THYROID HORMONE TUTORIAL: THYROID PATHOLOGY

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I. INTRODUCTION

Thyroid disorder is a general term representing several different diseases involving thyroid hormones and the thyroid gland. Thyroid disorders are commonly separated into two major categories, hyperthyroidism and hypothyroidism, depending on whether serum thyroid hormone levels (T_4 and T_3) are increased or decreased, respectively. Thyroid disease generally may be sub-classified based on etiologic factors, physiologic abnormalities, etc., as described in each section below.

More than 13 million Americans are affected by thyroid disease, and more than half of these remain undiagnosed. The American Association of Clinical Endocrinologists (AACE) has initiated a campaign to increase public awareness of thyroid disorders and educate Americans about key periods, from birth to advanced age, when people are at increased risk for developing a thyroid disorder (see below). The diagnosis of thyroid disease can be particularly challenging. Patients often present with vague, general clinical manifestations; in particular, the elderly may not associate the signs and symptoms with a disease process and thus may not bring them to the attention of their primary care provider.

The prevalence and incidence of thyroid disorders is influenced primarily by sex and age. Thyroid disorders are more common in women than men, and in older adults compared with younger age groups. The prevalence of unsuspected overt hyperthyroidism and hypothyroidism are both estimated to be 0.6% or less in women, based on several epidemiologic studies. Age is also a factor; for overt hyperthyroidism, the prevalence rate is 1.4% for women aged 60 or older and 0.45% for women aged 40 to 60. For men more than 60 years of age, the prevalence rate of hyperthyroidism is estimated to be 0.13%. A similar pattern is observed for the prevalence rate of hypothyroidism. The prevalence rate of overt hypothyroidism is 2% for women aged 70 to 80, 1.4% for all women 60 years and older, and 0.5% for women aged 40 to 60. In comparison, the prevalence rate of overt hypothyroidism is 0.8% for men 60 years and older. The estimated annual incidence of hyperthyroidism for women ranges from 0.36 to 0.47 per 1,000 women, and for men ranges from 0.087 to 0.101 per 1,000 men. In terms of hypothyroidism, the estimated incidence is 2.4 per 1,000 women each year. Overt thyroid dysfunction is uncommon in women less than 40 years old and in men <60 years of age.

Complications that can arise from untreated thyroid disease include elevated cholesterol levels and subsequent heart disease, infertility, muscle weakness, and osteoporosis. The issue of routine screening is controversial because cost-effectiveness has not been clearly proven. Although it may not be economically feasible or necessary to test all patients for thyroid dysfunction, there are instances when thyroid screening is appropriate. Pharmacists can counsel patients on the appropriateness of thyroid screening. The AACE advises TSH testing during the following times: (1) birth through adolescence, (2) the reproductive years (pregnancy), (3) midlife (menopause), and (4) the senior years (aging). Testing and screening may also be important for patients taking certain medications, herbal drugs and food supplements as described in the final section of this chapter.

- Birth: Routine screening for congenital hypothyroidism (which can cause cretinism, a growth and mental disorder caused by a lack of thyroid hormone) is performed on all newborns by administering a heel-pad test. Treatment of congenital hypothyroidism requires full doses of thyroid hormone as soon after birth as possible to prevent neurologic damage and impaired development. If treatment is delayed beyond 6 months after birth, full neurologic development is impaired and regression of neurologic deficits is not possible. Also, hypothyroidism may occur in the neonate if the mother ingests goitrogens (eg, cabbage or turnips) that inhibit normal feedback mechanisms for regulating thyroid hormone levels, or if the mother becomes hypothyroid through over-treatment with thionamides. The extent to which thioamide therapy is responsible for hypothyroidism in the fetus or neonate is controversial.

- Adolescence: Parents of older children need to be made aware that symptoms such as difficulty concentrating and inattentiveness at school, hyperactivity, unexplained daytime fatigue, delayed puberty, dry and itchy skin, and increased sensitivity to cold and heat all may be symptoms of an underlying thyroid condition. An initial diagnosis of attention deficit disorder (ADD) in a child or adolescent may prompt a parent to consult with a pharmacist about available treatment options. At this time, pharmacists can advise on thyroid screening to possibly rule out ADD.

- Reproductive Years (Pregnancy): The AACE advises expectant mothers to take a TSH test before pregnancy or as part of the standard prenatal blood work. Some studies have suggested that undiagnosed hypothyroidism impairs fertility, and in the pregnant patient, it results in a four times greater risk for miscarriage during the second trimester. Another opportunity or pharmacists to counsel on thyroid screening is when a woman is seeking advice on ovulation predictor kits and pregnancy tests.

- Midlife (Menopause): The symptoms of either hyperthyroidism or hypothyroidism, such as skin dryness, hot flashes, mood swings, depression, and weight gain, mimic the symptoms of menopause. If patients on hormone replacement therapies continue to experience mood swings, depression, or sleep disturbances, it would be appropriate to advise these women to request a thyroid function test. The AACE recommends that all women older than age 40 years have a TSH test, because studies have shown that 10% of these women have undiagnosed thyroid disease.

- Senior Years (Aging): Many seniors feel that the onset of symptoms such as fatigue, depression, forgetfulness, insomnia, and appetite changes are just part of the natural aging process. They often seek advice about over-the-counter vitamins or herbs (eg, ginkgo biloba) that can help alleviate these symptoms. At these times, pharmacists can inquire about thyroid screening. One of every five women older than age 65 years has an increased TSH, and approximately 15% of all hyperthyroid patients are older than 60 years.

II. THYROID FUNCTION TESTS: OVERVIEW

Several thyroid function tests (TFTs) are used to evaluate thyroid status. The development of sensitive TSH testing has been an important advance since the early 1990s. Before the sensitive TSH test was available, there was a gray zone between normal and abnormal thyroid function. The sensitive TSH test clearly defines thyroid disease and allows for precise titration of thyroid replacement therapy. Several key TFTs are discussed below and presented in Table 1.

- Thyroid-Stimulating Hormone: Assays to measure TSH are conducted using an extremely sensitive radioimmunoassay. The origin of hypothyroidism-whether at the level of the pituitary gland, hypothalamus, or thyroid gland-can be determined by using the test for TSH. Levels of TSH are used to diagnose or screen for hypothyroidism and to evaluate adequacy of replacement therapy.

- T_3 and T_4 Levels: Both T_3 and T_4 are measured by radioimmunoassay. Tests are available to directly or indirectly measure both bound and unbound hormone. The resin T_3 and T_4 uptake tests (RT_3U and RT_4U) estimate binding capacity to TBG and are used to calculate free T_3 and T_4 levels. The free T_3 index (FT_3I) and the free T_4 index (FT_4I), which can be calculated in several different ways, are used to correct for alterations in TBG.

- Antibodies: Autoantibodies of clinical interest in thyroid disease include thyroid-stimulating antibodies (TSAb), TSH receptor-binding inhibitory immunoglobulins (TBII), antithyroglobulin antibodies (Anti-Tg Ab) and the antithyroid peroxidase antibody (Anti-TPO Ab). Elevated levels of Anti-TPO A are found in virtually all cases of Hashimoto's thyroiditis and in approximately 85 percent of Graves' disease cases. Also, approximately 10 percent of asymptomatic individuals have elevated levels of Anti-TPO Ab that may suggest a predisposition to thyroid autoimmune diseases. Historically, Anti-TG Ab determinations were used in tandem with antimicrosomal Ab determinations to maximize the probability of a positive result in patients with autoimmune disease. Although the prevalence of Anti-TG Abs in thyroid autoimmune disease is significant (85 percent and 30 percent in Hashimito's thyroiditis and Graves' disease, respectively), it is much lower than the prevalence of the Anti-TPO Abs. Thyroid-stimulating antibodies (TSAb) are present in more than 90% of Grave's disease, and TSH receptor-binding inhibitory immunoglobulins (TBII) are present in atrophic form of Hashimoto's Disease, in maternal serum of pregnant women (predictive of congenital hypothyroidism) and myxedema

- Radioactive Iodine Uptake (RAIU): The RAIU test indicates iodine use by the thyroid gland but not hormone synthesis capacity or activity. A tracer dose of radioactive iodine (^{131}I or ^{123}I) is administered intravenously, and the thyroid gland is scanned for iodine uptake. A normal test result is 5% to 15% of the dose taken up within 5 hours and 15% to 35% within 24 hours. This test is primarily used for diagnosis of Graves' disease (increased uptake). In patients who are iodine deficient, results indicate a greater uptake of iodine, and in those with an iodine excess, lesser uptake. Additionally, after the administration of radioactive iodine, a thyroid scan can reveal "hot" or "cold" spots indicating areas of increased or decreased iodine uptake, which can be useful in the detection of thyroid carcinoma.

Table 1. Common Thyroid Function Tests

Test	Measures	Normals	Interference	Comments
Measurements of circulating thyroid hormone levels				
FT_4	Direct measure of free T_4	0.7-1.9 ng/mL (Analog)	Altered TBG do not interfere	Most accurate measure of free T_4
FT_4I	Calculated free T_4 level	6.5-12.5 T_4 (1.3-3.9)	Euthyroid sick syndrome	Estimates direct free T_4, compensates for altered TBG
TT_4	Total free + bound T_4	5.0-12 mg/dL	Alterations of TBG	Adequate if TBG is not altered
TT_3	Total free + bound T_3	70-132 ng/dL	Alterations of TBG; Euthyroid sick syndrome	Useful to detect early, relapsing and T_3 toxicosis
RT_3U	Indirect measure of TBG saturation	26-35%	Alterations of TBG	Used to calculate FT_3I and FT_4I
Tests of Thyroid Gland Function				
RAIU	Thyroid uptake of iodine	24 hr: 15-35%	< with Excess Iodine and > with iodine deficiency	Different. of hyperthyroidism
Scan	Size, shape & activity	----------	Thyroid and antithyroid drugs	Detect “Hot” vs “cold” nodules
Test Hypothalamic-Pituitary-Thyroid Axis				
TSH	Pituitary TSH levels	0.5-4.7 U/L	DA, glucocort-coids, TH, amiodarone	Most sensitive index for hyper-thyroidism & to monitor therapy
Tests of Autoimmunity				
ATgA	Antibodies to thyroglobulin	<8%	Non-thyroidal immune disease	Present in auto-immune thyroid disease; not present in remission
TPO	Thyroperoxidase antibodies	<100IU/mL	Non-thyroidal immune disease	More sensitive test; detectable during remission
TRab (TSAb)	Thyroid receptor IgG antibody	Titers negative	----------	Confirms Graves’ incl. neonatal
Thyroglobulin	Colloid protein of gland	5-25 mg/dL	Goiters, Inflam thyroid	Thyroid cancer marker

III. HYPERTHYROIDISM (Thyrotoxicosis)

A. Causes, Symptoms and Thyroid Function Tests

Hyperthyroidism represents a myriad of thyroid disorders (Table 1) characterized by elevated levels of circulating thyroid hormones. The annual incidence of hyperthyroidism is three per 1,000 in the general population, and the condition is eight times more common in women. Hyperthyroidism may result from generalized thyroid gland over-activity ("true" hyperthyroidism) or from causes other than over-activity of the gland. It is important to distinguish between these since the prognosis and treatment will be different. Once hyperthyroidism is suspected based on clinical presentation, and confirmed by thyroid hormone and TSH level determination (see below), the general form of disease can be differentiated by radioactive iodine uptake (RAIU) studies as indicated in Table 1. The normal RAIU over a 24 hour period ranges from 10%-35%.

"True" hyperthyroidism (Table 2) is caused by production of elevated levels of TSH (tumors, pituitary resistance), production of thyroid stimulators other than TSH (antibodies as in Graves' disease), or by thyroid autonomy (multinodular goiters). "True" hyperthyroidism is differentiated from other forms by elevated RAIU. The most common cause of hyperthyroidism is Graves' disease, a systemic autoimmune process in which the patient's body is producing autoantibodies against the thyrotropin (TSH) receptor. These autoantibodies called thyroid-stimulating immunoglobulins (TSH[stim]Abs) are present in 95% of patients with Grave's disease and activate the thyrotropin (TSH) receptor and stimulate the uncontrolled production and release of T_4 and T_3.

Hyperthyroidism caused by factors other than thyroid gland over-activity may result from inflammatory thyroid disease (subacute thyroiditis, "painless" thyroid), the presence of ectopic thyroid tissue (struma ovarii, metastatic follicular carcinoma) or by exogenous sources of thyroid hormone. These forms are differentiated from "true" hyperthyroidism by decreased RAIU. The different forms of hyperthyroidism are discussed in more detail in the sections that follow.

The major symptoms, physical findings and laboratory values associated with hyperthyroidism are outlined in Table 3 below. It is important to note that hyperthyroid patients may not exhibit all of these symptoms, and may display variable thyroid function test results depending on the form of the disease. Generally, however, hyperthyroidism results in acceleration of many physiologic functions are accelerated. The heart pounds, beats more quickly, and may develop an abnormal rhythm, leading to an awareness of the heartbeat (palpitations). Blood pressure is likely to increase. Many people with hyperthyroidism feel warm even in a cool room. Their skin may become moist as they tend to sweat profusely, and they may develop "myedema". Frequently there are also changes in the nails. Hyperthyroid patients may develop a fine tremor in their hands, and generally have good deep tendon reflexes. Many people feel nervous, tired, and weak, yet have an increased level of activity. Hyperthyroid patients may have an increased appetite, yet they lose weight due to the increased metabolic actions of thyroid hormone. Most hyperthyroid patients have frequent bowel movements, occasionally with diarrhea, and sleep poorly.

Table 2: Types and Causes Hyperthyroidism

Thyrotoxicosis associated with elevated Thyroidal RAIU:	
<u>TSH-Induced hyperthyroidism</u> • TSH-Secreting primary adenomas • Pituitary resistance to Thyroid Hormone (PRTH)	 ➔ TH overproduction from TSH hypersecretion (relatively rare) ➔ Resistance to suppressant effects of TH (relatively rare)
<u>Hyperthryoidism induced by mediators other than TSH</u> • Grave's Disease • Trophoblastic disease	 ➔ TSH-R[stim] Ab which stimulates TH overproduction ➔ High hCG levels which stimulate Thyroid TSH receptors resulting in TH overproduction
<u>Hyperthyroidism from Thyroid autonomy</u> • Toxic adenoma • Multinodular Goiters	 ➔ Functioning thyroid elements outside thyroid gland (rare) ➔ TH Overproduction: autonomous hyperfunction of thyroid gland portions
Thyrotoxicosis associated with suppressed Thyroidal RAIU:	
<u>Inflammatory Thyroid Disease</u> • Subacute Thyroiditis: • Painless Thyroid	 ➔ Transient disease caused by viral invasion of the thyroid ➔ Etiology unknown: postpartum
<u>Ectopic Thyroid Disease</u> • Struma Ovarii • Follicular Cancer	 ➔ Functioning thyroid elements outside thyroid gland (rare) ➔ TH Overproduction: autonomous hyperfunction
<u>Exogenous Source of Thyroid Hormone</u> • Medication • Food	 ➔ Ingestion of excessive exogenous TH
Thyrotoxicosis: Special Conditions	
• Graves Disease and Pregnancy • Neonatal/Pediatric Hyperthyroidism • Thyroid Storm	See Text below

Older people with hyperthyroidism may not develop these characteristic symptoms but have what is sometimes called "apathetic" or "masked" hyperthyroidism. They simply become weak, sleepy, confused, withdrawn, and depressed, symptoms often associated with aging. However, heart problems, especially abnormal heart rhythms, are seen more often in older people with hyperthyroidism.

Hyperthyroidism can cause changes in the eyes including puffiness around the eyes, increased tear formation, irritation, and unusual sensitivity to light. The person appears to stare. These eye symptoms disappear soon after the thyroid hormone secretion is controlled, except in people with Graves' disease, which causes unique eye problems as discussed below.

Hyperthyroidism is often associated with a goiter or thyroid nodules as discussed more in the sections that follow.

Table 3. Clinical and Laboratory Findings of Some Forms of Hyperthyroidism

Symptoms	Physical Findings	TFTs
- General: Weakness and fatigue - Heat intolerance - Nervousness, irritability and insomnia - Weight loss or gain (increased appetite) - Diarrhea, frequent bowel movements - Palpitations - Pedal edema - Tremor - Amenorrhea/light menses	- Thinning of hair - Plummer's nails - Ocular: Proptosis, lid lag, lid retraction, periorbital edema (exophthalmos in Grave's) - Diffusely enlarge goiter - Wide pulse pressure - Flushed, moist skin - Pretibial myxedema - Brisk deep tendon reflexes	- Suppressed TSH - Increased TH levels including TT_4, FT_4I, FT_4, TT_3, FT_3I - Positive antibodies (TRab, ATgA, TPO) - RAIU: >50% in "true" form - Decreased cholesterol - Increased Ca, AST, alkaline phosphatase

B. Characteristics of Various Forms of Hyperthyroidism

1. TSH-Induced Hyperthyroidism

TSH-induced hyperthyroidism may be caused by TSH-secreting pituitary adenomas or pituitary resistance to thyroid hormone. TSH-secreting adenomas may occur in females or males (8:7) typically 40 years or older. These tumors release TSH that induces elevated thyroid synthesis and release, and are not responsive to normal hormonal feedback control. Thus these patients present with many of the symptoms of hyperthyroidism. Diagnosis is confirmed by demonstrating a lack of TSH response to TRH stimulation and radiologic imaging of the pituitary. Imagining results may be misleading since some small tumors may not be detected, and some patients may have pituitary tumors without hyperthyroidism. Pituitary adenomas may also secrete prolactin and growth hormone and therefore also cause amenorrhea/galactorrhea or signs of acromegaly. The pituitary tumors may also effect the optic nerve and cause visual field defects. This condition is treated with transphenoid pituitary surgery followed by irradiation of the pituitary gland.

Pituitary resistance to thyroid hormone (PRTH) refers to resistance of the pituitary to thyroid hormone feedback control, perhaps resulting from receptor modification. This is a rare familial syndrome and is observed more commonly in women than men (2:1). PRTH patients typically present with multiple and varied symptoms including psychoses, retardation and developmental abnormalities. Diagnostically these patients display an appropriate increase in TSH in response to

TRH, and suppressed TSH in response to T_3. Patients with PRTH require treatment for the symptoms resulting from excessive thyroid hormone levels, but monitoring is difficult because TSH cannot be used to evaluate the adequacy of therapy.

2. Hyperthyroidism from Thyroid Stimulators Other than TSH: Graves' Disease and Trophoblastic Disease

The most common cause of hyperthyroidism is Graves' disease. This is an autoimmune syndrome resulting from the production of thyroid stimulating antibodies (TSAbs) capable of stimulating thyroidal TSH receptors, resulting in excessive thyroid hormone production and release, and overstimulation of gland growth. Autoantibodies that react with the orbital muscle of the eye and fibroblasts of skin are also produced and initiate the so-called "extrathyroidal" manifestations of Graves disease (see below). All of the autoantibodies produced in Grave's disease may arise from a genetic point mutation in the extracellular domain of the thyrotropin receptor. Evidence supporting a hereditary component in Graves' disease includes a 1). clustering of the disease in families and a 50% likelihood of a monozygotic (identical) twin developing the disease versus 9% in dizygotic (fraternal) twins, 2). The occurrence of other autoimmune diseases, such as Hashimoto's thyroiditis, is also higher in families with Graves' disease than in the general population and 3). There is an increased frequency of some human leukocyte antigens (HLAs) in patients with Graves' disease. Interestingly the production of autoantibodies in Grave's disease may decrease or disappear over time and this may result in a spontaneous remission of disease symptoms.

The majority of patients with Grave's disease or other thyroid abnormalities resulting in elevated thyroid hormones present with one or more of the following symptoms: resting tachycardia and palpitations, exercise intolerance, muscle weakness, cramping, fatigue, irregular menstrual cycles (women), impotence, weight loss (up to an average of 15% less than normal in spite of increased appetite), nervousness, exertional dyspnea, heat intolerance, irritability, tremor, sleep disturbance, increased perspiration, increased frequency of bowel movements, change in appetite, anxiety, warm/moist skin, hair loss, goiter and other “extrathyroidal” effects (see below). Additional tissue effects include accelerated metabolism, suppressed serum thyrotropin (TSH), low serum cholesterol (through interference with the cholesterol metabolism and excretion), increased bone turnover and reduced bone density with an increased risk of osteoporosis and fracture (particularly in postmenopausal women). **The primary characteristics of Graves' disease are diffuse thyroid enlargement (as much as two to three times the normal size, 40-60 grams), extrathyroidal manifestations (such as exophthalmus, pretibial myxedema or Grave’s dermopathy), and thyroid acropachy with confirming thyroid function tests**.

- Graves' dermopathy is characterized by subcutaneous swelling on the anterior portions of the legs and by indurated and erythematous skin. These effects may appear on the hands also. Dermopathy appears to be related to the infiltration and deposition of disease-related antibodies in the skin, usually over the shins. The thickened area may be itchy and red and feels hard when pressed with a finger. As with the ocular symptoms described below, these symptoms may begin before or after other symptoms of hyperthyroidism are noticed. Corticosteroid creams or ointments can help relieve the itching and hardness.

- Graves' ophthalmopathy may result from 1). Functional abnormalities resulting from TH-

induced hyperstimulation of the sympathetic nervous system or 2). Infiltrative changes involving the orbital contents and enlargement of the ocular muscles. Functional ocular abnormalities are present in most Graves' patients and include lid lag (upper eyelid behind globe on downward gaze). These abnormalities typically do not affect ocular function and resolve upon treatment for hyperthyroidism. Infiltrative ophthalmopathy involves lymphocytic infiltration, increased mucopolysaccharide content, fat and water in all retrobulbar tissue. It occurs in 50-70% of Grave's patients and is characterized by edema of the orbital contents, protrusion of the orbital globe (exophthalmos), paralysis of the extra-ocular muscles and damage to the retina and optic nerve. As a result of these pathologies, the Grave's patient may experience excess tearing and photophobia in milder cases, and diplopia, eye pain, and decreased visual acuity or blindness in more severe cases (retinal detachment, optic nerve damage). The cause of these manifestations is unknown, but it is suggested that antibodies may react with orbital muscle to cause or mediate development of exophthalmos (and fibroblast tissue to mediate skin changes). Also, current treatments for Grave's disease do not reverse these ocular effects, but they can stabilize them. Because the precise etiology of Graves'-related ophthalmopathy is not known, symptomatic and empiric therapies are often employed including corticosteroids.

In some patient populations unique complications of hyperthyroidism may be expressed. For example, Asians and Hispanics may present with recurrent muscle flaccidity ranging from mild muscle weakness to total paralysis, and markedly diminished deep tendon reflexes - a syndrome referred to as hypokalemic periodic paralysis. These symptoms are likely to occur after strenuous exercise or high carbohydrate diets and are related to hypokalemia resulting from a shift of potassium from extracellular to intracellular sites. Treatment of these patients involves correcting hyperthyroidism, administration of potassium, administration of spironolactone to conserve potassium and propranolol to minimize intracellular shifts.

Laboratory findings in Graves' disease and other forms of thyrotoxicosis include low to undetectable (depending on the sensitivity of the radioassay) TSH levels due to feedback inhibition by high thyroid hormone levels, and increased levels of both T_3 and T_4, with an increased ratio of T_3 relative to T_3. In some patients only the overproduction of T_3 will be noted (T_3 toxicosis). The hyper-production of thyroid hormones results in saturation of TBG and a marked increase in free T_3 and T_4 as evidenced by elevated RT_3U and FT_4I values. In addition, the vast majority of patients with Graves' disease will have significant titers of thyroid autoantibodies; however, the specific testing for autoantibodies is not routinely recommended. If the patient is not pregnant, a 24 hour RAIU should be obtained and will be significantly elevated. Untreated, patients with elevated thyroid hormone levels are at risk for reduced quality of life, atrial fibrillation, and osteoporosis. The objectives of treatment of thyrotoxicosis are to reduce the excess production and availability of thyroid hormones and to reduce or control symptoms of thyrotoxicosis. **There are currently three major treatment modalities for Graves' disease: antithyroid drug therapy, radioactive iodine, and surgical resection of the thyroid gland. The primary antithyroid drugs include propyltiouracil (PTU) and methimazole (MMI) which inhibit thyroid peroxidase (TPO) enzymes. Therapy is individualized on the basis of patient age, sex, other concurrent medical conditions, and response to previous therapy as discussed in a separate Tutorial.**

Others forms of hyperthyroidism resulting from the production of thyroid stimulators other than

TSH include trophoblastic diseases. As described in the Introductory Chapter, luteinizing hormone (LH), follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), and TSH all have very similar alpha-subunits, the subunit most important for TSH receptor binding. Most of these hormones have significantly lower affinity for TSH receptors; hCG has only 1/10,000 the receptor activity of TSH. But when very high levels of hCG (or LH or FSH) are produced, they may stimulate the thyroid directly and promote thyroid hormone release and hyperthyroidism. In patients with trophoblastic tumors hCG levels may reach 2000 U/ml compared to the 50 U/mL seen in normal pregnancy.

3. Hyperthyroidism from Thyroid Autonomy: Toxic Adenoma and Diffuse Toxic Goiter/Toxic Multinodular Goiter

An autonomous thyroid nodule is a discrete thyroid mass whose function is independent or normal pituitary control. These nodules may be toxic adenomas or “hot” nodules based on their uptake on radioiodine and appearance on a radioiodine thyroid scan (see "Nodules" section below). Toxic or hot nodules secrete thyroid hormones independent of the pituitary because this tissue contains mutated TSH receptors. Typically, the older the patient the larger the toxic nodules and the greater thyroid hormone release and degree of thyrotoxicosis. While T_4 levels typically are elevated in these patients, sometimes only T_3 levels are increased. Therefore if T_4 levels are normal in such patients, T_3 levels should be determined to rule out T_3 toxicosis. This form of hyperthyroidism may be treated by RAI, subtotal thyroidectomy or percutaneous injection of ethanol. The thionamide antithyroid drugs typically are not effective because they do not halt the proliferative process in the nodule. Typically autonomously functioning thyroid nodules are not cancerous.

The thyroid gland normally enlarges in response to an increased demand for thyroid hormones that occurs in puberty, pregnancy, iodine deficiency and immunologic, viral or genetic disorders. In these cases there is increased TSH secretion and a compensatory increase in thyroid follicles and thyroid hormone synthesis. Typically when the condition requiring more hormone subsides, TSH secretion subsides and the thyroid gland returns to normal size. However, irreversible changes may have occurred in some follicle cells so that they now can function autonomously relative to TSH. These autonomous follicles may (but not necessarily) produce excessive thyroid hormone unregulated by TSH, resulting in thyrotoxicosis. This condition is termed toxic multinodular goiter (Plummer’s Disease) and produces symptoms similar to Grave’s disease without infiltrative ocular manifestations or myxedema. The symptoms of hyperthyroidism related to toxic multinodular goiter typically develop slowly and predominantly affects older individuals with long-standing goiters. These patients may eventually present with the symptoms of “apathetic thyrotoxicosis” in the elderly as described below. Multinodular goiter patients can be diagnosed by radioiodine thyroid scan ("patches" of iodine uptake and autonomous function) and TSH and free thyroid hormone testing. The preferred treatments include RAI or surgery; surgery typically is used for patients whose goiters impinge on the esophagus or trachea. Alternatively percutaneous injection of 95% ethanol has been used.

4. Thyrotoxicosis associated with Inflammatory Thyroid Disease: Subacute Thyroiditis and "Painless" Thyroiditis

Subacute granulomatous (giant cell) thyroiditis ("painful", viral or deQuervain's thyroiditis) appears to result from viral invasion of the thyroid parenchyma and begins much more suddenly than Hashimoto's thyroiditis. Subacute granulomatous thyroiditis often may be mistaken initially for a dental problem, a throat or ear infection or the flu. Symptoms quickly worsen to include low-grade fever, severe myalgias, sore throat, ear pain, and tachycardia. The thyroid gland becomes increasingly tender, and the person usually develops a low-grade fever (99° F. to 101° F.) and most feel extremely tired. The pain may shift from one side of the neck to the other, spread to the jaw and ears, and pain may intensify when the head is turned or when the person swallows. Palpation may reveal a nodule, but in most patients, gland tenderness is so pronounced that they will not allow the physician to palpate it. The ear pain may be the principal complaint and is sometimes so dramatic that physicians treat for ear infection even though the ear appears normal. This form of thyroiditis often runs a triphasic course with 1). Inflammation resulting in initial hyperthyroidism and low TSH levels from release of preformed thyroid hormone, 2). Depletion of thyroid hormone stores resulting in mild hypothyroidism with elevation of TSH levels (see below) and 3). Recovery of normal thyroid hormone and TSH levels. Generally the condition is self-limiting, resolving within 2-6 months. Recurrence is rare, but rarely it may recur and, even more rarely, damages enough of the thyroid gland to cause permanent hypothyroidism. During the initial, hyperthyroid phase thyroid function test results include: high thyroid hormone levels, low TSH levels, and a thyroidal radioactive iodine uptake of 1% to 2%. The symptoms of subacute thyroiditis can be managed with beta-blockers to reverse the adrenergic actions of hyperthyriodism, along with aspirin or other NSAIDs to manage the pain. In more severe cases corticosteroids such as prednisone may be used to manage the inflammation. When corticosteroids are stopped abruptly, symptoms often return in full force, and thus they should be tapered off over 6 to 8 weeks. Thionamide antithyroid drugs are not appropriate in the treatment of this condition since the have minimal effect on preformed stores of thyroid hormone.

Painless (or silent or postpartum or lymphocytic) thyroiditis represents a major cause of hyperthyroidism (up to 15%) and occurs most commonly in women immediately after childbirth. The cause of this disease is not known and it runs the same triphasic course as painful thyroiditis. The typical symptoms of hyperthyroidism are present including lid lag, but not exophthalmos. The thyroid gland is diffusely enlarged, but not painful. Antithyroid antibodies and antimicrosomal antibody levels are elevated in more than 50% of patients. This form of thyroiditis is frequently occurs during the immediate postpartum period (3% to 5% of women in the United States) and patients may experience recurrences with subsequent pregnancies. Postpartum thyroiditis is now regarded as a form of Hashimoto's disease (see Hypothyroidism below), in which the immune system, quiescent during pregnancy, resumes a normal level of activity, resulting in a burst of thyrotoxicosis. Postpartum thyroiditis may be subclinical or produce only subtle clinical manifestations. Moreover, it lasts only a few weeks; indeed, it usually has resolved by the time the patient presents to her physician. If it is still present, thyroid function testing will show elevated thyroid hormone levels and a suppressed TSH level. After the thyrotoxicosis abates, the patient will be euthyroid for a few weeks. Then, because the thyroid has exhausted its store of hormone, hypothyroidism will ensue. In response, the TSH level begins to rise, and, in about a month, normal thyroid function is usually restored. Occasionally, the

hypothyroid phase may be prolonged by three to five months, but rarely is it permanent. Often, a beta-blocker such as propranolol is the only drug needed to control the symptoms during the period of hyperthyroidismand antithyroid drugs are ineffective. During the period of hypothyroidism, a person may need to take thyroid hormone, usually for no more than a few months. Hypothyroidism becomes permanent in about 10% of the people with silent lymphocytic thyroiditis.

Thyrotoxicosis caused by postpartum thyroiditis may be clinically identical to Graves' disease, which subsides during pregnancy and worsens immediately afterwards. Differentiating the two conditions obviously is important. The distinguishing feature is that in patients with Graves' disease, the thyroid actively produces hormone and so takes up radioiodine at three to five times the normal rate. In contrast, the thyroid releases hormone into the serum in patients with postpartum thyroiditis, and so radioiodine uptake is well below normal.

5. Thyrotoxicosis of Pregnancy

Thyrotoxicosis developing during pregnancy is usually due to Graves' disease, which is recognized by failure to gain weight and by other typical symptoms. Women with thyrotoxicosis often have scant menstrual periods or amenorrhea. It is important to distinguish the condition from early pregnancy. A condition that can mimic Graves' disease may occur in pregnant women with hyperemesis gravidarum. Placental human chorionic gonadotropin (hCG), whose levels normally increase during the first trimester, can functionally mimic TSH. The stimulation is not clinically evident except in women with hyperemesis gravidarum in whom the hCG level often is higher than usual. The free T_4 level may be elevated, but thyrotoxicosis usually does not occur, perhaps because the rise in T_4 is transient. The few women in whom mild thyrotoxicosis does occur generally do not require treatment because hyperemesis subsides spontaneously by the beginning of the second trimester.

Diagnosis of thyrotoxicosis is more difficult in pregnancy because some of its signs and symptoms mimic those of pregnancy (e. g., fatigue, heat intolerance, flushing, sweating, and tachycardia). Moreover, the total T_4 level normally rises above the upper limits of normal in early pregnancy; the increase is caused by an estrogen-induced rise in thyroid-binding globulin. Free T_4 and TSH levels remain normal, thereby verifying the patient's normal thyroid function. Diagnosis is even more difficult in women with hyperemesis gravidarum and abnormal thyroid function test results. Treatment of thyrotoxicosis in pregnant women is best left to physicians who are proficient in the management of thyroid disease.

Even mild thyrotoxicosis can prevent pregnancy. The more severe the thyrotoxicosis, the higher the likelihood of infertility. Since thyroid function tests (TSH and T_4) are a standard part of the infertility workup, patients with thyrotoxicosis are regularly identified. Such patients must be warned that while treatment for thyrotoxicosis can quickly restore fertility, becoming pregnant during treatment can be disastrous. A number of the medications cross the placenta, but radioiodine is particularly dangerous, since the fetal thyroid gland starts concentrating iodine at about 10 weeks.

6. Ectopic Thyroid Tissue: Struma Ovarii and Follicle Cancer

Struma ovarii is a teratoid tumor of the ovary that is capable of producing thyroid hormone. This is an extremely rare form of thyrotoxocosis and is evident by hyperthyroidism without thyroid gland enlargement and suppressed RAIU. The disease can be detected by whole body scanning with radioactive iodine. Both surgery and radioiodine therapy is required since the tissue is potentially malignant. It should be noted that not all cases of struma ovarii are associated with hyperthyroidism.

In metastatic follicular carcinoma with relatively preserved function sufficient thyroid hormone can be secreted to cause thyrotoxocosis. In most of these cases there was a previous diagnosis of thyroid malignancy. This disease is diagnosed with whole body radioiodine scanning and is treated with RAI.

7. Jod-Basedow Phenomenon/Iatrogenically-mediated Thyrotoxicosis

Jod-Basedow phenomenon is a form of iatrogenically-mediated thyrotoxicosis. The name combines the German word for iodine (jod) and a tribute to Karl Adolph von Basedow, a German contemporary of Robert Graves whose description of exophthalmic thyrotoxicosis may have preceded Graves' description. In some countries Graves' disease is known as Basedow's disease. Most patients with Jod-Basedow phenomenon have an asymptomatic multinodular goiter (see above). Thyrotoxicosis occurs a few weeks after a large dose of iodine is administered, typically in a contrast medium. In some patients, the free T_4, but not the free T_3 , level is elevated. Symptoms initially are subtle but become increasingly obvious. The thyrotoxicosis may be persistent or transient.

8. Exogenous Sources of Thyroid Hormone: Thyrotoxicosis factitia

Thyrotoxicosis factitia is the term used to describe hyperthyroidism resulting from the ingestion of thyroid hormone. Thyroid hormone is used for the treatment of hypothyroidism and non-toxic goiters, and also has been used for the treatment of non-thyroidal diseases including obesity (most common non-thyroidal use), menstrual irregularities, infertility, baldness, etc. When used for these conditions, excessive dosing of thyroid hormone can result in hyperthyroidism with many of the classic symptoms except for infiltrative ophthalmopathy or thyroid enlargement. In these patients RAIU will be low because the thyroid is suppressed by exogenous thyroid hormone. These patients may have low levels of thyroglobulin in the plasma (as opposed to higher thyroglobulin levels seen in thyroiditis). Thyrotoxicosis factitia is treated by dose reduction or termination and monitoring of TFTs within 4-6 weeks. Drugs such as amiodarone may induce hyperthyroidism or hypothyroidism. This drug has multiple and complex effects on the thyroid gland and thyroid hormone biosynthesis (see Drug Section)

9. Thyrotoxicosis in the Elderly

Thyrotoxicosis in the elderly manifests differently than in younger patients. Unlike Graves' disease, which waxes and wanes, multinodular goiter (Plummer's disease) in elderly patients progresses inexorably, for years or even decades, until florid thyrotoxicosis appears. Some investigators believe that thyrotoxicosis will develop in all patients with multinodular goiter if

they live long enough. When thyrotoxicosis occurs in the elderly, there is a long asymptomatic phase during which osteoporosis and cardiac abnormalities can develop unnoticed. The goiter itself may not be obvious on physical examination, especially when most of it is behind the sternum. When symptoms finally emerge, they may be limited to weight loss and heart failure complicated by atrial fibrillation, but may also include worsening congestive heart failure, anginal syndrome, proximal muscle myopathy and a peculiar form of delirium referred to "apathetic thyrotoxicosis". Apathetic thyrotoxicosis may occur in young patients but is more typical among those in their late 60s and 70s, especially women. In contrast to the dramatic symptoms seen in middle-aged thyrotoxic patients, elderly patients with apathetic thyrotoxicosis waste away over a period of months. The family often assumes that they are "fading" in preparation for death. In fact, apathetic thyrotoxicosis can be reversed completely with treatment. Thyroid function tests should be performed in all patients with apparent dementia.

The symptoms of hypermetabolism that are frequently present in younger patients (e. g., heat intolerance, nervousness, and tremor) occur in less than 20% of patients 75 to 95 years old. Physical signs common in young patients, including skin vibration, heart rate greater than 100 bpm, hyperreflexia, and lid lag, also occur in very few of the elderly. However, 33% of patients have atrial fibrillation, and an abnormal thyroid is only 32%. In older patients without symptoms and signs suggestive of hyperthyroidism and palpable thyroid abnormalities, only periodic screening of thyroid function will lead to the diagnosis.

Thyrotoxicosis resulting from multinodular goiter may be difficult to treat. First, the gland may be somewhat resistant to radioiodine therapy. Second, radioiodine therapy causes some radiation-induced thyroiditis, which can temporarily exacerbate an elderly patient's condition at a time when he or she is already quite ill.

10. Neonatal Hyperthyroidism

Some neonates may be hyperthyroid due to placental transfer of thyroid-stimulating antibodies which stimulates thyroid hormone production in utero and postpartum. Obviously, in these cases, the mother had high thyroid-stimulating antibody titers. The symptoms of neonatal hyperthyroidism typically appear within 7-10 days postpartum. Treatment with antithyroid thionamides (PTU or MMI) for 8-12 weeks is recommended – treatment must persist until the antibodies are cleared. Iodide salts may be used initially in therapy to acutely inhibit thyroid hormone release.

11. Thyrotoxic Crisis/Thyroid Storm

Thyroid storm is a relatively rare but life threatening worsening symptoms of thyrotoxicosis. While this condition may develop spontaneously it typically occurs in those with undiagnosed or only partially treated severe hyperthyroidism and have been subjected to excessive stress from infection, cardiovascular or pulmonary disease, dialysis or inadequate preparation for thyroid surgery. The symptoms include hyperthermia, tachycardia (especially atrial tachycardia) heart failure, agitation and delirium, dehydration and GI effects including nausea and vomiting and diarrhea. Treatment involves 1). Suppression of thyroid hormone synthesis and secretion with thionamides in high doses (particularly PTU), 2). anti-adrenergic therapy (IV beta-blockers) to block sympathetic actions of hyperthyroidism, 3). corticosteriods for high temperature and

stabilizing blood pressure (and possible adrenocorticoid insufficiency), and 4). treatment of associated complications or coexisting factors that may have precipitated the storm. Aspirin or NSAIDs should not be used for fever since these drugs displace protein bound thyroid hormone and may enhance hypothyroidism.

C. Screening for Hyperthyroidism and Thyroid Function Tests

The diagnosis of thyroid disease may be complicated because patients often present with vague, general clinical manifestations; in particular, the elderly may not associate the signs and symptoms with a disease process and bring them to the attention of their primary care provider. It has been suggested that patients should be screened for thyroid disorders with laboratory tests during routine clinic visits. The primary benefit of routine screening with thyroid function tests is relief of symptoms and improved quality of life. Another benefit is the potential abatement of progression to more serious consequences, such as atrial fibrillation and osteoporosis (in the case of subclinical hyperthyroidism) and hyperlipidemia (in the case of subclinical hypothyroidism). However, the issue of routine screening is controversial because, given the overall low incidence of thyroid disorders, the cost-effectiveness has not been clearly proven. Also, despite improved estimates of risk for other patient populations, the evidence that other groups benefit from early detection and treatment is still unclear. Possible groups to screen include:

- Women older than 50 years of age for unsuspected but symptomatic thyroid disease" with a sensitive thyrotropin (TSH) test.
- Neonates are routinely screened for congenital hypothyroidism, which undetected can lead to mental retardation.
- Pregnant women may be screened for thyroid disease to protect the outcome of the pregnancy and health of the fetus and neonate from the ill effects of uncontrolled hyperthyroidism (hypothyroidism during pregnancy is uncommon).

It is important to emphasize that hyperthyroidism/thyrotoxicosis should be diagnosed by measuring thyroid hormone and TSH levels. Radioiodine uptake studies, such as the RAIU scan, should not be used for initial documentation of thyrotoxicosis. They are expensive and unnecessary and may provide misleading results; for example, uptake may be normal despite the presence of hyperthyroidism. Such studies should only be used to determine the **cause** of thyrotoxicosis after thyroid function tests (TH and TSH) and clinical symptoms have established the diagnosis. RAIU can be very useful to identify thyroiditis, toxic multinodular goiter (Plummer's disease), etc.

After acknowledging that serum tests should be used to establish the diagnosis of thyrotox-icosis, the next question is which tests? T_4 is the principal secretory product of the thyroid, constituting about 90% of its hormonal output. Only about 10% of T_3 in the body is secreted by the thyroid gland; the remainder is derived by deiodination of T_4 in various tissues. Since the activity of the deiodinase enzymes involved in T_3 production may be affected by conditions unrelated to thyroid dysfunction, the serum T_3 level is not a very reliable indicator of thyroid status. Hence, status is best defined by measurements of T_3 rather than T_3. Thyroid hormones are tightly bound to plasma proteins, and the free rather than the bound T_4 reflects thyroidal status, so the free T_4 measurement is recommended.

Measurement of the TSH level in addition to the free T_4 level greatly enhances diagnostic

sensitivity. The negative feedback between free thyroid hormone concentrations and TSH secretion is very sensitively regulated; as little as a 20% increase in free T_4 may result in suppression of TSH secretion to undetectable levels as illustrated in subclinical hyperthyroidism. In this situation, although TSH is suppressed, serum levels of both free T_4 and free T_3 may be within the normal range, indicating that they were at least 20% lower before the patient's thyroid began to hypersecrete thyroid hormone. As thyroid hormone secretion progressively increases, the serum free T_4 level will rise above the normal range, and symptomatic hypermetabolism will develop.

Because multinodular goiter is one of the most common thyroid abnormalities, and iodinated contrast agents are widely used, iodide-induced hyperthyroidism may occur frequently. Indeed, it probably occurs more frequently than reported because these patients come for medical attention only when hypermetabolic symptoms develop, or atrial fibrillation occurs shortly after the diagnostic study is performed. Thus it is recommended serum free T_4 and TSH levels be measured several weeks after patients with thyroid nodules undergo any study involving iodinated contrast agents.

IV. HYPOTHYROIDISM (Myxedema)

A. Causes, Symptoms and Thyroid Function Tests

Decreased thyroid hormone synthesis and low levels of circulating thyroid hormones result in biochemical and/or clinical hypothyroidism. This condition occurs more frequently in women; the overall incidence is about 3% of the general population. The clinical presentation, particularly in elderly patients, may be subtle; therefore, routine screening of thyroid function tests is generally recommended for women more than 50 years of age. Hypothyroidism is classified as primary or secondary. Primary hypothyroidism results from 1). defective hormone biosynthesis resulting from Hashimoto's or autoimmune thyroiditis (most common), other forms of thyroiditis (acute thyroditis, subacute thyroiditis), endemic iodine deficiency, or antithyroid drug therapy (goitrous hypothyroidism); and 2). congenital defects or loss of functional thyroid tissue due to treatment for hyperthyroidism including radioactive iodine therapy or surgical resection of the thyroid gland.

In primary hypothyroidism the loss of thyroid function/tissue results in increased TSH secretion which promotes goiter formation. Secondary hypothyroidism may be caused by: 1). Insufficient stimulation of the thyroid from hypothalamic (decreased TRH secretion) or pituitary (decreased TSH secretion) disease, or 2). Peripheral resistance to thyroid hormones. Hypothyroidism secondary to pituitary or hypothalamic failure is relatively uncommon; most patients have clinical signs of generalized pituitary failure. The most common causes of secondary hypothyroidism are postpartum pituitary necrosis and pituitary tumor. The various sub-types of hypothyroidism are listed in Table 4 and discussed in more detail in subsequent sections.

Table 4. Types and Causes Hypothyroidism

Primary Hypothyroidism: Thyroid gland failure	
• Hashimoto's Disease	➔ Autoimmune destruction (acquired)
• Iatrogenic Hypothyroidism i.e Thyroid ablation (surgery/RAI in Graves' and radiation for head/neck cancer)	➔ Diminished TH synthesis/release
• Others: Iodine deficiency, Enzyme defects, Thyroid hypoplasia, Goitrogens	➔ Diminished TH synthesis/release:
Secondary Hypothyroidism	
• Pituitary Disease	➔ Deficient TSH secretion
• Hypothalamic Disease	➔ Deficient TRH secretion:
Hypothyroidism: Special Conditions	
• Myxedema Coma	➔ End-stage hypothyroidism
• Congenital Hypothyroidism	➔ Aplasia or hypoplasia of thyroid gland in infants and children
• Hypothyroidism in Pregnancy	➔ Defects in TH synthesis/action leading to impaired fetal development
• Hypothyroidism and Other Medications	➔ Disease may alter the kinetics of drugs used for other disease states

Hypothyroidism involves every organ in the body and so can produce dozens of signs and symptoms, many of which mimic those of other diseases (Table 5). Furthermore, a variety of factors can influence the presentation of hypothyroidism. Prominent among these are disease stage, severity and the patient's age. Recognition of the hypothyroidism is important not only because current treatments are very effective, especially if the diagnosis is made at an early stage, but also because lack of recognition has potentially disastrous consequences. Unless treated, the condition may progress from a biochemical abnormality (an elevated TSH level) to an irreversible structural change resulting in pleural or pericardial effusions or CAD.

Clinically, hypothyroid patients present with complaints of one or more of the following: fatigue, weakness, lethargy, cold intolerance, dry/coarse/cold skin, coarse hair, periorbital puffiness, hoarseness, constipation, weight gain, joint pain, muscle cramps and stiffness, mental impairment, depression, and menstrual disturbances. Upon examination, the patient may also have bradycardia, prolonged relaxation of deep-tendon reflexes, and hypercholesterolemia. Patients with low thyroid hormone levels have increased serum thyrotropin (TSH) levels because of the negative feedback relationship between the different hormones. Therefore, the results of the thyroid function tests for overt hypothyroidism are characterized by a low T_4 serum level and an elevated thyrotropin (TSH) serum level.

Table 5. Clinical and Laboratory Findings of Primary Hypothyroidism

Symptoms	**Physical Findings**	**TFTs**
- General: Weakness, lethargy and fatigue - Muscle cramps, aches and pains - Cold intolerance - Headache - Loss of taste/smell - Deafness - Hoarseness - No sweating - Modest weight gain - Dyspnea - Slow speech - Constipation - Menorrhagia - Galactorrhea	- Thin, brittle nails - Thinning of skin - Pallor - Puffiness of face and eyelids - Yellowing of skin - Thinning of outer eyebrows - Thickening of the tongue - Peripheral edema - Effusions: Pleural, peritoneal or pericardial - Decreased deep tendon reflexes - Goiter - CV: Hypertension, bradycardia, "myxedema heart"	- Increased TSH - Decreased TH levels including T_4, FT_4I, FT_4, TT_3, FT_3I - Antibodies (Hashimoto's) - RAIU: <10% - Increased cholesterol, CPK, LDH, AST - Decreased Na, Hct/Hgb

1. Hashimoto's Thyroiditis

Hashimoto's thyroiditis (autoimmune thyroiditis) is the most common type of thyroiditis and the most common cause of hypothyroidism. In 1912, Hakaru Hashimoto, a Japanese physician, described four women whose thyroid glands were enlarged and appeared to have been converted into lymphoid tissue. Although the women were not initially hypothyroid, they became so following thyroid surgery. Nearly 50 years later, the presence of antithyroid antibodies in patients with this disease was reported in the literature. Hashimoto's disease, or Hashimoto's thyroiditis, has since been characterized as a form of chronic autoimmune thyroiditis. For unknown reasons, the body initiates an autoimmune reaction, creating antibodies that attack the thyroid gland; T lymphocytes directed against normal antigens on the thyroid membrane probably interact with thyroid cell-membrane antigens, which leads to activation of B lymphocytes to produce antibodies. Thyroid peroxidase antibodies, which lead to cellular changes in the thyroid gland, are also found in almost all patients with Hashimoto's thyroiditis. Hashimoto's thyroiditis patients may develop a goiter or have thyroid atrophy. Patients with goiter may have antibodies that stimulate thyroid growth, whereas patients with an atrophic thyroid have antibodies that inhibit the trophic effects of TSH on the gland. Approximately 40% of women and 20% of men in the United States have some evidence of focal thyroiditis at autopsy. When more extensive thyroid involvement is used as a diagnostic criterion, the incidence of disease is 15% in women and 5% in men. Hashimoto's disease is more likely to occur in people with certain chromosomal abnormalities, including Turner's, Down, and Klinefelter's syndromes and tends to run in families. Also, many people with Hashimoto's thyroiditis have other endocrine disorders such as diabetes, an underactive adrenal gland, or underactive parathyroid glands, and other autoimmune diseases such as pernicious anemia, rheumatoid arthritis, Sjögren's syndrome, or systemic lupus erythematosus (lupus).

Hashimoto's thyroiditis often begins with a painless enlargement of the thyroid gland or a feeling of fullness in the neck. When doctors feel the gland, they usually find it enlarged, with a rubbery texture, but not tender; sometimes it feels lumpy. The thyroid gland is underactive in about 20 percent of the people when Hashimoto's thyroiditis is discovered; the rest have normal thyroid function. Thyroid function tests are performed to determine whether the gland is functioning normally, but the diagnosis of Hashimoto's thyroiditis is based on the symptoms, a physical examination, and the presence of antithyroid antibodies. No specific treatment is available for Hashimoto's thyroiditis. Most people eventually develop hypothyroidism and must take thyroid hormone replacement therapy for the rest of their lives. Thyroid hormone may also be useful in decreasing the enlarged thyroid gland.

2. Acute and Subacute Thyroiditis

Acute thyroiditis is caused by a bacterial infection of the thyroid gland and is a relatively rare disorder. Subacute thyroiditis is a non-bacterial inflammation of the thyroid often preceded by a viral infection as described earlier. These diseases state may have been preceded by hyperthyroidism (see hyperthyroidism section above) where the patient experiences fever and tenderness and enlargement of the thyroid gland. The hypothyroidism of these disease states results from inflammation secondary to infiltration of the gland by lymphocytes and leukoctyes. In most cases this form of hypothyroidism is transient and symptoms typically resolve within for 2-4 months. During this time patients may be treated with corticosteroids. Occasionally there may be sufficient injury to the thyroid gland to produce permanent hypothyroidism.

3. Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism is results from thyroid surgery, exposure of the thyroid to external radiation for neck carcinomas or from RAI to treat Grave’s disease. Typically hypothyroidism occurs within 1 month following total thyroidectomy, and within 1 year (sometimes in months) after RAI therapy for Grave’s disease.

4. Iodine Deficiency, Thyroid Enzyme Defects, Thyroid hypoplasia and Goitrogens

In adults, iodine deficiency or excess, and the ingestion of goitrogens may cause hypothyroidism on rare occasions by decreasing thyroid hormone synthesis or release. Iodine deficiency, thyroid enzyme defects, thyroid hypoplasia and goitrogens may cause thyroid hormone deficiency in a developing fetus, resulting in cretinism. This is discussed more in the following section.

5. Congenital Hypothyroidism

Congenital hypothyroidism (cretinism), a form of primary hypothyroidism, occurs in infants as a result of the absence of thyroid tissue (thyroid dysgenesis) and/or hereditary defects in thyroid hormone biosynthesis. Thyroid dysgenesis occurs more commonly in female infants and permanent abnormalities occur in 1 of every 4000 infants. Thyroid hormones are required for embryonic growth, particularly the growth of nerve tissue. Thus hypothyroid infants develop mental retardation due to poor development of synapses and poor myelination. In children, congenital hypothyroidism causes slowed bone growth and delayed skeletal maturation; growth hormone from the pituitary is depressed. Hypothyroidism also may occur in the neonate if the

mother ingests goitrogens (eg, cabbage or turnips) that inhibit normal feedback mechanisms for regulating thyroid hormone levels, or if the mother becomes hypothyroid through over-treatment with thionamides. The extent to which thionamide therapy is responsible for hypothyroidism in the fetus or neonate is controversial. If hypothyroidism is treated within 3 months of birth, cretinism is unlikely to occur. The primary therapy involves levothyroxine replacement therapy.

6. Hypothyroidism in Pregnancy

Hypothyroidism in pregnancy leads to an increase rate of stillbirths and possibly lower psychological and IQ scores in infants born to hypothyroid mothers. Thyroid hormone is required for fetal growth and must be obtained from the mother during the first two months of gestation. Hypothyroid mothers should be treated with levothyroxine to decrease TSH levels to I uU/mL and maintain free T_4 levels in the normal range. Typically higher doses of levothyroxine (increased by 36 ug/day) are required to maintain this level of euthyroidism during pregnancy due to 1). Increased production of thyroid hormone binding proteins, 2). Modification of peripheral thyroid hormone metabolism, and 3). Increased thyroid hormone metabolism by the fetal-placental unit.

7. Myxedema Coma

Myxedema coma is a rare consequence of untreated, longstanding hypothyroidism that may be caused by thyroid surgery, radiation therapy to thyroid gland, Hashimoto's thyroiditis, hypopituitarism. It is characterized by the classic symptoms of hypothyroidism (slowing of physical and mental activity, fatigue, apathy that mimics depression, slowed speech, cold intolerance, shortness of breath, decreased sweating, constipation, cool skin) but is a life-threatening condition due to associated hypothermia, bradycardia, respiratory failure, and cardiovascular collapse, delirium and coma. Patients should be treated immediately in the intensive care unit with intravenous levothyroxine, corticosteroids, and other supportive measures (ventilation, blood pressure, blood sugar, body temperature, etc.) to avoid mortality (60-70% mortality). Corticosteroids such as intravenous hydrocortisone (100 mg every 8 hrs) are given until coexisting adrenal suppression can be ruled out. Myxedema is characterized by low free T_3/T_4 and a high TSH (TSH not high in secondary hypothyroidism).

8. Secondary Hypothyroidism

Pituitary insufficiency or failure may be caused by pituitary tumors, metastatic tumors, infections, autoimmune diseases, surgery, radiation, postpartum pituitary necrosis (Sheehan's syndrome). In most of these cases, TSH deficiency will be accompanied with deficiencies of other pituitary hormones as well. In most hypothyroid patients with pituitary disease serum TSH levels are low or normal. Hypothalamic hypothyroidism is characterized by reduced TRH production and is very rare. It may be caused by comparable disease states.

C. Thyroid Function Testing for Hypothyroidism

The majority of hypothyroidism cases result from primary thyroid failure. The pituitary gland responds to that failure by secreting more TSH, raising serum TSH levels to 10 to 15 µU/mL well before there is a detectable decline in circulating thyroid hormones T_4 and tri-iodothyronine (T_3). Thus, elevated TSH level is the earliest and most definitive indicator of hypothyroidism. As thyroid failure progresses, T_4 and T_3 levels eventually become very low or even undetectable, and the TSH level increases to 100 µU/mL or more.

If the patient has obvious thyroid dysfunction, the free T_4 level should be measured in addition to the TSH level. Measuring the total T_4 level may not be necessary since its results are difficult to interpret; for example total T_4 consists largely of hormone that is bound to serum proteins or whose levels can be altered by drugs or nonthyroidal illness. Measurements of serum T_3 levels likewise have little diagnostic value because they can be lowered by so many other conditions, including aging, other illnesses, weight loss, and a number of drugs.

Low or normal TSH and free T_4 levels rule out hypothyroidism unless the patient has symptoms consistent with diminished pituitary function, in which case testing for hypopituitarism is indicated. Pituitary failure should be suspected when there are signs of gonadal dysfunction (e.g., cessation of menses), adrenal insufficiency (weight loss, nausea, diarrhea, postural hypotension), and hypothyroidism (a low TSH level).

If the TSH level is elevated, free T_4 levels should be determined. A low T_4 indicates hypothyroidism. A high TSH and normal T_4 indicate subclinical hypothyroidism and mandates testing for antithyroid antibodies; these patients may have no clinical signs of hypothyroidism. A TSH level greater than about 15 µU/mL or an antithyroid antibody titer greater than 1:1,500 (or a recent history of exposure to radioactive iodine or thyroid surgery) points to impending overt hypothyroidism. A TSH level of less than 15 µU/mL and an antibody titer of less than 1:1,500 in an asymptomatic patient is inconclusive. The TSH level should be measured again after six months, although one can opt for treatment if the patient has begun to experience symptoms.

Parenthetically, it should be noted that chronic severe thyroid hormone deprivation may lead to pituitary hyperplasia. In such cases, patients may have extremely high TSH levels (>100 µU/mL) and often an elevated prolactin level, which may result in galactorrhea. If the pituitary grows large enough, the optic nerve may be compressed.

Radioactive iodine uptake has limited applicability in hypothyroidism. Recall that thyroidal radioiodine uptake merely measures the activity of the thyroid gland's iodine pump, which responds to TSH by pulling iodine out of the blood and into the gland. Thyroid hormone synthesis may be impaired even though the iodine pump is responding normally, or even excessively, to TSH. Consequently, in patients with hypothyroidism uptake of radioiodine may be low, normal, or high. The radioiodine uptake test is most helpful when one suspects reversible hypothyroidism (e.g., Hashimoto's disease) or when certain forms of thyroiditis (postpartum, silent, or subacute) are suspected. Those disorders have a phase of transient hypothyroidism during which radioiodine uptake is normal or high (the opposite occurs with hyperthyroidism).
Measurement of free T_4 and TSH levels will not only confirm or eliminate the diagnosis of hypothyroidism, but will also provide insight into anatomic etiology. When the free T_4 level is

decreased and the TSH level increased, a diagnosis of hypothyroidism caused by thyroid disease is confirmed. If free T_4 is decreased and TSH is decreased or within the normal range, hypothyroidism caused by hypothalamic-pituitary disease is established. Many physicians do not know that the serum TSH level remains normal in about 50% of patients with hypothalamic-pituitary disease, probably because of minimal production of inadequately glycosylated TSH molecules that persist in the circulation but have no biologic activity.

V. THYROID NODULES AND GOITERS

A. Thyroid Nodules: Introduction

Simply put, thyroid nodules are "lumps" that commonly arise within an otherwise normal thyroid gland. Often these abnormal growths of thyroid tissue are located at the edge of the thyroid gland so they can be felt as a lump in the throat. When they are large or when they occur in very thin individuals, they can even sometimes be seen as a lump in the front of the neck. One in 12 to 15 women has a thyroid nodule while only one in 40 to 50 men have a thyroid nodule. More than 90% of all thyroid nodules are benign (non-cancerous growths). Some are actually cysts that are filled with fluid rather than thyroid tissue

Thyroid nodules increase with age and are present in almost ten percent of the adult population. Autopsy studies reveal the presence of thyroid nodules in 50% of the population, so they are fairly common. Ninety-five percent of solitary thyroid nodules are benign, and therefore, only five percent of thyroid nodules are malignant. Common types of the benign thyroid nodules are adenomas (overgrowths of "normal" thyroid tissue), thyroid cysts, and Hashimoto's thyroiditis. Uncommon types of benign thyroid nodules are due to subacute thyroiditis, painless thyroiditis, unilateral lobe agenesis, or Riedel's struma. Those few nodules which are cancerous are usually due to the most common types of thyroid cancers which are the differentiated" thyroid cancers. Papillary carcinoma accounts for 60%, follicular carcinoma accounts for 12%, and the follicular variant of papillary carcinoma accounting for 6%. These well-differentiated thyroid cancers are usually curable, but they must be found first.

Thyroid cancers typically present as a dominant solitary thyroid nodule that can be felt by the patient or even seen as a lump in the neck by his/her family and friends. It is important to differentiate benign nodules from cancerous solitary thyroid nodules. While history, physical examination, laboratory tests, ultrasound, and thyroid scans (see below) can all provide information regarding a solitary thyroid nodule, the only test that can differentiate benign from cancerous thyroid nodules is a biopsy. Thyroid tissues are easily accessible to needles, so rather than operating to remove a portion of the tissue, a very small needle can be used to remove cells for microscopic examination. This method of biopsy is called a fine needle aspiration biopsy, or "FNA".

The evaluation of a solitary thyroid nodule should always include history and examination. Certain aspects of the history and physical exam will suggest a benign or malignant condition as indicated in the Table below. However, a biopsy of some sort is the only way to know for sure. Thyroid hormone levels are usually normal in the presence of a nodule (unless "hot"), and normal thyroid hormone levels do not differentiate benign from cancerous nodules. But the presence of hyperthyroidism or hypothyroidism favors a benign nodule (that's why a "warm" nodule or a

"hot" nodule favors a benign condition). Thyroglobulin levels are useful tumor markers once the diagnosis of malignancy has been made, but are nonspecific in regard to differentiating a benign from a cancerous thyroid nodule. Ultrasound accurately determines thyroid gland volume, number and size of nodules; separates thyroid from nonthyroidal masses; helps guide fine needle biopsy when necessary; and can identify solid nodules as small as 3 mm and cystic nodules as small as 2 mm. Although several ultrasound features favor the presence of a benign nodule, and other ultrasound features favor the presence of a cancerous nodule. Ultrasound alone cannot be used to differentiate benign from malignant nodules. And since 15 percent of cystic thyroid nodules are malignant, ultrasound determination that a nodule is cystic does not rule out thyroid cancer (Table 6).

Table 6. Features favoring benign versus malignant nodules

Features favoring a benign thyroid nodule	**Features increasing the suspicion of a malignant nodule:**
• family history of Hashimoto's thyroiditis • family history of benign thyroid nodule or goiter • symptoms of hyperthyroidism or hypothyroidism • pain or tenderness associated with a nodule • a soft, smooth, mobile nodule • multinodular goiter without a predominant nodule (lots of nodules, not one main nodule) • "warm" nodule on thyroid scan (produces normal amount of hormone) • simple cyst on ultrasound	• age less than 20 • age greater than 70 • male gender • new onset of swallowing difficulties • new onset of hoarseness • history of external neck irradiation during childhood • firm, irregular and fixed nodule • presence of cervical lymphadenopathy (swollen hard lymph nodes in the neck) • previous history of thyroid cancer • nodule that is "cold" on scan (the nodule does not make hormone) • solid or complex on ultrasound

Ionizing radiation has been known for a number of years to be associated with a small increased risk of developing thyroid cancer. There is typically a delay of 20 years or more between radiation exposure and the development of thyroid cancer. Radiation was used occasionally between the 1920's and 1950's to treat certain neck infections such as recurrent tonsillitis as well as certain skin conditions such as severe acne. In July 1997 the U.S. government announced that nuclear weapons testing in the Southeast U.S. from 1945 through the 1970's would likely increase the amount of thyroid cancers seen in Americans over the next several decades. The risks are substantially greater for those patients living nearby the test sites for many years. Fortunately these cancers will likely be of the well differentiated type which have an excellent prognosis; the vast majority of these can be cured. There is no evidence that children are at increased risk of developing thyroid cancer, the small increase risk appears to be limited to those that were directly exposed in the past. Despite these increased risks, thyroid cancer is still relatively uncommon and usually curable.

B. Symptoms and Diagnosis of Thyroid Nodules

Most thyroid nodules cause no symptoms at all. Nodules are usually found by patients who feel a lump in their throat or see it in the mirror. Occasionally, a family member, friend or physician will notice a strange lump in the neck of someone with a thyroid nodule. Occasionally, nodules may cause pain, and even rarer still are those patients who complain of difficulty swallowing when a nodule is large enough and positioned in such a way that it impedes the normal passage of food through the esophagus (which lies behind the trachea and thyroid).

Three questions that should be answered about all thyroid nodules: 1). Is the nodule one of the few that are cancerous? 2). Is the nodule causing trouble by pressing on other structures in the neck ? 3). Is the nodule making too much thyroid hormone? After an appropriate work-up, if any of the above questions are answered "yes", then medical or surgical treatment is required. However, most thyroid nodules will yield an answer of "no" to all of the above questions. In this most common situation, there is a small to moderate sized nodule that is simply an overgrowth of "normal" thyroid tissue, or even a sign that there is too little hormone being produced. Patients with a diffusely enlarged thyroid (called a goiter) will present with what is perceived at first to be a nodule, but later found to be only one of many benign enlarged growths within the thyroid. Thyroid nodules are evaluated by fine needle aspiration biopsy (FNA), radioiodine uptake, ultrasound examination and as described below.

Using RAI and other methods, nodules are classified as cold, hot or warm. If a nodule is composed of cells which do not make thyroid hormone (don't absorb iodine) then it will appear "cold" on the x-ray film after RAI administration. A nodule which is over-producing thyroid hormone will show up darker and is called "hot". Eighty-five percent of thyroid nodules are cold, 10% are warm, and 5% are hot. Also, that 85% of cold nodules are benign, 90% of warm nodules are benign, and 95% of hot nodules are benign. Although thyroid scanning can give a probability that a nodule is benign or malignant, it cannot truly differentiate benign or malignant nodules and usually should not be used as the only basis for recommending treatment of the nodule, including thyroid surgery.

The ultrasound test is quick, accurate, cheap, painless, and completely safe, and thus is routinely performed. This test usually takes only about 10 minutes and the results can be known almost immediately. This simple test uses sound waves to image the thyroid. The sound waves are emitted from a small hand-held transducer that is passed over the thyroid. As sound waves hit structures they bounce back like an echo. The probe detects these reflections to make a "sonogram". This test will usually determine if a nodule has a low chance of being cancer (has characteristics of a benign nodule), or that it has some characteristics of a cancerous nodule and therefore should be biopsied. While the ultrasound alone cannot differentiate between benign or cancerous nodules, but generally benign nodules will have the following characteristics:

- Nice sharp edges are seen all around the nodule
- Nodule filled with fluid and not live tissue (a cyst)
- Lots of nodules throughout the thyroid (almost always a benign multi-nodular goiter)
- No blood flowing through it (not live tissue, likely a cyst).
- Complex nodule with some portions being cystic and others contain live nodular tissue.

Thyroid fine needle aspiration (FNA) is the first, and in the vast majority of cases, the only test required for the evaluation of a solitary thyroid nodule, other than a TSH and T_4 determination.

Thyroid ultrasound and thyroid scans are usually not required for evaluation of a solitary thyroid nodule. FNA biopsy is the only non-surgical method that can differentiate malignant and benign nodules in most, but not all, cases. The FNA procedure is very simple, takes less than 30 seconds, is virtually pain free, and can be very accurate. In this test, a very small needle is passed into the nodule and some cells are aspirated .The cells are placed on a microscope slide, stained, and examined by a pathologist. The nodule is then classified as nondiagnostic, benign, suspicious or malignant:

- Nondiagnostic indicates that there are an insufficient number of thyroid cells in the aspirate and no diagnosis is possible. A nondiagnostic aspirate should be repeated, as a diagnostic aspirate will be obtained approximately 50% of the time when the aspirate is repeated. Overall, five to 10% of biopsies are nondiagnostic, and the patient should then undergo either an ultrasound or a thyroid scan for further evaluation.

- Benign thyroid aspirations are the most common and consist of benign follicular epithelium with a variable amount of thyroid hormone protein (colloid).

- Malignant thyroid aspirations can diagnose the following thyroid cancer types: papillary, follicular variant of papillary, medullary, anaplastic, thyroid lymphoma, and metastases to the thyroid. Follicular carcinoma and Hurthle cell carcinoma cannot be diagnosed by FNA biopsy. This is an important point. Since benign follicular adenomas cannot be differentiated from follicular cancer (~12% of all thyroid cancers) these patients often end up needing a formal surgical biopsy, which usually entails removal of the thyroid lobe which harbors the nodule.

- Suspicious cytologies make up approximately 10% of FNA's. The thyroid cells on these aspirates are neither clearly benign nor malignant. Twenty five percent of suspicious lesions are found to be malignant when these patients undergo thyroid surgery. These are usually follicular or Hurthle cell cancers. Therefore, surgery is recommended for the treatment of thyroid nodules from which a suspicious aspiration has been obtained.

Treatment of nodules depends on the clinical situation. For example, "hot" nodules may suppress the other lobe of the thyroid so that there is no excess production of thyroid hormone and no therapy other than monitoring is required. However, in a toxic "hot" nodule where the rest of the gland is not suppressed and the patient will be hyperthyroid and require therapy. In this case surgery or RAI ablation is preferred; antithyroid drugs would not 'resolve" the thyroid problem. If the nodule is "cold" and benign, no therapy beyond continued monitoring is required, although some recommend thyroxine suppressive therapy may be used to shrink the nodule (although this approach has been only marginally successful). If the "cold" nodule is cancerous or "suspicious" upon pathologic examination, surgery is recommended.

C. Goiters

The term nontoxic goiter refers to enlargement of the thyroid that is not associated with overproduction of thyroid hormone or malignancy. The normal thyroid gland resides in the neck, with both lobes wrapping gently around the trachea. When thyroid becomes enlarged (goiter), it can grow a number of different directions. Usually, they will grow within the neck and can become very large so that it can easily be seen as a mass in the neck. Less commonly, a thyroid will grow down the trachea into the chest. This can become a more significant problem since the chest is surrounded by a very rigid bone structure (the chest cavity including ribs, spinal column, clavicles, and sternum. When an enlarged thyroid grows within the chest region it can compress the soft tissue structures trachea, lungs, and blood vessels. This is why the presence of a sub-sternal goiter requires special attention. A chest x-ray or CT scan can reveal displacement in the position of the trachea or esophagus in the presence of a sub-sternal goiter, as well as compression of the lungs.

There are a number of factors that may cause the thyroid to become enlarged. A diet deficient in iodine can cause a goiter but this is rarely the cause in the US these days because of the readily available iodine in our diets. A more common cause of goiter in the US is an increase in thyroid stimulating hormone (TSH) in response to a defect in normal hormone synthesis within the thyroid gland. This enlargement usually takes many years to become manifest.

Most small to moderate sized goiters can be treated with thyroid hormone. Thyroid hormone therapy results in suppression of the pituitary so that less TSH is released and this may result in stabilization in size of the gland. This technique often will not cause the size of the goiter to decrease but will usually keep it from growing any larger. Patients who do not respond to thyroid hormone therapy are often referred for surgery if it continues to grow.

In larger neck or substernal goiters, the enlarged gland may compress the trachea and esophagus leading to symptoms such as changes in voice, coughing, waking up from sleep with compromised breathing, and the sensation that food is getting stuck in the upper throat. The enlarged gland can even compress the blood vessels of the neck. Once a goiter grows to the point of obstructing these structures, surgical removal is the only means to relieve the symptoms. Interestingly, it is a misconception that all sub-sternal thyroids require that the sternum be split to allow it to be removed. In fact, this is extremely rare. Essentially all sub-sternal thyroids can be removed through a conventional thyroid neck incision.

Suspicion of malignancy in an enlarged thyroid is an indication for removal of the thyroid. There is often a dominant nodule within a multinodular goiter which can cause concern for cancer. It should be remembered that the incidence of malignancy within a multinodular goiter is usually significantly less than 5%. If the nodule is cold on thyroid scanning, then it may be slightly higher than this. For the vast majority of patients, surgical removal of a goiter for fear of cancer is not warranted. A less common reason to remove a goiter is for cosmetic reasons. Often a goiter gets large enough that it can be seen as a mass in the neck and it may not cause symptoms of obstruction or hyper- or hypothyroidism. The surgical procedures performed on thyroid nodules and goiters are described in more detail in the "Thyroid Surgery" Tutorial.

VI. THYROID CARCINOMA

Thyroid carcinoma is relatively rare (ca. 16,000 cases annually), but is the most common endocrine malignancy. While the causes of this form of cancer are not precisely understood, it is known that iodine deficiency, long-term use of goitrogenic drugs and exposure to ionizing radiation are risk factors for thyroid hyperplasia and ultimately malignancy. Thyroid carcinoma may be discovered as a small thyroid nodule or a metastatic tumor arising from lung, brain or bone cancer. Most individuals with thyroid carcinoma have normal thyroid hormone levels (are euthyroid). This cancer is detected by changes in the voice or swallowing due to tumor growth impinging on the trachea or esophagus. Treatment for thyroid carcinoma remains controversial but may involve partial or total thyroidectomy, TSH suppression therapy with levothyroxine, or radioactive iodine therapy (iodine concentrating tumors). Post-operative radiation therapy and chemotherapy also may be employed. More information on this subject is available in the "Thyroid Cancer" Tutorial.

VII. EUTHYROID SICK SYNDROME

In the euthyroid sick syndrome (or "sick euthyroid syndrome"), thyroid tests are abnormal even though the thyroid gland is functioning normally. This syndrome is very common and, in fact, may be found in up to 70% of hospitalized patients. The euthyroid sick syndrome commonly occurs in patients who have a non-thyroid, severe illness such as heart failure, chronic renal failure, liver disease, stress, starvation, surgery, trauma, infections, and autoimmune diseases, as well as in patients using a number of drugs. In euthyroid sick syndrome patients, the degree of reduction in thyroid hormone levels appears to be correlated with the severity of nonthyroidal illness and may predict prognosis in some cases. For example, some studies have shown that, of hospitalized intensive care patients, the mortality rate correlates with degree suppression of serum T_4 levels.

It is not clear whether thyroid hormone changes reflect a protective response in the face of serious illness or a maladaptive process that needs to be corrected. However, thyroid function tests generally return to normal when the nonthyroidal illness is resolved. When people are ill, are malnourished, or have had surgery, the T_4 form of thyroid hormone isn't converted normally to the T_3 form. Large amounts of reverse T_3 (rT_3), an inactive form of thyroid hormone, accumulate. Despite this abnormal conversion, the thyroid gland continues to function and to control the body's metabolic rate normally. Because no problem exists with the thyroid gland, no treatment is needed. Laboratory tests show normal results once the underlying illness resolves.

Sick euthyroid syndrome may take one of several diagnostic forms as outlined below:

- Low T_3: This is the most commonly encountered abnormality in nonthyroidal illness. T_3 levels fall rapidly within 30 minutes to 24 hours of onset of illness, while rT_3 levels increase. TSH and total and free T_4 levels are usually normal. Low T_3 syndrome is thought to be due to a decrease in T_4 conversion to T_3 by the hepatic deiodinase system, possibly by production of interleukin-6 (IL-6) which functions as a deiodinase inhibitor. Surgery and acute respiratory infections acutely elevate IL-6 concentrations. The finding of increased rT_3 levels differentiates this syndrome from true hypothyroidism, in which rT_3, T_3, and T_4 levels would likely all be low (except in AIDs where rT_3 is already low).
- Low T_3 and low T_4: In patients who are moderately ill, low T_3 levels are accompanied by low

T_4 levels. This has been described in up to 20% of patients treated in intensive care units. Free thyroid hormone levels are usually normal but may be decreased in patients treated with dopamine hydrochloride (Intropin) or corticosteroids. TSH levels also may be normal or low (see below). The mechanism involved may be a deficiency in TBG, which leads to low total thyroid hormone levels. Another possibility is the presence of a thyroid hormone-binding inhibitor, which lowers total thyroid hormone levels.

- Low TSH, low T_3, and low T_4: This abnormality occurs in patients with the most severe nonthyroidal illness. Although most of these patients have TSH levels at the low end of normal, TSH may be undetectable in some, even when third-generation assays are used. The finding of low TSH and low total T_4 and T_3 levels suggests altered pituitary or hypothalamic responsiveness to circulating thyroid hormone levels. During the recovery period, TSH levels return to normal or may even rise transiently.

- Elevated T_4: In this condition, the total T_4 level is elevated, TSH level is normal or elevated, and T_3 level is normal or high. It may be seen in primary biliary cirrhosis and acute and chronic active hepatitis, in which TBG synthesis and release are increased. Elevated levels of total and free T_4 also have been reported in patients with acute psychiatric illness. Drugs such as amiodarone (Cordarone), propranolol (Inderal), and iodinated contrast agents also elevate T_4 levels by inhibiting peripheral conversion of T_4 to T_3.

The mechanisms leading to thyroid hormone abnormalities are not yet clear, but hypothalamic and pituitary suppression have been implicated. Other causes that have been postulated are decreased T_4 to T_3 conversion, alterations in serum binding of thyroid hormones, and a decrease in the level of TSH or its effect on the thyroid. Cytokines (tumor necrosis factor-alpha, interleukin-1 (IL-1), interleukin-6 (IL-6)), free fatty acid, cortisol, and glucagon have been studied as possible mediators.

Whether active intervention using thyroid hormone supplements is beneficial or not in patients with euthyroid sick syndrome remains controversial and controlled trials are limited. A study assessing treatment of such patients with levothyroxine sodium showed no benefit, which may be due to the inability of these patients to convert administered T_4 to the metabolically active T_3. Other studies in which liothyronine sodium was administered to patients undergoing coronary bypass procedures showed improvement in cardiac output and lower systemic vascular resistance in one group of 142 patients and no benefit in another group of 211 patients. However, no difference in the need for inotropic drugs or improvement in survival was evident in patients of either group.

In patients who are moderately ill, no intervention is recommended, aside from careful monitoring. Thyroid function tests should be reevaluated when the nonthyroidal illness is resolved. Even though no harm has been reported when T_3 deficiencies are corrected, evidence does not support the use of thyroid hormone supplements in patients with sick euthyroid syndrome.

VIII. THE EFECT OF HYPOTHYROIDISM ON MEDICATIONS AND OTHER DISEASE STATES.

Hypothyroidism may effect the metabolism and efficacy of a number of medications. During hypothyroidism, digitalis preparations have reduced volume of distribution, resulting in increased sensitivity to the digitalis effect. Therefore many hypothyroid patients may require lower digitalis doses. Also, the metabolism of insulin is slowed during hypothyroidism and thus lower doses are often appropriate. Hypothyroidism also delays the metabolic inactivation of clotting factors. Thus if a patient is stabilized on warfarin is made euthyroid with levothyroxine, the patient's response to anticoagulants may be delayed. Nitrates may precipitate hypotension and syncope un hypothyroidism because these patients have a low circulating blood volume. Respiratory depressants such as the phenothiazines, barbiturates and narcotic analgesics should be avoided because hypothyroid patients are more sensitive to these agents resulting in increased carbon dioxide retention and precipitating of myxedema coma.

Severe hypothyroidism may exacerbate or unmask other disease states, especially cardiovascular diseases. For example, hypothyroid patients may present with symptoms of congestive heart failure including cardiomegaly, dyspnea, edema, pericardial effusions and abnormal cardiogram. But these symptoms may be caused by “myxedema heart” caused by hypothyroidism related deposition of mucopolysaccharides in the myocardium. Also, elevations of enzymes such as aspartate aminotransferase (AST), creatinine kinase (CK) and lactate dehydrogenase (LDH) suggestive of myocardial infarction (MI) may actually result from chronic skeletal or cardiac muscle damage or from decreased enzyme clearance associated with hypothyroidism. The symptoms of angina may be masked by the low oxygen and metabolic demands of hypothyroidism and treatment with thyroxine may cause angina symptoms to emerge or worsen.

IX. THE EFFECTS OF DRUGS ON THRYOID HORMONE LEVELS

It is not surprising that many drugs can have an effect on the thyroid and thyroid hormones, and therefore have an effect on the results of thyroid function tests. The prevalent role of thyroid hormones throughout the human body lends itself to a multitude of potential drug interactions. Drugs that decrease thyrotropin (TSH) secretion and thereby decrease TSH serum concentrations include dopamine (at doses >1mcg/kg per minute), short-course corticosteroids (eg, hydrocortisone doses >100 mg/day), and octreotide (doses >100 mcg/day). Certain medications are known to decrease thyroid hormone production or secretion. Included are methimazole (MMI) and propylthiouracil (PTU) which are used therapeutically to treat hyperthyroidism. Long-term therapy with lithium, which disrupts thyroid hormone synthesis and secretion, results in goiter in up to 50% and overt hypothyroidism in up to 20% of patients.

Drugs that contain iodine (eg, inorganic iodide, amiodarone, aminoglutethimide, radiographic contrast agents) decrease the conversion of T_4 and T_3; whether the effect is persistent or temporary depends on the patient’s clinical thyroid status. Drugs containing iodine also can cause hyperthyroidism in euthyroid patients with certain thyroid disorders (eg, multinodular goiter, hyperfunctioning thyroid adenoma). The antiarrhythmic amiodarone may cause thyroid dysfunction via several different mechanisms: (1) it contains iodine; (2) it can cause thyroiditis; (3) it may decrease conversion of T_4 to T_3; and (4) it may inhibit the activity of T_3. Most patients treated with amiodarone remain clinically euthyroid despite altered thyroid hormone levels, although 2% to 6% of patients experience either hyperthyroidism or hypothyroidism.

The presence of environmental goitrogens was suggested by the resistance of endemic goiters to iodine prophylaxis and iodide treatment in Italy and Colombia. In the past, endemic outbreaks of hypothyroidism have pointed to calcium as a source of water-borne goitrogenicity, and it is presently believed that calcium is a weak goitrogen able to cause latent hypothyroidism to come to the surface.