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Euthyroid Sick Syndrome

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Introduction

Euthyroid sick syndrome is a reversible abnormality of thyroid function tests in the presence of an acute or chronic nonthyroidal illness (NTI) or an altered physiologic state such as starvation. These abnormalities result from disturbances in the hypothalamo-pituitary-thyroid axis, thyroid hormone binding to serum proteins, tissue uptake of thyroid hormones, and/or thyroid hormone metabolism. After recovery from an NTI, abnormal thyroid function tests are usually completely reversible and normalized.[1] (*See Figures 1 and 2.*) Low serum triiodothyronine (T3) and elevated reverse T3 (rT3) are the most prominent and frequent abnormalities. Depending upon the severity and duration of the NTI, thyroid-stimulating hormone (TSH), thyroxine (T4), free T4, and free T4 index (FTI) also are affected in variable degrees. (*See Table 1.*)

Several diseases may be associated with abnormal thyroid function tests. (*See Table 2.*) In many patients with NTI, drugs administered for treatment may also affect the regulation and metabolism of thyroid hormone levels. It is difficult to assess and interpret thyroid function in patients with nonthyroidal illness because changes can occur at all levels of the hypothalamic-pituitary-thyroid axis raising suspicion of the presence of central hypothyroidism.[2] The magnitude of abnormalities in thyroid function tests reflects the severity of NTI, and extremely low T3 and T4 and high rT3 levels may indicate poor prognosis.

This review will discuss the changes in thyroid hormone metabolism that are seen in patients with euthyroid sick syndrome. It also will discuss the current controversies in treatment of euthyroid sick syndrome with the administration of thyroid hormone.

Epidemiology

Low serum total T3 is the most common abnormality, observed in about 70% of hospitalized patients with NTI. Serum

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total T3 may vary from undetectable to normal in patients with systemic illness, and the mean value is approximately 40% of the normal level.[2] As the severity of NTI progresses, T4 and TSH levels also decline.

The magnitude of thyroid test abnormalities depends on the severity of NTI, regardless of type of illness. The decline in T4 level follows lowering of T3 as the severity of illness worsens, and thus, mortality frequently correlates with T4 level. With serum total T4 level of less than 4 mcg/dL, the probability of death is 50% and rises to 80% with levels below 2 mcg/dL.[3,4] Moreover, the lack of improvement in T4, T3, and rT3 levels on repeated determinations denotes a poor prognosis resulting in death. In one of our studies, we examined the effect of improvement in clinical state on thyroid hormone concentrations in 44 cirrhotic patients. Low serum T4 and T3 as well as raised rT3 were observed in cirrhotic patients with advanced liver dysfunction alone. Serum T3 and rT3 correlated significantly with liver function tests. T4, T3, and rT3 normalized on improvement in clinical status and liver function tests. The lowest levels of T4 and T3 with extremely high rT3 were seen in patients with extremely advanced liver dysfunction. In these patients, the mortality was high.[5] People of all races are affected equally in NTI.

Thyroid function test results in both sexes are affected equally in NTI. NTI can affect people at any age. Since chronic illnesses are common in individuals of an advanced age, altered metabolism might be responsible for abnormal findings on thyroid function tests in elderly patients. However, lack of similar changes in healthy elderly people refutes the effect of aging alone on the changes in thyroid hormone levels. Several investigators report lowering of T3 and/or a rise in reverse T3 (rT3) in elderly subjects. To assess the possible effect of aging, we studied T3 resin uptake, T4, free T4, T3, and rT3 concentrations in 152 euthyroid healthy adult subjects. These subjects were selected carefully and were therefore devoid of any illness, acute or chronic, and were not treated with any medications at the time of study. No significant alterations were noted in any of the thyroid hormone concentrations in subjects divided into groups according to age. Nor was there a significant difference in these parameters between men and women of any individual age group or for all ages combined. Therefore, old age per se may not influence thyroid hormone metabolism and, hence, may not induce changes in serum thyroid hormone concentrations.[6]

Physiology

Pituitary-thyroidal Axis During Systemic Illness. Secretion of thyroid hormones from the thyroid gland is regulated by the hypothalamic pituitary thyroid gland axis involving the secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus, pituitary thyrotropin/thyroid-stimulating hormone (TSH) from pituitary, and negative feedback from T3 and thyroxine.[7] In normal individuals, 80% of circulating T3 is generated from peripheral deiodination of thyroxine in the liver, kidney, and other tissues, whereas 20% is contributed by local deiodination of T4 to T3 in the thyroid gland. About 99% of T4 and T3 is bound to thyroxine-binding globulin (TBG), prealbumin (TBPA), and albumin. Free T3 is the major metabolically active preferential hormone. It binds to a nuclear receptor in the cell and regulates transcription of thyroid hormone-responsive genes, thereby inducing the physiological effect of hormone.[7] Free T4 also has the ability to be active, especially in the absence of or with extremely low circulating T3.

In critical illness there are multiple complex metabolic, immunologic, and endocrine alterations. The initial neuroendocrine response to acute illness is increased secretion of anterior pituitary hormones. After several days of systemic illness, reduced hypothalamic stimulation leads to impaired pulsatile release of several anterior pituitary hormones and reduced stimulation of the respective target tissues. Many abnormalities in the pituitary-thyroid axis have been demonstrated in critical illness, including attenuated TRH release, decreased level of TBG, decreased total T4 and T3 levels, low tissue uptake of thyroid hormones, and/or interference with its binding to thyroid hormones because of increased FFAs resulting in altered thyroid hormone metabolism.[8-10]

Although patients with nonthyroidal illness may present with a variety of abnormalities in thyroid function tests, most of these abnormalities can be classified into two major groups: low T3 state; and low T3 and T4 state. The following section describes the alterations in thyroid hormone levels in NTI in further detail.

Thyroid Hormones in Nonthyroidal Illness

Triiodothyronine and Serum Reverse Triiodothyronine. Thyroid hormone (T4 and T3) concentrations in target tissues are greatly influenced by the activity of iodothyronine deiodinases.

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Figure 1. Relationship Between Severity and Duration of Nonthyroidal Illness (NTI) and Thyroid Hormone Levels

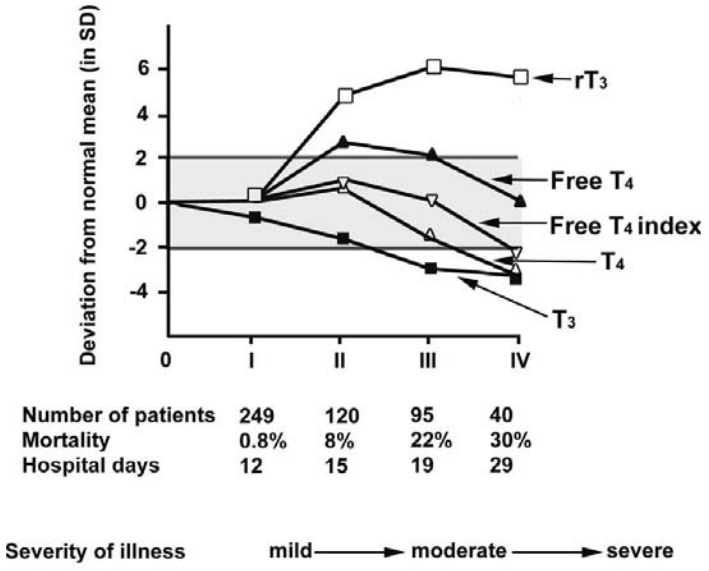

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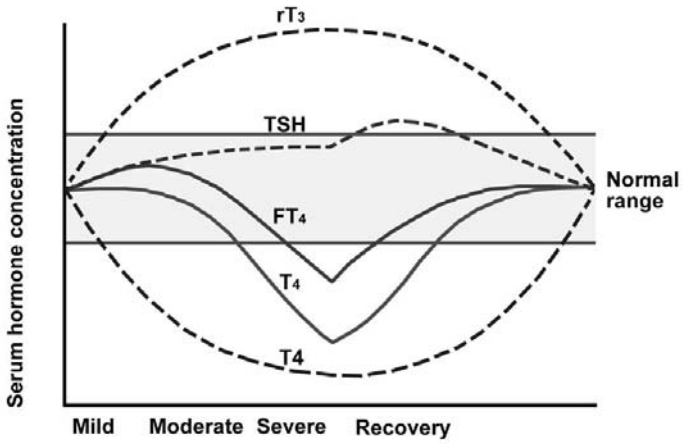
Figure 2. Relation Between Serum Thyroid Hormone Concentrations and Severity of Nonthyroidal Illness (NTI)



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Type 1 and 2 deiodinases generate T3 from T4, while deiodinase type 3 (D3) transforms T4 and T3 to inactive metabolites. The enzyme 5'-deiodinase catalyzes the monodeiodination of circulating T4 to produce the active hormone T3. Inhibition of 5'-deiodinase is believed to occur in nonthyroidal illness, resulting in a decrease in T4 to T3 conversion and low serum T3 concentrations.[11] With impairment of 5'-deiodinase activity, more T4 substrate is available for 5-deiodinase action via the inactivating pathway and hence more is converted to rT3. In addition, 5'-deiodinase ordinarily converts rT3 to T2, and reduced activity of 5'-deiodinase slows the conversion of rT3, further elevating its level. The clearance of reverse T3 to diiodothyronine (T2) is also reduced in nonthyroidal illness because of inhibition of the 5'-monodeiodinase activity.[15] So, serum rT3 concentrations are high in patients with nonthyroidal illnesses, except in those with renal failure[16] and some with AIDS.[17]

Regulation of T3 is achieved by the sequential removal of iodine moieties from the thyroid hormone molecule. Recent studies have revealed the induction of high D3 activity in diverse animal models of tissue injury including starvation, cryolesion, cardiac hypertrophy, infarction, and chronic inflammation. By analyzing serum and tissues taken from hospitalized patients at the time of death, investigators have also documented the robust induction of D3 activity in several human tissues suggesting a role of D3 in the tissue response to injury and in the derangement of thyroid hormone homeostasis commonly observed during critical illness.[18]

Low serum T3 is the most common manifestation of altered thyroid economy in nonthyroidal illness. It is useful to measure serum T3 in hospitalized patients who have a low serum TSH concentration. The serum T3 value is high in hyperthyroidism, but low in nonthyroidal illness. Measurement of serum rT3 is occasionally useful in hospitalized patients to distinguish between nonthyroidal illness and central hypothyroidism. In patients with mild hypothyroidism, serum rT3 concentrations may be normal or even slightly high, thus limiting its usefulness.[18] The values are low in patients with central hypothyroidism because of reduced production of the substrate (T4) for rT3.

Several mechanisms can contribute to low serum T3 concentrations in nonthyroidal illness[2] (*see Figure 3*):

- High endogenous serum cortisol concentrations and exogenous glucocorticoid therapy;[19]
- Circulating inhibitors of deiodinase activity, such as free fatty acids;[20]
- Drugs that inhibit 5'-monodeiodinase activity, such as amiodarone and high doses of propranolol;
- Cytokines (tumor necrosis factor, interferon-alfa, NF-kB, and interleukin-6).[21] Cytokines, such as IL-1 beta, TNF-alpha, and interferon-gamma, also affect the deiodinase activity. Soluble TNF-alpha, soluble TNF-alpha receptor, soluble IL-2 receptor antagonist, and IL-6 have been shown to be inversely correlated with serum T3 levels. These cytokine changes may play a pathogenic role through mechanisms that are not yet clearly defined.[12-14]

Glucagon. Some studies have suggested that glucagon may play a role in T4 monodeiodination in some states such as starvation and uncontrolled diabetes mellitus. In several studies, glucagon administration induced lowering of serum T3 and a rise in reverse T3 in euthyroid healthy subjects even while receiving thyroid hormone. We concluded in a study that hyperglucagonemia may be a major contributor of thyroid hormone alterations observed in several euthyroid sick states, not associated with

Table 1. Thyroid Hormone Concentration During Acute Illness

STAGE OF ILLNESS	T4	T3	RT3	FT4	TSH	Δ TSH
I (Mild)	N or ↑ or ↓	↓	↑	N	N	N
II (Severe)	N or ↓	↓↓	↑↑	N	N	↓
III (Critical)	↓↓	↓↓↓	↑↑↑	N	↓	↓↓
IV (Early recovery)	↓	↓	↑	N	↑	↑
V (Post recovery)	N	N	N	N	N	N

N = Normal; ↓ = Decreased; ↑ = Increased

stress, and may enhance these changes during euthyroid sick syndrome associated with stressful crises.[22] It is apparent that most of these mechanisms induce these changes in circulating thyroid hormone levels via two pathways, one being the direct effect on deiodinases and the other causing inhibition of hypothalamic pituitary thyroid axis with decreased production of thyroid hormones by the thyroid gland itself. It may be further attributed by the effect of TSH on T4 metabolism in nonthyroidal tissues.

Catecholamines. Dopamine directly inhibits anterior pituitary function through inhibitory dopamine receptors, resulting in diminished TSH release. In a study of children with meningococcal septic shock who received dopamine, significantly lower TSH levels and TSH/FT4 ratios were found than in those who did not receive dopamine.[23] Also dopamine infusion has been shown to induce or aggravate the euthyroid sick syndrome in critical illness.

Thyroxine. Approximately 15-20% of hospitalized patients and up to 50% of patients in intensive care units have low serum T4 concentrations (low T4 syndrome). The concentration is low because of reduction in the serum concentrations of one or more of the three thyroid hormone-binding proteins (thyroxine-binding globulin [TBG], transthyretin [TTR], or thyroxine-binding prealbumin [TBPA]), and albumin. Small reductions in binding proteins should not alter serum free T4 index values, and these values are usually normal in patients whose illness is not severe. However, when the concentrations of binding proteins are very low, the T3-resin uptake test fails to correct for the binding-protein deficiency adequately, and the serum free T4 index is low.[24] Patients with more critical illness also have other circulating substances that inhibit T4 from binding to the binding proteins. This results in further reduction in serum total T4 concentrations, and frequently low serum free T4 concentrations and low serum free T4 index values.[25]

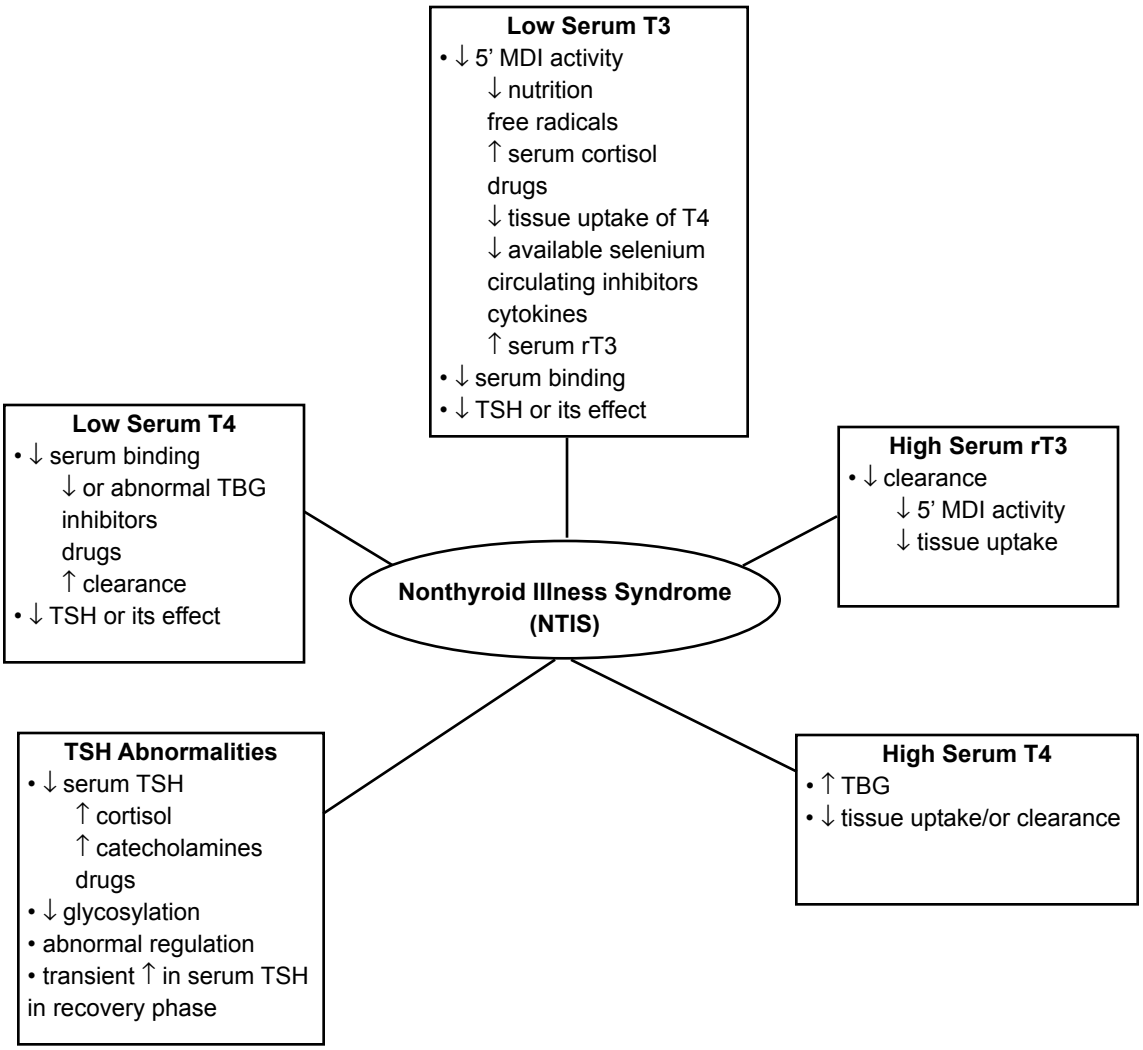
The results of free T4 assays in NTI are method-dependent and may be influenced by many variables. Several methods can be used to measure free T4 directly, including equilibrium dialysis (with undiluted serum), a two-step immunoextraction technique, a one-step (analog) method, FTI (T3 resin-binding ratio), and ultrafiltration. Equilibrium dialysis usually is the preferred technique. The serum free T4 fraction measured by equilibrium dialysis may be normal or even slightly high in these patients.[26,27]

Table 2. Examples of Illnesses During Which Thyroid Hormone Changes Can Occur

Gastrointestinal diseases
Renal diseases
Pulmonary diseases
Cardiovascular diseases
Myocardial infarction
Infiltrative and metabolic disorders (diabetes mellitus)
Inflammatory conditions
Starvation
Sepsis
Burns
Trauma
Surgery
Malignancy
Bone marrow transplantation

Thyrotropin. Depending upon the etiology of the underlying nonthyroidal illness, TSH levels may be low, but only on rare occasions are TSH levels undetectable due to nonthyroidal illness alone. Serum TSH assays that have a detection limit of 0.01 mU/L should be used in assessing thyroid function in critically ill patients.[28] Responsiveness of the pituitary to TRH during NTI varies; some patients respond normally, while many have a less-than-normal response. Normal responsiveness in the presence of low TSH may suggest that a hypothalamic abnormality is causing the low TSH and low T4. Almost all patients who have a subnormal but detectable serum TSH concentration (greater than 0.05 mU/L and less than 0.3 mU/L) will be euthyroid when reassessed after recovery from their illness. Approximately 75% of patients with undetectable serum TSH concentrations (< 0.01 mU/L) have hyperthyroidism. Some hospitalized patients have transient elevations in serum TSH concentrations (up to 20 mU/L) during recovery from nonthyroidal illness.[28] Few of these

Figure 3. Some Factors that May Contribute to Major Abnormalities of NTIS



Used with permission from: Chopra IJ. Euthyroid sick syndrome: Is it a misnomer? *J Clin Endocrinol Metab* 1997;82:329-334, Figure 1.

patients have hypothyroidism when reevaluated after illness, and patients with serum TSH concentrations over 20 mU/L usually have permanent hypothyroidism.[29]

Transient Central Hypothyroidism

Patients with severe nonthyroidal illness may also have a transient central hypothyroidism. A prospective study evaluating changes in thyroid function in patients undergoing bone marrow transplantation found that serum TSH concentrations fell coincident with decline in serum T4 concentration.[30] Another study of critically ill patients recovering from nonthyroidal illness demonstrated that a rise in serum TSH concentration preceded normalization of serum T4 concentration.[31] Patients with nonthyroidal illness (similar to those with central hypothyroidism from other causes) have a blunted nocturnal rise in serum TSH concentrations, but usually have a normal serum TSH response to TRH.[32] TRH infusion in patients with critical illness can raise serum TSH, T4, and T3 concentrations.[33]

Alteration in Thyroid Hormones in Specific Clinical Conditions

Cardiac Disorders and Coronary Artery Bypass Graft (CABG). Alterations in thyroid function tests in cardiac disorders are frequently observed with myocardial ischemia, congestive heart failure, and after coronary artery bypass grafting. Decreased T3, increased rT3, and decreased TSH and T4 have been found in acute myocardial infarction and unstable angina. Also, the degree of T3 decrease and rT3 increase has been found to be proportional to the severity of illness. A prospective study investigating thyroid function in cardiac arrest found total and free T3 to be significantly lower in patients after cardiac arrest induced by acute coronary syndrome as compared with patients who had acute uncomplicated myocardial infarction or healthy

control subjects. There were no significant differences between total T4, free T4, and TSH levels among the groups. Much lower values of free and total T3, free and total T4, and TSH were found in those who sustained prolonged cardiac arrest than in those whose duration of cardiac arrest was shorter, and thyroid function tests normalized at 2 months in those who survived.[34]

The prevalence of a nonthyroidal illness syndrome in congestive heart failure is approximately 18% according to a prospective trial[35] and may be as high as 23%.[36] Deaths in heart failure patients who have nonthyroidal illness syndrome are significantly more frequent than in heart failure patients who have normal thyroid function tests. TSH level above the upper limit of normal but with a normal free T4 is even more prevalent than nonthyroidal illness syndrome in patients who have NYHA class II-III congestive heart failure.[36] Low T3 has also been shown to be an independent predictor of mortality in hospitalized cardiac patients.[37] Heart transplant normalizes thyroid function tests in patients who have heart failure and nonthyroidal illness syndrome. A recent study aimed at assessing the short-term effects of synthetic L-T3 replacement therapy in patients with low-T3 syndrome and ischemic or nonischemic dilated cardiomyopathy found that short-term synthetic L-T3 replacement therapy significantly improved neuroendocrine profile and ventricular performance.[41] However, the data regarding survival are sparse.

There is no evidence that thyroid hormone replacement is beneficial for patients undergoing CABG whose serum T3 concentrations are known to decrease in the perioperative period. During and after cardiopulmonary bypass, there is a transient decrease in serum T3 concentrations.[38] While animal data and anecdotal clinical experience have suggested that T3 repletion might improve outcomes after cardiopulmonary bypass,[39] clinical trials have not demonstrated such a benefit.[40] In a trial of 142 patients with coronary heart disease undergoing CABG who were randomly assigned to intravenous T3 therapy for six hours at the completion of the surgery or placebo, the mean cardiac index was higher and systemic vascular resistance lower in the T3 group compared to placebo.[42] Also, there were no differences between the groups in the incidence of arrhythmia and the need for inotropic or vasodilator drugs during the 24 hours after surgery or in the perioperative morbidity and mortality rates.

Diabetes. Several studies have demonstrated that the uncontrolled diabetic state in both type I as well as type II diabetes mellitus is characterized by altered thyroid hormone metabolism, which results in the lowering of serum T3 levels and a reciprocal elevation of rT3 levels. A study of 220 type II diabetics from 40-85 years of age was conducted to assess the influence of aging and metabolic control on thyroid hormone levels and found that serum thyroxine (T4), free T4, T3 resin uptake, and TSH measurements in diabetic patients were not significantly altered compared with 37 young normal control subjects, irrespective of age or the grade of metabolic control. Serum T3 levels declined and rT3 levels rose in the diabetic patients with worsening of the metabolic control. However, with comparable metabolic control, the levels were not significantly different from the younger patients.[43] Another study has shown that T3 and rT3 concentrations may serve as indicators of metabolic control in diabetes mellitus.[56]

Infection, Sepsis, and HIV. Infection and sepsis cause decreased TSH secretion from the pituitary, reduced thyroidal secretion of T4 and T3, and impaired peripheral T4 to T3 conversion. These changes contribute to low T4, free T4, T3, and TSH and occur early in the course of sepsis. Cytokines play a role in the development of nonthyroidal illness syndrome in the setting of sepsis and severe inflammatory states. There is evidence to suggest that cytokines interleukin (IL)-1β, tumor necrosis factor–alpha, and nuclear factor κB suppress TSH in sepsis.[12,44] Nutritional deprivation during sepsis and severe illness also contribute to these abnormalities.[45] The degree of thyroid hormone alterations also directly relates to the sepsis severity.[46]

In most patients with HIV, thyroid function tests including T3, free T4, and TSH remain normal unless severe disease is present with low CD4 cell counts.[47] Increases in TBG have been observed in the HIV population for reasons that remain unclear, although likely to be either due to low levels or interference of binding of TBG to circulating thyroid hormones. A study of patients who had *Pneumocystis carinii* pneumonia and AIDS showed that low serum T3 values were associated with increased mortality. In another study of HIV-infected patients receiving highly active antiretroviral therapy, 23 out of 182 patients (12.6%) demonstrated lower free T4 and higher TSH levels, which is suggestive of subclinical or mild hypothyroidism.[48] This could be due to immune reconstitution with the unmasking of underlying Hashimoto disease that was previously quiescent.

Renal Disease. T3 levels are decreased in the nephrotic syndrome due to loss of TBG in the urine along with other proteins.[49] TBG levels, however, are normal in many patients who have nephrotic syndrome and a preserved glomerular filtration rate (GFR) rate.[50] Serum rT3 levels typically are normal to low in nephrotic syndrome. Glucocorticoids given to treat nephrotic syndrome may complicate the interpretation of thyroid function tests (they lower TSH secretion and decrease T4 to T3 conversion). Free T4 and free T3 usually are normal in nephrotic syndrome. Thyroid hormone supplementation should be reserved for patients who have at least mild TSH elevations as a consequence of large-scale proteinuria and excess thyroid hormone wasting in the urine or with low serum free T4 in the setting of glucocorticoid use.

End-stage renal disease (ESRD) leads to decreased total and free T3 because of reduced T4 to T3 conversion. Chronic metabolic acidosis in ESRD may contribute to low free T3 levels. ESRD also alters the hypothalamic-pituitary-thyroid hormone axis.[51] Hemodialysis does not tend to normalize the abnormal thyroid function parameters observed in ESRD, but these alterations largely are reversed after renal transplant. Interpretation of thyroid function test in the renal transplant population is complicated by chronic post-transplant glucocorticoid use in many recipients.[51] Low free T3 has been shown to be an independent predictor of mortality in hemodialysis patients.[52] Total and free T4 are generally slightly decreased or normal, but free T4 may be increased in the setting of heparin used for anticoagulation

during hemodialysis because heparin is known to inhibit T4 binding.[53] Also, rT3 levels are most commonly normal in ESRD.[54] Although the clearance rate of serum rT3 is impaired in ESRD, the apparent redistribution of rT3 from vascular to extravascular spaces and enhanced intracellular entry of rT3 may account for normal rT3 levels. ESRD may affect the plasma half-life of TSH, and the TSH response to TRH is typically blunted (indicative of hypothalamic dysfunction) with a delayed peak and prolonged return to baseline, perhaps due to reduced renal clearance of TSH, TRH, or both.[55]

Starvation, Fasting, and Burns. In several pathophysiologic states (i.e., cirrhosis of liver, protein calorie malnutrition, starvation, carbohydrate deprivation, etc.), thyroid hormone metabolism is reported to be altered with a decrease in serum T3 and a reciprocal increase in rT3.[56] Fasting state causes a down-regulation in the hypothalamic-pituitary-thyroid axis and decreased thyroid hormone levels. Many acute and chronic diseases can cause a relative state of starvation. In the fasting state, substantial decreases in serum total and free T3 are seen within 24-48 hours primarily due to the down-regulation of peripheral 5'-deiodination of T4 to T3. The increase in rT3 during fasting is mainly due to decreased metabolic degradation of rT3 by 5'-deiodinase rather than increased rT3 production from 5-deiodination of T4 to rT3.[57] The total T4 concentration may change little, and free T4 levels most commonly remain unchanged or may show a slight increase due to fasting-induced elevation in plasma free fatty acids, which inhibit binding to TBG.[58] Free T4 returns to normal within 2 weeks of continued fasting, although total T4 may steadily decrease due to a fall in thyroid binding globulin. At the central level, decreased stimulation of TSH production occurs due to suppression of TRH expression within the hypothalamic paraventricular nucleus.[59] Leptin has been hypothesized to be a factor causing a fall in TRH expression. It may act directly via leptin receptors on TRH neurons or indirectly via the hypothalamic melanocortin pathway.[60] The exact mechanisms by which leptin modifies TRH expression or TSH secretion are still unclear.

Thyroid function is also affected by dietary composition. Reduced carbohydrate intake causes decreased T3, increased rT3, and decreased thyroid binding globulin levels.[61] Restoring serum T3 to the normal range during starvation may increase muscle catabolism. Evidence suggests that in fasting subjects, refeeding with 50 g of carbohydrate (200 kcal) can reverse fasting-induced changes in T3 and rT3, but refeeding with protein and fat cannot normalize T3 levels.[62] Also, an increase in protein intake may lower T3 levels secondary to a rise in glucagon, inhibiting T4 to T3 conversion. However, the effect of weight loss with low carbohydrate diet is not sustained long term due to decreased T4 to T3 conversion with less availability of active thyroid hormone T3, thus limiting its usefulness alone.

In a randomized trial of burn patients with low free T4 index and free T3 index levels, T3 replacement had no effect on mortality or metabolic rate when compared to placebo.[63]

Hepatic Disease. The liver is the principal site of T4 to T3 conversion via 5'-deiodination, thyroid hormone carrier protein (TBG and albumin) synthesis, T4 uptake, and secondary T4 and T3 release into the blood. The most common thyroid function test abnormalities in cirrhosis are low total T3, low free T3, and elevated rT3. The plasma T3: rT3 ratio is inversely related to the severity of cirrhosis.[64] Free T4 may increase and total T4 may decrease secondary to changes in TBG and albumin binding to the thyroid hormone.

In acute hepatitis, increased amounts of TBG is released from the liver as an acute-phase reactant resulting in elevated total T3 and total T4 levels. Free T4 and TSH are mostly normal, but elevation in rT3 and reduction in free T3 may also be observed.[65] There is evidence to suggest that the rT3:T3 ratio may have a value in assessing the severity of hepatitis and the prognosis of patients who have fulminant disease.[66]

In chronic autoimmune hepatitis and primary biliary cirrhosis, serum TBG levels are elevated, with an associated increase in total T4 and T3 concentrations similar to acute hepatitis. Because these forms of liver dysfunction have an autoimmune etiology, there is a higher incidence of coexisting autoimmune thyroid disease that must be distinguished from nonthyroidal illness syndrome. Up to 34% of patients who have primary biliary cirrhosis have antithyroid microsomal antibodies, and 20% have antithyroglobulin antibodies.[67] Such patients are likely to have Hashimoto thyroiditis and a propensity to develop subclinical or overt hypothyroidism. The degree of thyroid function abnormalities in chronic autoimmune hepatitis and primary biliary cirrhosis may not correlate with the severity of liver dysfunction.

Effect of Drugs

Certain pharmacologic agents may alter the serum concentration of thyroid hormones and confound the interpretation of thyroid function tests. (*See Table 3.*) Some drugs that are commonly used in severe systemic illness and ways in which they can alter the thyroid function parameters are discussed below.

Glucocorticoids. Glucocorticoids affect the hypothalamic-pituitary-thyroid axis at multiple levels. They cause suppression of TSH secretion, down-regulation of T4 to T3 conversion by 5'-deiodinase, and decrease of TBG concentration and hormone-binding capacity. This can result in low TSH, low T3, low T4, and normal to slightly low free T4.[68]

Amiodarone. Amiodarone induces predictable changes in thyroid function tests that are largely explained in terms of the physiological effects of iodide excess and inhibition of deiodinase activity.[70] Patients with underlying autoimmune thyroid disease are more likely to develop amiodarone-induced hypothyroidism, while in patients with underlying multinodular goiter or latent Graves' disease, hyperthyroidism may occur. The excess iodine from the amiodarone provides increased substrate, resulting in enhanced thyroid hormone production.

Amiodarone may increase or decrease thyroid hormone secretion and inhibits T4 to T3 conversion by 5'-deiodinase, resulting in decreased T3 and increased rT3 levels.[69] Amiodarone slows T4 metabolism, leading to T4 and free T4 elevations, and may cause short-term TSH increase.[69] Although the T4 changes may persist, T3 and TSH generally normalize after

Table 3. Drugs that Can Alter Thyroid Function

DRUGS THAT DECREASE THYROID HORMONE SECRETION
• Lithium
• Iodide
• Amiodarone
DRUGS THAT DECREASE THYROID-STIMULATING HORMONE SECRETION
• Dopamine
• Glucocorticoids
DRUGS THAT INCREASE THYROID HORMONE SECRETION
• Iodide
• Amiodarone
DRUGS THAT DECREASE THYROXINE ABSORPTION
• Aluminum hydroxide
• Ferrous sulfate
• Sucralfate
DRUGS THAT INCREASE SERUM THYROXINE-BINDING GLOBULIN CONCENTRATION
• Estrogens
• Tamoxifen
DRUGS THAT DISPLACE THYROXINE FROM PROTEIN-BINDING SITES
• Furosemide
• Salicylates
DRUGS THAT DECREASE SERUM THYROXINE-BINDING GLOBULIN CONCENTRATION
• Androgens
• Anabolic steroids
• Glucocorticoids
DRUGS THAT INCREASE HEPATIC METABOLISM OF THYROXINE AND TRIIODOTHYRONINE
• Rifampin
• Phenytoin
• Carbamazepine

several months on amiodarone.[46] The reported incidence of amiodarone-induced hypothyroidism varies widely, ranging from as high as 13% in countries with a high dietary iodine intake, to as low as 6% in countries with low or intermediate iodine intake. The risk of developing hypothyroidism is independent of the daily or cumulative dose of amiodarone, but is enhanced in elderly and female patients.[70] There are two types of amiodarone-induced thyrotoxicosis occurring in either an abnormal (Type I) or normal (Type II) thyroid gland. Type I is typically seen in patients with pre-existing multinodular goiter or latent Graves' disease, while Type II is a destructive thyroiditis that results in excess release of T4 and T3, without increased hormone. In the United States, the majority of cases are type II. Common presenting symptoms and signs include the development or redevelopment of atrial arrhythmias, exacerbation of ischemic heart disease or heart failure, or unexplained weight loss, restlessness, or low-grade fever. Color flow Doppler sonography (CFDS) may help distinguish type I (increased vascularity) from type II (absent vascularity) hyperthyroidism.

Phenytoin. Phenytoin increases the rate of hepatic metabolism of T4 and T3 and may cause decreases in free T4 and rT3. The effects of phenytoin on T3 and free T3 are variable, and these parameters may be depressed or remain normal in patients receiving this medication.[71]

Iodine. Iodine acutely reduces thyroid hormone secretion and exacerbates hypothyroidism. In large doses iodine can precipitate thyrotoxicosis in patients who have underlying autonomous thyroid function.[11]

Dopamine. Prolonged use of dopamine (for many days) can result in TSH suppression and low T4, free T4, T3, and free T3, which may lead to secondary hypothyroidism with worsening prognosis until thyroid hormone replacement is given.[72]

Furosemide. High doses of furosemide can cause a transient elevation in free T4 and a decrease in T4 due to the displacement of T4 from TBG. This also depends upon serum concentrations of albumin, which bind furosemide.[73]

Salicylates. In high doses, salicylates can cause a transient increase in free T4 due to inhibition of T3 and T4 binding to TBG.[74]

Differential Diagnosis

Several disease states are associated with abnormal thyroid function tests like acute hepatitis, hepatoma, acute intermittent porphyria, acromegaly, nephrotic syndrome, Cushing' s syndrome, acute psychosis, and depression. Some patients with acute psychiatric illnesses, particularly schizophrenia, have transient elevations in serum T4 concentrations with or without low serum TSH concentrations.

Differentiation between central hypothyroidism (pituitary or hypothalamic) and euthyroid sick syndrome may also be difficult. Both conditions present with decreased levels of total T4, T3, and TSH. Many chronically ill patients are edematous, have associated infections, or have cardiopulmonary disorders that could easily mask evidence of thyroid dysfunction. Additional tests, including obtaining basal and/or stimulated cortisol, and prolactin levels may be of help in such cases. If the serum cortisol level is normal or elevated, euthyroid sick syndrome is probably the cause, rather than pituitary dysfunction. If serum cortisol is low, pituitary dysfunction is likely and treatment with corticosteroids and thyroid hormone supplementation may be initiated. In some instances, it may be difficult to exclude hyperthyroid patients, who may present with suppressed TSH levels and normal T4 and T3 levels in the presence of infection or other catabolic illness. Hyperthyroid patients who are chronically ill or malnourished may have hypoproteinemia and low levels of TBG inducing low T4 and T3 levels. In such patients, an elevated free-T4 level and an undetectable TSH level may confirm the diagnosis of hyperthyroidism. A previous history of thyroid disorder, a history of external radiation, or the presence of goiter and/or a midline neck scar and presence of antithyroid antibodies may indicate a primary thyroid condition.

Treatment

With recovery from underlying illness, thyroid abnormalities in patients with euthyroid sick syndrome normalize. Randomized controlled studies reporting the benefits of T3 replacement are sparse.[76] The administration of T4 to critically ill adults has failed to demonstrate a reduction in the mortality rate.[75] The lack of beneficial effect with T4 treatment may be due to the inability of these patients to convert administered T4 to metabolically active T3. Several controlled studies in which T3 was administered to adult and pediatric patients have also provided equivocal results. Thyroid hormone replacement in patients who have ESRD also has been shown to have no beneficial effects.[80]

In one study, in patients undergoing coronary bypass procedures, T3 administration improved cardiac output and decreased systemic vascular resistance and resulted in improvement in cardiac indexes and decreased inotropic requirements, postoperative ischemia, mortality rate, and length of hospital stay.[77] Another study examined the effect of T3 administration on pulmonary function in sepsis. This study showed an improvement in respiratory drive, pulmonary histologic integrity, and surfactant availability.[78] However, other studies have shown little or no benefit from short-term administration of T3. Although no harm has been reported with the administration of T3 to critically ill patients, the evidence fails to support the use of thyroid hormone supplements to correct thyroid hormone abnormalities.

If administration of thyroid hormone replacement is to be considered in a patient with deteriorating clinical status and thyroid function test results suggestive of hypothyroidism, intravenous T3 administration is preferred over T4 due to reduced 5'-deiodinase activity and, hence, decreased conversion of T4 to metabolically active T3 in the sick patient. However, in a study in the intensive care unit, administration of intravenous T4 in patients sufficient to normalize T4 and free T4 found no survival benefit in comparison to those who did not receive thyroxine.[79] Therefore, IV administration of thyroid hormone is generally not warranted in sick subjects with hypothyroidism. Oral supplementation with gradually increasing dosage appears to be appropriate because of the well proven safety of this approach, especially in the elderly as well as in patients with coronary artery disease.

Conclusions

Euthyroid sick syndrome is a manifestation of transient hypothalamic-pituitary dysfunction along with altered thyroid hormone metabolism. It is not prudent to rely solely on a single thyroid test in the evaluation of thyroid function of patients with critical illness, and a careful assessment of multiple tests may be needed. It is reasonable to delay the final diagnosis for several days to weeks, or after recovery from the acute illness, to determine the appropriate thyroid status. Thyroid hormones have been used in the setting of NTI in various settings with T4 and T3 replacement and still remain controversial in the absence of prospective studies to demonstrate benefit. Assessing thyroid function in patients with severe illness such as those in the ICU is difficult. Many of them have low serum concentrations of thyroxine (T4), free T4, and triiodothyronine (T3), and their serum thyrotropin (TSH) concentrations also are frequently low. Thyroid function tests need not be assessed in seriously ill patients unless there is a strong suspicion of thyroid dysfunction. Also, measurement of serum TSH alone is inadequate for the evaluation of thyroid function and, in this scenario, free T4 and T3 along with TSH are recommended. The methods for assessing free T4 levels are unreliable in severe critical illness, and a free T4 by equilibrium dialysis in undiluted serum is least likely to provide ambiguous results. Treating patients with critical illness with low serum T3 and/or low T4 concentrations with no other clinical signs of hypothyroidism is not commonly recommended. Patients may receive thyroid hormone replacement if there is additional evidence to suggest a diagnosis of hypothyroidism (such as a TSH over 20 mU/L with low free T4 and/or history, symptoms, and signs of hypothyroidism), in which case cautious administration of thyroid hormone is appropriate.

Finally, thyroid functions should not be assessed in critically ill patients in the absence of a suspicion of thyroid dysfunction as these abnormalities are not a true reflection of actual hormonal activity at the cellular level and treatment of these patients with thyroid hormones is of little benefit and sometimes may be harmful.

References

1. Aytug S. Euthyroid sick syndrome. eMedicine.com. Available at http://www.emedicine.com/med/topic753.htm.
2. Chopra IJ. Euthyroid sick syndrome: Is it a misnomer? *J Clin Endocrinol Metab* 1997; 82:329.
3. De Groot L. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *J Clin Endocrinol Metab* 1999;84:151-164.
4. Maldonado LS, Murata GH, Hershman JM, et al. Do thyroid function tests independently predict survival in the critically ill? *Thyroid* 1992;119-123.
5. Kabadi UM, Premachandra BN. Serum T3 and reverse T3 levels in hepatic cirrhosis: Relation to hepatocellular damage and normalization on improvement in liver dysfunction. *Am J Gastroenterol* 1983; 78:750-755.
6. Kabadi UM, Rosman PM. Thyroid hormone indices in adult healthy subjects: no influence of aging. *J Am Geriatr Soc* 1988;36:312-316.
7. Larsen PR. Thyroid-pituitary interaction: Feedback regulation of thyrotropin secretion by thyroid hormones. *N Engl J Med* 1982;306: 23-32.
8. Wong TK, Hershman JM. Changes in thyroid function in nonthyroidal illness. *Trends Endocrinol Metab* 1992;3:8-12.
9. McIver B, Gorman CA. Euthyroid sick syndrome: An overview. *Thyroid* 1997;7:125-132.
10. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996;24: 1580-1590.
11. Burman KD, Wartofsky L. Endocrine and metabolic dysfunction syndromes in the critically ill: Thyroid function in the intensive care unit setting. *Crit Care Clin* 2001; 43-57.
12. Monig H, Arendt T, Meyer M, et al. Activation of the hypothalamo-pituitary-adrenal axis in response to septic or non-septic diseases—implications for the euthyroid sick syndrome. *Intensive Care Med*

1999;1402-1406.
13. Cannon JG, Tompkins RG, Gelfand JA, et al. Circulating interleukin-1 and tumor necrosis factor in septic shock and experimental endotoxin fever. *J Infect Dis* 1990;161:79-84.
14. Van der Poll T, Van Zee KJ, Endert E, et al. Interleukin-1 receptor blockade does not affect endotoxin-induced changes in plasma thyroid hormone and thyrotropin concentrations in man. *J Clin Endocrinol Metab* 1995;1341-1346.
15. Chopra IJ. An assessment of daily turnover and significance of thyroidal secretion of reverse T3. *J Clin Invest* 1975;58:32.
16. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. *Endocr Rev* 1996;17:45.
17. Ricart-Engel W, Fernandez-Real JM, Gonzalez-Hulx F, et al. The relation between thyroid function and nutritional status in HIV-infected patients. *Clin Endocrinol* 1996;44:53.
18. Huang SA, Bianco AC. Reawakened interest in type III iodothyronine deiodinase in critical illness and injury. *Nat Clin Pract Endocrinol Metab* 2008;4:148-155.
19. Burmeister LA. Reverse T3 does not reliably differentiate hypothyroid sick syndrome from euthyroid sick syndrome. *Thyroid* 1995; 5:435.
20. Chopra IJ, Williams DE, Orgiazzi J, et al. Opposite effects of corticosteroids on serum concentrations of 3,3',5' triiodothyronine (reverse T3) and 3,3',5 triiodothyronine (T3). *J Clin Endocrinol Metab* 1975;41:911.
21. Chopra IJ, Huang TS, Beredo A, et al. Evidence for an inhibitor of extrathyroidal conversion of thyroxine to 3,5,3' triiodothyronine in sera of patients with nonthyroidal illness. *J Clin Endocrinol Metab* 1985;60:666.
22. Nagaya T, Fujieda M, Otsuka G, et al. A potential role of activated NF-kappa B in the pathogenesis of euthyroid sick syndrome. *J Clin Invest* 2000;106:393.
23. Kabadi UM, Dragstedt LR 2nd. Glucagon-induced changes in plasma thyroid hormone concentrations in healthy dogs resemble "euthyroid sick syndrome." *J Endocrinol Invest* 1991;14:269-275.
24. den Brinker M, Joosten KF, Visser TJ et al. Euthyroid sick syndrome in meningococcal sepsis: The impact of peripheral thyroid hormone metabolism and binding proteins. *J Clin Endocrinol Metab* 2005;90:5613-5620.
25. Chopra IJ, Solomon DH, Hepner GW, et al. Misleadingly low free T4 index (FT4I) and usefulness of reverse T3 (rT3) measurement in nonthyroidal illnesses. *Ann Intern Med* 1979;90:905.
26. Wong TK, Pekary AE, Soo Hoo G, et al. Comparison of methods for measuring free thyroxin in nonthyroidal illness. *Clin Chem* 1992;38:720.
27. Docter R, Krenning EP, de Jong M, et al. The sick euthyroid syndrome: Changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol* (Oxf) 1993;39:499.
28. Chopra IJ, Trong UT, Le A. Simultaneous measurement of free thyroxine and free 3,5,3'-triiodothyronine in undiluted serum by direct equilibrium dialysis/radioimmunoassay: evidence that free triiodothyronine and free thyroxine are normal in many patients with the low triiodothyronine syndrome. *Thyroid* 1998;8:249.
29. Spencer CA, LoPresti JS, Patel A, et al. Application of a new chemiluminometric thyrotropin assay to subnormal measurement. *J Clin Endocrinol Metab* 1990;70:453.
30. Attia J, Margetts P, Guyatt G. Diagnosis of thyroid disease in hospitalized patients: A systematic review. *Arch Intern Med* 1999; 159:658.
31. Wehmann RE, Gregerman RI, Burns WH, et al. Suppression of thyrotropin in the low-thyroxine state of severe nonthyroidal illness. *N Engl J Med* 1985;312:546.
32. Hamblin PS, Dyer SA, Mohr VS, et al. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. *J Clin Endocrinol Metab* 1986;62:717.
33. Romijn JA, Wiersinga WM. Decreased nocturnal surge of thyrotropin in nonthyroidal illness. *J Clin Endocrinol Metab* 1990; 70:35.
34. Van den Berghe G, Wouters P, Weekers F, et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab* 1999;84:1311.
35. Iltumur K, Olmez G,Ariturk Z,et al. Clinical investigation: Thyroid function test abnormalities in cardiac arrest associated with acute coronary syndrome. *Crit Care* 2005;R416-R424.
36. Opasich C, Pacini F, Ambrosino N. Sick euthyroid syndrome in patients with moderate-to-severe chronic heart failure. *Eur Heart J* 1996;17:1860-1866.
37. Manowitz NR, Mayor GH, Klepper MJ, et al. Subclinical hypothyroidism and euthyroid sick syndrome in patients with moderate-to-sever congestive heart failure. *Am J Ther* 1996;3:797-801.
38. Iervasi G, Pingitore A, Landi P, et al. Low T3 syndrome: A strong prognostic predictor of death in patients with heart disease. *Circulation* 2003;107:708-713.
39. Gardner DF, Kaplan MM, Stanley CA, et al. Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *N Engl J Med* 1979;300:579.
40. Broderick TJ, Wechsler AS. Triiodothyronine in cardiac surgery. *Thyroid* 1997;7:133.
41. Bennett-Guerrero E, Jimenez JL, White WD, et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. Randomized, double-blind, placebo-controlled trial. *JAMA* 1996;275:687.
42. Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: A randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2008;93:1351-1358.
43. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary-artery bypass surgery. *N Engl J Med* 1995;333:1522.
44. Kabadi UM, Premachandra BN. Low triiodothyronine and raised reverse triiodothyronine levels in patients over fifty years of age who have type II diabetes mellitus: Influence of metabolic control, not age. *J Am Geriatr Soc* 1984;32:375-379.
45. Nagaya T, Fujieda M, Otsuka G, et al. A potential role of activated NF-kB in the pathogenesis of euthyroid sick syndrome. *J Clin Invest* 2000;106:393-401.
46. Richmand DA, Molitch ME, O'Donnell T. Altered thyroid hormone levels in bacterial sepsis: The role of nutritional adequacy. *Metabo-*

lism 1980;29:936-942.
47. Cavalieri RR. The effects of disease and drugs on thyroid function tests. *Med Clin North Am* 1991;75:27-39.
48. Grunfeld C, Pang M, Doerrier W, et al. Indices of thyroid function and weight loss in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Metabolism* 1993;42: 1270-1276.
49. Madeddu G, Spanu A, Chessa F, et al. Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): A longitudinal study. *Clin Endocrinol* (Oxf) 2006;64:375-383.
50. Afrasiabi MA, Vaziri ND, Gwinup G, et al. Thyroid function studies in the nephrotic syndrome. *Ann Intern Med* 1979;90:335-338.
51. Gavin LA, McMahon FA, Castle JN, et al. Alterations in serum thyroid hormones and thyroxine-binding globulin in patients with nephrosis: Qualitative aspects. *J Clin Invest* 1978;46:125-130.
52. Kaptein EM. Thyroid hormone metabolism and thyroid disease in chronic renal failure. *Endocr Rev* 1996;17:45-63.
53. Zoccali C, Mallamaci F, Tripepi G, et al. Low triiodothyronine and survival in end-stage renal disease. *Kidney Int* 2006;70:523-528.
54. Silverberg DS, Ulan RA, Fawcett DM, et al. Effects of chronic hemodialysis on thyroid function in chronic renal failure. *Can Med Assoc J* 1973;109:282-286.
55. Kaptein EM, Feinstein E, Nicoloff JT, et al. Serum reverse triiodothyronine and thyroxine kinetics in patients with chronic renal failure. *J Clin Endocrinol Metab* 1983;57:181-189.
56. Duntas L, Wolf CF, Keck FS, et al. Thyrotropin-releasing hormone: Pharmacokinetic and pharmacodynamic properties in chronic renal failure. *Clin Nephrol* 1992;38:214-218.
57. Kabadi UM, Premachandra BN, Maayan M. Low serum 3, 5, 3'-triiodothyronine (T3) and raised 3, 3', 5'-triidothyronine (reverse T3 or RT3) in diabetes mellitus: normalization on improvement in hyperglycemia. *Acta Diabetol Lat* 1982; 19:233-242.
58. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: The "euthyroid sick syndrome." *Endocr Rev* 1982;3:164-217.
59. Lim CF, Doctor R, Visser TJ, et al. Inhibition of thyroxine transport into cultured rat hepatocytes by serum of nonuremic critically ill patients: Effects of bilirubin and non-esterified fatty acids. *J Clin Endocrinol Metab* 1993;76:1165-1172.
60. Weintraub BD, Gesundheit N, Taylor T, et al. Effect of TRH on TSH glycosylation and biological action. *Ann NY Acad Sci* 1989; 553:205-213.
61. Kim MS, Small CJ, Stanley SA, et al. The central melanocortin system affects the hypothalamo-pituitary thyroid axis and may mediate the effect of leptin. *J Clin Invest* 2000;105:1005-1011.
62. Danforth Jr E, Burger AG. The impact of nutrition on thyroid hormone physiology and action. *Annu Rev Nutr* 1989;9:201-227.
63. Azizi F. Effect of dietary composition on fasting-induced changes in serum thyroid hormones and thyrotropin. *Metabolism* 1978;27: 935-942.
64. Becker RA, Vaughan GM, Ziegler MG, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. *Crit Care Med* 1982; 10:870.
65. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. *Q J Med* 2002;95:559-569.
66. Gardner DF, Carithers RL, Galen EA, et al. Thyroid function tests in patients with acute and resolved hepatitis B infection. *Ann Intern Med* 1982;96:450-452.
67. Kano T, Kojima T, Takahashi T, et al. Serum thyroid hormone levels in patients with fulminant hepatitis: Usefulness of rT3 and the rT3/T3 ratio as prognostic indices. *Gastroenterol Jpn* 1987;22: 344-353.
68. Elta GH, Sepersky RA, Goldberg MJ, et al. Increased incidence of hypothyroidism in primary biliary cirrhosis. *Dig Dis Sci* 1983;28: 971-975.
69. Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med* 1995;333:1688-1694.
70. Melmed S, Nademance K, Reed AW, et al. Hyperthyroxinemia with bradycardia and normal thyrotropin secretion after chronic amiodarone administration. *J Clin Endocrinol Metab* 1981;53:997-1001.
71. Newman CM, Price A, Davies DW, et al. Amiodarone and the thyroid: A practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998;79:121-127.
72. Smith PJ, Surks MI. Multiple effects of 5, 5-diphenylhydantoin on the thyroid hormone system. *Endocr Rev* 1984;5:514-524.
73. Heinen E, Herrmann J, Konigshausen T, et al. Secondary hypothyroidism in severe non-thyroidal illness? *Horm Metab Res* 1981; 13:284-288.
74. Stockigt JR, Topliss DJ. Assessment of thyroid function during high-dose furosemide therapy. *Arch Intern Med* 1989;149:973.
75. Kabadi UM, Danielson S. Misleading thyroid function tests and several homeostatic abnormalities induced by "disalcid" therapy. *J Am Geriatr Soc* 1987;35:255-257.
76. Slag MF, Morley JE, Elson ME, et al. Hypothyroxinemia in critically ill patients as a predictor of high mortality. *JAMA* 1981;245: 43-45.
77. Novitzky D, Cooper DK, Swanepoel A. Inotropic effect of triiodothyronine ([T.sub.3]) in low cardiac output following cardioplegic arrest and cardiopulmonary bypass: An initial experience in patients undergoing open heart surgery. *Eur J Cardiothorac Surg* 1989;3:140-145.
78. Mullis-Jansson SL, Argenziano M, Corwin S, et al. A randomized

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. *J Thorac Cardiovasc Surg* 1999;117:1128-1134.
79. Dulchavsky SA, Hendrick SR, Dutta S. Pulmonary biophysical effects of triiodothyronine augmentation during sepsis-induced hypothyroidism. *J Trauma* 1993;35:104-108.
80. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *J Clin Endocrinol Metab* 1986;63:1.
81. Lim VS, Tsalikian E, Flanigan MJ. Augmentation of protein degradation by L-triiodothyronine in uremia. *Metabolism* 1989;38: 1210-1215.

Physician CME Questions

5. Which of the following can contribute to lowering the T3?
   A. Glucocorticoids
   B. Free fatty acids
   C. Amiodarone
   D. Propranolol
   E. All the above

6. Which of the following can be a cause of nonthyroidal illness?
   A. Sepsis
   B. Trauma
   C. Surgery
   D. Malignancy
   E. All the above

7. Which one of the following is *not* associated with increased hepatic metabolism of thyroid hormones?
   A. Rifampin
   B. Furosemide
   C. Phenytoin
   D. Carbamazepine

8. Which of the following is most helpful in differentiating central hypothyroidisms from euthyroid sick syndrome?
   A. Decreased level of total T4
   B. Edema
   C. Cortisol and prolactin levels
   D. Cardiopulmonary disorders

CME Answer Key

5. E
6. E
7. B
8. C

Correction

In the July issue of *Primary Care Reports* ("Obesity: Dormant Volcano Waiting to Erupt"), on page 70 in the top left column, the sentence should read: "In one, obesity is divided into two main types: hyperplastic, which is increased fat cell number calculated as total body fat divided by adipose cell size, usually over 84 x 10^9)..."

In Future Issues:

Chiropractic Care

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Bird Flu Vaccine Looks Promising

In This Issue: Baxter Bioscience has developed a whole-virus, two dose vaccine against avian flu; warning label now on antipsychotics regarding an increased risk of mortality in elderly patients treated for dementia-related psychosis; vitamin D for men with heart disease on horizon? A new oral anticoagulant may soon be available for prevention of thrombotic complications of hip or knee surgery; FDA Actions

An effective two dose vaccine has been developed against the avian flu (H5N1 virus) according to a recent study in the *New England Journal of Medicine*. Researchers from Baxter Bioscience have developed a whole-virus vaccine that was tested on 275 volunteers between the ages of 18 and 45 years. Four different strengths of the vaccine were tested with and without adjuvant. The most effective regimen was a dose of either 7.5 µg or 15 µg of hemagglutinin given without adjuvant 21 days apart. The vaccine was effective at inducing neutralizing antibody response against three different viral strains. Mild pain at the injection site and headache were the most common adverse effects. The authors conclude that a two dose vaccine regimen of either 7.5 µg or 15 µg induced neutralizing antibodies against diverse H5N1 viral strains in a high percentage of subjects (*NEJM*. 2008;358:2573-2584).

Boxed warning now required for antiphychotics for elderly with dementia

The FDA is requiring a boxed warning for conventional antipsychotics regarding an increased risk of mortality in elderly patients treated for dementia-elated psychosis. This expands the warning on the newer atypical antipsychotics which was issued in April 2005 to include the older, more conventional antipsychotics. The new warning includes medication such as haloperidol (Haldol), thioridazine (Mellaril), and chlorpromazine (Thorazine). The warning specifically states that elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are at increased risk of death. Antipsychotic drugs are not approved for the treatment of dementia-related psychosis, and physicians who prescribe antipsychotics for elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patient's families, and caregivers. It was previously thought only the newer, atypical antipsychotics were associated with increased mortality; however, multiple studies have now shown that the older antipsychotics also increase the risk. The warning can be found on the FDA web site at www.FDA.gov.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

Vitamin D for men with heart disease?

Men may be asking about prevention of heart disease with vitamin D based on this reports of recent studies. In a follow-up from the Health Professionals Follow-up Study (HPFS) from the Harvard School of Public Health, plasma 25-hydroxyvitamin D levels were measured on over 18,000 male health-care professionals age 40 to 75 years, who were free of diagnosed cardiovascular disease at blood collection. In 10 years of follow-up, 450 men had nonfatal myocardial infarction or fatal coronary heart disease. After adjustment for matched variables, and men deficient in 25-hydroxyvitamin D (≤ 15ng/ml) were at increased risk of MI compared to those considered to be sufficient (≥ 30ng/ml) (RR 2.42; 95% CI, 1.53-3.84; *P* <.001 for trend). After adjustment for family history and multiple risk factors, the relationship remains significant. Even those with levels 22.6 to 29.9 ng/ml were at higher risk than those with levels over 30 ng/ml. The authors conclude that "low levels of 25-hydroxyvitamin D are associated with a higher risk of myocardial infarction in a graded manner even after controlling for factors noted to be associated with coronary disease." The mechanism for this relationship is unclear but may be related to vitamin D, its effect on vascular smooth muscle proliferation, inflammation, vascular calcification, and blood pressure. Whether vitamin D supplementation reverses these findings remains be seen, but it is clear that men with low vitamin D levels will require more than the current recommended daily allowance of 200-600 IU/d, perhaps even as much as 3000 IU/day (*Arch Int Med*. 2008;168:1174-1180). Another study with similar conclusions was recently published (*Arch Intern Med*. 2008;168:1340-1349).

New oral anticoagulant tested for patients with hip or knee surgery

A new oral anticoagulant may soon be available for prevention of thrombotic complications of hip or knee surgery. Rivaroxaban is an oral direct inhibitor of factor Xa that is in phase 3 trials by Bayer and Ortho-McNeil Pharmaceutical. The drug has the advantage of being highly bioavailable when given orally and has a standard 10-mg dose given once a day. In 3 recent trials, rivaroxaban was compared to subcutaneous enoxaparin after total hip arthroplasty and total knee arthroplasty. Over 7000 patients were randomized to receive rivaroxaban 10 mg daily beginning after surgery or subcutaneous enoxaparin 40-mg once daily beginning the day before or the day of surgery. A third study compared long-term use of rivaroxaban with short-term use of enoxaparin. The primary outcomes included deep venous thrombosis, pulmonary embolism, and all cause mortality. In all 3 studies thromboprophylaxis with rivaroxaban was significantly more effective than enoxaparin, while toxicity, specifically major bleeding, was the same in both groups. The authors conclude that a once-daily 10-mg oral dose of rivaroxaban is significantly more effective than a 40 mg subcutaneous dose of enoxaparin in preventing thrombotic complications in patients undergoing total hip or total knee arthroplasty (*NEJM.* 2008;358:2765-2775, 2776-2786. *Lancet* 2008 published early online 25 June 2008). While rivaroxaban is not yet approved in this country, the prospect of an orally active direct Xa inhibitor that could take the place of parenteral heparin compounds and perhaps even warfarin is exciting to clinicians.

FDA Actions

The FDA has approved a new pentavalent vaccine for children age 6 weeks through 4 years. The new vaccine combines diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenza type b. It is given as a 4 dose series at 2, 4, 6 and 15-18 months of age. The vaccine is marketed by Sanofi Pasteur as "Pentacel." GlaxoSmithKline has also received approval for a combination vaccine with diphtheria, tetanus, acellular pertussis, and polio for children 4 to 6 years old who require their fifth DTaP and fourth polio shot. The combination vaccine may prevent additional injections for these children. This four vaccine combination will be marketed as "Kinrix."

The FDA has issued warning letters to 23 US companies and two foreign individuals regarding the marketing of fake cancer cures on the Internet. The products which include tablets, tonics, black salves, and creams are fraudulently promoted, claiming to prevent and cure cancer. The products contained in treating such is bloodroot, shark cartilage, coral calcium, cesium, Cat's Claw, herbal tea and mushrooms. A complete list of companies and individuals concluded and the warning can be found at www.fda.gov/cder/news/fakecancercures.htm. ■