

Chapter 7

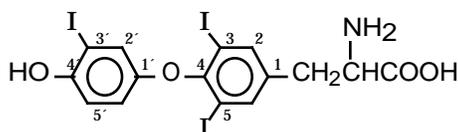
The Thyroid Gland

Introduction

The thyroid gland is the endocrine gland responsible for producing thyroid hormone, a regulator of growth, development, and basal metabolic rate, and calcitonin, a regulator of calcium homeostasis (described in Chapter 8).

The structures of the two thyroid hormones, triiodothyronine (T3) and thyroxine (T4), are shown in Figure 1. In effect, T3 is the actual hormone, since T3 has a much higher affinity for the thyroid hormone receptor than does T4; T4 is thought to act primarily a precursor for T3. In the following discussion, however, the term “thyroid hormone” will be used to refer to both compounds.

Triiodothyronine (T3) = 3,5,3'-triiodothyronine



Thyroxine (T4) = 3,5,3',5'-tetraiodothyronine

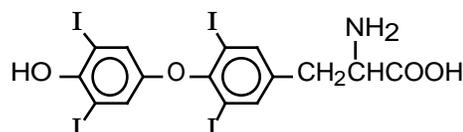


Figure 1. The structures of the thyroid hormones.

Note the numbering of the ring carbons in the T3 structure in Figure 1. The sole difference between T3 and T4 is that T3 is missing the iodine at the 5' position. This relatively subtle difference has a profound physiological effect.

Each T3 molecule contains three iodines, and each T4 contains four. This implies that the thyroid must be able to obtain iodine to incorporate into the thyroid hormones it produces. The thyroid has an active uptake mechanism that concentrates iodine about 30-fold over the serum levels. The thyroid is very efficient: 20-40% of an administered dose of iodine is trapped by the gland, and the gland contains over 90% of the total amount of iodine present in the body. The fact that the thyroid is the sole organ that uses iodine is important in therapy; low levels of radioactive iodine can be used to image the thyroid (*e.g.*, to look for uneven uptake, which is often observed in thyroid disorders), and a high level of radioactive iodine can be used to destroy the thyroid without directly affecting the rest of the body.

There are four isotopes of iodine that are relevant clinically. The short $t_{1/2}$ of ^{123}I makes it most useful for imaging, while ^{131}I is used for imaging and for thyroid ablation therapy; ^{125}I is used in research as a radioisotope label. The stable isotope ^{127}I is the form normally taken in in the diet.

	Amount used:	
^{123}I $t_{1/2}$ = 13 hours	<u>Imaging</u>	<u>Ablation</u>
^{125}I $t_{1/2}$ = ~60 days	2 - 10 mCi	30 - 200 mCi
^{127}I $t_{1/2}$ = stable		(to total dose
^{131}I $t_{1/2}$ = ~8 days		of 500 mCi)

Thyroid Hormone Synthesis

The synthesis of thyroid hormone occurs in the follicles of the thyroid. The follicles are spherical groupings of specialized epithelial cells surrounding a central lumen containing a protein-rich colloid. The major protein in the colloid is thyroglobulin (TG), a large (~660 kDa) homodimeric glycoprotein that acts as the thyroid hormone synthesis and storage site. Mature TG contains T3 and T4 as modified tyrosine residues. Each TG peptide monomer contains at most two thyroid hormone molecules out of a total of 2748 amino acids.

Thyroglobulin mRNA is translated in the rough endoplasmic reticulum. TG is glycosylated during translation, and is iodinated during transport through the Golgi and in the vesicles prior to release into the lumen. Although TG has about 70 tyrosine residues, only four are substrates for iodination.

The reactions that produce the thyroglobulin-bound thyroid hormone are all catalyzed by a single enzyme, thyroid peroxidase (TPO). TPO first activates the iodine (actually present as the ionic form iodide), and then incorporates the activated iodine into TG. Finally, TPO catalyzes the coupling reaction, which forms an ether link between the two rings, and yields thyroid hormone bound to TG. The reactions catalyzed by TPO require hydrogen peroxide; hydrogen peroxide generation appears to be a key regulatory step in the iodination process. The reactions and the pathway for thyroid hormone release are shown in Figure 2.

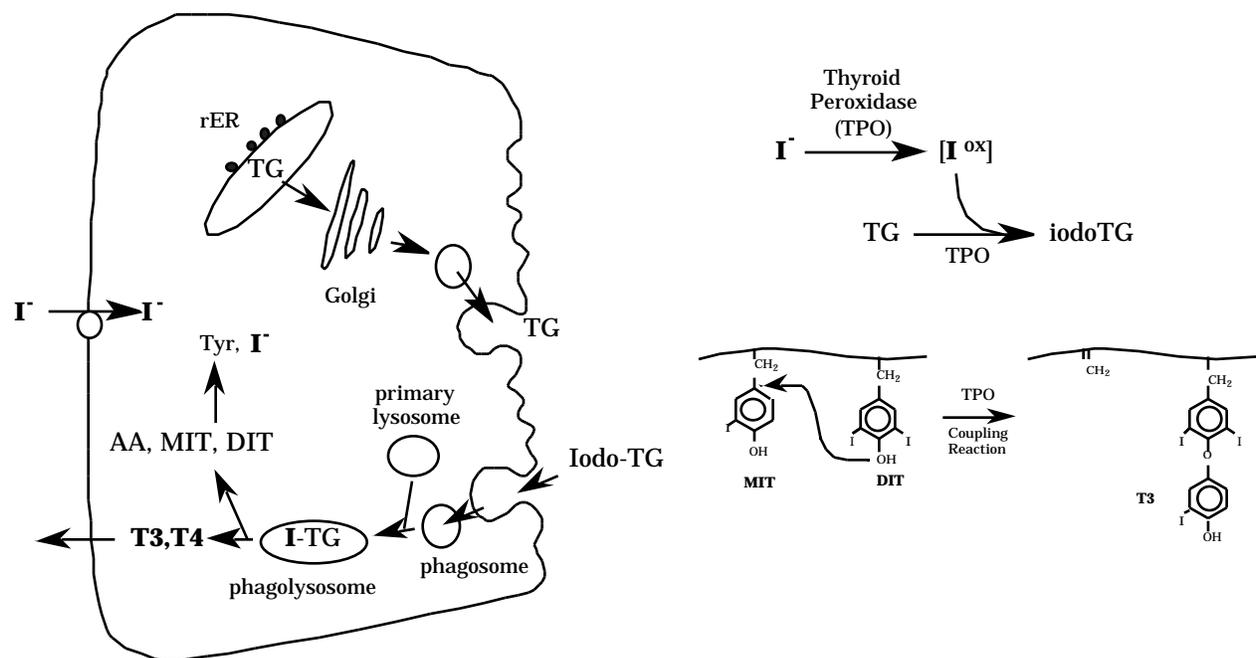


Figure 2. The production of thyroid hormone. TG is produced in the cells of the follicle and secreted into the lumen. TPO, a membrane bound enzyme, begins its reactions in the transport vesicles, and continues in the lumen. When stimulated to release thyroid hormone, the follicle cell internalizes the iodinated-TG and hydrolyzes it to form free T3 and T4 for release into circulation, and free MIT, DIT, and amino acids which are recycled.

The tyrosine residues affected by TPO are iodinated at the 3 and 5 positions to form diiodotyrosine (DIT); about one out of 40 is iodinated only at the 3 position, to form monoiodotyrosine (MIT). In the coupling reaction the phenolic hydroxyl of one DIT attacks the 1 position of another DIT (or sometimes of an MIT). This forms a bound thyroid hormone residue. Even when MIT is present, the attack of MIT on DIT does not occur, and therefore most, if not all, thyroid hormone synthesized has either four iodines, or three, with the non-iodinated position located on the outer ring.

The iodinated, coupled TG is taken up by the follicle cells in a phagocytotic process. The phagosome fuses with a lysosome, forming a secondary lysosome (also called a phagolysosome). The lysosomal proteases hydrolyze the TG to release free thyroid hormone, MIT, DIT, and free amino acids. The MIT and DIT are further metabolized to release the iodide and free tyrosine, both of which can be used to produce more TG. The T3 and T4, like the steroid hormones, enter the blood stream by passive diffusion.

There are large amounts of iodinated TG in the thyroid; a normal adult can go for about two months without iodine intake before serum thyroid hormone levels begin falling. When necessary, the thyroid can alter the ratio of T3:T4 released in order to conserve iodine, further protecting against hypothyroidism.

Thyroid Hormone Transport

Like cortisol, most thyroid hormone circulates bound to serum proteins. However, even less thyroid hormone is free than cortisol: only 0.3% of T3 and 0.03% of T4 are free in solution. This is reflected in the half-lives of the hormones: cortisol (~5% free) has a $t_{1/2}$ of 1-2 hours, while T3 has a $t_{1/2}$ of about 24 hours, and T4 has a $t_{1/2}$ of about 6 days. The majority of the thyroid hormone circulates bound to Thyroxine Binding Globulin (TBG), with the remainder bound to transthyretin and serum albumin. TBG has the highest affinity for thyroid hormone, and is induced by estrogen and thyroid hormone. Transthyretin (formerly called thyroxine binding pre-albumin or TBPA) is present in both serum and cerebrospinal fluid, and has a somewhat lower affinity; serum albumin has a rather low affinity for thyroid hormone, but is present in large amounts in serum.

Table I.
Physiological Thyroid Hormone Levels

Compound	Amount secreted ($\mu\text{g}/\text{day}$)	Total concentration ($\mu\text{g}/\text{dL}$)	Free concentration ($\mu\text{g}/\text{dL}$)
T3	5	0.12	0.0004
T4	95	8	0.002

As a result of the very small free concentration and relatively low rate of metabolism of thyroid hormone, and of the fact that circulating T4 acts as a

reservoir for T₃, T₃ has a long period of action. The levels of thyroid hormone normally change very slowly.

Synthesis and release of TBG are affected by several hormones: glucocorticoids and androgens reduce the amount of TBG, while estrogens increase TBG levels, especially during pregnancy. These observations are of some clinical relevance for individuals being treated with thyroid hormone, since the levels of exogenous thyroid hormone required will be affected by the presence of other hormones. As an example, patients with Graves' disease may have their disorder exacerbated by concurrent androgen therapy (*e.g.*, for metastatic breast cancer).

Thyroid Hormone Metabolism

The major pathway of thyroid hormone inactivation is via deiodination, although conjugation with glucuronic acid or sulfates are also observed. About 85% of T₄ and 50% of T₃ are deiodinated; the reactions occur in thyroid, pituitary, kidney, liver, placenta, and a number of other tissues. There appear to be 3 classes of deiodinase: Type I, which is inhibited by the antithyroid drug propylthiouracil (PTU), and can remove iodine from both rings, and Types II and III, which are PTU insensitive, and remove iodine from only outer ring or inner ring (respectively).

<p>The Type I deiodinase has an unusual amino acid, selenocysteine, which is required for its function. From a biochemical point of view this is interesting, because it is an example of incorporation of an amino acid other than one of the normal 20; the incorporation of "unnatural" amino acids is a goal to allow certain types of structure-function studies of proteins. Of more clinical relevance, a selenium deficient diet results in altered thyroid hormone metabolism due to decreased Type I deiodinase activity.</p>

The 5'-deiodination (*i.e.* removal of iodine from the outer ring) of T₄ produces T₃, the more active form of thyroid hormone. This conversion of T₄ to T₃ occurs largely in peripheral tissues as a result of the action of the Type I deiodinase; it also occurs in the pituitary as a result of the action of the PTU-insensitive Type II deiodinase. The 3-deiodination of T₄ (*i.e.* loss of an iodine from the inner ring) produces a compound called reverse T₃ (rT₃, or 3,3',5'-triiodothyronine) which is inactive. The product of any deiodinase acting on T₃ is also inactive. The deiodinated products may be further stripped of iodine (for recovery by the thyroid) or excreted.

Deiodination in peripheral tissues is thought to be one mechanism by which tissues alter their response to thyroid hormone. During starvation, T₄ levels remain fairly constant, but T₃ levels decrease, and rT₃ levels increase. This alteration in T₃ levels is probably important in preventing excessive degradation of muscle protein.

Drugs that induce hepatic enzymes may also induce thyroid hormone metabolism. Under normal conditions, the thyroid can respond to the decreased thyroid hormone levels by increasing thyroid hormone production, but increased hepatic metabolism may be a cause of problems in patients with thyroid insufficiency or by resulting in a chronic stimulation of the thyroid that can lead to thyroid neoplasia.

Regulation of Thyroid Hormone Release

The major regulator of the thyroid is Thyroid Stimulating Hormone (TSH), a glycoprotein hormone of the hCG/LH/FSH family. TSH stimulates a number of processes in the thyroid leading to thyroid hormone secretion. As with ACTH, these effects fall into four major groups: 1) **short term effects** (minutes): increased phagocytosis and processing of iodo-TG to T₃ and T₄; 2) **intermediate term effects** (hours): increased uptake and activation of iodide, increased hydrogen peroxide generation, increased TG synthesis and transport, increased T₃:T₄ ratio, and increased recovery of iodide from free mono- and diiodotyrosine by thyroid deiodinases; 3) **long term effects** (days to weeks): thyroid hypertrophy and hyperplasia; and 4) **life-time effects**: TSH is required to prevent thyroid atrophy.

The effects of TSH are mediated by cAMP and phosphatidyl inositol hydrolysis. The effects on TG transcription require protein synthesis, implying a secondary transcriptional event following production of a transcription factor protein. In contrast, the TSH-stimulated increase in TPO transcription does not require protein synthesis, and typically occurs much more rapidly, suggesting a direct cAMP-mediated effect on the TPO gene. The proteins phosphorylated by the TSH-generated second messenger-activated kinases are not known.

Under normal physiological conditions TG gene expression is close to maximal (additional stimulation by TSH has minimal effect); however, decrease in TSH below normal levels results in a marked decrease in TG synthesis.

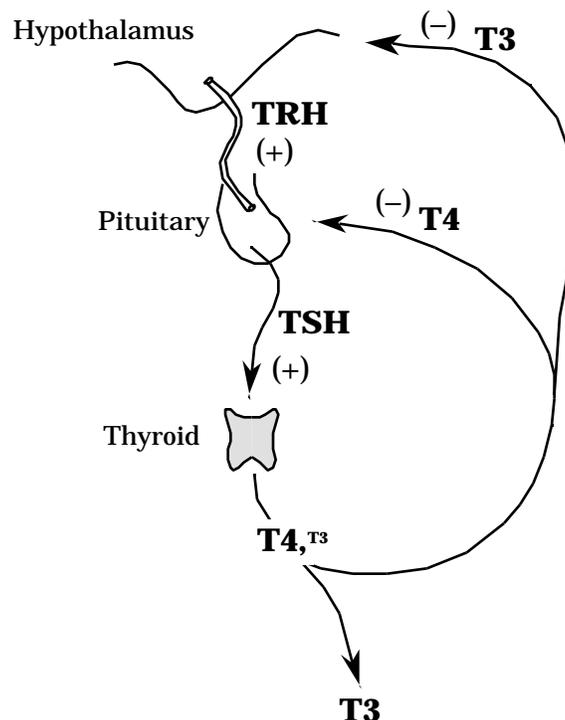


Figure 3. Control of thyroid hormone secretion.

TSH is released from the pituitary in response to TRH (thyrotropin [= TSH] releasing hormone) produced in the hypothalamus (Figure 3). The central nervous system plays a role in determining the need for increased thyroid hormone production. However, this process is very poorly understood. High levels of T3 (produced by peripheral conversion of T4 to T3) decrease the rate of TRH gene expression.

In contrast to the T3 control of TRH secretion, it is primarily high serum T4 levels that lead to decreased TSH release by the pituitary. The pituitary has the ability to trap T4; although T3 is the main form of the hormone that binds the thyrotropic thyroid hormone receptor, the pituitary primarily responds to T4, since it has an active 5'-deiodinase. The hypothalamus-pituitary-thyroid forms another example of a closed negative feedback loop system for the control of hormone release.

Mechanism of Thyroid Hormone Action

All known actions of thyroid hormones appear to be mediated by the thyroid hormone receptor. The thyroid hormone receptors are members of the steroid hormone receptor superfamily (see Chapter 1).

T3 and T4 enter cells by passive diffusion, and bind a cytoplasmic binding protein. Once inside the cell, T4 is deiodinated to T3, which moves to the nucleus (either facilitated by the binding protein or by diffusion), and binds to the thyroid hormone receptor. In general, the thyroid hormone receptors are constitutively active as repressors in the absence of hormone, although repression of gene expression can also be hormonally regulated (as in the case of the α and TSH β sub-unit genes). The non-hormone binding thyroid hormone receptor-2 is probably a constitutive repressor (see box) and apparently acts as a competitive inhibitor of the binding of other thyroid hormone receptor isoforms to DNA.

Two genes for the thyroid hormone receptor have been identified, and localized to different chromosomes (TR α on chromosome 17, and TR β on chromosome 3). Both are thought to code for active proteins, and both have been shown to yield more than one product mediated by alternate splicing events during mRNA maturation. In the case of TR β two of the forms, TR β 2 and TR β 2v, are incapable of binding T3; in contrast, the two known forms of TR α have differ only at their N-termini, and therefore both bind thyroid hormone normally. It appears that all forms of both gene products can bind thyroid hormone response elements (TRE), and may act positively or negatively either alone or in conjunction with retinoic acid receptors. TRs may also act as repressors at estrogen response elements. The non-T3 binding TR (TR β 2 and TR β 2v) forms are probably constitutive repressors; however, it is possible that the differences in their C-termini mediate the types of heterodimers that the proteins form, and it is possible that heterodimers between these proteins and ligand binding-competent receptors (*e.g.*, retinoic acid receptors) are capable of activating gene transcription. Note, however, that most of the studies regarding TR expression have been performed in rats and mice, and there may be differences between TR expression in those species and humans.

There is evidence for tissue-specific differential regulation of TR expression. TR β 2 expression is

largely confined to the brain, and its levels appear to be controlled by T3 and TRH. TR₂ may be the primary pituitary-specific form responsible for regulation of TSH secretion. Both major TR forms (TR₁ and TR₂) and TR₁ are expressed in nearly all tissues, albeit at varying levels. The ratio of TR₁ to TR₂ may be controlled, at least in part, by transcription of Rev-erbA RNA, which is transcribed from the opposite orientation of the TR₂-specific exon, and therefore consists of antisense RNA to the TR₂ exon; increased Rev-erbA results in an increased TR₁ to TR₂ ratio. The relative amount of the different forms of the receptor is probably important in regulating which genes are affected by thyroid hormone in different tissues.

The role of phosphorylation of the various forms of TR is not yet understood, although all forms are thought to be phosphorylated.

Heterodimers formed with various other partners (retinoid-X-receptors, retinoic acid receptors, and probably others) have higher affinity for DNA than TR homodimers. The retinoid-X-receptors appear to be the most favored partners in forming heterodimers. Altering the equilibrium between favoring heterodimer and homodimer formation by TR is probably an important mechanism by which thyroid hormone affects transcription of different genes within the same tissue.

Physiological Actions of Thyroid Hormone

The effects of thyroid hormone are relatively long lasting and take some time to manifest themselves. This is a consequence both of the fact that the major mode of action is alterations in gene transcription, and of the buffering capacity of TBG – the levels of free thyroid hormone cannot change rapidly in either direction. Thyroid hormone has a wide range of physiological effects. These fall into three main classes:

1) General thermogenesis: thyroid hormone increases the basal metabolic rate of most tissues (brain, spleen, lungs, gonads, and lymphocytes appear to be exceptions). This results in increased oxygen utilization and in heat generation. The mechanism for this action is unknown, although thyroid hormone appears to increase mitochondrial oxidative phosphorylation. Thyroid hormone also increases cardiac output and respiration rate.

Although incompletely understood, one mechanism for the action of thyroid hormone in cardiac tissue is the alteration of relative amounts of different isozymes of myosin. Thyroid hormone stimulates an elevated β to myosin ratio; myosin has greater ATPase activity and mediates stronger contractions. Thyroid hormone also increases the number of β -adrenergic receptors as well as increasing post-receptor actions by increasing the amount of adenylyl cyclase. The potentiation of catecholamine action in hyperthyroid states is responsible for a number of the symptoms of the disorder. These actions of thyroid hormone are reversed in hypothyroid states.

2) General metabolic effects: thyroid hormone stimulates protein turnover (acute effects are largely synthetic; chronic effects lead to increased breakdown), lipid turnover, and carbohydrate metabolism. These effects are probably a result of up-regulation of key enzyme gene transcription. Some of the effects are probably indirect; thyroid hormone also potentiates the effects of both insulin and epinephrine, and increases growth hormone secretion.

In adipose tissue, the main effects of thyroid hormone appear to involve potentiation of catecholamine action. High levels of thyroid hormone increase the levels of β -adrenergic receptors, and probably also enhance post-receptor effects (such as coupling of the receptor to adenylyl cyclase and decreasing cAMP inactivation); the enhanced lipolysis that occurs as a result is one mechanism by which elevated thyroid hormone levels result in weight loss.

3) Growth and developmental effects: thyroid hormone is required for normal development, especially for growth and for development of the brain during fetal and postnatal development. Maternal hypothyroid status due to lack of iodine must be corrected prior to *conception* to completely prevent fetal abnormalities (due to both direct effects of insufficient thyroid hormone in the fetus and from indirect effects of hypothyroid maternal metabolism). Absence of thyroid hormone synthesis during the “critical period”, which includes at least the last trimester of gestation and the first 1-2 years of postnatal life, and probably also includes the entire period of pregnancy, results in irreversible deficits in brain function due to impaired development. Athyroid fetuses are currently only incompletely treatable, since although maternal thyroid hormone crosses the placenta to the fetus, the levels are usually insufficient to completely support development. Fetal hypothyroid status during this period (*i.e.* thyroid hormone is present, but only at low levels), also has long lasting effects; however, over a period of several years treatment can eventually reverse most of the deficits.

Thyroid hormone also stimulates growth, probably both directly and via increasing both growth hormone levels (the growth hormone gene has a TRE) and IGF-I levels (and probably other growth factors as well). In addition, thyroid hormone is required for normal brain functioning throughout life.

Relatively little specific information is available on the mechanism by which these effects are mediated.

The Thyroid During Pregnancy

During pregnancy, estrogen levels rise markedly. Probably as a result of this, TBG levels increase by ~3-fold. In most women, free T3 and T4 levels remain fairly constant; in some cases, the levels decrease slightly (~10%) but these individuals usually maintain euthyroid status. The increase in TBG requires increased thyroid stimulation to maintain free T3 and T4 levels. The resulting increase in thyroid hormone production, combined with increased levels of thyroid hormone metabolism (and consequent loss of iodine in urine) and with fetal iodine uptake for its own thyroid hormone synthesis means that maternal iodine requirement rises somewhat during pregnancy. In the United States this is rarely a problem in normal women. In parts of Europe and in developing countries where iodine deficiency is much more common, this may result in hypothyroidism and fetal developmental abnormalities.

The necessity for increased thyroid hormone synthesis during pregnancy may also produce overt hypothyroidism in women apparently normal prior to conception, especially in early cases of Hashimoto's syndrome (discussed below). Women being

treated with thyroid hormone for thyroid insufficiency prior to conception require increased supplementation during pregnancy.

The placental hormone hCG can activate the TSH receptor. Although in most women this merely results in euthyroid status with decreased TSH levels, the hCG effect can result in pregnancy-induced hyperthyroidism. While the hyperthyroidism often resolves as hCG levels decline following the first trimester, the individuals may require some treatment during that period; pregnancy-induced hyperthyroidism may also be a symptom of a sub-clinical thyroid disorder. In addition, hCG-stimulation of the TSH receptor may exacerbate pre-existing Graves' disease (see below).

Clinical Manifestations of the Thyroid

Thyroid disorders are fairly common, striking about 2% of the population in the United States. Excluding pregnancy-related thyroid disorders, the most common (about 50% of the total) is Graves' disease.

A normal individual is euthyroid. Euthyroid status means that the individual does not exhibit any thyroid-related disorders. That sounds obvious, but a number of individuals have thyroid hormone levels that are well outside the normal range, yet are not in need of treatment. In some cases these individuals have been treated anyway, with unpleasant results. An example of this is provided by individuals that lack thyroxine binding globulin (TBG). As a result, their serum *total* thyroid hormone levels are very low, although their *free* thyroid hormone levels are normal, and they do not exhibit any symptoms. Hyperthyroid and hypothyroid conditions are similarly defined by the symptoms exhibited rather than by the total thyroid hormone levels.

Serum levels of TSH are generally used as indicators of thyroid status. In individuals with normal pituitary function, measurement of TSH levels is usually informative; however, other abnormalities may complicate the clinical picture (*e.g.*, an enlarged thyroid may produce normal levels of thyroid hormone at sub-normal levels of TSH), and therefore even results from properly performed TSH assays must be interpreted with considerable caution.

Hyperthyroid Disorders

Hyperthyroidism (also called thyrotoxicosis) is caused by elevated free T3 and T4 levels, and is characterized by nervousness, hyperactivity, restlessness, tachycardia and cardiac arrhythmia, and weight loss due to increased BMR. Some of these symptoms are due to increased sensitivity to catecholamines. Hyperthyroid individuals typically have difficulty tolerating exercise, probably due, at least in part, to alterations in the cardiovascular system, and to thyrotoxic myopathy (muscle weakness and atrophy) which often occurs in severe cases. High levels of thyroid hormone increase chances of myocardial infarction, increase risk for osteoporosis, and may increase insulin requirements in diabetics.

There are number of underlying causes of hyperthyroidism.

Graves' disease: Graves' disease is an autoimmune disorder in which antibodies (TS Ab) against the TSH receptor act to stimulate the thyroid in the absence of TSH. This usually results in goiter formation due to chronic and uncontrolled thyroid stimulation, with T3 levels usually increased more than those of T4. More than 80% of cases are female. Onset is often associated with stress; incidence in susceptible individuals (DR3 HLA type) increases at menarche and menopause. There is also some evidence that some types of infection can trigger Graves' disease in susceptible individuals.

Although, paradoxically, treatment with T4 can in some cases alleviate symptoms of Graves' disease, including exophthalmos (possibly by decreasing levels of TSH receptor, and thereby decreasing the immune response that causes the disorder), the preferred treatment for Graves' disease in most cases is ^{131}I ablation. Surgery to remove the thyroid is less commonly used (except in cases of large goiters, which are less responsive to radioiodine), and may result in damage to the larynx or to the parathyroids. PTU (propylthiouracil) inhibits the coupling reaction (and therefore thyroid hormone synthesis) and Type I deiodinase (and therefore peripheral, but not pituitary, conversion of T4 to T3). PTU is frequently used to treat hyperthyroid conditions, especially during pregnancy, because, unlike radioiodine (which crosses the placenta and will damage the thyroid of the fetus), PTU crosses the placenta only to a limited extent. Less of the antithyroid drug is required during the second and third trimesters of gestation when the symptoms of Graves' disease usually decrease or even disappear, due to estrogen-stimulated increases in TBG and to immunosuppression by the hormonal changes associated with pregnancy. During the first trimester, and in the immediate postpartum period, however, the disorder generally intensifies.

Graves' disease is often (25-50% of cases) accompanied by **exophthalmos**, an autoimmune-induced inflammation of the tissue behind the eyes resulting in protrusion of the eyes; autoimmune attack on the ocular tissue occurs in nearly all patients, sometimes leading to impaired vision. In some cases radiotherapeutic destruction of the thyroid worsens the autoimmune attacks, probably by causing the release of thyroid antigens resulting in stimulation of the immune system.

Toxic adenoma: Thyroid adenomas are non-malignant but produce T3 and T4 autonomously. As might be expected, these patients present with high T4, very high T3, and low TSH. Most characterized toxic adenomas have been shown to contain mutant forms of the TSH receptor which constitutively stimulate cAMP production (although apparently not phosphatidyl inositol hydrolysis). This may be due to a dominant genetic abnormality, or to a somatic cell mutation.

Thyrotoxicosis facticia: Hyperthyroid status may be a result of thyroid hormone ingestion (*e.g.*, from eating bovine thyroid, or from abusing or being overdosed with prescription thyroid hormone). Thyroid hormone levels usually change slowly, and the effects of thyroid hormone have slow onset; therefore hyperthyroidism due to ingested thyroid hormone may not exhibit overt symptoms for one to three weeks.

Thyroid malignancy: Thyroid cancer usually has very markedly decreased ability

to produce thyroid hormone (<1% of normal tissue). Hyperthyroid status resulting from thyroid cancer thus usually requires large (kilogram size) tumor. In the rare cases of hyperthyroidism associated with tumors, the tumor usually overproduces T3 preferentially. In some cases this is treatable by reducing iodine intake. In cases of thyroid hormone-producing thyroid cancer, ^{131}I is often used as a supplement to surgery, especially in cases of metastatic disease. In cases of tumors that do not produce thyroid hormone, ^{131}I is generally ineffective due to very low or absent iodine uptake by the tumor. High level (>500 mCi total) ^{131}I therapy may have adverse effects on other organs; this is especially evident in cases of metastatic tumors (in which the ^{131}I is concentrated in proximity to other organs). Thyroid hormone-producing malignancies are in some cases treated by T4 suppression of TSH (TSH is mitogenic for thyroid cells). It should be noted that the dose of T4 required places the patient in the low hyperthyroid range, and may thus have adverse health consequences. The prognosis for thyroid tumors is significantly worse for patients that exhibit Graves' disease, probably due to the mitogenic effects of the TS Ab. Thyroid medullary carcinoma does not synthesize thyroid hormone; instead, it is usually associated with elevated calcitonin levels.

Pituitary adenoma: Some pituitary adenomas secrete TSH, resulting in hyperthyroid condition and goiter. The adenomas usually do not respond to TRH.

Hypothyroid Disorders

Hypothyroid disorders are characterized by mental and physical slowness, cold skin, mild weight gain (although usually not obesity), and decrease in basal metabolic rate. Hypothyroid status also results in decreased cardiac function which can lead to congestive heart failure. Hypothyroidism can lead to both hypertension and hypercholesterolemia, and is associated with increased risk for development of atherosclerosis.

In addition to treatment for the underlying disorder, it is usually necessary to supplement with exogenous thyroid hormone. Poor compliance has been observed, especially in adolescents; this can result in developmental abnormalities.

Severe (non-thyroid) illness may reduce T3 levels to apparent hypothyroid levels (a phenomenon known as **euthyroid sick syndrome**). In many cases, however, these patients are not, in fact, hypothyroid, and upon resolution of the illness, the thyroid hormone levels return to normal.

Cretinism: Hypothyroid conditions during fetal development result in impairment of growth and brain functioning. The hypothyroidism may be due to iodide deficiency or to congenital defects, such as lack of TSH receptor. The result is a mentally retarded, dwarfed newborn.

Goiter: The thyroid is capable of massive increases in size, resulting in a visually obvious bulge in the neck. Goiter formation usually results from excessive stimulation of the thyroid by TSH (see also Graves' disease, above). In hypothyroid conditions, this is usually due to low thyroid hormone production, as a result of iodide deficiency (fairly common in the developing world, but rare in the United

States due to sodium iodide supplementation of table salt) or from goitrogens, which are usually compounds that interfere with iodide uptake. Goitrogens are found in high concentrations in turnips and related vegetables (excessive consumption of which can result in goiter formation, although the goitrogens can be inactivated by cooking). Another type of goitrogen is a compound that stimulates hepatic clearance of thyroid hormone. As with other thyroid conditions, goiters are much more common in women (about 8:1).

Congenital goiter: Defects in thyroglobulin synthesis or structure, or in iodide incorporation (probably as a result of TPO defects) cause neonatal goiter and hypothyroidism. In some cases increased T3 synthesis leads to low euthyroid status, allowing essentially normal growth, but not alleviating the mental symptoms. Defects in TG may result in the presence of proteins iodinated on tyrosine and histidine in urine (in the absence of TG, TPO uses a variety of other proteins as substrates). In some cases the defect alters the three-dimensional structure of the TG protein, and therefore although iodination is normal, coupling is inhibited.

Excess iodide: Paradoxically, too much dietary iodide can result in decreased thyroid hormone production, although the thyroid usually compensates. However, the fetus responds to excess iodide by shutting down thyroid hormone production, resulting in goiter, hypothyroid disorders, and problems during labor.

Idiopathic myxedema: Myxedema, a condition of puffy skin characteristic of hypothyroidism, is in some cases not associated with any obvious cause. One possible cause is the presence of antibodies that act as antagonists rather than the agonist-type action of TS Ab (see Graves' disease, above).

Hashimoto's syndrome: Hypothyroidism can result from an autoimmune attack on the thyroid (as with all autoimmune disorders, this is much more common in women than in men). It is often subclinical, especially in early stages, due to compensating hypertrophy and hyperplasia of undamaged thyroid tissue, and to increases in secretion of T3 (*i.e.* an increased T3:T4 secretion ratio). The disorder generally progresses from normal T3/low T4/high TSH, to low T3/low T4/very high TSH, with enlarged thyroid and myxedema. There is some evidence that some types of thyroid-destructive autoimmune attack can be stimulated by environmental insults such as exposure to polyhalogenated biphenyls, and that some types of infection can trigger Hashimoto's disease in susceptible individuals. Autoimmune attack on the thyroid may be associated with other autoimmune disorders, such as Addison's disease and Type I diabetes mellitus.

Interferon: About 10% of individuals treated with interferon- (*e.g.*, for hepatitis C) develop autoimmune-related thyroid disorders, with Hashimoto's being more common than Graves' disease. Interferon treatment is also associated with exacerbation of existing autoimmune-induced thyroid dysfunction, suggesting that patients undergoing interferon therapy may require examination for effects on the thyroid.

Generalized resistance to thyroid hormone: Rare individuals exhibit resistance to thyroid hormone due to a genetic defect in the thyroid hormone receptor- gene. In autosomal recessive cases, the disorder is due to a gene deletion. In autosomal

dominant cases, the disorder is due to a point mutation that results in decreased affinity for thyroid hormone. GRTH is a disorder characterized by elevated free and (usually) total T3 and T4 levels, with either normal or high levels of TSH. The normal levels are probably a consequence of the fact that the thyroid has become sufficiently hyperplastic as to be capable of producing elevated levels of thyroid hormone from normal levels of TSH. Although some have claimed that the disorder is asymptomatic, most individuals present with somatic abnormalities suggestive of hypothyroid status, as well as low IQ, dyslexia, short stature, and low BMR. About 50% of affected individuals also exhibit attention deficit disorder and hyperactivity. However, individuals diagnosed with attention deficit disorder usually do not have GRTH.

The reason for the recessive form of thyroid hormone resistance is obvious: there are two defective alleles of a gene coding for a required protein. The reason for the dominant disorder is more complex. While not fully understood, it is probably a result of the fact that the thyroid hormone receptor binds to the DNA as a dimer. In individuals with a single mutant form of the receptor, the presence of the mutant receptor as one component of the dimer is enough to inhibit proper functioning. Recall that the thyroid hormone receptor acts as a repressor in the absence of hormone; presumably dimers formed from one normal and one mutant protein are incapable of being activated, and therefore act as constitutive repressors, *regardless* of the presence of hormone. In addition, wild-type TR homodimers dissociate upon binding T3; this dissociation is required for normal formation of heterodimers. In most mutants, the heterodimers exhibit normal activity, but lack of dissociation of homodimers prevents heterodimer formation required for proper functioning.

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