosine with iodine in positions 3,3' and 5'.

Solitary nodule - Localized enlargement of a portion of the thyroid gland.

T_3 - Thyroid hormone with iodine atoms in positions 3,5 and 3' (triiodotyrosine).

T_3 suppression test - A test used to establish the presence of thyroid autonomy. A 24-hour radioiodine uptake is obtained before and after oral administration of T_3.

T_4 - Thyroid hormone with iodine atoms in positions 3,5,3' and 5' (tetraiodotyrosine).

Thyroglobulin - A glycoprotein of molecular weight 660.000 daltons produced by the follicular cells and containing the precursors of T_3 and T_4.

Thyroid binding globulin (TBG) - A glycoprotein of alpha-mobility that transports thyroid hormone in the blood.

Thyroid colloid - The material found within the follicles of the thyroid gland containing thyroglobulin and thyroid hormone.

Thyroid dermopathy - Pretibial myxedema, a condition involving the dorsum of the legs or feet in patients with an autoimmune thyroid disease. The skin is infiltrated and generally has a raised or thickened appearance (peau d'orange) and may be associated with pruritus or hyperpigmentation. Often it may be confused with erythema nodosum.

Thyroiditis - A general term for inflammation of the thyroid gland.

Thyrotoxicosis - Condition caused by excess thyroid hormone secretion, often used as synonym for hyperthyroidism.

TRH - Thyroid-releasing hormone; a tripeptide that promotes release of TSH.

TRH stimulation test - This test measures the TSH response to TRH administration and may be used to differentiate primary, secondary, and tertiary hypothyroidism. It may also be used to evaluate suspected hyperthyroidism.

TSH - Thyroid stimulating hormone, the glycoprotein composed of alpha- and beta-subunits released from the pituitary gland, which promotes thyroid hormone production and release.

TSH stimulation test - A test used to differentiate primary from secondary hypothyroidism.

TSI - Thyroid-stimulating immunoglobulin.