

THYROID TODAY

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RESISTANCE TO THYROID HORMONE

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Disease states may be regarded as microscopes that nature provides to divulge its innermost secrets. Thus, it is not surprising that, over the years, endocrinologists have made use of these valuable instruments to elucidate some of the more complex pathways of hormone physiology. In the field of thyroidology, for example, studies of inborn errors of hormonogenesis helped scientists unravel the normal steps of thyroid hormone synthesis, and research on abnormalities of thyroxine-binding globulin (TBG) provided a means for understanding the mechanism of thyroid hormone* transport in blood and its delivery to peripheral tissues. Hence, there are reasons to believe that studies in patients with peripheral resistance to thyroid hormone might shed light on the mode of its action. The ultimate hope is that such knowledge can be applied to develop therapeutic measures to correct the defect.

Suggestions of the possible occurrence of resistance to thyroid hormone can be found in scattered reports. The earliest serious contention for the existence of such an abnormality appeared in a 1967 report of 3 siblings, the products of a consanguineous marriage, who presented a syndrome of deaf-mutism, delayed bone age with stippled epiphyses, goiter and high levels of protein-bound iodine (PBI), in the absence of stigmata compatible with thyro-

**The term "thyroid hormone" or "the hormone" is used throughout the article to designate the two naturally occurring, and metabolically active hormones: L-tetraiodothyronine (T4) and L-triiodothyronine (T3).*

Other abbreviations used: thyrotropin (TSH); thyrotropin-releasing hormone (TRH); thyroxine-binding globulin (TBG); basal metabolic rate (BMR).

toxicosis.¹ Subsequently, variants of the syndrome were described in 18 additional patients, bringing the total number of cases to 21. Three were sporadic²⁻⁴ and the remaining 15 were members of 3 unrelated families.⁵⁻⁷ Furthermore, the author had the opportunity to review data, yet unpublished, from 15 cases who appeared to be affected. Four were sporadic and eleven were members of two unrelated families.⁸

Proof of Resistance to Thyroid Hormone Action in Man.

Since the mechanism of thyroid hormone action remains unknown, and because no single test is available that could determine with specificity the level of peripheral tissue responses to the hormone, demonstration of hormonal resistance requires the execution of a large number of tedious, if not complex, studies. They are summarized in Table I and have been carried out in the original cases. Results published in great detail served to establish criteria for diagnosis.^{1,9-12}

Similarities and Differences in the Syndrome of Resistance to Thyroid Hormone Action.

The hallmark feature, common to all cases with the syndrome thus far described, is an elevation of the circulating levels of free thyroid hormone in the face of clinical euthyroidism. This observation alone, however, is inadequate for establishing a diagnosis of thyroid hormone resistance. Unfortunately, the methods employed for the evaluation and description of cases lack uniformity. The conclusion that each case represents a distinct entity is probably erroneous.^{2,3,6,7,13} Such logic can be equated to a similar assumption made in early studies on the disorder of androgen receptor with male phenotype or Reifenstein syndrome.

Although, for reasons stated above, an all inclusive critical analysis of all cases is not possible, several common features can be identified (Table II). In no instance has a defect in the conversion of T4 to T3 been demonstrated. When measured, serum T3 has always been found to be elevated. Administration of supraphysiologic doses of thyroid hormone have uniformly failed to produce the

expected metabolic effects which were variably determined by measuring changes in serum cholesterol,^{3,9} caloric intake,^{2,9} BMR,^{2,9} sleeping pulse,^{4,9} or urinary excretion of hydroxyproline.^{3,4,9} When sought, no evidence for the presence of pituitary tumor could be demonstrated.^{2-4,6,9} Under basal conditions, serum TSH levels were normal or mini-

mally elevated in all cases.^{2-7,9,11} Variable degrees of serum TSH suppression in response to the administration of T3 were observed, but the response of TSH to TRH was preserved in all cases tested, despite elevated thyroid hormone levels.^{2,3,5-7,11} In one case, T3 treatment produced a paradoxical enhancement of the TSH response to TRH.¹¹

Table 1
Proof of Resistance to Thyroid Hormone Action in Man

CRITERIA	TESTS
1. Authenticity of the circulating thyroid hormone	Binding of serum T4 and T3 to specific antisera and to TBG. Characterization of the circulating iodoproteins by chromatography. Coprecipitation of endogenously labeled hormones to constant specific activity. Digestion of serum T4 and T3 with L-amino acid oxidase.
2. Secretion of excessive amounts of thyroid hormone metabolized through normal pathways	In vivo T4 and T3 turnover kinetics. Conversion of T4 to T3 by peripheral tissues in vivo and/or in vitro.
3. Transfer of excessive amounts of thyroid hormone from blood to tissues	Kinetic parameters of the rapidly exchangeable cellular T4 and T3 pools (disappearance of simultaneously injected labeled T4 or T3 and albumin). In vitro studies of hormone transfer into patient's lymphocytes or fibroblasts.
4. Absence of hypermetabolism or evidence of hypothyroidism	Evaluation of growth, dentition, bone age, strength, endurance and caloric intake. Sleeping pulse rate. Basal metabolic rate (BMR). Achilles tendon reflex relaxation time. Serum cholesterol, lipids, tyrosine, carotene and creatinine phosphokinase. Urinary excretion of hydroxyproline and creatine.
5. Absence or inadequate metabolic responses to the administration of pharmacological doses of thyroid hormone	Evaluation of criteria listed under 4 and 6, in response to the acute and chronic administration of supraphysiologic doses of thyroid hormones.
6. Feedback regulation of pituitary TSH resistant selectively to thyroid hormone	Repeated determinations of basal serum TSH. TSH and prolactin responses to TRH before and after administration of full replacement and supraphysiologic amounts of thyroid hormone and of glucocorticoids. Serum T4 response to exogenous T3.
7. Evidence for TSH induced thyroid hyperactivity	Criteria listed under 9. Bioassay of circulating TSH. Changes in serum T4 and T3 in response to TRH induced TSH secretion. Thyroidal radioiodide uptake.
8. Possible defect of thyroid hormone receptors or their interaction with thyroid hormone	Thyroid hormone binding kinetics to nuclei obtained from patient's lymphocytes, fibroblasts or other tissues.
9. Exclusion of other thyroid diseases	Tests for inborn errors of hormonogenesis (ex. perchlorate discharge). Tests for autoimmune thyroid diseases (thyroid microsomal and thyroglobulin antibodies, thyroid stimulating immunoglobulins). Thyroid biopsy. Response to the administration of iodide.
10. Exclusion of TSH producing pituitary adenoma	Pituitary function tests. Pituitary polytomography.

Goiter was present in all cases except one.⁴

Reported differences in the syndrome involved the mode of presentation, including familial occurrence, symptoms and signs, retardation of bone maturation, and prior therapy (Table III). These discrepancies may not represent different entities but actual variability in the severity of the affliction. For example, delayed bone maturation was found in 5 patients from 3 unrelated families.^{1,4,5} All were younger than 13 years and possibly exhibited a more severe form of the defect as judged by the clinical presentation and the degree of serum hormone elevation. Administration of prednisone either totally¹¹ or partially² suppressed the TSH response to TRH, or had no effect.⁶

The response to antithyroid drugs is difficult to assess because of the great variability in the preparation, doses and duration of therapy. More importantly, demonstration of a nuclear receptor abnormality has not been a uniform finding. However, only two laboratories have studied T3-binding to lymphocyte nuclei, one showing an important defect in the receptor affinity,¹² while the other reported conflicting data.^{14,15}

Diagnostic Evaluation.

Since the clinical presentation of the syndrome is variable, a high degree of suspicion is a prerequisite for its detection. Patients are most likely to present with a small

Table II
Similarities Among Published Cases

Author and Reference No.	Metabolic Responses to Thyroid Hormone							Pituitary Tumor	Basal TSH	TSH Response to TRH		Goiter
	↑ T3	Cholesterol	Caloric Intake	BMR	Sleeping Pulse	Urinary Hydroxyproline Response	Basal			on T3		
Familial												
Refetoff et al ^{9,11}	+++	-	-	-	-	↓	-	Nor ↑	+	↑	+	
Lamberg et al ⁷	+							N	++		+	
Elewaut et al ⁶	+						-	Nor ↑	++		+	
Agerbaek ⁵	+							Nor ↑	+		+	
Sporadic												
Lamberg ³	++	-					-	N	+	↓	+	
Bode et al ²			-	-			-	N	+	↓	+	
Schneider et al ⁴					-	↓	-	Nor ↑			-	

+ present; - absent; ↑ increased; ↓ decreased; N normal

Table III
Differences Among Published Cases

Author and Reference No.	Familial	Consanguinity	Age (yrs)	Bone Age Retardation	Severity	Glucocorticoid Effect on TSH Response to TRH	Nuclear T3 Binding to Lymphocytes	
							Affinity	Capacity
Familial								
Refetoff et al ^{1,11,12}	+	+	<1-12	Yes (3/3)	+++	↓↓	↓↓	↓
Lamberg et al ^{7,15}	+	-	18-56		+		↓ or N	N
Elewaut et al ⁶	+		6/73		+	-		
Agerbaek ⁵	+	-	7->46	Yes (1/4)	++			
Sporadic								
Lamberg et al ^{3,15}	-	-	25	No	+		N	N
Bode et al ²	-	-	8	No	+	↓		
Schneider et al ⁴	-	-	13	Yes	++			

+ present; - absent; ↑ increased; ↓ decreased; N normal

Table IV
Suggested Course of Diagnostic Procedures

Usual presentation: Goiter and high serum T4 without thyrotoxicosis. (compensated euthyroidism)

Confirm the elevated serum levels of free thyroid hormones (T4 and T3). (absence of thyroid hormone transport defects)

Exclude the existence of common thyroid diseases. (a critical review of the case)

Demonstrate the presence of TSH in serum and its response to TRH. ("inappropriate secretion of TSH")

Exclude the presence of pituitary adenoma by radiographic procedures and possibly pituitary function tests.

Demonstrate the absence or inadequacy of metabolic responses to the administration of pharmacological doses of thyroid hormone. (resistance to thyroid hormone action)

Study thyroid hormone—receptor interaction and in vitro tissue responses.

goiter and a high serum T4 level in a clinical setting of euthyroidism. The suggested procedure of diagnosis involves a stepwise process of elimination (Table IV).

The presence of elevated serum T4 concentration needs to be confirmed by repeating the test, and ruling out the possibility of inherited or acquired increase in TBG¹⁶ by measuring its concentration in serum and by estimating the circulating free T4 level. Confirmation of high serum T3 levels is also of value, since a defect in the peripheral conversion of T4 to T3 occasionally may be associated with a transient elevation in serum total and free T4.¹⁷

At this point of the diagnostic study, it is useful to critically review the case to determine if subtle signs and symptoms of the more common thyroid diseases might have been overlooked. Particular attention should be given to the presence of a toxic nodular goiter and to clinical stigmata of Graves' disease. The existence of autoimmune thyroid disease could be confirmed easily by the presence of circulating antibodies directed against thyroid microsomes or thyroglobulin.

In the absence of specific tests for the quantitative evaluation of peripheral tissue responses to thyroid hormone, the simplest diagnostic approach to be undertaken next is measurement of the serum TSH level and its response to TRH. Under most circumstances, patients with elevated serum levels of thyroid hormone have virtually undetectable serum TSH levels with characteristic failure to respond to TRH. This is true even when the magnitude of thyroid hormone excess is minimal and thus subclinical in nature.¹⁷ The combination of elevated serum levels of thyroid hormone and non-suppressed TSH narrows the differential diagnosis to a handful of rather rare conditions designated by Gershengorn and Weintraub as "inappropriate secretion of TSH."¹⁸ Their presumed pathophysiologies are illustrated in Figure 1. All share in common a state of TSH hypersecretion inappropriate for the level of circulating thyroid hormone and a preservation of the TSH response to the administration of TRH. If these criteria are satisfied, theoretically possible causes include: (a) excessive stimulation of pituitary TSH by an endogenous source of TRH; (b) autonomous secretion of TSH; and (c) inability

of thyroid hormone to suppress TSH release.

A demonstration of a pituitary tumor by polytomography or by computerized tomography of the sella turcica is suggestive of a TSH-producing adenoma.¹⁹⁻²³ In some instances, patients present with acromegaly due to the concomitant hypersecretion by the tumor of growth hormone.^{21,23} Ectopic production of TSH, indistinguishable from the pituitary glycoprotein, is a theoretical possibility but has never been demonstrated. However, tumors of trophoblastic origin have been shown to produce substances with thyroid stimulating activity.^{24,25} Failure to demonstrate a pituitary abnormality by radiographic means does not exclude the presence of a small adenoma. Nevertheless, under such circumstances, it has been conjectured that the TSH hypersecretion might be due to excessive stimulation by endogenous TRH²⁶ or to a decreased sensitivity of the TSH producing cells to thyroid hormone: a "selective resistance" of the pituitary gland.^{18,21,27} Thus, in the absence of demonstrable pituitary tumor, further investigation should center on the evaluation of the metabolic state of the patient.

As diagrammatically shown in Figure 1, with only one exception, the elevated levels of thyroid hormone associated with all conditions of inappropriate TSH secretion give rise to thyrotoxicosis. This exception is characteristic, if not pathognomonic, of the syndrome of resistance to thyroid hormone action. Proving the existence of peripheral tissue resistance to the hormone is not a simple matter. Proof requires not only establishment that the patient is eumetabolic on clinical grounds, but also pursuit of a long term clinical investigation, preferably under controlled conditions which allow the direct observation of the patient. Since the resistance to the hormone is usually partial and variable in different organ tissues, no single test measuring a particular aspect of thyroid hormone action on peripheral tissues is sufficient. As a matter of fact, no specific group of tests can be recommended. The choice rests with local laboratory facilities since some of the more valuable tests, such as the basal metabolic rate (BMR), formerly used for the diagnosis of thyroid dysfunction, may not be readily available to the physician. In practice, a spectrum of tests currently available (see Table I, no. 4) should be carried out in the basal state and repeated over a prolonged course (weeks or months) of thyroid hormone administration in graded suprphysiological doses (full to 5-fold or more replacement). Failure to observe the expected changes is compatible with tissue resistance to the hormone.

Demonstration of a preserved TSH response to TRH during the course of thyroid hormone administration is of particular value. Although non-suppressibility or only partial suppression of the response is typical of the syndrome, it only indicates that the resistance is shared by the pituitary gland. Suppression of the TSH response to TRH during the administration of glucocorticoids indicates the presence of a resistance selective for thyroid hormone. However, resistance to thyroid hormone but not to the glucocorticoid mediated suppression of TSH release is common to all conditions of inappropriate secretion of TSH (Figure 1) and thus is not diagnostic of the syndrome.

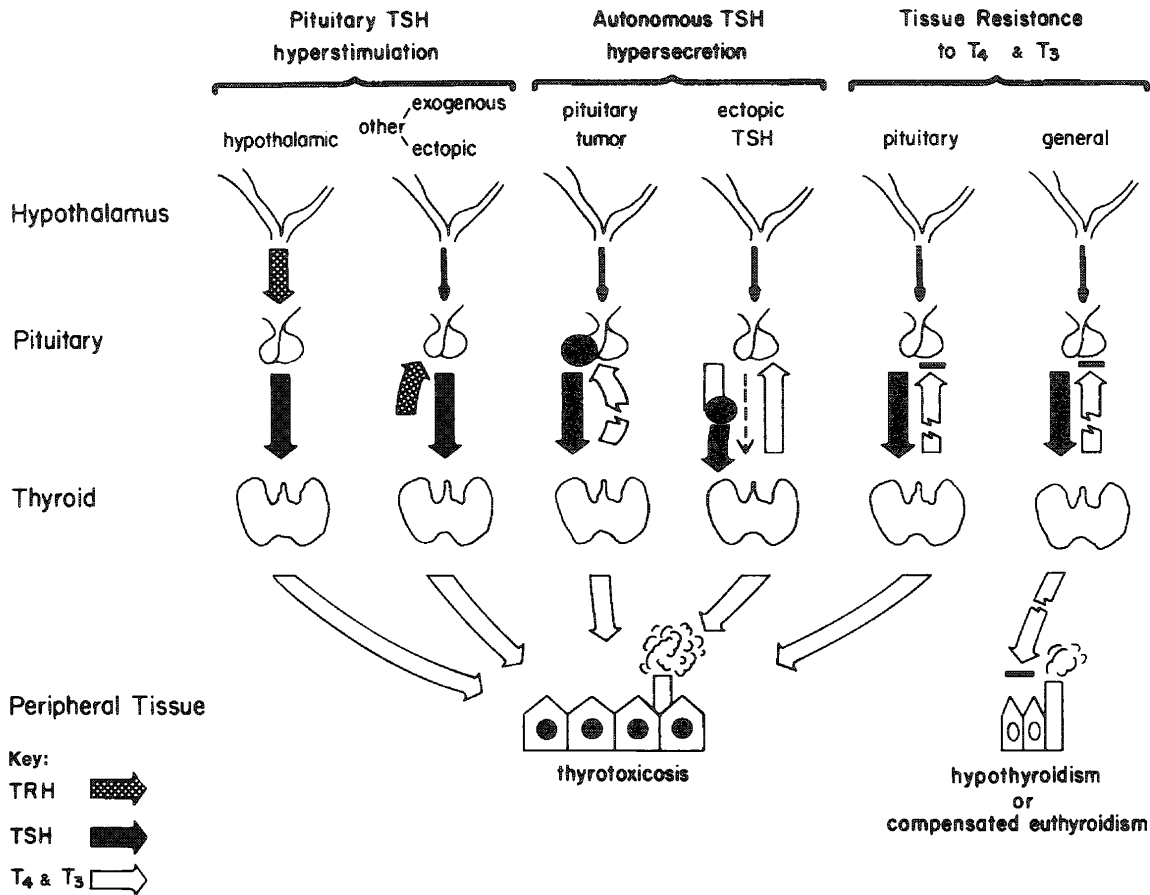


Figure 1: "Inappropriate Secretion of TSH." A diagrammatic presentation of real and hypothetical causes for the coexistence of high serum levels of free T₄ and T₃ without TSH suppression. Broken arrows indicate defective feedback and, together with a black bar, resistance to the action of thyroid hormone. For details, see text.

Evidence has accumulated that thyroid hormone interacts with putative nuclear protein receptors present in virtually all tissues.²⁸⁻³⁰ Although there is no direct proof that thyroid hormone actions are mediated through nuclear binding, several lines of evidence suggest that this may be the case.³⁰ Since the relatively large amounts of fresh tissue required for binding studies cannot be readily obtained from man, peripheral lymphocytes and fibroblasts grown in tissue culture have been used. Available results from studies on nuclear T₃-binding are limited to 3 isolated cases presumed to be resistant to thyroid hormone. Data are conflicting, showing either a clear cut abnormality¹² or only minimal changes.^{14,15} Although measurements of nuclear T₃-binding capacity and affinity in lymphocytes and in fibroblasts cannot be used as the sole test, a demonstration of binding abnormalities is a useful diagnostic adjunct. It is hoped that with future experience, this and other tests measuring intracellular events involved in the expression of thyroid hormone action will facilitate and simplify the diagnostic process.

Speculations on the Origin of the Defect.

The defect, best described as variable tissue resistance to the action of thyroid hormone, appears to be either

inherited^{1,5,7} or acquired,^{2,4} with the tendency for gradual amelioration over an extended period of observation, usually more than 5 to 10 years. Consanguinity is known to be present in only 1 of the 6 families. The largest number of affected subjects in a single family is 8; the overall male to female ratio 2 to 1; and the ethnic background varied (European, Mexican and American Indian). The pituitary must share the resistance for the defect to be detected. Otherwise, the circulating hormone could not attain supranormal levels. Since the hormone has been found to be normal stereochemically, to undergo the normal pathways of degradation, and to adequately penetrate peripheral tissues, the defect should reside in the cellular level, at the site of hormonal action. Thus, abnormalities of the receptor, in the interaction between the hormone and its receptor, or defects at some post receptor-binding step are plausible hypotheses. Unfortunately, current methodologies are unable to localize the defect more precisely. In view of the discrepancy in the findings from early attempts to localize the defect at the receptor level,^{12,14,15} it is possible that the syndrome represents the manifestation of a number of defects, beginning at the hormone-receptor interaction and encompassing all subsequent steps leading to the expression of thyroid hormone action.

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