MEDICAL GRAND ROUNDS
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THYROTOXICOSIS

Thyrotoxicosis is an extremely common endocrine disease. Because it is a multisystem disorder, patients may be seen by physicians in a variety of specialities. Diagnosis is not always easy because thyroid function studies can be influenced by a number of unrelated illnesses and drugs. Choice of treatment varies with the clinical situation. In this review I will briefly cover: thyroid hormone physiology and actions, clinical picture, causes of thyrotoxicosis, diagnostic procedures and treatment.

I. Thyroid hormone physiology and actions

1. Regulatory network for thyroid hormone secretion. Thyroid hormone production is normally tightly controlled by a signal network linking the brain, hypothalamus, pituitary and thyroid glands (1). A skeletal outline is shown in Fig. 1.

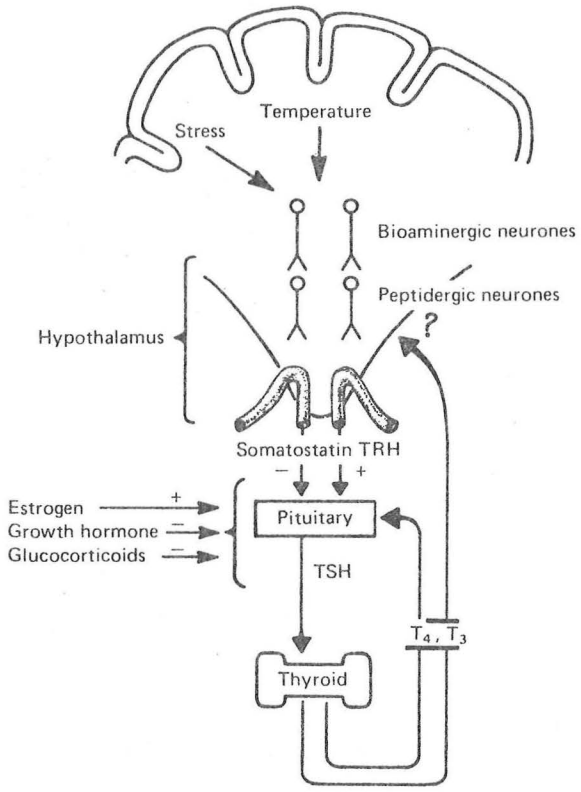


Fig. 1 (ref. 1)

FIG. 1 This is a schematic outline of a number of elements involved in neural control of the pituitary–thyroid axis, summarizing current concepts. TSH secretion is inhibited by thyroid hormones acting at the pituitary level. TSH secretion is stimulated by the hypothalamic hormone TRH, and inhibited by the hypothalamic hormone somatostatin. Secretion of both somatostatin and TRH is believed to be controlled by an intermediary set of bioamnergic neurones. These in turn come under the influence of the remainder of the brain (principally the limbic system). Other hormones may feed back on this system. Estrogens sensitize the pituitary to TRH effects, corticoids reduce pituitary sensitivity, as does growth hormone. Glucocorticoids also act on the hypothalamus to inhibit TRH release.

Thyroid stimulating hormone (TSH) secretion is regulated by the circulating level of thyroid hormone with feedback inhibition exerted at the pituitary level and probably also in the hypothalamus. Current thought favors triiodothyronine (T_3) as the primary inhibiting agent

with the T_3 derived from intrapituitary deiodination of thyroxine (T_4). The latter enters the gland from plasma (2,3). Basically when T_4/T_3 levels are normal or high, TSH release from the pituitary is blocked both directly and by inhibition of thyroid releasing hormone (TRH) secretion. When thyroid hormone levels fall in plasma, TRH release increases, pituitary inhibition is removed and TSH secretion is stimulated. TRH effects on the pituitary are very rapid (1-2 minutes) in contrast to the inhibitory effects of T_4 or T_3 which take several hours *in vivo*. This may reflect the fact that TRH acts via a cyclic AMP dependent protein kinase while the inhibitory effect of thyroxine requires new protein synthesis (1). It is important to note that when TRH (positive effector) and thyroid hormone (negative effector) are present simultaneously, the negative effector dominates. This is the basis for the TRH test for thyrotoxicosis wherein administration of TRH intravenously fails to produce a rise in TSH. As shown in the figure, growth hormone and glucocorticoids desensitize the pituitary to TRH while estrogens enhance responsiveness. The role of somatostatin is uncertain. While clearly capable of blocking TSH release, it has not been shown to be a primary regulator of thyrotropin response in physiologic or pathologic situations.

The contribution of the brain to control of TRH and TSH release is murky. Presumably signals arising in the limbic region reach the hypothalamus via bioaminergic and peptidergic neurones to stimulate or inhibit TRH production or secretion. For example lowered environmental temperature would signal the need for heat production thereby activating the TRH → TSH → T_4 sequence.

The effects of TSH on the thyroid are profound, altering both its morphology and every aspect of function. The initial step appears to involve binding to a specific receptor on the plasma membrane which is followed by the generation of cyclic AMP. An excellent brief review of TSH actions has been provided by Field in the Werner-Ingbar text (4). For our purposes it is sufficient to say that TSH stimulates the uptake of iodine by the gland, enhances T_3 and T_4 synthesis and accelerates the release of both hormones.

2. *Thyroid hormone interrelationships.* It is now known that thyroid hormone exists in three major forms in tissue and plasma (other derivatives, less important, also exist): *thyroxine* (3,5,3',5'-tetraiodothyronine), *triiodothyronine* (3,5,3'-triiodothyronine) and *reverse* T_3 (3,3',5'-triiodothyronine). The "prime" notation distinguishes positions on the outer phenolic ring from those on the inner. The formulas are shown in Fig. 2.

Fig. 2 (ref. 5)

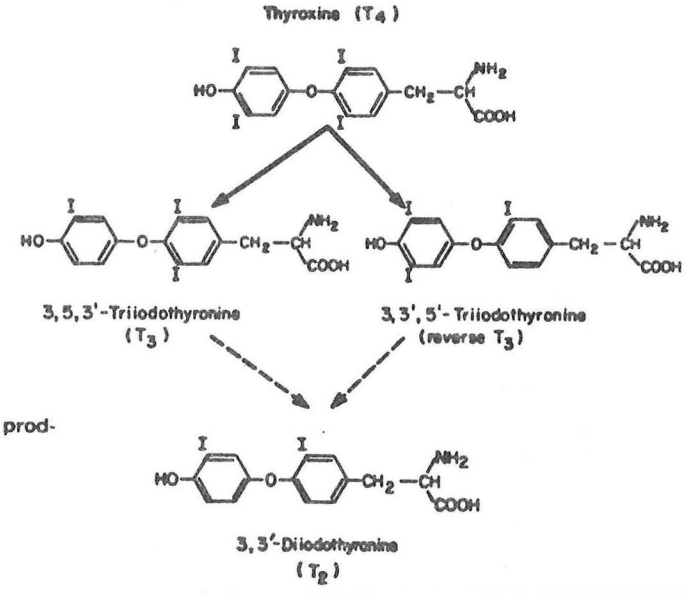


Figure Structural formulas of thyroxine and several of the products of thyroxine deiodination.

Note that T_3 is produced by removal of the 5' iodine while reverse T_3 ($\underline{rT_3}$) is formed by cleavage of the 5 iodine.

All thyroxine is made by the thyroid gland, the usual production rates being 80-100 μG per day (5,6). About 20-25% of triiodothyronine is produced directly by the thyroid, the remainder coming from peripheral conversion of $T_4 \rightarrow T_3$, primarily in liver (Fig. 3). Normal production rates are 30-40 μG per day. T_3 is thought to be the active form of thyroid hormone with T_4 functioning as a prohormone. About 98% of reverse T_3 is formed peripherally from T_4; in the normal human its production rate is equivalent to that of T_3, about 30-40 μG per day. (The turnover of rT_3 is more rapid than that of T_3 and plasma levels are lower.)

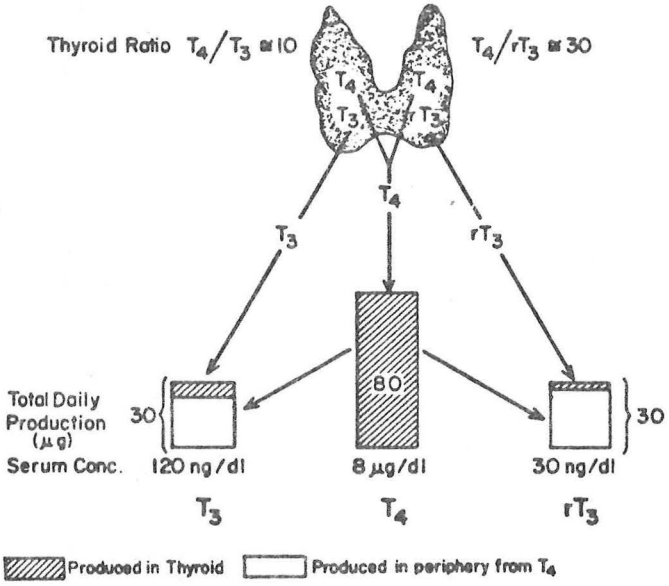


Fig. 3 (ref. 5)

Figure Quantitative outline of thyroidal secretion and peripheral conversions of thyroxine (T_4) and thyroidal and peripheral production of triiodothyronine (T_3) and reverse triiodothyronine (rT_3). The approximate serum concentrations (*Conc*) and the relative proportion of the serum concentrations of T_3 and rT_3 derived from thyroidal and peripheral production are also shown.

Reverse T_3 is metabolically inactive (6). In a variety of acute and chronic illnesses, particularly those accompanied by semi-starvation and weight loss, there is a fall in T_3 production and a rise in rT_3 concentration. The net effect is that tissue metabolism falls during catabolic states, minimizing caloric wastage and loss of body mass. These changes are caused by a decrease in activity of the 5' deiodinase that converts $T_4 \rightarrow T_3$ and $rT_3 \rightarrow T_2$. (Thus T_3 levels fall because of decreased production while rT_3 levels rise because of decreased degradation) (see Fig. 4). It has been claimed that rT_3 inhibits $T_4 \rightarrow T_3$ conversion (7), but this effect is not accepted by all investigators. The alteration in peripheral metabolism of T_4 produced by serious illness is an important cause of misdiagnosis of thyrotoxicosis, since a fall in T3 production results in activation of the TRH → TSH → thyroid axis which may be sufficient to cause an absolute elevation of plasma T_4 concentrations in euthyroid patients (see below).

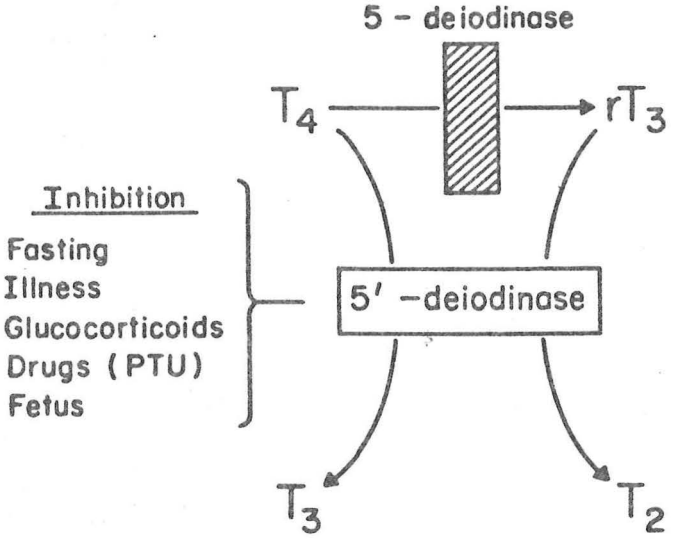


Fig. 4 (ref. 5)

Figure One hypothetical scheme of thyroxine and 3,3',5'-triiodothyronine (reverse T_3 [rT_3]) deiodination by a single 5'-deiodinase. Some of the situations and agents that inhibit 5'-deiodination and therefore result in decreased peripheral T_3 production are listed. PTU=Propylthiouracil.

3. Mechanism (s) of action of thyroid hormone. The mechanism(s) of action of thyroid hormone is not precisely understood despite intensive study (8,9). Permissive amounts are clearly needed for body growth and development of the central nervous system. Inadequate thyroxine neonatally leads to cretinism or stunted growth. Thyroid hormone is likewise permissively involved in hematopoiesis and probably all cellular renewal processes. Apart from its role in growth, major emphasis has been placed on thyroid-induced changes in oxygen consumption and thermogenesis. Clinically, it has long been known that hypothyroidismn can lead to hypothermia and that in thyroid storm body temperatures are high. Even in the absence of fever, thyrotoxicosis or exogenous thyroid increases basal oxygen uptake, implying increased heat production. A second major effect of thyroid hormone, important in hyperthyroidism, is its capacity to cause tachycardia and increased cardiac output. These two major facets of its activity can now be partially explained.

a. Effect of thyroid hormone on oxygen uptake and heat production. Life is sustained by the continual production of the high energy compound called adenosinetriphosphate (ATP). Under normal circumstances free energy released during the oxidation of carbohydrate, lipid or protein is tightly coupled to the production of ATP which can then be used for numerous energy requiring reactions in the body. The bulk of the ATP is generated intramitochondrially in the electron transport chain by oxidation of NADH or succinate as shown in Fig. 5 (next page). The rate of electron flux through the chain (and the simultaneous requirement for oxygen) is primarily determined by concentrations of ATP, ADP and Pi. If ATP stores are high, ADP and Pi will be low and electron transport and oxygen uptake are slow. If ATP concentrations fall, there is a rise in phosphate acceptor (ADP) such that electron flow and oxygen uptake are stimulated. Chemicals such as 2,4-dinitrophenol have the capacity to "uncouple" oxidative phosphorylation. It was early suggested that thyroid hormone functioned as an uncoupler. For a variety of reasons this theory has been largely abandoned. More recently Edelman and his colleagues have suggested that the primary thermogenic action of thyroid hormone is not to reduce ATP

Fig. 5 (ref. 8)

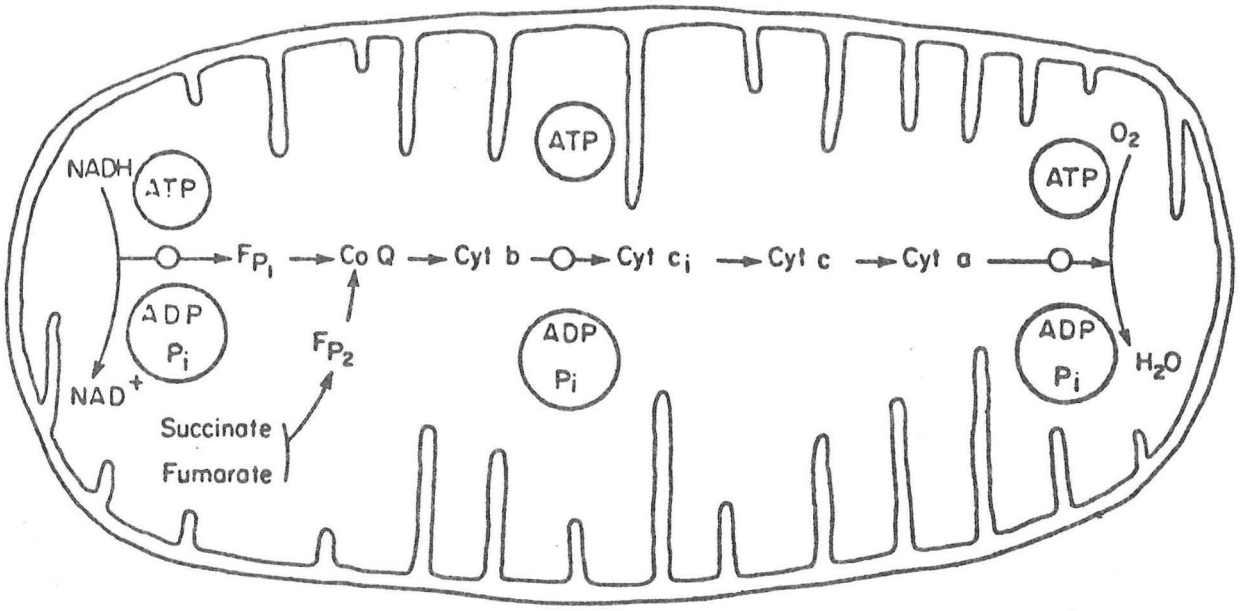


Figure Mitochondrial Oxidative Phosphorylation.

Reduced nicotinamide adenine dinucleotide (NADH) and succinate are products of glucose metabolism. Oxidation of these intermediates is coupled to ATP synthesis from ADP and P, at the indicated steps. The electron transport system consisting of the flavo proteins (F_p), coenzyme (CoQ) and the cytochromes (Cyt) links the oxidation of the intermediates to reduction of O_2.

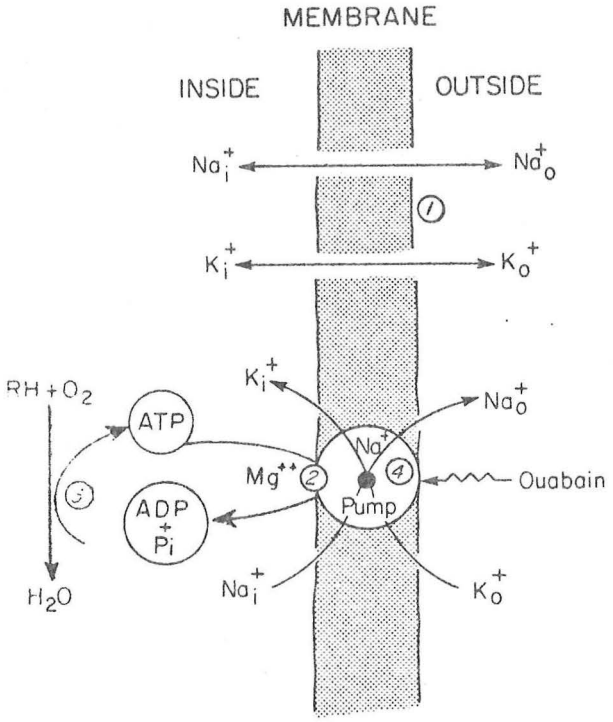


Fig. 6 (ref. 8)

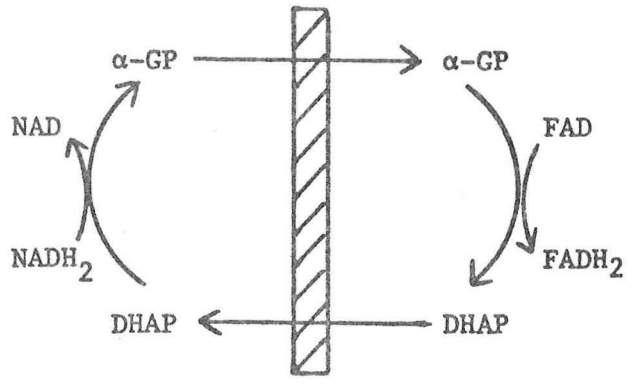
Figure Sites of Regulation of Na^+ Transport across Cell Membrane.

Site 1 indicates passive Na^+ and K^+ permeability channels. Site 2 is the coupling of ATP hydrolysis to active Na^+ transport (or Na^+:K^+ linked transport). Site 3 designates the regeneration of ATP coupled to oxidation of reduced substrates (e.g., NADH, succinate). Site 4 indicates actions on the Na^+ pump either by stimulation of a set of pre-existing pumps or by increasing the number of pumps.

synthesis but to increase ATP breakdown. They believe that the primary functional ATPase is the specific (Na^+, K^+)-ATPase of the plasma membrane (8,10-12). This enzyme, which is sensitive to inhibition by the cardiac glycoside ouabain, is responsible for the exclusion of sodium from the cell via an exchange reaction with potassium - the sodium pump (see Fig. 6, previous page). In thyroid responsive tissues it has been found that 40-100% of the increased oxygen uptake induced by thyroid hormone is inhibitable by ouabain. Thyroid hormone increases the synthesis of (Na^+, K^+)-ATPase without altering its rate of degradation (10,11). It is thought that in hyperthyroidism the increased amount of enzyme accelerates ATP breakdown in purposeless fashion (i.e., it functions as a "futile cycle"). Increased breakdown of ATP would result in wastage of its energy as heat and stimulation of oxygen uptake over the electron transport chain. The increased weight loss, negative nitrogen balance and increased food intake of thyrotoxicosis can be considered the consequence of increased requirements for substrate in the face of continual energy (ATP) drain (substrate oxidation allows regeneration of ATP). Note that thyroxine effects on (Na^+, K^+)-ATPase may not be the sole means whereby heat is generated and oxygen uptake stimulated. For example, thyroid hormone tremendously increases the content of another enzyme, intramitochondrial α-glycerophosphate dehydrogenase (glycerol-3-phosphate dehydrogenase, NAD^+)(13). Without going into detail it can be said that this enzyme functions in a "shuttle" that allows transfer of reducing equivalents from the cytoplasm of the cell into the mitochondria (which are impermeable to NADH). This shuttle is shown in Fig. 7.

Fig. 7

(1)



Dihydroxyacetonephosphate is reduced to α-glycerophosphate (sn-glycerol-3-phosphate) in the cytosol of the cell with oxidation of NADH. The α-glycerophosphate then crosses the mitochondrial membrane and is reoxidized to dihydroxyacetonephosphate by the intramitochondrial α-glycerophosphate dehydrogenase (glycerol-3-phosphate dehydrogenase). The important point is that the intramitochondrial enzyme uses a flavoprotein (FAD) as electron receptor rather than NAD. As shown in Fig. 5, oxidation of NADH in the mitochondria produces three moles of ATP, but oxidation of FADH bypasses the first ATP production site. The

net effect is that oxidation of a mole of FADH yields only 2 moles of ATP and the energy which would ordinarily be used for the third mole is wasted as heat. This again would result in increased oxygen uptake and accelerated thermogenesis.[1]

b. Thyroid hormone and catecholamines. Physiologists have long recognized that thyroid hormone was important in the regulation of catecholamine effects on metabolism and circulation. Moreover, many of the symptoms of thyrotoxicosis are known to resemble hyperactivity of the sympathetic nervous system (17). It has now been shown that thyroid hormones increase the number of β-adrenergic receptors in the heart (18,19) and enhance the affinity of catecholreceptors in other tissues (20). These findings almost certainly account for the dynamic circulatory changes (as well as tremor and sweating) of the thyrotoxic state.

c. Molecular mechanism of thyroid hormone action. Evidence is now strong that T_3 is preferentially bound to receptors located on nuclear chromatin where it exerts its effects (20-24)[2]. As shown in Fig. 8, T_4 is deiodinated to T_3 in the cytosol of the cell. The T_3 is then bound to specific receptors in the nucleus and the receptor-T_3 complex activates transcription of specific messenger RNA(s) which code for new protein synthesis. Amongst the proteins induced are the (Na^+, K^+)-ATPase, the mitochondrial α-glycerophosphate dehydrogenase and the β-receptor for catecholamines as discussed. While T_3 can bind to mitochondria, as shown, it is not certain that this binding has physiologic importance despite championing by Sterling (25).

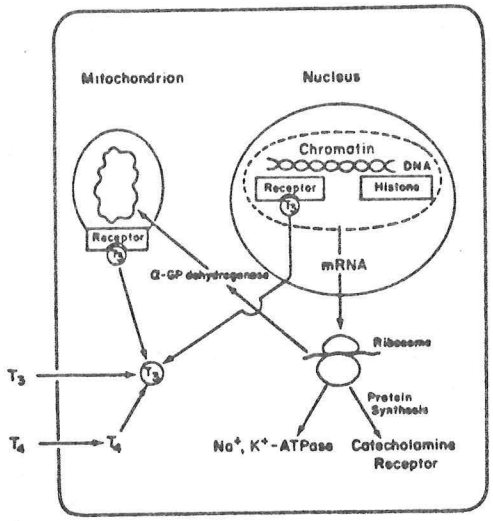


Fig. 8

MECHANISM OF ACTION OF THYROID HORMONE CELL

[1] It is of interest that obesity is associated with a decrease in both the membrane (Na^+, K^+)-ATPase and intramitochondrial α-glycerophosphate dehydrogenase (14-16). This may partially account for the efficient metabolism (and marked propensity to gain weight) seen in massively obese subjects.

[2] Thyroid hormones may also exert effects on plasma membranes, but these are probably not of major physiologic importance. See: Segal, J. and S. H. Ingbar. Direct and synergistic interactions of 3,5,3'-triiodothyronine and the adrenergic system in stimulating sugar transport by rat thymocytes. J. Clin. Invest. 65:958-966, 1980.

An important question is whether an increase in the number of enzyme units in and of itself (given constant substrate levels) can result in sufficient increased activity of a given reaction (e.g., ATP breakdown during exchange of sodium and potassium by (Na^+, K^+)-ATPase) to account for the energy wastage known to occur in thyrotoxicosis. It is conceivable that the enzyme is also modified in some way to increase its cycling. A prototype of such a change is seen in the (Na^+, K^+)- ATPase of tumor tissue which has a high rate of aerobic glycolysis because of accelerated ATP breakdown. The (Na^+, K^+)-ATPase consists of α and β subunits. Phosphorylation of a tyrosine residue(s) on the β-subunit of the tumor enzyme causes loss of efficiency in sodium pumping, requiring increased cycling to maintain extrusion of sodium from the cell (26). This is accompanied by accelerated ATP breakdown. It is not yet known whether (Na^+, K^+)-ATPase might be modified in some similar fashion by thyroid hormone, but the possibility is attractive.

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II. Prevalence and Clinical picture

The prevalence of thyrotoxicosis is about 37 per 100,000 females and 8 per 100,000 males (27). The disease may exist as an almost asymptomatic state or cause death. The signs and symptoms in a series of 247 patients are shown in Table 1.

Table I (ref. 28)

TABLE INCIDENCE OF SYMPTOMS AND SIGNS OBSERVED IN 247 PATIENTS WITH THYROTOXICOSIS

Symptom	Per Cent	Symptom	Per Cent
Nervousness	99	Increased appetite	65
Increased sweating	91	Eye complaints	54
Hypersensitivity to heat	89	Swelling of legs	35
Palpitation	89	Hyperdefecation (without diarrhea)	33
Fatigue	88	Diarrhea	23
Weight loss	85	Anorexia	9
Tachycardia	82	Constipation	4
Dyspnea	75	Weight gain	2
Weakness	70		
Sign	**Per Cent**	**Sign**	**Per Cent**
Tachycardia*	100	Eye signs	71
Goiter†	100	Atrial fibrillation	10
Skin changes	97	Splenomegaly	10
Tremor	97	Gynecomastia	10
Bruit over thyroid	77	Liver palms	8

*In other studies thyrotoxic patients with normal pulse rate have been observed.
†The data shown in this table are taken from Williams, R. H.: *J. Clin. Endocr.* 6:1, 1946. In the experience of the present authors, enlargement of the thyroid is lacking in approximately 3 per cent of patients with thyrotoxicosis.

1. Symptoms. Nervousness, sweating, heat intolerance, palpitations, fatigue and weight loss are almost universal (27,28). Increased appetite is usual, but not invariant. There is a tendency to eat sweets and a high carbohydrate diet. Rarely patients eat enough to overcome the tendency to weight loss and a few even gain weight. The nervousness, tachycardia and sweating are thought to be due to the aforementioned sensitization and increased number of catecholamine receptors. Epinephrine and norepinephrine production rates are not increased in thyrotoxicosis (29,30). The heat intolerance and weight loss are caused by futile cycling of the (Na^+, K^+)-ATPase (and, to a lesser extent, other enzymes)as described. The major site of heat generation is probably the liver.

The primary cause of weakness is thyrotoxic myopathy. A prevalence of 70% is listed in Table 1, but more recent figures place the percentage at greater than 80% (31). About three-quarters of patients have only proximal disease, but in the remainder both proximal and distal muscles are involved. Weakness of the thigh muscles is often very striking such that the patient cannot arise from the squatting position. Electromyographic abnormalities are seen in 80 to 100% of untreated subjects. Creatine phosphokinase levels are not increased despite severe muscle involvement in contrast to hypothyroidism where elevation of muscle enzymes is usual (31). It is probable that two processes are operative, one biochemical, producing weakness in the absence of atrophy, and the second causing muscle destruction (32). The biochemical lesion has not been identified, but atrophy may be due to activation of tissue proteases (33).

Hyperdefecation is common and occasionally a devastating diarrhea resembling cholera may occur. The cause is uncertain but increased intestinal motility and accelerated production of bile acids may both play a role (34,35). While not well recognized thyrotoxicosis can produce steatorrhea (34,36).

Oligo-amenorrhea is common in women, but the cause remains a mystery. The hypothalamic-pituitary axis for gonadotropins appears intact (37). Gynecomastia occurs in about 5% of male patients. Its cause is likewise unknown, though it almost certainly represents a relative or absolute increase in estrogen to androgen production as is true in all other forms of male breast enlargement (38). One possible

explanation would be altered hepatic blood flow resulting in diversion of androstenedione and testosterone to peripheral tissues for conversion to estrogens analogous to the situation in cirrhosis of the liver.

Dyspnea is fairly frequent and is generally postulated to be the consequence of muscle weakness (39). Dependent edema is said to be due to increased capillary permeability (39). Both symptoms may occur in the absence of heart failure. The latter, when it occurs, is usually high output in type (rapid circulation time, increased venous pressure). Heart failure may be due to hyperthyroidism alone, but in older patients underlying cardiac disease may be a major contributing factor.

2. Signs. While almost all patients with thyrotoxicosis have a goiter (or palpable nodule), 2-5% may have no apparent enlargement of the gland. Eye signs (proptosis, inflammation, lid-lag, stare, muscle imbalance) are present in about 70% of patients. Causes and treatment of exophthalmos will not be covered here but several recent articles are listed for interested readers (40-42). Tachycardia, tremor, velvety skin, fine hair and bruits over the thyroid gland are almost always found. Atrial fibrillation is probably more common than the 10% indicated in Table 1, especially in older patients. Occasionally a cardiac scratch resembling a friction rub is noted. Splenomegaly occurs but is not common.

Nail changes (onycholysis) occur in a high percentage of cases. As noted by Plummer the upper surface of the nail is flattened or slightly concave with elevation of the distal end ("scoop shovel" appearance). There is an irregular separation of the nail from underlying soft tissue and often a black irregular band of dirt is seen. Thyroid dermopathy (pretibal myxedema) is relatively rare. It may present as raised erythematous nodules, resembling erythema nodosum, a diffusely elevated plaque with a peau d'orange appearance, or a diffuse, bilateral, woody, infiltrative process similar to lymphedema (43). Vitiligo is present in 6-7% of patients; it has the unusual characteristic of affecting palms and soles (44). Thyroid acropathy consists of clubbing of the fingers and toes, periosteal new bone formation in the fingers and distal long bones, and soft tissue swelling overlying the bony lesions. How thyroid hormone excess causes hair, skin, nail and bone changes is unknown.

An unusual sign is choreo-athetosis (45). Easy bruising or purpura is another rare presenting complaint (46). It is due to thrombocytopenia.

3. Variant presentations. Some older patients with hyperthyroidism lack the usual manifestations of thyrotoxicosis and present with a placid or depressed appearance, disproportionate weight loss and atrial fibrillation or congestive heart failure. Myopathy tends to be severe. Exophthalmos is almost never present but ptosis of the eyelids is frequently observed. This syndrome is usually termed apathetic hyperthyroidism (47). Thyroid storm represents the extreme of thyrotoxicosis and is frequently fatal. It has been recently reviewed in these Grand Rounds (48). The cardinal manifestations are: (1) fever, (2) cardiovascular signs, (3) CNS dysfunction and (4) GI abnormalities (49,50). Thyrotoxicosis may present as primary muscle disease: hypokalemic periodic paralysis (in Orientals and Latin Americans) or myasthenia gravis (31). The former is much more common in men than women. Myasthenia may occur in up to 1% of thyrotoxic patients, while

3-5% of myasthenics have Graves' disease.

4. Accompanying abnormalities. A variety of laboratory abnormalities accompany hyperthyroidism. The following are the most frequent.

a. Hypercalcemia. Hypercalcemia (usually of mild degree) is seen in 15 to 20% of hyperthyroid patients (43). It is thought to be due to a direct effect of thyroid hormone on bone resorption (51). Ordinarily this slight hypercalcemia results in inhibition of parathyroid hormone release with the result that serum levels of 1,25-dihydroxy-vitamin D_3 fall (52), blunting calcium absorption in the gut (53,54). Occasionally PTH levels are high, suggesting the presence

TABLE Clinical and biochemical data on the patients with thyroid disorders

Parameter	Normal controls (A)	Hyperthyroid patients (B)	Hypothyroid patients (C)	Significance B *vs.* C[a]
No.	81	23	12	
Sex (males/females)	23/58	4/19	1/11	
Mean age (yr)	37	41	47	NS
Range	18–64	19–59	28–77	
Cholesterol (mg/dl)[b]	190 ± 20	147 ± 32[c]	307 ± 59[c]	0.001
T_4[b] (μg/dl)	8.7 ± 1.6	22.2 ± 5.6[c]	2.2 ± 1.6[c]	0.001
Free T_4 index[b]	9.0 ± 2.1	40.7 ± 19.9[c]	2.0 ± 1.5[c]	0.001
T_3[b] (ng/dl)	115 ± 18	404 ± 128[c]		
TSH (μU/ml)[b]	2.6 ± 1.0		52 ± 22[c]	
Calcium (mg/dl)	9.7 ± 0.4	9.78 ± 0.66	9.17 ± 0.54[c]	0.001
Phosphorus (mg/dl)	3.7 ± 0.7	4.1 ± 0.7[d]	3.2 ± 0.5[d]	0.001
PTH (mU/liter)[b]	26 ± 9	20 ± 10[d]	53 ± 17[c]	0.001
$25OHD_3$ (μg/liter)	14.4 ± 4.0	13.1 ± 2.9	11.8 ± 6.0	NS
$1,25\text{-}(OH)_2D_3$ (ng/liter)	42 ± 13	28.0 ± 10.6[c]	73.4 ± 28.5[c]	0.001
DBP (mg/liter)	325 ± 64	352 ± 35	381 ± 52[e]	0.05
$1,25\text{-}(OH)_2D_3$:DBP molar ratio × 10^5	1.8 ± 0.4	1.1 ± 0.4[c]	2.6 ± 0.9[c]	0.001
$1,25\text{-}(OH)_2D$:$25OHD_3$ molar ratio × 10^3	2.7 ± 0.8	2.0 ± 0.6[c]	6.2 ± 2.3[c]	0.001

Table 2 (ref. 52)

[a] The statistical significance was calculated using Student's *t* test. At least a similar degree of significance was found using the Mann-Whitney U test, except for DBP when the two-tailed *P* value was then only 0.14.

[b] The normal range of these parameters is based on a different group of at least 90 normal adults.

[c] $P < 0.001$ *vs.* normal controls (by Student's *t* test).

[d] $P < 0.01$ *vs.* normal controls (by Student's *t* test).

[e] $P < 0.05$ *vs.* normal controls (by Student's *t* test).

of hyperparathyroidism (55). However in the two reported cases PTH values fell to normal after treatment of thyrotoxicosis, indicating that the high concentrations were the consequence of thyroid hormone excess. A possible mechanism would be sensitization to catecholamine stimulation of PTH release.

b. Hyperglycemia. Hyperglycemia is more frequent in thyroid storm than uncomplicated thyrotoxicosis but can occur in the latter as well. The cause has not been definitively worked out. It has been claimed that glucagon receptors are increased in hyperthyroidism (56) and that hepatic glucose production shows a sustained response to glucagon and epinephrine (57). Insulin resistance has been postulated as well (58). The effect of thyroid hormone on insulin release is controversial, since both inhibition (59) and enhancement have been claimed (57,58). The problem with all the studies is that they are not controlled for counterregulation making interpretation difficult; i.e., when insulin levels change other hormones change in response and vice versa. The only practical point is that hyperglycemia, increased appetite and weight loss might suggest (erroneously) the presence of diabetes in a thyrotoxic patient particularly since mild polyuria may normally accompany thyroid gland hyperfunction. This ordinarily is not a real problem.

c. Anemia. Anemia is relatively unusual in uncomplicated thyrotoxicosis. If present it may be normocytic, hypochromic microcytic or macrocytic. Normochromic abnormalities may be caused by poor utilization of iron or decreased red cell survival (60,61). Hypochromic anemia could be the consequence of decreased gastric acidity with impaired iron absorption but pyridoxine deficiency may play a role in some patients (61). Macrocytic anemia may be due to either folate or B_{12} deficiency, since their turnover is increased by thyrotoxicosis. However, it must be remembered that pernicious anemia occurs in about 3% of thyrotoxic patients, apparently the consequence of the same type of immune disturbance that causes Graves' disease (61,62).

d. Abnormal liver functions. Elevated alkaline phosphatase concentrations are common, the source being both liver and bone (63). SGOT may also be high. In severe cases hypoalbuminemia may be severe (43). Jaundice may also occur, though it has been speculated that it usually represents thyrotoxicosis-induced exaccerbation of some mild underlying abnormality such as Gilbert's disease (64). The endocrine service at Parkland has seen a number of cases where jaundice could not be accounted for by underlying disease, heart failure or acquired liver disease.

e. Electrocardiographic abnormalities. Atrial fibrillation is well known, but it is perhaps not as well known that prolongation of PR intervals and complete heart block can accompany thyrotoxicosis (43). The reports of heart block preceded advent of modern diagnostic techniques and the cause may well have been something other than the thyrotoxicosis which was present.

f. Hypergastrinemia. Eleven of 24 hyperthyroid patients had elevations of serum gastrin and 7 had coexistent atrophic gastritis (62). Gastrin levels could be normally suppressed by infusion of acid into the stomach and reverted to normal after treatment of thyrotoxicosis.

III. Causes of thyrotoxicosis

The causes of thyrotoxicosis are listed in Table 3. A division is made between those conditions characterized by sustained overproduction

Table 3

Causes of thyrotoxicosis

1. Sustained overproduction of thyroid hormone
   - a. Diffuse toxic goiter
   - b. Toxic multinodular goiter
   - c. Toxic adenoma (single hot nodule)
   - d. Increased TSH production
   - e. Trophoblastic tumor
   - f. Iodine induced (Jodbasedow)

2. No sustained overproduction of thyroid hormone
   - a. Subacute thyroiditis
   - b. Chronic thyroiditis with transient thyrotoxicosis
   - c. Factitious and iatrogenic thyrotoxicosis
   - d. Struma ovarii

of hormone by the thyroid gland and those in which thyroidal production is normal and the hormone is derived from glandular leakage (secondary to tissue damage) or an extraglandular source. The term hyperthyroidism refers to thyrotoxicosis due to thyroid gland overactivity while thyrotoxicosis is the general term used for the clinical syndrome regardless of source of hormone.

1. Diffuse toxic goiter. This is the most common cause of hyperthyroidism. If ophthalmopathy is present (with or without dermopathy) the term Graves' disease may legitimately be used. The cause is thought to be one (or more) of a series of antibodies directed against the thyroid gland that are now called human thyroid-stimulating immunoglobulins (hTSI) (26,65-67). Long-acting thyroid stimulator (LATS) is only one of these antibodies. Some workers subdivide into hTSI for globulins that stimulate adenylate cyclase activity in target tissues and TBII (TSH binding inhibitory IgG) for those that inhibit binding of radioactive TSH to receptor membranes (67). The relationship (if any) between the two types of immune globulins and how they induce thyrotoxicosis remains a mystery. Nor is it known what predisposes to their development. There does appear to be a relationship with certain HLA phenotypes, HLA B_8 and DR_3 predisposing to thyrotoxicosis and other autoimmune endocrinopathies (68). It is thought that increased antibody formation is due to a suppressor T cell deficiency (69).

2. Toxic multinodular goiter (Plummer's disease). This condition is to be distinguished from toxic adenoma where thyrotoxicosis is due to a single hyperfunctioning nodule. The disease begins with a multinodular goiter which is non-toxic for many years (43). Natural progression is toward thyrotoxicosis for reasons that are still unknown. Prior to development of frank hyperthyroidism, TSH levels are lower than in diffuse non-toxic goiter (70). Up to 25% of patients with plasma T_4 and T_3 values in the normal range show no stimulation of TSH after TRH, implying autonomy (71). Two patterns are seen by scintiscan. In the first radioiodine uptake is irregular but generalized; neither TSH nor exogenous thyroid change the pattern of uptake. In the second, discrete hot nodules are present with intervening areas which do not take up iodine (i.e., they are suppressed by the autonomously functioning areas). After TSH treatment the quiet areas respond by taking up isotope.

No thyroid stimulating immunoglobulins have been identified in this disease (72). Hyperthyroidism is clinically milder than in diffuse toxic goiter.

3. Toxic adenoma. Single nodules are not infrequent in the general population, but only a few function autonomously (i.e., fail to suppress radioiodine uptake after exogenous thyroid hormone). Autonomously functioning nodules are only 1/50 as common as diffuse toxic goiter and only 13% progress to thyrotoxicosis (73). Nodules greater than 3 cm have a greater tendency to become toxic. They produce larger amounts of T_3 (relative to T_4) than does normal thyroid tissue.

4. Increased TSH production. Recently a number of thyrotoxic patients have been reported in whom plasma TSH levels are not low but high (74). Probably half or more have small pituitary tumors (74-76). Elevation of the common alpha subunit of pituitary hormones (the beta subunit gives specificity to TSH, FSH, LH, chorionic gonadoropin) may be the best laboratory test of a TSH secreting tumor (76). The other syndrome of TSH excess appears to represent partial resistance of the

pituitary to inhibition of TSH release by thyroid hormone (77). The excess TSH then drives the thyroid to produce clinical thyrotoxicosis. The syndrome of TSH-induced thyrotoxicosis should not be confused with generalized resistance to thyroid hormone (pituitary and peripheral tissues) in which a euthyroid state is associated with inappropriate TSH levels (78,79). In some patients TSH levels may not be high in absolute terms but are inappropriate for the elevated levels of T_4 in plasma. The euthyroid state is the consequence of peripheral resistance to the elevated thyroid hormones, a situation that does not apply in patients who have resistance limited to the pituitary and thus get thyrotoxicosis. Excess production of TRH has also been postulated to cause TSH-induced hyperthyroidism, but the supporting evidence is relatively soft (80,81). Thyroid-stimulating immunoglobulins are not elevated in hyperthyroidism due to TSH stimulation (74).

5. Trophoblastic tumors. Hyperthyroidism may occur in association with hydatidiform mole, choriocarcinoma or embryonal carcinoma of the testis (82-84). The thyroid stimulator in these cases mimics the action of TSH but is not that hormone. It is uncertain whether the stimulating molecule is HCG itself or a distinct (perhaps derivative) component (84). Affected patients have increased levels of T_4 and T_3 in plasma and TSH response to TRH is blunted.

6. Iodine induced hyperthyroidism. This condition results from iodine intake in patients with iodine deficient goiters or autonomously functioning thyroid glands (incipient diffuse toxic or multinodular goiters) (86). Amiodarone, an iodine-containing antiarrhythmic drug used in Europe, may produce hyperthyroidism by release of iodine (87).

7. Thyrotoxicosis without hyperthyroidism. The hallmark of this syndrome is clinical evidence for thyrotoxicosis, including elevated levels of T_4 and T_3 in plasma, but depressed uptake of radioiodine by the thyroid gland. In subacute thyroiditis and Hashimoto's disease with transient thyrotoxicosis the cause is probably loss of storage capacity and leakage of thyroid hormone due to inflammatory disease in the thyroid gland. The syndrome is easy to recognize with painful subacute disease but is more difficult when no pain is present and goiter is absent, a not uncommon presentation (88). This has led to the suggestion that all patients with thyrotoxicosis have an RAI uptake, since treatment for thyrotoxicosis is inappropriate for thyroiditis (89). Factitious thyrotoxicosis gives a similar picture, although if the patient takes T_3, plasma T_4 levels will be low (because of suppression of TSH). Factitious disease should be considered in medically related personnel or in family members of a patient taking thyroid hormone for hypothyroidism. Iatrogenic thyrotoxicosis may not be recognized by the patient if thyroid hormone is given by the physician without identification (as by doctors specializing in weight loss). Ectopic production of thyroid hormones by struma ovarii is rare.

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IV. Diagnostic procedures in thyrotoxicosis and variant syndromes.

The diagnoses of thyrotoxicosis is ordinarily not difficult, but on occasion there are problems. While the chemical picture is often highly suggestive, confirmation requires tests of thyroid function. These include static measurements of thyroid hormones in blood, stimulation and suppression tests and assessment of radioactive iodine uptake (90-93).

1. Thyroid hormones in blood. Both T_4 and T_3 can be measured directly in blood by radioimmunoassay. The tests are ordinarily quite accurate. Normal values vary from laboratory to laboratory, but at Parkland ranges are 5.5-10.5μG.dl^{-1} for T_4 and 70-160 ng.dl^{-1} for T_3. The problem is that concentrations are influenced by the levels of several proteins in plasma that bind iodothyronines (both T_4 and T_3): thyroid binding globulin (TBG), thyroid-binding prealbumin and albumin. Since free and bound thyroid hormones are in equilibrium, it follows that an increase or decrease in thyroid binding proteins will be reflected by changes in total concentrations measured by immunoassay (which includes both bound and free forms). Thus an increase in TBG (because of pregnancy, say) would cause an increase in T_4 which might be interpreted as indicating thyrotoxicosis if not corrected for. Free (unbound) hormone can be determined by dialysis techniques, but this procedure is too time consuming for ordinary clinical use (only about 0.02% of T_4 and about 0.20% of T_3 is unbound). In most cases similar information can be

obtained by doing a T_3 resin uptake (T_3RU) and utilizing the result to correct the T_4 and T_3 measured by immunoassay for binding to plasma proteins. This calculation is called the free thyroxine index (FTI) or free triiodothyronine index (FT_3I). There is a good deal of confusion about these tests. Nomenclature should be that of the American Thyroid Association (93). The description of the tests is as follows:

a. T_3 resin uptake: Radioactive T_3 is incubated with the patient's serum, allowing binding to free sites on TBG and other proteins. Then an inert resin is added with further incubation. The resin will only bind radioactive thyroid hormone that has not been bound by TBG. The resin is then separated and counted with the test reported as percent of added radioactivity (see Fig.9). It is obvious from the figure that the T_3 resin uptake may be high either because thyroid binding globulin is highly saturated in vivo (thyrotoxicosis) or because thyroid binding globulin is low. A low T_3 resin uptake indicates either hypothyroidism (binding sites on TBG are unsaturated) or increased levels of TBG in plasma (e.g., estrogen treatment or pregnancy). Common conditions altering thyroid binding globulin are shown in Table 4, next page.

b. T_3 resin uptake ratio. This method, which is used at Parkland and is strongly recommended by the American Thyroid Association, simply compares the T_3 resin uptake in the patient to a pooled sample from a group of normal subjects. The ratio is then used for calculation of FTI and FT_3I (see next section). It corrects for day to day variation in the assay. The T_3 resin uptake ratio is obtained by dividing the T_3 resin uptake (patient) by T_3 resin uptake of a pooled sample of sera from 20 control (euthyroid) subjects.

c. Free thyroxine index (FTI). This is calculated by multiplying the T_4 by immunoassay by the T_3 resin uptake ratio. An example follows: A woman on birth control pills has a T_4 of 14.4 $\mu g.dl^{-1}$

Fig. 9

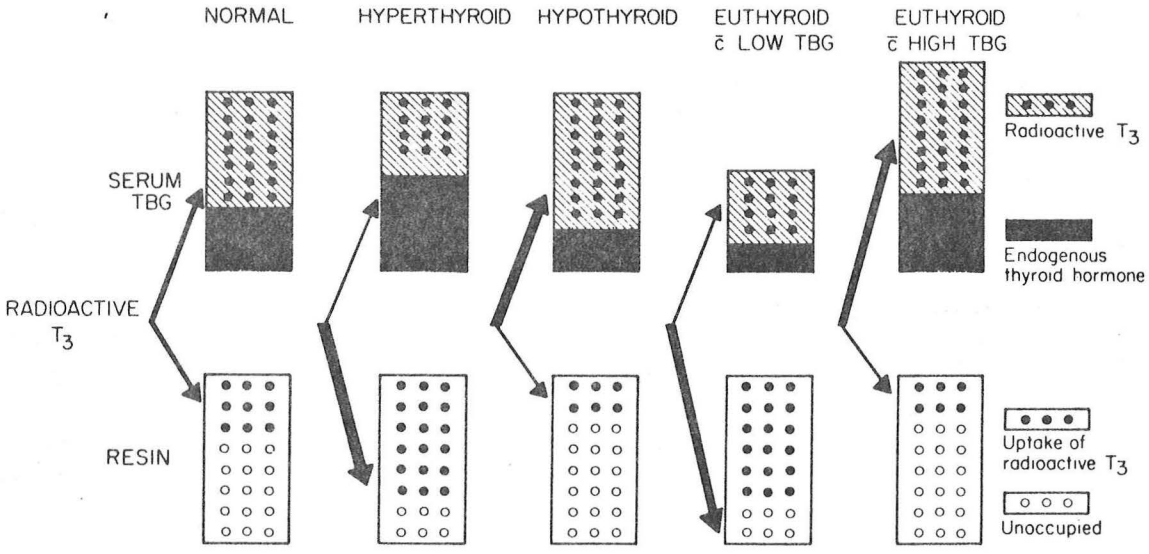

Figure T_3 uptake test: diagram of the principle and changes in thyroid and non-thyroid disease. Radioactive T_3, added to patient's serum, binds to the binding sites on TBG that are unoccupied by endogenous thyroid hormone, predominantly T_4. The radioactive T_3 not bound to TBG is taken up by the resin. Results of T_3 uptake are expressed as percent of the total radioactivity that has been taken up by the resin. Solid dots represent radioactive T_3. (From Chopra, I. J. and Solomon, D. H.: Pharmacology and Therapeutics, C. *1*:367, 1976.)

Table 4

Conditions and drugs that alter the level of thyroid binding globulin (TBG)

Increased TBG	Decreased TBG
Pregnancy	Androgens & antibiotic steroids
New born state	Large doses of glucocorticoids
Oral contraceptives & other estrogens	Chronic liver disease
Acute intermittent porphyria	Severe systemic illness
Chronic liver disease	Active acromegaly
Acute hepatitis	Nephrotic syndrome
Genetic	Genetic

(normal 5.5-10.5 $\mu g.dl^{-1}$). Her T_3 resin uptake is 33% (normal 35-51%). The T_3 resin uptake in a pooled sample of 20 controls is 47%. Thus the T_3 resin uptake ratio is 33%/47% = 0.7 and the FTI = 0.7 X 14.4 = 10.1 $\mu g.dl^{-1}$. The the low T_3 resin uptake ratio indicates a high TBG level and the corrected T_4 is in the normal range.

d. Free triiodothyronine ratio (FT_3I). This is done in exactly the same way as the FTI except that the T_3 by immunoassay rather than the T_4 is multiplied by the T_3 resin uptake ratio (94). The correlation of the FTI and FT_3I with measured concentrations of free T_4 and T_3 is shown in Fig. 10.

Fig. 10 (ref. 94)

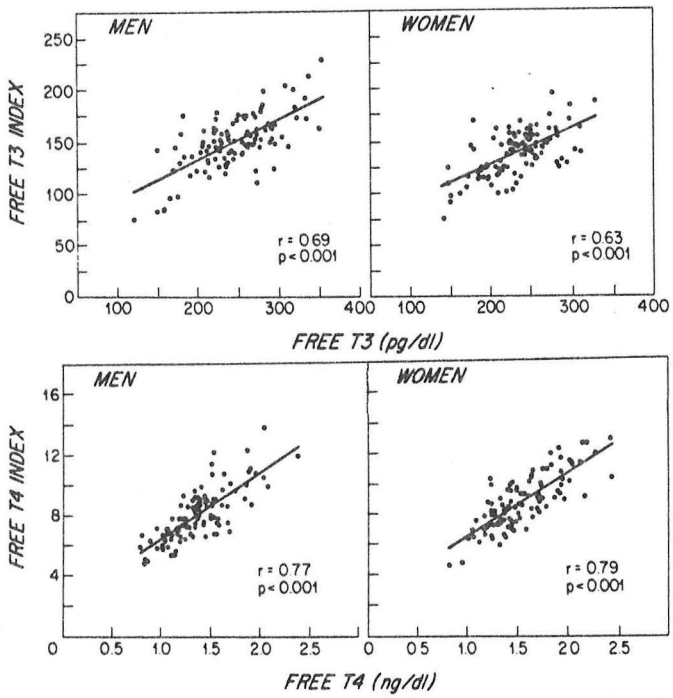

Figure Correlation of the free T_3 index with the free T_3 (*top*) and of the free T_4 index with the free T_4 (*bottom*) in normal adult men and women.

2. Thyroid stimulating hormone (TSH). Levels are measured by radioimmunoassay. In the past they were utilized primarily for TRH stimulation tests in the diagnosis of thyrotoxicosis. Some physicians feel that they should now be obtained in all patients because of the problem of TSH secreting tumors. My current feeling is that this is not necessary because such microadenomas are relatively rare and because I would not treat with transsphenoidal hypophysectomy even if such a lesion was present.

3. Radioactive iodine uptake. The radioactive iodine uptake is still useful in the diagnosis of thyrotoxicosis and particularly in differentiating hyperthyroidism and thyroiditis. Thus in hyperthyroidism the radioactive iodine uptake will be high together with an elevated T_4 (and FTI) while in thyroiditis the uptake will be low even though T_4 concentrations are increased. Thyroid scans are not indicated in the workup of thyrotoxicosis unless a nodule(s) is palpated and one wishes to determine its (their) activity for diagnostic or therapeutic purposes (e.g., larger amounts of ^{131}I will be needed for treatment of multinodular goiter than for diffuse toxic goiter).

Values for radioactive iodine uptake have progressively fallen over the last few years such that in many laboratories a 24 hour uptake of 30% is now in the hyperthyroid range. It is thought that an increase in the iodine content of the American diet has caused this change, but other factors could be operative. The effect of iodine intake on radioactive iodine uptake is shown in Fig. 11.

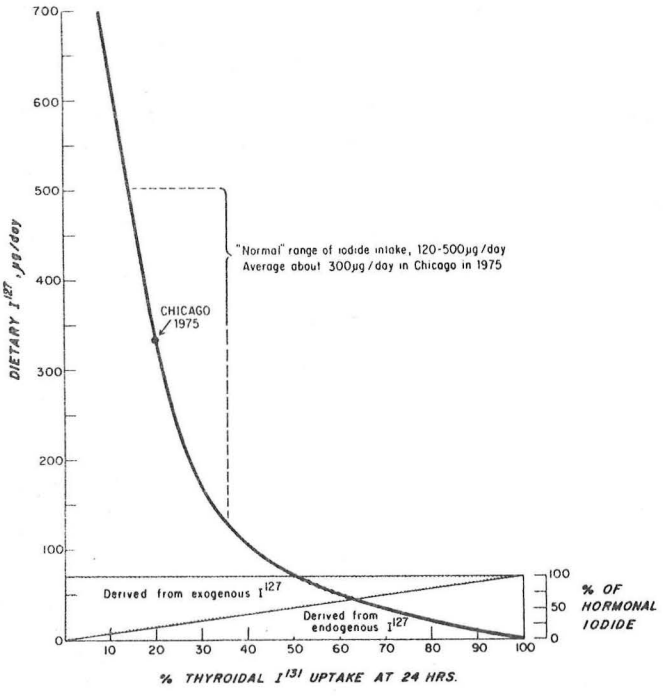

Fig. 11 (ref. 39)

Fig. *Relation of thyroidal radioiodide uptake (RAIU) to dietary content of iodine.* The uptake increases with decreasing dietary iodine. With iodine intake below the amount provided from thyroid hormone degradation, the latter contributes a larger proportion of the total iodine taken up by the thyroid. Under current dietary habits in the United States, the average 24-hour thyroidal RAIU is below 20 percent. (From DeGroot et al., The Thyroid and Its Diseases. New York, John Wiley, 1975, with permission.)

By 1975 the average 24 hour RAI uptake in the United States was 20%, corresponding to an iodine intake of about 300 µg per day. Complete suppression of uptake requires much higher doses: 30 mg of iodide initially and 15 mg daily thereafter (95). (This is the amount of iodide

required in case of nuclear accident. The amounts listed are for iodide itself; the equivalent amounts of sodium iodide would be 36 and 18 mg respectively). Some characteristic kinetic curves for radioiodine uptake are shown in Fig. 12.

Fig. 12 (ref. 39)

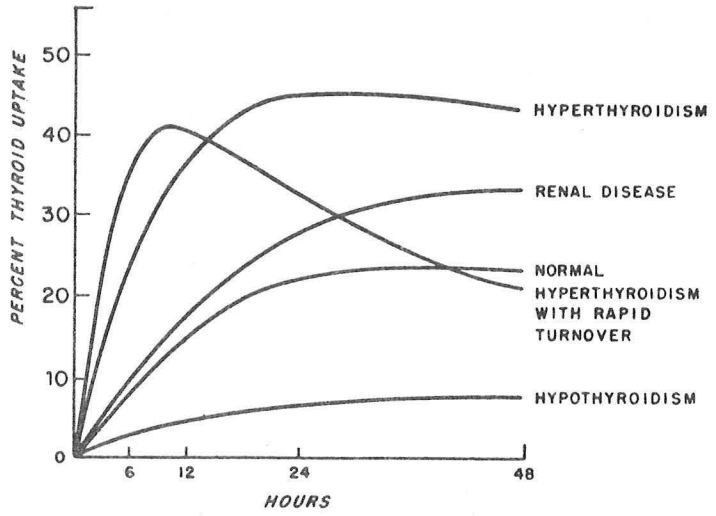

Fig. 12. *Examples of thyroidal RAIU curves under various pathological conditions.* Note the prolonged uptake in renal disease due to decreased urinary excretion of the isotope and the early decline in thyroidal radioiodide content in some patients with thyrotoxicosis associated with a small but rapidly turning over intrathyroidal iodine pool. (From DeGroot et al., The Thyroid and Its Diseases. New York, John Wiley, 1975, with permission.)

Fig. 13

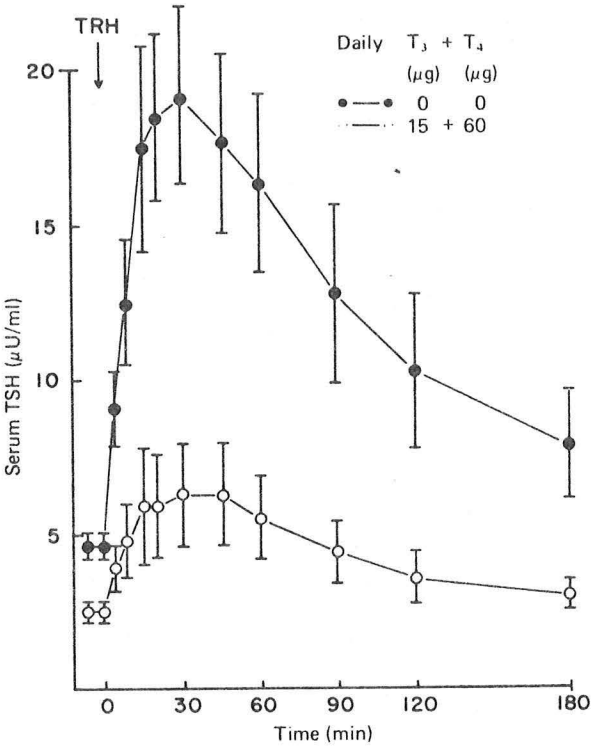

FIG. 13. Inhibitory effect of chronic (20–30 days) administration of 15μg T_3/day and 60μg T_4/day on the serum TSH response to TRH in normal subjects. The vertical bars indicate ± SEM. (Modified from Snyder PJ, Utiger RD: J Clin Invest 51:2077, 1972)

Renal disease tends to elevate the RAI uptake because of decreased isotope excretion. A few hyperthyroid patients have higher 6 hour than 24 hour values.

4. TRH stimulation test. This test has become the most widely used procedure to test for the presence of thyrotoxicosis in equivocal cases. It will be recalled that in thyrotoxicosis basal TSH levels are low because the pituitary release of TSH is inhibited by high circulating levels of thyroid hormone and that this inhibition cannot be overcome by administration of TRH. Thus a patient who has thyroid hormone levels at the upper limit of normal yet appears thyrotoxic or the person who has high plasma concentrations of T_4 but looks euthyroid can be given 500 μg of TRH (generic name: protirelin; trademarks: Thypinone; Relefact TRH) with measurement of TSH at zero time, 20 and 30 minutes. A normal response is a rise in TSH to greater than 7 $\mu U.ml^{-1}$. The shape of the TSH response curve to TRH and its suppressibility by exogenous thyroid hormone is shown in Fig. 13(see above). Failure to rise suggests the presence of thyrotoxicosis. The TRH test may remain abnormal after treatment of thyrotoxicosis and induction of remission with antithyroid drugs; 16% of 110 patients in one series had long-term TRH non-responsiveness (96). If both impaired TSH response to TRH and abnormal thyroid suppression are found, the chances are good that clinical thyrotoxicosis will recur (97). Abnormality of only one test does not imply that relapse is likely.

5. Thyroid suppression test. In hyperthyroidism the thyroid gland is autonomous, meaning that its dependence on TSH for regulation is impaired. A normal thyroid gland shows diminished RAI uptake when TSH release is suppressed by exogenous thyroid but this response is lost in hyperthyroidism. The suppression test is ordinarily done by administering 75 to 100 μg of T_3 orally for a week to 10 days followed by measurement of 24 hour RAI uptake. If the patient cannot take medications orally, T_4 can be given intramuscularly at 200 μg per day to accomplish the same end (there is no parenteral preparation of T_3). Most authors accept a suppression of 50% (from baseline RAI) as normal, but we prefer to see the 24 uptake suppressed to less than 5% for the test to be unequivocally normal. A variant procedure is to administer 3 mg of L-thyroxine as a single dose with measurement of RAI uptake 8 days later (98). The advantage is that the dose can be given in the doctor's presence, avoiding false results due to failure to take T_3 for 1 week. It is said to be tolerated well. Neither version of the test should be used in patients with coronary artery disease in my opinion.

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V. Problems in diagnosis.

In most patients with thyrotoxicosis the clinical picture and laboratory findings are consistent. In a surprising number of cases, however, the differentiation of thyrotoxicosis and euthyroidism is difficult. An illustrative case follows:

V.N. is a 26 y/o black woman with a history of persistent vomiting for 8-9 years requiring multiple admissions to Parkland Memorial

Hospital. Her course was complicated by intermittent presence of hallucinations and several suicide attempts. In 1979 she was found to have a slightly elevated T_4. Her sequential thyroid function tests were as follows:

	9/79	10/79	12/79	1/80	8/80	3/81
T_4 ($\mu g.dl^{-1}$)	10.4	11.3	10.8	10.2	23.3	13.2
T_3 RU(%)	43.1	44.8	46.7	55.3	28.3	40.7
FTI($\mu g.dl^{-1}$)	9.3	10.6	10.6	13.1	15.6	17.2
RAI uptake(%)	-	-	41.4	-	-	-
T_3($ng.dl^{-1}$)	-	-	-	106	-	-

She was noted to have a goiter and approximately a 30 pound weight loss. She was admitted to rule out thyrotoxicosis. Physical exam showed a depressed, wasted young woman with a pulse of 132. She had a diffusely enlarged thyroid gland but no other signs of thyrotoxicosis. Routine laboratory was unremarkable except for a metabolic alkalosis (HCO_3^- 34 $meq.l^{-1}$), volume depletion (hematocrit 49.8%) and mild hypercalcemia (10.8 $mg.dl^{-1}$) thought to be the consequence of volume depletion. Her initial thyroid functions were:

T_4 - 15.6 $\mu g.dl^{-1}$
T_3 RU - 42.1%
FTI - 15.5 $\mu g.dl^{-1}$
RAI uptake - 32.1%

These values suggested hyperthyroidism, but clinically she appeared euthyroid. That conclusion was confirmed by the following: T_3 by immunoassay: 138 $ng.dl^{-1}$, TRH stimulation test: 0 - 4mIU.ml^{-1}, 20 min - 12mIU.ml^{-1}, 30 min - 15mIU.ml^{-1}; T_4 suppression test (200 μg T_4 I.M. X 5days because of vomiting): RAI uptake 2.2%. Final diagnoses were: (1) psychogenic vomiting (2) secondary anorexia nervosa (3) schizophrenia (4) non-toxic goiter (5) "euthyroid sick" syndrome.

Repeat thyroid function studies in Endocrine clinic 5-20-81 were: T_4, 12.9 $\mu g.dl^{-1}$; T_3RU, 31.1%; FTI 9.3 $\mu g.dl^{-1}$; T_3 by immunoassay, 220 $ng.dl^{-1}$. She had gained 5# in weight.

Some of the common diagnostic problems will be outlined.

1. Euthyroid patient with elevated thyroid function tests suggesting hyperthyroidism. The most common problem is that illustrated in the case report, the so-called euthyroid sick syndrome. As noted earlier a variety of acute and chronic illnesses block the conversion of $T_4 \rightarrow T_3$ (5,99,100). This results in a compensatory increase in T_4 production by the thyroid gland secondary to release of TSH. In most ill patients the picture is that of a normal or slightly low T_3 and normal T_4, but some develop an absolute elevation of TSH, RAI uptake and T_4 concentration. This is illustrated in Fig. 14 where the findings in a patient with alcoholic hepatitis is presented (102). The same results can be produced by the gall bladder dye iopanoic acid (Telepaque) with effects lasting for weeks (103). The laboratory picture can be further confused because TBG may be increased with liver disease (104) and because inhibitors of T_4 binding to TBG may appear in acute and chronic illness (105).

It has been suggested that clinical thyrotoxicosis can exist under circumstances where T_4 is elevated but T_3 is normal (106). The evidence is that some patients with elevated T_4 and FTI but normal T_3 and FT_3I do not respond to TRH administration with a rise in TSH.

Fig. 14 (ref. 102)

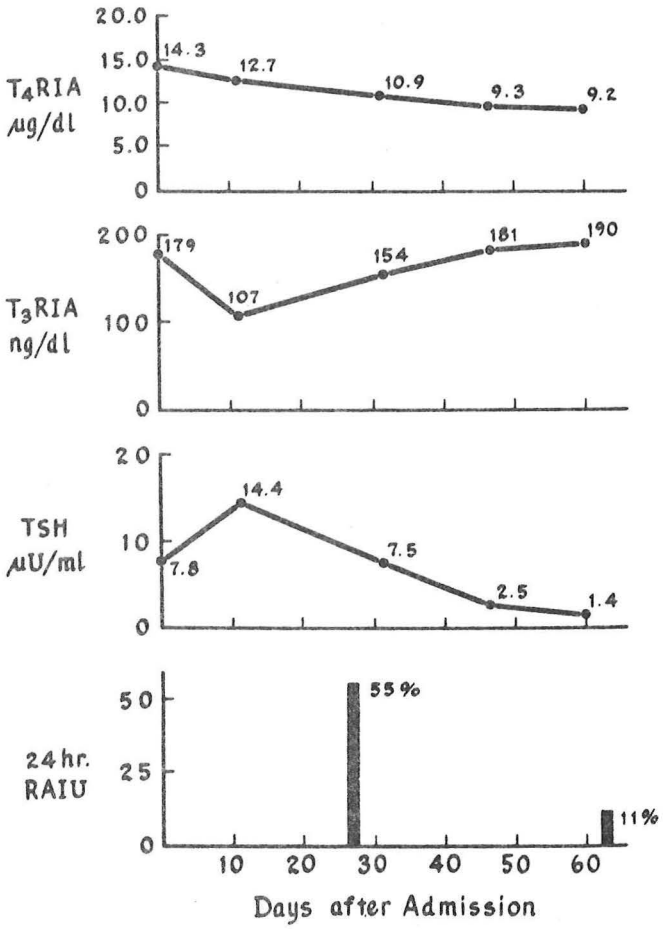

Figure 14 Serum total thyroxine (*T_4RIA*), total triiodothyronine (*T_3RIA*), thyrotropin (*TSH*), and thyroidal radioiodine tracer uptake (*24 hr RAIU*) monitored sequentially without therapy.

It is possible that there is a syndrome of T_4 toxicosis, but the idea is unattractive to me because the evidence seems convincing that T_3 is the active thyroid hormone and T_4 a prohormone. Certainly the euthyroid sick with high T_4 values do not have signs of thyrotoxicosis. In the cited study (106) 6 of 13 patients had RAI uptakes and only two were significantly elevated. The presence of high RAI values in these two patients cannot be considered definitive for a diagnosis of hyperthyroidism since elevated TSH values can be produced by a block in $T_4 \rightarrow T_3$ conversion (see Fig. 14). It has been speculated that these patients actually do have thyrotoxicosis together with some intercurrent illness that blocks $T_4 \rightarrow T_3$ conversion. The presumption would be that recovery from the putative second illness would bring a rise in T_3 and the usual chemical picture of uncomplicated thyrotoxicosis. A second possibility is that TRH responsiveness in these patients is impaired by severe stress. They would thus be examples of "euthyroid sick" with the

additional problem of blocked TSH release. Glucocorticoids are known to produce such a block (5,106) and the same phenomenon can be seen with uremia, acromegaly and the use of levodopa or salicylates in large doses (106). I tend to favor this explanation at present. A third possibility, entirely speculative, is that there could be increased production of T_3 in tissues but failure of back-leak into plasma. Such a phenomenon has never been described,but there are no theoretical reasons why it might not occur.

Until clarification is forthcoming I would be very hesitant to treat "T_4 toxicosis" definitively with radioiodine or surgery. If therapy is required, antithyroid drugs should be used.

2. Hyperthyroid patients with normal thyroid function tests suggesting euthyroidism. There are two conditions in which true thyrotoxicosis may be associated with normal T_4 concentrations. The first is T_3 toxicosis (107) and the second is thyroid binding globulin deficiency (108). In regard to the former, it is now known that ordinary hyperthyroidism is associated with increased production of T_3 relative to T_4 (109); it is thought by many that the syndrome of T_3 toxicosis simply represents a stage in the development of ordinary hyperthyroidism (107,108). The syndrome may be more common in elderly patients; it also may occur in thyrotoxicosis produced by metastatic thyroid cancer (110). Diagnosis should be straightforward: T_3 concentration by immunoassay is elevated, T_4 concentration is normal, FT_3I is increased, RAI uptake is high and TRH stimulation (or T_3 suppression) is abnormal.

Deficiencies in thyroid binding globulin may occur sporatically or be familial. Inherited disease appears to be sex-limited, affecting males (108). For some reason familial thyroid-binding globulin deficiency predisposes to development of thyrotoxicosis (5 of 12 cases in the cited study). While T_4 tends to be normal, FTI and total T_3 concentrations are elevated (Fig. 15).

Fig. 15 (ref. 108)

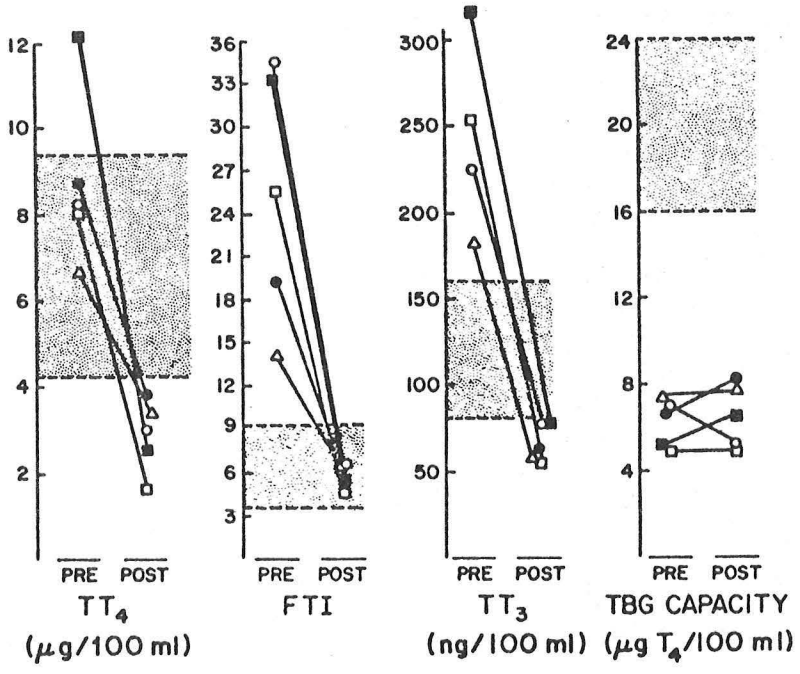

FIG. Serum TT_4, FTI, TT_3 and TBG capacity in the 5 cases with thyrotoxicosis before (pre) and at least one month after achievement of euthyroidism (post). Stippled area is the normal range (mean ± 2 SD). Solid square (■) is Case 1, open square (□) case 2, open circle (○) case 3, closed circle (●) case 4, and open triangle (△) case 5.

The diagnosis of TBG deficiency in euthyroid patients is suggested by high T_3RU with low total T_4 values while hyperthyroidism in subjects with TBG deficits would demonstrate high T_3RU, normal T_4, elevated T_3 high FTI and a dysfunctional TRH or suppression test. An interesting variant has been described in a patient with hyperthyroidism, normal T_4, normal T_3, elevated T_3RU and a RAI uptake of 60%. Thyrotoxicosis was due to a hot nodule with suppression of the remainder of the gland. These findings pointed to a deficiency of TBG, but measurement by immunoassay showed normal values (111). The authors thus speculated that the TBG molecule was present in normal amounts (and was immunologically competent) but unable to bind thyroid hormones.

3. Workup of suspected thyrotoxicosis. I prefer the following sequence in patients who are seriously suspected to be hyperthyroid: (1) T_4, T_3RU, T_3. The T_3 is included in the routine screen because it likely is as good a discriminator as the TRH test in routine cases (112). If hyperthyroidism is not really suspected but thyroid screening is thought necessary (e.g., in patients with new onset atrial fibrillation), a T_4 and T_3RU is probably sufficient. (2) If the tests in (1) are positive, then a 24 hour RAI uptake will differentiate hyperthyroidism from thyrotoxicosis without hyperthyroidism (thyroiditis, factitious thyrotoxicosis, struma ovarii). A scan would be entertained only if a nodule is present. (3) In equivocal cases (discrepancy between clinical and laboratory findings) the simplest differential test is the TRH procedure, although it is my impression that T_3 suppression is the gold standard for diagnosis. One or both of these should be done if there is a serious question. Attempts to simplify diagnosis by graphical-mathematical procedures have been suggested (113) but I am not persuaded they are helpful.

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V. Treatment

1. Radioactive iodine. The therapy of choice for hyperthyroidism in most patients is radioactive iodine, although some authorities continue to feel that surgery or antithyroid drugs should be used in children and adults through the reproductive years (114). Treatment appears to be safe in the sense that no excess of malignant tumors has occurred when carefully looked for in large series (115,116). There is no evidence that RAI induces genetic damage in offspring of treated patients, but it remains conceivable that subtle changes would not manifest themselves for several generations. The possibility of genetic injury, though remote, has to be kept open (114). The only significant late complications of ^{131}I therapy is hypothyroidism. In an excellent paper comparing treatment by radioiodine, surgery and antithyroid drugs, the cumulative incidence of ^{131}I-induced hypothyroidism was 19% at 5 years and 32% at ten years (117). The time course is shown in Fig. 16, next page. Some representative figures in other series are shown in Table 5, next page. The incidence of late hypothyroidism rises with larger doses; there is also a suggestion that ^{125}I induces a greater degree of thyroid destruction than comparable doses of ^{131}I (118). Many authors now feel that it is preferable to deliberately ablate the gland and then treat for hypothyroidism rather than attempt to produce a euthyroid state (119). It has been pointed out that low dose radioiodine is more hazardous from the standpoint of producing malignancy than higher dose therapy, presumably because a number of cells are injured (mutagenized) but not killed(114).

If the patient is not acutely ill, radioactive iodine can be given immediately upon diagnosis followed by initiation of antithyroid drugs 5 to 7 days later. If the patient is sick (e.g., fast atrial fibrillation, congestive heart failure, extreme wasting), control should be initiated with antithyroid drugs and radioactive iodine administered some months

later after partial or complete recovery.

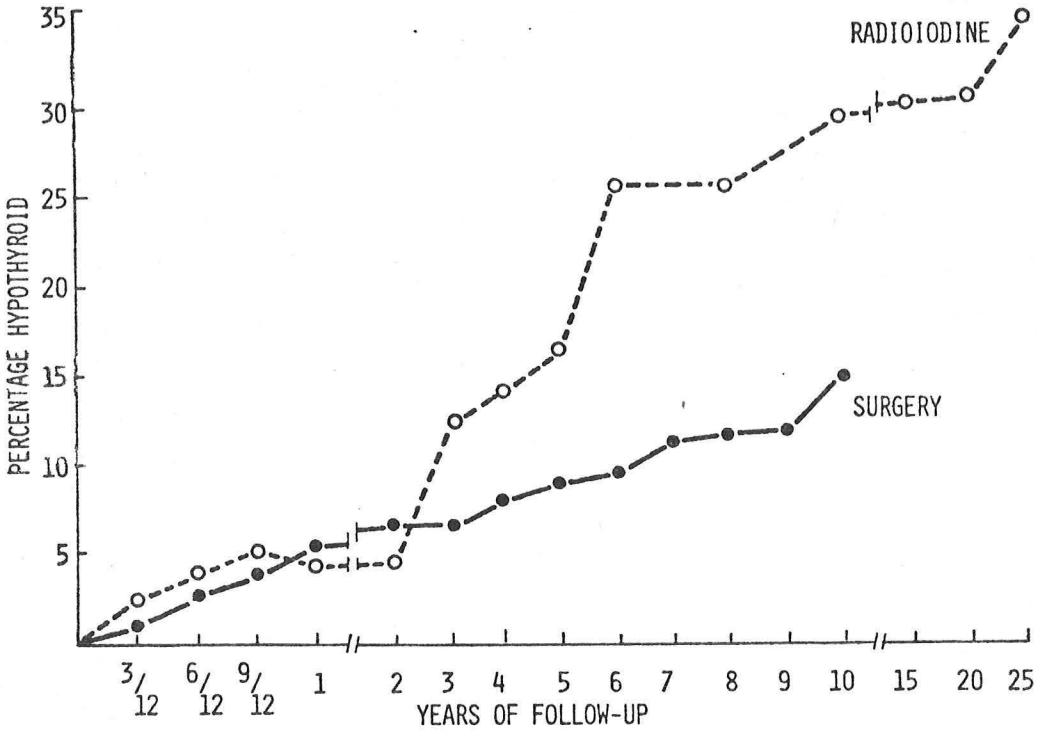

Fig.16 (ref.117

FIG. Cumulative incidence of hypothyroidism following surgery (n = 266) and radio-iodine (n = 43).

Table 5 (ref. 117)

TABLE . *Rising incidence of hypothyroidism with increased duration of follow-up after radio-iodine*

Author	Year	No. of patients	Average first dose	Per cent hypothyroid	Maximum period of follow-up yrs.
Balls	1955	180	7·5 microcuries	18·3	6
Green & Wilson	1964	925	7000 rads	28·8	12
Nofal *et al.*	1966	828	185 microcuries/gram	51	16
Present series	1979	43	7·2 microcuries	36·1	12

2. Antithyroid drugs. Antithyroid drugs are still a perfectly acceptable form of treatment for thyrotoxicosis and recommended as first choice by some authorities (119). The only problem is that rates of relapse are extremely high (Fig. 17 and Table 6, next page). The cumulative figure for recurrence in the Dublin series (carbimazole therapy) was 70% and ranged in other reports from 30 to 59% (117). Permanent remission is also rare (11-14%) with propylthiouracil or methimazole (120). A report of higher remission rates utilizing short term therapy with a single daily dose of methimazole should not be taken seriously (121). In initiation of treatment propylthiouracil has a slight advantage over methimazole initially since it inhibits conversion of $T_4 \rightarrow T_3$ in peripheral tissues while methimazole does not (e.g., 122,123). Its

Fig. 17 (ref. 117)

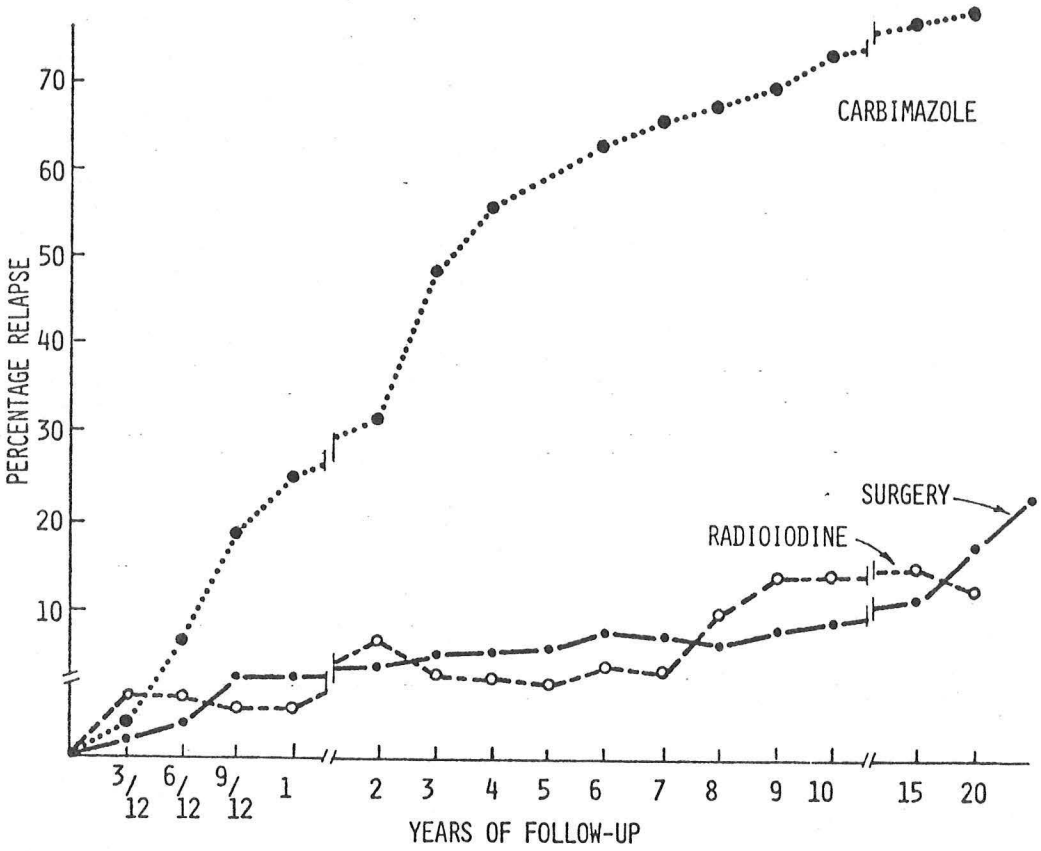

FIG. Cumulative incidence of relapse following carbimazole ($n = 272$), surgery ($n = 266$) and radio-iodine ($n = 43$).

Table 6 (ref. 117)

TABLE *Previous studies of patients treated with antithyroid drugs or surgery*

Antithyroid drugs				Surgery				
Author	No. of patients	Yrs. followed	% relapse	Author	No. of patients	Yrs. followed	% relapse	% hypo-thyroid
Solomon *et al.*	101	4 or more	30–45	Cattell	1000	0–6	2·4	4·5
McCullagh & Cassidy	60	4–6	34	Wade	119	1–3½	0	4·5
Douglas & Kennie	187	?–5	55	Beahrs and Sakulsky	355	5–10	3·3	42·8
Goodwin *et al.*	94	1–4	59	Roy *et al.*	84	2–9	11	5
Trotter	157	10	55	McNeill & Thomson	123	8–15	11·4	6·5
Reveno & Rosen-baum	167	4–19	43	Murley & Rigg	204	½–13	0	4·1
Hershman *et al.*	176	6–20	46	Hedley *et al.*	146	2–21	6·2	36·3
Present series	272*	0–25	69·9	Present series	266	0–25	28·3	26·5

* Combined 2 yrs., >2 yrs. and <2 yrs. course of carbimazole.

disadvantage is that it has to be given frequently. It is important to start therapy with high doses (150-300 mg g 6h) until thyrotoxicosis is brought under control following which a gradual decrement in dosage can be undertaken. Maintenance therapy may be carried out with methimazole which has the advantage of a longer half-life and lower dosage requirements (fewer pills). Treatment probably should be carried out for 2 years before testing for remission (117).

3. Surgery. Surgery is usually recommended for young persons and some pregnant patients when the diagnosis is made early. Results in 266 patients in the series of Sugrue et al (117) were as follows (see also Figs. 16 & 17).

State	Percent
Remission (10 years)	72
Relapse (10 years)	10
Hypothyroidism (10 years)	18
Vocal cord paralysis (permanent)	3.4
Hypocalcemia (permanent)	1.9

In a smaller series of 100 patients followed for only 12 months, Toft et al (124) found normal thyroid function in 20, normal T_4 and T_3 but elevated TSH in 40, temporary hypothyroidism with subsequent reversion to euthyroidism in 20, permanent hypothyroidism in 14 and relapse to hyperthyroidism in 6. There was 1 case of permanent vocal cord paresis but no hypoparathyroidism. Some of the patients with normal T_4 and T_3 but elevated TSH may yet develop permanent hypothyroidism.

Surgery should not be carried out until the patient is euthyroid. Traditionally this has meant treatment with antithyroid drugs for 4-6 weeks (or longer) with iodine (SSKI or Lugol's) given 7-10 days prior to operation to decrease vascularity of the gland. Recently propranolol or propranolol plus iodides have been recommended for rapid, effective pre-operative preparation (124,125). While the reported results were favorable, we have had only limited experience with this approach at Parkland and cannot offer firm recommendations for or against. The inclination is to stay with proven therapy, though there would be no objection to adding propranolol to reduce blood loss at operation (124).

4. Propranolol. Propranolol should be considered adjuvant rather than primary treatment in thyrotoxicosis. The drug will control symptoms produced by catecholamines, especially tachycardia and tremor, but has minimal effects on hypermetabolism (126,127). Propranolol does impair $T_4 \rightarrow T_3$ conversion (128,129) but the effect appears to be insufficient to overcome the thyroidal overproduction of hormones. The drug is contraindicated in thyrotoxicosis of pregnancy since it may cause intrauterine growth retardation, prolonged labor, fetal respiratory depression at birth, postnatal hypoglycemia and bradycardia (130,131). It should also be used with great caution (if at all) in patients with thyrotoxic heart failure since the depressant effect on left ventricular function is much greater than in normal subjects (132,133). Larger doses are required for therapeutic effect in hyperthyroidism since the turnover of propranolol is increased under these circumstances (134,135).

5. Choice of treatment. Considerable emotion tends to be generated in any discussion of treatment for thyrotoxicosis. My personal

recommendations follow, although different approaches may be dictated by clinical considerations or personal choice in a given patient.

1. Surgery: all children and young adults to age 25 if no surgical contraindication is present.

2. Radioiodine: all adults above the age of 25 except pregnant women and persons actively anticipating reproduction (114).

3. Antithyroid drugs: all acutely ill patients prior to definitive therapy. Probably also the therapy of choice in pregnancy (136-138). (Note: in treatment of pregnant women it is preferable to maintain mild thyrotoxicosis). I treat relatively few patients long-term with antithyroid drugs - the exceptions being a patient's desire for this course or some contraindication to surgery or radioactive iodine.

Appendix: Most European journals now report thyroid hormone values in molar terms. The conversion factors are as follows:

$$T_4 : \quad 1\ \mu g.dl^{-1} = 12.87\ nmol.l^{-1}$$

$$T_3 : \quad 1\ ng.dl^{-1} = 1.536\ nmol.l^{-1}$$

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