Rakel & Bope: Conn's Current Therapy 2008, 60th ed.

Chapter 161 – Hypothyroidism

Method of:
John T. Nicoloff, MD
Jonathan S. LoPresti, MD, PhD

Diagnosis and treatment of **hypothyroidism** is an extremely rewarding experience both for the patient and clinician because lifelong restoration of a euthyroid state can be safely and economically achieved with the appropriate use of oral l-thyroxine (T_4) replacement therapy. Although there are many potential causes for **hypothyroidism** (Table 1), autoimmune thyroiditis (chronic thyroiditis, lymphocytic thyroiditis, Hashimoto's thyroiditis) represents most spontaneously occurring cases of primary **hypothyroidism**. The initial phases of the disease often start in early adolescence; the incidence of **hypothyroidism** often reaches its peak in older patient populations in which some degree of biochemical **hypothyroidism** becomes demonstrable in approximately 8% of males and 20% of females by the age of 70 years. This pattern is the result of the inherently slow, progressive, and unremitting nature of the underlying destructive autoimmune process. Unfortunately, establishing a clinical **diagnosis** of **hypothyroidism** generally is a difficult task, especially during the early stages of the disease. The insidious character of thyroid destruction and the lack of specific symptoms that raise suspicion in either the patient or physician make the **diagnosis** of **hypothyroidism** problematic. However, this diagnostic limitation can be overcome by establishing the presence of what is most often termed *biochemical* or *subclinical* or *mild* **hypothyroidism** as defined by consistent elevations in serum thyroid-stimulating hormone (TSH) concentrations when serum free thyroxine (FT_4) levels still remain within the normal range. This **diagnosis** may be further bolstered by the additional findings of detectable serum antithyroperoxidase (anti-TPO) antibodies and the presence of a small, firm goiter. Therefore, the **diagnosis** of **hypothyroidism** secondary to chronic autoimmune thyroiditis can definitively be diagnosed at the earliest stages of the disease before the development of significant morbidity occurs. Furthermore, advances in technology have both reduced the cost and improved the accuracy of serum TSH measurements, thereby making it possible to perform cost-effective serum TSH screening on large *at-risk* populations. Therefore, the challenge for the clinician is to identify populations that are likely to be *at risk* for developing **hypothyroidism**, establish a **diagnosis** of subclinical disease, and initiate oral T_4 therapy before overt signs and symptoms of **hypothyroidism** become clinically apparent.

TABLE 1 -- Etiology of Hypothyroidism

Primary Hypothyroidism
• Chronic autoimmune thyroiditis (Hashimoto's, lymphocytic) • Iatrogenic: ^{131}I therapy, thyroidectomy, external radiation • Drugs: methimazole (Tapazole), PTU, perchlorate, lithium, amiodarone • Immune modulators: interferon-α, interleukins, postpartum period • Congenital: complete or partial thyroid gland absence, peroxidase deficiency • Severe dietary iodine deficiency • Thyroid infiltrative diseases (rare): lymphoma, Riedel's struma, amyloidosis, hemochromatosis
Central Hypothyroidism

• Pituitary TSH deficiency (secondary **hypothyroidism**): Sheehan's syndrome, pituitary tumors, hypophysitis, trauma (surgery, radiation, head injury), empty sella syndrome • Hypothalamic TRH deficiency (tertiary **hypothyroidism**): tumor, craniopharyngioma, Sheehan's syndrome, infiltrative diseases (sarcoidosis, tuberculosis, histiocytosis, lymphoma, eosinophilic granuloma)
Transient Hypothyroidism
• Subacute thyroiditis • Postpartum thyroiditis
Congenital Thyroid Hormone Resistance (Genetic)
• Peripheral variant • Central variant

Abbreviations: ^{131}I = iodine-131; PTU = propylthiouracil; TRH = thyrotropin releasing hormone; TSH = thyroid-stimulating hormone.

Etiology

PRIMARY **HYPOTHYROIDISM**

Chronic autoimmune thyroiditis is responsible for most spontaneously occurring cases of thyroid gland failure. As its name implies, chronic autoimmune thyroiditis results from an immunologic process characterized by the insidious, cell-mediated destruction of the thyroid gland. Lymphocytic thyroiditis and Hashimoto's thyroiditis represent specific pathologic terms that describe histologic variants of this autoimmune thyroid gland destruction. The disorder is characterized by progressive infiltration of the thyroid by lymphocytes, lymphoid follicles, and other inflammatory cells over many years, ultimately producing a remnant scar where the gland was located. The onset of the disease commonly occurs in early adolescence and primarily in females (5:1 female-to-male ratio) who display a small, irregular, firm, nontender goiter (so-called adolescent goiter) in an otherwise healthy young adult. Even in this initial phase of the disease, serum TSH concentrations can become persistently elevated; and serum anti-TPO antibodies are frequently detectable. The former is responsible for the compensatory goiter formation, and the latter serving as a nonspecific marker of the underlying thyroid autoimmunity. With advancing age, the cumulative incidence of **hypothyroidism** gradually rises in both females and males with the female-to-male ratio declining from an initial value of 5:1 to a 2:1 ratio by age 70 years. This latter finding is consistent with the concept of a genetic predisposition for developing autoimmune thyroiditis with thyroid dysfunction displayed earlier in the female population. It is noteworthy that this same age/sex pattern is commonly observed with other autoimmune diseases as well. Exposure to iodine-containing drugs such as intravenous (IV) contrast dyes and to immune modulating agents such as interferon can precipitate or exacerbate this underlying autoimmune process in susceptible individuals, occasionally producing an abrupt onset of thyroid gland failure and development of **hypothyroidism**. However, on withdrawal of these agents, thyroid function usually returns to the pretreatment status. In a similar context, postpartum thyroiditis represents a transient autoimmune exacerbation of thyroid dysfunction occurring during early postpartum in women with either preexisting or the genetic tendency for autoimmune thyroid disease. Although most of these women subsequently experience a spontaneous resolution of this mild and transient form of biochemical **hypothyroidism** within a few weeks, they should be considered to be an at-risk population for developing spontaneous **hypothyroidism** in the future.

UNCOMMON CAUSES OF PRIMARY **HYPOTHYROIDISM**

Severe dietary iodine deficiency, surgical thyroidectomy, iodine-131 (^{131}I) ablation, and excessive antithyroid drug administration represent obvious and anticipated causes of primary **hypothyroidism** and therefore should not represent either a diagnostic or therapeutic problem for the clinician. Approximately one third of patients with subacute thyroiditis will experience a mild to moderate primary **hypothyroidism** from 6 weeks to 6 months following the onset of this virally mediated destruction of the thyroid. However, in contrast to chronic autoimmune thyroiditis, this form of **hypothyroidism** is transient in character; eventual full recovery of thyroid gland function and histology is the norm. Neonatal **hypothyroidism**, or cretinism, represents a rare but important treatable cause of infant mental retardation. Although clinically difficult to recognize at birth, the widespread use of neonatal thyroid screening testing and early T_4 replacement therapy has essentially abolished this form of **hypothyroidism** in medically advanced countries. Fortunately, thyroid neonatal screening programs are also rapidly spreading to the underdeveloped regions of the world to address this treatable form of **hypothyroidism**.

CENTRAL **HYPOTHYROIDISM**

Central **hypothyroidism** is a rarely encountered entity representing less than 1% of all cases of **hypothyroidism**. It results from a wide variety of pathologic conditions that impair pituitary TSH, secondary **hypothyroidism**, and/or hypothalamic thyrotropin-releasing hormone (TRH), tertiary **hypothyroidism** production, or secretion resulting in a decline in function of the thyroid gland. Common causes of central **hypothyroidism** include pituitary tumors, empty sella syndrome, trauma, postpartum pituitary necrosis (Sheehan's syndrome), hypophysitis, whole-brain radiation, and a variety of infiltrative diseases (see Table 1). Of considerable diagnostic importance is that the biologic properties of the TSH secreted in secondary **hypothyroidism** are often altered (because of impaired TRH action on TSH formation) resulting in forms of TSH that have markedly reduced bioactivity while retaining normal immunoactivity. This phenomenon often results in falsely normal TSH values reported in patients who are otherwise biochemically and clinically hypothyroid. Therefore, the utility of serum TSH measurements by immunoassay in accurately assessing thyroid status is essentially lost either for establishing the initial **diagnosis** or monitoring the adequacy of T_4 replacement therapy in patients with secondary **hypothyroidism**.

Diagnosis

The clinical **diagnosis** of **hypothyroidism** is inherently difficult to establish because the classic features of this condition only become fully evident in the latest stages of the disease. Furthermore, the classic signs and symptoms of **hypothyroidism** such as weight gain, hypertension, dry skin, hair loss, cold intolerance, chronic fatigue, constipation, and fluid retention are nonspecific in character and commonly occur in populations without **hypothyroidism**. Only the presence of an asymptomatic, small, firm goiter and delayed deep tendon reflexes provide findings of some diagnostic utility and specificity. However, these signs are usually not routinely assessed unless a suspicion that the patient is at risk for developing **hypothyroidism** is present. Common risk factors include a positive family history of thyroid or other autoimmune diseases and the detection of an elevated serum TSH value with routine blood tests.

CURRENT DIAGNOSIS

- **Hypothyroidism** presents with nonspecific signs and symptoms. Therefore, **hypothyroidism** requires biochemical **diagnosis**.
- Screening of all adults older than 35 years of age should be considered.
- Definitive indications for screening include a positive family history and/or the presence of a goiter on exam.
- Routine screening tests include a serum TSH level and anti-TPO titer.
- Primary **hypothyroidism** is confirmed by elevated serum TSH levels and low T_4 values.
- Secondary **hypothyroidism** is diagnosed by low serum T_4 levels.

- Subclinical **hypothyroidism** is defined as a normal T_4 and a minimally elevated TSH level.

Abbreviations: anti-TPO = antithyroperoxidase; T_4 = l-thyroxine; TSH = thyroid-stimulating hormone.

AT-RISK POPULATIONS FOR PRIMARY **HYPOTHYROIDISM**

Because the propensity for the development of autoimmune diseases is strongly influenced by genetic factors, it is not surprising to find that **hypothyroidism** secondary to chronic thyroiditis is a familial disorder. Therefore, eliciting a family history either of an *underactive* or *overactive* thyroid condition, the use of thyroid medications, or the presence of a goiter all point toward the possibility of the patient harboring an occult thyroid disorder. If any of these conditions are present in the family, undertaking of a more careful neck examination palpating for a goiter, eliciting deep tendon reflexes evaluating for a slow relaxation phase, and measuring serum TSH and anti-TPO levels can be justified. A positive family history for other autoimmune disorders such as vitiligo, pernicious anemia, myasthenia gravis, Addison's disease, and type 1 diabetes mellitus increases the risk of developing autoimmune **hypothyroidism**. The discovery of such a history of familial autoimmunity is considerably useful because it raises the probability of detecting subclinical **hypothyroidism**.

LABORATORY DETECTION OF SUBCLINICAL **HYPOTHYROIDISM**

Measurement of serum TSH levels occupies a central role in establishing the laboratory **diagnosis** of primary **hypothyroidism**, especially in its earliest subclinical stage. Because thyroxine secretion declines as a result of the progressive destruction of the thyroid gland from chronic thyroiditis, even a small decrease in serum FT_4 concentration within the normal range promptly produces a reciprocal increase in the serum TSH value. Importantly, the relative magnitude of this serum TSH rise far exceeds the fall in FT_4 resulting from an *amplified* hypothalamic–pituitary negative feedback response, for example, a two-fold change in FT_4 produces a 100-fold change in TSH. Therefore, this isolated elevation in serum TSH not only serves as an early marker for impending thyroid gland failure but also acts to stimulate the preferential secretion of more biologically active triiodothyronine (T_3) by the thyroid gland, thereby masking the onset of the signs and symptoms of **hypothyroidism**. This latter phenomenon helps, in part, to explain the subclinical character of this syndrome. When such an isolated elevation in serum TSH is detected, the serum TSH determination should be repeated along with a serum anti-TPO measurement for diagnostic verification and as an indicator of the underlying autoimmune nature of the process. If not already performed, complete a careful family history, as characterized earlier; a careful neck examination for the presence of a goiter; and an assessment of deep tendon reflexes.

WHEN ARE SERUM THYROID-STIMULATING HORMONE ELEVATIONS SIGNIFICANT?

In ambulatory, clinically well individuals, any persistent serum TSH elevation should be considered as strong evidence for the presence of primary **hypothyroidism**, even when the serum FT_4 values remain within the normal range. With a normal reference range of serum TSH concentration of 0.5 to 3.5 mU/L, individuals displaying TSH increases from 3.5 to 10 mU/L or even higher are often remarkably free of hypothyroid symptoms, particularly in younger patients. However, bolstered by the additional findings of detectable anti-TPO antibodies, a positive family history for thyroid or other autoimmune diseases as well as the presence of a small firm goiter, this suspicion evolves into the realm of diagnostic certainty, even with modest rises in serum TSH levels. If, however, these additional confirmatory findings are absent but serum TSH elevations persist, some clinicians may choose to defer making a **diagnosis** of primary **hypothyroidism**, especially if the rise in serum TSH is minimal (less than 10 mU/L). In this case, the physician should continue to monitor serum TSH concentrations at 6- to 12-month intervals to ascertain the persistence and progression of **hypothyroidism** rather than to initiate lifelong oral T_4 therapy. Keep in mind, however, that many patients with mild subclinical **hypothyroidism** may experience unexpected symptomatic benefit as well as lowering of serum lipid levels following the initiation of T_4 replacement therapy. In this sense, *subclinical* **hypothyroidism** may represent a misnomer.

TRANSIENT SERUM THYROID-STIMULATING HORMONE ELEVATIONS ASSOCIATED WITH SYSTEMIC ILLNESSES

In contrast to the relatively stable serum TSH values encountered in healthy ambulatory populations, serum TSH values can become quite labile with acute illnesses where serum TSH values are commonly in the range characteristic of both hyper- and **hypothyroidism**. Generally, as the illness worsens, serum TSH concentrations become suppressed whereas during recovery they can rebound to elevated values. Obviously, these transient changes in serum TSH levels greatly impair the utility of serum TSH determination as a diagnostic tool. Therefore, greater reliance must be placed on serum FT_4 measurements in sick patients.

Interestingly, the therapeutic use of both glucocorticoids and dopamine will also cause dramatic transient reductions in serum TSH levels during their acute administration, followed by rebound elevations when these agents are withdrawn. It is believed that this results from direct inhibitory action on the release of TSH from the pituitary. Presumably, a similar inhibitory action from the endogenous cortisol increase on TSH secretion in response to major stress is responsible for the spontaneous decline in serum TSH in acute illness. When such transient changes in serum TSH occur in ambulatory patient populations, acute therapeutic glucocorticoid administration most often proves to be the culprit, such as asthma therapy. However, when chronic glucocorticoid therapy is employed, serum TSH concentrations generally remain in the normal range in the euthyroid patient.

THYROID-STIMULATING HORMONE SCREENING OF ADULT POPULATIONS

Serum TSH screening of adult populations is cost effectively performed because of technological advances made in the automation of TSH assay methods. This fact has led the American Thyroid Association to recommend screening of the entire population for thyroid disease starting at age 35 years and at 5-year intervals thereafter if initial screening results are normal. Other more restrictive population screening recommendations include testing the entire prenatal population and all the adult population starting at age 60 years. Certainly, all individuals providing a familial history of thyroid or other autoimmune diseases also make up a logical group deserving of TSH screening, as well. In the final analysis, it comes down to what is perceived to be the cost-to-benefit ratio of such an undertaking. Presently, a broad consensus in the medical community on this subject has not yet been formed regarding screening for thyroid disease in the population.

Treatment

ORAL L-THYROXINE ALONE AS THE SOLE FORM OF THYROID HORMONE REPLACEMENT THERAPY

The advantages of employing oral LT_4 (Synthroid) as the sole thyroid replacement therapy are many and include the following:

- The availability of several well-standardized, competitively priced brands of synthetic oral LT_4 (Table 2)
- A long biological half-life approximating 7 days, thereby making day to day compliance less critical
- Production of remarkably stable circulating levels of FT_4, which can be easily and accurately measured by routine laboratory testing methods
- Production of stable physiologic circulating levels of triiodothyronine (T_3), the active form of thyroid hormone, derived from the peripheral tissue conversion from T_4
- Allows the physiologically adaptive regulation of T_4 to T_3 conversion to occur in response to alterations in nutrition and stresses associated with illness and injury

TABLE 2 -- Thyroid Hormone Preparations

Generic Name	Brand Name

Generic Name	Brand Name
Levothyroxine sodium (LT_4)	• Levothroid • Levoxyl • Unithroid
Liothyronine sodium (LT_3)	Cytomel
Liotrix (LT_4 and LT_3 combination)	Thyrolar
Thyroid USP (LT_3 and LT_4 extract)	Armour Thyroid

Abbreviations: LT_4 = levothyroxine; LT_3 = liothyronine.

In contrast, the use of oral LT_3 (Cytomel) alone or in combination with LT_4 possesses none of these important advantages and therefore is not recommended for use as standard hormone replacement therapy.

INITIATION AND MAINTENANCE OF OPTIMAL LT_4 REPLACEMENT THERAPY IN PRIMARY **HYPOTHYROIDISM**

It is important to initiate oral LT_4 replacement therapy slowly, starting with a LT_4 dose of 25 µg daily and subsequently increasing the dose by 25 µg every 6 weeks until the serum FT_4 levels reach the midnormal range. A total daily LT_4 dose ranging between 50 and 125 µg usually is required to achieve this goal of a normal FT_4 value (a daily dose of 125 mg of LT_4 is needed for full replacement in an adult with no residual thyroid function). This deliberate treatment approach is essential to allow sufficient time for the myriad of metabolic alterations produced by T_4 therapy to take place. After achieving this initial goal of normal serum FT_4 levels, serial serum TSH levels can be measured to achieve an optimal individualized TSH target value ranging between 0.5 to 2.0 mU/L. However, with each LT_4 dosage adjustment, it is important to allow a period of at least 6 weeks for a new metabolic equilibrium to be achieved before serum TSH is remeasured. As noted, this LT_4 titration process requires that considerable time and patience be practiced by both by the clinician and patient. Once the final optimal serum TSH level is achieved, this daily oral LT_4 dose requirement rarely changes as long as the patient remains compliant and the brand of T_4 medication is not altered. One possible exception to this rule is that a slight reduction in LT_4 dose requirement often occurs after the age of 60 years presumably in association with a general slowing of overall metabolism.

CURRENT THERAPY

- Treatment of choice for **hypothyroidism** should be a nongeneric levothyroxine preparation.
- Interchanging of brands is contraindicated because each levothyroxine preparation has a unique absorption profile.
- Levothyroxine sodium (Synthroid) dosing should start at 25 µg daily and be increased slowly until the ideal dose is reached as determined by a serum TSH level.

- Goal of levothyroxine therapy in primary **hypothyroidism** is a serum TSH value between 0.5 mU/L and 2.0 mU/L.
- Goal of therapy in secondary **hypothyroidism** is a normal T_4 level.
- Treatment of subclinical **hypothyroidism** should be determined on a case-by-case basis.

Abbreviations: T_4 = l-thyroxine; TSH = thyroid-stimulating hormone.

TREATMENT OF CENTRAL **HYPOTHYROIDISM**

The initiation of oral LT_4 therapy in patients with central **hypothyroidism** is essentially the same as detailed previously for primary **hypothyroidism**. However, before starting LT_4 therapy, special care must be exercised to ensure adequate glucocorticoid replacement as thyroid hormone may accelerate glucocorticoid disposal and thereby may precipitate an Addisonian crisis. Additionally, because the measurement of serum TSH concentrations cannot serve as a useful therapeutic end-point in patients with central **hypothyroidism**, the adequacy of LT_4 replacement therapy must then rely on normalizing serum FT_4 values.

COMMON PITFALLS IN OPTIMAL ORAL L-THYROXINE THERAPY

The clinician should become suspicious that a problem likely exists in the management of LT_4 therapy when marked variability in serum TSH values occurs on a fixed LT_4 maintenance dose. The three most likely causes for this phenomenon are as follows:

1. Noncompliance: Poor compliance represents the most commonly encountered problem causing suboptimal LT_4 maintenance therapy. The principal reason for noncompliance usually relates to the fact that patients do not experience any immediate change in their state of health when stopping LT_4 therapy. This often results in patients missing their daily LT_4 dose or when they run out of their T_4 supply, not promptly replacing it. To compound the problem, when the patients are asked, “Are you taking your thyroid medication?” they can honestly say, “Yes,” because they may have recently restarted therapy in anticipation of the next physician visit. Therefore, one might ask, “How often do you forget to take your thyroid medication?” to remove the stigma from noncompliance. Patients often look puzzled when queried in such a manner but they then rapidly understand when their physician reassures them, “We all forget to take our medication at some time—I certainly do.” Experience indicates that such misinformation is the most common cause for physicians inadvertently prescribing excessive dosages of oral LT_4 therapy
2. Drugs and other factors altering T_4 absorption and metabolism: Table 3 lists some of the most common causes leading to a need for an increase in oral LT_4 dose requirements. Drugs or conditions that reduce gastric acidity also decrease T_4 absorption because the hormone is more readily absorbed in its acidic form. Because T_4 is highly lipophilic, drugs that interfere with fat absorption also will impair thyroxine absorption, as well. Still other drugs act to accelerate hepatic T_4 disposal by the so-called hepatic “first pass effect.” Administering oral LT_4 separately in the morning before taking drugs that interfere with GI absorption can mitigate this problem. Otherwise, compensatory increases in the oral LT_4 dosing schedule will be required.

3. Switching oral LT_4 brands: The T_4 content of oral thyroxine preparations is well standardized and carefully monitored by the FDA. However, variations in tablet dissolution characteristics and other features of the tablet structure appear to influence the efficiency of T_4 gastrointestinal absorption. These facts make it desirable not to switch the brand of an oral LT_4 preparation once the optimal dose has been ascertained for any given patient. For the same reason, generic T_4 brands should be avoided because the source of the T_4 tablets may vary over time.

TABLE 3 -- Common Causes Requiring Oral Levothyroxine Dosage Adjustment

Increased LT_4 Administration Required
• Poor compliance • Decreased gastrointestinal absorption: oral iron, lipid-binding drugs, sucralfate, calcium carbonate, achlorhydria, proton-blocking drugs • Altered T_4 metabolism: phenobarbital, phenytoin, carbamazepine, rifampin, HAART • Pregnancy • Nephrotic syndrome
Decreased LT_4 Administration Required
• Aging

Abbreviations: HAART = highly active antiretroviral therapy; LT_4 = levothyroxine; T_4 = L-thyroxine.

Special Situations

PREGNANCY

Women with **hypothyroidism** who become pregnant usually require substantial increases in their oral LT_4 maintenance dose. Such upward dose adjustments must be performed very early in pregnancy because normal fetal brain development in the first 12 weeks of gestation depends on maternal thyroxine as its source of thyroid hormone. Furthermore, there is strong circumstantial evidence that a deficiency in maternal T_4 at this stage of pregnancy is associated with a subsequent reduction in intelligence quotient in the offspring. It is noteworthy that one possible cause for this increased oral LT_4 requirement results from the concurrent use of oral iron supplements, which interfere with T_4 absorption (Table 3). To reduce this effect of iron on T_4 absorption, it is advisable to take the oral LT_4 dose and the iron at separate times.

SURGICAL PROCEDURES

Surgery usually does not present a special problem for hypothyroid patients who have received adequate preoperative oral LT_4 replacement therapy. The failure to receive oral medications for a few days postoperatively also is not a therapeutically important problem by virtue of the long 7-day half-life of thyroxine. However, in rare cases of prolonged restriction of oral intake, LT_4 can then be administered as a 500 µg IV

bolus every 5 days until oral intake can be restarted. In the untreated or inadequately treated hypothyroid patient requiring elective surgery, surgery should be deferred until a euthyroid state is restored with LT_4 therapy to significantly reduce operative and postoperative morbidity. In those instances of surgical emergenciesor in patients with severe coronary artery disease, surgery should proceed because such surgery is reasonably well tolerated if IV LT_4 therapy is administered in the immediate postoperative period.

MYXEDEMA COMA

Myxedema coma is a somewhat imprecise term in that this syndrome should be more appropriately termed *decompensated* **hypothyroidism**. Myxedema coma does not simply represent the natural progression of severe **hypothyroidism** but signifies an instance where intervening illness or events are responsible for precipitating a significant deterioration in mental status (i.e., acute psychosis, confusion, stupor, and coma) and producing cardiovascular collapse in the patient. The key to therapy is determining the precipitating cause and promptly initiating appropriate therapy. Occult infection and sepsis represent the most common etiologies of decompensation, but a long list of primary and contributing causes includes blood loss, excessive use of diuretics, carbon dioxide retention, oversedation with medications, overuse of tranquilizers and narcotics, and so forth. The use of IV LT_4 at an initial dose of 500 μg undoubtedly plays a positive role in marshalling an improved host response but is only useful in conjunction with the identification and reversal of the precipitating event(s).