DTIC
ELECTE
APR 08 1994
S D
F

AD-A277 947

94-10602

12pg

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.[1-3] This response includes elevated body temperature, high cardiac output, and decreased peripheral resistance,[4] 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[5] 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.[6] 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.[7] 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[8] and hypermetabolic[9,10] 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.[11-25] 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,[26-53] as well as in food deprivation.[54-61] This set of illnesses is often called "nonthyroidal illness" or "NTI."

Triiodothyronine and Thyroxine

The changed pattern of serum thyroid hormones in NTI is often labeled the "low T_3 syndrome" to represent the most common feature,

From the U.S. Army Institute of Surgical Research, Internal Medicine Branch, Ft Sam Houston, TX.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Reg 70-25 on Use of Volunteers in Research.

Research was conducted in compliance with Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and in adherence with the Guide for the Care and Use of Laboratory Animals, *NIH publication 80-23, 1985 edition.*

Address reprint requests to George M. Vaughan, MD, Col. MC., Chief, Internal Medicine Branch, Bldg 2653, U.S. Army Institute of Surgical Research, Fort Sam Houston, TX 78234-5012.

This is a government work. There are no restrictions on its use.

0270-9295/93/1304-0002$0.00/0

94 4 2 012

This document has been approved for public release and sale; its distribution is unlimited

QUALITY INSPECTED 3

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[26-61] 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 (T_4) and/or free T_4 (FT_4) levels, with variable changes in serum triiodothyronine (T_3) and thyrotropin (TSH).[33,37-39,45,47] 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 T_4 and/or T_3 by virtue of release of hepatic stores of T_4-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 T_3 and usually less depression of T_4 levels. With greater severity of illness, T_3 and free T_3 are even more depressed, but T_4 may also decrease, generating the term "low T_4-T_3 syndrome." In human illness, this is opposite of the pattern in bonafide hypothyroidism due to intrinsic thyroid disease, wherein serum T_3 at first tends to be preserved as T_4 falls, with a rise in TSH.[62] Because of this and the frequent additional observations of normal levels of free T_4 (FT_4) and TSH even in low T_4-T_3 NTI, critical illness is widely considered to be under the rubric of the euthyroid sick syndrome. However, it should be noted that low T_4 has been an index of greater mortality in critically ill medical,[47,50,51] surgical,[52,53] and burn[24] 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 T_4[41] or of burn patients with T_3[14] did not appear to prevent morbidity or mortality. T_4 treatment of septic rats may have worsened their condition.[63]

Thyroid Hormone Disposal

Another difference of human NTI from the hypothyroidism of thyroid disease is found in the pattern of changes in T_3 and the metabolically inactive product of T_4, reverse T_3 (rT_3). A disproportionately greater decrease in serum T_3 than in T_4 may result from NTI-induced inhibition of outer ring monodeiodination of T_4 to T_3 in peripheral tissues, though abnormalities in other pathways in T_4 disposal may be involved.[36,37,47,64-69] This peripheral conversion to T_3 normally supports serum T_3 concentration, because T_4 is the principal iodothyronine secreted from the thyroid. In contrast, in hypothyroidism, serum T_3 may be preferentially supported by the rise in TSH and less diminution of T_3 than of T_4 secretion by residual thyroid activity. NTI may raise rT_3 by inhibiting its monodeiodination and delaying its clearance. In contrast, hypothyroidism may produce low rT_3 from lack of substrate T_4.

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.[37,45,47,65-67] The metabolic clearance rates of T_4 and T_3 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 T_4 (FT_4), 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.[70-79] The most commonly used FT_4 estimate involves determining an index of the unbound fraction of radiotracer T_3 (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.[80-86] 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_3D is frequently low. Non-esterified fatty acids (NEFA) from augmented lipolysis in NTI have been implicated as the hormone-binding inhibitor.[83-86] Artifactual binding deficiency can be produced by use of heparin, which stimulates lipase activity in samples.[85]

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,[87] human red blood cells,[88] $HepG_2$ cells of human hepatoma origin,[89] as well as to exogenous binding matrices in the T_3U test[87] that is used in obtaining the FT_4I. This suggested reduction of T_4 availability to tissues was reflected in much better prediction of $HepG_2$ cellular uptake of T_4 by the FT_4I than by the FT_4D in NTI patients.[89] 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.[25]

Control of Thyrotropin

Hypothyroidism at the tissue level is most readily sensed in the pituitary to produce an elevated thyrotropin (TSH) level in serum.[62] 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.[47] 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).[90,91] Depressed serum TSH in NTI relative to controls is best seen in nocturnal samples,[92,93] particularly in fatal cases,[94] 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[95] 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 restrainable by lower thyroid hormone levels.[34] Augmentation of the TSH response to TRH is normally seen after iodide-induced slowing of thyroid secretion. This augmentation was blunted in NTI.[25] In a rat model of NTI (transplanted carcinoma), depression of serum free T_4 and T_3 was associated with reduced pituitary T_3.[96] 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 thyroidectomy 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[97] and a deficient thyroid to serum iodide concentration ratio,[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.[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.[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.[47] Indeed, in mice, administration of either tumor necrosis factor (TNF) or interleukin-1[101] reduced T_4 and T_3 levels. In normal humans, TNF injection lowered serum T_3 and TSH and raised rT_3.[102] However, in NTI patients, serum TNF concentrations were usually not elevated and did not correlate with serum T_4, T_3, or rT_3.[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_3 and T_4 in groups of burn patients and burn animal models is well documented.[11-25] Burn size provides a convenient index of the extent of illness. The depression of serum T_4 and T_3 and their free estimates is proportional to burn size.[24,25] Additional depression of these variables in patients is exerted by sepsis[11] or non-survival,[24,25] independent of the extent of burn. In uncomplicated patients with burns of less than 20% of the total body surface, T_4 variables were usually not depressed. In survivors, recovery of T_4 variables (if depressed) generally followed rises in TSH and preceded recovery of T_3 variables, the latter occurring gradually over variable periods of up to 2 to 3 months in the patients with more extensive burns.[12,24,99] In a group of non-survivors, mean values for T_4 and T_3 variables and TSH gradually descended to very low levels in the days to weeks before demise.[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 T_3 (*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 T_4 to T_3 conversion has not been directly measured in burns, the mean 1.5- to 2-fold greater proportional decrement of T_3 than of T_4 concentration variables in burned patients (relative to respective mean normal) resembles the pattern of inhibited T_4 to T_3 conversion seen in other forms of human NTI.[24,25] Interestingly, in burned rats, the relative decrease in serum T_4 is the same or greater than that of T_3.[18,20-22,24,25] This conforms to the pattern seen in other rat NTI models,[96,97,104,105] 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 rT_3 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 rT_3 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 rT_3 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 rT_3 in burn patients is not known. Burned rats have an opposite response of serum rT_3 from that of humans with burns or NTI, in that a burn-size-related depression of rT_3 occurs in rats.[25] However, the relevance of normal rat skin as a potential source of rT_3 in explaining this is uncertain. In another rat NTI model, turpentine injection also lowers rT_3.[105] In mouse models, bacterial infection or injection of cytokines also lower rT_3.[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 FT_4D concentration was reduced significantly below the unburned matched control mean, the serum-binding defect (elevated DFT_4) was present but insufficient to offset the low T_4 and normalize the mean FT_4D. Less prominently elevated T_3U (than DFT_4) was indicated by somewhat lower FT_4I in burns than in controls at any given projected FT_4D over the range of values exhibited.[25] The relatively lesser binding of tracer in these burn samples to the exogenous T_3U matrix than expected from the magnitude of the serum protein-binding defect determines a somewhat more accentuated burn-induced depression of free T_4 concentration as estimated by the FT_4I than by the FT_4D. 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 T_3U (and FT_3I) was used also in conjunction with the DFT_3 and FT_3D. Very similar results in both species, with the same kind of disparity between T_3U- and T_3 dialysis-derived variables, indicated that observation of the binding deficiency to both serum protein and T_3U matrix did not depend on whether T_3 or T_4 dialysis-derived variables were used in the comparisons.

This pattern mimics the findings in other NTI in which the FT_4D overestimated the concentration of T_4 available to cells, the latter apparently more closely estimated by the FT_4I.[25] It has not yet been determined whether the factor in burn samples that inhibits iodothyronine binding to serum proteins and to an exogenous T_3U 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,[25] 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 FT_4I were depressed by 6 hours and markedly so at 24 hours when TSH became elevated.[22] Partial restoration of T_4 and FT_4I (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 FT_4D was also shown to be depressed in other rats with this size burn. In rats with only a 17% burn, T_4, FT_4I, FT_4D, T_3, FT_3I, and FT_3D were depressed at 6 and 24 hours. TSH, elevated at 24 and 48 hours, normalized FT_4 and FT_3 by 48 hours.[22] Thus, the initial decrease in thyroid hormones is not TSH-dependent, 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 T_4 (11 μg/100 g per day) by subcutaneous osmotic minipump during the 6 days post-burn before sampling.[22] Normal regulation was defined in sham burn and in thyroidectomized rats. In rats not receiving T_4, mean FT_4 was depressed in the burn group, though TSH was not. Primary alteration of T_4 produced a negative relationship between FT_4I (or FT_4) and TSH in the burns as it did in the various controls (Fig 1). However, at a given FT_4I or FT_4, serum TSH was lower in the burn group. This was not due to augmented serum T_3, because T_3 and FT_3D 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 NTI model with use of different techniques.[96]

Local pituitary conversion of serum T_4 to T_3 (via Type II 5'deiodinase) provides the T_3 stimulus for negative feedback on TSH, and a rise in pituitary and brain 5'deiodinase activity provides a sensitive index of low serum T_4 as sensed by these particular tissues in the hypothyroid rat. In three different non-burn rat models of NTI, serum TSH was frankly depressed.[97] No change was observed in pituitary 5'deiodinase activity in any of the models. This suggests that depression of TSH secretion does not occur via augmented conversion of T_4 to T_3 in the pituitary and that the pituitary does not sense the low thyroid hormones as hypothyroidism.

Pituitary 5'deiodinase has not been assessed in burned rats, though brain T_4 to T_3 conversion has.[24] 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

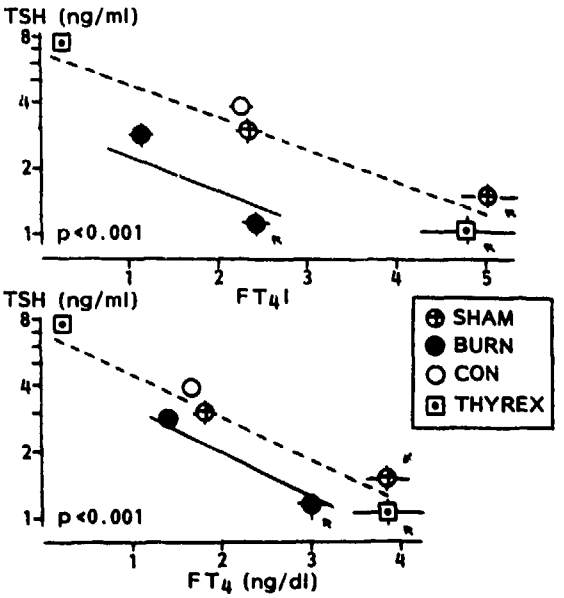

Fig 1. Mean ± SE and analyses of covariance of log serum TSH with FT_4I (top) and FT_4 (by tracer dialysis) (bottom) between burn groups and other (combined) groups of rats.[22] Small arrows point to the groups receiving T_4. THYREX indicates thyroidectomized and CON is unoperated controls. TSH was measured by RIA in 0.2-mL samples with the NIDDK antibody and RP2 standard from the National Hormone and Pituitary Program, Baltimore, MD. The least detectable TSH was 0.5 to 1.0 ng/mL in buffer in these studies. The slopes within each plot above were not significantly different, and the significances for the positional differences are indicated.

has been documented to result from burn injury or other NTI. 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.[109-112] Large doses of iodine (or iodide) initially block thyroid hormone synthesis and secretion, acutely lowering T_4 and/or T_3 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

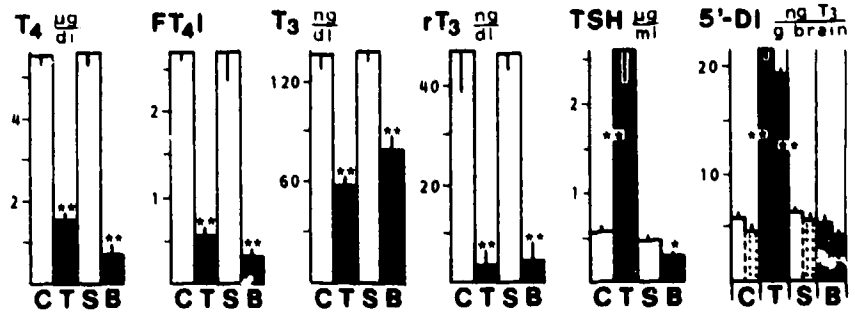

Fig 2. Serum thyroid hormones, serum TSH, and in vitro brain (telencephalon and diencephalon) 5'-deiodinase (5'-DI) activity (T_4 to T_3) in adult male rats subjected to thyroidectomy, 60% full-thickness burn, or sham burn (mean ± SE).[20,24] RP1 standard was used in the TSH assay. Activity of 5'-DI was taken as the difference in T_3 (RIA of ethanol extracts) for a brain homogenate between separate aliquots with T_4 (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.

may largely depend on different predisposing conditions.[109]

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.[112] Beyond 6 weeks of continuing exposure, serum T_4, FT_4I, and T_3 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.[113-116] Burn patients treated with this topical agent for days or weeks have occasionally exhibited metabolic acidosis and a fatal outcome.[113,114] 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.[114] 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.[115-118] Patterns of serum T_4, T_3, rT_3, and TSH did not appear to differ from what might be expected in burn patients, though there may possibly have been some depression of T_4 and/or T_3 and elevation of TSH due to the agent. Should a suspected thyroid disease require further investigation in such a patient, thyroidal radioiodine 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.

REFERENCES

1. Cuthbertson DP: The disturbance of metabolism produced by bony and non-bony injury, with notes of certain abnormal conditions of bone. Biochem J 24:1244-1263, 1930

2. Taylor FHL, Levenson SM, Davidson CS, et al: Abnormal nitrogen metabolism in patients with thermal burns. N Engl J Med 229:855-859, 1943

3. Moore FD, Langohr JL, Ingebretson M, et al: The role of exudate losses in the protein and electrolyte imbalance in burned patients. Ann Surg 132:1-19, 1950

4. Pruitt BA, Mason AJ Jr, Moncrief JA: Hemodynamic changes in the early postburn patient: The influence of fluid administration and of a vasodilator (hydralazine). J Trauma 11:36-46, 1971

5. Cope O, Nardi GL, Quijano M, et al: Metabolic rate and thyroid function following acute thermal trauma in man. Ann Surg 137:165-174, 1953

6. Trofimov GA: Changes of thyroid function in burn disease. Fed Proc (Trans) 22, Pt II:T1181-T1183, 1963

7. Reichlin S, Lieberman ZH: Effects of thermal injury and of skin removal on thyroid function in the rat. Am J Physiol 195:659-662, 1958

8. Sellers EA, You SS, You RW: The influence of adrenal cortex and thyroid on the loss of nitrogen in urine after experimental burns. Endocrinology 47:148-155, 1950

9. Herndon D: Mediators of metabolism. J Trauma 21: 701-705, 1981

10. Caldwell FT Jr, Osterholm JL, Sower ND, et al: Metabolic response to thermal trauma of normal and thyroprivic rats at three environmental temperatures. Ann Surg 150:976-988, 1959

11. Becker RA, Wilmore DW, Goodwin CW Jr, et al: Free T_4, free T_3, and reverse T_3 in critically ill, thermally injured patients. J Trauma 20:713-721, 1980

12. Becker RA, Vaughan GM, Goodwin CW, Jr, et al: Plasma norepinephrine, epinephrine, and thyroid hormone interactions in severely burned patients. Arch Surg 115: 439-443, 1980

13. Smeds S, Kågedal B, Liedén G, et al: Thyroid function after thermal trauma. Scand J Plast Reconstr Surg 15: 141-148, 1981

14. Becker RA, Vaughan GM, Ziegler MG, et al: Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med 10:870-875, 1982

15. Calvano SE, Chiao J, Reaves LE, et al: Changes in free and total levels of plasma cortisol and thyroxine following thermal injury in man. J Burn Care Rehabil 5:143-151, 1984

16. Vaughan GM, Mason AD Jr, McManus WF, et al: Alterations of mental status and thyroid hormones after thermal injury. J Clin Endocrinol Metab 60:1221-1225, 1985

17. Vaughan GM, Becker RA, Unger RH, et al: Nonthyroidal control of metabolism after burn injury: Possible role of glucagon. Metabolism 34:637-641, 1985

18. Shirani KZ, Vaughan GM, Pruitt BA Jr, et al: Reduced serum T_4 and T_3 and their altered serum binding after burn injury in rats. J Trauma 25:953-958, 1985

19. Vaughan GM, Shirani KZ, Vaughan MK, et al: Hormonal changes in burned hamsters. Endocrinology 117: 1090-1095, 1985

20. Vaughan GM, Pruitt BA Jr, Shirani KZ, et al: The thyroid axis and brain 5'-monodeiodination of thyroxine in the burned rat model of nonthyroidal illness. Neuroendocrinol Lett 8:221-226, 1986

21. Scott DE, Vaughan GM, Pruitt BA Jr: Hypothalamic neuroendocrine correlates of cutaneous burn injury in the rat: I. Scanning electron microscopy. Brain Res Bull 17: 367-378, 1986

22. Vaughan GM, Vaughan MK, Waymack JP, et al: Role of thyroid hormones in burn pathophysiology: The rat model of nonthyroidal illness, in Annual Research Progress Report. Fort Sam Houston, TX, U.S. Army Institute of Surgical Research, 1990, pp 257-270

23. Doleček R: The pituitary-thyroid axis, in Doleček R, Brizio-Molteni L, Molteni A, et al (eds): Endocrinology of Thermal Trauma. Philadelphia, PA, Lea & Febiger, 1990, pp 132-147

24. Vaughan GM: Neuroendocrine and sympathoadrenal response to thermal trauma, in Doleček R, Brizio-Molteni L, Molteni A, et al (eds): Endocrinology of Thermal Trauma. Philadelphia, PA, Lea & Febiger, 1990, pp 267-306

25. Vaughan GM, Pruitt BA Jr, Mason AD Jr: Burn trauma as a model of severe illness, in Doleček R, Brizio-Molteni L, Molteni A, et al (eds): Endocrinology of Thermal Trauma. Philadelphia, PA, Lea & Febiger, 1990, pp 307-349

26. Shambaugh GE III, Beisel WR: Early alterations in thyroid hormone physiology during acute infection in man. J Clin Endocrinol 27:1667-1673, 1967

27. Chopra IJ, Chopra U, Smith SR, et al: Reciprocal changes in serum concentrations of 3,3',5'-triiodothyronine (reverse T_3) and 3,3'5-triiodothyronine (T_3) in systemic illness. J Clin Endocrinol Metab 41:1043-1049, 1975

28. Brandt MR, Skovsted L, Kehlet H, et al: Rapid decrease in plasma-triiodothyronine during surgery and epidural analgesia independent of afferent neurogenic stimuli and of cortisol. Lancet 2:1333-1336, 1976

29. Spector DA, Davis PJ, Helderman JH, et al: Thyroid function and metabolic state in chronic renal failure. Ann Intern Med 85:724-730, 1976

30. Lim VS, Fang VS, Katz AI, et al: Thyroid dysfunction in chronic renal failure: A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. J Clin Invest 60:522-534, 1977

31. Rudman D, Fleischer AS, Kutner MH, et al: Suprahypophyseal hypogonadism and hypothyroidism during prolonged coma after head trauma. J Clin Endocrinol Metab 45:747-754, 1977

32. Ljunggren J-G, Kallner G, Tryselius M: The effect of body temperature on thyroid hormone levels in patients with non-thyroidal illness. Acta Med Scand 202:459-462, 1977

33. Wartofsky L, Burman KD, Dimond RC, et al: Studies on the nature of thyroidal suppression during acute fal-

ciparum malaria: Integrity of pituitary response to TRH and alterations in serum T_3 and reverse T_3. J Clin Endocrinol Metab 44:85-90, 1977

34. Utiger RD: Decreased extrathyroidal triiodothyronine production in non-thyroidal illness-benefit or harm. Am J Med 69:807-810, 1980

35. Kaplan MM, Larsen PR, Crantz FR, et al: Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. Am J Med 72:9-16, 1982

36. Wartofsky L, Burman KD: Alterations in thyroid function in patients with systemic illness: The "euthyroid sick syndrome." Endocrine Rev 3:164-217, 1982

37. Chopra IJ, Hershman JM, Pardridge WM, et al: Thyroid function in nonthyroidal illnesses. Ann Intern Med 98:946-957, 1983

38. Borst GC, Eil C, Burman KD: Euthyroid hyperthyroxinemia. Ann Intern Med 98:366-378, 1983

39. Zaloga GP, Smallridge RC: Thyroidal alterations in acute illness. Semin Respir Med 7:95-107, 1985

40. Zaloga GP, Chernow B, Smallridge RC, et al: A longitudinal evaluation of thyroid function in critically ill surgical patients. Ann Surg 201:456-464, 1985

41. Brent GA, Hershman JM: Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab 63:1-8, 1986

42. Faber J, Kirkegaard C, Rasmussen B, et al: Pituitary-thyroid axis in critical illness. J Clin Endocrinol Metab 65: 315-320, 1987

43. Surks MI, Hupart KH, Pan C, et al: Normal free thyroxine in critical nonthyroidal illnesses measured by ultrafiltration of undiluted serum and equilibrium dialysis. J Clin Endocrinol Metab 67:1031-1039, 1988

44. Tang WW, Kaptein EM: Thyroid hormone levels in the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex. West J Med 151:627-631, 1989

45. Kaptein EM: Abnormal thyroid function tests in euthyroid persons, in Becker KD (ed): Principles and Practice of Endocrinology. Philadelphia, PA, Lippincott, 1990, pp 293-300

46. Palazzo MG, Suter PM: Delivery dependent oxygen consumption in patients with septic shock: Daily variations, relationship with outcome and the sick-euthyroid syndrome. Intensive Care Med 17:325-332, 1991

47. Nicoloff JT, LoPresti JS: Nonthyroidal illness, in Braverman LE, Utiger RD (eds): Werner and Ingbar's The Thyroid, 6th ed. Philadelphia, PA, Lippincott, 1991, pp 357-368

48. Raffi F, Brisseau J-M, Planchon B, et al: Endocrine function in 98 HIV-infected patients: A prospective study. AIDS 5:729-733, 1991

49. Chopra IJ, Wu S-Y, Teco GNC, et al: A radioimmunoassay for measurement of 3,5,3'-triiodothyronine sulfate: Studies in thyroidal and nonthyroidal diseases, pregnancy, and neonatal life. J Clin Endocrinol Metab 75: 189-194, 1992

50. Slag MF, Morley JE, Elson MK, et al: Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 245:43-45, 1981

51. Kaptein EM, Weiner JM, Robinson WJ, et al: Relationship of altered thyroid hormone indices to survival in nonthyroidal illnesses. Clin Endocrinol 16:565-574, 1982

52. Phillips RH, Valente WA, Caplan ES, et al: Circulating thyroid hormone changes in acute trauma: Prognostic implications for clinical outcome. J Trauma 24:116-119, 1984

53. Baue AE, Günther B, Hartl W, et al: Altered hormonal activity in severely ill patients after injury or sepsis. Arch Surg 119:1125-1132, 1984

54. Gardner DF, Kaplan MM, Stanley CA, et al: Effect of triiodothyronine replacement on the metabolic and pituitary responses to starvation. N Engl J Med 300:579-584, 1979

55. Burman KD, Wartofsky L, Dinterman RE, et al: The effect of T_3 and reverse T_3 administration on muscle protein catabolism during fasting as measured by 3-methylhistidine excretion. Metabolism 28:805-813, 1979

56. Henson LC, Heber D: Whole body protein breakdown rates and hormonal adaptation in fasted obese subjects. J Clin Endocrinol Metab 7:316-319, 1983

57. Borst GC, Osburne RC, O'Brian JT, et al: Fasting decreases thyrotropin responsiveness to thyrotropin-releasing hormone: A potential cause of misinterpretation of thyroid function tests in the critically ill. J Clin Endocrinol Metab 57:380-383, 1983

58. Spencer CA, Lum SMC, Wilber JF, et al: Dynamics of serum thyrotropin and thyroid hormone changes in fasting. J Clin Endocrinol Metab 56:883-888, 1983

59. Kaptein EM, Fisler JS, Duda MJ, et al: Relationship between the changes in serum thyroid hormone levels and protein status during prolonged protein supplemented caloric deprivation. Clin Endocrinol 22:1-15, 1985

60. Kalk WJ, Hofman KJ, Smit AM, et al: Thyroid hormone and carrier protein interrelationships in children recovering from kwashiorkor. Am J Clin Nutr 43:406-413, 1986

61. Unger J: Fasting induces a decrease in serum thyroglobulin in normal subjects. J Clin Endocrinol Metab 67:1309-1311, 1988

62. Larson PR: Thyroid hormone concentrations, in Ingbar SH, Braverman LE (eds): Werner's The Thyroid, 5th Ed. Philadelphia, PA, Lippincott, 1986, pp 479-501

63. Little JS: Effect of thyroid hormone supplementation on survival after bacterial infection. Endocrinology 117: 1431-1435, 1985

64. Cavalieri RR, Rapoport B: Impaired peripheral conversion of thyroxine to triiodothyronine. Ann Rev Med 28:57-65, 1977

65. Pittman CS, Suda AK, Chambers JB, et al: Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. J Clin Endocrinol Metab 48:854-860, 1979

66. Kaptein EM, Robinson WJ, Grieb DA, et al: Peripheral serum thyroxine, triiodothyronine and reverse triiodothyronine kinetics in the low thyroxine state of acute nonthyroidal illnesses. J Clin Invest 69:526-535, 1982

67. Engler D, Burger AG: The deiodination of the iodothyronines and of their derivatives in man. Endocrine Rev 5:151-184, 1984

68. Chopra IJ, Huang T-S, Beredo A, et al: Evidence

for an inhibitor of extrathyroidal conversion of thyroxine to 3,5,3'-triiodothyronine in sera of patients with nonthyroidal illnesses. J Clin Endocrinol Metab 60:666-672, 1985

69. Huang, T-S, Boado RJ, Chopra IJ: The effect of free radicals on hepatic 5'-monodeiodination of thyroxine and 3,3',5'-triiodothyronine. Endocrinology 121:498-503, 1987

70. Chopra IJ, Van Herle AJ, Teco GNC, et al: Serum free thyroxine in thyroidal and nonthyroidal illnesses: A comparison of measurements by radioimmunoassay, equilibrium dialysis, and free thyroxine index. J Endocrinol Metab 51:135-143, 1980

71. Slag MF, Morley JE, Elson MK, et al: Free thyroxine levels in critically ill patients. JAMA 246:2702-2706, 1981

72. Melmed S, Geola FL, Reed AW, et al: A comparison of methods for assessing thyroid function in nonthyroidal illness. J Clin Endocrinol Metab 54:300-306, 1982

73. Konno N, Hirokawa J, Tsuji M, et al: Concentration of free thyroxin serum during nonthyroidal illness—Calculation or measurement? Clin Chem 35:159-163, 1989

74. Csako G, Zweig MH, Glickman J, et al: Direct and indirect techniques for free thyroxin compared in patients with nonthyroidal illness. I. Effect of free fatty acids. Clin Chem 35:102-109, 1989

75. Csako G, Zweig MH, Glickman J, et al: Direct and indirect techniques for free thyroxin compared in patients with nonthyroidal illness. II. Effect of prealbumin, albumin, and thyroxin-binding globulin. Clin Chem 35:1655-1662, 1989

76. Csako G, Zweig MH, Ruddel M, et al: Direct and indirect techniques for free thyroxin compared in patients with nonthyroidal illness. III. Analysis of interference variables by stepwise regression. Clin Chem 36:645-650, 1990

77. Midgley JEM, Sheehan CP, Christofides ND, et al: Concentrations of free thyroxin and albumin in serum in severe nonthyroidal illness: Assay artefacts and physiological influences. Clin Chem 36:765-771, 1990

78. Tikanoja SH, Liewendahl BK: New ultrafiltration method for free thyroxin compared with equilibrium dialysis in patients with thyroid dysfunction and nonthyroidal illness. Clin Chem 36:800-804, 1990

79. Wong TK, Pekary AE, Hoo GS, et al: Evaluation of different free T_4 assays in nonthyroidal illness. Clin Chem 38:720-724, 1992

80. Oppenheimer JH, Squef R, Surks MI, et al: Binding of thyroxine by serum proteins evaluated by equilibrium dialysis and electrophoretic techniques. Alterations in nonthyroidal illness. J Clin Invest 42:1769-1782, 1963

81. Lutz JH, Gregerman RI, Spaulding SW, et al: Thyroxine binding proteins, free thyroxine and thyroxine turnover interrelationships during acute infectious illness in man. J Clin Endocrinol Metab 35:230-249, 1972

82. Woeber KA, Maddux BA: Thyroid hormone binding in nonthyroid illness. Metabolism 30:412-416, 1981

83. Chopra IJ, Huang T-S, Solomon DH, et al: The role of thyroxine (T_4)-binding serum proteins in oleic acid-induced increase in free T_4 in nonthyroidal illnesses. J Clin Endocrinol Metab 63:776-779, 1986

84. Mendel CM, Frost PH, Cavalieri RR: Effect of free fatty acids on the concentration of free thyroxine in human serum: The role of albumin. J Clin Endocrinol Metab 63: 1394-1399, 1986

85. Mendel CM, Frost PH, Kunitake ST, et al: Mechanism of the heparin-induced increase in the concentration of free thyroxine in plasma. J Clin Endocrinol Metab 65: 1259-1264, 1987

86. Mendel CM, Frost PH, Cavalieri RR: Effect of free fatty acids on concentrations of iodothyronines in plasma during nonthyroidal illness (letter). Clin Chem 34:1368-1371, 1988

87. Oppenheimer JH, Schwartz HL, Mariash CN, et al: Evidence for a factor in the sera of patients with nonthyroidal disease which inhibits iodothyronine binding by solid matrices, serum proteins, and rat hepatocytes. J Clin Endocrinol Metab 54:757-766, 1982

88. Mendel CM, Cavalieri RR: Red blood cell thyroxine in nonthyroid illnesses and in heparin-treated patients. J Clin Endocrinol Metab 58:1117-1124, 1984

89. Sarne DH, Refetoff S: Measurement of thyroxine uptake from serum by cultured human hepatocytes as an index of thyroid status: Reduced thyroxine uptake from serum of patients with nonthyroidal illness. J Clin Endocrinol Metab 61:1046-1052, 1985

90. Wehmann RE, Gregerman RI, Burns WH, et al: Suppression of thyrotropin in the low-thyroxine state of severe nonthyroidal illness. N Engl J Med 312:546-552, 1985

91. Boles J-M, Morin J-F, Garre MA: Ultrasensitive assay of thyroid stimulating hormone in patients with acute non-thyroidal illness. Clin Endocrinol 27:395-401, 1987

92. Romijn JA, Wiersinga WM: Decreased nocturnal surge of thyrotropin in nonthyroidal illness. J Clin Endocrinol Metab 70:35-42, 1990

93. Bartalena L, Martino E, Brandi LS, et al: Lack of nocturnal serum thyrotropin surge after surgery. J Clin Endocrinol Metab 70:293-296, 1990

94. Arem R, Deppe S: Fatal nonthyroidal illness may impair nocturnal thyrotropin levels. Am J Med 88:258-262, 1990

95. Samuels MH, Lillehei K, Kleinschmidt-Demasters BK, Stears J, et al: Patterns of pulsatile pituitary glycoprotein secretion in central hypothyroidism and hypogonadism. J Clin Endocrinol Metab 70:391-395, 1990

96. Tibaldi JM, Surks MI: Animal models of nonthyroidal disease. Endocrine Rev 6:87-102, 1985

97. Boado R, Chopra IJ, Huang T-S, et al: A study of pituitary thyrotropin, its subunits, and messenger ribonucleic acids in nonthyroidal illness. Metabolism 37:395-399, 1988

98. Bacci V, Schussler GC, Kaplan TB: The relationship between serum triiodothyronine and thyrotropin during systemic illness. J Clin Endocrinol Metab 54:1229-1235, 1982

99. 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 62:717-722, 1986

100. Holland FW II, Brown PS Jr, Weintraub BD, et al: Cardiopulmonary bypass and thyroid function: A "Euthyroid sick syndrome." Ann Thorac Surg 52:46-50, 1991

101. Fujii T, Sato K, Ozawa M, et al: Effect of interleukin-1 (IL-1) on thyroid hormone metabolism in mice: Stimulation by IL-1 of iodothyronine 5'deiodinating activity (Type I) in the liver. Endocrinology 124:167-174, 1989

102. van der Poll T, Romijn JA, Wiersinga WM, et al: Tumor necrosis factor: A putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab 71: 1567-1572, 1990

103. Chopra IJ, Sakane S, Teco GNC: A study of the serum concentration of tumor necrosis factor-α in thyroidal and nonthyroidal illnesses. J Clin Endocrinol Metab 72: 1113-1116, 1991

104. Lim VS, Henriquez C, Seo H, et al: Thyroid function in a uremic rat model—Evidence suggesting tissue hypothyroidism. J Clin Invest 66:946-954, 1980

105. Huang TS, Chopra IJ, Boado R, et al: Effect of turpentine oil on thyroid economy in the rat: A model for the human syndrome of nonthyroidal illness. Clin Res 34: 426A, 1986 (abstr)

106. Huang T-S, Chopra IJ, Beredo A, et al: Skin is an active site for the inner ring monodeiodination of thyroxine to 3,3',5'-triiodothyronine. Endocrinology 117:2106-2113, 1985

107. Harrison TS, Seaton JF, Feller I: Relationship of increased oxygen consumption to catecholamine excretion in thermal burns. Ann Surg 165:169-172, 1967

108. Wilmore DW, Long JM, Mason AD Jr, et al: Catecholamines: Mediator of the hypermetabolic response to thermal injury. Ann Surg 180:653-669, 1974

109. Nuovo JA, Wartofsky L: Adverse effects of iodide, in Becker KD (ed): Principles and Practice of Endocrinology. Philadelphia, PA, Lippincott, 1990, pp 300-305

110. Chopra IJ: Nature, sources and relative biologic significance of circulating thyroid hormones, in Braverman LE, Utiger RD (eds): Werner and Ingbar's The Thyroid, 6th ed. Philadelphia, PA, Lippincott, 1991, pp 126-128

111. Alexander NM, Nishimoto M: Protein-linked iodotyrosines in serum after topical application of povidone-iodine (Betadine). J Clin Endocrinol Metab 53:105-108, 1981

112. Ader AW, Paul TL, Reinhardt W, et al: Effect of mouth rinsing with two polyvinylpyrrolidone-iodine mixtures on iodine absorption and thyroid function. J Clin Endocrinol Metab 66:632-635, 1988

113. Matsuda T, Kharwadkar R, Hanumadass M, et al: Topical povidone-iodine for burns may result in iodine toxicity. Am Fam Physician 15:183, 1977 (abstr)

114. Pietsch J, Meakins JL: Complications of povidone-iodine absorption in topically treated burn patients. Lancet 1:280-282, 1976

115. Balogh D, Bauer M, Riccabona G: The influence of povidone-iodine treatment on thyroid hormones in severe burns. J Hosp Inf 6:147-153, 1985 (suppl)

116. Bugyi S, Steen M, Zellner PR, et al: Alterations of iodine metabolism in patients with burns treated by cutaneous therapy with PVP iodine. Unfallchirurgie [Ger] 11:58-64, 1985 (English Abstr)

117. Habermann J, Pickardt CR, Scriba PC, et al: Thyroid function during treatment of burn injuries with polyvinylpyrrolidone iodine complex. Unfallheilkunde [Ger] 85:253-256, 1982 (English Abstr)

118. Preissler P: Changes in thyroid hormone levels in severely burned patients treated topically with povidone-iodine. Lagenbecks Arch Chir [Ger] 360:9-15, 1983 (English Abstr)

Accesion For
NTIS CRA&I ☑
DTIC TAB ☐
Unannounced ☐
Justification .....
By .....
Distribution /
Availability Codes
Dist | Avail and / or Special
A-1 | 20