

NONTHYROIDAL ILLNESS SYNDROME:

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DEFINITIONS

Serum thyroid hormone levels drop during starvation and illness. In mild illness, this involves only a decrease in serum triiodothyronine (T₃) levels. However, as the severity and length of the illness increases, there is a drop in both serum T₃ and thyroxine (T₄). This decrease of serum thyroid hormone levels is seen in starvation, sepsis, surgery, myocardial infarction, bypass, bone marrow transplantation, and in fact probably any severe illness.¹⁻⁹ The condition has been called the *euthyroid sick syndrome* (ESS). An alternative designation, which does not presume the metabolic status of the patient, is *nonthyroidal illness syndrome*, or NTIS.

For more than 3 decades the interpretation of these changes has been debated. Many observers have considered the changes in hormone level to be laboratory artifacts, or if valid, not representative of true hypothyroidism, or if hypothyroidism was present, that it was a beneficial response designed to “spare calories” (1-21). More recently evidence has accumulated that central hypothyroidism, and altered peripheral metabolism of T₄ and T₃, combine to produce a state marked by diminished serum and tissue supplies of thyroid hormones. Nevertheless, some observers accept the low hormone levels as valid, but maintain that this is a (unique) situation in which such lack of hormone is not truly hypothyroidism (i.e.,

the “euthyroid sick syndrome”). Lastly, there is even greater uncertainty about hormone replacement therapy, in considerable part because the opinion that replacement treatment should not be given has been repeated so many times, even though there is effectively no factual support for that view. We need controlled clinical trials in order to answer the question. It can not be solved by oft-stated opinions.

Low T₃ States

Starvation, and more precisely carbohydrate deprivation, appears to rapidly inhibit deiodination of T₄ to T₃ by type 1 iodothyronine deiodinase in the liver, thus inhibiting generation of T₃ and preventing metabolism of reverse T₃ (rT₃).¹⁰ Consequently there is a drop in serum T₃ and elevation of reverse T₃. Since starvation induces a decrease in basal metabolic rate,¹¹ it has been argued, teleologically, that this decrease in thyroid hormone represents an adaptive response by the body to spare calories and protein by inducing some degree of hypothyroidism. Patients who have only a drop in serum T₃, representing the mildest form of the NTIS, do not show clinical signs of hypothyroidism. Nor has it been shown that this decrease in serum T₃ (in the absence of a drop in T₄) has an adverse physiologic effect on the body or that it is associated with increased mortality.

Nonthyroidal Illness Syndrome With Low Serum T₄

As the severity of illness, and often associated starvation, progresses, there is the gradual development of a more complex syndrome associated with low T₃ *and* usually low T₄ levels. Generally thyroid-stimulating hormone (TSH) levels are low or normal despite the low serum hormone levels, and rT₃ levels are normal or elevated. A large proportion of patients in an intensive care unit setting have various degrees of severity of NTIS with low T₃ and T₄. Plikat et al. found that 23% of patients admitted to an ICU during a 2-year period had low free T₃, low free T₄, and low or normal TSH, and that these findings gave a greatly increased risk of death.¹² Girvent et al. note that NTIS is highly prevalent in elderly patients with acute surgical problems and is associated with poor nutrition, higher sympathetic response, and worse postoperative outcome.¹³ Surprisingly, during the past 4 decades, some endocrinologists have assumed that NTIS is a beneficial physiologic response,¹⁴⁻¹⁷ but factual evidence for this view is unavailable. However it seems illogical to consider NTIS as an evolutionarily derived physiologic response, since survival with the severity of illness seen in NTIS patients would be almost impossible except in modern ICUs.

A marked decrease in serum T₃ and T₄ in NTIS is associated with a high probability of death. NTIS was found in a group of 20 patients with severe trauma, among whom 5 died, and the drop in T₃ correlated with the Apache II score.¹⁸ NTIS found in patients undergoing bone marrow transplantation was associated with a high probability of fatal outcome.¹⁹ NTIS was typical in elderly patients undergoing acute surgery and was associated with a worse prognosis.²⁰ All of 45 non-dopamine-treated children with meningococcal septicemia had low T₃, T₄, and thyroxine-binding globulin (TBG), without elevated TSH. When serum T₄ levels drop below 4 g/dL, the probability of death is about 50%, and with serum T₄ levels below 2 g/dL, the probability of death reaches 80%.²¹⁻²³ Obviously such associations do not prove that hypothyroidism is the cause of these complications or deaths, but the fact of hypothyroidism must at least raise the consideration of treatment.

Interpretations of NTIS

Several conceptual explanations of NTIS can be followed through the literature:

1. The abnormalities represent test artifacts, and assays would indicate euthyroidism if proper tests were employed.
2. The serum thyroid hormone abnormalities are due to inhibitors of T₄ binding to proteins, and the tests do not appropriately reflect free hormone levels.

Proponents of this concept may or may not take the position that a binding inhibitor is present throughout body tissues, rather than simply in serum, and that the binding inhibitor may also inhibit uptake of hormone by cells or prevent binding to nuclear T₃ receptors and thus inhibit action of hormone.

3. In NTIS, T₃ levels in the pituitary are normal because of enhanced local deiodination. In this concept the pituitary is actually euthyroid, while the rest of the body is hypothyroid. This presupposes enhanced intrapituitary T₄ > T₃ deiodination as the cause.
4. Serum hormone levels are in fact low, and the patients are biochemically hypothyroid, but this is (teleologically) a beneficial physiologic response and should not be altered by treatment.
5. Lastly, NTIS is in part a form of secondary hypothyroidism, the patient's serum and tissue hormone levels are truly low, tissue hypothyroidism is present, this is probably disadvantageous to the patient, and therapy should be initiated if serum thyroxine levels are depressed below the danger level of 4 µg/dL.

SERUM HORMONE LEVELS AND TISSUE HORMONE SUPPLIES IN NTIS

Serum T₃ and Free T₃

With few exceptions, reports on NTIS indicate that serum T₃ and free T₃ levels are low.²⁴⁻³⁰

Liver Iodothyronine D1 normally produces up to 80% of circulating T₃ via T₄>T₃ deiodination, the remainder coming from the thyroid directly, or by a contribution from ID2 in muscle as noted below. ID1 in liver is down-regulated in severe illness, and this is certainly an important contributor to the low T₃ in blood. One presumed cause is reduced nutrition, especially of carbohydrate, but direct effects of cytokines on liver may also be involved. The problem presumably is exacerbated by hypothyroidism, which also down-regulates ID1.

Chopra and co-workers reported that free T₃ levels were low (Fig. 1),³¹ or in a second report, often normal.³² However, it is important to note that in the second report, the patients with "NTIS" actually had average serum T₄ levels that were *above* the normal mean and did not have significant NTIS. Sapin et al. compared free T₃ levels found in patients with NTIS by direct dialysis, microchromatography, analogue, two-step immune extraction, and a labeled antibody RIA method.³⁰ Results were significantly below normal by five of the methods and low in the most severe cases by one method. Faber et al. evaluated thyroid hormone levels in 34 seriously ill patients, most of whom had low T₄ and free T₄ index values, and found generally normal free T₃ and free T₄ using an ultrafiltration technique.³³ A point to consider is that some ultrafiltration techniques fail to exclude thyroid hormone-binding proteins from the filtrate and give spuriously high free hormone values.³⁴

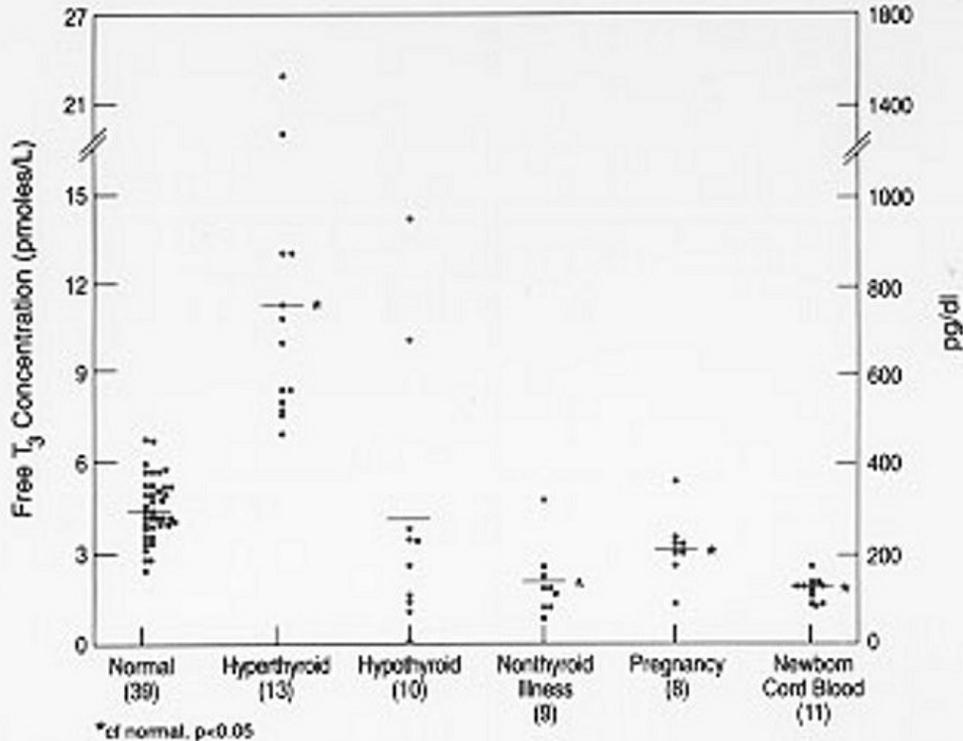


Figure 1. Free T₃ concentrations in different groups of patients, as reported by Chopra et al, reference 32. In this report, patients with NTIS have significantly lowered Free T₃ levels than do normal subjects.

Serum rT₃ may be reduced, normal, or elevated and is not a reliable indicator of abnormal thyroid hormone supply. While it may be expected that rT₃ should always be elevated, this is not true, and often it is within the normal range. Peeters et al.³⁵ found in patients with NTIS, serum TSH, T₄, T₃, and the T₃/rT₃ ratio were lower, whereas serum rT₃ was higher than in normal subjects (P < 0.0001). Liver D1 is down-regulated, and D3 (which is not evident in liver and skeletal muscle of healthy individuals) is induced, particularly in disease states associated with poor tissue perfusion. The level of rT₃ reflects the action of several enzymes and presumably, as well, tissue metabolic function. Induction of D3 would tend to increase rT₃. Degradation of rT₃ is reduced by decreased function of the same D1 enzyme that generates T₃. However, formation of rT₃ is limited by the low level of substrate (T₄) in serum and in tissues and perhaps by inhibition of T₄ entry into cells. Personal experience treating patients with NTIS (unpublished) shows that when T₄ is given and repletes serum hormone levels, generation of rT₃ rapidly increases, and levels often become significantly elevated.

Serum T₄

Serum T₄ levels are reduced in NTIS in proportion to the severity and, probably, length of the illness.²⁴⁻³⁵ In acute, short-term trauma such as cardiac bypass³⁶ or in short-term starvation,³⁷ there is no drop in serum T₄. However, with increasing severity of trauma, illness, or infection, there is a drop in T₄ which may become extreme. As indicated, serum T₄ levels below 4 µg/dL are associated with a marked increased risk of death (up to 50%), and once T₄ is below 2, prognosis becomes extremely guarded. In neonates, low total T₄ and TSH are associated with a

greater risk of death and severe intraventricular hemorrhage. It is suggested that thyroid hormone supplementation might be a potential benefit in infants with the lowest T_4 values.²⁷

Total serum T_4 is reduced in part because of a reduction in TBG. One reason for this reduction appears to be because of cleavage of TBG. Schussler's group recognized a rapid drop in TBG to 60% of baseline within 12 hours after bypass surgery, and their data suggest that this is due to cleavage of TBG by protease, which causes TBG to lose its T_4 -binding activity.³⁸ Further studies by this group demonstrated the presence of a cleaved form of TBG present in serum of patients with sepsis.³⁹

The impact of meningococcal sepsis on peripheral thyroid hormone metabolism and binding proteins was studied in 69 children with meningococcal sepsis. All children had decreased total T_3 and total T_3/rT_3 ratios without elevated TSH. Lower total T_4 levels were related to increased turnover of TBG by elastase. Lowered TBG is a partial explanation for lower total T_4 and T_3 in NTIS.⁴⁰

Serum Free Thyroxine

A major problem in understanding NTIS is in analyzing data on the level of free T_4 . Free T_4 is believed by most workers to represent hormone availability to tissues, although it is in fact intracellular T_3 that binds to the receptors. The results of free T_4 assays in NTIS are definitely method dependent. They may be influenced by a variety of variables, including (alleged) inhibitors present in serum or the effect of agents such as drugs, metabolites, or free fatty acids in the serum or assay. Assays which include an estimate of TBG capacity to estimate free hormone typically return low values for calculated free thyroxine in NTIS. Methods using T_3 analogs in the assay also give levels that are depressed. The free T_4 level determined by dialysis varies widely, as does T_4 measured by ultrafiltration²⁵⁻²⁹; the majority of reports are of low values, but in some samples normal or rarely elevated values.^{25,26,41-43}

In theory, methods utilizing equilibrium dialysis may allow dilution of dialyzable inhibitors. Compounds such as 3-carboxy-4-methyl-5-propyl-2-furan-propanoic acid, indoxyl sulfate, and hippuric acid, can accumulate in severe renal failure.⁴⁴ However, these compounds probably do not interfere with serum hormone assays. Free fatty acids, if elevated to 2 to 5 mmol/L, can displace T_4 binding to TBG and elevate free T_4 . Free fatty acids almost never reach such levels in vivo.^{45,46} However, even small quantities of heparin (0.08 units/kg given IV, or 5000 units given SC), commonly given to patients in an ICU, can lead to in vitro generation of free fatty acids during extended serum dialysis for "free T_4 " assay and falsely augment apparent free hormone levels.⁴⁷ This is probably a common and serious problem, which explains many instances of apparently elevated free T_4 levels in patients with acute illness.

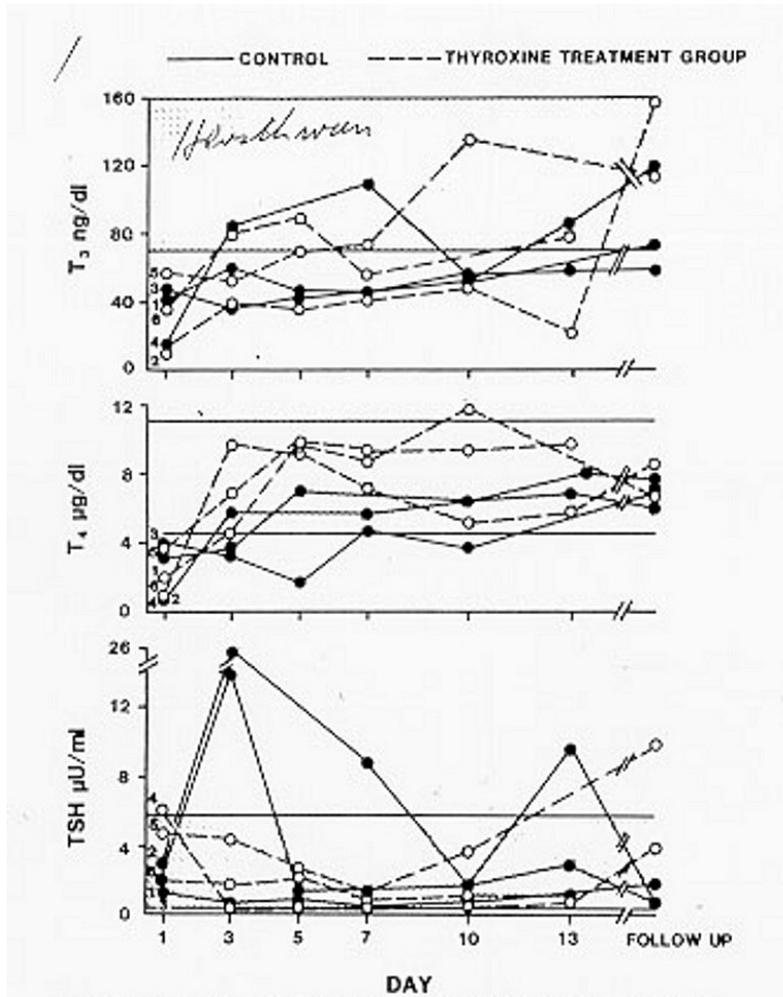
Results obtained using ultrafiltration also are variable. Wang et al.⁴⁸ found that in patients with NTIS, free T_4 measured by ultrafiltration was uniformly low (average of 11.7 ng/L), but when measured by equilibrium dialysis, free T_4 was near normal, at 18 ng/L. By ultrafiltration, free T_3 was also (not surprisingly) found to be low and similar to free T_3 by radioimmune assay. Chopra³² found levels below the normal mean, ± 2 SD, when measured by dialysis; 6 of 9 were low when measured by ultrafiltration, and 7 of 9 were low when measured by standard resin-uptake-corrected free T_4 . The means of the NTIS patients in this study were clearly below the mean of normals.

Thus, although free T_4 is low in most assays that involve a correction for TBG levels, there is still some question as to the true free T_4 in patients with NTIS. It is of interest that this problem does not carry over to estimates of free T_3 , which are depressed in most studies. There might be two reasons for this difference. Firstly, the depression of total T_3 is proportionately greater than of total T_4 . Secondly, factors which affect thyroid hormone binding are more apt to alter T_4 assays than T_3 , since T_4 is normally more tightly bound to TBG than is T_3 .

IS THERE EVIDENCE FOR SUBSTANCES IN SERUM WHICH CAN AFFECT T₄ BINDING TO PROTEINS?

Mendel et al.⁴⁹ carefully review the studies that have claimed the presence of dialyzable inhibitors of binding and point out that many of these studies must be viewed with caution^{44,45,50-53}. Numerous artifacts are present in both dialysis assays and ultrafiltration assays. They also point out that while the low free T₄ by resin uptake assays found in NTIS generally do not agree with the clinical status of the patient, it is equally true that clinical assessment generally does not fit with the high free T₄ results found by some equilibrium dialysis assays in NTIS.

An argument that completely refutes the importance of factors in serum inhibiting binding of thyroid hormone is provided in the clinical study of Brent and Hershman (Fig. 2).⁵⁴ These



Legend Figure 2. Patients with severe NTIS were randomized and left untreated or given T₄ iv over two weeks. Serum T₃, T₄, and TSH concentrations are shown for the survivors of the control (filled circles), and T₄-treated (empty circles), groups during the study period and at the time of follow-up. Upper and lower lines designate the normal range. Note the prompt recovery of T₄ values to the normal range immediately following i.v. treatment with T₄. Also note the elevated TSH levels in some patients. T₃ levels did not return to normal following T₄ treatment for up to two weeks. (Reference 54)

researchers gave 1.5 µg of T₄ per kg body weight daily to 12 of 24 patients with severe NTIS and followed serum hormone levels over 14 days. T₄ levels returned to the normal range within

3 days of therapy. Thus the serum thyroxine pool was easily replenished, and T_4 levels reached normal values. Not surprisingly, because of reduced $T_4 \rightarrow T_3$ deiodination, T_3 levels did not return to the normal range until the end of the study period in the few patients who survived. However, the ability of intravenous thyroxine in replacement doses to promptly restore the plasma pool to normal clearly shows that neither a loss of serum TBG nor an inhibitor of binding could be the main cause of low serum T_4 in this group of severely ill patients.

With growing acceptance of decreased thyroid secretion and decreased peripheral t_3 production as causes of low T_4 and T_3 , there has been little emphasis on serum T_4 binding inhibitors in recent literature. Some contribution by low TBG levels may, or may not (see below) play a role, but any role for binding inhibitors in producing this syndrome must be marginal.

TSH LEVELS

Serum TSH in NTIS is typically normal or reduced and may be markedly low, although usually not less than $0.05 \mu\text{U/mL}$.^{16,24,25,28,29,31,55} However, to use usual endocrinology logic, these TSH levels are almost always inappropriately low for the observed serum T_4 and T_3 . Third-generation assays with sensitivity down to 0.001 U/mL may allow differentiation of patients with hyperthyroidism from those with NTIS, although there can be overlap in these very disparate conditions.⁵⁶ Serum TSH in patients with NTIS may have reduced biological activity, perhaps because of reduced thyrotropin-releasing hormone (TRH) secretion and reduced glycosylation. Some patients are found with a TSH level above normal, and elevation of TSH above normal commonly occurs transiently if patients recover from NTIS (Fig. 3).^{29,54} This elevation of TSH strongly suggests that the patients are recovering from a hypothyroid state, during which the ability of the pituitary to respond had been temporarily inhibited.

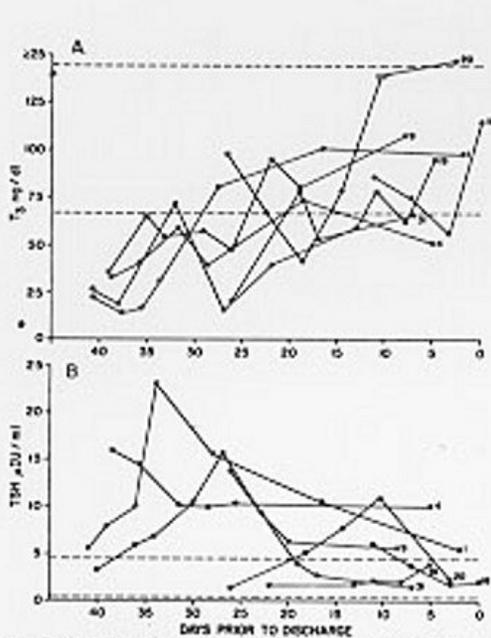


FIG. 1. T_3 and TSH concentrations in patients with nonthyroid illness who were eventually discharged. Patients are identified by case number. The broken lines indicate ± 2 SD of the mean value in the normal subjects. Divide T_3 by 65 to convert to nmol/liter .

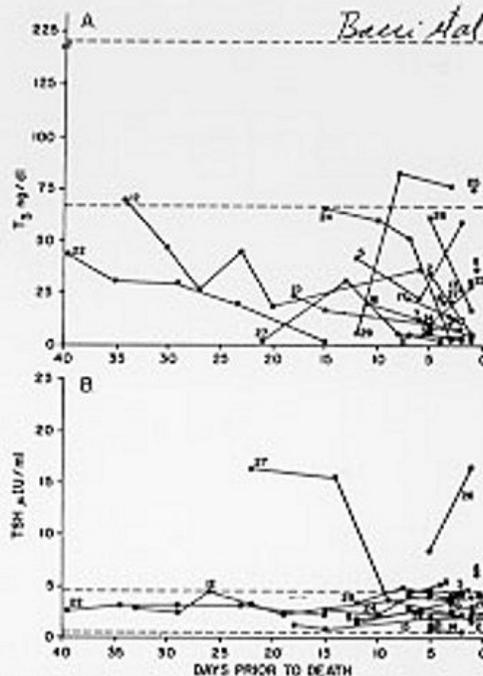


FIG. 2. T_3 and TSH concentrations in patients with nonthyroid illness who died. Numbers and broken lines as in Fig. 1.

Figure 3. T_3 and TSH concentrations are shown in patients with nonthyroidal illness who were eventually discharged from hospital (left panels). The broken line indicates $\hat{A} \pm 2$ SD of the mean value in the normal

subjects. The right panel displays T3 and TSH concentrations in patients with NTIS who died. Subjects are indicated by numbers. Note the elevated TSH in some patients who recovered, and the generally dropping T3 and low TSH levels in patients who died. (Reference 29)

Responsiveness of the pituitary to TRH during NTIS is variable: many patients respond less than normal,⁵⁷ and others respond normally.⁵⁸ "Normal" responsiveness in the presence of **low** TSH may suggest that there is a hypothalamic abnormality as a cause of the low TSH and low T₄. There is also a diminution or loss of the diurnal rhythm of TSH,⁵⁹ and in some studies, there is evidence for reduction of TSH glycosylation, with lower TSH bioactivity.⁶⁰ A logical explanation is that the low TSH is in fact the proximate cause of the low thyroid hormone levels. Hypothalamic function is impaired in patients with NTIS and TRH mRNA is low, resulting in low TSH and thus low output of thyroid hormones by the thyroid.

There is other evidence of diminished hypothalamic function in patients with serious illness. Serum testosterone drops rapidly, as do follicle-stimulating hormone (FSH) and luteinizing hormone (LH).^{61,62} Typically serum cortisol is elevated as part of a stress response, and because metabolism of cortisol is reduced. Some patients develop hypotension in association with apparent transient central hypoadrenalism, have low or normal serum ACTH, and cortisol levels under 20 µg/dL. Some of these patients respond dramatically to cortisol replacement and may manifest normal adrenal function at a later time if they recover.

Centrally mediated hyposomatotropism, hypothyroidism, and pronounced hypoandrogenism were observed in a study of patients in the catabolic state of critical illness. In these patients, pulsatile LH secretion and mean LH secretions are very low, even in the presence of extremely low circulating total testosterone and low estradiol. Pulsatile growth hormone (GH) and TSH secretion are also suppressed. Interleukin 1 β (IL-1β) levels are normal, whereas IL-6 and tumor necrosis factor α (TNF-α) are elevated. Exogenous IV gonadotropin-releasing hormone (GnRH) partially return serum testosterone levels toward normal but do not completely overcome hypoandrogenism, suggesting that combined deficiency of GH, GnRH, and TSH secretagogues may be important in this low androgen syndrome.⁶³

THYROID HORMONE TURNOVER

Kaptein et al.^{64,65} studied a group of patients who were critically ill, all of whom had total T₄ below 4 µg/dL, low fT₄ index, low normal free T₄ by dialysis, and TSH which was normal or slightly elevated. In these patients, the mean T₄ by dialysis was significantly below the normal mean. There was on average a 35% decrease in thyroxine disposal per day (Table 1). The T₄ production rate in NTIS was significantly below the mean of 17 normal subjects (p < 0.005). In a similar study of T₃ kinetics,⁶⁵ free T₃ was found to be 50% of normal serum values. The production rate of T₃ was reduced by 83% (Table 2). These two studies document a dramatic reduction in provision of T₄ and T₃ to peripheral tissues, which would logically indicate that the effects of hormone lack (hypothyroidism) should be present. A third study reported dramatically reduced total T₄ and T₃ turnover, with normal thyroïdal secretion of T₃ in patients with NTIS due to uremia.⁶⁶ However, this was a calculated rather than directly measured value of T₃ secretion, was highly variable, and does not negate the extreme reduction in T₃ supply due to diminished T₄ > T₃ conversion in peripheral organs.

T₄ ENTRY INTO CELLS AND GENERATION OF T₃

Thyroid hormone is transported actively into tissues by several specific transporters including MCT8, and in the pituitary OATP1C1. In the cell it is metabolized by enzymes which activate it to T₃, or inactivate it to rT₃, or promote excretion via sulfation or glucuronidation. Iodotyrosine deiodinase type 1 (ID1) is found in liver, kidney and thyroid, and the enzyme present in liver is considered a main source of T₃, possibly providing 80% of the total, the remainder coming largely from the thyroid. ID1 is down-regulated in hypothyroidism, and in NTIS, reducing serum

T3 levels. ID2 is present in brain and pituitary, and is responsible for local production of T3 in those tissues. Recent data show that D2 present in muscle may also contribute to serum T3. ID2 is up-regulated by hypothyroidism, and is up-regulated in NTIS. The third enzyme, ID3, deiodinates the inner thyronine ring, converting T4 to rT3 and T3 to T2. It's activity in liver is up-regulated in NTIS.

Using deiodination of T₄ as an index of cellular transport of T₄ into rat hepatocytes, Lim et al.⁶⁷ and Vos et al.⁶⁸ found that serum from patients with NTIS inhibited T₄ uptake. Sera from critically ill NTIS patients caused reduced T₄ uptake compared to control sera in one study, and the authors considered elevated nonesterified fatty acids (NEFA) and bilirubin and reduced albumin to play a role. Serum from patients with mild NTIS did not cause impaired deiodination of T₄ and T₃.⁶⁹ Inhibition of uptake of T₄ into hepatocytes caused by sera of patients with NTIS also was observed by Sarne and Refetoff.⁷⁰ There is a diminution in the “reducing equivalents” available for the deiodination of T₄ to T₃ in liver, and presumably elsewhere, thus lowering transport and the function of the type 1 iodothyronine deiodinase.⁷¹ In animals, and probably in man, there is also a drop in the level of type 1 iodothyronine deiodinase enzyme, apparently due to hypothyroidism, since it can be reversed by giving T₃. Recently a study was performed on blood, liver, and skeletal-muscle biopsies of patients immediately after death in intensive care unit settings. Liver T₄ deiodinase 1 was found to be down-regulated, and deiodinase 3 was induced in liver and muscle, especially in situations associated with poor tissue perfusion. These changes contribute to the low generation of T₃ and its increased metabolism in NTIS, thus lowering the intracellular T₃ levels.³⁵

Table 1. T₄ Kinetics in the Low T₄ State of Nonthyroidal Illness⁶⁴

Case Number	TT ₄ (µg/dL)	FT ₄ (ng/dL)	PR (µg/d/m ²)
Normal Subjects (n = 19)			
Mean	7.1	2.21	50.3
±SE	0.4	0.13	3.4
Sick Patients			
1	2.7	2.05	32.4
2	3.0	1.23	51.1
3	1.2	0.48	39.0
4	1.4	1.04	23.7
5	1.3	0.75	22.2
6	3.0	1.35	34.6
7	1.9	1.33	36.6
8	2.0	1.88	25.3
9*	0.4	0.28	10.0
10*	1.5	1.50	13.7
11*	1.6	1.70	18.4
Mean	1.8	1.24	27.9
±SE	0.2	0.17	3.7
P	<0.001	<0.001	<0.001

FT₄, Free thyroxine; PR, production rate; TT₄, total thyroxine.

*Patients receiving dopamine.

All P values are for unpaired t tests.

Table 2. T₃ Kinetics in the Low-T₄ State of Nonthyroidal Illness⁶⁵

Case Number	TT ₃ (ng/dL)	FT ₃ (pg/dL)	PR (µg/d/m ²)
Normal Subjects (n = 12)			
Mean	162	503	23.47
±SE	5	46	2.12
Sick Patients			
3	30	272	6.18
5	42	247	5.67
6	25	151	5.41
7	34	266	8.39
12*	45	282	6.07
Mean	35	244	6.34
±SE	4	24	0.53
P	<0.001	<0.001	<0.005

FT₃, Free triiodothyronine; PR, production rate; TT₃, total triiodothyronine. *Patient receiving dopamine.

In theory, reduced cellular uptake (acting alone) would cause tissue hypothyroidism, reduced T₃ generation and serum T₃ levels, and elevated serum T₄, which is not observed. It is likely that reduced hormone supply in NTIS is caused by multiple factors, and that reduced cell uptake, if present, is one of the factors. T₄ is converted to T₃, although at a reduced rate. In addition, T₄ is rapidly converted to rT₃ by an intracellular process, suggesting that entry into cells is not seriously impaired, but the pathways of intracellular deiodination are abnormal.

THYROID HORMONE IN TISSUES

There are increasing data on thyroid hormone in tissues of patients with NTIS.⁷² In one study, there was of a dramatically reduced level of T₃ in tissues (Table 3). While most samples had very low levels of T₃ compared to normal tissues, some patients with NTIS showed sporadically and inexplicably high levels of T₃ in certain tissues, especially skeletal muscle and heart.

Table 3. Tissue T₃ Concentrations in Nonthyroidal Illness Syndrome (nmol of T₃/kg of Wet Weight)⁷²

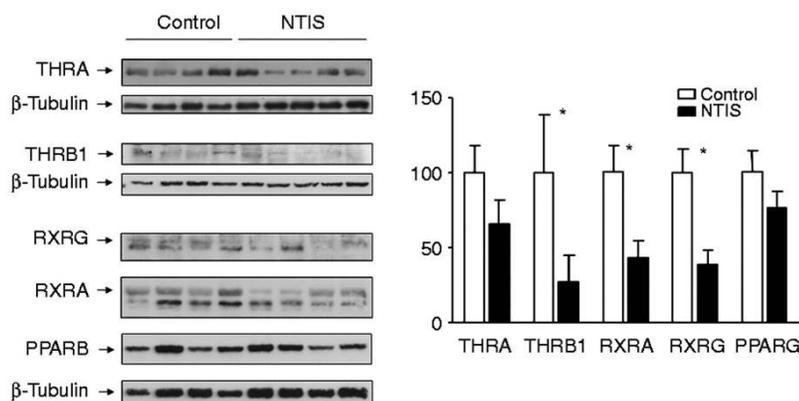
Tissue	Control Group			NTI Group	
	Mean	SD	P	Mean	SD
Cerebral cortex	2.2	0.9	<.05	1.2	1.1
Hypothalamus	3.9	2.2	<.01	1.4	1.2
Anterior pituitary	6.8	2.5	<.005	3.7	1.1
Liver	3.7	2.3	<.01	0.9	0.9
Kidney	12.9	4.3	<.001	3.7	2.8
Lung	1.8	0.8	<.01	0.8	0.5
Skeletal muscle	2.3	1.2	NS	> 10.9	
Heart	4.5	1.5	NS	> 16.3	

NS, Not significantly different; NTI, nonthyroidal illness; T₃, triiodothyronine. *Patients receiving dopamine.

Peeters et al.⁷³ investigated 79 patients who died after intensive care, some of whom received thyroid hormone treatment. Tissue iodothyronine levels were positively correlated with serum levels, indicating that the decrease in serum T₃ during illness is associated with decreased levels of tissue T₃. Higher serum T₃ levels in patients who received thyroid hormone treatment were accompanied by higher levels of liver and muscle T₃, with evidence for tissue-specific regulation. Tissue rT₃ and the T₃/rT₃ ratio were correlated with tissue deiodinase activities. Monocarboxylate transporter 8 expression was not related to the ratio of the serum/tissue concentrations of the different iodothyronines.⁷³

TR LEVELS

Information on expression of TRs in human tissues during illness is limited. Increased expression of the messenger ribonucleic acid (mRNA) for thyroid hormone receptors α 1, α 2, and β 1 has been reported in cardiac tissue of patients with dilated cardiomyopathy; α 1 and α 2 isoforms also had increased expression in ischemic heart disease.⁷⁴ Rodriguez-Perez et al. studied subcutaneous fat and skeletal muscle in patients with septic shock.⁷⁵ In muscle, mRNA for TR β 1 and RXR gamma was reduced, and mRNA for RXR alpha was increased, compared to normals. In adipose tissue, MCT8, TR β 1, TR α 1, and RXR gamma mRNAs were lower. The authors conclude that in these patients, tissue responses were related to decreased hormone levels and decreased hormone action. In animals, starvation and illness are associated with a reduction in thyroid hormone receptor levels. In experimental studies in mice, LPS induces NTIS, and this is associated with an early decrease in binding of the RXR/TR dimer to DNA due to limiting amounts of RXR, and later an up to 50% decrease in levels of RXR and TR protein. Lado-Abeal and co workers found in humans with prolonged NTIS that expression of TRbeta1, TRalpha1, and RXRgamma in striated muscle were reduced compared to normals, and that these changes were unrelated to expression of NFkB1(FIGURE 4)(78).



Lado-Abeal J et al. Eur J Endocrinol 2010;163:765-773

FIGURE 4 . THRA, THRB1, RXRG, RXRA, AND PPARG PROTEIN LEVELS WERE EVALUATED BY WESTERN BLOTTING.

ORGAN SPECIFIC RESPONSES IN NTIS

In contrast to a uniform whole body response, there are wide variations in responses to thyroid hormone supply and action in different tissues, and between the response to acute illness and chronic illness. These multifactorial systems involve serum TH levels, TH transporters, deiodinases, TH receptors, and enzyme responses which are under different regulation in individual tissues (79). In reviewing these data it is useful to note that meaning of data often must be “interpreted”, and that this can depend on the mind-set of the reviewer.

In the hypothalamus in an animal model of NTIS, TH transporters MCT10 and OATP1C1 (but not MCT8) were increased, and hypothalamic D2, considered a major source of local T3, was up-regulated, but there was no corresponding increase in tissue T3. TR α and beta mRNA expression levels were not altered (Figure 4)(80). Tissue levels of T3 and T4 are reduced in chronic NTIS in both experimental models and in humans. Thus the known low TRH mRNA levels in the hypothalamus reflect the action of neural signals, and not an hypothesized local tissue hyperthyroidism. On the other hand, the “low normal” T3 levels in the hypothalamus, in the presence of low serum T3 levels, presumably reflect the action of D2, and may provide a partial explanation of why TSH is not usually elevated in NTIS.

Data on the pituitary are few. D2 levels have not shown consistent changes. In animal models TR β 2 levels are reported to be reduced in acute NTIS. In humans with fatal illness, pituitary T3 levels were low. The overall picture is of central down-regulation of the hypothalamus and pituitary and low levels of tissue T3 despite increments in transporter activity and D2 deiodinase (Figure 5). These findings fit with the observed correction of TSH and TH levels in human NTIS through administration of TRH.

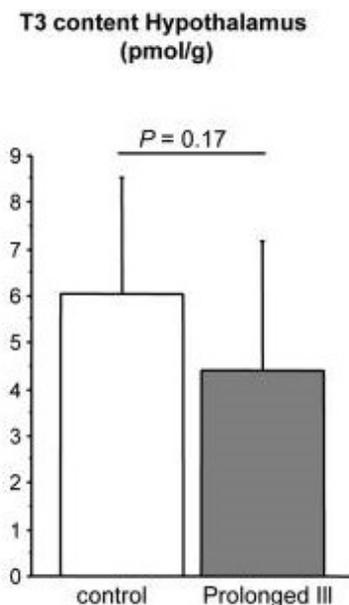


Figure 5 . T3 and T4 content in Hypothalamus of chronically ill animals with NTIS.(From Mebis et al(80).

Liver D1 and D3 activity are reduced in acute NTIS. In man MCT8 and MCT10 may be reduced in acute but not chronic NTIS. Several enzymes that are responsive to TH have reduced activity in acute NTIS in animals. The data fit with reduced metabolic activity in this organ. In chronic NTIS in man, reduced serum T3 and T4 and normal or elevated RT3 are characteristic. Liver T3 is low in chronic human NTIS, and is directly related to serum T3. MCT8, but not MCT10, are increased in liver and muscle in prolonged NTIS (81). Expression levels of TR α and β mRNA are reported to be reduced, or increased. Metabolic activity is probably reduced, but in relation to oxygenation and nutrients as well as TH activity. In a rabbit model of chronic NTIS, serum and liver T3 and liver D1 activity were low. Interestingly replacement with basal levels T4 or T3 did not reverse these abnormalities, but 3-5 fold increments, or TRH administration, did so (82). This study offers several interesting points. There was a very strong correlation between serum and tissue hormone levels, so tissue entry was not a problem. The requirement for more than replacement dose T4 to restore tissue hormone is mainly due to depletion of very diminished stores of T4, in this 6 day treatment protocol. No evidence was found for an important role of T4-sulfo conjugates.

The response in muscle is less well defined. D2 increases and D3 is decreased in acute NTIS in an animal model, and there is evidence for decreased TR expression. Changes in enzyme responses do not show a consistent pattern. In chronic NTIS, human muscle D3 is augmented, while D2 has been found low, or increased. Muscle MCT8 is increased (81), and this has been proposed as a response to hypothyroidism, since TH treatment in a rabbit model of NTIS returns the transporters to normal. Enzymatic activity is presumed low but good data are lacking. Prolonged infusion of lipopolysaccharide in pigs induced a severe NTIS state, associated with generally low tissue TH levels, reduced TH transporters, and low TR- β levels, suggesting reduced TH sensitivity and hypothyroidism(83).

ARE PATIENTS WITH NTIS CLINICALLY HYPOTHYROID?

It is straightforward that the typical clinical parameters of severe hypothyroidism are absent in patients with NTIS. However, these patients usually present with a serious illness and are diagnostically challenging in view of their complicated state. Many are febrile, have extensive edema, have sepsis or pneumonia, may have hyper metabolism associated with burns, have severe cardiac or pulmonary disease, and in general have features that could easily mask evidence of hypothyroidism. Further, the common clinical picture of hypothyroidism does not develop within 2 to 3 weeks of complete thyroid hormone deprivation, but rather requires a much longer period for expression. General laboratory tests are also suspect. Thus starvation or disease-induced alterations in cholesterol, liver enzymes, TBG, creatine kinase, and even basal metabolic rate generally rule out the use of these associated markers for evidence of hypothyroidism. Angiotensin-converting enzyme levels are low,⁸⁴ as seen in hypothyroidism, while high-affinity testosterone-binding globulin (TeBG) and osteocalcin levels are not altered.⁸⁵ Antithrombin III levels are reduced in a septic rat model of NTIS. T₃ supplementation returned the sepsis-induced decrease in antithrombin III levels toward normal.⁸⁶

MECHANISM OF THYROID HORMONE SUPPRESSION IN NTIS

It is probable that the cause of NTIS is multifactorial and may differ in different groups of patients. Specifically, the changes in liver disease and renal disease are probably somewhat different from those occurring in other forms of illness. Certainly one important cause of the drop in serum T₃ is a decreased generation of T₃ by type 1 iodothyronine deiodinase.⁸⁷ Reduced

entry of T_4 into cells is not a major problem. Some studies have suggested that individuals with NTIS may have selenium deficiency, and this may contribute to a malfunction of the selenium-dependent iodothyronine deiodinase. However, supplements of 500 μg of selenium given to patients in a surgical ICU during the first 5 days after serious injury caused only modest changes in thyroid hormones. The data did not suggest a major role for selenium deficiency in this condition.⁸⁸

The overall daily metabolic consumption of thyroid hormone, both thyroxine and T_3 , is radically diminished in the NTIS syndrome in the presence of low hormone serum levels. The reduced degradation cannot *produce* the lowering of serum hormone levels; a primary reduction in degradation would increase serum hormone. The change in degradation must be due to the low hormone supply, and other factors. Schussler and co-workers have observed a sharp drop in TBG levels during cardiac bypass surgery, which their studies indicate is due to some selective consumption of TBG. It is possible that this occurs because of activation of serine protease inhibitors (serpins) at sites of inflammation, which cleave the TBG into an inactive form.³⁸

Considerable evidence suggests that an alteration in hypothalamic and pituitary function causes the low production of T_4 , which in turn causes the low production of T_3 . In rats, starvation reduces hypothalamic mRNA for TRH, reduces portal serum TRH, and lowers pituitary TSH content.⁸⁹ A recent study documents low TRH mRNA in hypothalamic paraventricular nuclei⁹⁰ in NTIS patients (Fig. 6). Responses to administered TRH vary in different reports, being suppressed or even augmented.^{57,58} Administration of TRH has been suggested as an effective

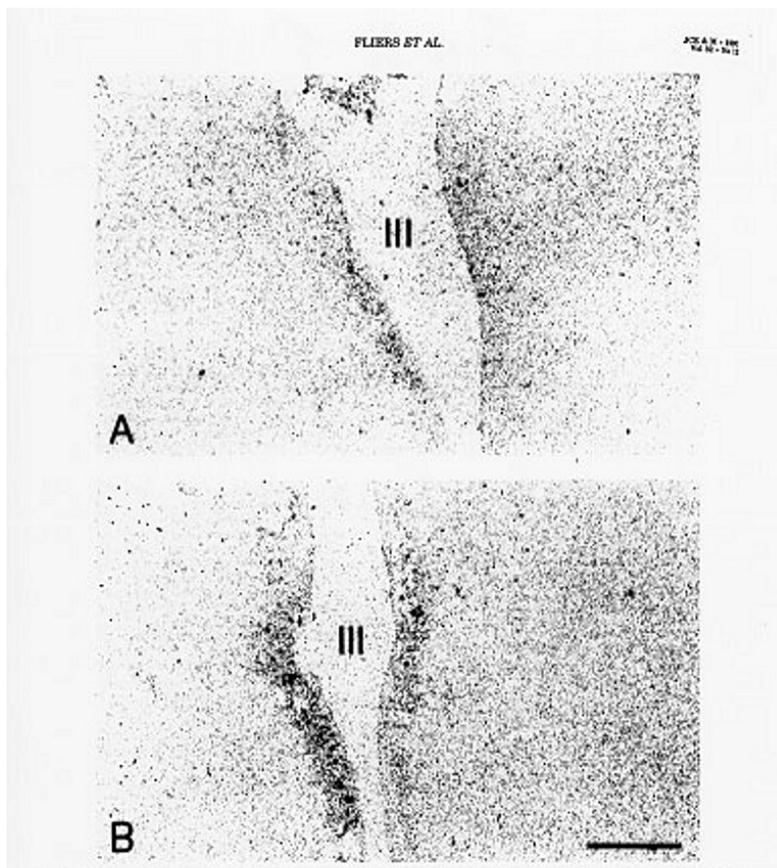


Figure 6. In situ hybridization study demonstrating mRNA for TRH in the periventricular nuclei of a subject who died with NTIS in Panel A, and a subject who died accidentally in Panel B. mRNA for TRH is significantly reduced in patients with NTIS. (Reference 90)

means of restoring serum hormone levels to normal in individuals with NTIS. A recent report by Van den Berghe and co-workers proves that administration of TRH to patients with severe NTIS leads directly to increased TSH levels, increased T_4 levels, and increased T_3 levels.⁹¹ This data is strong support (albeit not proof) for the role of diminished hypothalamic function as a crucial factor in NTIS.

Quite possibly the production of TRH, and responses to TRH, are reduced by cytokines (to be discussed later) or by glucocorticoids.⁹² The diurnal variation in glucocorticoid levels at least in part controls the normal diurnal variation in TSH levels, perhaps by affecting pituitary responsiveness to TRH.⁹³ High levels of glucocorticoids in Cushing's disease suppress TSH and cause a modest reduction in serum hormone levels.⁹⁴ High levels of glucocorticoids are known to suppress pituitary response to TRH in man.⁹² Stress-related elevation of glucocorticoids in animals causes suppression of TSH and serum T_4 and T_3 hormone levels.⁹⁵ Thus stress-induced glucocorticoid elevation may be one factor affecting TRH and TSH production.

Why should pituitary production of TSH be diminished in the presence of low serum thyroid hormone levels? One idea was that augmented intrapituitary conversion of T_4 to T_3 allowed the pituitary to remain suppressed while the rest of the body was actually hypothyroid. While some data supported this idea in a uremic rat model of NTIS⁹⁶, careful studies in both experimental animals (82,83) and man, described above, disprove this concept.

Another suggestion is that some other metabolite of thyroxine may be involved in control of pituitary responsiveness. For example, possibly triiodothyroacetic acid (triac) or tetraiodothyroacetic acid (tetrac) generated by metabolism of thyroxine could control pituitary responsiveness,⁹² but there is no experimental proof of this idea, and even if true, it would mean that the pituitary was normal but the rest of the body hypothyroid. As suggested earlier, elevated serum cortisol levels could play a role. The most obvious possibility is that low TSH stems from diminished TRH production, as previously described. It must also be remembered that the defect in pituitary function is not restricted to TSH, but that LH and FSH are also suppressed in seriously ill patients, and testosterone is reduced, in contrast to the generally augmented glucocorticoid levels. Quite possibly these changes are the effect on the hypothalamus of neural integration of multiple factors including stress, starvation, glucocorticoids, and cytokines.

Van den Berghe has stressed that the changes in endocrine function seen during severe illness have a biphasic course. Possibly the initial suppression of T_3 levels represents a genetically engineered adaptive response of the organism, allowing reduced metabolic rate and conservation of energy and protein stores for a longer period of time, while the animal or man goes through a period of starvation. However, the circumstances surrounding severe illness, and the resuscitative efforts applied in an intensive care unit over 1 or more weeks, seem to be a different response. This second phase of the syndrome, with associated suppression of thyroid hormone and other pituitary hormones and a variety of other changes, may represent a maladaptive response. Patients in this situation tend to have elevated insulin levels, nitrogen wasting, retention of fats if calories are made available, and a variety of other metabolic abnormalities that include neuropathy and cardiomyopathy. These authors consider that provision of multiple hormonal support, including thyroid hormone, growth hormone, and androgens, may be beneficial.^{97,98}

CYTOKINES IN NTIS

In a series of septic patients studied shortly after admission to an ICU, total T_4 , free T_4 , total T_3 , and TSH were depressed, and IL-1 β , soluble interleukin-2 receptor (sIL-2R), IL-6, and TNF- α were elevated.⁹⁹ The hypothalamo-pituitary-adrenal axis was activated as expected. The data suggest central suppression of TSH as the cause of the problem, but the relation to cytokines is unclear, as seen in the following reports. Hermus et al.¹⁰⁰ showed that continuous infusion of IL-1 in rats causes suppression of TSH, T_3 , and free T_4 . Higher doses of IL-1 were accompanied by a febrile reaction and suppression of food intake, which presumably played some role in the altered thyroid hormone economy. IL-1 did not reproduce the diminution in hepatic 5'-deiodinase activity believed to be so characteristic of NTIS. IL-1 is also known to impair thyroid hormone synthesis by human thyrocytes and is enhanced in many diseases associated with NTIS.¹⁰¹ van der Poll et al.¹⁰² studied the effect of IL-1 receptor blockade in human volunteers to determine if it could alter the NTIS induced by endotoxin. Blockade of IL-1 activity was achieved by infusing recombinant human IL-1 receptor antagonist, but this did not prevent the drop in T_4 , free T_4 , T_3 , and TSH or the rise in r T_3 caused by endotoxin. This is evidence against an important role for IL-1.

Interferon γ

Interferon- γ (IFN- γ) 100 $\mu\text{g}/\text{m}^2$ administered subcutaneously to normal volunteers did not alter TNF- α levels, caused a small elevation of IL-6 levels, and thus did not support a role for IFN- γ in the pathogenesis of the euthyroid sick syndrome in humans.¹⁰³

Tumor Necrosis Factor

TNF is another proinflammatory cytokine that is thought to be involved in many of the illnesses associated with NTIS. Infusion of recombinant TNF in man by van der Poll et al.¹⁰⁴ produced a decrease in serum T_3 and TSH and an increase in r T_3 . Free T_4 was transiently elevated in association with a significant rise in FFA levels. These studies suggest that TNF could be involved in producing NTIS. Recombinant IL-6 given to humans activates the hypothalamic pituitary-adrenal axis, and this could play a role in suppressing TSH production. However, Chopra et al.¹⁰⁵ did not find TNF to be closely correlated with hormone changes in NTIS. van der Poll et al.¹⁰⁶ gave human subjects endotoxin, which caused lowering of T_4 , free T_4 , T_3 , and TSH. TNF blockade by a recombinant TNF receptor-IgG fusion protein did not alter the response, indicating that TNF did not cause the changes in hormone economy induced by administration of endotoxin. Nagaya et al.¹⁰⁷ proposed a mechanism through which TNF could reduce serum T_3 . TNF- α was found during in vitro studies to activate nuclear factor kB (NF-kB), which in turn inhibits the T_3 -induced expression of 5'-DI, which would lower T_3 generation in liver. However, as noted above, activation of liver NFkB is not seen in NTIS.

Interleukin 6

Serum IL-6 is often elevated in NTIS,¹⁰⁸ and its level is inversely related to T_3 levels. Stouthard et al.¹⁰⁹ gave recombinant human IL-6 chronically to human volunteers. Short-term infusion of IL-6 caused a suppression of TSH, but daily injections over 42 days caused only a modest decrease in T_3 and a transient increase in r T_3 and free T_4 concentrations. IL-6 could be involved in the NTIS syndrome, although the mechanism was not defined. In an animal model of NTIS studied by Wiersinga and collaborators,¹¹⁰ antibody blockade of IL-6 failed to prevent the induced changes in thyroid hormone economy typical of NTIS. Boelen et al. studied the levels of IFN, IL-8, and IL-10 in patients with NTIS and found no evidence that they had a pathogenic role.¹¹¹ Short-term administration of recombinant IFN- γ to normal subjects caused a minimal elevation of IL-6, no alteration in TNF, and did not significantly alter thyroid hormone levels. Michalaki et al. observed that serum T_3 drops early after abdominal surgery as an early manifestation of the NTIS syndrome, prior to an increase in serum IL-6 or TNF- α , suggesting that these changes in cytokines do not induce the drop in T_3 .¹¹³

The potential interaction between cytokines and the hypothalamic-pituitary-thyroid axis is certainly complicated, and cytokines themselves operate in a network. For example, IL-1 and TNF can stimulate secretion of IL-6. Activation of TNF and IL-1 production is associated with the occurrence of cytokine inhibitors in serum, which are actually fragments of the cytokine receptor or actual receptor antagonists. Soluble TNF receptor and IL-1 RA are receptor antagonists, which can inhibit the function of the free cytokines. These molecules are increased in many infectious, inflammatory, and neoplastic conditions. Boelen et al.¹¹³ found evidence that the NTIS is “an acute phase response” generated by activation of a cytokine network. Soluble TNF, soluble TNF receptor, soluble IL-2 receptor antagonist, and IL-6 all inversely correlated with serum T₃ levels.

While the studies noted fail to pinpoint one cytokine as the crucial mediator, we can be convinced that striking changes in cytokines co-occur during NTIS and probably play a pathogenic role by mechanisms yet undefined.

OTHER FACTORS ALTERING SERUM T₄ SUPPLY

Altered CNS Metabolism

In healthy men going through two 4.5-hour-long sessions of induced hypoglycemia, TSH, fT₃ and fT₄ are significantly reduced.¹¹⁴ Perinatal asphyxia, recognized by low Apgar scores, is associated with a depression of TSH, T₄, and T₃, and the reductions are greatest in infants with hypoxic/ischemic encephalopathy. In this study, 6 of 11 infants with fT₄ < 2ng/dL died. These data suggest, not surprisingly, that reduced substrate or O₂ supply to the CNS could induce hypothalamic/pituitary dysfunction.^{114,115}

Glucagon

Administration of glucagon to dogs caused a significant fall in serum T₃, suggesting that stress-induced hyperglucagonemia may be a contributor to the NTIS syndrome by altering intracellular metabolism of T₄.¹¹⁶

Dopamine

Dopamine given in support of renal function and cardiac function must play a role in many patients who develop low hormone levels while in an intensive care unit setting. Dopamine inhibits TSH secretion directly, depresses further the already abnormal thyroid hormone production, and induces significant worsening of the low hormone levels. Withdrawal of dopamine infusion is followed by a prompt dramatic elevation of TSH, a rise in T₄ and T₃, and an increase of the T₃/rT₃ ratio. All of these changes suggested to Van den Berghe et al.¹¹⁷ that dopamine makes some patients with NTIS hypothyroid, inducing a condition of iatrogenic hypothyroidism, and that treatment (presumably by administering thyroid hormone), “should be evaluated.”

Leptin

Leptin plays a key role in control of thyroid hormone levels during starvation in animals. During starvation, leptin levels drop. With this there is diminished stimulation of TRH, thus diminished secretion of TSH, and lowered thyroid hormone levels. Administration of leptin appears to work via the arcuate nucleus of the hypothalamus to induce production of pro-opiomelanocortin (POMC), and thus α -melanocyte-stimulating hormone (α MSH), and reduce Agouti-related protein (AgRP). Normally α MSH stimulates the melanocortin 4 receptor (MC4R), whereas AgRP suppresses it. Presumably through these actions, a lack of leptin during starvation leads to diminished stimulation of the MC4R receptor on the TRH neurons in ventricular nuclear centers and thus diminished TRH secretion. Administration of leptin partially reverses this sequence.¹¹⁸ These actions appear to be part of an energy-conserving scheme related to thyroid changes during starvation and are associated with leptin-induced increase in appetite, decreased energy expenditure, and modified neuroendocrine function. The relevance of this to human physiology is as yet unclear, but the data strongly suggest that leptin is involved in the down-regulation of thyroid function during acute starvation.¹¹⁸⁻¹²⁰ In clinical trials, stimulation of growth hormone

secretion by GH secretagogues lead to increased insulin and leptin levels in severely ill ICU patients. To date, studies of leptin levels in patients with NTIS have indicated they are normal or elevated, not low.¹²¹

Atrial Natriuretic Peptides

Atrial natriuretic peptides, including amino acids 1 to 30, amino acids 31 to 67 (known as *vessel dilator*), 79 to 98 (kaliuretic hormone), and 99 to 126 (atrial natriuretic hormone), derived from the ANH prohormone, significantly decreased circulating concentrations of total T₄, free T₄, and free T₃, when given to healthy humans for 60 minutes. A reciprocal increase in TSH lasted for 2 or 3 hours after cessation of the administration of these hormones, suggesting that the effect was a direct inhibition of thyroid hormone release from the thyroid gland rather than an action of the hormones upon the hypothalamus or pituitary. No data are available on these factors in NTIS¹²² (Table 4).

DIAGNOSIS

Typically the endocrinologist is presented with a severely ill patient in whom there is no prior history suggestive of pituitary disease, in whom clinical findings of hypothyroidism are either absent or masked by other disorders, with a T₄ and FTI (by an index method) that are low, a low or normal TSH, and, if measured, a low T₃. If T₄ is below 4 µg/dL in this setting, the diagnosis of NTIS, associated with a potentially fatal outcome, may be assumed; rT₄ may be normal or elevated and is not diagnostic. An elevated TSH suggests the presence of prior hypothyroidism, which should be treated. Finding positive antithyroid antibody titers supports the diagnosis of primary hypothyroidism but does not prove it.

Serum cortisol should be measured. Transient, apparently central, hypoadrenalism may occur in severe illness.¹²³⁻¹²⁵ Cortisol should be above 20 µg/dL, and commonly is above 30. If below 20, ACTH should be drawn, and the patient may be given supportive cortisol therapy. Serum cortisol should certainly be determined if thyroid hormone is to be given. Since CBG may be reduced, it is advisable to measure serum free cortisol if possible. It is useful to determine FSH in postmenopausal women as a sign of pituitary function, but this is less clearly valuable in men. If there is a reason to consider hypopituitarism, a CAT scan of the pituitary is appropriate, or at least a skull film.

Use of aspirin, dilantin, and carbamazepine should be noted, since they can lower T₄ and FTI as measured by several "index" methods. Dopamine used in the setting of severe illness can induce clear-cut hypothyroidism. Hyperthyroidism is the typical cause of suppression of TSH below 0.1 µU/mL, but it is rarely difficult to exclude this diagnosis in the setting of severely depressed T₄ and T₃.

IS THYROID HORMONE TREATMENT OF NTIS ADVANTAGEOUS OR DISADVANTAGEOUS?

Two valuable studies are available on replacement therapy using thyroid hormone in patients with NTIS. In the study by Brent and Hershman,⁵⁴ replacement with 1.5 µg T₄ IV per kilogram body weight daily, in 12 patients, promptly returned serum T₄ levels to normal (thereby proving that a binding defect was not the cause of the low T₄) but did not normalize T₃ levels over a period of 2 to 3 weeks. However, in both the treated and control group, mortality was 80%.⁵⁴ Clearly this excellent small study, which used for primary therapy what would now be considered the wrong hormone, failed to show either an advantageous or disadvantageous effect. It is possible that the failure to show a positive effect was due to the failure of T₃ levels to be restored to normal. In a study of severely burned patients given 200 µg T₃ daily, again there was no evidence of a beneficial or disadvantageous effect.¹²⁶ Mortality was not so great, as in the Brent and Hershman study, but it is entirely possible that the high levels of T₃ given worsened the hypermetabolism known to be present in burn patients and could have, at these levels, been disadvantageous.

An important study by Acker et al. certainly advises caution regarding T₄ therapy in patients with acute renal failure. Numerous studies in animals have documented a beneficial effect of T₄ therapy in experimental acute renal failure.¹²⁷ In a randomized, controlled prospective study of patients with acute renal failure (ARF), treated patients received 150 µg of thyroxine a total of four times intravenously over 2 days.¹²⁸ The single difference recognized in the subsequent laboratory data was a suppression of TSH. T₄ treatment had no effect on any measure of ARF severity. Among other questions, it is not clear that serum T₃ levels were ever altered. However, mortality was higher in the thyroxine group (43% versus 13%) than in the control group. It is of interest that, as the authors state, "the observed mortality in the controls in this study was less than that typically seen in our institution in ARF and ICU patients, whereas the 43% mortality noted in the thyroid group better approximates both our experience and that reported in the literature for ICU patients." It will be difficult to replicate this study (although this reader believes it should be replicated). But it is uncertain whether the small dose of thyroxine administered over 2 days actually is related to the mortality, considering that the mortality in the treated group was that usually observed, whereas the control happened to have a much lower mortality.¹²⁸ The same group has also studied the effect of thyroid hormone treatment on posttransplant acute tubular necrosis. T₃ treatment during the posttransplant period did not alter outcome in a beneficial or derogatory manner.¹²⁹

Studies from animals are often quoted in the literature as an argument against treatment of NTIS or for the therapy. A study of sepsis induced in animals showed no difference in mortality with treatment, but some animals treated with thyroid hormone died earlier than did those that were untreated.¹³⁰ Chopra et al. induced NTIS in rats by injection of turpentine oil. The reduction in T₄, T₃, free T₄ index, and TSH were associated with no clear evidence of tissue hypothyroidism, and urinary nitrogen excretion was normal. Thyroid hormone replacement with T₄ or T₃ did not significantly alter enzyme activities or urinary nitrogen excretion.¹³¹ Healthy pigs were subjected to 20 minutes of regional myocardial ischemia by Hsu and collaborators,¹³² and this was associated with a drop in T₃, free T₃, and elevated rT₃. Some animals were treated with 0.2 µg T₃ per kilogram for five doses over 2 hours. While myocardial infarction size was not altered, the pigs treated with T₃ showed a more rapid improvement in cardiac index. Oxygen consumption did not alter. It should be noted that the T₃ levels fell back to normal levels within 4 hours of the last T₃ dose, suggesting that more prolonged therapy might have been beneficial. Katzeff et al.¹³³ studied a model of NTIS induced by caloric restriction in young rats. In these animals, T₃ was reduced, and there was a decrease in LV relaxation time, SERCA2 mRNA, and αMHC mRNA. All changes were reversed to normal values by supplementation with T₃, suggesting that the low-T₃ syndrome was related to the pathologic cardiac changes. Sepsis and multisystem organ failure are often associated with disseminated intravascular coagulation and consumption of coag inhibitors such as antithrombin III. Chapital studied a model of sepsis in rats and showed that T₃ supplementation reduced the decrease in antithrombin III levels, which presumably would reflect a beneficial effect.¹³⁴ Dogs subjected to hemorrhagic shock recovered more cardiovascular function when given T₃ intravenously than did untreated animals.¹³⁵ Neurologic outcome after anoxia is improved in dogs by T₃ treatment.¹³⁶ Short-term studies on T₃ replacement of patients in shock, in patients with respiratory disease, in subjects who are brain dead and potential organ donors, and in patients undergoing coronary artery bypass grafts all suggest modest cardiovascular benefits from the administration of T₃. One study reports benefit by replacing T₃ to elevate the depressed T₃ levels in premature infants.¹³⁷ Other studies found no apparent effects. Children treated with T₃ postoperatively when they have undergone cardiac surgery also require less cardiac support (138). T₃ administration (one dose of approximately 6 µg IV) did not alter cardiac performance in brain-dead transplant donors.¹³⁹ Coronary artery bypass, as studied by Klemperer and collaborators,³⁶ was associated with a drop in serum T₃; IV administration of T₃ elevated T₃ above normal, augmented cardiac output, and reduced the need for pressor support but had no other effect. In

this study, however, the patients had a very favorable prognosis and minimal NTIS, so the study primarily shows that administration of T₃ had no adverse effect under these circumstances. In a study of patients after heart transplant, patients with the low T₃ syndrome (NTIS) had higher mortality, higher incidence of acute rejection, highest number of re-operations, and higher incidence of infections, compared to those without NTIS (140). In a study reported several years ago, T₃ administration to critically ill neonates with severe respiratory distress appeared to improve survival. Infants of less than 37 weeks gestational age or weighing less than 220 grams were given prophylactic doses of thyroxine and T₃ daily and had a lower mortality rate than untreated infants.¹³⁷ Use of thyroid hormone replacement in children after cardiac surgery has been extensively reviewed by Haas et al., with the conclusion that it is a desirable treatment option, especially in high-risk patients.¹⁴¹ Goarin et al. studied the effect of T₃ administration in brain-dead organ donors and found that although it returned T₃ levels to normal, it did not improve hemodynamic status or myocardial function.¹⁴² Pingitore et al. gave T₃ by IV infusion for 3 days to patients with chronic heart failure. Heart rate, plasma nor-epinephrine (down 52%), natriuretic peptide, and aldosterone (down 23%) were all significantly diminished, and ventricular performance improved, without side effects.¹⁴³ In a randomized study of patients for 24 hours after coronary bypass, correction of the usual drop in serum T₃ by IV T₃ infusion had no beneficial or deleterious effect on cardiac parameters.¹⁴⁴ Of interest, it also did not affect leucine flux or urinary nitrogen excretion, contrary to the usual assumption that a drop in serum T₃ should spare body protein. Novitsky (145) studied three conditions in which NTIS and myocardial functional depression have been documented - i) transient regional myocardial ischemia and reperfusion, ii) transient global myocardial ischemia in patients undergoing cardiac surgery on cardiopulmonary bypass, and iii) transient inadequate global myocardial perfusion in brain-dead potential organ donors. Under all three conditions, in models and in man, following administration of T₃/T₄, the myocardial dysfunction was rapidly reversed. Cautious use of thyroid hormonal therapy to any patient with the ESS and/or a stunned myocardium was advocated. The general outcome of these studies is that they weakly support the use of T₃, and none of the studies found evidence of damage caused by treatment.¹⁴⁴⁻¹⁵⁰

In summary, it can be stated that there is no clear evidence that thyroxine or triiodothyronine treatment of NTIS in animals or man is disadvantageous, but no certain proof that it is advantageous. In the acute NTIS syndrome associated with operations, short term treatment with T₃ augments cardiac function, but has not been shown to alter the already low mortality (150). However, what evidence there is suggests TH may be beneficial. The argument has been raised that administration of thyroid hormone in NTIS would prevent the elevation in TSH commonly seen in recovering patients. This seems rather specious. More objectively, the elevation of TSH is another suggestion that the few patients who survive the ordeal were hypothyroid and left untreated. Lastly, it is unlikely that administration of replacement hormone during NTIS would be harmful, even if all of the evidence presented suggesting hypothyroidism was erroneous, and the patients were in fact euthyroid.

IF THYROID HORMONE REPLACEMENT IS GIVEN, WHAT SHOULD IT BE?

Clearly the high mortality rate in patients in the chronic phase of NTIS, with T₄ under 4 µg/dL, suggests that this is a target group in whom thyroid hormone administration should be considered. In this group of patients, there appears to be no obvious contraindication to replacement therapy, with the possible exception of people who have cardiac decompensation or arrhythmias. Even here, the evidence is uncertain. There is no clear evidence that administration of replacement doses of T₃ to patients with low cardiac output is disadvantageous, and in fact current studies using intravenous T₃ in these patients indicate it is well tolerated and may be beneficial.¹⁵¹ Arrhythmias obviously also raise a question, but again, there is no evidence that replacement of thyroid hormone to a normal level would cause trouble in control of arrhythmias. Low free T₃ levels are reported to be associated with an increased

incidence of fibrillation after cardiac surgery in elderly patients.¹⁵² Thus even in this group of patients, it is reasonable to suggest therapy. It should also be noted that among patients with NTIS, there will certainly be patients who are clearly hypothyroid—based on known disease, treatment with dopamine, or elevated TSH—who need replacement therapy by any standard.

If therapy is to be given, it cannot be thyroxine alone, since this would fail to promptly elevate T_3 levels.⁵⁴ Treatment should include oral, or if this is impractical, intravenous T_3 , and probably should be at the replacement level of approximately 50 $\mu\text{g}/\text{day}$ given in divided doses. It may be appropriate to give slightly higher doses, such as 75 $\mu\text{g}/\text{day}$ for 3 to 4 days to increase the body pool more rapidly, followed by replacement doses as described. Coincidentally, it is appropriate to start replacement with T_4 . Serum levels of T_4 and T_3 should be followed at frequent intervals (every 48 hours) and dosages adjusted to achieve a serum T_3 level at least low normal (70 to 100 ng/dL) prior to the next scheduled dose. If treatment is successful, T_3 administration can gradually be reduced, and thyroxine administration can be increased to replacement levels as deiodination increases. Because of the marked diminution in T_4 to T_3 deiodination, and shunting of T_4 toward r T_3 , replacement with T_4 may initially only lead to elevation of r T_3 and have very little effect upon T_3 levels, or physiologic action. In this situation, continued administration of T_3 would be preferred.

An alternate therapy, giving TRH to stimulate TSH production and TH release, has been shown to be effective in raising TH levels during short term treatment. This is described below. No prolonged treatment, or effects on survival have so far been reported.

ADDITIONAL SUPPORTIVE HORMONAL THERAPY TO CONSIDER

Although this discussion concentrates on the potential value of treating patients with NTIS with replacement thyroid hormone, several important recent studies expand the concept to other areas, including treatment of the associated hyperglycemia, relative adrenal insufficiency, use of beta blockers in burn patients, and possible use of GHRH and testosterone.

Van den Berghe and co-workers have suggested that the acute and prolonged critical illness responses are entirely different neuroendocrine conditions. In protracted severe illness, patients are kept alive with conditions that previously caused death. However, this process has unmasked a variety of nonspecific wasting syndromes that include protein loss, accumulation of fat stores, hyperglycemia and insulin resistance, hypoproteinemia, hypercalcemia, potassium depletion, and hypertriglyceridemia. In prolonged illness, cortisol values are elevated, although ACTH levels are low, indicating that other mechanisms are driving the steroid response. Growth hormone secretory pulses are reduced, and the mean GH concentration is low in prolonged critical illness. FSH and LH are reduced, and testosterone levels are reduced. These authors maintain that the reduced neuroendocrine drive, present in the chronic phase of illness in an intensive care setting, is unlikely to be an evolutionary preserved beneficial process. They suggest that the administration of hypothalamic physiotropic releasing peptides may be a safer strategy than the administration of peripherally active hormones.¹⁵³⁻¹⁵⁶

NTIS is typically associated with poor nutrition unless supportive measures are taken, and undernutrition is a known inducer of NTIS. Yet nutritional support is not uncomplicated. Parenteral feeding of rabbits (in contrast to fasting) in a model of chronic NTIS resulted in a normalization of low T_3 levels, but did not correct low T_4 levels (157). Use of early parenteral alimentation for patients in the ICU with NTIS was recommended by Perez-Guisado et al (158), who found it decreased length of hospital stay. However a study by Langouche et al (159) found, in contrast, that adding parenteral nutrition sooner than one week in the ICU increased complications and delayed recovery.

Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Van den Berghe et al carried out a prospective randomized study on ICU patients on mechanical ventilation, maintaining blood glucose at a level between 80 and 110 mg/dl, versus allowing glucose to range between a level of 180 – 200 mg/dl. Intensive

insulin therapy reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care (98). This strict blood sugar control can lead to bouts of hypoglycemia, and higher controlled values are currently aimed for. In isolated brain injury patients, intensive insulin therapy reduced mean and maximal intracranial pressure while identical cerebral perfusion pressures were obtained with eightfold less vasopressors. Seizures and diabetes insipidus occurred less frequently. At 12 months follow-up, more brain-injured survivors in the intensive insulin group were able to care for most of their own needs. Preventing even moderate hyperglycemia with insulin during intensive care protected the central and peripheral nervous systems, with clinical consequences such as shortening of intensive care dependency and possibly better long-term rehabilitation. Prevention of catabolism, acidosis, excessive inflammation, and impaired innate immune function may explain previously documented beneficial effects of intensive insulin therapy on outcome of critical illness.

Severe burns are known to be associated with a hypermetabolic state and a strong sympathetic response. Beta blockade given as propranolol to reduce the resting heart rate by 20% decreased resting energy expenditure and increased net muscle protein balance significantly in a group of burn patients. It is logical that this would be a significant benefit (160). Severe sepsis, which is of course associated with NTIS, is frequently associated with relative adrenal insufficiency, and possibly systemic inflammation-induced glucocorticoid receptor resistance. In a prospective randomized study, Annane et al studied a seven day treatment of patients with septic shock, by giving hydrocortisone, 50 mg q6h, and 9-alpha-fludrocortisone, 50 mg once daily. The risk of death in this treated group was significantly reduced without increasing any adverse effects. The treatment was most beneficial in individuals who responded poorly to a 250 mg ACTH test, which was conducted prior to the therapy. Non-response was defined as a response of 9 mg/dl or less, between the lowest, and highest concentration taken after the ACTH injection. Samples were taken in this study at 30 and 60 minutes (161). The severity of the illness was suggested by the statistics that 63% died in the placebo group, and 53% in the corticosteroid treatment group. The authors recommend that all patients with catecholamine dependent septic shock should be given a combination of hydrocortisone and fludrocortisone as soon as a short corticotrophin stimulation test is performed, and the treatment should be continued for seven days in non-responders. Hamrahian et al advise caution in using total serum cortisol measurements in patients with serum albumin levels below 21.5gm/dl. They observed that these patients may have low total cortisol because of low CBG, but have normal or elevated free cortisol levels (162)

In contrast to the generally beneficial effects of hormonal therapy described above, high levels of growth hormone given to critically ill patients were found by Takala et al to augment mortality. The dosage used was 0.1 mg/kg bw, for up to 21 days. Mortality rate was nearly double. These authors suggest that GH may have an adverse effect upon immunity, cause fluid retention, and cause hyperglycemia (163).

TREATMENT WITH HYPOTHALAMIC RELEASING HORMONES

Van Den Berghe and collaborators have pioneered studies on the effects of hypothalamic releasing hormones in patients with severe NTIS. The logic supporting this approach is that it corrects a major cause of the low hormonal state, and may allow normal feed-back control and peripheral regulation of hormones, thus being more physiological than replacing the peripheral hormone deficit directly. Extensive studies document restoration of T4 and T3 levels following administration of TRH and GH secretagogue (153). In a rabbit model of NTIS treatment with

GHRP-2 and TRH reactivated the GH and TSH axes and altered liver deiodinase activity, driving T₄ to T₃ conversion.

In NTIS there are suppressed pulsatile GH, TSH, LH secretion in the face of low serum concentrations of IGF-I, IGFBP-3 and the acid-labile subunit (ALS), thyroid hormones, and total and estimated free testosterone levels, whereas free estradiol (E₂) estimates are normal. Ureagenesis and breakdown of bone tissue are increased. Baseline serum TNF- α , IL-6 and C-reactive protein level and white blood cell (WBC) count are elevated; serum lactate is normal. Coadministration of GHRP-2, TRH and GnRH reactivated the GH, TSH and LH axes in prolonged critically ill men and evoked beneficial metabolic effects which were absent with GHRP-2 infusion alone and only partially present with GHRP-2 + TRH. These data underline the importance of correcting the multiple hormonal deficits in patients with prolonged critical illness to counteract the hypercatabolic state (154).

Contrary to expectation, intensive insulin therapy suppressed serum IGF-I, IGFBP-3, and acid-labile subunit concentrations. This effect was independent of survival of the critically ill patient. Concomitantly, serum GH levels were increased by intensive insulin therapy. The data suggest that intensive insulin therapy surprisingly suppressed the somatotrophic axis despite its beneficial effects on patient outcome. GH resistance accompanied this suppression of the IGF-I axis. To what extent and through which mechanisms the changes in the GH-IGF-IGFBP axis contributed to the survival benefit under intensive insulin therapy remain elusive (155). While outcome studies using this approach are not available, it is quite possible that treatment of NTIS by use of hypothalamic releasing hormones may be a preferred approach.

CONCLUSIONS

This review has presented the arguments for administration of replacement T₃ and T₄ hormone in patients with NTIS. However, it is impossible to be certain at this time that it is beneficial to replace hormone, or whether this could be harmful. Other recent reviews on this topic are available (164). Only a prospective study will be adequate to prove or disprove the value of hormone replacement, and probably this would need to involve hundreds of patients. Tragically, many ICU patients continuing to die with NTIS (we do not know if this is from NTIS) and we have now waited over 40 years for the proper controlled study to be done. One cannot envisage that replacement of thyroxin or T₃ can “cure” patients with NTIS. The probable effect, if any is achieved, will be a modest increment in overall physiologic function and a decrease in mortality. Perhaps this would be 5%, 10%, or 20%. If effective, thyroid hormone replacement will be one of many beneficial treatments given the patient, rather than a single magic bullet which would reverse all the metabolic changes going wrong in these severely ill patients. Ongoing studies document the beneficial effects of hormone replacement in these acutely and severely ill patients. Possibly therapy will ultimately involve replacement of peripheral hormones, or may instead be via growth hormone-releasing peptide (GHRP), TRH, GnRH, insulin, adrenal steroids, and leptin.

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