HISTORY

135 | Thyroid Disease

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Definition

Patients with abnormalities of thyroid gland function or structure come to medical attention for several reasons. They present with symptoms attributable to physiologic effects of increased or decreased plasma concentrations of thyroid hormone (hyperthyroidism or hypothyroidism, respectively). They may also present with symptoms related to localized or generalized enlargement of the gland (diffuse goiter, multinodular goiter, or single thyroid nodule). These changes may result from functional abnormalities or neoplasia, benign or malignant.

The following symptoms are typical problems that may eventually be diagnosed as specific thyroid diseases or syndromes. For diagnoses related to hyperthyroidism (thyrotoxicosis), these complaints may include weight loss, anxiety or nervousness, increased sweating, tremulousness, diarrhea, palpitations, muscular weakness, heat intolerance, or history of treatment of an "overactive" thyroid. For diagnoses related to hypothyroidism, typical problems include fatigue, weight gain, depression, lethargy, dry skin, cold intolerance, voice change, change in menses, muscle cramps, or treatment of a thyroid condition. Thyroid enlargement (goiter) may present in the context of hyper- or hypothyroidism. It may also occur in a patient with normal thyroid hormone production (euthyroid patient). Typical complaints related to thyroid enlargement include generalized neck swelling (diffuse goiter), neck mass (uninodular or multinodular goiter), dysphagia, neck pain, or hoarseness. Finally, patients may be referred with no complaints but with "abnormal thyroid function tests" that lead to a search for symptoms and signs of thyroid dysfunction.

Thyroid storm refers to an increasingly rare but still highly dangerous form of thyrotoxicosis that, in addition to the other complaints of hyperthyroidism, is marked by extreme temperature elevation and/or change in mental status, ranging from extreme agitation to coma. *Hypothyroid crisis* refers to advanced thyroid hormone deficiency manifested by hypothermia and obtundation.

Technique

Initial questions directed at patients to uncover thyroid problems should be somewhat general. Ask: Have you or any member of your family been told you have had a thyroid condition or a goiter? Have you taken thyroid medication? Have you been told that you have an underactive or an overactive thyroid gland? Have you ever received radiation treatments to the head or neck? Have you noted a change in weight? Have you noticed a change in your skin or hair? Have you been more uncomfortable in hot or cold weather? Has there been a change in your bowel habit (constipation or diarrhea)? Has there been a change in your mood? Has there been a change in your strength and energy? Have you noticed any change in your neck? Have you had any pain or discomfort in your neck?

For symptoms more specific for hyperthyroidism and diseases causing hyperthyroidism, ask: Have you been bothered by increased nervousness or irritability? Do you sweat more? Have you lost weight despite an increase in appetite or food intake? Are you more uncomfortable in the heat, or do you prefer cooler weather? Is this different from previously? Do you have more frequent bowel movements? Are you more "shaky" or tremulous? Have you noticed a change for the worse in your handwriting? Do you notice your heart racing? Do you have difficulty rising from a chair or from a kneeling position? Are you more breathless after exercise?

For symptoms more specific for hypothyroidism and diseases causing hypothyroidism, ask: Have you experienced gain in weight despite eating less? Do you tire more easily? Have you noticed dryness of your skin? Are you more constipated? Has there been a change in your voice? Are you more sensitive to cold weather than previously? Do you have muscle aches, pains, or cramping? Do you feel depressed? Are you able to perform your usual job as previously? Are you losing your memory?

For symptoms of an enlarging thyroid, ask: Have you noted any changes in the appearance of your neck? Do your shirt collars feel tight? Any sense of a lump in your throat or difficulty swallowing when you eat? Has there been a change in your voice? Have you experienced any pain or tenderness in your neck? Have you noticed any swelling or lumps in your neck?

Basic Science

The understanding of thyroid disease and the interpretation of thyroid function tests requires an understanding hypothalamic–pituitary–thyroid feedback control (see Figure 135.1). It also demands an appreciation of thyroid hormone transport and the response of cells to non-protein-bound thyroid hormone. The hypothalamic hormone, thyrotropin releasing hormone (TRH), modulates the release of pituitary thyroid stimulating hormone (TSH). TSH interacts with specific receptors on thyroid follicular cells to stimulate thyroid hormone production [approximately 80% thyroxine (T4) and 20% triiodothyronine (T3)]. T4 and T3 are transported in blood bound to serum proteins. The remainder of T3 production (80%) comes from the conversion of T4 in peripheral tissues. T3 is the most active form of thyroid hormone. Non-protein-bound thyroid hormones, representing a minor fraction of the total circulating thyroid hormones, enter peripheral cells and interact with a specific nuclear binding protein. This interaction leads to induction of many enzymes to finally express the effect of the thyroid hormones. Circulating levels of T4 and T3 are sensed by the pituitary gland and perhaps by the hypo-

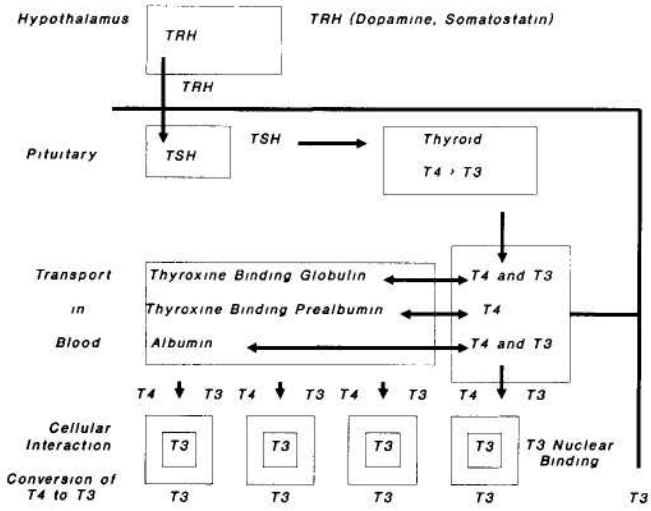

Figure 135.1
Hypothalamic–pituitary–thyroid axis. Thyroid hormone transport and tissue effects.

thalamus to control the secretion of TSH and thereby maintain blood levels of thyroid hormones within normal limits. Disturbances in many aspects of this complex system can present the physician with clinical and laboratory findings of hyper- or hypothyroidism, goiter, or apparent abnormalities of thyroid function testing without definite clinical correlates. Often, the discordance between clinical findings and laboratory testing makes the diagnosis of thyroid disorders challenging and stimulating.

Noniatrogenic causes of thyroid dysfunction include inflammation (acute or subacute thyroiditis), autoimmune disease (Hashimoto's thyroiditis and Graves' disease), inherited metabolic defects (mono- and di-iodotyrosine deiodinase deficiency), malignancy (follicular, papillary, anaplastic, and parafollicular or C cell), and nutritional deficiencies (iodine or protein deficiency).

Thyroid problems may also directly result from medical or surgical therapies of the thyroid gland or indirectly from treatment of nonthyroid conditions. Examples include hypothyroidism after radioactive iodine or surgery for Graves' disease, and thyroid cancer after x-ray therapy to the head or neck. Hypothyroidism and hyperthyroidism have been reported after treatment of arrhythmias with Amiodarone, which contains iodine.

Although enlargement of the thyroid gland may suggest thyroid disease, physiologic and temporary enlargement of the thyroid gland associated with pregnancy and adolescence is normal. It is occasionally confused with abnormal enlargement and must be considered in the differential diagnosis of goiter.

The thyrotoxic patient (see Table 135.1) suffers from signs and symptoms attributable to the metabolic effects of excessive thyroid hormone, many of which appear related to increased activity of the sympathetic nervous system. These must be differentiated from non-thyroid-related causes of actual or apparent hypermetabolism and sympathetic overactivity, such as pheochromocytoma, cocaine abuse, and nonspecific anxiety. The use of beta-sympathomimetic blocking drugs in treating thyrotoxicosis relieves many of the symptoms attributable to the sympathetic nervous system without decreasing, at least acutely, the increased consumption of oxygen characteristic of the hypermetabolic state.

Table 135.1
Thyrotoxicosis: Thyroid Morphology and Etiological Features[a]

Thyroid examination	Pathogenic mechanism
Diffuse goiter	Thyroid stimulating immunoglobulins Chorionic gonadophin-like thyroid stimulator TSH (pituitary adenoma)
Toxic adenoma Toxic multinodular goiter	Autonomous thyroid function
Normal or small thyroid	Ectopic thyroid tissue Exogenous thyroid hormone
Enlarged and/or tender thyroid	"Injury" with transient excess hormone release

[a]Excess thyroid hormone with somatic manifestations.

In contrast to hyperthyroidism, the hypothyroid patient's signs and symptoms are attributable to decreased circulating concentrations of thyroid hormone (see Table 135.2). Hypothyroid individuals demonstrate a decreased oxygen consumption with an overall impression of reduced sympathetic activity. Weight gain and psychomotor retardation are related to the decreased metabolic rate due to decreased thyroid hormone. In addition, hypothyroidism results in a decreased clearance of metabolic products such as cholesterol and triglyceride and enzymes such as creatine phosphokinase (CPK). Therefore, serum concentrations of these substances are increased. Furthermore, metabolic clearance of medications is decreased so that there is increased risk for toxicity from commonly used medications such as sedatives or digitalis preparations.

Genetic predisposition to thyroid disease is apparent in autoimmune thyroid disorders. Specific enzyme deficien-

Table 135.2
Hypothyroidism: Thyroid Morphology and Etiological Features[a]

Thyroid examination	Pathogenic mechanism
Goiter	*Primary hypothyroidism (elevated TSH)* Inherited defects in thyroid hormone synthesis Nutritional Iodide Deficiency Goitrogens (e.g., PTU)
Goiter with/without tenderness	"Injury" due to thyroiditis
Normal, small, or absent thyroid	Thyroid stimulating hormone Receptor Blocking Antibody Radioiodide, surgical Congenital thyroid absence *Secondary hypothyroidism (pituitary or hypothalamic dysfunction) low TSH*

[a]Insufficient thyroid hormone with somatic manifestations.

cies related to concentrating iodine, synthesizing thyroid hormone, or reclaiming iodotyrosine iodine are clearly inherited. Certain forms of thyroid cancer (parafollicular) may also have a genetic component. Thus, a family history of thyroid disease or goiter may direct attention to a subtle or overlooked thyroid problem. Conversely, a goiter requires that data be gathered concerning a possible family history of thyroid abnormalities.

If hypothyroidism is caused by pituitary or hypothalamic dysfunction rather than by primary thyroid disease, symptoms and findings of other endocrine "end organ" dysfunction are usually present. If pituitary disease is present, clinical manifestations include hypogonadism (amenorrhea, decreased libido, impotence), growth hormone deficiency (short stature in children), postpartum agalactia, and hypoadrenalism (nausea, vomiting, diarrhea, hyponatremia, and decreased tolerance to medical stress).

Hypothalamic abnormalities may also cause hypothyroidism by interfering with TRH secretion and cause many of the same features seen in pituitary failure. In hypothalamic dysfunction (and also in primary hypothyroidism), hyperprolactinemia may occur in association with hypogonadism. In hypothalamic disease, the absence of pituitary lactotroph inhibiting factor, dopamine, leads to unregulated prolactin secretion and hyperprolactinemia. In primary hypothyroidism, increased TRH secretion or sensitivity causes pituitary lactotrophs to secrete large amounts of prolactin. Marked enlargement of the pituitary gland may occur in primary hypothyroidism and may simulate a prolactinoma. However, the hyperprolactinemia and pituitary enlargement resolve with reversal of the hypothyroidism by supplying adequate replacement thyroid hormone.

Thyroid problems also include interpretation of abnormal thyroid function tests, either obtained to confirm the presence of thyroid disease or as screening procedures to detect thyroid dysfunction. Difficulties in evaluating these tests are related to marked elevations or reduction in thyroxine binding serum proteins, to changes in thyroxine production and clearance (phenytoin effect or response to acute or chronic illness) or to unusual inherited states in which there is resistance to the effects of thyroid hormone.

Only a tiny fraction of the total serum concentrations of thyroxine (T4) and triiodothyronine (T3) circulate "free" in the blood. The cellular response to thyroid hormone is determined by this non-protein-bound fraction (0.03% for T4; 0.3% for T3). The majority of T4 is bound to three plasma proteins: thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA), and albumin. T3 is primarily bound to thyroxine binding globulin and albumin, with only a tiny amount bound to TBPA. Thyroid function tests that measure the total amount of circulating thyroid hormone are affected by physiologic events that alter the amount of these binding proteins. Thus, somewhat increased or decreased total serum concentrations of T4 or T3 may be associated with normal amounts of "free" thyroid hormones. If the hypothalamic–pituitary axis is intact, low circulating concentrations of "free T4" are associated with increases in pituitary thyroid stimulating hormone (TSH), and there is increased responsiveness of the pituitary gland to exogenously administered thyrotropin releasing hormone (TRH). Thus, primary hypothyroidism often results in generalized thyroid enlargement. There is an exception to this, however. In autoimmune thyroiditis, blocking antibodies to the TSH receptors on thyroid cells may prevent TSH stimulation and thyroid atrophy may occur even in primary hypothyroidism. Conversely, when concentrations of "free T4" are increased, TSH is decreased and response to TRH is blunted. Indirect measures of "free" non-protein-bound thyroxine such as the free thyroxine index (FTI) or direct measures such as "free T4 by equilibrium dialysis" are used to further assess true elevations or reductions of free thyroxine. In rare instances, however, even elevated "free T4" values may not be associated with hyperthyroidism, as there are increasing numbers of patients identified as having peripheral resistance to thyroid hormone. These patients may be asymptomatic; they require these elevations in order to maintain normal metabolic function. This subgroup of patients with peripheral resistance to thyroid hormone was identified because astute clinicians refused to accept a diagnosis of thyrotoxicosis on the basis of abnormally elevated concentrations of free T4 in patients with goiter who had no symptoms of hyperthyroidism. By the same token, patients who appear euthyroid but who have low total T4 or T3 values may have a congenital deficiency of TBG but normal "free" hormone concentrations. In short, thyroid function tests should not be obtained and certainly should not be interpreted in a definitive fashion without correlating them with the symptoms and signs manifested by the patient.

The concentrations of physiologically active T4 and T3 also depend on nutritional status and general health. The most active form of thyroid hormone, triiodothyronine (T3), may be replaced by increased amounts of "reverse T3," an alternate form of T3 with little biologic activity. Medications such as corticosteroids and clinical states such as starvation or chronic illness ("euthyroid sick" syndrome) may increase this inactive form of thyroid hormone with associated reductions in T3 (see Table 135.3).

An enormous range of clinical tests are available to the clinician to confirm the presence of hyper- or hypothyroidism. The most commonly used are measures of total circulating thyroid hormone, particularly T4 by radioimmunoassay (RIA), in screening for thyroid dysfunction. Total T3 by RIA and reverse T3 are also available. Concentrations of "free" T4 can be inferred from the total T4, and measurements of thyroxine binding such as the T3 resin uptake which are used to calculate a "free thyroxine index," which is proportional to the "free" T4. A similar index can be calculated for "free" T3. Pituitary TSH in conjunction with total T4 provides the basis for differen-

Table 135.3
"Euthyroid Sick" Syndrome[a]

Findings	Mechanisms
Normal thyroid morphology	
Severity of illness and mortality rate inversely related to T4 concentration	
Chemical findings	TRH response decreased
Low Total T4	Decreased TBG
Normal, low, high free T4[b]	
Low T3	Decreased conversion of T4 to T3 and increased reverse T3 (medication: steroid, beta-blockade; starvation)
Increased Reverse T3	
Low TBG	
Elevated T3 resin uptake	
Normal TSH	
Blunted response to TRH	Block to cellular uptake T4

[a]Associated with acute and chronic illness.
[b]Depends on method.

tiating between primary hypothyroidism (thyroid gland failure) and secondary hypothyroidism (hypothalamic or pituitary failure causing hypothyroidism). TRH stimulation tests are useful in assessing patients with autonomous thyroid hyperfunction (for example, deciding when Graves' disease is in remission, when "euthyroid" Graves' disease is present, or when patients are on an adequate suppressive dose of thyroid hormone after thyroid ablation for cancer). At present, the TSH by RIA is being supplanted by the ultrasensitive TSH by radioimmunometric assay (IRMA). The TSH by RIA was an adequate tool for monitoring elevated concentrations of TSH. It was a relatively insensitive test, however, for monitoring the low concentrations of TSH seen in thyrotoxicosis due to all causes except rare situation of a TSH secreting pituitary adenoma. Thus, TSH by IRMA replaces the TRH stimulation test and the T3 suppression test for diagnosing thyrotoxicosis.

Thyroid function can also be assessed by the capacity of thyroid tissue to take up and incorporate iodide or other similar compounds (radioiodine scan and uptake), technetium pertechnetate scan). The distribution of the scanning material also helps to assess general and localized thyroid malfunction. Ultrasound, computed tomographic (CT) scanning, and, more recently, magnetic resonance imaging (MRI) assist in determining the nature of thyroid nodules. Needle aspiration is now being utilized to define the nature of these nodules and assist in the preoperative diagnosis of malignancy. Tests for antithyroglobulin and antimicrosomal antibodies assist in the identification of patients with autoimmune thyroiditis. Antibodies to TSH receptors are now clinically available, both TSH-like thyroid stimulating antibodies (TSI) and thyroid blocking immunoglobulins, to diagnose Graves' disease and atrophic hypothyroidism.

Clinical Significance

Thyroid-related medical problems are exceedingly common. As the symptoms of hyper- or hypothyroidism are nonspecific, often they are attributed to other medical or psychiatric illness. Furthermore, the signs and symptoms may develop over such a long period of time that friends, family, and even personal physicians adapt to the changes and do not perceive the abnormalities. Both conditions tend to prevent the patient from functioning normally in a work or family environment and thus eventually come to medical attention. Both conditions are difficult to diagnose in the elderly.

The diagnosis of thyroid disease is of great benefit to the patient. Hyper- and hypothyroidism can be extremely disabling. Graves' disease may progress to thyroid storm. Blindness may be occur because of the associated ophthalmopathy. Profound weakness is associated with the wasting of the hypermetabolic state. Hypokalemic periodic paralysis, mostly in Orientals but also in other groups, may be associated with profound periodic muscle weakness. It is treated by using beta-blockers and by reversing the hyperthyroid state. Graves' disease complicating pregnancy is associated with increased fetal wastage. In contrast, hypothyroidism may be associated with central respiratory failure. Pericardial effusion causing pericardial tamponade may occur. Hypothyroidism may be the unrecognized cause of infertility or hypertension. It may cause profound depression. It probably accelerates the progression of atherosclerosis, because of the hypercholesterolemia associated with it. Autoimmune thyroiditis is associated in greater frequency with other autoimmune diseases such as Type I diabetes mellitus.

Although most thyroid diseases are chronic and often debilitating, they are treatable. A host of medications are available to control the signs and symptoms of hyperthyroidism by controlling the sympathetic stimulatory effects of thyroid hormone (beta-sympatholytic drugs such as propranolol), by controlling the uptake and synthesis of thyroid hormone (propylthiouracil, methimazole, iodide, or lithium), by decreasing its release (iodide), or by decreasing the conversion of T_4 to T_3 in peripheral tissues (propylthiouracil, propranolol, and glucocorticoids). Radioiodide can be used to treat hyperthyroidism and disseminated thyroid cancer. Surgery is also effective in treating both conditions, although it is being used less frequently in thyrotoxicosis because of the availability of effective drugs and radioiodide. In hypothyroidism, thyroid replacement therapy with thyroid hormone is effective and relatively inexpensive.

Symptoms related to thyroid dysfunction are nonspecific but sensitive. Thus, while weight gain, constipation, and cold intolerance are frequently found in hypothyroidism, only a few patients complaining of obesity or constipation or cold intolerance are hypothyroid. Nonetheless, each additional complaint renders such a diagnosis more likely, particularly if physical findings suggestive of hypothyroidism are also present. Further confirmatory evidence comes from the laboratory demonstrating, for example, a low total T_4 and an elevated TSH, indicating primary thyroid failure. Similarly, symptoms related to hyperthyroidism are individually sensitive; however, only in aggregate are they specific.

Hyperthyroidism may be relatively easy to diagnose in a symptomatic patient with all of the characteristic physical features of Graves' disease (diffuse toxic goiter), which include prominent exophthalmos (protruding eyes), blepharospasm (a stare), a prominent diffuse goiter, a tremor, weight loss, a rapid pulse, and a hyperdynamic circulation (wide pulse pressure, rapidly rising pulse wave, prominent apical pulse), and hyperreflexia. One is less likely to think of hyperthyroidism in those without clear-cut Graves' disease, particularly in elderly or pregnant patients or in those with other forms of thyrotoxicosis. Hyperthyroidism in the elderly may only be manifested by weight loss and refractory cardiac arrhythmias or chronic diarrhea. Patients with thyrotoxicosis in pregnancy may be missed because so many normal women complain of heat intolerance, fatigue, irritability, and tachycardia. In addition, mild diffuse thyroid enlargement is normally found in pregnancy. Conversely, thyrotoxicosis may still be mistakenly diagnosed in pregnancy because of the above findings if a serum thyroxine, elevated because of an increase in circulating thyroxine binding globulin (TBG), is thought to confirm thyrotoxicosis. This is one of several forms of euthyroid hyperthyroxinemia (see Table 135.4). Some assessment of free thyroxine ("free" T_4 or FTI) must be made to establish the diagnosis in pregnancy. Nevertheless, thyrotoxicosis is common in pregnancy and increases the risk of an adverse outcome for both mother and fetus. There is an increased risk of thyroid storm for the mother; there is increased fetal wastage and an increased frequency of babies small for gestational age. Thyrotoxicosis probably related to "thyroiditis," a condition which is usually transient, is now being seen with increasing frequency in the pregnant patient. A rare form of thyrotoxicosis found only in pregnancy is that associated with a hydatidiform mole or with choriocarcinoma. In this instance, human chorionic gonadotropin, which has

Table 135.4
Euthyroid Hyperthyroxinemia: Thyroid Morphology and Etiological Features[a]

Thyroid morphology	Pathogenic mechanism
Normal thyroid	Transport protein abnormality (normal free T4 and TSH) Increased TBG Increased TBPA Dysalbuminemia Antibody to thyroid hormones
Goiter	Pituitary and peripheral resistance to thyroid hormone (receptor or post-receptor abnormality)
Normal thyroid	(?) Transient block in conversion of T4 to T3 (medication, hyperemesis gravidarum, psychiatric)
Depends on underlying thyroid problem	Thyroxine replacement therapy

[a]Increased T4 without thyrotoxicosis.

weak TSH properties, is produced in enormous amounts and is able to cause thyroid enlargement and increased production of thyroid hormone, leading to thyrotoxicosis. It is diagnosed by recognizing excessively rapid uterine growth in a presumably pregnant patient and demonstrating the lack of fetal parts with an ultrasound examination. Thyrotoxicosis in these patients is cured by evacuation of the tumor.

Other causes of thyrotoxicosis include single or multiple autonomous nodules (which in most cases are palpable), abuse of thyroid hormone by neurotic patients, and inappropriate dosages of thyroid hormone administered for thyroid replacement or suppression. Rare causes of thyrotoxicosis are pituitary adenomas secreting TSH, autonomous hypersecreting thyroid tissue in the ovary (struma ovarii), or widespread thyroid hormone secreting follicular carcinoma.

Reliance on screening populations for hyperthyroidism using thyroid function tests as part of health maintenance surveys is relatively expensive and inefficient. For asymptomatic euthyroid patients with elevated thyroxine binding pre-albumin (TBPA) or with an abnormal thyroxine binding albumin or patients with increased peripheral resistance to thyroid hormone, screening tests may lead to unnecessary treatment for hyperthyroidism. Screening for hypothyroidism may be worthwhile for certain populations. There is a good argument for screening newborns for hypothyroidism because of the devastating effects of this condition on the central nervous system. These are prevented with early thyroid hormone replacement. Screening has also been advocated in the elderly because of the high frequency of hypothyroidism, particularly in elderly women. Nevertheless, screening of thyroid function will reveal many individuals, particularly those with chronic illness ("euthyroid sick"), who have apparent hypothyroidism by their low total T4 measurements. In these persons, treatment of their underlying condition is the key to rational therapy.

In summary, the symptoms related to hyper- or hypothyroidism should be correlated with physical findings. Clinical diagnoses should be further supported by appropriate laboratory testing of thyroid function. Discordances between clinical findings and laboratory testing require explanation, and complete diagnoses require that such inconsistencies be resolved.

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