Endo

THE DILEMMA OF ABNORMAL THYROID FUNCTION TESTS: IS THYROID DISEASE PRESENT OR NOT?

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I. INTRODUCTION

The endocrine service is frequently consulted to interpret the incidental finding of abnormal thyroid function tests in patients without obvious thyroid disease. Only a fraction of these abnormal tests involve abnormalities in the well understood changes associated with altered levels of thyroid hormone binding globulin (TBG). In the remainder of patients it is necessary to decide whether subtle hypo-or hyperthyroidism exists or whether the abnormal values are somehow spurious. In spite of the ready availability of assays of serum triiodothyronine (T_3) and thyrotropin (TSH) and of the ability to test the pituitary-thyroid axis by assessing the response of TSH to thyrotropin releasing hormone (TRH) stimulation, the diagnosis of subtle hypo- or hyperthyroidism is still a problem in clinical endocrinology. Since thyroid disease is quite common in the adult population with a prevalence of noniatrogenic hypo- or hyperthyroidism of about 4% in women (1), it is important to have a high index of suspicion.

This review will consider the new insight into thyroid hormone physiology gained by studies of peripheral metabolism of thyroid hormones during the last 10 years and discuss the problems of interpretation of thyroid function tests. The spectrum of confounding conditions includes not only the variety of changes in circulating thyroid hormone that may accompany the so-called "euthyroid sick syndrome", but an increasing variety of drug effects on thyroid hormones and thyroid function as well as the seemingly "new" familial causes of euthyroid hyperthyroxinemia. Several recent reviews are recommended for additional reading (2-6).

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II. NORMAL THYROID HORMONE DYNAMICS

Ingested iodine is absorbed and taken up by the thyroid gland where it is organified by incorporation into mono- and diiodotyrosines. Thyroxine (T_4) is formed by coupling of two diiodotyrosyl molecules, and T_3 by coupling a

monoiodotyrosyl and diiodiotyrosyl residues in thyroglobulin, the storage protein for thyroid hormones. When thyroglobulin is resorbed into thyroid cells, T_4 and T_3 are released into the circulation. It is now clear that most of the circulating T_3 is produced by monodeiodination of T_4 in peripheral tissues (7,8). About 80% of T_4 is successively monodeiodinated in either the 5' or 5 positions to form the various iodothyronines (Fig. 1). About one third of the T_4 secreted each day is metabolized via 5'-deiodination to give rise to about 80% of the plasma T_3 (Fig. 2). Most of this conversion occurs in liver and kidney (11, 12) with the T_3 formed released into plasma. The remaining 20% of T_3 production comes from direct secretion by the thyroid gland. In most systems T_3 has about 10 times the potency of T_4 (9,10). Since under physiological conditions almost all the activity of T_4 can be accounted for by the T_3 formed from it, T_4 can be considered a prohormone.

The alternate monodeiodination product of T_4 formed by removal of an inner ring iodine is 3,3',5'-triiodothyronine or reverse T_3 (rT_3) (Fig. 1). It is also largely produced extrathyroidally with a little more than a third of secreted T_4 being initially converted to this metabolite (Fig. 2) (13). Serum rT_3 concentrations are lower than T_3 concentrations (Fig. 2) because of the more rapid metabolic clearance of rT_3. Reverse T_3 has little or no thyroid hormone biological activity (14,15). Both T_3 and rT_3 are further deiodinated to 3,3'-diothyronines (Fig. 1) as well as other diodo- and monoiodothyronines (reviewed in 16). Direct measurement of thyroidal vein iodothyronines supports the secretion of T_3 and rT_3 and their estimated relative contributions to peripheral levels as depicted in Fig. 2 (17).

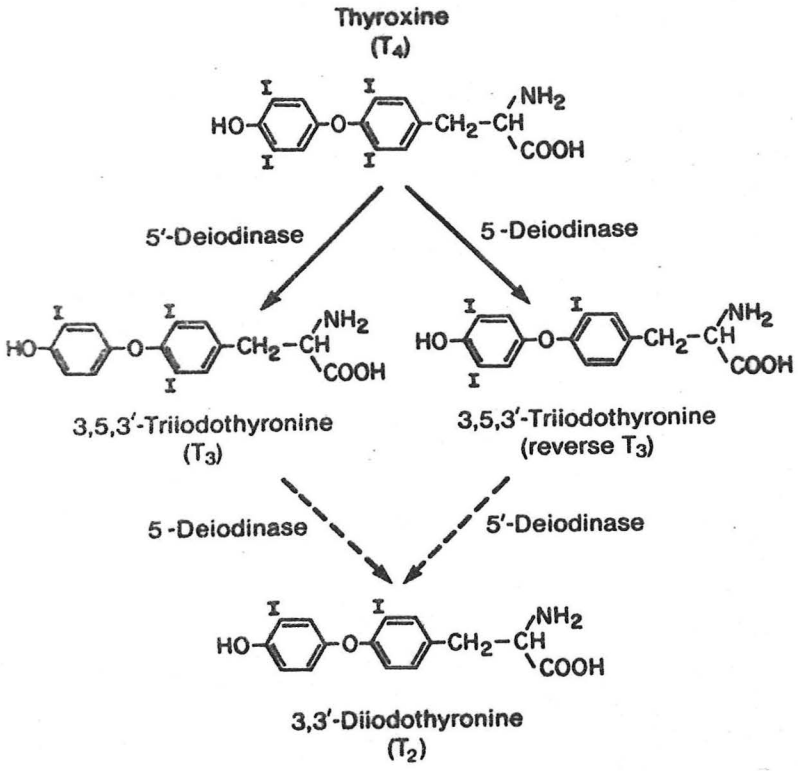

Figure 1

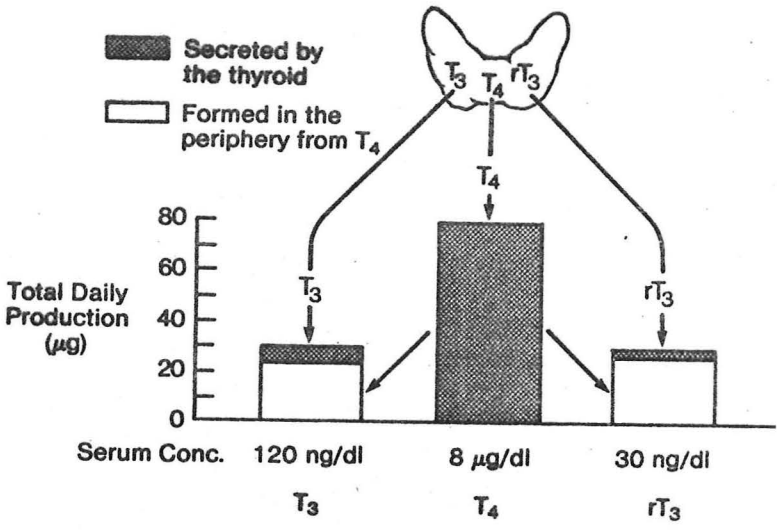

Figure 2

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III. T_4 TO T_3 CONVERSION AND REGULATION OF TSH SECRETION

A. 5'-Deiodinase of Kidney and Liver

The conversion of T_4 to T_3 in liver and kidney has been studied primarily in the rat. Studies of this reaction have shown the requirement of a sulfhydryl-containing cofactor in the cytosol to activate this membrane-bound enzyme (18). The reaction is inhibited by propylthiouracil (18), a drug known to impair T_4 to T_3 conversion in man (19). Likewise fasting the rats prior to measuring the 5'-deiodinase in vitro resulted in decreased enzymatic activity (20) in keeping with the observed lower T_3 levels in starved humans (21). Moreover, the activity of the liver and kidney 5'-deiodinase were shown to increase in hyperthyroid animals and decrease in hypothyroid animals (22) consistent with the increased fractional rate

of degration of T_4 in hyperthyroidism and the decreased rate in hypothyroidism. Since starvation was known to be accompanied by increased rT_3 levels (23) it was interesting to note that the activity of 5'-deiodinase in liver and kidney for rT_3 (Fig. 1) seemed to have similar properties to the enzyme metabolizing T_4 suggesting the presence of a single 5'-deiodinase in these tissues (24). Additional studies of the mechanism of reduced 5'-deiodinase activity in fasted animals suggested that the defect might reside in depletion of intracellular glutathione (25,26) since addition of glutathione could partially (25) or completely (26) restore activity.

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B. 5'-Deiodinase of Anterior Pituitary, Brain, and Brown Adipose Tissue

Binding of T_3 to a nuclear thyroid hormone receptor is thought to initiate most of the effects of T_3 in tissues (27). Of all tissues studied anterior pituitary had the highest concentration of nuclear thyroid hormone receptors (Fig. 3) (9). Fig. 4 shows the time course of nuclear T_3 binding and plasma TSH after administration of a single IV dose of T_3 to chronically hypothyroid rats (28). The response is rapid with plasma TSH levels significantly decreasing within one to two hours.

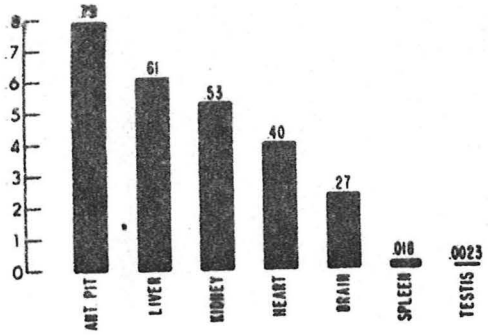

Figure 3. T_3 Nuclear Binding Capacity (Nanograms per Milligram of DNA) in Various Rat Tissues.

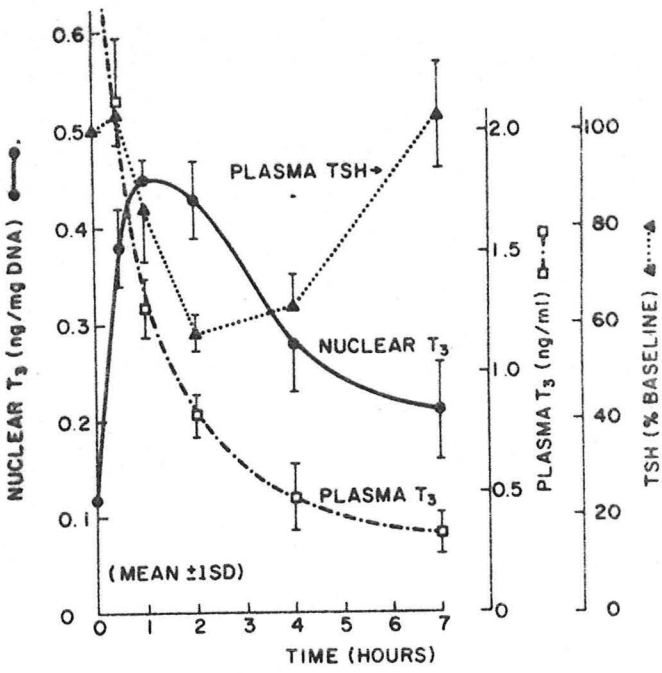

FIG. 4. Time course of pituitary nuclear T_3 and TSH after administration of a single iv dose of 70 ng T_3/100 g BW to thyroidectomized rats. Each point is the mean ± SD for four rats. The gravimetric T_3 quantities were calculated from the specific activity of the injected dose and the [^{125}I]T_3 found specifically bound to the nucleus or in trichloroacetic acid precipitates of plasma.

Infusion of T_4 also suppresses TSH but it requires a 10-fold higher dose. After T_4 infusion TSH remains suppressed for up to 22 hours while serum T_3 levels at seven hours are insufficient to account for the suppression (29). Furthermore, treatment of the rats with PTU, an agent known to block T_4 to T_3 conversion in liver and kidney did not prevent the suppression of TSH by T_4. These observations might seem to imply that T_4 to T_3 conversion is not critical for suppression of TSH. However, when labelled T_4 was given to rats 80 to 100% of the iodothyronine bound to the pituitary nuclear receptors was T_3 within two to three hours (30). This T_3 does not originate from plasma T_3 but from T_4 converted to T_3 within the pituitary (30). For unexplained reasons PTU inhibits T_4 to T_3 conversion in liver and kidney but not in the pituitary (30). In contrast the oral cholecystographic agent iopanoic acid inhibits T_4 to T_3 conversion in all tissues studied. When T_4 is given to hypothyroid rats pretreated with iopanoic acid no acute suppression of TSH is seen (Fig. 5) (31). However, T_3 given to similarly treated animals caused TSH suppression indicating that the drug iopanoic acid did not prevent the change in TSH in some nonspecific manner (Fig. 5) (31).

Studies of euthyroid rats have shown that only 40 to 50% of nuclear T_3 in the pituitary originates from circulating T_3. Production of T_3 from T_4 within the pituitary accounts for the majority of T_3 occupying nuclear receptors (Fig. 6) (32). This extra quantity of locally produced T_3 results in nuclear receptors that are about 80% saturated in the euthyroid state compared to about 50% for liver or kidney (Fig. 6) (32). Thus, in the euthyroid state plasma T_4 is a more important source of intracellular T_3 in the anterior pituitary than in the liver or kidney.

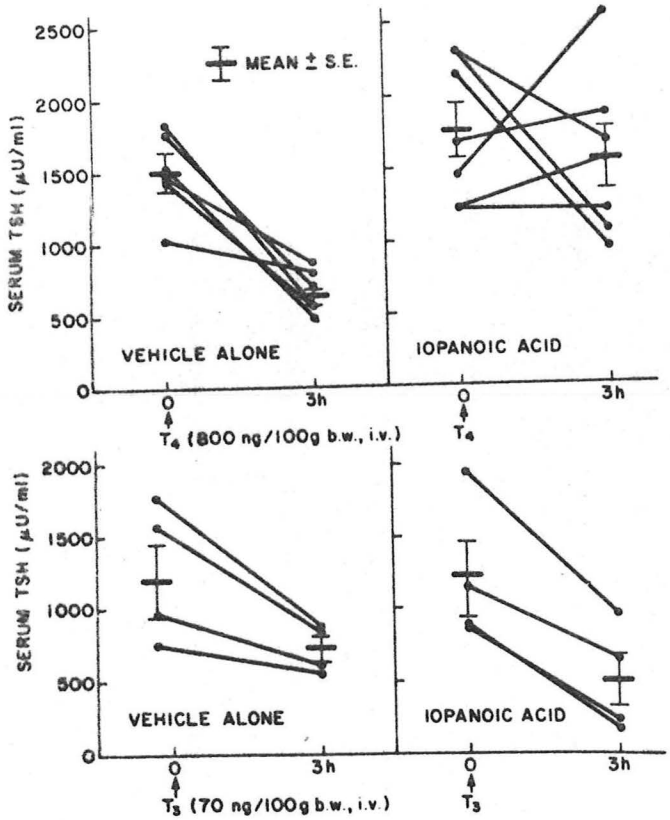

FIG. 5. Acute response of chronically hypothyroid rats to 800 ng T_4 or 70 ng T_3/100 g BW iv. One group received three injections of iopanoic acid, 5 mg/100 g BW ip 24, 16, and 1½ h before injection of iodothyronines, whereas the other group received vehicle alone.

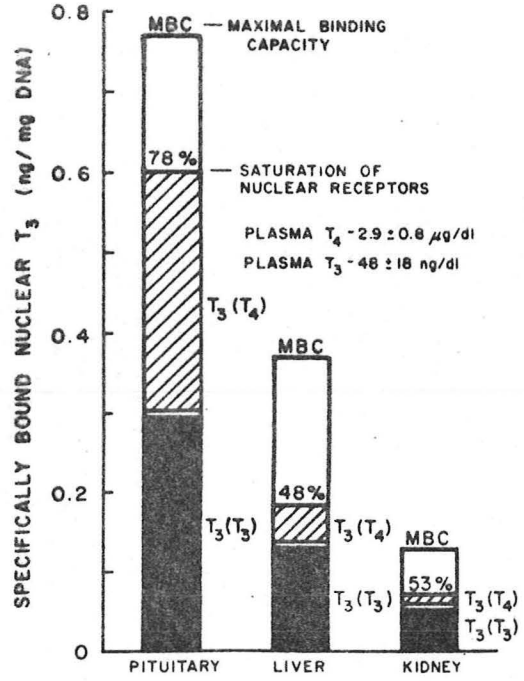

FIG. 6. Sources of nuclear T_3 in anterior pituitary, liver, and kidney of euthyroid rats based on results of tracer distribution studies. The maximal T_3 binding capacity of euthyroid rats for each tissue is indicated by the height of the bar. The component of the nuclear T_3 present deriving from either plasma T_3 [$T_3(T_3)$] or from intracellular T_4 5'-monodeiodination [$T_3(T_4)$] within each tissue is indicated by the coded areas within each bar. The gravimetric quantities of T_3 from these two sources are determined from the mean of results obtained 18 and 24 h after [^{125}I]T_4 injection. The gravimetric quantities of plasma T_3 and T_4 were measured by RIA in the same animals before tracer iodothyronine injection.

An understanding of the differences in sources of nuclear T_3 in the pituitary helps explain some of the previously difficult to understand phenomena of clinical thyroidology such as the elevation of serum TSH in early hypothyroidism when T_3 levels are not decreased but T_4 levels are slightly below normal (33).

The findings of differences in T_4 deiodination in pituitary compared with liver and kidney prompted more extensive evaluations of the enzyme characteristics and nuclear binding in vitro. Studies of cultured pituitary fragments showed that T_4 supplied in the medium was a better source of nuclear T_3 than T_3 supplied in the medium (34). Moreover, in contrast to liver tissue from fasting or PTU-treated animals intrapituitary T_4 to T_3 conversion was not decreased (34). While hypothyroidism depressed and thyroxine treatment stimulated liver 5'-deiodinase active, these manipulations had the opposite effect on the pituitary enzyme. In contrast iopanoic acid inhibited both pituitary and liver 5'-deiodinases (34). The enzyme was then studied in pituitary homogenates and the changes associated with thyroid status and pattern of drug inhibition confirmed (35). In addition the pituitary enzyme was shown to have thiol dependence like the liver enzyme (35,36), but the pituitary enzyme differed from the hepatic and renal reaction in requiring a 20-to 50-fold higher concentration of dithiothreitol as the thiol agent and in having a markedly lower Km for T_4 (35).

In a series of elegant papers from Dr. Larsen's lab in the last few years the effects of hypothyroidism and T_4-treatment, substrate specificity, and PTU-sensitivity have been used to demonstrate the presence of two 5'-deiodinase

enzymes in rat pituitary, brain and brown adipose tissue (37-40). These studies have shown that one of the 5'-deiodinase activities in these tissues resembles that seen in liver, kidney, and epididymal fat pad, prefers reverse T_3, and predominates in euthyroid pituitary tissue in vitro. The other 5'-deiodinase activity predominates in hypothyroid pituitary and brain tissue, is rapidly responsive to changes in thyroid hormone availability, and appears to account for all the T_3 produced locally in vivo (37-40). These enzymatic capacities have been termed 5'-deiodinase I and II. Their differing characteristics are summarized in Table I.

Table I
Characteristics of 5'-Deiodinases in Rat Tissues

	5'-Deiodinase I	5'-Deiodinase II
Location	Liver and Kidney (Pituitary, Brain and Brown Adipose Tissue)	Pituitary, Brain, and Brown Adipose Tissue
Inhibition by PTU	Yes	No
Effect of Hypothyroidism	Decreased	Increased
Effect of Hyperthyroidism	Increased	Decreased
Effect of Fasting	Decreased	No Change
Inhibition by Iopanoic Acid	Yes	Yes
Substrate Preference	Reverse T_3	T_4
Km for T_4	High	Low

Several recent papers from Dr. Larsen's lab have examined the mechanism of thyroid hormone inhibition of 5'-deiodinase II (41), the distribution of 5'-deiodinase II in various pituitary cell types (42), and the contribution of 5'-deiodinase II to circulating T_3 in chronic hypothyroidism (43). Interestingly, the T_3-mediated rapid fall in 5'-deiodinase II does not result from a change in rate of enzyme synthesis but instead appears to be mediated by a posttranscriptional mechanism that ultimately increases the rate of degradation or inactivation of the enzyme (41). In populations of pituitary cells enriched for somatotrophs, mammotrophs, thyrotrophs and gonadotrophs, it appears that changes in somatotrophs and mammotrophs primarily account for the majority of increased whole pituitary levels of 5'-deiodinase in hypothyroidism (42). Since somatotrophs depend on T_3 for growth hormone secretion, this would appear beneficial. If thyrotrophs had as great an increase in T_3 generation, this might be maladaptive in blunting TSH response to try to compensate for decreased thyroid hormone levels (42). Finally, in hypothyroid rats because of decreased liver and kidney 5'-deiodinase I activity and enhanced 5'-deiodinase II activity, this second type of deiodinase actually contributes significantly to the extracellular T_3 pool (43).

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IV. CIRCULATING THYROID HORMONES AND THEIR DELIVERY TO TISSUES UNDER NORMAL CONDITIONS

Iodothyronines in the circulation are largely protein bound to thyroid-hormone binding globulin (TBG), thyroid-hormone binding prealbumin (TBPA) and albumin. In routine assessment of thyroid status we usually measure the total T_4 concentration and correct it for an in vitro assessment of thyroid hormone binding in plasma (the T_3 uptake ratio) to derive a free T_4 index. Although this is commonly only done for T_4 levels, it can also be applied to total T_3 levels to derive a free T_3 index (44). In both instances within the usual variation of thyroid hormone binding globulin levels these free hormone estimates correlate fairly well with actual free hormone concentrations measured by equilibrium dialysis. However, in extreme alterations in TBG levels the T_3 uptake ratio tends to undercorrect the total T_4 so that with near absence of TBG the elevated T_3 uptake ratio might not bring the decreased total T_4 up to a normal free T_4 index. The relative distribution of T_4 and T_3 among plasma proteins at equilibrium under normal conditions is shown in Table II (45,46).

Table II
Distribution of T_4 and T_3 Among Plasma Proteins at Equilibrium

Fraction	T_4	T_3
	%	
TBG-bound	70	70
TBPA-bound	20	<5
Albumin-bound	10	30
Free (dialyzable)	0.03	0.3

Until the recent past it was felt that only the free fraction of largely protein bound steroid and thyroid hormones was available for entry into tissues and thus "active". This concept must be reassessed in light of the work of Dr. Pardridge in the last five years. He has developed a model for studying bioavailability of plasma protein bound thyroid hormones, steroid hormones, and drugs by measuring the transport into brain and liver following in vivo injections in animals (47). This "free intermediate" model for the transport of protein-bound substances into tissues

emphasizes three factors: the transit time, the rate of unidirectional dissociation of ligand from plasma protein (K_{off}), and the rate of ligand diffusion through the membrane (Fig. 7) (47). Since the half times of dissociation of T_4 and T_3 from albumin are each <1 second and the half times of dissociation from TBG are about 39 and 4 sec, respectively, based on the different brain (as an example of peripheral nonhepatic tissues) and liver transit times (Fig. 7) bioavailable T_3 would be predicted to be much greater than the dialyzable fraction. In measurements from Dr. Pardridge's lab bioavailable T_3 in brain was found to be equal to 10% of the albumin-bound T_3 while bioavailable T_3 in liver was equal to all of the albumin-bound fraction and more than half of the TBG-bound fraction (48-50). The bioavailable T_4 in brain is probably similar to T_3 while the bioavailable T_4 in liver is primarily just the albumin-bound fraction.

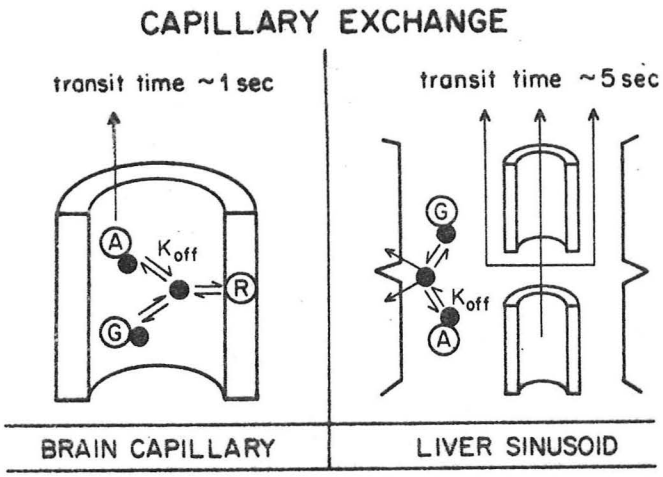

Figure 7. The "free intermediate" model for the transport of protein-bound substances into tissues emphasizes the three major factors underlying the transport process: the transit time; the rate of unidirectional dissociation of ligand from the plasma protein (K_{off}); and the rate of ligand diffusion through the membrane. Ligand diffusion may occur via either a lipid-mediated mechanism (for example, steroid or thyroid hormone transport into liver), or a receptor (carrier)-mediated mechanism (for example, thyroid hormone transport through the brain capillary wall)—that is, the blood-brain barrier. Plasma proteins distribute instantaneously across the sinusoidal wall and come into direct contact with the immediate interstitial space surrounding the hepatocyte cell membrane. From Pardridge , reproduced with permission from *Endocrine Reviews*. A = albumin; G = globulin; R = carrier.

Although estimates of "free" hormone concentrations by the free T_4 index may not have relevance to what is bioavailable in vivo, they continue to be commonly used and provide a useful tool for understanding actual thyroid status when TBG concentrations are altered for a variety of reasons (Table III). The problems that develop in using the free T_4 index to assess thyroid status in other conditions will be discussed below. In addition free hormone concentrations by dialysis do correlate with clinical hyper- and hypothyroidism.

Table III
Conditions and Drugs that Alter the Level of Thyroid Hormone Binding Globulin (TBG)

Increased TBG	Decreased TBG
Pregnancy	Androgen and anabolic steroids
Newborn state	Large dose of glucorticoids
Oral contraceptives and other sources of estrogens	Chronic liver disease
Chronic liver disease	Severe systemic illness
Acute hepatitis	Active acromegaly
Genetically determined	Nephrotic syndrome
Methadone, heroin and clofibrate	Genetically determined
	L-Asparaginase

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49. Pardridge WM, Mietus LJ: Influx of thyroid hormones into rat liver in vivo: differential availability of thyroxine and triiodothyronine bound by plasma proteins. J. Clin. Invest. 66:367-374, 1980.

50. Pardridge WM, Mietus LJ: Transport of thyroid and steroid hormones through the blood-brain barrier of the newborn rabbit: primary role of protein-bound hormone. Endocrinology 107:1705-1710, 1980.

V. NONTHYROIDAL ILLNESS WITH A NORMAL T_4 (LOW T_3 SYNDROME)

A. Frequency of Decreased T_3 Levels in Hospitalized Patients

The most common abnormality of thyroid function tests in nonthyroidal illness is not usually appreciated since the routine screening tests (total T_4 and T_3 uptake ratio) are within the normal ranges. About 10 years ago acutely ill patients with a variety of medical problems were noted to have serum total T_3 levels below the normal range (51-54). As many as 70% or more of patients in these series had low serum T_3 levels, and the abnormalities could not usually be accounted for by decreased plasma binding or the recognized decline in T_3 levels with advanced age (54). In general total T_4 levels were normal but the mean values somewhat lower while the free T_4 levels were somewhat higher than a control population due to an increased dialyzable fraction. Mean TSH levels and the TSH response to TRH levels in these patients was also within the normal range. Serum reverse T_3 levels were noted to be elevated in similar patient populations (55,56). The change in rT_3 levels was shown not to be due to increased binding but to decreased clearance (13). And the alterations in serum T_3 and reverse T_3 were noted to be reversible on recovery from the acute illnesses when such observations were possible (53,55,56). These changes were most compatible with a decreased extrathyroidal T_4 to T_3 conversion.

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54. Bermudez F, Surks MI, Oppenheimer JH: High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J. Clin. Endocrinol. Metab. 41:27-40, 1975.

55. Chopra IJ, Chopra U, Smith SR, Reza M, Solomon DH: Reciprocal changes in serum concentrations of 3,3',5'-triiodothyronine (reverse T_3) and 3,3'5-triiodothyronine (T_3) in systemic illnesses. J. Clin. Endocrinol. Metab. 41:1043-1049, 1975.

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B. Low T_3 Levels in Specific Medical Illnesses and Following Surgery

1. Effects of Fasting in Normal Subjects

Soon after it was recognized that T_3 levels were low in patients suffering from a variety of medical illnesses investigators noticed that an experimental model for the low T_3 syndrome was starvation (57). Total caloric deprivation resulted in greater than a 50% decrease in total and free T_3 levels without major changes in total or free T_4 levels, serum TSH, or TSH response to TRH (57). As with nonthyroidal illness serum rT_3 levels increased about 50% with starvation (58). When volunteers ingested hypocaloric diets with no carbohydrate only the fall in T_3 was observed (59). Studies of the production and metabolism of T_3 and rT_3 in fasting subjects demonstrated a generalized decrease in iodothyronine deiodination, especially at the 5'-position thus reducing both T_3 production and rT_3 clearance (60).

57. Portnay GI, O'Brian JT, Bush J, Vagenakis AG, Azizi F, Arky RA, Ingbar SH, Braverman LE: The effect of starvation on the concentration and binding of thyroxine and triiodothyronine in serum and on the response to TRH. J. Clin. Endocrinol. Metab. 39:191-194, 1974.

58. Vagenakis AG, Burger A, Portnay GI, Rudolph M, O'Brian JT, Azizi F, Arky RA, Nicod P, Ingbar SH, Braverman LE: Diversion of peripheral thyroxine metabolism from activating to inactivating pathways during complete fasting. J. Clin. Endocrinol. Metab. 41:191-194, 1975.

59. Spaulding SW, Chopra IJ, Sherwin RS, Lyall SS: Effect of caloric restriction and dietary composition on serum T_3 and reverse T_3 in man. J. Clin. Endocrinol. Metab. 42:197-200, 1976.

60. Suda AB, Pittman CS, Shimizu T, Chambers JB Jr.: The production and metabolism of 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine in normal and fasting subjects. J. Clin. Endocrinol. Metab. 47:1311-1319, 1978.

2. Acute and Chronic Liver Disease

In both acute and chronic inflammatory disease of the liver the primary alteration of thyroid function tests is an increased total T_4 due to an increased release of TBG from hepatocytes (61,62). Free T_4 index values are usually normal (i.e. the decreased T_3 resin uptake ratio corrects the total T_4 for the alteration in TBG). Serum total T_3 levels are normal or increased (due to the increased TBG levels) while free T_3 index values are decreased (61,62). An example of the values of several parameters of thyroid function in a group of 20 patients during acute viral hepatitis and during recovery is shown in Table IV (62).

Table IV
Thyroid Function Tests in Acute Viral Hepatitis

	T_4	T_3	T_3UR	FT_4I	FT_3I	TSH	TBG
	µg/dl	ng/dl				µU/ml	µg/ml
Normal range	5-12	70-159	0.85-1.15	5-12	70-150	<1-8	15-35
Acute hepatitis	12.5±0.6	163±14	0.57±0.04	6.9±0.4	94±10	2.6±0.4	55.6±2.0
During recovery	7.4±0.3	138±5	1.04±0.05	7.4±0.3	144±9	2.0±0.3	34.2±1.2
p value	<0.001	NS	<0.001	NS	<0.001	NS	<0.001

Thus the low T_3 state in inflammatory liver disease may be masked by increased TBG levels. The authors of the report of subjects with chronic inflammatory liver disease stress the importance of considering the coexistence of autoimmune thyroiditis since they found several patients with probable subclinical hypothyroidism based on elevated TSH and antithyroid antibodies (61).

In patients with chronic alcoholic liver disease and cirrhosis, TBG levels are more commonly depressed (and the T_3 uptake ratio increased) than elevated. The primary abnormality is a reduction in total and free serum T_3 (63-66). The degree of decrease of T_3 seems to correlate with the severity of the liver abnormalities as assessed by serum albumin, prothrombin time, and survival. Although one report (63) seemed to indicate significant elevations of serum TSH, this has not been consistently seen (64-66). Kinetic studies in patients with cirrhosis confirmed decreased 5'-deiodinase activity with preservation of 5-deiodination (67).

61. Schussler GC, Schaffner F, Korn F: Increased serum thyroid hormone binding and decreased free hormone in chronic active liver disease. N. Engl. J. Med. 299:510-515, 1978.

62. Gardner DF, Carithers RL Jr., Utiger RD: Thyroid function tests in patients with acute and resolved hepatitis B virus infection. Ann. Intern. Med. 96:450-452, 1982.

63. Nomura S, Pittman CS, Chambers JB Jr., Buck MW, Shimizu T: Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. J. Clin. Invest. 56:643-652, 1975.

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65. Hepner GW, Chopra IJ: Serum thyroid hormone levels in patients with liver disease. Arch. Intern. Med. 139:1117-1120, 1979.

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3. Chronic Renal Failure

The changes in thyroid function tests in patients with renal disease are similar in many respects to patients with other nonthyroidal illnesses. In an extensive study of 38 chronic dialysis patients serum total and free T_4 and TBG levels were normal, but 43% had a low total T_3 and 54% a low free T_3 (68). Another study of 46 patients before and after institution of hemodialysis and after renal transplantation confirmed decreased extrathyroidal T_4 to T_3 conversion and noted in addition that a normal basal serum TSH was associated with a blunted response to TRH (69). The major unique feature of the abnormal thyroid function tests in renal disease is the consistent observation of a normal rather than increased serum level of reverse T_3 (70). Kinetic studies of rT_3 metabolism suggested that a normal rT_3 production (similar to nonrenal nonthyroidal illness) is coupled with a normal serum MCR of rT_3 (in contrast to other nonthyroidal illness). Abnormalities of serum binding was similar to other nonthyroidal illness (see below) whereas the fractional rate of rT_3 exit from the serum was increased instead of reduced in renal disease (70). A shift of rT_3 from vascular to extravascular sites is postulated (70).

Changes of thyroid function tests in acute oliguric renal failure are similar to that seen in chronic renal failure (71). Patients with nephrotic syndrome and normal glomerular filtration rates without other diseases (e.g. diabetes) have some abnormalities of thyroid hormone binding but may not have impaired T_3 production (72).

68. Spector DA, Davis PJ, Helderman JH, Bell B, Utiger RD: Thyroid function and metabolic state in chronic renal failure. Ann. Intern. Med. 85:724-730, 1976.

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

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71. Kaptein EM, Levitan D, Feinstein EI, Nicoloff JT, Massry SG: Alterations of thyroid hormone indices in acute renal failure and in acute critical illness with and without acute renal failure. Am. J. Nephrol. 1:138-143, 1981.

72. Feinstein EI, Kaptein EM, Nicoloff JT, Massry SG: Thyroid function in patients with nephrotic syndrome and normal renal function. Am. J. Nephrol. 2:70-76, 1982.

4. Diabetes Mellitus

Diabetic patients with both type I and type II disease have impaired T_4 to T_3 conversion with low serum T_3 levels, and the degree of impaired T_3 production seems to correlate with the severity of the metabolic abnormality (73-75). Thus the ratio of serum T_3 to T_4 can be correlated with fasting serum glucose levels in randomly selected diabetic clinic patients (Fig. 8) (73). With attempted better diabetic control thyroid hormone metabolism returns toward normal but at a slow rate. Often it takes 5 to 14 days of rigorous diet and insulin therapy to return T_3 levels to normal (74,76), and even then measured T_3 production may remain lower than the normal range (74). The nature of the decreased T_3 production from T_4 in liver may be different than the depletion of the sulfhydryl-containing cofactor abnormality demonstrated in the fasting model since addition of dithiothreitol does not restore deiodinase activity (77).

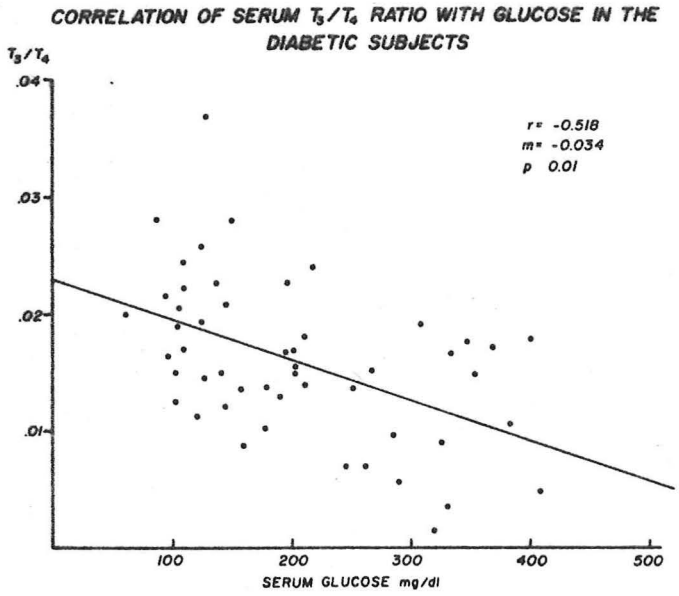

Figure 8.
Comparison of serum T3 and fasting glucose levels in the diabetic clinic population.

Diabetic ketoacidosis may complicate the interpretation of thyroid function tests in additional ways. The TSH response to TRH may be blunted in euthyroid patients with this diabetic complication (76), and serum T_3 may not be elevated in patients with actual hyperthyroidism until recovery from the ketoacidosis (78).

73. Pittman CS, Suda AK, Chambers JB Jr, Ray GY: Impaired 3,5,3'-triiodothyronine (T_3) production in diabetic patients. Metabolism 28:333-338, 1979.

74. Pittman CS, Suda AK, Chambers JB Jr. McDaniel HG, Ray GY, Preston BK: Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. J. Clin. Endocrinol. Metab. 48:854-860, 1979.

75. Kabadi UM, Premachandra BN: Low triiodothyronine and raised reverse triiodothyronine levels in patients over fifty years of age who have type II diabetes mellitus: influence of metabolic control, not age. J. Am. Geriatr. Soc. 32:375-379, 1984.

76. Naeije R, Clumeck N, Somers G, Golstein J, Meinhold H, Wenzel KW, Vanhaelst L: Pituitary-thyroid axis in diabetic coma. Eur. J. Clin. Invest. 7:222, 1977.

77. Pittman CS, Lindsay RH, Senga O, Chambers JB Jr., Hill JB Jr.: The effects of diabetes mellitus on the 3,5,3'-triiodothyronine production. Life Sciences 28:1677-1682, 1981.

78. Mayfield RK, Sagel J, Colwell JA: Thyrotoxicosis without elevated serum triiodothyronine levels during diabetic ketoacidosis. Arch. Intern. Med. 140:408-410, 1980.

5. Acute Infections

Serum T_3 levels fall and serum rT_3 levels rise in conjunction with acute febrile episodes associated with infection (79,80). The role of nutritional support in severly ill patients with bacterial sepsis was studied by comparison of T_3 levels in patients receiving only 5% dextrose versus total parenteral nutrition (81). Septic patients receiving total parenteral nutrition had significantly higher serum T_3 levels than those given 5% dextrose and were not significantly different than a control group (81).

79. Wartofsky L, Burman KD, Dimond RC, Noel GL, Frantz AG, Earll JM: Studies on the nature of thyroidal suppression during acute falciparum malaria: integrity of pituitary response to TRH and alterations in serum T_3 and reverse T_3. J. Clin. Endocrinol. Metab. 44:85-90, 1977.

80. Talwar KK, Sawhney RC, Rastogi GK: Serum levels of thyrotropin, thyroid hormones and their response to thyrotropin releasing hormone in infective febrile illnesses. J. Clin. Endocrinol. Metab. 44:398-403, 1977.

81. Richmand DA, Molitch ME, O'Donnell TF: Altered thyroid hormone levels in bacterial sepsis: the role of nutritional adequacy. Metabolism 29:936-942, 1980.

6. Acute Myocardial Infarction

Following acute myocardial infarction serum T_3 levels fall reaching their nadir on about day 3 post infarct (82-84). Simultaneously, serum rT_3 levels increase reaching peak values at about the same time (82-84). One group was able to show a significant correlation with the maximal decrease in serum T_3 and infarct size as assessed by peak SGOT (83). In another study an investigator found a better correlation of the plasma cortisol with the decrease in serum T_3 levels, but those with the higher cortisols also had the larger infarcts by CPK values (84).

82. Westgren U, Burger A, Levin K, Melander A, Nilsson G, Pettersson U: Divergent changes of serum 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine in patients with acute myocardial infarction. Acta Med. Scand. 201:269-272, 1977.

83. Wiersinga WM, Lie KI, Touber JL: Thyroid hormones in acute myocardial infarction. Clin. Endocrinol. 14:367-374, 1981.

84. Kahana L, Keidar S, Sheinfeld M, Palant A: Endogenous cortisol and thyroid hormone levels in patients with acute myocardial infarction. Clin. Endocrinol. 19:131-139, 1983.

7. Following Surgery

Within the first 24 hours following major surgery there is a fall in serum T_3 levels to almost 50% of baseline with gradual return to normal within a week (85-88). This change occurs even if epidural anethesia is used to prevent a rise in serum cortisol (86). Serum rT_3 levels change in a reciprocal fasion to those of T_3 (85-88). Interestingly, during the surgical procedure there is a brief elevation of total and free T_4 (87,88). Serum TSH does not show a consistent change (87,88).

85. Burr WA, Griffiths RS, Black EG, Hoffenberg R, Meinhold H, Wenzel KW: Serum triiodothyronine and reverse triiodothyronine concentrations after surgical operation. Lancet 2:1277-1279, 1975.

86. Brandt MR, Kehlet H, Skovsted L, Hansen JM: Rapid decrease in plasma-triiodothyronine during surgery and epidural analgesia independent of afferent neurogenic stimuli and of cortisol. Lancet 2:1333-1335, 1976.

87. Chan V, Wang C, Yeung RTT: Pituitary-thyroid responses to surgical stress. Acta Endocrinol. 88:490-498, 1978.

88. Kehlet H, Klauber PV, Weeke J: Thyrotropin, free and total triiodothyronine, and thyroxine in serum during surgery. Clin. Endocrinol. 10:131-136, 1979.

C. Changes at the Tissue Level and Other Parameters of Thyroid Status

A major question of the low T_3 state is whether patients with major reductions in serum T_3 (total and free) have tissue hypothyroidism. The fact that serum TSH values are not usually elevated would seem to argue against it. However, one could postulate that there is impaired hypothalamic TRH secretion masking actual thyroid hormone deficiency. One approach to consider events at the tissue level is to assess tissue uptake and binding of thyroid hormones. This has been studied extensively in the fasting rat model. In addition there are a number of tissue responses to thyroid hormones such as catabolic effects, cardiac parameters, and dynamics tests of feedback at the hypothalamic pituitary level that have been investigated.

1. Altered Tissue Uptake of Thyroid Hormones with Fasting

Fasting in rats results in a 30 to 50% reduction of the maximal binding capacity of liver (89-91) and kidney (91) nuclear T_3 receptors without a change in receptor affinity. In an isolated perfused liver model fasting resulted in a greater than 50% decrease in liver T_4 uptake that could account for decreased T_3

production even without a decrease in 5'-deiodinase (92). In addition rats on a nutritionally deficient diet with increased (rather than decreased) serum T_3 levels were found to have decreased cellular uptake of T_3 (93). Whether the decrease in nuclear receptors or perhaps an abnormality of cell surface receptor binding sites for T_3 (94) is responsible for decreased tissue uptake of thyroid hormones is not known. These alterations would seem to enhance the effect of any decreased serum T_3 concentrations at the tissue level.

It is unclear whether these changes in tissue uptake seen in the rat starvation model are applicable to man. Although patients with chronic wasting diseases eventuating in death had reduced tissue T_3 concentrations (95), this might be more an example of changes in a subset of patients with the more severe abnormalities of the low T_4 syndrome (see below). Examination of mononuclear leukocyte nuclear T_3 receptors in humans before and after fasting did not disclose any decrease in T_3 binding with fasting (96).

89. Burman KD, Lukes Y, Wright FD, Wartofsky. Reduction in hepatic triiodothyronine binding capacity induced by fasting. Endocrinology 101:1331-1334, 1977.

90. Schussler GC, Orlando J: Fasting decreases triiodothyronine receptor capacity. Science 199:686-688, 1978.

91. Thompson P Jr, Burman KD, Lukes YG, McNeil JS, Jackson BD, Latham KR, Wartofsky: Uremia decreases nuclear 3,5,5'-triiodothyronine receptors in rats. Endocrinology 107:1081-1084, 1980.

92. Jennings AS, Ferguson DC, Utiger RD: Regulation of the conversion of thyroxine to triiodothyronine in the perfused rat liver. J. Clin. Invest. 64:1614-1623, 1979.

93. Okamura K, Taurog A, DiStefano JJ III: Elevated serum levels of T_3 without metabolic effect in nutritionally deficient rats, attributable to reduced cellular uptake of T_3. Endocrinology 109:673-675, 1981.

94. Maxfield FR, Willingham MC, Pastan I, Dragsten P, Cheng S-Y: Binding and mobility of the cell surface receptors for 3,3',5-triiodo-L-thyronine. Science 211:63-65, 1981.

95. Reichlin S, Bollinger J, Nejad I, Sullivan P: Tissue thyroid hormone concentration of rat and man determined by radioimmunoassay: biologic significance. Mt. Sinai J. Med. 40:502-510, 1973.

96. Buergi U, Larsen PR: Nuclear triiodothyronine binding in mononuclear leukocytes in normal subjects and obese patients before and after fasting. J. Clin. Endocrinol. Metab. 54:1199-1205, 1982.

2. Tissue Response Parameters of Thyroid Status

When patients with decreased serum T_3 levels during a fast are given exogenous T_3 replacement, muscle protein catabolism is enhanced as evidenced by urinary urea, ammonia, and 3-methylhistidine excretion (97-99). This is perhaps shown best in the studies of Gardner et al. in which 5 μg T_3 every three hours was given orally to fasting normal men during one of two 80 hour fasts (Fig. 9 and 10) (98). Serum T_3 levels remained slightly above baseline levels during the T_3-

supplemented fast, and urinary urea excretion increased during the T_3 fast compared to the control fast. This has been taken as evidence of a protein sparing effect of the low T_3 levels in starvation.

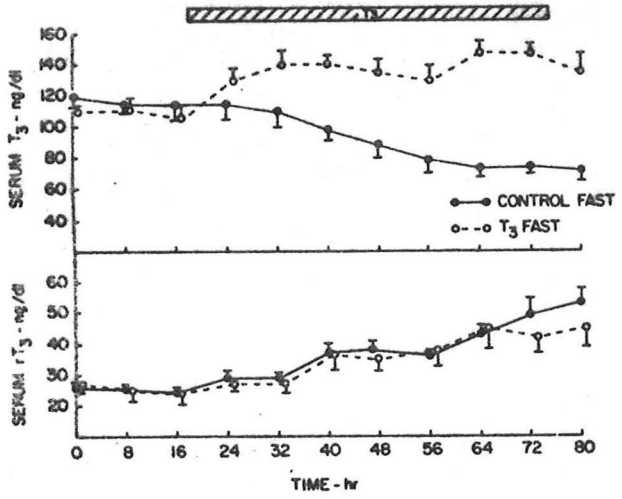

Figure 9. Serial Changes in Mean Serum T_3 (Upper Panel) and rT_3 (Lower Panel) Concentrations in Seven Normal Men during Control and T_3 Fasts.

Each point represents the mean ± S.E. In this and subsequent figures, the horizontal line at the top indicates the period during which T_3, in a dose of 5 μg every three hours by mouth, was given.

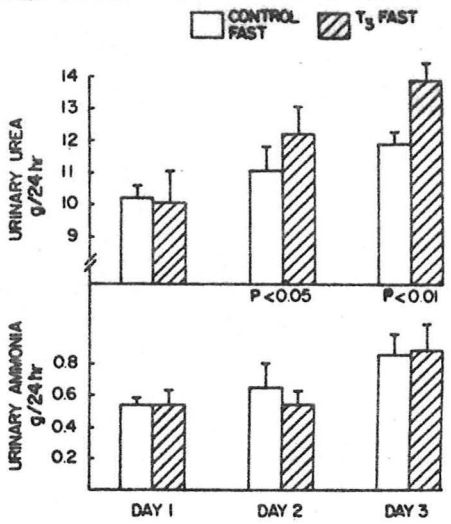

Figure 10 Mean (± S.E.) 24-Hour Urinary Urea (Upper Panel) and Ammonia (Lower Panel) Excretion in Seven Normal Men during the Control and T_3 Fasts.

In the early clinical observations of patients with the low T_3 syndrome (51,68) basal metabolic rate, pulse wave arrival time and achilles half-relaxation time were all in the normal range, again suggesting euthyroidism at the tissue level. Recently the degree of possible effect of the low T_3 levels on resting metabolic rates was reassessed (100). This study was prompted by the thought that perhaps a decreased metabolic rate associated with a low T_3 during weight loss in obese women might account for their resistance to further weight loss. After 5 weeks of a very low energy diet (472 cal/day) when serum T_3 levels had fallen almost 50%, resting metabolic rate had declined only about 9% and was still within the normal range for lean or overweight women on ad lib diets (938-1533 cal/day) (Table V) (100).

Table V
Effect of Very Low Energy Diet on Mean Body Weight, RMR and Serum Thyroid Hormone Concentrations in Six Women

	Baseline	5th week of diet
Wt (kg)	90.7±4.2	79.9±4.2
RMR (cal/day)	1522±45	1380±88
Serum T_4 (μg/dl)	8.6±0.6	7.6±0.5
Serum T_3 (ng/dl)	121±11	65±11

Thus, the "hypometabolic" response to weight loss cannot explain the failure of obese subjects to lose weight on weight-reducing regimens.

Although the studies of Gardner et al. demonstrated no significant differences between baseline TSH response to TRH and the response to TRH in the control fast but a major suppression of baseline TSH and response to TRH during the T_3-supplemented fast (Fig. 11) (98), others have continued to study normality of TSH in fasted subjects. Many subjects appear to have a blunted TSH response to TRH during fasting, and T_3 seems to be less effective in inhibiting the TSH response in such fasted subjects compared with the fed state (Fig. 12) (101).

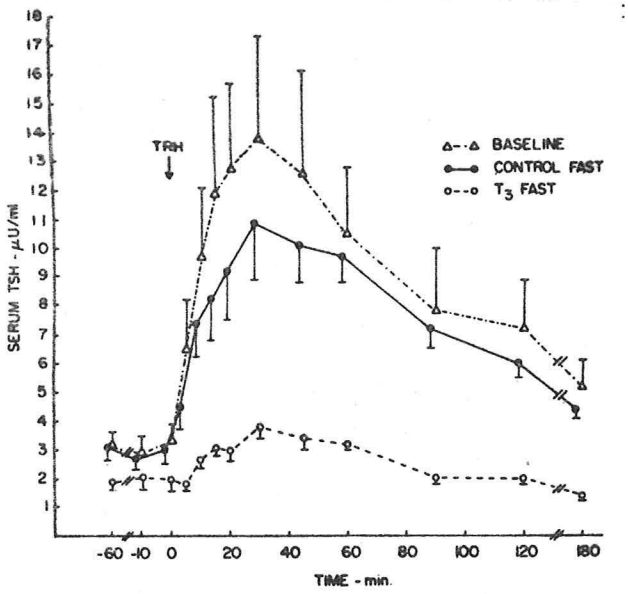

Figure 11. Serum TSH Responses to TRH after an Overnight Fast (Base Line) and at the Conclusion of the Control and T_3 Fasts.
The subjects were the same as in the previous figures. Each point represents the mean ± S.E.

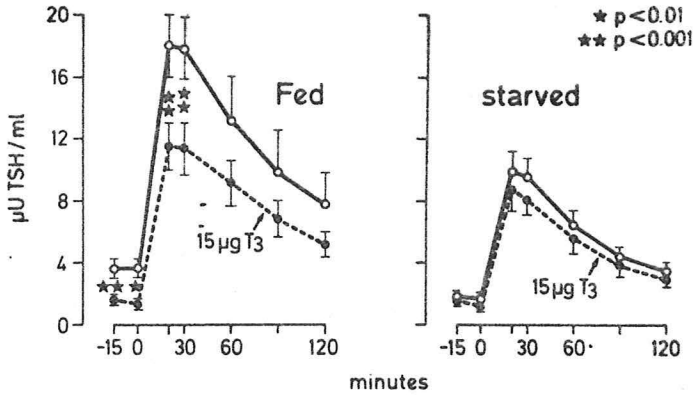

FIG. 12. Effect of T_3 on the TSH response to TRH. TRH (200 μg) was injected at zero time iv. *Left panel,* TRH tests were performed on subjects fasted overnight. T_3 was injected 24 h before the test. *Right panel,* TRH tests were performed in the same individuals but after 48 h of starvation. By analysis of variance, the two areas of TSH response are only significantly different ($P < 0.005$) when the subjects ate normally. The significance of the individual time points are shown (°, $P < 0.01$; **, $P < 0.001$).

The study in Fig. 12 differed from that in Fig. 11 in that only those subjects with an apparent blunting of the TSH response to TRH during a fast (10 of 13) were included in the figure, and the subjects were given 15 μg T_3 IV 24 hours before the TRH test. These observations were interpreted as supporting a partial resistance to target organs to T_3 in starvation (101). However, a recent study suggests that intrapituitary T_4 to T_3 conversion is more likely involved in the explanation of diminished TSH response to TRH during a fast since ipodate administration restored the TSH response to TRH in fasted subjects (102). In addition, 5 μg of T_3 every 4 hours while fasting abolished the TSH rise in response to TRH either when given alone or with ipodate (102). These observations plus the augmentation of TSH response to TRH in response to small decreases in T_4 induced by iodide (98) support a normal pituitary feedback response to both intrapituitary and extrapituitary T_3 in fasting.

Whether these studies in fasted subjects can be applied to interpretation of TSH response in systemic illness is not clear. During recovery from systemic illness in some patients serum TSH rises before T_3 levels have returned to normal suggesting that TSH secretion might have been inhibited by the stress of the systemic illness (103). In addition, in contrast to studies in fasted subjects (98), an augmented TSH response to TRH in response to small reductions in serum T_4 and T_3 levels induced by iodides occurred in only about half of 23 patients with

nonthyroidal illness (104). This did not seem to be related to the low T_3 levels and may indicate that the TSH level may not be a reliable indicator of the euthyroid state in these patients (104).

97. Vignati L, Finley RJ, Hagg S, Aoki TT: Protein conservation during prolonged fast: a function of triiodothyronine levels. Trans. Assoc. Am. Physicians 91:169-178, 1978.

98. Gardner DF, Kaplan MM, Stanley CA, Utiger RD: Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. N. Engl. J. Med. 300:579-584, 1979.

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102. Burman KD, Smallridge RC, Burge JR, Carlson D, Wartofsky L: Ipodate restores the fasting-induced decrement in thyrotropin secretion. J. Clin. Endocrinol. Metab. 57:597-602, 1983.

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

104. Maturlo SJ, Rosenbaum RL, Pan C, Surks MI: Variable thyrotropin response to thyrotropin-releasing hormone after small decreases in plasma free thyroid hormone concentrations in patients with nonthyroidal diseases. J. Clin. Invest. 66:451-456, 1980.

In summary, the nonthyroidal illness associated with a normal T_4 and low T_3 is common. Many of the changes seen in this condition are similar to those observed with fasting in normal subjects. Although some subtle abnormalities of pituitary regulation can be demonstrated in sick patients, there is little evidence for significant hypothyroidism at the tissue level, and the impaired T_4 to T_3 conversion is probably beneficial in sparing protein catabolism.

VI. NONTHYROIDAL ILLNESS WITH A LOW T_4

While nonthyroidal illness with a normal T_4 is not usually a problem to clinicians, nonthyroidal illness with a low T_4 certainly is. As will be discussed the basic underlying changes are similar to the low T_3 syndrome but with some superimposed changes on thyroid hormone binding. In addition some drugs can cause a decreased free T_4 index in the absence of hypothyroidism.

A. Prevalence in Hospitalized Patients and Results of Various Assay Methods

In the initial studies of thyroid function tests in nonthyroidal illness some patients were noted to have a frankly low total T_4 and free T_4 index (51,54,61,63). This was more often seen in the "critically ill" than the mildly "sick" patients. When such patients were not specifically excluded about 27% of 47 hospitalized patients with nonthyroidal illness in one study had a decreased free T_4 index and would thus present a diagnostic problem following routine thyroid function tests (Fig. 13) (105). In each of two larger studies of consecutive patients admitted to a medical service (175 patients total), 11% of patients had a decreased free T_4 index (106,107). In the one study where sufficient followup was obtained to be certain of the diagnosis, only 2 of the 11 patients with low free T_4 index values had actual thyroid disease (106). The pattern of the abnormal thyroid function tests in the low T_4 syndrome (or "euthyroid sick") is perhaps best seen in the series patients reported by Chopra et al. (Fig. 13) (105).

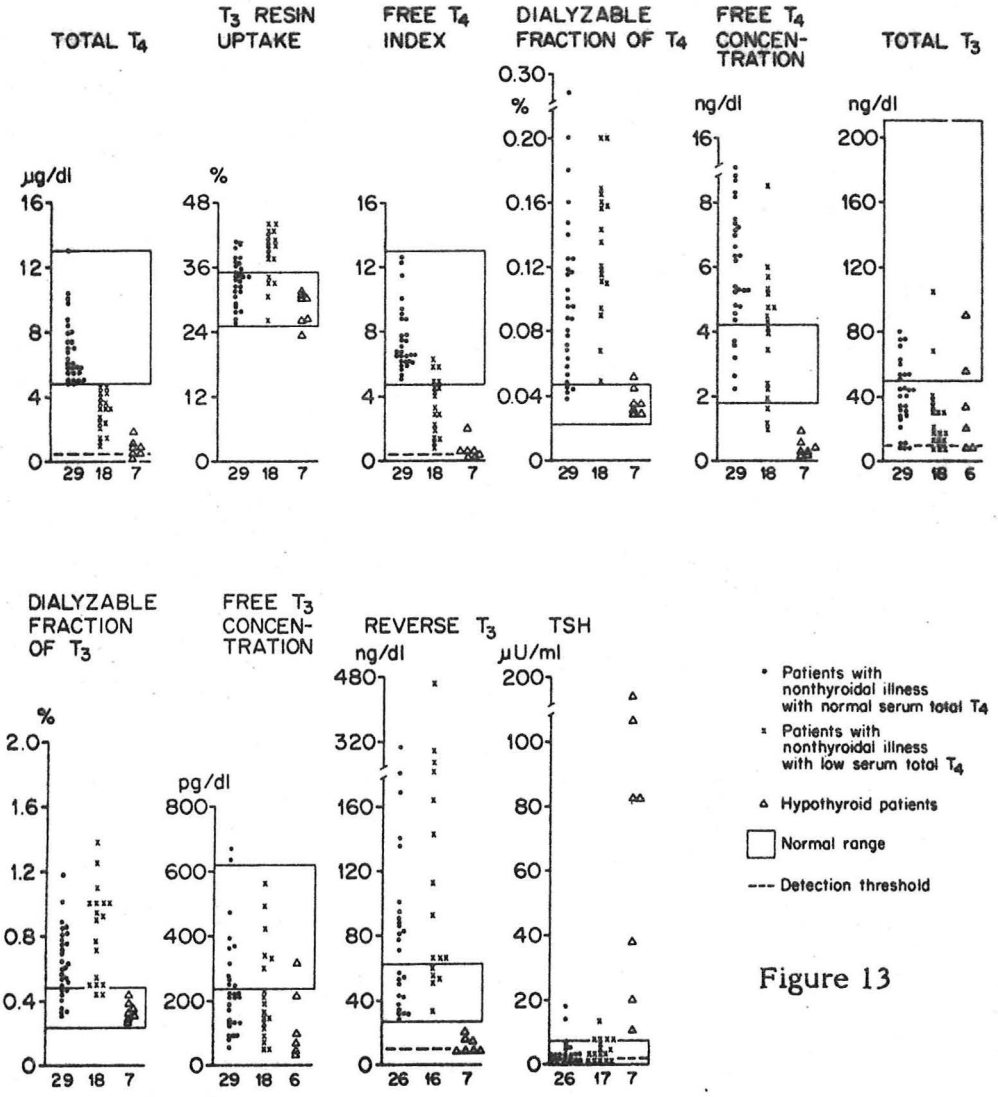

Figure 13

An even greater fraction of patients had a low total T_4 level than those with a low free T_4 index. And 75% and 57% had a low total and free T_3 level, respectively. These values and the elevated reverse T_3 levels are similar to the low T_3 syndrome.

Serum TBG levels were normal or slightly decreased. The striking abnormality noted in this study is that in spite of mild elevations in the T_3 resin uptake in some of the patients (which resulted in 5 patients with a low total T_4 having a normal free T_4 index), the majority of patients had a normal or absolutely increased free T_4 concentration. This resulted from the greatly increased (in some instances fivefold) dialyzable fraction of total T_4. Thus this is a situation in which the standard T_3 uptake correction of the total T_4 and T_3 does not result in a free hormone index closely approximating the free hormone concentration. A number of studies have appeared testing the various commercial kits for estimating free T_4 levels for how they relate to free T_4 levels measured by the tedious method of equilibrium dialysis (108-110). In one series of patients, kits made by Abbott and Clinical Assays gave a similar number of low free T_4 estimates in patients with nonthyroidal illness and decreased total T_4 levels as free T_4 concentrations by equilibrium dialysis (Fig. 14) (109).

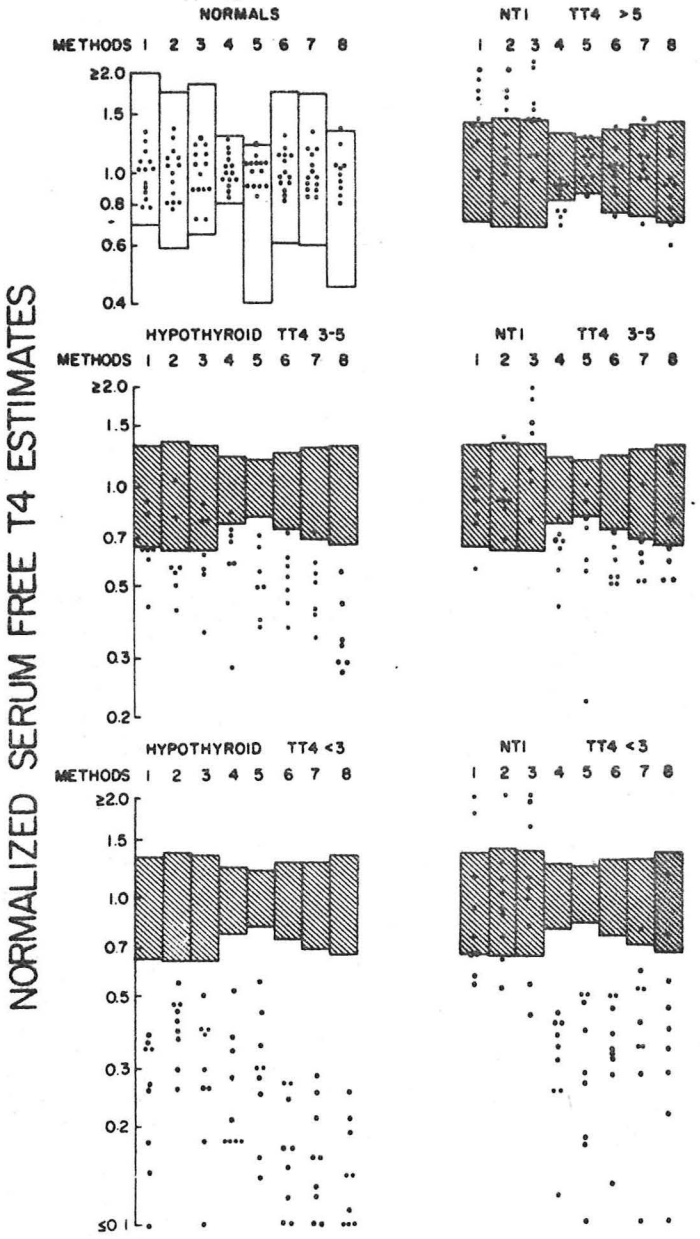

FIG. 14 Distribution of normalized free T_4 estimates within normal, NTI and hypothyroid groups. □, Reference ranges for normal subjects; ▨, calculated 95% confidence intervals from the 14 normal subjects studied. Number 1, Equilibrium dialysis; 2, Abbott; 3, Clinical Assays; 4, Corning; 5, Damon; 6, FT_4I; 7, new FT_4I; and 8, TBG index.

Compare lanes 1,2 and 3 with the standard free T_4 index in lane 6 in the lower two panels for hypothyroid and nonthyroid illness with total T_4 <3 μg/dl. However, two of nine patients with nonthyroidal illness had low values by even these methods. In a later larger study of 14 MICU patients with total T_4 <5 μg/dl 13 patients with chronic liver disease, and 32 ambulatory chronic hemodialysis patients, although the free T_4 estimate by Clinical Assays more closely approximated the free T_4 by dialysis, a substantial percentage of patients with nonthyroidal illness had free T_4 estimates overlapping those of hypothyroid patients by any method (Fig. 15) (110).

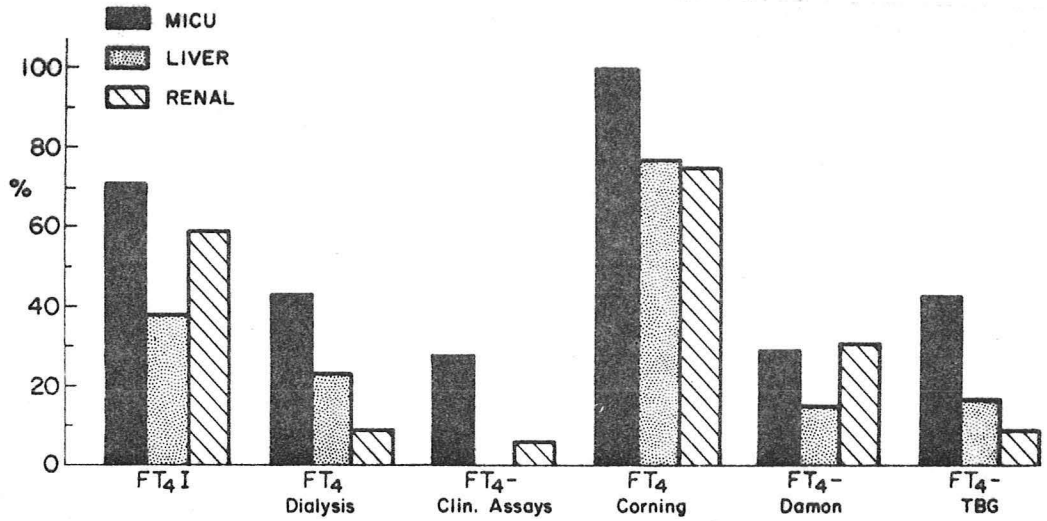

Fig. 15. Percentage of patients with subnormal results for the various FT_4 assays in each group of NTI patients tested.

In contrast to the various in vitro assays attempting to measure free T_4 concentrations or approximate them in which free hormone levels on average tend to be normal in these patients, the assay of "bioavailable" thyroid hormones in the low T_4 syndrome indicates no alteration in the hepatic bioavailable fraction of T_4 or T_3 (Fig. 16) (111). Since the total serum T_4 is reduced this should indicate that T_4 delivery to the liver is reduced (if tissue binding of T_4 in the liver is unchanged).

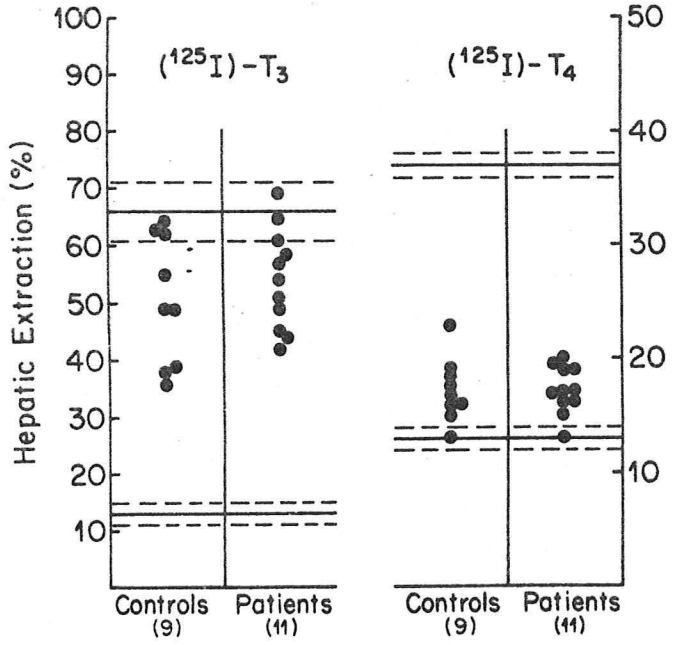

Figure 16 The extraction of unidirectional influx of [125I]T3 and [125I]T4 into rat liver in vivo is shown for three types of portal vein injection vehicles: [1] 0.1 g/100 mL bovine albumin (*upper horizontal bars*); [2] human serum (●); and [3] T4- or T3-specific rabbit antiserum (*lower horizontal bars*). Injection vehicles [1] and [3] represent extractions when 100% and 0%, respectively, of labeled hormone is available for transport into liver The horizontal bars represent the mean ± SE (n = 6 rats).

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106. Kaplan MM, Larsen PR, Crantz FR, Dzau VJ, Rossing TH, Haddow JE: Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. Am. J. Med. 72:9-16, 1982.

107. Gooch BR, Isley WL, Utiger RD: Abnormalities in thyroid function tests in patients admitted to a medical service. Arch. Intern. Med. 142:1801-1805, 1982.

108. Chopra IJ, Van Herle AJ, Chua Teco GN, Nguyen AH: Serum free thyroxine in thyroidal and nonthyroidal illnesses: a comparison of measurements by radioimmunoassay, equilibrium dialysis, and free thyroxine index. J. Clin. Endocrinol. Metab. 51:135-143, 1980.

109. Kaptein EM, MacIntyre SS, Weiner JM, Spencer CA, Nicoloff JT: Free thyroxine estimates in nonthyroid illness: comparison of eight methods. J. Clin. Endocrinol. Metab. 52:1073-1077, 1981.

110. Melmed S, Geola FL, Reed AW, Pekary AE, Park J, Hershman JM: A comparison of methods for assessing thyroid function in nonthyroidal illness. J. Clin. Endocrinol. Metab. 54:300-306, 1982.

111. Pardridge WM, Slag MF, Morley JE, Elson MK, Shafer RB, Mietus LJ: Hepatic bioavailability of serum thyroid hormones in nonthyroidal illness. J. Clin. Endocrinol. Metab. 53:913, 1981.

B. Studies of Thyroid Hormone Kinetics in the Low T_4 Syndrome

Peripheral T_4, T_3, and rT_3 kinetics have been studied in the low T_4 syndrome associated with critical nonthyroidal illness (Fig. 17) (112,113). The total T_4 levels were low as a criteria for studying the patients. The increased dialyzable fraction of T_4 almost offset the decrease in total T_4 to result in a normal free T_4 level in more than half the patients. The T_4 fractional catabolic rate and metabolic clearance rate was increased in keeping with decreased thyroid hormone binding. The resultant calculated production rate of T_4 was normal in most patients not receiving dopamine infusions (see below). If one were to postulate a defect in T_4 binding similar to that seen in congenital TBG deficiency, the rate at which tracer was transferred to the extravascular compartment (Ki) should have been increased. This was not seen (Fig. 17). Since the estimated total T_4 pool size was decreased to one-fourth that of normal, it is postulated that the explanation is decreased extravascular binding, perhaps analogous to the studies reporting decreased tissue uptake found in starved rats (see above). Not shown in the figure is a decreased T_3 production rate (about 25% of normal) which was felt to be due to decreased 5'-deiodinase rather than decreased T_4 availability. The data also suggested an extravascular binding impairment of T_3 comparable to that found in serum. In any case the normal T_4 production rate is reassuring for supporting the fact that these patients are actually euthyroid.

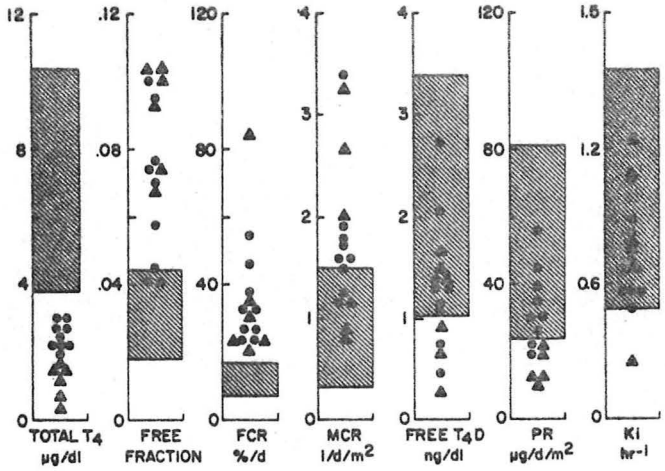

Figure 17. Graphic representation of thyroxine (*T4*) kinetics in 15 patients with severe nonthyroidal illnesses. The *shaded bars* represent the normal range of values and the *solid diamonds* represent patients who were receiving intravenous dopamine for treatment of shock at time of study. FCR = fractional catabolic rate; MCR = metabolic clearance rate; PR = production rate; Ki = rate at which the injected T4 tracer is transferred from the vascular to extravascular tissue sites.

112. Kaptein EM, Grieb DA, Spencer CA, Wheeler WS, Nicoloff JT: Thyroxine metabolism in the low thyroxine state of critical nonthyroidal illnesses. J. Clin. Endocrinol. Metab. 53:764-771, 1981.

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C. Role of Tissue Derived Inhibitors in Producing the Low T_4

The finding of an abnormally high dialyzable fraction of total serum T_4 in patients with the low T_4 syndrome suggested the possibility of a circulating inhibitor of T_4 binding since TBG levels were essentially normal or only minimally reduced. When serum from patients with nonthyroidal illness was added to normal serum, the dialyzable fraction of T_4 increased with increasing amounts of patient serum in contrast to the decrease seen when additional normal serum was added (114). The factor was not dialyzable, and the inhibition of binding by solid matrices was noted in addition to the inhibition of binding by serum proteins (115). The inhibitor appeared to be present in almost three-fourths of sera from patients with nonthyroidal illness (115). The possibility that this inhibitor might be a tissue derived factor leaked into the serum in severely ill patients was studied by assessing effect of the addition of small amounts of rat or human tissue extracts on the dialyzable fraction of T_4 in normal serum (116). The addition of small amounts of rat tissue protein markedly increased the dialyzable fraction of T_4 (Fig. 18) (116). Similar results were obtained with human liver and kidney. Both the serum inhibitor and the tissue factors are nondialyzable, heat labile, more effective in inhibiting binding of T_4 than T_3, and precipitate with ammonium sulfate and elute from gel filtration columns in a similar manner (116). Moreover the tissue inhibitor seems to alter the binding affinity of the serum proteins for T_4 without decreasing the number of binding sites. Interestingly, the serum binding inhibitor appears to also decrease tissue uptake of T_4 by isolated rat hepatocytes (115). The uptake of

T_4 was lower in the presence of nonthyroidal illness serum than would have been predicted by the equilibrium dialysis changes. This would be in keeping with the decreased extravascular binding found in the in vivo kinetic studies (see above).

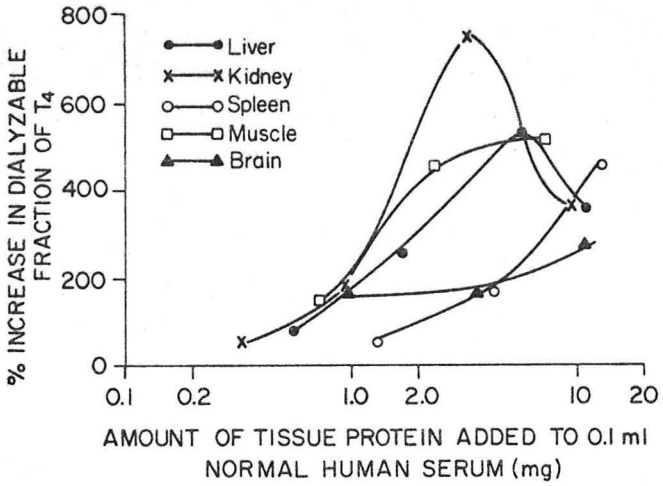

Figure [18] **increases in the dialyzable fraction of T4-125I caused by the addition of homogenates of various rat tissues to 0.1 mL aliquots of a pooled normal human serum. From Chopra and colleagues.**

Recently Chopra has reported a competitive ligand binding assay for measurement of the thyroid hormone-binding inhibitor in serum and tissues (117). It depends on the ability of the inhibitor to reduce the competitive ability of charcoal-treated iodothyronine-free human serum to decrease the binding of labelled T_4 to an anti-T_4 antibody. Values of binding inhibitor activity correlated fairly well with the inhibition found in dialysis assays ($r=0.58$, $p<0.001$) (117). Inhibitor activity in this assay was present in ether extracts of pooled sera of critically ill patients with parallel inhibition by arachidonic acid. Extracts of particulate fractions of rat tissues, especially small intestine, had the greatest inhibitor activity. Activity of intestine homogenates changed little after treatment with trypsin or protease inhibitors but was enhanced by treatment of homogenates with phospholipases. The fact that fatty acids may be affected by temperature and could circulate with macromolecules may make these recent observations not inconsistent with heat sensitivity and nondialyzable characteristics noted above.

An alternative explanation for at least a portion of the changes in dialyzable fraction of T_4 has been offered by the observation that the relative proportion of a desialylated form of TBG is increased in the sera of patients with the low T_4 syndrome (118). This "slow" TBG apparently binds T_4 less well than TBG, and increases in content of slow TBG in mixtures of normal and patient sera result in an increased dialyzable fraction of T_4 (118). These observations have yet to be confirmed.

114. Chopra IJ, Chua Teco GN, Nguyen AH, Solomon DH: In search of an inhibitor of thyroid hormone binding to serum proteins in nonthyroidal illnesses. J. Clin. Endocrinol. Metab. 49:63-69, 1979.

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

116. Chopra IJ, Solomon DH, Chua Teco GN, Eisenberg JB: An inhibitor of the binding of thyroid hormones to serum proteins is present in extrathyroidal tissues. Science 215:407-409, 1982.

117. Chopra IJ, Huang T-S, Hurd RE, Beredo A, Solomon DH: A competitive ligand binding assay for measurement of thyroid hormone-binding inhibitor in serum and tissues. J. Clin. Endocrinol. Metab. 58:619-628, 1984.

118. Reilly CP, Wellby ML: Slow thyroxine binding globulin in the pathogenesis of increased dialysable fraction of thyroxine in nonthyroidal illnesses. J. Clin. Endocrinol. Metab. 57:15-18, 1983.

D. Relation of the Low T_4 State to Survival in Critically Ill Patients

Two large studies totalling almost 300 patients have shown a striking correlation of the total serum T_4 level and survival of patients requiring admission to a medical intensive care unit (119,120). In each study patients with the lowest ranges of total T_4 (e.g. < 3 µg/dl) had greater than a 70% mortality, those with a total T_4 of 3-5 µg/dl about a 45% mortality, and those with T_4 levels > 5.0 µg/dl (i.e. normal) about a 15% mortality (119,120). The correlation of survival was also seen for the free fraction or dialyzable fraction of T_4. Nonsurvivors also had lower total T_3 levels than survivors. However, the free T_4 concentrations, total rT_3, and TSH values were similar in the survivors and nonsurvivors. Discriminant function analysis indicated that total T_4 was the best prognostic indicator with an overall classification accuracy of 70% (120).

An interesting study of the time course of changes in T_4 and T_3 levels in patients with acute trauma who had been previously well has also identified a low total T_4 as a prognostic factor for survival (121) (Fig. 19). Of 19 trauma patients admitted, four died within 48 hours. The T_3 levels (Fig. 19A) decreased to below normal levels in the survivors by the time of admission and continued to be decreased during recovery. T_3 levels in the fatalities were not lower than the survivors. In contrast serum total T_4 (Fig. 19B) and free T_4 were normal on admission and remained normal in the survivors throughout observation while levels decreased progressively in the fatalities.

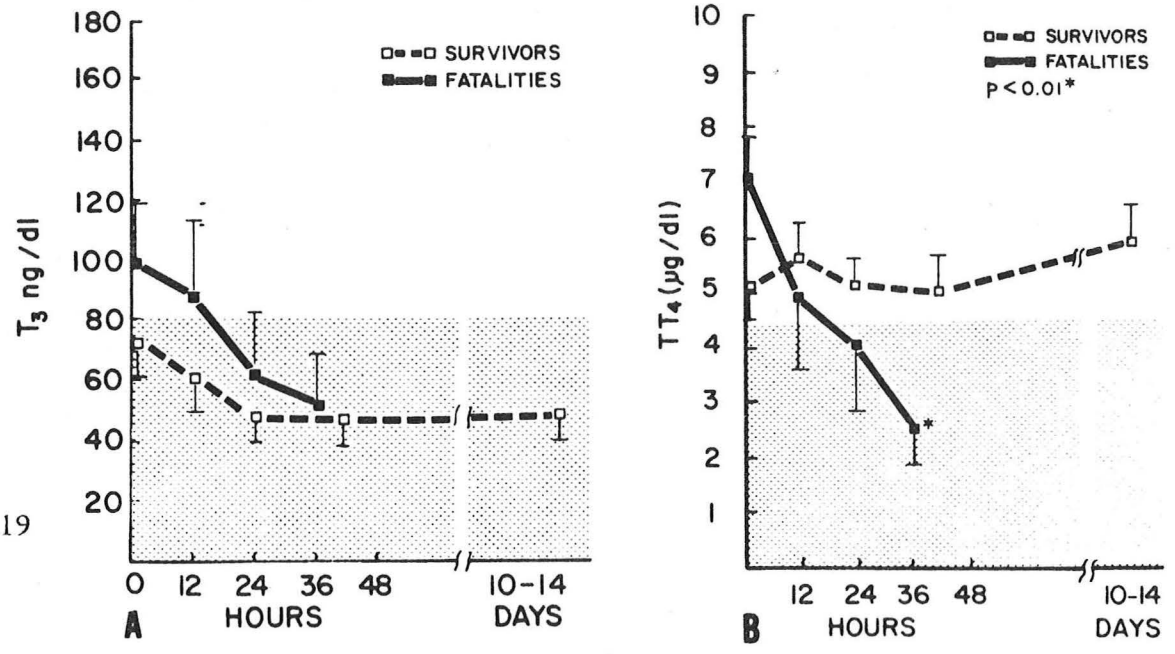

Figure 19

Chopra has proposed that one mechanism for a causal link of the proposed tissue inhibitor of thyroid hormone binding and survival in critical nonthyroidal illness is that the tissue inhibitor might impair phagocytosis (5). Preliminary observations from his lab suggest that rat intestine, liver and kidney have tissue components that impair human polymorphonuclear leukocyte phagocytosis of E. coli, and that this phagocytosis inhibitor may have properties of heat inactivation and nondialyzability similar to the inhibitor of thyroid hormone binding (122).

119. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB: Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 245:43-45, 1981.

120. Kaptein EM, Weiner JM, Robinson WJ, Wheeler WS, Nicoloff JT: Relationship of altered thyroid hormone indices to survival in nonthyroidal illnesses. Clin. Endocrinol. 16:565-574, 1982.

121. Phillips RH, Valente WA, Caplan ES, Connor TB, Wiswell JG: Circulating thyroid hormone changes in acute trauma: prognostic implications for clinical outcome. J. Trauma 24:116-119, 1984.

122. Huang TS, Hurd RE, Chopra IJ, Solomon DH, Stevens P, Young L: Coexistence of inhibitors of thyroid hormone binding and phagocytosis in extrathyroidal tissues. 58th Meeting of the American Thyroid Association, 1982, p. T-28, (abstract).

E. Drugs Which Lower T_4 Levels in Euthyroid Individuals

In addition to the effects of drugs on the level of TBG (see above), drugs can alter T_4 levels in a manner that may not be detected by alterations of the T_3 uptake ratio (i.e., the free T_4 index is also decreased) in patients who are euthyroid by clinical parameters.

A number of drugs inhibit the binding of T_4 and T_3 to TBG and, in a manner analogous to the serum inhibitor in patients with nonthyroidal illness, result in an increased free fraction of total T_4 and a normal to increased free T_4 concentration. Such drugs include salicylates and furosemide in high doses, the antiinflammatory agents phenylbutazone and fenoclofenac, the hypolipidemic agent halofenate, the cancer chemotherapeutic agents mitotane (o,p'-DDD) and 5-fluorouracil, and the anticonvulsant phenytoin (2, 123-126). Large doses of salicylates in the range of 4-5 g aspirin per day to yield serum salicylate levels of 20-25 mg/dl are required for this effect (123). Salicylates also appear to interfere with T_4 to T_3 conversion (125). The furosemide effect was detected in patients with acute oliguric renal failure and could be a factor resulting in the low T_4 syndrome in some critically ill patients (126). The effects of salicylate and furosemide are probably not detected in the T_3 uptake determinations because of altered drug binding to serum proteins with serum dilutions resulting in dilution of a reservoir to sustain free drug concentrations (123-126).

Phenytoin, in contrast to the other inhibitors of T_4 binding, does not actually result in increased free T_4 concentrations but lower free T_4 levels (123,124). This is because phenytoin has the additional effect of enhancing the cellular uptake of T_4. Patients on chronic phenytoin treatment with therapeutic serum levels have a 20-30% reduction in total T_4 levels (124). Occasionally the total T_4 values fall as low as 2-3 µg/dl with a similar fall in free levels in spite of a normal T_4 production rate. Phenytoin apparently does not effect the conversion of T_4 to T_3 but probably

enhances transport of T_4 into tissues and enhances T_4 metabolism through induction of enzymes in the smooth endoplasmic reticulum. In general patients appear clinically euthyroid with normal basal TSH levels. A recent report has suggested that there may be some depression in the integrated response to TRH in control subjects given phenytoin (127). While phenobarbital appears not to alter T_4 levels in normal subjects it may alter the T_4 requirement in hypothyroid individuals. The precipitation of clinical hypothyroidism by phenytoin with major elevation of TSH in an individual with known hypothyroidism on replacement L-thyroxine suggests that phenobarbital and phenytoin might turn subclinical compensated partial thyroid insufficiency into frank hypothyroidism (128).

The effect of heparin therapy is to elevate free T_4 levels without lowering total T_4 levels. In studies of red blood cell T_4 levels, heparin appears to act as an inhibitor of cellular T_4 binding (129). The patients remain clinically euthyroid.

123. Larsen PR: Salicylate-induced increases in free triiodothyronine in human serum: evidence of inhibition of triiodothyronine binding to thyroxine-binding globulin and thyroxine-binding prealbumin. J. Clin. Invest. 51:1125-1134, 1972.

124. Cavalieri RR, Gavin LA, Wallace A, Hammond ME, Cruse K: Serum thyroxine, free T_4, triiodothyronine, and reverse-T_3 in diphenylhydantoin-treated patients. Metabolism 28:1161-1165, 1979.

125. Chopra IJ, Solomon DH, Chua Teco GN, Nguyen AH: Inhibition of hepatic outer ring monodeiodination of thyroxine and 3,3',5'-triiodothyronine by sodium salicylate. Endocrinology 106:1728-1734, 1980.

126. Stockigt JR, Lim C-F, Barlow JW, Stevens V, Topliss DJ, Wynne KN: High concentrations of furosemide inhibit serum binding of thyroxine. J. Clin. Endocrinol. Metab. 59:62-66, 1984.

127. Surks MI, Ordene KW, Mann DN, Kumara-Siri MH: Diphenylhydantoin inhibits the thyrotropin response to thyrotropin-releasing hormone in man and rat. J. Clin. Endocrinol. Metab. 56:940-945, 1983.

128. Blackshear JL, Schultz AL, Napier JS, Stuart DD: Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. Ann. Intern. Med. 99:341-342, 1983.

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

F. Clinical Decisions of Thyroid Status in Patients with Low T_4 Levels

The interpretation of low total T_4 levels accompanied by low free T_4 index values in the acutely ill patient can be difficult. Although one might feel that use of one of the newer kits for estimating free T_4 levels that more closely approximate free T_4 concentrations by equilibrium dialysis might result in less confusion, it is clear that even these assays find low values in some patients with nonthyroidal illness (see above). In addition some of these newer kits may add to confusion by giving a significantly greater number of free T_4 values higher than the normal range in patients with low total T_4 levels (109). I feel that it is still appropriate to screen for abnormalities of thyroid function only with a total T_4 and

a T_3 uptake ratio. If the free T_4 index is low and the patient is not receiving salicylates or phenytoin as the likely explanation, then one has to consider ways to rule out hypothyroidism as an alternative explanation than the more common problem of altered thyroid hormone binding.

Since secondary hypothyroidism (i.e. pituitary disease) is much less common than primary hypothyroidism, the serum TSH is the most useful measurement. As shown in Fig. 13 (105) and reported by other groups (112), in contrast to the few nonthyroidal illness patients with small elevations in TSH, patients with primary hypothyroidism have major elevations of TSH, usually greater than 20 μU/ml. One study measured TSH values in acutely ill elderly women and found transient elevations in 4% (130). In three of these four patients the free T_4 index was normal, and the transient increase in TSH was greater than 20 μU/ml in only one patient. I think this just indicates that screening measurements of TSH should not be done (130). The reason for slight elevations in TSH in sick patients is unclear, but it could be appropriate compensation for generalized impaired T_4 to T_3 conversion. Thus major elevation of TSH in the setting of a low free T_4 index suggests primary hypothyroidism.

If the serum TSH is normal (or low) then either secondary hypothyroidism is present or the serum binding abnormality is the explanation. If the patient is receiving high doses of glucocorticoids (131) or dopamine infusions (132), it is possible for a normal TSH level to be associated with actual primary hypothyroidism due to suppression of pituitary TSH secretion by the drug (Fig. 20) (132). TRH testing is not recommended since it is recognized that a moderate decrease in TSH response may be present (see above), and it would not eliminate the possibility of low TSH levels because of hypothalamic disease (e.g. following head trauma) (133).

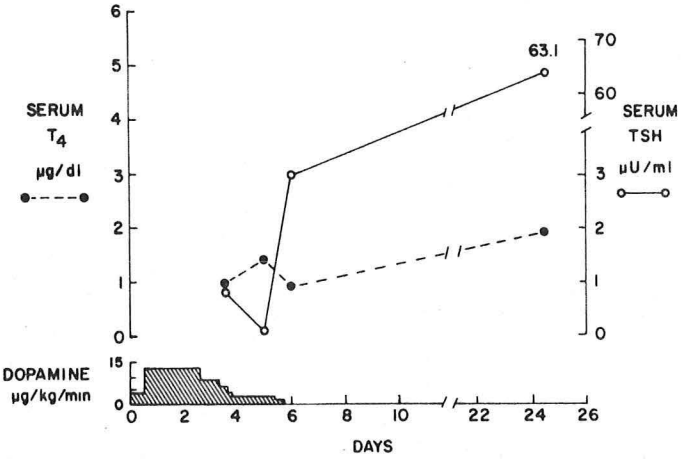

FIG. 20. Serial serum T_4 (●--●) and TSH (○—○) values in one critically ill patient during and after DA administration for shock. The serum TSH value on day 24 is compatible with a diagnosis of primary hypothyroidism.

If the free T_4 index is very low (e.g. less than 2) or if hypothalamic or pituitary disease is suspected, then one can determine if the serum cortisol is appropriately elevated for a normal stressed patient (i.e. greater than 20 μg/dl). If the serum cortisol is not appropriately elevated, then it may be appropriate to give stress replacement doses of glucocorticoids and thyroid hormone until a more definitive evaluation can be performed. Even if the cortisol level is appropriate for stress, the physician may not wish to wait the several days or more required to

obtain a TSH result in a critically ill patient if thyroid disease seems a distinct possibility. In all such patients, especially those with hypothermia or hypoventilation, the best course of action is to give replacement thyroid hormone (e.g. 100 to 200 μg sodium L-thyroxine intravenously initially followed by 100 μg daily). Euthyroid patients will not be harmed by such therapy, and the hypothyroid patient may be helped.

130. Wong ET, Bradley SG, Schultz AL: Elevations of thyroid-stimulating hormone during acute nonthyroidal illness. Arch. Intern. Med. 141:873-875, 1981.

131. Re RN, Kourides IA, Ridgway EC, Weintraub BD, Maloof F: The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. J. Clin. Endocrinol. Metab. 43:338-346, 1976.

132. Kaptein EM, Spencer CA, Kamiel MB, Nicoloff JT: Prolonged dopamine administration and thyroid hormone economy in normal and critically ill subjects. J. Clin. Endocrinol. Metab. 51:387-393, 1980.

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

VII. EUTHYROID CONDITIONS WITH A HIGH T_4

In contrast to decreased T_4 levels in euthyroid subjects which primarily occur in very sick patients, an elevated total T_4 and free T_4 index may be found in subjects who would not be considered "ill" and in whom the elevated thyroid hormone levels are an incidental finding. The causes of an elevated T_4 in spite of euthyroidism include: increased thyroid hormone binding in the plasma, acute medical illness, acute psychiatric illness, generalized resistance to thyroid hormones, and drugs.

A. Increased Thyroid Hormone Binding in the Plasma

The most common cause of increased thyroid hormone binding in the plasma is an elevated level of TBG. The common causes of an increased TBG level are listed in Table III. In practice estrogen effects and acute hepatitis (Table IV) probably account for the majority of instances of increased TBG levels. As discussed above detection of this phenomenon is not usually difficult since the T_3 uptake ratio is decreased and the resultant calculated free T_4 index is normal. What is of greater concern and interest is elevation of the free T_4 index in euthyroid subjects due to abnormal binding in the plasma.

Recently, families have been reported in which there is the autosomal dominant transmission of a condition characterized by an increased T_4 and free T_4 index (usually both in the range of 12 to 20), normal free T_4 by equilibrium dialysis, normal total T_3, and normal TSH response to TRH (134-138). On electrophoresis of serum there is increased T_4 binding to albumin. Serum albumin concentrations are normal, and the abnormality appears to be an abnormal albumin with increased affinity for T_4 (134,137). Although this syndrome has only been recognized in the last five years it may be relatively common since one major thyroid center found 26 patients in one year (136). More than 20 families have been reported in the literature. The affinity of albumin binding for T_3 is normal. Since T_3 is usually used in determining the uptake ratio, this explains why an abnormal free T_4 index is obtained. The condition has been termed dysalbuminemic hyper-thyroxinemia

(136). A modification of the T_3 resin uptake test has been proposed as a means of detecting this variant of normal plasma T_4 binding (138). This involves addition of unlabelled T_4 to displace radiolabelled T_4 from lower capacity normal binding proteins but not exceeding the capacity of the abnormal proteins.

Another form of abnormal thyroid hormone binding in the plasma that appears to be limited to T_4 has been described in a father and son from one family (139). The total T_4 and free T_4 index were elevated while the total T_3 and the free T_4 by dialysis were normal. In spite of the similarity of the abnormalities to those in the patients, with the abnormal albumin described above, these patient's sera were not found to have increased albumin binding but instead enhanced T_4 binding to prealbumin as studied on electrophoresis. The measured concentration of prealbumin in the father's serum was almost twice normal. Recall that there is normally very little binding of T_3 to prealbumin (Table II). This would then explain the lack of increase in total T_3. The affinity of T_4 binding to prealbumin has not been reported, and this condition may be primarily a problem of increased prealbumin formation, but the prealbumin concentration in the son's serum was not increased (139). Thus a qualitative abnormality may be the actual problem similar to dysalbuminemic hyperthyroxinemia. This binding abnormality can also be distinguished from normal by the T_4-loaded T_4-resin uptake test described above (138).

One final mechanism of increased T_4 levels due to abnormal binding in the plasma is the rare occurrence of anti-T_4 antibodies (140). The calculated T_4 may be high or low depending on the assay method used to separate bound and free. With double antibody techniques very high values can be obtained, while resin or charcoal separation methods give low values. The antibodies may also bind T_3 (140).

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135. Stockigt JR, Topliss DJ, Barlow JW, White EL, Hurley DM, Taft P: Familial euthyroid thyroxine excess: an appropriate response to abnormal thyroxine binding associated with albumin. J. Clin. Endocrinol. Metab. 53:353-359, 1981.

136. Ruiz M, Rajatanavin R, Young RA, Taylor C, Brown R, Braverman LE, Ingbar SH: Familial dysalbuminemic hyperthyroxinemia: a syndrome that can be confused with thyrotoxicosis. N. Engl. J. Med. 306:635-639, 1982.

137. Borst GC, Premachandra BN, Burman KD, Osburne RC, Georges LP, Johnsonbaugh RE: Euthyroid familial hyperthyroxinemia due to abnormal thyroid hormone-binding protein. Am. J. Med. 73:283-289, 1982.

138. Stockigt JR, White EL, Barlow JW: Differences between familial hyperthyroxinemia syndromes (Letter). N. Engl. J. Med. 307:824, 1982.

139. Moses AC, Lawlor J, Haddow J, Jackson IMD: Familial euthyroid hyperthyroxinemia resulting from increased thyroxine binding to thyroxine-binding prealbumin. N. Engl. J. Med. 306:966-969, 1982.

140. Ginsberg J, Segal D, Emrlich RM, Walfish PG: Inappropriate triiodothyronine (T_3) and thyroxine (T_4) radioimmunoassay levels secondary to circulating thyroid hormone autoantibodies. Clin. Endocrinol. 8:133-139, 1978.

B. Acute Medical Illness

In most series of nonthyroidal illness patients with an abnormal free T_4 index, the free T_4 index is more often decreased than increased. This was certainly the case in the series of 98 patients reported by Kaplan et al. in which only 2% had an increased index while 11% had a decreased value (106). However, in the other large series of patients admitted to a medical service almost 12% had an increased free T_4 index (107). The endocrine service at PMH feels that our experience is more like the latter series with at least as many medical admissions (not limited to critically ill patients) having an increased free T_4 index as those with a decreased value. Additional series of patients with transient isolated T_4 elevations have been reported (141-143). In general serum T_3 levels are not as low as in patients with the low T_4 syndrome (107). The mechanism for the elevated T_4 levels in nonthyroidal illness is uncertain. Clinical signs of hyperthyroidism are absent. Some authors have proposed that the elevated T_4 levels may represent compensatory increases in T_4 secretion in response to transient increase in TSH associated with decreased T_4 to T_3 conversion (144). Certainly elevations of serum TSH are not commonly seen. Alternatively the increase in T_4 can be postulated to result from decreased T_4 disposal without associated increased production. Dr. Larsen has proposed that such patients may have some underlying mild thyroid autonomy explaining why the T_4 levels don't decrease appropriately when T_4 disposal is impaired (6).

The main issue of concern is the possibility of these patients having thyrotoxicosis with the nonthyroidal illness decreasing serum T_3 levels to the normal or low range as described for some patients with diabetic ketoacidosis (see above). Patients with hyperthyroidism with normal or low serum T_3 levels usually have clinical signs and symptoms of thyrotoxicosis (142,143). However, elderly patients with hyperthyroidism may have an apathetic presentation, and nonthyroidal illness patients may have fever, tremor, and tachycardia suggesting thyrotoxicosis.

In a study of 124 patients with elevated free T_4 index values, 16% of the 83 patients proven to be hyperthyroid had isolated elevations of the free T_4 index (145). Thus "T_4 toxicosis" may not be rare. However, a third of the 124 patients in this series had nonthyroidal illness as the explanation of the elevated T_4 values. In general the euthyroid patients had smaller elevations in the free T_4 index than did the hyperthyroid patients. Serum total T_3 levels were generally less than 160 ng/dl. In this series euthyroid patients were defined by those having an increase in TSH following TRH injection of at least 2 μU/ml. As discussed above, nonthyroidal medical illness may blunt but does not usually abolish some response to TRH.

141. Burrows AW, Shakespear RA, Hesch RD, Cooper E, Aickin CM, Burke CW: Thyroid hormones in the elderly sick: "T_4 euthyroidism". Br. Med. J. 4:437-439, 1975.

142. Birkhauser M, Burer T, Busset R, Burger A: Diagnosis of hyperthyroidism when serum-thyroxine alone is raised. Lancet 2:53-56, 1977.

143. Gavin LA, Rosenthal M, Cavalieri RR: The diagnostic dilemma of isolated hyperthyroxinemia in acute illness. JAMA 242:251-253, 1979.

144. Stuart DD, Schultz AL: Thyroid function tests simulating Graves' Disease in alcoholic hepatitis. Ann. Intern. Med. 89:514-515, 1978.

145. Caplan RH, Pagliara AS, Wickus G: Thyroxine toxicosis: a common variant of hyperthyroidism. JAMA 244:1934-1938, 1980.

C. Acute Psychiatric Illness

Perhaps the most commonly encountered and puzzling cause of transient elevations of the free T_4 index is acute psychiatric illness. In four series of patients admitted to acute psychiatric hospital units over 11% had elevations of the free T_4 index (Table VI) (146-149). However, one very recent report did not find this high incidence (150).

Table VI
Frequency of an Elevated Free T_4 Index in Patients Admitted for Acute Psychiatric Disorders

Series (ref. no.)	Total Patients	Number with increased free T_4 index	%
Cohen and Swigar (146)	480	39*	8.1
Levy et al. (147)	150	11	7.3
Morley and Shafer (148)	386	29	7.5
pratt et al. (149)	559	100	17.9
	1575	179	11.4

*Not including 3 patients receiving T_4 and one subsequently diagnosed as thyrotoxic.

In those patients followed by sequential measurements of T_4, the free T_4 index usually returned to normal within a few weeks. Serum T_3 levels were variable but usually normal. One series noted an even greater incidence of elevated free T_3 index values than T_4 values (148). Although not consistent among the series, one group seemed to identify a higher incidence of thyroid hormone elevations in patients with paranoid schizophrenia and phencyclidine or amphetamine-induced psychosis (148). Almost three-fourths of patients with hyperemesis gravidarum have an elevated free T_4 index that returns to normal on resolution of the condition (151). Since there are psychiatric components to hyperemesis gravidarum, such patients should probably be considered to represent a part of this phenomenon in acute psychiatric illness.

Unfortunately the TRH test is of little help in patients with acute psychiatric illness unless it is normal since TRH testing demonstrated a flat response in over half the patients with an increased free T_4 index in one series (149). In this same series a similar per cent of newly-admitted patients with a normal free T_4 index had abnormal TRH tests. As many as a fourth of all psychiatric patients without thyroid disease have a blunted or absent response to TRH, perhaps more commonly in unipolar or bipolar depression (149).

The mechanism for the increased free T_4 index in acute psychiatric disease is not known. An interesting proposal for a possible mechanism has come from the observations that patients with amphetamine-induced psychoses have increased T_4 values and that acute amphetamine administration to monkeys results in elevations of TSH within 30 min. followed by elevations of T_4 levels within 2 to 3 hours (152). Since amphetamines increase the excretion of phenylethylamine in monkeys (153), and paranoid schizophrenics seem to excrete higher amounts of phenylethylamine in the absence of a drug effect (154), one might suggest that patients with certain forms of acute psychiatric illness have an abnormal release of phenylethylamine that is responsible for the increased T_4 perhaps via central nervous system effects on catecholamines (155). Elevated serum TSH values (as seen in monkeys given amphetamines) have not been observed in acute psychiatric illness (147,149), but perhaps transient elevations were missed.

146. Cohen KL, Swigar ME: Thyroid function screening in psychiatric patients. JAMA 242:254-257, 1979.

147. Levy RP, Jensen JB, Laus VG, Agle DP, Engel IM: Serum thyroid hormone abnormalities in psychiatric disease. Metabolism 30:1060-1064, 1981.

148. Morley JE, Shafer RB: Thyroid function screening in new psychiatric admissions. Arch. Intern. Med. 142:591-593, 1982.

149. Spratt DI, Pont A, Miller MB, McDougall IR, Bayer MF, McLaughlin WT: Hyperthyroxinemia in patients with acute psychiatric disorders. Am. J. Med. 73:41-48, 1982.

150. Kramlinger KG, Gharib H, Swanson DW, Maruta T: Normal serum thyroxine values in patients with acute psychiatric illness. Am. J. Med. 76:799-801, 1984.

151. Bouillon R, Naesens M, Van Assche FA, De Keyser L, De Moor P, Renaer M, De Vos P, De Roo M: Thyroid function in patients with hyperemesis gravidarum. Am. J. Obstet. Gynecol. 143:922-926, 1982.

152. Morley JE, Shafer RB, Elson MK, Slag MF, Raleigh MJ, Brammer GL, Yuwiler A, Hershman JM: Amphetamine-induced hyperthyroxinemia. Ann. Intern. Med. 93:707-709, 1980.

153. Chuang L-W, Karoum F, Perlow MJ: A study on the acute effect of amphetamine on the urinary excretion of biogenic amines and metabolites in monkeys. Br. J. Pharmacol. 74:571-577, 1981.

154. Potkin SG, Karoum F, Chuang L-W, Cannon-Spoor HE, Phillips I, Wyatt RJ: Phenylethylamine in paranoid chronic schizophrenia. Science 206:470-471, 1979.

155. Perlow MJ, Chiueh CC, Lake CR, Wyatt RJ: Increased dopamine and norepinephrine concentrations in primate CSF following amphetamine and phenylethylamine administration. Brain Res. 186:469-473, 1980.

D. Generalized Resistance to Thyroid Hormones

An uncommon cause of an increased total serum T_4 and free T_4 index in a euthyroid individual is generalized resistance to thyroid hormone action (156-160).

The term "generalized" resistance to thyroid hormone is used to distinguish this disorder from an even less common condition in which the resistance to thyroid hormone action is limited to the pituitary (161). These latter patients actually have hyperthyroidism and present in a manner very similar to those uncommon patients with a pituitary tumor secreting TSH (161). Generalized resistance to thyroid hormones was first described in 1967 by Refetoff in three siblings of consanguineous parentage who had clinical features of hypothyroidism (delayed bone age, epiphyseal stippling, and low hydroxyproline excretion) in conjunction with an increased thyroxine concentration and increased thyroid hormone production (reviewed in 156). All the subsequent reports have been of either sporadic cases or families with patterns of transmission more consistent with autosomal dominant inheritance (157) and have not included such severe manifestations of clinical hypothyroidism. Examples of the thyroid function tests of eight affected members from one kindred are shown in Table VII (157).

Table VII
Thyroid Function Tests in a Family with Generalized Thyroid Hormone Resistance

Patient	Age (yr)	Total T_4 (μg/dl)	Free T_4 (ng/dl)	Total T_3 (ng/dl)	Free T_3 (pg/dl)	TSH (μ U/ml)	T_3 Uptake (%)	RAIU (%)
JR	3.5	21.8	6.9	329	1701	2.3	36	38
CR*	27	19.9	5.1	279	1385	6.3	37	45
HC*	64	17.6	5.2	261	799	13.3	34	28
AS	40	21.1	5.2	290	727	1.7	31	26
WC	33	20.5	6.5	258	828	0.5	40	41
SC	8	20.7	4.6	357	1085	1.0	40	45
BC	5	25.1	5.2	404	1061	4.5	34	34
PC	20	21.9	4.5	406	1485	1.0	30	26
Normal Adult		5-12	1.3-3.8	80-160	220-660	0.5-4.0	25-35	10-30

***Prior subtotal thyroidectomy**

Note that in this study using a sensitive TSH assay with a lower limit of normal the basal serum TSH was inappropriately normal in light of the elevated T_4 and T_3. Response of TSH to TRH was normal except in CR and HC who had an exaggerated response. There are now more than 60 individuals from 25 families with generalized thyroid hormone resistance reported in the literature, most of them in the last few years. The commonest presentation has been that of goiter and elevated thyroid hormone levels in phenotypically normal patients without clinical evidence of thyrotoxicosis. Several patients have been treated inappropriately either surgically or medically for suspected thyrotoxicosis (157,158). The defect appears to be either a receptor or a postreceptor defect in thyroid hormone action (160,161).

Studies of the hypothalamic-pituitary axis demonstrate that these patients are resistant to thyroid hormones. Basal serum TSH levels and the TSH response to TRH are normal or increased in the presence of high endogenous free T_4 and T_3 concentrations and show a variable but usually incomplete suppression with exogenous thyroid hormone administration. The problem in diagnosis stems from

the lack of sensitivity of the routine clinical TSH assays. Since these assays cannot distinguish normal from low serum TSH levels, measurement of basal levels in these patients are not interpreted as inappropriately normal in light of the increased thyroid hormone levels. Correct diagnosis requires a high index of suspicion of lack of clinical thyrotoxicosis in spite of the increased free T_4 and T_3 index and demonstration of normal or increased response of TSH to TRH.

156. Refetoff S: Syndromes of thyroid hormone resistance. Am. J. Physiol. 243:E88-E98, 1982.

157. Brooks MH, Barbato AL, Collins S, Garbincius J, Neidballa RG, Hoffman D: Familial thyroid hormone resistance. Am. J. Med. 71:414-421, 1981.

158. Bantle JP, Seeling S, Mariash CN, Ulstrom RA, Oppenheimer JH: Resistance to thyroid hormones: a disorder frequently confused with Graves' Disease. Arch. Intern. Med. 142:1867-1871, 1982.

159. Cooper DS, Ladenson PW, Nisula BC, Dunn JF, Chapman EM, Ridgway EC: Familial thyroid hormone resistance. Metabolism 31:504-509, 1982.

160. Daubresse J-C, Dozin-Van Roye B, De Nayer P, De Visscher M: Partial resistance to thyroid hormones: reduced affinity of lymphocyte nuclear receptors for T_3 in two siblings. In Thyroid Research VIII: Proceedings of the Eighth International Thyroid Congress, Sydney, Australia, 3-8 February, 1980. JR Stockigt, S Nagataki, E Meldrum, JW Barlow, PE Harding (eds), Canberra, Australian Academy of Science, 1980, pp. 295-298.

161. Eil C, Fein HG, Smith TJ, Furlanetto RW, Bourgeois M, Stelling MW, Weintraub BD: Nuclear binding of [^{125}I]triiodothyronine in dispersed cultured skin fibroblasts from patients with resistance to thyroid hormone. J. Clin. Endocrinol. Metab. 55:502-510, 1982.

162. Weintraub BD, Gershengorn MC, Kourides IA, Gein H: Inappropriate secretion of thyroid-stimulating hormone. Ann. Intern. Med. 95:339-351, 1981.

E. Drug-Induced Elevation of the Free T_4 Index

All of the drugs that result in a high T_4 have as at least one of their mechanisms of action impairment of T_4 to T_3 conversion. Drugs that impair T_4 to T_3 conversion can be grouped into two classes depending on whether the site of action is only on the 5'-deiodinase I predominantly in liver and kidney or whether the drug affects both 5'-deiodinase I and 5'-deiodinase II in the anterior pituitary and brain (see above). Propylthiouracil is the prototype for the drugs acting on 5'-deiodinase I. However, dexamethasone (163,164) and propranolol (164) also have this effect and lower serum T_3 levels. Propranolol is the only drug in this category which will raise serum T_4 levels, and only when given in high doses (usually greater than 160 mg per day) (165). The mechanism of propranolol's action appears to be a membrane stabilizing effect, probably only in liver and kidney, to result in decreased T_3 formation (166). Other β-blockers such as atenolol and sotolol, which have no membrane-stabilizing activity, do not inhibit T_3 formation. Presumably at high concentrations propranolol can decrease the disposal rate of T_4 sufficiently to result in elevated T_4 levels (167).

163. Duick DS, Warren DW, Nicoloff JT, Otis CL, Croxson MS: Effect of single dose dexamethasone on the concentration of serum triiodothyronine in man. J. Clin. Endocrinol. Metab. 39:1151, 1974.

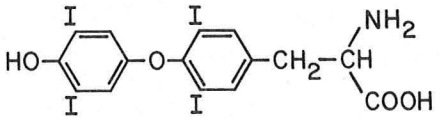
164. Chopra IJ, Williams DE, Orgiazzi J, Solomon DH: Opposite effects of dexamethasone on serum concentrations of 3,3',5'-triiodothyronine (reverse T_3) and 3,3',5-triiodothyronine (T_3). J. Clin. Endocrinol. Metab. 41:911-920, 1975.

165. Cooper DS, Daniels GH, Ladenson PW, Ridgway EC: Hyperthyroxinemia in patients treated with high-dose propranolol. Am. J. Med. 73:867-871, 1982.

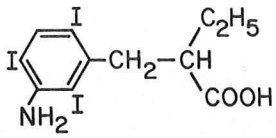
166. Heyma P, Larkins RG, Campbell DG: Inhibition by propranolol of 3,5,3'-triiodothyronine formation from thyroxine in isolated rat renal tubules: an effect independent of β-adrenergic blockade. Endocrinology 106:1437-1441, 1980.

167. Lumholtz IB, Siersbaek-Nielsen K, Faber J, Kirkegaard C, Friis TH: Effect of propranolol on extrathyroidal metabolism of thyroxine and 3,3',5-triiodothyronine evaluated by noncompartmental kinetics. J. Clin. Endocrinol. Metab. 47:587-589, 1978.

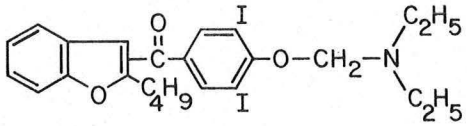
The second category of drugs, i.e. those that inhibit 5'-deiodinase in all tissues studied, is characterized by drugs with iodine in their structure and some resemblance to part of the structure of thyroxine, iopanoic acid and amiodarone being protypes (Fig. 21). It is presumed that these drugs inhibit T_3-formation from T_4 in the anterior pituitary and result in increased TSH secretion and elevated T_4 levels.



THYROXINE



IOPANOIC ACID



AMIODARONE

Figure 21

Iopanoic acid (Telepaque) and sodium ipodate (Oragrafin) are two radiographic contrast agents used for the performance of an oral cholecystogram. Studies of the pituitary-thyroid axis after a typical dose of iopanoic acid demonstrate a fall in serum T_3, rise in rT_3, and rise in TSH in the first 3 to 5 days after the dose (168-170). Serum T_4 levels rise about 25% (as high as 16 μg/dl) by 1 week and may not return to baseline until six weeks after the drug is given. The response of TSH to TRH is enhanced during the period of low T_3 levels, and the change in TSH can be prevented by T_3 administration (170). In addition cholecystographic agents may elevate T_4 levels by inhibiting hepatic uptake and binding of T_4 in vivo (171).

Amiodarone, an antiarrhythmic drug, induces may of the same changes in thyroid function tests described for iopanoic acid above (172,173). The elevated serum TSH levels present initially return to normal with chronic amiodarone therapy (173). However, during chronic therapy the serum T_4, free T_4 index, and free T_4 concentrations remain elevated and do not return to normal until about 6 weeks after stopping the drug (173). The patients usually remain clinically euthyroid in spite of an 80% increase in T_4 production rate (174). (This contrasts to the almost 5-fold increase in T_4 production rate in patients with classical hyperthyroidism in the same study.) These authors felt that the increased T_4 levels were primarily a result of the decrease in T_4 metabolic clearance rate.

Because of the amount of iodine administered in amiodarone (75 mg per 200 mg tablet) and the storage of the drug in adipose tissue and muscle some patients develop either iodide-induced hypo- or hyperthyroidism after taking the drug for a period of time(175,176). Hypothyroidism resulting from amiodarone may relate to underlying thyroid disease as suggested by a positive family history and/or the presence of antithyroid antibodies (175). Hypothyroidism is detected by an elevated basal and TRH-stimulated serum TSH in the presence of an inappropriately low normal T_4 and free T_4 index (175,176). In one study reporting both patients with a low iodine intake and patients with a sufficient iodine intake, the incidence of hypothyroidism was 5% and 22%, respectively (176). Patients with a low iodine intake would be anticipated to be at risk for iodine-induced thyrotoxicosis, and the incidence of thyrotoxicosis in this group was 9.6% compared to 2% in the iodine sufficient group in this same study (176). Hyperthyroidism was manifested by greater increases in T_4 levels than the clinically euthyroid patients and by increased T_3 levels. However, there was overlap of the T_4 values in the hyperthyroid and euthyroid amiodarone-treated groups indicating a need to monitor T_3 levels.

168. Burgi H, Wimpfheimer C, Burger A, Zaunbauer W, Rosler H, Lemarchand-Beraud T: Changes of circulating thyroxine, triiodothyronine and reverse triiodothyronine after radiographic contrast agents. J. Clin. Endocrinol. Metab. 43:1203-1210, 1976.

169. Kleinmann RE, Vagenakis AG, Braverman LE: The effect of iopanoic acid on the regulation of thyrotropin secretion in euthyroid subjects. J. Clin. Endocrinol. Metab. 51:399-403, 1980.

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172. Burger A, Dinichert D, Nicod P, Jenny M, Lemarchand-Beraud T, Vallotton MB: Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxin, and thyrotropin: a drug influencing peripheral metabolism of thyroid hormones. J. Clin. Invest. 58:255-259, 1976.

173. Melmed S, Nademanee K, Reed AW, Hendrickson JA, Singh BN, Hershman JM: Hyperthyroxinemia with bradycardia and normal thyrotropin secretion after chronic amiodarone administration. J. Clin. Endocrinol. Metab. 53:997-1001, 1981.

174. Lambert MJ, Burger AG, Galeazzi RL, Engler D: Are selective increases in serum thyroxine (T_4) due to iodinated inhibitors of T_4 monodeiodination indicative of hyperthyroidism? J. Clin. Endocrinol. Metab. 55:1058-1065, 1982.

175. Amico JA, Richardson V, Alpert B, Klein I: Clinical and chemical assessment of thyroid function during therapy with amiodarone. Arch. Intern. Med. 144:487-490, 1984.

176. Martino E, Safran M, Aghini-Lombardi F, Rajatanavin R, Lenziardi M, Fay M, Pacchiarotti A, Aronin N, Macchia E, Haffajee C, Odoguardi L, Love J, Bigalli A, Baschieri L, Pinchera A, Braverman L: Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. Ann. Intern. Med. 101:28-34, 1984.

F. Clinical Decisions of Thyroid Status

When confronted with a patient who has an elevated free T_4 index and does not appear thyrotoxic, after considering the possibility of a recognized drug effect (above), the most useful additional test is the serum T_3 determination. As described above most patients with acute nonthyroidal illness associated with an increased free T_4 index have a serum total T_3 level less than 160 ng/dl (assuming a normal T_3 uptake ratio). If the serum T_3 is greater than160 ng/dl, one should be concerned that the patient may have hyperthyroidism associated with nonthyroidal illness. It is possible for critical nonthyroidal illness to lower T_3 levels below 160 ng/dl in hyperthyroid patients, and thus a normal T_3 does not rule out the diagnosis in such patients. The presence of a goiter should signal the possibility of thyrotoxicosis since it is absent in only a few per cent of hyperthyroid patients.

If clinical suspicion of severe thyrotoxicosis is high appropriate treatment with propylthiouracil, iodides, and perhaps glucocorticoids should be instituted in critically ill patients pending results of confirmatory lab tests. Such treatment could be lifesaving in a patient with impending thyroid storm and will most likely not harm patients who are not thyrotoxic.

If the serum T_3 is normal or low the possibility of one of the abnormalities of thyroid hormone binding in the plasma or unrecognized psychiatric disease might be considered in addition to acute medical illness. The T_4-loaded T_4 resin uptake may help identify individuals with abnormal thyroid binding in plasma. As mentioned the rare patients with generalized thyroid hormone resistance may have a goiter with an elevated T_3 but lack symptoms of thyrotoxicosis. When the thyroid status is still uncertain after measuring the T_3 level, a TRH test may be helpful. After a baseline TSH sample, 500 µg of TRH is given intravenously and another TSH sample is obtained at 20 to 30 minutes. Any significant increase in TSH following TRH (probably 2 µU/ml in our assay) rules out hyperthyroidism. However, absence of a response to TRH does not necessarily prove that hyperthyroidism is present since elderly men and psychiatric patients not uncommonly have a blunted or absent response. A radioactive iodine uptake may be helpful in some patients, and still others may require a trial of antithyroid therapy.