Thyroid Function in Critical Illness and Burn Injury

By George M. Vaughan and Basil A. Pruitt, Jr

The marked and protracted hypermetabolic and catabolic response in major burn and other severe traumatic injury has been appreciated for most of this century. This response includes elevated body temperature, high cardiac output, and decreased peripheral resistance, and resolves in survivors as the wounds heal over weeks to months. During this time before wound closure, a condition resembling thyrotoxicosis is thus present. Because of this and the long-standing speculation that “stress” is the etiology of hyperthyroidism, Oliver Cope et al recognized the importance of determining whether the post-burn hypermetabolic condition is a function of transient hyperthyroidism. They found that thyroidal radioactive iodine uptake (RAIU) and serum protein bound iodine measurements were normal in burn patients and concluded that hyperthyroidism was not present and was not the mediator of the hypermetabolism. Later, others found a widely varying thyroidal RAIU in burn patients. However, in their patients with the most severe burns, a low RAIU clearly predominated during the 3 months after injury and ultimately resolved in survivors. RAIU measurements could have been influenced by a number of variables such as changing fluid and circulatory status, and thyroidal and renal iodide delivery, or iodine exposure or deprivation before or during the hospital course.

Others indirectly assessed thyroidal secretion in rats with small burns (10% to 20% body surface area) by loading the thyroid with radioactive iodine, following the decay of thyroidal radioactivity, and comparing this with the decay exhibited before the burn. Thyroid secretion appeared to be slowed in the first 1 to 2 days after the burn, then returned toward normal. In contrast, secretion appeared to be accelerated in control rats with simple removal of a similar area of skin, a reaction interpreted as the normal response to cold exposure. The protein catabolic and hypermetabolic response to burn injury still occurs in thyroprivic experimental animals, confirming that it is not thyroid-dependent. However, the resting energy expenditure level and post-burn indices of this response were both lower in animals previously rendered hypothyroid, suggesting that the thyroid gland is involved to some extent in the metabolic response to injury. This gland may continue to function at some level after injury, though interestingly, that level may be reduced.

Are Patients with Non-Thyroidal Illness Hypothyroid?

Subsequent measurement of thyroid-axis hormones in burn patients and animal burn models with more recent technology has confirmed that an increase in thyroid function does not occur following major burns. In fact, the opposite question of whether hypothyroidism occurs in this setting has arisen. Burn injury produces a pattern of thyroid function that has now been seen to occur in virtually every severe and protracted illness, whether medical, surgical, or traumatic, as well as in food deprivation. This set of illnesses is often called “non-thyroidal illness” or “NTI.”

Triiodothyronine and Thyroxine

The changed pattern of serum thyroid hormones in NTI is often labeled the “low T₃ syndrome” to represent the most common feature.
or more commonly "euthyroid sick syndrome." The latter label prejudges a normal, effective thyroid hormone-related status of the tissues. That is, so far, it has been difficult to characterize the effects of altered thyroid hormone levels as adverse or deleterious.

Nevertheless, the patterns of thyroid hormone changes and the plethora of conditions in which they are exhibited provoke important questions about the metabolic economy of illness and injury and the control of the thyroid axis. Some acute and usually time-limited conditions, as widely divergent as infections and psychotic episodes, may occasionally raise serum total thyroxine (T4) and/or free T4 (FT4) levels, with variable changes in serum triiodothyronine (T3) and thyrotropin (TSH). Little is known about the generation or metabolic consequences of this response, but it has been classified as a form of "euthyroid hyperthyroxinemia." In some cases, euthyroid hyperthyroxinemia involves a component of hepatitis that may raise T4 and/or T3 by virtue of release of hepatic stores of T4-binding globulin (TBG), without major disturbance of the metabolically active free hormone concentrations.

However, hyperthyroxinemia does not characterize severe illness or trauma and has not been a feature of major burn injury. Indeed, most NTI, particularly in patients requiring critical care, is characterized by low concentrations of serum T3 and usually less depression of T4 levels. With greater severity of illness, T3 and free T3 are even more depressed, but T4 may also decrease, generating the term "low T4-T3 syndrome." In human illness, this is opposite of the pattern in bonafide hypothyroidism due to intrinsic thyroid disease, wherein serum T3 at first tends to be preserved as T4 falls, with a rise in TSH. Because of this and the frequent additional observations of normal levels of free T4 (FT4) and TSH even in low T3-T4 NTI, critical illness is widely considered to be under the rubric of the euthyroid sick syndrome. However, it should be noted that low T3 has been an index of greater mortality in critically ill medical, surgical, and burn patients. These relationships to mortality have not been dependent on use of exogenous corticosteroids or dopamine, which may additionally depress the thyroid by inhibiting TSH secretion. On the other hand, replacement therapy of medical patients with T4 or of burn patients with T3 did not appear to prevent morbidity or mortality. T4 treatment of septic rats may have worsened their condition.

**Thyroid Hormone Disposal**

Another difference of human NTI from the hypothyroidism of thyroid disease is found in the pattern of changes in T3 and the metabolically inactive product of T4, reverse T3 (rT3). A disproportionately greater decrease in serum T3 than in T4 may result from NTI-induced inhibition of outer ring monodeiodination of T4 to T3 in peripheral tissues, though abnormalities in other pathways in T4 disposal may be involved. This peripheral conversion to T3 normally supports serum T3 concentration, because T3 is the principal iodothyronine secreted from the thyroid. In contrast, in hypothyroidism, serum T3 may be preferentially supported by the rise in TSH and less diminution of T3 than of T4 secretion by residual thyroid activity. NTI may raise rT3 by inhibiting its monodeiodination and delaying its clearance. In contrast, hypothyroidism may produce low rT3 from lack of substrate T4.

Though these differences underscore a basic dissimilarity between hypothyroidism and NTI-induced thyroid axis changes, they do not directly address the issue of whether an underlying hypothyroidism exists at the tissue level in NTI. Thyroid hormone kinetic studies have shown results that suggest reduced availability of thyroid hormones to tissues in NTI. The metabolic clearance rates of T4 and T3 appear to be accelerated despite inhibited one-way transfer from serum to tissue pools, and production rates appear reduced. Tissue pool sizes appear diminished. However, such changes may not distinguish deficient tissue delivery of thyroid hormone from an attempt to prevent excessive delivery and may simply reflect the increased metabolic rate in resuscitated injured patients.

**Free Thyroid Hormones and Serum-Binding Defect**

Clinically significant hypothyroidism from intrinsic disease of the thyroid axis is usually indicated by depressed free T4 (FT4), the concen-
tration unbound to serum proteins. Most methods used to estimate \( FT_4 \) levels agree closely in their ability to disclose abnormalities of the pituitary-thyroid axis outside the setting of NTI. However, the many different methodological types of \( FT_4 \) estimates give varying results (compared with normal) in samples from patients with NTI. \(^7\) The most commonly used \( FT_4 \) estimate involves determining an index of the unbound fraction of radiotracer \( T_1 \) (in vitro \( T_3 \) uptake, \( T_3U \), on an exogenous binding matrix in competition with serum thyroxine-binding proteins) and multiplying this by the serum \( T_4 \) concentration. This product gives an index, the \( FT_4I \). Other \( FT_4 \) estimates involve determining the dialyzable or ultrafilterable fraction of \( T_4 \) tracer (\( DFT_4 \) or \( UFT_4 \)). This multiplied by the \( T_4 \) gives the \( FT_4D \) or \( FT_4U \), which are considered the most reliable estimates of free \( T_4 \) concentration, least likely confounded by artifacts resulting from abnormalities in serum constituents. Other \( FT_4 \) estimates, based on competitive binding of tracer \( T_4 \) or an analogue, show variable extents of adventitial effects from serum abnormalities.

Mostly by use of \( FT_4D \) procedures, it has been known for a number of years that the free fraction of \( T_4 \) (\( DFT_4 \)) is elevated in NTI. \(^8\) A similar deficit in serum \( T_3 \) binding is also observed. This widely observed NTI-induced serum thyroid hormone-binding defect can compensate for low (total) \( T_4 \) levels, normalizing the \( FT_4 \) concentration. In this situation, it is not uncommon to observe a low \( FT_4I \). However, \( FT_4D \) has also sometimes been low in critical NTI and \( FT_4D \) is frequently low. Non-esterified fatty acids (NEFA) from augmented lipolysis in NTI have been implicated as the hormone-binding inhibitor. \(^9\) Artifactual binding deficiency can be produced by use of heparin, which stimulates lipase activity in samples. \(^10\)

**Thyroid Hormone Availability to Tissues**

It can be argued that the NTI-induced thyroid hormone-binding defect results from a serum constituent that not only reduces binding to serum proteins, but also inhibits thyroid hormone in NTI samples from in vitro binding to rat hepatocytes. \(^7\) human red blood cells. \(^8\) HepG2 cells of human hepatoma origin, \(^9\) as well as to exogenous binding matrices in the \( T_3U \) test \(^7\) that is used in obtaining the \( FT_4I \). This suggested reduction of \( T_4 \) availability to tissues was reflected in much better prediction of HepG2 cellular uptake of \( T_4 \) by the \( FT_4I \) than by the \( FT_4D \) in NTI patients. \(^10\) It is possible that altered \( FT_4I \) might better reflect altered availability to tissues than the free \( T_4 \) concentration. Thus, the more often depressed \( FT_4I \) may bespeak low \( T_4 \) tissue availability in critical NTI. If there is low thyroid hormone availability in severe NTI, tissues might respond as if there is hypothyroidism. However, low metabolic rate has not characterized most NTI, and high \( O_2 \) consumption is often present. \(^10\)

**Control of Thyrotropin**

Hypothyroidism at the tissue level is most readily sensed in the pituitary to produce an elevated thyrotropin (TSH) level in serum. \(^11\) However, in a large population of hospitalized patients assessed with a sensitive and specific assay, 85% had normal TSH and twice as many had low as had high levels. \(^12\) Critically ill patients with low \( T_3 \) and \( T_4 \) levels are more likely to have a frankly low TSH and/or a blunted response to its releasing hormone (TRH). \(^13\) Depressed serum TSH in NTI relative to controls is best seen in nocturnal samples, particularly in fatal cases, which disclose blunting or obliteration of the nocturnal rise in TSH. The tendency to lower TSH often could not be explained by inadequate caloric intake or use of drugs (eg, glucocorticoids, dopamine) known to depress TSH. Absence of elevated TSH suggests that the pituitary does not interpret the low thyroid hormone levels in human NTI as hypothyroidism. Blockade of the nocturnal surge of TSH is a finding in central hypothyroidism \(^14\) and suggests the possibility of an adaptation at the pituitary-hypothalamic level in NTI.

Additionally, the above results suggest that NTI exerts a relative inhibitory influence on TSH secretion, perhaps resetting TSH release to be retrainable by lower thyroid hormone levels. \(^15\) Augmentation of the TSH response to TRH is normally seen after iodide-induced slowing of thyroid secretion. This augmentation was blunted in NTI. \(^16\) In a rat model of NTI (transplanted carcinoma), depression of serum free \( T_3 \) and \( T_4 \) was associated with reduced pituitary \( T_1 \). \(^17\) The latter, mostly converted locally from serum \( T_4 \),
is the principal factor providing negative feedback to inhibit TSH secretion. Nevertheless, neither serum TSH nor its response to further lowering of thyroid hormones (by additional thyroidec- tomy or chemical thyroid blockade) was augmented in the tumor-bearing rats. Thus, they were able to regulate TSH around a setting relatively low for the available thyroid hormones. Furthermore, rat NTI models have had low pituitary TSH mRNA\textsuperscript{97} and a deficient thyroid to serum iodide concentration ratio,\textsuperscript{96} the latter considered a reflection of reduced TSH effect. The implications are that in NTI, thyroid hormone has an augmented ability to suppress TSH secretion and that pituitary-thyroid function is set at a new (low) level but not eliminated. Normal or even mildly elevated levels of serum TSH in NTI might indicate relatively deficient TSH for the thyroid hormone milieu, even though some degree of response is maintained.

The lower setting for TSH secretion may contribute to relative lowering of thyroid function in NTI. This formulation is supported by the return of serum thyroid hormones toward normal in patients recovering from NTI in association with prior rises of TSH to values near or above the upper limit of normal.\textsuperscript{98,99} A role of elevated levels of endogenous cortisol and dopamine in NTI to produce the relative inhibition of TSH secretion is suspected. Contrariwise, intercurrent hypothermia may raise serum TSH.\textsuperscript{98,100}

Assessment of TSH, like that of tissue thyroid hormone availability, suggests a genuine suppression in thyroid axis function in NTI. However, lack of hypometabolism, resetting of TSH control, and lack of apparent benefit of thyroid hormone replacement point toward a physiological adaptation to illness rather than pathological hypothyroidism.

Cytokines

NTI usually involves activation of cells that promote host defense, inflammatory changes, and tissue repair. In that cytokine products of these cells can produce many of the concomitants of illness including augmented cortisol and NEFA levels, it has been suspected that cytokines may also mediate the thyroid axis changes of NTI.\textsuperscript{97} Indeed, in mice, administration of either tumor necrosis factor (TNF) or interleukin-1\textsuperscript{101} reduced T\textsubscript{4} and T\textsubscript{3} levels. In normal humans, TNF injection lowered serum T\textsubscript{3} and TSH and raised rT\textsubscript{3}.\textsuperscript{102} However, in NTI patients, serum TNF concentrations were usually not elevated and did not correlate with serum T\textsubscript{4}, T\textsubscript{3}, or rT\textsubscript{3}.\textsuperscript{103} Because current technology may not yet allow measurement with sufficient sensitivity and specificity to detect relevant changes in circulating cytokines, it is too early to discount their mediation in the thyroidal and other changes of NTI.

**BURNS AS A MODEL OF NON-THYROIDAL ILLNESS**

Many of the changes discussed above that occur in the composite spectrum of non-burn NTI have been detected with variable frequency in various non-burn conditions. Relationships of interest among the possible changes have not always been well defined. Studies of burn patients and animal models of burn injury have allowed detailed observation of many of the changes seen in other critical illnesses.

**Thyroid Axis Suppression**

The depression of mean values for circulating concentrations of T\textsubscript{3} and T\textsubscript{4} in groups of burn patients and burn animal models is well documented.\textsuperscript{11-25} Burn size provides a convenient index of the extent of illness. The depression of serum T\textsubscript{4} and T\textsubscript{3} and their free estimates is proportional to burn size.\textsuperscript{24,25} Additional depression of these variables in patients is exerted by sepsis\textsuperscript{11} or non-survival,\textsuperscript{24,25} independent of the extent of burn. In uncomplicated patients with burns of less than 20% of the total body surface, T\textsubscript{3} variables were usually not depressed. In survivors, recovery of T\textsubscript{4} variables (if depressed) generally followed rises in TSH and preceded recovery of T\textsubscript{3} variables, the latter occurring gradually over variable periods of up to 2 to 3 months in the patients with more extensive burns.\textsuperscript{12,24,99} In a group of non-survivors, mean values for T\textsubscript{4} and T\textsubscript{3} variables and TSH gradually descended to very low levels in the days to weeks before demise.\textsuperscript{24} This decrease was initiated independently of drugs known to depress thyroid function. These findings in burns show dramatically the profound suppression of the entire thyroid axis that is possible in NTI. However, such suppression may not represent true hypothyroidism, requiring thera-
peutic correction. In 28 young men, 17 to 23 years of age, with large burns (18% to 93% body surface), random double-blind assignment to full replacement of T₃ (vs placebo) throughout their course resulted in the same mortality (4/14) in both groups with the same distribution of burn size.¹⁴

Relative Alterations of Iodothyronines

Although T₄ to T₃ conversion has not been directly measured in burns, the mean 1.5- to 2-fold greater proportional decrement of T₃ than of T₄ concentration variables in burned patients (relative to respective mean normal) resembles the pattern of inhibited T₄ to T₃ conversion seen in other forms of human NTI.²⁴·²⁵ Interestingly, in burned rats, the relative decrease in serum T₄ is the same or greater than that of T₃.¹⁸·²⁰·²²·²⁴·²⁵ This conforms to the pattern seen in other rat NTI models,³⁶·⁹⁷·¹⁰⁴·¹⁰⁵ including fasting, infection, uremia, transplanted carcinoma, turpentine inflammation, and diabetes mellitus. The cause of this difference from the human NTI response pattern is not yet understood.

Elevation of mean serum rT₃ in groups of burn patients is often present, and a weak-positive relationship to burn size and/or mortality has sometimes been noted.¹¹·¹³·¹⁴·¹⁶·²³·²⁴ The less predictable response of rT₃ in burns compared with a number of other forms of human NTI is not understood. Studies in the normal rat indicated that the skin is the major site of rT₃ formation and storage in this species.¹⁰⁶ Whether destruction of parts of this site in humans would partly interfere with an NTI-induced increase in serum rT₃ in burn patients is not known. Burned rats have an opposite response of serum rT₃ from that of humans with burns or NTI, in that a burn-size-related depression of rT₃ occurs in rats.²⁵ However, the relevance of normal rat skin as a potential source of rT₃ in explaining this is uncertain. In another rat NTI model, turpentine injection also lowers rT₃.¹⁰³ In mouse models, bacterial infection or injection of cytokines also lower rT₃.¹⁰¹ It is apparent that burn injury faithfully reproduces NTI hormonal patterns even when they diverge between species.

Serum Iodothyronine Binding

In a group of burn patients (burn size 17% to 68%, studied mainly in the second and third week post burn) whose mean FT₄ D concentration was reduced significantly below the unburned matched control mean, the serum-binding defect (elevated DFT₄) was present but insufficient to offset the low T₄ and normalize the mean FT₄ D. Less prominently elevated T₃ U (than DFT₄) was indicated by somewhat lower FT₃ I in burns than in controls at any given projected FT₄ D over the range of values exhibited.²³ The relatively lesser binding of tracer in these burn samples to the exogenous T₃ U matrix than expected from the magnitude of the serum protein-binding defect determines a somewhat more accentuated burn-induced depression of free T₄ concentration as estimated by the FT₄ I than by the FT₄ D. These relationships were confirmed in rats at 8 and 14 days after a 60% burn,¹⁸ with essentially identical results. Furthermore, in the above patients and rats, the T₃ U (and FT₃ U) was used also in conjunction with the DFT₃ and FT₃ D. Very similar results in both species, with the same kind of disparity between T₃ U- and T₃ Dialysis-derived variables, indicated that observation of the binding deficiency to both serum protein and T₃ U matrix did not depend on whether T₃ or T₄ dialysis-derived variables were used in the comparisons.

This pattern mimics the findings in other NTI in which the FT₄ D overestimated the concentration of T₄ available to cells, the latter apparently more closely estimated by the FT₄ I.²⁵ It has not yet been determined whether the factor in burn samples that inhibits iodothyronine binding to serum proteins and to an exogenous T₃ U matrix also limits hormone availability to tissues. Nevertheless, evidence for inhibition of binding to both serum protein and matrix suggests that the post-burn samples contained a binding inhibitor(s) and that the serum-binding defect does not result entirely from a deficiency of serum-binding proteins. Burn patients usually have normal levels of thyroxine-binding globulin, though the other less avidly binding proteins may be diminished.²⁵ Thus, as in other NTI, the identity of a binding inhibitor and the relative role for it versus abnormalities of binding proteins in burn injury are not yet known.

Control of Metabolism

Conveniently, both the depression of thyroid hormones and an elevation of resting metabolic
rate are proportional to burn size over approximately the same time course. 24 This very divergence of thyroid function and metabolism itself indicates that non-thyroid mediators are primarily responsible for the hypermetabolic drive. A large array of changes occurs in the endocrine milieu of burn patients, most of which changes often occur also in other forms of NTI, 25 including elevation of catecholamines, cortisol, and glucagon. Correlation of post-burn hypermetabolism with urine catecholamine excretion and blunting of hypermetabolism with beta-adrenergic blockade suggested mediation by catecholamines. 107,108 Resting supine levels of plasma norepinephrine and epinephrine were found to be correlated inversely with serum $T_3$ in hypermetabolic patients with large burns. 12 Treatment of these patients with $T_3$ lowered plasma norepinephrine without changing the metabolic rate. This suggested that in the low thyroid functional state of NTI, resting metabolism is elevated at least partly by a regulated rise in sympathetic activity.

In another study 17 of patients with large burns, weekly measurements of fasting resting metabolic rate were negatively correlated with thyroid hormones, but were positively correlated not only with plasma norepinephrine but also with glucagon and cortisol. These and the previously mentioned results have allowed the tentative conclusion that resting metabolism after burn injury (and probably in other hypermetabolic NTI) is removed from control by the thyroid gland and placed under the influence of a set of anti-insulin hormones that may include catecholamines, cortisol, and glucagon, but not growth hormone.

Caloric deprivation produces some of the changes of NTI, such as the thyroid axis changes, suppression of the reproductive system, and elevation of cortisol, glucagon, lipolysis, and gluconeogenesis. 25 Thus, an element of starvation may contribute to the thyroidal changes seen in some NTI patients. However, this is not the case in the above discussed studies of burn patients, because they usually received vigorous hyperalimentation. Furthermore, critical illness and major burn injury are fundamentally different from starvation, 26 the former hypermetabolic and the latter hypometabolic in terms of $O_2$ consumption. In primary fuel deprivation, proteolysis is diminished to minimize net muscle loss possibly mediated by the low $T_3$, and high glucagon and cortisol are secondary to relative hypoglycemia and promote elevation of glycogenolysis, lipolysis, and gluconeogenesis. In contrast, in illness and burns, proteolysis is accelerated and the stimulation of catecholamines, glucagon, cortisol, gluconeogenesis, and lipolysis is characteristically independent of hypoglycemia and might be mediated by cytokines from areas of tissue damage and repair. In this case, the reduction in thyroid activity again appears adaptive, though the adaptive advantage is not yet clear.

Control of Thyrotropin

Though the changes in thyroid hormones in human burn injury, including the accentuated depression of $T_3$, may involve elements other than depression of TSH secretion, the latter appears to be involved. Depression of TSH appears mainly as altered TSH regulation in burn survivors in whom serum TSH can remain in or near the normal range and respond normally to TRH despite reduced availability of $T_3$ and often of $T_4$. TSH can be frankly depressed on replacement of thyroid hormone or in nonsurvivors. 12,14,24

Characteristics of this altered TSH regulation have been defined with use of a non-lethal, full-thickness burned rat model. After a 60% burn, serum $T_4$ and FT4 were depressed by 6 hours and markedly so at 24 hours when TSH became elevated. 22 Partial restoration of $T_4$ and FT4 (though still depressed) at 48 hours accompanied the reduction of TSH back to normal levels. Thereafter, all three variables fell in parallel. TSH was significantly depressed (vs sham burn) at the end of the first and second weeks, when FT4 was also shown to be depressed in other rats with this size burn. In rats with only a 17% burn, $T_4$, FT4, FT3, $T_3$, FT3, and FT3 were depressed at 6 and 24 hours. TSH, elevated at 24 and 48 hours, normalized FT4 and FT3 by 48 hours. 22 Thus, the initial decrease in thyroid hormones is not $T_3$-independent, and TSH initially responds as if the animals were hypothyroid. The altered TSH regulation appeared in the rats with a larger
burn, and then only after 2 days with progressive accentuation thereafter for at least 2 weeks.

Further characterization of the altered TSH regulation was obtained in 25% burned rats receiving placebo or T4 (11 μg/100 g per day) by subcutaneous osmotic minipump during the 6 days post-burn before sampling. Normal regulation was defined in sham burn and in thyroidectomized rats. In rats not receiving T4, mean FT4 was depressed in the burn group, though TSH was not. Primary alteration of T4 produced a negative relationship between FT4 and TSH in the burns as it did in the various controls (Fig 1). However, at a given FT4 or FT4, serum TSH was lower in the burn group. This was not due to augmented serum T3, because T3 and FT3 were lower in the burn groups than in comparable control groups. The altered regulation of TSH in burn rats can be viewed as an augmented ability of thyroid hormone to restrain TSH, a conclusion similar to that obtained in another rat NT1 model with use of different techniques.

Local pituitary conversion of serum T4 to T3 (via Type II 5'eiodinase) provides the T3 stimulus for negative feedback on TSH, and a rise in pituitary and brain 5'eiodinase activity provides a sensitive index of low serum T4 as sensed by these particular tissues in the hypothyroid rat. In three different non-burn rat models of NT1, serum TSH was frankly depressed. No change was observed in pituitary 5'eiodinase activity in any of the models. This suggests that depression of TSH secretion does not occur via augmented conversion of T4 to T3 in the pituitary and that the pituitary does not sense the low thyroid hormones as hypothyroidism.

Pituitary 5'eiodinase has not been assessed in burned rats, though brain T4 to T3 conversion has. Figure 2 shows that although the brain sensed hypothyroidism after thyroidectomy, it apparently did not sense hypothyroidism after burns, despite dramatic reductions in thyroid hormones.

In sum, a post-burn diminution of TSH secretion relative to the reduced availability of thyroid hormones may contribute to the depressed thyroid function. These changes resolve on healing of the wounds. Despite these changes, it appears that neither bonafide hyper- nor hypothyroidism has been documented to result from burn injury or other NT1. The decrease in thyroid axis activity may represent an adaptation that provides an as yet undocumented advantage. At any rate, no currently available data support the clinical use of replacement therapy in this situation.

**TOPICAL IODINE TREATMENT**

In areas of iodine sufficiency, iodine intake in the population usually ranges from 45 to 700 μg/d. Normal serum iodine is about 4 to 8 μg/dL, most of which is incorporated into tyrosine residues of thyroid hormones or of albumin and a small amount is circulating iodide. Large doses of iodine (or iodide) initially block thyroid hormone synthesis and secretion, acutely lowering T4 and/or T3 levels that are restored by a rise in TSH secretion with continued iodine exposure in normal persons. Rare development of goiter and hypothyroidism or of hyperthyroidism
Fig 2. Serum thyroid hormones, serum TSH, and in vitro brain (telencephalon and diencephalon) 5'-deiodinase (5'-DI) activity (T₄ to T₃) in adult male rats subjected to thyroidectomy, 60% full-thickness burn, or sham burn (mean ± SE). RP1 standard was used in the TSH assay. Activity of 5'-DI was taken as the difference in T₃ (RIA of ethanol extracts) for a brain homogenate between separate aliquots with T₄ (1 µg/mL) added before and after incubation; the 2-hour incubation always included 25 mM dithiothreitol. In the 5'-DI plot, the left side of each bar represents incubation without and the right side with 1 mM propylthiouracil. The predominance of propylthiouracil-resistant 5'-DI activity in all groups, and the similar pattern between this and total activity across groups suggest that the 5'-DI changes mainly reflect the type II 5'-DI enzyme typically predominant in brain. C, controls; S, sham burn; T, 2 weeks after thyroidectomy; B, 2 weeks after 60% burn. *P < .05; **P < .001; T versus C, or B versus S.

Topical treatment with povidone-iodine raises serum iodine. For example, daily povidone-iodine mouth washes for treatment of gingivitis may largely depend on different predisposing conditions.  

Topical treatment with povidone-iodine raises serum iodine. For example, daily povidone-iodine mouth washes for treatment of gingivitis raised total serum iodine 2- to 3-fold, serum iodide about 10-fold, and urinary iodine excretion about 15-fold, presumably reflecting a similarly increased absorption. Beyond 6 weeks of continuous exposure, serum T₄, FT₄, and T₃ were unchanged from baseline, though TSH remained slightly but significantly elevated.

Topical treatment of large burns with povidone iodine may produce serum iodine levels 125- to 8,000-fold more than normal. Burn patients treated with this topical agent for days or weeks have occasionally exhibited metabolic acidosis and a fatal outcome. Though the course in these patients was confounded by a pattern of prerenal failure, renal failure, and/or sepsis, nevertheless an absence of lactic acidemia was noted in some cases. These authors hypothesized that there was iodine toxicity with possible consumption of bicarbonate to produce iodide and periodate and impairment of renal acid excretion. Though these possibilities remained largely untested, they recommended against the use of povidone-iodine in situations predisposing to acidosis, in renal failure, and in patients with burns larger than 20% of body surface area. The likelihood of iodine toxicity in these settings remains uncertain.

Investigators measuring thyroid function in patients with large burns treated for days to weeks with topical povidone-iodine have usually not reported results for comparison in similar patients not so treated. Patterns of serum T₄, T₃, rT₃, and TSH did not appear to differ from what might be expected in burn patients, though there may possibly have been some depression of T₄ and/or T₃ and elevation of TSH due to the agent. Should a suspected thyroid disease require further investigation in such a patient, thyroidal radiiodine uptake and scan studies most likely would not be interpretable because of the iodine exposure. As a separate issue, it is unknown whether burn injury can change the likelihood that large excesses of iodine exposure for a few weeks may cause overt thyroid disease. In the absence of burn, this likelihood is usually very low, especially without predisposing factors such as chronic iodine deficiency or underlying thyroid abnormalities. Because thyroidal and extrathyroidal effects of large doses of iodine in the setting of burn injury remain undetermined, iodine-containing topical agents probably should not be used in this setting.
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