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Dangerous Dogmas in Medicine: The Nonthyroidal Illness Syndrome

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For more than 3 decades it has been known that serum thyroid hormone levels drop during starvation and illness. In mild illness, this involves only a decrease in serum T_3 levels. However, as the severity of the illness increases, there is a drop in both serum T_3 and T_4 (1). This decrease in serum thyroid hormone levels is seen in starvation (2), sepsis (3, 4), surgery (5), myocardial infarction (6, 7), bypass (8), bone marrow transplantation (9), and, in fact, probably any severe illness. Based on the conviction that patients with these abnormalities are not hypothyroid despite the low hormone levels in blood, the condition has been called the euthyroid sick syndrome. An alternative designation, which does not presume the metabolic status of the patient, is nonthyroidal illness syndrome (NTIS). NTIS seems a preferable name in light of present knowledge and will be used in this review.

Low T_3 states

Starvation in man and animals causes a prompt decline in serum T_3 and serum free T_3 along with a drop in basal metabolic rate (BMR). As noted previously, almost any severe infection, trauma, or illness likewise causes a drop in serum T_3 levels, but it is often difficult to differentiate the effects of these problems from short term starvation. Starvation, more precisely carbohydrate deprivation, appears to rapidly inhibit deiodination of T_4 to T_3 by type 1 iodothyronine deiodinase in the liver, thus inhibiting the generation of T_3 and preventing the metabolism of rT_3 (10). Consequently, there is a drop in serum T_3 and an elevation in rT_3. As starvation induces a decrease in the BMR (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 hypothyroidism. This would logically be a beneficial response for an otherwise well animal or man facing temporary starvation. Patients who have only a drop in serum T_3, representing the mildest form of NTIS, do not show clinical signs of hypothyroidism, nor has it been shown that this decrease in serum T_3 has an adverse physiological effect on the body or that it is associated with increased mortality.

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NTIS with low serum T_4

As the severity of illness, and often the associated starvation, progresses, there is the gradual development of a more complex syndrome associated with low T_3 and low T_4 levels. In this state serum free T_4 levels are commonly below normal, but may be normal or above normal, as described below. Generally, TSH levels are low or normal despite the low serum hormone levels, and rT_3 levels are normal or elevated. The depression of serum T_3 alone represents the least marked abnormality in NTIS, but there is no clear separation of this response from the more severe syndrome. Rather, there seems to be a gradual progression from a low T_3 level to the most advanced condition in serious illness, associated with extremely low T_3 and T_4 levels. Most patients with serious illness in the hospital have low serum T_3 levels. A large proportion of patients in an intensive care unit setting have various degrees of severity of NTIS with low T_3 and T_4 levels.

The reason for interest in this syndrome is not simply to understand its physiology. A marked decrease in serum T_4 is associated with a high probability of death. When serum T_4 levels drop below 4 μg/dL, the probability of death is about 50%; with serum T_4 levels below 2 μg/dL, the probability of death reaches 80% (12–15). Obviously, this raises the question of whether replacement of thyroid hormone would be beneficial in such patients and could increase their chance of survival. The dogma in endocrinology, accepted and supported by most individuals in the field over the past 3 decades (15–17), has been that this is a beneficial physiological response and that "it is difficult to advocate or even defend treatment of NTI patients" (18). However, as described below, there is no factual basis for this dogma.

Physiological interpretations of NTIS

Five conceptual explanations of NTIS can be followed through the literature. 1) The abnormalities represent test artifacts, and assays would indicate euthyroidism if a proper test were employed. 2) The serum thyroid hormone abnormalities are due to inhibitors of T_4 binding to proteins, and 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 T_3 receptors, and thus inhibit the action of hormone. 3) In NTIS, T_3 levels in the pituitary are normal because of enhanced local deiodination. Thus, the pituitary is actually euthyroid, whereas the rest of the body is hypothyroid. This

presupposes enhanced intrapituitary $T_4 \rightarrow T_3$ deiodination as the cause. 4) Serum hormone levels are, in fact, low, and the patients are biochemically hypothyroid, but this is (teleologically) a beneficial physiological response and should not be altered by treatment. 5) Lastly, 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 T_4 levels are depressed below the danger level of 4 μg/dL.

What are the serum hormone levels and tissue hormone supplies in NTIS?

Serum T_3 and free T_3. With few exceptions, reports on NTIS indicate that serum T_3 and free T_3 levels are low (19–24). Chopra and co-workers have recently reported that free T_3 levels were low (Fig. 1) (25) or, in a second report, normal (26). However, it is important to note that in the latter report the patients with "NTIS" actually had average serum T_4 levels that were above the normal mean. Although it is uncertain which study should be given precedence, it is clear that most of the subjects in the latter report did not have severe NTIS.

Serum T_4. Serum T_4 levels are reduced in NTIS in proportion to the severity and probably the length of the illness (17–21). In acute, short term trauma, such as cardiac bypass (27), or short term starvation (28), there is no drop in serum T_4. However, with increasing severity of trauma, illness, or infection, there is a drop in T_4, which may become extreme. As indicated, serum T_4 levels below 4 μg/dL are associated with a marked increased risk of death (up to 50%), and once T_4 is below 2, the prognosis becomes extremely guarded.

Serum free T_4. The major problem in understanding the 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. The results of free T_4 assays in NTIS are definitely method dependent and 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 (FFA) in the serum or assay. Assays that employ a resin uptake method to estimate free hormone usually return low values for calculated free T_4 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 ultrafiltration (19–23), but the majority of reports are of normal or low, and in some samples even elevated, values.

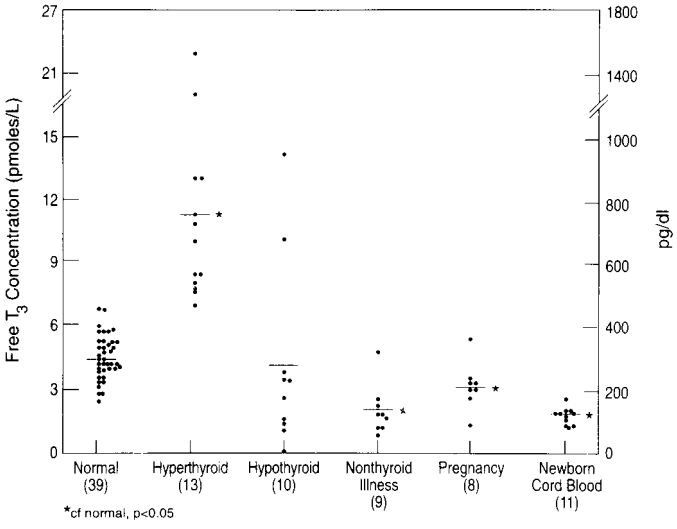

FIG. 1. Free T_3 concentrations in different groups of patients, as reported by Chopra *et al.* (25). In this report, patients with NTIS have significantly lowered free T_3 levels than those in normal subjects.

In theory, methods using equilibrium dialysis may allow dilution of dialyzable inhibitors, including compounds such as 3-carboxy-4-methyl-5-propyl-2-furan-propanoic acid, indoxyl sulfate, and hippuric acid, which can accumulate in severe renal failure (29). However, in the absence of renal failure, these compounds are not present in serum at a sufficiently high level to interfere in any assay. FFA, if elevated to 2–5 mmol/L, can displace T_4 binding to albumin and elevate free T_4. FFA almost never reach such levels *in vivo* (30, 31). However, even small quantities of heparin (0.08 U/kg, iv, or 5000 U, sc) can lead to *in vitro* generation of FFA during extended serum dialysis and falsely augment apparent free hormone levels (32). As heparin is so universally employed for the prevention of thrombotic episodes in patients in intensive care units and in other settings during severe illness, this is probably a widespread and serious problem, which may explain many instances of apparently elevated free T_4 levels in patients with acute illness.

One of the most thorough comparative studies of serum T_4 assays was reported in 1982 by Melmed *et al.* (20). Free T_4 was measured by six methods, including dialysis, and was found to be uniformly reduced as measured by all methods in patients in the MICU, whereas results were more variable for patients with liver disease or chronic renal failure (see below). A problem to be noted in reviewing these reports has to do with the categorization of patients. Patients reported with NTIS who have normal serum T_4 typically will not have reduced free T_4 by most assay methods. However, when patients with low serum T_4 are studied separately, the results become more uniform. In an extensive comparison of methods by Kaptein and associates (21), free T_4, measured by five methods, was extremely low in patients with NTIS who had a serum T_4 level under 3 μg/dL. However, free T_4 was in the normal range in patients when measured by two commercial methods and by equilibrium dialysis. Uchimura *et al.* (33) studied the effect of dilution of serum on free T_4 and found that it caused up to a 30% reduction in apparent free T_4. This reduction caused by dilution of course also applied to serum standards. Thus, values obtained by study of undiluted serum or diluted serum or using indirect methods for establishing the free T_4 concentration all gave values that closely correlated. Nelson and Weiss (34) also studied the effect of serum dilution on free T_4. They found that using a tracer dialysis method, there was progressive reduction in free T_4 values with serum dilution. The change with dilution of free T_4 in serum from a normal patient and from a patient with NTIS varied in parallel. Thus, by this method, despite dilution, values for the NTIS patient appeared low. However, using a method that they believe is more appropriate, measuring T_4 in the dialysate by direct RIA, sera from patients with low T_3 syndrome frequently gave high values when

undiluted and normal or even low values when diluted. Nelson and Weiss are convinced that the direct RIA method is correct, and that the alterations reflect the presence of dialyzable inhibitors in the serum altering the measurement of free T_4.

Results obtained using ultrafiltration also are variable. Wang *et al.* (35) found that in patients with NTIS, free T_4 measured by ultrafiltration was uniformly low (average, 11.7 ng/L), but when measured by equilibrium dialysis, free T_4 was near normal (18 ng/L). By ultrafiltration, free T_3 also, not surprisingly, was found to be low and similar to free T_3 by RIA. The researchers suggest that the observations with ultrafiltration are more apt to be erroneous due to the effect of inhibitors of binding, in contrast to the results of dialysis, which they assume are correct. Chopra *et al.* (25) recently reported free T_3 measured by dialysis in patients with NTIS and found free T_3 to be markedly reduced, whereas free T_4 was within the normal range. However, it must be noted that in this study, their patients had an average T_4 in the normal range (6.9 μg/dL), and these patients would not be expected to have low free T_4 levels. The second study from this group recently published is noted above. Surks *et al.* (19) studied T_4 levels by equilibrium dialysis and ultrafiltration of undiluted serum. Although the researchers report that the results in patients with NTIS were "similar to or higher than those in 12 normal subjects," in fact seven of nine patients had levels below the normal mean ($\pm$2 SD) when measured by dialysis, six of nine were low when measured by ultrafiltration, and seven of nine 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 normal mean.

Thus, it is still a question as to whether the free T_4 in patients with NITS is actually low or normal, and even sometimes elevated. 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 that of total T_4. Secondly, factors that affect thyroid hormone binding are more apt to alter T_4 assays than T_3, as T_4 is normally more tightly bound to TBG than is T_3.

Is there evidence for substances in serum that can affect T_4 binding to proteins?

In patients with advanced renal disease who have not been recently dialyzed, there is possibly an accumulation of substances, as noted above, that can alter binding of T_4 (29). These materials could be dialyzed out promptly during assays of free hormone and therefore cause the assay to record an apparently low free T_4. Evidence for dialyzable and nondialyzable inhibitors of T_4 binding has been presented by Chopra (36). The material in serum was thought possibly to be fatty acids. In contrast, Mendel and colleagues (37) found no evidence for an inhibitor of T_4 binding to serum proteins in a study of a series of 111 patients from acute care wards. It should be noted that almost all subjects had T_4 values within the normal range. Only 3 had values below 4 μg/dL. Thus, the patients may not have been optimal for studying evidence of a binding inhibitor. As reviewed by Mendel *et al.* (37), one of the main concerns regarding an inhibitor of binding is the potential effect of elevated FFA levels in starving NTIS patients. Levels of FFA above 5 mmol/L, with a molar ratio of FFA to albumin of more than 5, may produce this abnormality. In the patients studied by Liewendahl (30) and Csako *et al.* (38) and in the study by Mendel *et al.* (37), FFA levels were below this level. Thus, FFA levels in serum samples taken from patients ordinarily are not high enough to cause a problem, although remarkably elevated FFA levels were found in the series of patients reported by Chopra *et al.* (39). A more serious problem may occur if low doses of heparin have been given, as noted above. FFA can be generated during the incubation procedure, as reported by Jaume *et al.* (32). In this situation, there may be a progressive increase in FFA during prolonged dialysis, causing a spurious increase in the free T_4 fraction. Mendel *et al.* (37) carefully reviewed 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. Numerous artifacts are present in both dialysis assays and ultrafiltration assays. They also point out, that although the low free T_4 levels found by resin uptake assays 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 T_4 results found by some equilibrium dialysis assays in NTIS.

A strong argument against the importance of factors in serum inhibiting binding of thyroid hormone is provided in the clinical study of Brendt and Hershman (Fig. 2) (40). These researchers gave 1.5 μg T_4/kg BW to 12 of 24 patients with severe NTIS and followed serum hormone levels over 14 days. T_4 levels returned to the normal range within 3 days of therapy. Thus, the T_4 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 that survived. However, the ability of intravenous T_4 to restore the plasma pool to normal clearly shows that an inhibitor of binding could not be the predominant cause of low serum T_4 in this group of severely ill patients.

TSH levels

Serum TSH in NITS is typically normal or reduced and may be markedly low, although it is usually not less than 0.05 μU/mL (19, 20, 22, 25; reviewed in Refs. 17 and 41). However, to use usual endocrinological logic, these TSH levels are almost always inappropriately low for the observed serum T_4. Third generation assays with sensitivities as low as 0.001 μU/mL may allow differentiation of patients with hyperthyroidism (a rare problem in differential diagnosis) to be separated from those with NTIS, although there can be overlap in these very disparate conditions (42). There is a suggestion that serum TSH in patients with NTIS may have reduced biological activity, perhaps because of reduced TRH secretion and reduced glycosylation. Some patients are found with a TSH level above normal, and elevation of TSH above normal commonly occurs if patients recover (Fig. 3) (17, 23, 40). This elevation of TSH strongly suggests that the patients are recovering from a hypothyroid state.

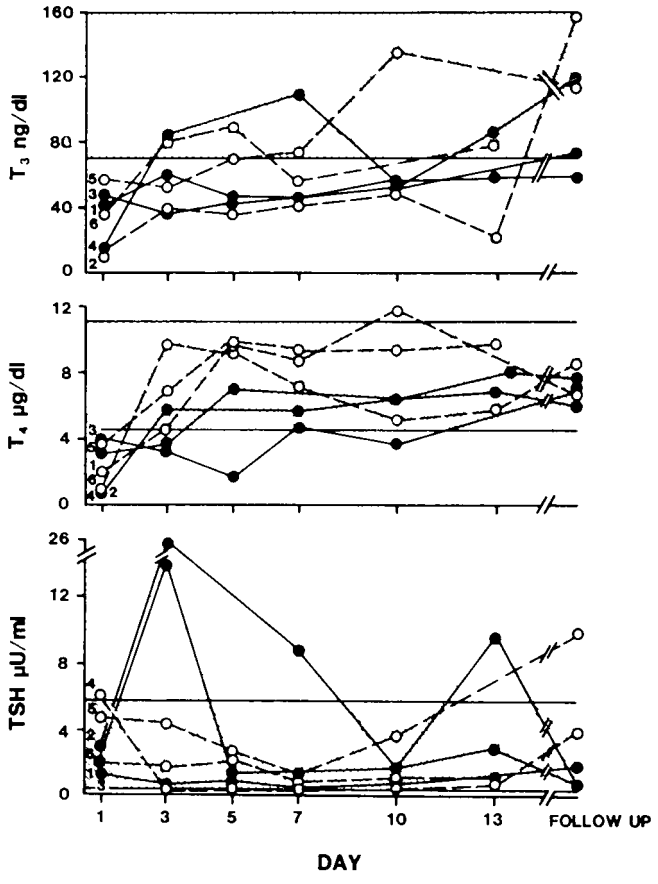

FIG. 2. Patients with severe NTIS were randomized and left untreated or were given T_4 iv over 2 weeks. Serum T_3, T_4, and TSH concentrations are shown for the survivors of the control (●; 1–3), and T_4-treated (○; 4–6) groups during the study period and at the time of follow-up. The *shaded area* designates the normal range. Note the prompt recovery of T_4 values to the normal range immediately after iv treatment with T_4. Also note the elevated TSH levels in some patients. T_3 levels did not return to normal after T_4 treatment for up to 2 weeks (40).

Responsiveness of the pituitary to TRH during NTIS is variable; many patients have a less than normal response (43), and others respond normally (44). Normal responsiveness in the presence of low TSH may suggest that there is a hypothalamic abnormality that is a cause of the low TSH and low T_4. There is also a diminution, or loss, of the diurnal rhythm of TSH (45), and in some studies there is evidence for a reduction of TSH glycosylation with lower TSH bioactivity (46). That TSH is not elevated in the presence of low T_4 is taken to mean that the patients are not hypothyroid. An easy and perhaps more logical alternative explanation is that the low TSH is, in fact, the proximate cause of the low thyroid hormone levels. As will be shown later, there is reason to believe that hypothalamic function is impaired in patients with NITS, and that this may, because of low TRH, result 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 does FSH and LH (47, 48).

Thyroid hormone turnover

The daily turnover (tissue supply) of thyroid hormone can be estimated from the serum hormone concentration and the disappearance curve of injected isotopically labeled T_4 or T_3. Daily degradation of T_4 and T_3 has long been considered the most exact method for analyzing the supply of thyroid hormone to the body tissues. In numerous studies, there is a marked correlation with clinical status in patients with normal function or hyper- or hypothyroidism. There are few studies of T_4 and T_3 metabolism in patients with NTIS. Among those available are the outstanding studies by Kaptein *et al.* (49, 50), who studied a group of patients who were critically ill, all of whom had total T_4 below 4 μ/dL, low free T_4 index, free T_4 by dialysis that was low normal, and TSH that was normal or slightly elevated. In these patients, the mean T_4 determined by dialysis was significantly below the normal mean. There was, on the average, a 35% decrease in T_4 disposal per day. Although the researchers state that the T_4 production rate was normal, the T_4 production rate in NTIS was significantly below the mean of 17 normal subjects ($P < 0.005$; Table 1). The MCR of T_4 from serum was more rapid in the critically ill patients, which may in part be related to reduced TBG levels. In a similar study of T_3 kinetics (50), free T_3 was found to be 50% of normal serum values. The production rate of T_3 was reduced by 83% (Table 2). The MCR of T_3 during the period after initial distribution was actually slower than that in normal subjects, in contrast to the findings with T_4. These two studies document a dramatic reduction in provision of T_4 and T_3 to peripheral tissues, which would logically indicate that the effects of a lack of hormone (hypothyroidism) should be present. However, the researchers observe that "use of T_4 therapy would not appear to be appropriate, since there is no proof of an overt deficiency of free T_4," and the "low T_3 levels may be of adaptive significance in reducing protein catabolism, potentially making T_3 therapy detrimental" (50). The reasons to object to this teleological analysis have been given, and whether reduced protein catabolism could be beneficial will be discussed below. One study reported normal thyroidal secretion of T_3 in patients with NTIS due to uremia (Table 3) (51). However, this was a calculated, rather than directly measured, value, was exceedingly variable, and did not negate the extreme reduction in T_3 supply due to diminished $T_4 \rightarrow T_3$ conversion.

T_4 entry into cells

Using deiodination of T_4 as an index of cellular transport of T_4 into rat hepatocytes, Lim *et al.* (52) and Vos *et al.* (53) found that serum from critically ill NTI patients caused reduced uptake compared to control serum and considered elevated nonesterified fatty acids and bilirubin, and reduced albumin, to play a role. Serum from patients with mild NTIS did not cause impaired deiodination of T_4 and T_3 (54). Inhibition of uptake of T_4 into hepatocytes caused by sera of patients with NTIS also was observed by Sarne and Refetoff (55). In theory, reduced cellular uptake would cause tissue hypothyroidism, reduced T_3 generation and serum T_3 levels, and elevated serum T_4. Except for the serum T_4 levels, this hypothesis would explain many of the changes in hormone economy seen in NTIS and would also suggest a need for

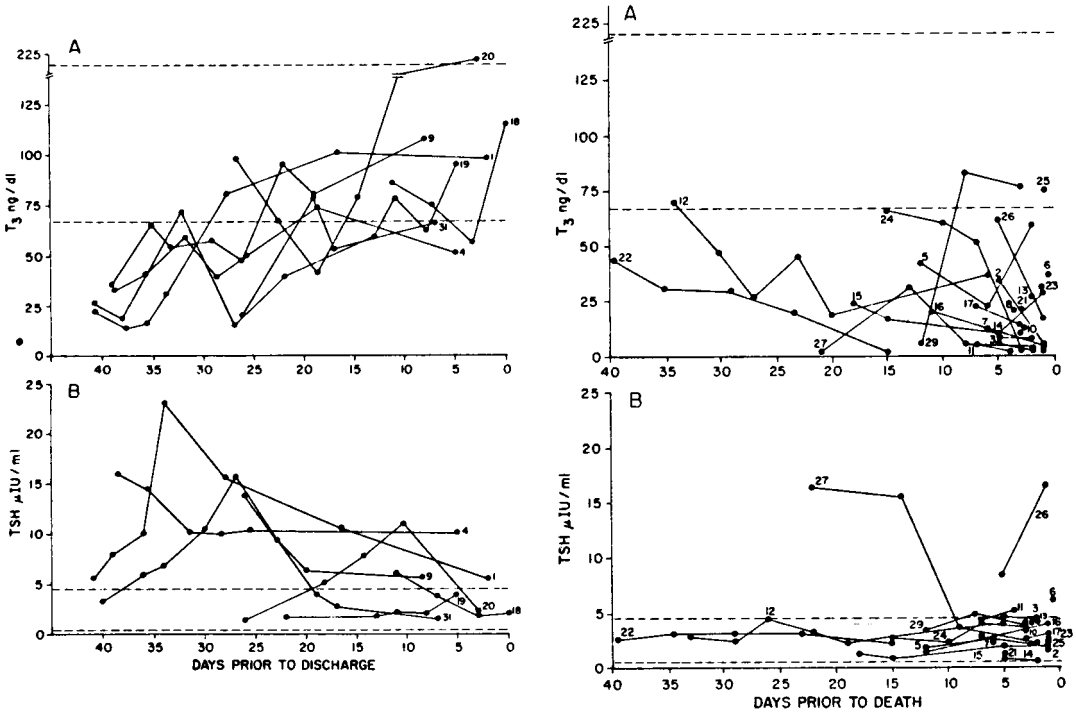

FIG. 3. T_3 and TSH concentrations are shown in patients with nonthyroidal illness who were eventually discharged from hospital (*left panels*). The *broken line* indicates ±2 SD of the mean value in the normal subjects. The *right panel* displays T_3 and TSH concentrations in patients with NTIS who died. Subjects are indicated by numbers. Note the elevated TSH in some patients who recovered, and the generally dropping T_3 and low TSH levels in patients who died (23).

TABLE 1. T_4 kinetics in the low T_4 state of nonthyroidal illness

Case No.	TT_4 (μg/dL)	Free T_4 (ng/dL)	PR (μg/day · 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[a]	0.4	0.28	10.0
10[a]	1.5	1.50	13.7
11[a]	1.6	1.70	18.4
Mean	1.8	1.24	27.9
±SE	0.2	0.17	3.7
P^b	<0.001	<0.001	<0.001

Data are from Ref. 50.
[a] Patients receiving dopamine.
[b] All P values are for unpaired t tests.

TABLE 2. T_3 kinetics in the low T_4 state of nonthyroidal illness

Case No.	Total T_3 (ng/dL)	Free T_3 (pg/dL)	PR (μg/day · 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[a]	45	282	6.07
Mean	35	244	6.34
±SE	4	24	0.53
P^b	<0.001	<0.001	<0.005

Data are from Ref. 50.
[a] Patients receiving dopamine.
[b] All P values are for unpaired t tests.

replacement hormone therapy. It is likely that the reduced hormone supply in NTIS is caused by multiple factors, and that reduced cell uptake is one of the factors.

Thyroid hormone in tissues

Only one study has provided significant data on thyroid hormone in tissues of patients with NTIS (56). The general finding was of a dramatically reduced level of T_3 in all tissues (Table 4). Although most samples had very low levels of T_3 compared to normal tissues, some patients with NTIS showed sporadically and inexplicably high levels of T_3 in certain tissues, especially skeletal muscle and heart. These levels exceeded a level that could be brought about by contamination with serum T_3 and suggest, if the assays are correct, that there may have been, for some reason, a deposition of T_3 in these tissues. This mysterious and important observation awaits clarification, but the main finding of this study is the generally low level of T_3 in tissues.

Are patients with NTIS hypothyroid?

It is clear that the usual clinical parameters of hypothyroidism are absent in patients with NTIS. However, these

TABLE 3. Turnover rates of T_4 and T_3 and thyroidal secretion of T_3 before L-T_4 replacement in uremic patients

Group and patient	T_4 metabolism		T_3 metabolism		T_3 secreted by thyroid	
	TT_4 (μg/100 mL)	D (μg/day)	TT_3 (ng/100 mL)	D (μg/day)	μg/day	% of DT_3
Normal						
D.B.	6.0	88	136	31.8	1.1	3.5
T.C.	6.7	66	146	22.5	1.1	4.9
F.K.	5.6	77	142	24.6	0.6	2.5
W.S.T.	6.5	87	130	28.0	3.5	12.5
E.S.	8.0	82	145	22.5	2.4	10.7
Mean ± SD	6.6 ± 0.9	80 ± 9	140 ± 7	25.9 ± 4.0	1.8 ± 1.2	6.9 ± 4.4
Before HD						
W.S.	5.4	59	72	12.2	5.2	42.6
W.A.	4.3	43	55	5.6	1.2	21.4
D.M.	5.2	53	88	13.7	5.8	42.3
M.A.S.	3.4	41	58	9.0	2.5	27.8
Mean ± SD	4.6 ± 0.9	49 ± 9	68 ± 15	10.1 ± 3.6	3.7 ± 2.2	33.5 ± 10.5
P^a	NS	NS	<0.01	<0.01	NS	<0.01

The turnover rates (D) of T_4 and T_3 were calculated from the respective MCR determined during L-T_4 replacement and the TT_4 and TT_3 concentrations measured before L-T_4 treatment. The amount of T_3 secreted by the thyroid gland was derived from turnover rates of T_4 and T_3 and the percentage of T_4 converted to T_3. Individual values from all four groups were analyzed by ANOVA and summarized as F ratio, degree of freedom, and *P* values. Data are from Ref. 51.

[a] The significance of the difference between the means of each patient group and the controls (*P*) was derived by using the mean square within value.

TABLE 4. Tissue T_3 concentrations in NTIS (nmol T_3/kg wet wt)

	Control group			NTI group	
	Mean	SD	*P*	Mean	SD
Cerebral cortex	2.2	0.9	<0.05	1.2	1.1
Hypothalamus	3.9	2.2	<0.01	1.4	1.2
Anterior pituitary	6.8	2.5	<0.005	3.7	1.1
Liver	3.7	2.3	<0.01	0.9	0.9
Kidney	12.9	4.3	<0.001	3.7	2.8
Lung	1.8	0.8	<0.01	0.8	0.5
Skeletal muscle	2.3	1.2	NS	>10.9	
Heart	4.5	1.5	NS	>16.3	

Data are from Ref. 56.

patients usually present with an acute illness and are diagnostically challenging in view of their complicated states. Many are febrile, have extensive edema, have sepsis or pneumonia, may have hypermetabolism 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 even 2–3 weeks, but requires a much longer period for expression (57).

General laboratory tests are also suspect. Thus, starvation or disease-induced alterations in cholesterol, liver enzymes, TBG, creatine phosphokinase, and even BMR generally rule out the use of these associated markers for evidence of hypothyroidism. Angiotensin-converting enzyme levels are low (58), as seen in hypothyroidism, whereas TEBG and osteocalcin levels are not altered (59).

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 (see below).

Certainly, one important cause of the drop in serum T_3 is a decreased generation of T_3 by type 1 iodothyronine deiodinase in liver and a reduced degradation of rT_3. The net result is a drop in serum T_3 and, if substrate T_4 is present in sufficient amount, an increment in serum levels of rT_3. This drop in T_3 is induced by starvation, especially by carbohydrate starvation, and is possibly related to the reduction in reducing equivalents needed in the liver in the enzymatic process for T_4 deiodination to T_3 (60). Possibly, as described above, entry of thyroid hormone into cells is abnormal, so that T_4 substrate is not adequately provided to the intracellular enzymes. However, it is logical to assume that if reduced entry into cells was a primary event and the major problem, then serum T_4 levels would become elevated rather than suppressed. Some studies have suggested that individuals with NTIS may have selenium deficiency and that this may contribute to a malfunction of the selenium-dependent iodothyronine deiodinase (61). However, the bulk of evidence does not favor selenium deficiency.

As described above, another major hypothesis is that part of the change in serum hormone levels is due to the presence of inhibitors of binding of T_4, and perhaps T_3, to serum proteins. This evidence has been discussed above and need not be reviewed again here. The most compelling evidence against this concept as a major problem in humans is the observations by Brendt and Hershman (40). Repletion of T_4 iv served to elevate hormone levels to normal in patients with NTIS. Seemingly, this rules out a binding inhibition as a major factor in the depression of hormone levels.

An alteration in binding of hormones to serum might logically affect turnover. In fact, as described above, the MCR (liters of serum cleared of thyroid hormone per day) for T_4 is augmented in patients with NTIS, and that for T_3 is normal. The changes recognized in the study by Kaptein *et al.* (49, 50) are modest and may reflect only an alteration in serum binding protein levels rather than another effect. However, it is the total micrograms of T_3 and T_4 produced each day, rather than the kinetics, that correlate with the metabolic effect.

The overall degradation of thyroid hormone, both T_4 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 secondary to the low hormone supply.

Considerable evidence suggests that an alteration in hypothalamic and pituitary function causes the low production of thyroid hormone. In rats, starvation reduces hypothalamic messenger ribonucleic acid (mRNA) for TRH, reduces portal serum TRH, and lowers pituitary TSH content (62). A recent study documents low TRH mRNA in hypothalamic paraventricular nuclei (63) in NTI patients (Fig. 4). Responses to administered TRH vary in different reports, being suppressed or even augmented (43, 44). Administration of TRH has been suggested as an effective means of restoring serum hormone levels to normal in individuals with NTIS. A recent report of great significance 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 (Fig. 5) (64). These data are strong documentation of the role of diminished hypothalamic function as a, or perhaps the, cause of NTIS.

Quite possibly the production of TRH and responses to TRH are induced by cytokines, to be discussed below, or glucocorticoids (65). 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 (66). High levels of glucocorticoids in Cushing's disease suppress TSH and cause a modest reduction in serum hormone levels (67). High levels of glucocorticoids are known to suppress the pituitary response to TRH in man (65). Stress-induced elevation of glucocorticoids in animals causes suppression of TSH and serum T_4 and T_3 hormone levels (68).

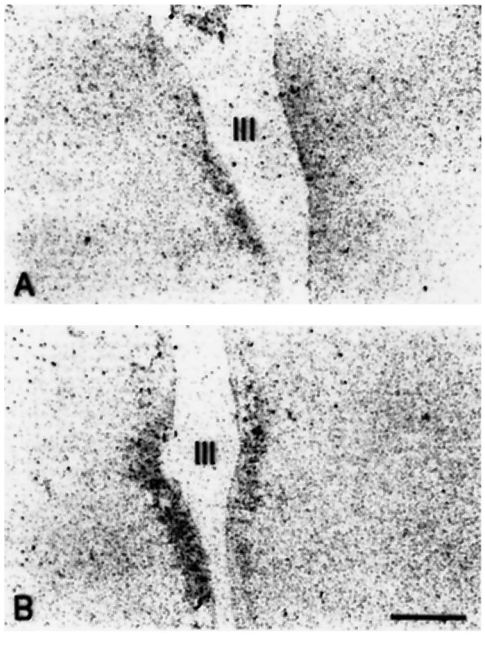

FIG. 4 *In situ* hybridization study demonstrating mRNA for TRH in the periventricular nuclei of a subject who died with NTIS (A) and a subject who died accidentally (B). The level of mRNA for TRH is significantly reduced in patients with NTIS (63).

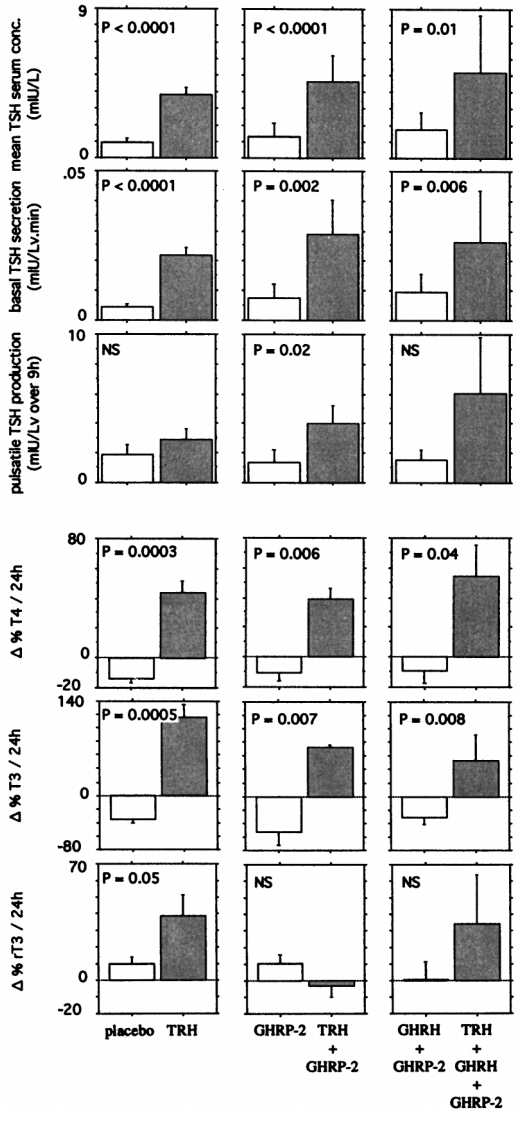

FIG. 5. The study demonstrates the effect of infusion of 1 μg/kg·h TRH compared with placebo, TRH plus GHRP-2 (1 μg/kg·h), or the combined treatment. Values for mean serum TSH and basal and pulsatile TSH secretion are shown in the *upper panel*, and 24-h changes in peripheral thyroid hormone levels in the three study groups are shown in the *lower panel*. TRH infusion increased TSH secretion and TSH, T_4, T_3, and rT_3 levels (64).

Thus, possibly, stress-induced glucocorticoid elevation may be one factor affecting TRH and TSH production.

Pituitary production of TSH is probably radically suppressed in most patients with the euthyroid sick syndrome, who have low levels of TSH in the presence of reduced levels of serum T_3 and T_4. At a minimum, pituitary responsivity must be abnormal, considering that TSH is normal or suppressed when it should be elevated, in the presence of low serum hormone levels. As we have been able to ascertain, no studies on the effect of administered human TSH have been reported to date (NTIS may constitute yet another use of recombinant human TSH.)

Why should pituitary production of TSH be diminished in the presence of low serum thyroid hormone levels? One idea, without proof, is that it represents a response to hyperthy-

roidism, which has not been documented. Another possibility is that there is augmented intrapituitary conversion of T_4 to T_3, thus allowing the pituitary to remain "euthyroid" while the rest of the body is actually hypothyroid. There is experimental support for this idea in a uremic rat model of NTIS (69). Another suggestion is that some other metabolite of T_4 may be involved in the control of pituitary responsiveness. For example, possibly Triac or Tetrac generated by metabolism of T_4 could control pituitary responsiveness (70), 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 was hypothyroid. As suggested above, elevated serum cortisol levels could play a role. The most obvious possibility is that low TSH stems from diminished TRH production, as described above. It must also be remembered that the defect in pituitary function is not restricted to TSH, but LH and FSH are also suppressed in seriously ill patients, and testosterone is reduced, in contrast to the generally augmented glucocorticoid response. Quite possibly these changes are the effect on the hypothalamus of neural integration of multiple factors, including stress, starvation, glucocorticoids, and cytokines.

Cytokines in NTIS

Much current attention is centered on the role of cytokines in developing the euthyroid sick syndrome through an effect on the hypothalamus, the pituitary, or possibly elsewhere. Hermus *et al.* (71) showed that continuous infusion of interleukin-1 (IL-1) in rats caused 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 (73). Vanderpool *et al.* (74) studied the effect of IL-1 receptor blockade in human volunteers to determine whether 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 rT_3 caused by endotoxin. This is evidence against an important role for IL-1.

Tumor necros factor-α (TNFα) is another proinflammatory cytokine that is thought to be involved in many of the illnesses associated with NTIS. Infusion of recombinant TNFα in man, as reported by Vanderpool *et al.*, produced a decrease in serum T_3 and TSH and an increase in rT_3. Free T_4 was transiently elevated in association with a significant rise in FFA levels. These studies suggest that TNFα could be involved when recombinant IL-6, given to humans, activates the hypothalamic pituitary axis, and as noted above, this could secondarily suppress TSH production. However, Chopra *et al.* (76) did not find TNFα to be closely correlated with hormone changes in NTIS.

Serum IL-6 is often elevated in NTIS (77), and its level is inversely related to T_3 levels (78). Stouthard *et al.* (79) 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

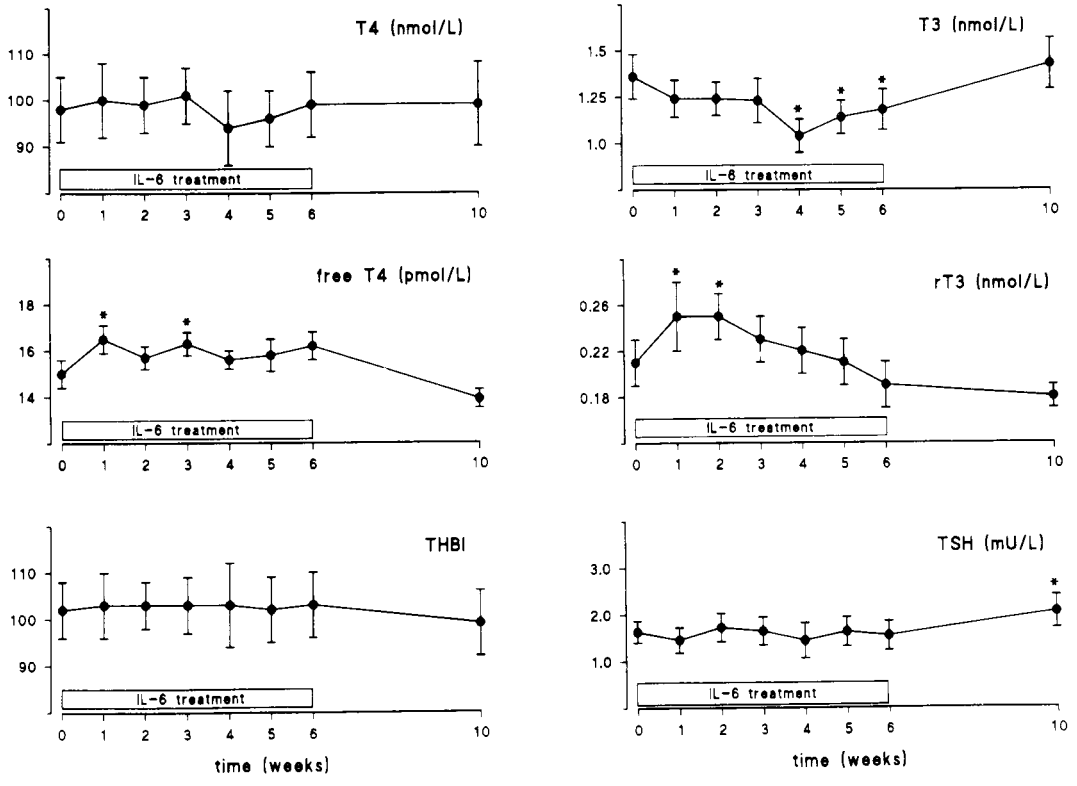

FIG. 6. IL-6 was administered over 6 weeks, and changes in thyroid hormone levels and TSH were recorded. Except for a transient elevation in rT_3 and a minimal suppression of T_3, no significant alteration in hormone levels was produced.

in T_3 and a transient increase in rT_3 and free T_4 concentrations (Fig. 6). 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 (80), 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 interferon-γ, IL-8, and IL-10 in patients with NTIS and found no evidence that they had a pathogenic role (81).

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 TNFα can stimulate the secretion of IL-6. Activation of TNFα 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 TNFα receptor and IL-1 receptor antagonist are receptor antagonists that can inhibit the function of the free cytokines. These molecules are increased in many infectious, inflammatory, and neoplastic conditions. Boelen *et al.* (82) found evidence that NTIS is an acute phase response generated by activation of a cytokine network. Soluble TNFα, soluble TNFα receptor, soluble IL-2 receptor antagonist, and IL-6 all inversely correlated with serum T_3 levels. The researchers concluded that the elevations of soluble TNFα receptor and IL-6 were independent determinants of serum T_3 and accounted for 35% and 14%, respectively, of the change in T_3. At least we can be convinced that these cytokine changes cooccur with changes in T_3 and may play a pathogenic role by mechanisms yet unknown.

Other factors altering serum T_4 supply

Administration of glucagon to dogs caused a significant fall in serum T_3, suggesting that the stress-induced hyperglucagonemia may be a contributor to the NTIS syndrome by altering intracellular metabolism of T_4 (83).

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 T_4 and T_3, and an increase in the T_3/rT_3 ratio (78). All of these changes suggested to Van den Berghe *et al.* (84) that dopamine makes some patients with NTIS hypothyroid, inducing a condition of iatrogenic hyperthyroidism, and that treatment (presumably by administering thyroid hormone) "should be evaluated."

Thyroid hormone changes in patients with liver and renal disease

Patients with alcoholic liver disease, as reported by Walfish *et al.* (85), tend to have low serum T_3 levels, slightly reduced T_4 levels, and elevated free T_4 indexes because of low binding proteins. These changes were associated with increased mortality. In chronic biliary cirrhosis and chronic active hepatitis, as studied by Liewendahl (86), elevated TBG may be found associated with normal free T_3 and free T_4 levels. Chopra *et al.* (87) studied patients with hepatic cirrhosis and found free T_4 to be significantly elevated, T_3 to be markedly reduced, free T_3 to be low, and TSH to be slightly above normal. Assessment of a variety of clinical parameters suggested that the patients were euthyroid. The researchers concluded that in this instance, euthyroidism is maintained by the high normal or slightly elevated serum free T_4 levels. It should be noted that the mean free T_4 level in the patients studied by Chopra was 3.9 ng/100 mL, which falls well within the range of normal reported by the researchers of 1.8–4.2 ng/dL and is not characteristic of NTIS. It is probable that some of the distinctive effects of liver disease on thyroid hormone economy are due to changes in the synthesis of TBG, possibly the effect of hyperestrogenism, and probably reduced deiodination of T_4 to T_3 in the liver.

Kaptein *et al.* (88) studied patients with acute renal failure and found decreased serum T_4 and T_3 levels and normal or elevated levels of free T_4 and TSH in patients with acute renal failure, but not in those with critical illness. In this group of patients, rT_3 levels tended to be normal. Ramirez *et al.* (89) studied patients receiving chronic hemodialysis and found a striking prevalence of goiter (58%) and low serum T_4, T_3, and TSH levels. TRH caused an increase in serum TSH and T_3 levels, suggesting a suppression of pituitary function in these patients. Lim and co-workers (90) studied the thyroid hormone supply in a uremic rat model and found changes similar to those seen in uremic man, including low serum T_3, low serum T_4, low serum TSH, and low liver T_3 content. T_3 treatment of the animals increased low liver enzyme activity, and the researchers conclude that the reduction in liver T_3 content in the uremic rat and the low enzyme activity indicate hypothyroidism. The T_3 nuclear receptor binding capacity was also reduced in uremic rat livers. Further studies found that the pituitary T_3 content was normal. Thus, they hypothesized that pituitary type 2 deiodinase maintains an adequate level of T_3 so that the pituitary is euthyroid while the rest of the body is hypothyroid. In further studies, they presented data that intrapituitary $T_4 \rightarrow T_3$ deiodination is selectively increased in these animals (69). Not surprisingly, administration of 0.8 μg T_3/kg daily to uremic men increased nitrogen excretion, from increased protein catabolism (91). Presumably, this is evidence for repair of hypothyroidism and, if it represents a significant problem, could be covered by increased protein intake.

Is the hypothesis that NTIS is due to a test artifact valid?

Clearly, the question of exact free T_4 levels in patients with NTIS remains uncertain and most likely will be shown to be variable. In many patients, all tests indicate that the hormone levels are low. Considering the range of assays applied and their different response to inhibitors, it seems unlikely that inhibitors of T_4 and T_3 binding to serum proteins are universally important, causing a test artifact. There is no clear-cut evidence for the role of any specific inhibitor, except possibly in uremic patients or in patients previously treated with heparin (whose sera develop elevated FFA levels during *in vitro* dialysis). In point of fact, if the concept of heparin-induced FFA generation during dialysis procedures is valid, it would produce an artifact contrary to that commonly of-

fered to explain serum hormone discrepancies. In this case, the usual T_4 and free T_4 index measurements would be reliable, but the determination of free T_4 would be falsely elevated. Further, the test artifact hypothesis cannot explain the low T_3, the suppressed TSH, or the low production of T_4 and T_3 in patients with NTIS.

Is the binding inhibitor hypothesis a possible explanation for NTIS?

The arguments against the binding inhibitor playing an important role have been spelled out above and in previous sections of this review. The salient points are that a binding inhibitor could not explain more than a fragment of the observed abnormalities, because it does not explain the reduced generation of T_3, the low T_3 levels, the low TSH levels, or the low production of T_4 and T_3. Most importantly, it is contradicted by the direct observation that replacement of T_4 in patients with NTIS causes a return of serum levels to normal in the patients reported by Brendt and Hershman (40).

Is there evidence that tissue hypothyroidism is present and is a physiological adaptive response?

There is suggestive evidence that tissue hypothyroidism occurs because of low supplies of serum T_4 and T_3, low production levels of T_4 and T_3, and low tissue levels of T_4 and T_3. Much of the current research involving cytokines suggests the ability of these agents to induce a condition that is associated with low hormone supply in tissues. Nevertheless, absolute proof that tissues are chemically hypothyroid in humans with NTIS is clearly lacking as of this moment, primarily because such tissue markers are not available.

Assuming for the sake of argument that tissue hypothyroidism is present, can we assume that this is physiologically beneficial? We cannot take it for granted that metabolic changes occurring during illness are beneficial. Thus, hyponatremia, hypoventilation, fever, hypermetabolism of burn injury, and an endless array of other effects of illness are physiologically maladaptive. There are only two possible ways that we can know that the changes in NTIS are beneficial. The first is "revelation" and implies that we are given information, from a source that designed the system, that it is a beneficial response. This is not readily available! The second approach would be by obtaining convincing experimental evidence that the changes in thyroid economy lead to better physiological performance. In contrast, the changes in thyroid hormone levels in NTIS, when they are extreme, are clearly associated with a marked increase in morbidity. If anything, the changes are associated with maladaptation (decreased survival) rather than beneficial adaptation. Of course, correlation does not prove causation.

Much of the basis for the argument that the changes are an adaptive mechanism has to do with the modest changes in thyroid hormone levels occurring in starvation. Even here, the evidence is at best cloudy. With caloric restriction and weight loss, there is a modest drop in the resting metabolic rate of about 10%, whereas serum T_3 levels drop nearly 50% (92, 93). In animals, starvation induces a reduction in the T_3 binding capacity of the T_3 nuclear receptors in liver due to a reduction in the quantity of nuclear receptor protein present (94). In rats, the adaptation to starvation includes a decrease in TRH levels in hypothalamic portal blood and thus decreased hypothalamic TRH synthesis and release, leading to decreased TSH production (62). Sanchez found that in the brain, starvation did not alter the content or binding capacity for T_3, but illness (diabetes) did cause a decrease in the thyroid hormone receptor content and T_3 binding capacity of glial cell nuclei (95). This suggests that a decline in serum T_3 during hypocaloric feeding is like hypothyroidism, and obviously this could be adaptive. The fall in serum T_3 during hypocaloric feeding in humans was shown by Osburne *et al.* (96) to cause apparent hypothyroidism, as determined by timing of the arterial sounds and a decrease in pulse rate. Replacement doses of T_3 (30 μg/day) or T_4 (100 μg/day) promptly reversed these abnormalities. Gardener *et al.* found that fasting in normal males decreased serum T_3 (97). Administration of 5 μg T_3 every 3 h (40 μg/day) brought T_3 back to slightly higher than normal prefasting levels, and urea excretion was augmented. These researchers suggested that the fasting-induced reduction in T_3 spared nitrogen. Burman *et al.* (98) conducted similar studies and showed decreased muscle catabolism during fasting, which was reversed by feeding doses of T_3 that induced mild hyperthyroidism (60–100 μg/day). Byerley and Heber (99) presented contrasting data. During starvation in normal subjects, the metabolic rate and CO_2 production decreased, but did not increase after T_3 supplementation. Urinary nitrogen excretion decreased during fasting and did not increase with T_3 supplementation (30 μg T_3 daily). Their data suggest that the drop in T_3 does not mediate the protein sparing found in fasting.

Thus, it is clear that the fasting induces a drop in BMR, reduces nitrogen loss, and tends to decrease T_3 levels, but replacement of T_3 does not return the BMR to normal or necessarily alter protein metabolism. From these studies it cannot be proven that a drop in T_3 exerts a specific adaptive, physiological, protein-sparing effect during fasting, although this remains a reasonable possibility. Even granted that this is true, any relationship of this to NTIS is extremely problematical. The changes in thyroid hormone supply induced by short term fasting in man are very modest and are not comparable to the severe drop in hormone supply found in severely ill patients with T_4 levels below 4 μg/dL, nor is there any evidence that these small decreases in T_3 increase the probability of death, as occurs in severe NTIS. Aside from the uncertainty about the relationship of T_3 to protein sparing, and the lack of comparability to severe NTIS, a third more important point argues against the relevancy of this information in considering therapy for NTIS. Although short term starvation is allowed in patients undergoing mild surgical intervention or who present to the hospital with acute illness, starvation is not allowed to continue during illness. Patients are promptly supplemented with glucose, vitamins, lipids, amino acids, and every factor needed by every route possible to maintain appropriate nutrition. Thus, although starvation may occur, it is not an accepted part of medical management of patients with NTIS, and in general, NTIS patients are not, or at least should not be, starving.

Is there evidence that treatment of NTIS is disadvantageous?

The data from observations of man are restricted. In the study by Brent and Hershman (40), replacement with 1.5 μg T_4/kg BW, iv, in 12 patients promptly returned serum T_4 levels to normal, but did not normalize T_3 levels over a period of 2–3 weeks. However, in both treated and control groups, mortality was 80% (40). 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. One can argue that the failure to show a positive effect was due to the failure of T_3 levels to be restored to normal. In a study of severely burned patients given 200 μg daily, there was again no evidence of a beneficial or a disadvantageous effect (100). Mortality was not as great as in the Brent and Hershman study, but it is entirely possible that the high levels of T_3 worsened the hypermetabolism known to be present in burn patients and could have, at these levels, been disadvantageous.

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, but some animals treated with thyroid hormone died earlier than those that were untreated (101). Chopra *et al.* induced NTIS in rats by injection of turpentine oil. The reductions in T_4, T_3, free T_4 index, and TSH were associated with no clear evidence of tissue hypothyroidism, and urinary nitrogen excretion was normal. Thyroid hormone replacement with T_4 or T_3 did not significantly alter enzyme activities or urinary nitrogen excretion (102). Healthy pigs were subjected to 20 min of regional myocardial ischemia by Hsu and collaborators (103), and this was associated with drops in T_3, free T_3, and elevated rT_3. Some animals were treated with 0.2 μg T_3/kg for five doses over 2 h. While myocardial infarction size was not altered, the pigs treated with T_3 showed a more rapid improvement in cardiac index (103). Oxygen consumption did not change. It should be noted that the T_3 levels returned to normal levels within 4 h of the last T_3 dose, suggesting that more prolonged therapy might have been beneficial.

Coronary artery bypass, as studied by Klemperer and collaborators (27), was associated with a drop in serum T_3. Administration of T_3 iv altered in a positive manner some indexes of postoperative cardiac function, but had no other effect. In this study, however, the patients had a very favorable prognosis and minimal NTIS, and the study primarily shows that administration of T_3 had no adverse effect under these circumstances. T_3 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 g were given prophylactic doses of T_4 and T_3 daily and had a lower mortality rate than untreated infants (104). Dogs subjected to hemorrhagic shock recover more cardiovascular function when given T_3 iv than did untreated animals (105). Neurological outcome after anoxia is improved in dogs by T_3 treatment (106).

In summary, it can be stated that there is no clear evidence that T_4 or T_3 treatment of NTIS in animals or man is disadvantageous, but there is no certain proof that it is advantageous. However, what evidence there is suggests that it may be beneficial. The argument has been raised that administration of thyroid hormone in NTIS would prevent the elevation of 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 originally 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 above suggesting hypothyroidism was erroneous, and the patients were, in fact, euthyroid (Table 5).

If treatment is given, what should be the method?

Clearly, the high mortality rate in patients with T_4 levels below 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 subjects who have cardiac decompensation or arrhythmias. Even here the evidence is uncertain. There is no clear evidence that administration of replacement doses of T_3 to patients with low cardiac output is disadvantageous, and in fact, current studies using iv T_3 in these patients indicate that it is well tolerated and may be beneficial (107). 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 the control of arrhythmias. 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 levels, who need replacement therapy by any standard.

If therapy is to be given, it cannot be T_4 alone, because this would fail to promptly elevate T_3 levels (40). Treatment must

TABLE 5. Summary of observations in NTIS

1. Hypothalmic mRNA for TRH is reduced, and cytokines may be involved.
2. TSH levels are inappropriately low for serum hormone levels, presumably because of reduced secretion.
3. TRH injection causes an elevation of TSH, T_4, and T_3, reversing many aspects of the syndrome and suggesting that low TRH secretion may be a primary problem.
4. Measured serum levels of apparent free T_4 and T_3 may be low, normal, and in some assays even elevated, but no assay can be certified to be free of artifact.
5. Inhibitors of T_4 and T_3 binding to serum proteins, and possibly receptors, have been postulated, but remain of unproven significance.
6. T_4 and T_3 production rates have been clearly demonstrated to be markedly reduced.
7. Based on scant data, levels of hormone in most tissues are greatly reduced.
8. Replacement hormone therapy has not been shown to be disadvantageous, and in some studies appears to be beneficial.
9. Serum hormone was, in the one study available, restored by administration of physiological doses of hormone.

be with oral, or if this is impractical, iv T_3 and probably should be at the replacement level of approximately 50 μg/day given in divided doses. It may be appropriate to give slightly higher doses, such as 75 μg/day, for 3–4 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 h), and dosages should be adjusted to achieve a serum T_3 level approximating at least low normal (70–100 ng/dL) before the next scheduled dose. If treatment is successful, T_3 administration can gradually be reduced, and T_4 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 rT_3, replacement with T_4 may initially only lead to elevation of rT_3 and have very little effect on T_3 levels or physiological action. In this situation, continued administration of T_3 would be preferred.

Conclusion

I argue for the administration of replacement T_3 and T_4 hormone in patients with NTIS as the most logical way to "do no evil." However, it is impossible to be certain at this time that it is beneficial to replace hormone, or whether this could be harmful. Only a prospective study will be adequate to prove this point, and probably this would need to involve hundreds of patients (1). One cannot envisage that replacement of T_4 or T_3 would cure all patients with NTIS. The probable effect, if any is achieved, will be a modest increment in overall physiological 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 to the patient, rather than a single magic bullet that would reverse all of the harmful metabolic changes occurring in these severely ill patients.

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