SYNDROMES OF THYROID HORMONE RESISTANCE

Department of Internal Medicine

Grand Rounds

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I. Introduction

I reviewed the subject of thyroid hormone resistance for Endocrine Rounds more than nine years ago (1). In considering a topic for today's rounds, I initially dismissed the possibility of reviewing this same subject, in spite of the many advances in almost a decade, because of the thought that the condition was uncommon and had not been seen at this institution. However, I then recalled that I had been consulted by a physician on the SWIS line concerning a family who seemed to have generalized resistance to thyroid hormone. Then I recognized toward the end of January that I was seeing another family with thyroid hormone resistance, a mother and daughter who probably had the other form of the disorder in which the pituitary is predominantly or selectively affected.

Thyroid hormone resistance is like other better known hormone resistance states in that normal or increased hormone concentrations are not associated with the expected hormone effects. There are now more than 200 reported individuals with generalized resistance to thyroid hormone and 32 patients with pituitary resistance to thyroid hormone. The two families mentioned above and described subsequently as well as a number known to the NIH (personal communication, B. Weintraub) are not reported and suggest that the condition is not rare. The development of sensitive TSH assays has made it likely that many additional patients with thyroid hormone resistance will be recognized in the future. Several reviews are available (2-6).

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4. Refetoff S. The syndrome of generalized resistance to thyroid hormone (GRTH). Endocr Res 15:717-743, 1989

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II. The Hypothalamic-Pituitary-Thyroid Axis

The function of the thyroid gland is regulated mainly by TSH (7). TSH stimulates the thyroid by interacting with specific cell surface receptors on thyroid follicular cells. The regulation of TSH secretion by the pituitary is primarily under the dual control of the hypothalamic tripeptide thyrotropin-releasing hormone (TRH) and thyroid hormones (Fig. 1). Like other hypothalamic releasing hormones, TRH reaches the anterior pituitary via the hypothalamic-pituitary portal circulation. TRH interacts with specific receptors on pituitary thyrotrophs to release TSH and on mammotrophs to release prolactin. The release of TRH is controlled by central nervous system

mechanisms. TRH is probably released in a pulsatile fashion, since pulsatile TSH secretion has been identified. The ability of the thyrotroph to respond to TRH with increased TSH release is controlled by the feedback inhibition of thyroid hormones (Fig. 1). Either T_4 or T_3 is capable of inhibiting TSH secretion; however, T_3 formed in the pituitary by 5'-deiodination of circulating T_4 appears to be a more important source of thyroid hormone to occupy nuclear receptors and mediate this feedback inhibition than is circulating T_3 (8). It is not known whether thyroid hormones also inhibit TRH release.

In addition to TRH and thyroid hormone, other substances of hypothalamic origin play some role in regulating TSH secretion. Somatostatin, another hypothalamic hormone, can inhibit TSH secretion. The neurotransmitter dopamine may be responsible for tonic inhibition of TSH release since dopamine antagonists cause elevation of serum TSH levels in normal subjects. It is not known by what mechanism dopamine inhibits TSH; it may act via effects on somatostatin. Finally, glucocorticoids, when present at supraphysiological levels, lead to partial inhibition of TSH secretion.

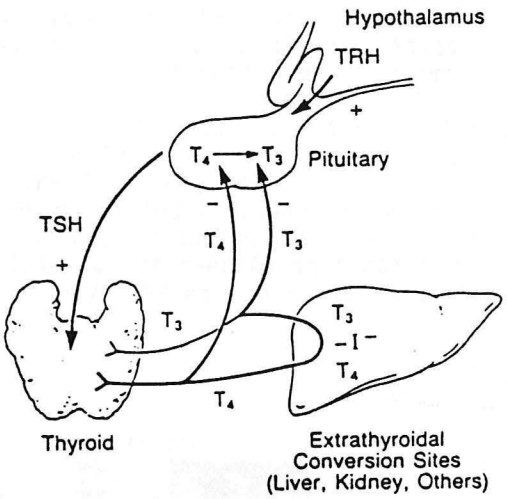

Figure 1

7. Griffin JE. The Thyroid. In Textbook of Endocrine Physiology, J.E. Griffin, SR Ojeda, Eds. Oxford University Press, New York, 1988 pp. 222-244.

8. Larsen PR. Thyroid-pituitary interaction. N Engl J Med 306:23-32, 1982

III. Mechanism of Thyroid Hormone Action

Thyroid hormones are important for the normal growth and development of the maturing human. In the adult, thyroid hormones maintain metabolic stability by regulating oxygen requirements, body weight, and intermediary metabolism. They have unique functions in a variety of organs including the heart, liver, and pituitary (see above). Most of the effects of thyroid hormones occur at the level of gene expression, and are mediated by nuclear thyroid hormone receptors (for review see 9-11).

The nuclear thyroid hormone receptor was first described in December 1986 when two separate groups reported that c-erbA, the product of the cellular homologue of the viral oncogene v-erbA, has the ability to bind T_3 with high affinity and specificity (12,13). This rapidly advanced our understanding of thyroid hormone action since attempted purification of the receptor had not been successful. Since v-erbA had been shown to be structurally related to steroid receptors, this confirmed that the thyroid hormone receptor belonged to the same families of intracellular receptors. Subsequently vitamin D and retinoic acid receptors were shown to have a similar structure. This superfamily of intracellular hormone receptors even includes orphan receptors for yet to be identified candidate hormones (14). Each receptor interacts with its specific hormone as well as with the subset of genes responsive to that hormone. DNA binding to target genes is mediated by two highly conserved "zinc finger" structures, formed by the tetrahedral coordination of zinc with four cysteine residues (14). The hormone-binding regions of the receptor are less well conserved and located closer to the carboxyl termini of the individual receptor proteins.

The most fascinating aspect of the thyroid hormone receptor is that multiple thyroid hormone receptors exist in a given species (15). These different thyroid receptors (TR) are divided into α and β forms on the basis of sequence similarities and chromosomal location (Fig. 2). The TRβ2 (or c-erbAβ2), like TRβ1 has been localized to human chromosome 3, but differs in that it appears to be pituitary specific. The TRα1 has been localized to human chromosome 17 and is widely distributed like TRβ2 (Fig. 2). Alternative splicing of the TRα gene transcript yields a species called c-erbAα2 or TR variant I which is identical to TRα2 for 370 amino acids, including the DNA-binding domain, then diverges completely (Fig. 2). This latter c-erbAα does not bind T_3 and is thus not a TR (11). However, it is widely present and shows regulation by T_3 as do the true TRs (16).

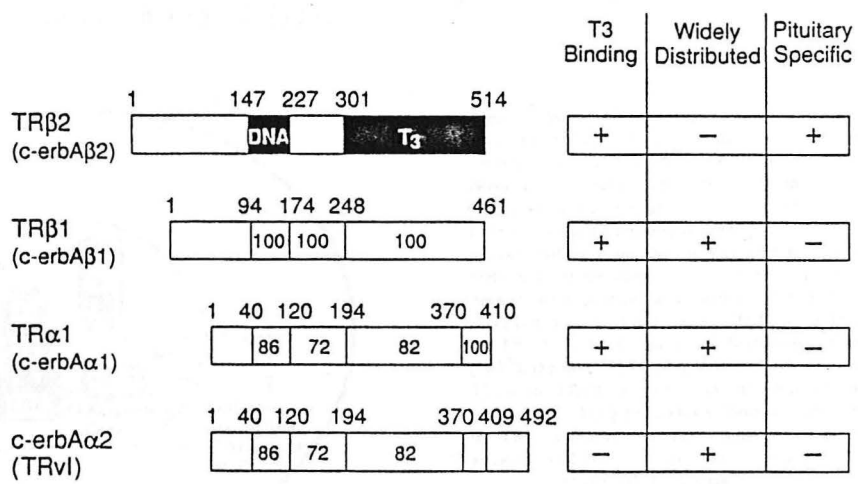

Figure 2

In addition to binding T_3, a true TR must also be able to bind to a thyroid hormone response element (TRE) in target tissues. Furthermore, binding to T_3 and

the TRE must be combined with activation of gene transcription. TRβ1, TRβ2, and TRα1 all bind T_3 in a similar manner. The transcriptional activation of the rat growth hormone (rGH) gene by T_3 is due to a TRE (17, 18). The binding of TRs to TREs appears to be independent of T_3. Interestingly, c-erbAα2 also binds to the rGH TRE (11). All three TRs are able to confer T_3-responsiveness when expressed in cells that normally do not respond to T_3. In contrast, c-erbAα2 does not produce a T_3 dependency of transcription of reporter genes bearing TREs. Instead, it inhibits the action of the TRs in a concentration dependent manner (19). A similar dominant negative effect is caused by the v-erbA protein (20). This effect of v-erbA requires its DNA-binding domain. Moreover the unliganded TRα-1 may actually decrease basal T_3-responsive gene expression, presumably by binding to the TRE (20).

The retinoic acid (RA) receptor, which is more similar to the TR than any other receptor, in the unliganded form also inhibits T_3-responsive gene expression, presumably due to interference with TRE binding. In the presence of RA, the RAR activates transcription from TRE-containing genes, in keeping with its ability to bind to the TRE (21). Formation of TR-RAR heterodimers has been demonstrated in vitro (21), and a putative dimerization domain containing a leucine zipper-like heptad in the region of the ligand binding domain has been identified in the TRs and RARs (22). It is not clear whether TRs can form homodimers or heterodimers with each other as has been shown for the estrogen receptor or whether this is required for DNA binding or transcriptional activation. Artificial mutants containing the putative dimerization domain but lacking a DNA-binding domain were able to function in a dominant negative manner to block transactivation by TR and RAR, suggesting that the heptad repeats mediate the formation of inactive mutant/wild type heterodimers (22). This dimer formation could be the mechanism of the inhibition shown by the nonhormone binding c-erbAα2 and v-erbA.

An overall model for mediation of T_3 action by nuclear thyroid hormone receptors is shown in Fig. 3 (11).

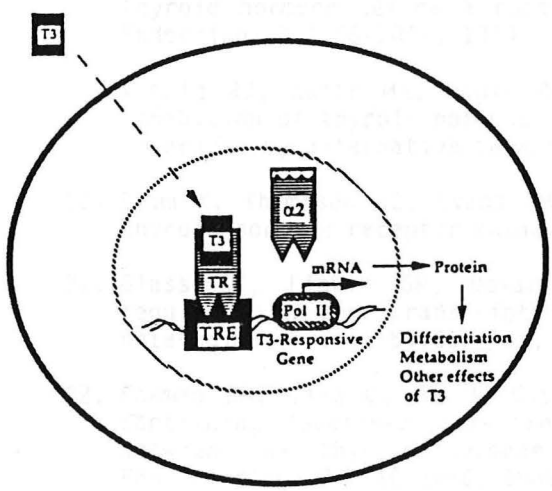

Figure 3 Model of the mediation of T3 action by nuclear thyroid hormone receptors. T3 either enters the cell (as depicted) or is derived from intracellular deiodination of T4. Nuclear interaction between a T3-bound TR and a thyroid hormone-responsive element (TRE) results in increased or decreased activity of RNA polymerase II (pol II) on a T3-responsive gene. The TRE is indicated as containing two half-sites, and the TR may bind as a dimer. Effects on mRNA levels are translated into increased or decreased cellular concentrations of proteins so as to promote differentiation, metabolic processes, and other cell-specific effects of T3. In the absence of T3, the TRE-bound TR may repress basal transcription. c-erbAα2 ("α2"), the non-T3-binding splice variant, can inhibit the effects of T3-bound TRs by a mechanism which has not been established, probably involving heterodimer formation and/or competition for the TRE. A similar mechanism is likely to explain the dominant negative effect of the *v-erbA* oncoprotein and mutated TRs, as in the syndromes of generalized resistance to T3.

Figure 3

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IV. Generalized Resistance to Thyroid Hormone

As mentioned in the introduction, resistance to the actions of thyroid hormone can be classified as generalized (i.e. involving most tissues) or limited to the pituitary. In some instances the distinction is difficult because the generalized resistance is of variable severity in different tissues. The separation into the two groups is useful since the clinical presentations and differential diagnoses are quite different.

A. The Clinical Syndrome

The existence of thyroid hormone resistance was first recognized in 1967 by Refetoff and his colleagues (23) in three patients who were products of a consanguineous marriage and who demonstrated some clinical features of hypothyroidism in the presence of thyroid hormone concentrations typical of hyperthyroidism (23-26). These patients had sensorineural deafness, delayed bone age with stippled epiphyses and decreased urinary hydroxyproline. In most other respects, however, the patients appeared to be euthyroid (i.e., BMR, cholesterol, serum enzymes, dentition, and intelligence were normal). Total and free thyroid hormone concentrations, RAIU, and nonsuppressability of RAIU were typical of hyperthyroidism. The constellation of findings was thought to be most compatible with thyroid hormone resistance. This family has proved to be atypical in regard to the autosomal recessive inheritance and the presence of some clinical manifestations of hypothyroidism. Most families reported subsequently have had an autosomal dominant mode of inheritance and individuals have been clinically euthyroid (27-40, only selected more detailed reports are referenced). Dr. Refetoff has continued to catalog the patients with generalized resistance to thyroid hormone (GRTH) and claims that 27 unpublished patients studied at his institution brings the total to 205 (Table 1) (5).

Table 1. Subjects with GRTH according to Refetoff (5)

	Number of individuals	Number of families
Familial	181	47
Sporadic	8	8
Unknown		
adopted	5	5
families not studied	11	11
TOTAL	205	71

The sex ratio is about equal, in contrast to the female predominance in most thyroid disease. The condition appears to have wide geographic distribution and has been reported in whites, asians, and blacks.

The following patient summary, kindly provided at my request by Dr. Bryant Boyd for use in these rounds, is fairly typical of the presentation of GRTH. Since Dr. Refetoff was sent blood on the patient and his mother, these individuals probably contribute to Table 1.

A 15 year old white male was seen by this family practice physician for a second opinion regarding proposed surgery for his goiter. He gave a history of being initially evaluated at age eight for a goiter and being diagnosed as having Graves' disease with increased free thyroxine index and RAIU and was given methimazole. However, no evidence of thyrotoxicosis was documented on physical exam at that time. The patient felt that his goiter became larger on methimazole. After five years in the drug he was switched to PTU for "failure to respond." Serum thyroxines were 14-18 µg/dl while on therapy, and TSH was not suppressed. While on PTU 100 mg t.i.d., T_4 was 14.7 µg/dl, T_3-RIA 236 ng/dl, and TSH 10.0 µU/ml.

On Dr. Boyd's initial physical exam there was no evidence of thyrotoxicosis but a large symmetrical goiter was present. Laboratory assessment while on a small dose of PTU was similar to that listed above. At this point Dr. Boyd contacted me and discontinued the PTU. He then evaluated the nature of the patient's mother's history of thyroid disease. She reported possible "thyroid trouble" since childhood. She was treated with antithyroid drugs for two years after a diagnosis of "thyrotoxicosis" was made following her first pregnancy. At age 27 a RAIU was elevated, and she was given methimazole, up to 80 mg daily, followed by a subtotal thyroidectomy six months later. She had not had symptoms of typical thyrotoxicosis. Four months postop her T_4 was again elevated. Eight months after her surgery RAIU was again increased, and methimazole was restarted and continued for seven years. During this time T_4 remained elevated and a single TSH value was 16.4 µU/ml (normal then <10µU/ml). Eight years post subtotal thyroidectomy a repeat elevated RAIU prompted treatment with ^{131}I. Six months later levothyroxine 0.15 mg/day was initiated and continued for four years at which point she was seen by Dr. Boyd. On this dose of levothyroxine her free T_4 index was high normal whereas her TSH was 84 µU/ml.

This family indicates not only the usual presentation of individuals with GRTH, i.e. asymptomatic goiter with elevated thyroid hormone levels, but also the usual effect of physician evaluation. Most physicians cannot believe that someone with such elevated thyroid hormone levels and a goiter is not thyrotoxic even if they do not have a history of hyperphagia with weight loss, nervousness, and palpitations or physical findings of tachycardia and other signs of thyroid hormone excess. This mistake has been repeatedly pointed out in the literature (28,31,33,36,38). Prior to the availability of immunoradiometric TSH assays, this diagnosis required a high index of suspicion since TSH values by the former TSH RIA were usually normal and not distinguisable from patients with thyrotoxicosis. Then it required the performance of a TRH test to demonstrate an "inappropriate" normal response in an individual suspected of having thyrotoxicosis (41). In contrast, with the immunoradiometric TSH assays now available in almost all clinical labs, endogenous or exogenous thyroid hormone excess is associated with a serum TSH that is below the normal range and usually undetectable in individuals with normal response to thyroid hormone (42) and in the absence of a TSH-secreting pituitary tumor (see below).

The resistance to thyroid hormones is presumed to be incomplete. The resistance can be completely overcome by increased levels of thyroid hormones which are the result of the "inappropriate" levels of TSH. In some organs the increased thyroid hormone levels only partially compensate for the resistance.

Giving graded doses of exogenous triiodothyroxine results in partial suppression of the basal and TRH-stimulated TSH (27). Only in Refetoff's original family was there apparent inability to inhibit the TRH response with exogenous T_3 (26). In all patients tested glucocorticoids suppress TSH normally.

The pedigree shown in Fig. 4 is from one of the larger families with GRTH studied extensively (38).

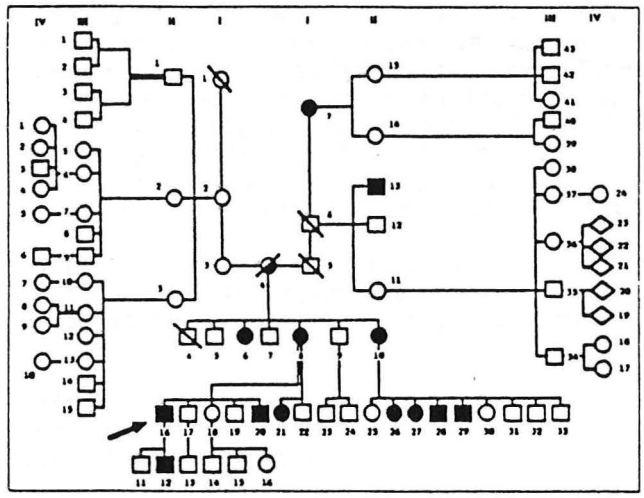

Figure 4 Pedigree of a family with thyroid hormone resistance. Closed symbols are affected members, shaded symbols are unaffected, and open symbols are untested. Diamonds indicate undetermined sex. Patient I-4 had premortem elevated T_4 and free T_4 index, with no TSH determination. Arrow indicates propositus. Diagonal line across a symbol indicates that the person is deceased.

Figure 4

Some of the thyroid function tests from affected members of the family are shown in Table 2.

Table 2. Thyroid function tests in 14 affected members of a family with GRTH (38).

Patient	Age/Sex	T_4 (µg/dl)	FT_4 (ng/dl)	T_3 (ng/dl)	FT_3 (pg/dl)	TSH (µU/ml)
I-4	67-5	17.6				
I-7	65-F	14.2	4.2	198	672	2.4
II-6	50-5	18.5				
II-8	44-F	16.2	3.4	222	492	3.6
II-10	33-F	14.2	3.8	219	525	1.6
II-13	40-M	15.7		212		1.9
III-16*	25-M	13.7		241		14.9
III-20	22-M	20.0		259		1.8
III-21	10-F	14.4	4.5	315	747	2.5
III-26	12-F	14.6	4.7	239	581	2.6
III-27	10-F	12.6	4.1	260	684	4.3
III-28	8-M	14.2	4.1	286	635	3.6
III-29	6-M	12.8	4.3	272	680	5.7
IV-12	5-M	13.2	4.8	233	726	3.0
Upper limits of normal		12.1	3.8	220	480	4.0

*Values obtained following ^{131}I before becoming hypothyroid.

Of interest, as shown in Table 2, only the individual with destructive therapy to the thyroid gland (III-16) had a serum TSH that was unequivocally elevated (i.e. more than twice the upper normal limit). Thus if the goiter were small (as it was in some individuals in this family) and only routine TFTs and TSH were obtained one might attribute a serum thyroxine and free T_4 index in the 14 to 16 range coupled with a normal TSH as being indicative of dysalbuminemic hyperthyroxinemia (41). Only the recognition of a goiter and the elevated T_3 would provide a clue to the correct diagnosis (as would the FT_4 or free T_4 by equilibrium dialysis). The extensive neuropsychological studies in this extended pedigree cast doubts on previous reports of a variety of psychological and behavioral abnormalities including learning disabilities, emotional instability, and hyperactivity in patients with GRTH. Mild impairments in many areas were detected by testing in this large extended family. However, when unaffected family members were studied, impairments were not specific for affected persons. Significant differences were only present between households (38).

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B. <u>In Vivo Diagnostic Studies</u>

In the typical patient as described above the absence of signs and symptoms of thyrotoxicosis limits the need to consider other causes of inappropriate secretion of TSH such as a TSH-producing pituitary adenoma or selective pituitary resistance to thyroid hormone (PRTH) (see below for differential diagnosis of these conditions). Although the effect of exogenous thyroid hormone on the pituitary response to TRH can be used to assess pituitary resistance to thyroid hormone (43), no sensitive tests are available which specifically measure the effects of thyroid hormones on peripheral tissues.

A number of parameters have been suggested as possible markers of thyroid hormone action on peripheral tissues including serum sex hormone binding globulin (SHBG), ferritin, angiotensin-converting enzyme, cholesterol, CPK, urine hydroxyproline, sleeping pulse, BMR, cardiac contractility, deep tendon relaxation time (38, 44, 46). Unfortunately none of these measurements is sensitive or specific enough to reliably discriminate subjects with GRTH from those in whom the tests are not altered by mild degrees of thyrotoxicosis or from those in whom the tests are affected by other factors (5).

Dr. Refetoff's group feels that SHBG change in response to 100 µg/day of T_3 therapy provides the best discrimination when euthyroid, hypothyroid and hyperthyroid controls are used (Fig. 5) (47).

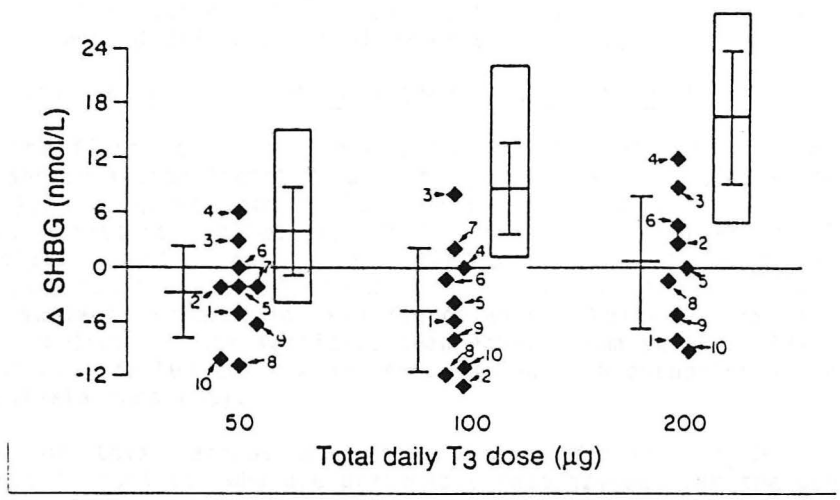

Figure 5 Serum SHBG responses to graded doses of T_3 in patients with GRTH and nonresistant subjects. Each T_3 dose level was given for 3 consecutive days and was administered as a split dose every 12 hours. Open bars represent the full range of values in 21 nonresistant subjects (euthyroid, hypothyroid and thyrotoxic) and the vertical lines, means ± SD for each group. Numbered diamonds indicate individual patients with GRTH. Note the reduction of serum SHBG concentration, which was significant in 6 of the 10 subjects with GRTH while receiving 100 µg T_3 daily (Reprinted from Sarne et al.[43] with permission.)

Figure 5

With the intermediate dose of T_3, a significant increase in serum SHBG concentration was observed in 95% of nonresistant subjects irrespective of their baseline thyroid state. A similar response occurred in only one of ten subjects with GRTH. Furthermore, a paradoxic decline of serum SHBG was observed in more than one half of subjects with GRTH.

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C. In Vitro Studies of Thyroid Hormone Binding and Action at the Cellular Level

Whereas the first study carried out in the original family with recessive inheritance showed a significant reduction in T_3-binding affinity to the nuclear receptor (25), subsequent studies have been disappointing (30,31,35,37,40,48, 49). By Dr. Refetoffs tabulation, studies in 12 laboratories on 35 patients from 22 unrelated families have demonstrated an abnormality in affinity and/or capacity in only about one third of subjects studied in mononuclear cells and in one half of subjects studied in skin fibroblasts. Weintraub has stressed the kinetic binding data is more sensitive than equilibrium studies (49). However, even these studies failed to show any correlation with purported variability in clinical manifestations (35).

In light of this perhaps not unexpected difficulty in demonstrating a binding defect in subjects who are presumably heterozygous for the gene causing the defect and who would thus be expected to have normal receptor coded for by the normal allele, attempts have been made to demonstrate T_3 effects in cultured cells. In a small study of 3 controls and 3 GRTH patients, T_3 failed to stimulate LDL degradation in cultured fibroblasts (50). Although the mean decrease in glycosaminoglycan accumulation in fibroblasts in response to T_3 treatment was less in GRTH patients than controls, there was considerable overlap (51). The most reliable marker of thyroid hormone action in cultured fibroblasts studied thus far has been the inhibition of fibronectin synthesis (52). In this report six of seven patients with GRTH had much less suppression of fibronectin synthesis in their fibroblasts than did seven controls (Fig. 6) (52). Interestingly, the single GRTH patient who appeared to be similar to controls is the same outlier as in Fig. 5 and is reported to have only "mild" peripheral resistance (47).

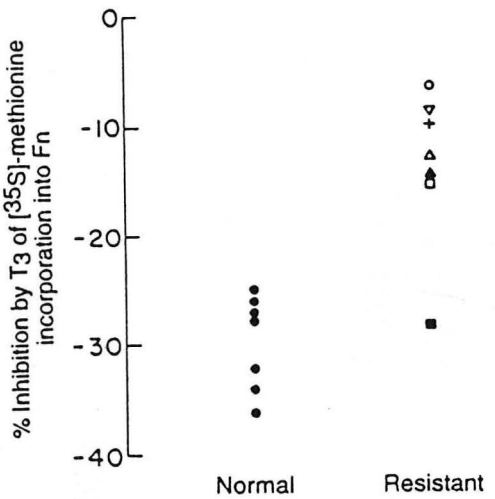

Figure 6 Inhibitory effect of T_3 on fibronectin (Fn) synthesis by fibroblasts from patients with GRTH (resistant) compared to those from normal subjects. Cultures were exposed to 10^{-9} M free T_3 and Fn was measured by incorporation of [^{35}S]-methionine into Fn. Results are expressed as percent inhibition compared to each subject's fibroblasts cultured without added T_3. (Reprinted from Ceccarelli et al.,[52] with permission.)

Figure 6

48. 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

49. Menezes-Ferreira MM, Eil C, Wortsman J, Weintraub BD. Decreased nuclear uptake of [^{125}I] triiodo-L-thyronine in fibroblasts from patients with peripheral thyroid hormone resistance. J Clin Endocrinol Metab 59:1081-1087, 1984

50. Chait A, Kanter R, Green W, Kenny M. Defective thyroid hormone action in fibroblasts cultured from subjects with the syndrome of resistance to thyroid hormones. J Clin Endocrinol Metab 54:767-772, 1982

51. Murata Y, Refetoff S, Horwitz AL, Smith TJ. Hormonal regulation of glycosaminoglycan accumulation in fibroblasts from patients with resistance to thyroid hormone. J Clin Endocrinol Metab 57:1233-1239, 1983

52. Ceccarelli Paola, Refetoff S, Murata Y. Resistance to thyroid hormone diagnosed by the reduced response of fibroblasts to the triiodothyronine-induced suppression of fibronectin synthesis. J Clin Endocrinol Metab 65:242-246, 1987

D. The Molecular Defect

Several reports of studies of the molecular defect in families with GRTH have appeared in the last two years, following the discovery of the gene for the TR described above. Initially RFLPs showed tight linkage to the TRβ gene on chromosome 3 in one kindred (53). Subsequently, the molecular defect has been defined in four families (54-58). The initial family in which the specific defect was identified had a glycine to arginine substitution at amino acid position 345 in the hormone binding domain as a result of a point mutation G → C (Fig. 7A) (54). The recreated mutant receptor did not bind hormone (Fig. 7C).

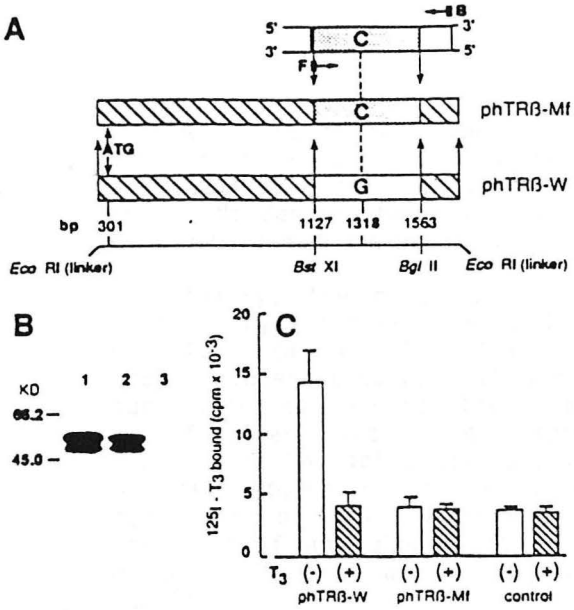

Figure 7 Characterization of the properties of the mutant TRβ gene (Mf) following its in vitro expression. A. Strategy of plasmid construction for in vitro transcription. Filled boxes and arrows indicate the position of primers B and F and the direction of elongation in the amplification reaction.
B. Molecular size determination of TRs synthesized in vitro by translation of the transcribed normal (W, lane 1) and mutant (Mf, lane 2) genes and in the absence of mRNA (lane 3). The position of protein size markers of 66.2 KD (bovine serum albumin) and 45.0 KD (ovalbumin) are indicated. Note that both genes yielded two protein products (55,000 and 52,000 daltons) as a result of translation initiation at two different methionines, 31 amino acids apart.
C. ^{125}I-T_3 binding to the products of translation without (-) and with (+) addition of an excess (10,000 fold) unlabeled T_3. The control is rabbit reticulocyte lysate processed without the addition of mRNA. For details, see text. (Reprinted from Sakurai et al.[17] with permission.)

Figure 7

The second mutation identified in a kindred studied at the NIH was also in the hormone binding domain but further toward the carboxy terminus at position 453 changing a proline to a histidine as a result of a base substitution C → A (55). Subsequent recreation of this mutation has shown that it binds T_3 but with reduced affinity, $4.5X10^{9}M^{-1}$ compared with $2.3X10^{10}M^{-1}$ for the wild-type TBβ translation product (56). These authors went on to study binding of this mutant TR to the TRE in the rGH and the human TSHβ promoters (Fig. 8) (56). These two TREs bound to the mutant TR with comparable or perhaps greater avidity than to an equivalent amount of wild type TR. This type of observation would support the ability of mutant TRs to act like excess unliganded c-erbAα2 or v-erbA in causing a dominant negative effect as described above.

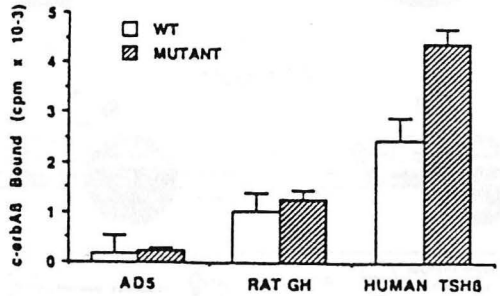

Figure 8 Binding of the wild-type human placental c-erbAβ and Kindred A *in vitro* receptors to DNA fragments containing the TSHβ segment -12 to +43 and rat growth hormone gene segment -188 to -160. The negative control was a DNA fragment containing the adenovirus 5 long terminal repeat. The avidin-biotin DNA binding assay was employed with one picomole of the respective biotinylated DNA fragment and equivalent amounts of ^{35}S-labeled wild-type and Kindred A *in vitro* translation products were used as quantitated by SDS-polyacrylamide gel electrophoresis.

Figure 8

The third mutation described, also in TRβ, is only 5 amino acids in the amino terminal direction in the hormone binding domain from the first mutation and involves a point mutation leading to a glutamine to histidine substitution (57). No description of the hormone or DNA binding properties of a recreation of the mutation has been reported.

Finally, the most recent report includes a screening of 19 unrelated families by Refetoff's group for possible presence of the first two described mutations, in exons 7 and 8 of TRβ respectively, by PCR study of these two exons (58). Interestingly, although no other families with these mutations were identified, primers for the normal sequence of exons 7 and 8 were amplified in all families except the original autosomal recessive family of Refetoff. Subsequent DNA blot analysis revealed absence of all coding exons. Thus there was major deletion both TRβ alleles in affected members of this family. This total loss of both the hormone and DNA binding domains could thus account for the lack of any abnormalities in heterozygotes since they would not have a mutant allele to act as a dominant negative as in the autosomal dominant families.

The overall mechanism for the effect of mutant TRs on gene activation in the usual dominant form of GRTH is depicted schematically in Fig. 9 (58). In A in the figure mutant TR competes with TR for TRE, and inhibits response of gene expression by interaction with TRE, whereas in B formation of inactive heterodimers reduce the functional capacity of both normal TR and T_3.

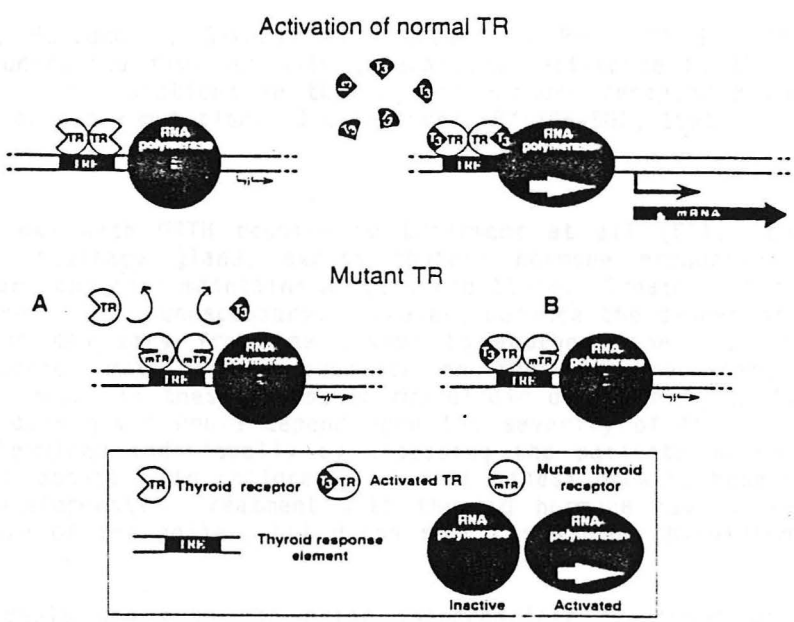

Figure 9 Diagrammatic representation of gene activation through interaction of the TR-T_3 complex with TRE. A and B are examples of postulated interactions of the mutant TR with the hormone, the normal TR and its TRE. For details, see text.

Figure 9

53. Usala SJ, Bale AE, Gesundheit N, Weinberger C, Lash RW, Wondisford FE, McBride OW, Weintraub BD. Tight linkage between the syndrome of generalized thyroid hormone resistance and the human c-erbAβ gene. Molecular Endocrinology 2:1217-1220, 1988

54. Sakurai A, Takeda K, Ain K, Ceccarelli P, Nakai A, Seino S, Bell GI, Refetoff S, DeGroot LJ. Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor β. Proc Natl Acad Sci, USA 86:8977-8981, 1989

55. Usala SJ, Tennyson GE, Bale AE, Lash RW, Gesundheit N, Wondisford FE, Accili D, Hauser P, Weintraub BD. A base mutation of the c-erbAβ thyroid hormone receptor in a kindred with generalized thyroid hormone resistance. J Clin Invest 85:93-100, 1990

56. Usala SJ, Wondisford FE, Watson TL, Menke JB, Weintraub BD. Thyroid hormone and DNA binding properties of a mutant c-erbAβ receptor associated with generalized thyroid hormone resistance. Biochem Biophys Res Commun 171:575-585, 1990

57. Usala SJ, Menke JB, Watson TL, Bernard J, Edward W, Bradley C, Bale AE, Lash RW, Weintraub BD. A new point mutation in the 3,5,3'-triiodothyronine-binding domain of the c-erbAβ thyroid hormone receptor is tightly linked to generalized thyroid hormone resistance. J Clin Endocrin Metab 72:32-38, 1991

58. Takeda K, Balzano S, Sakurai A, DeGroot LJ, Refetoff S. Screening of nineteen unrelated families with generalized resistance to thyroid hormone for known point mutations in the thyroid hormone receptor β gene and the detection of a new mutation. J Clin Invest 87:496-502, 1991

E. Therapy

Most patients with GRTH require no treatment at all (59). Because GRTH involves the pituitary gland, excess thyroid hormone production occurs in response to TSH, and this maintains a euthyroid state. Treatment with exogenous thyroid hormone is thus unnecessary. However, because the degree of resistance to the hormone can vary from one tissue to another, the increased thyroid hormone production may not be adequate to meet the requirements of all peripheral tissues. In these cases, pharmacologic doses of T_4 or T_3 should be given. The doses given would depend upon the severity of the resistance and should be determined individually by assessing the patients metabolic status (see section B above). In children, one must assess growth, bone maturation, and mental development. Treatment with thyroid hormone may be justified to reduce the size of the goiter, but doses that cause hyperthyroidism should be avoided.

In individuals who have had prior inappropriate treatment with subtotal thyroidectomy or radioactive iodine and who are unable to compensate as evidenced by an unequivocally elevated (as opposed to seemingly inappropriately normal) TSH, thyroid hormone should be given in sufficient amounts to suppress the elevated serum TSH levels to alleviate symptoms of hypermetabolism. Failure to correct such therapeutic mistakes, particularly if the thyroid ablative

therapy was given early in life may lead to irreversible damage to the patient (33).

59. Dulgeroff AJ, Hershman JM. Generalized resistance to thyroid hormone. In Current Therapy in Endocrinology and Metabolism 4th ed., C. Wayne Bardin Ed. B.C. Decker Inc., Philadelphia, 1991 pp.102-104.

V. Selective Pituitary Resistance to Thyroid Hormone

A. The Clinical Syndrome

In contrast to patients with GRTH, who usually come to medical attention because of a goiter (or rarely symptoms of hypothyroidism), patients with selective pituitary resistance to thyroid hormone (PRTH) present with signs and symptoms of thyrotoxicosis. The severity of the thyrotoxicosis is usually only moderate, but presence of heat intolerance, weight loss, palpitations, nervousness, and emotional lability is generally unequivocal allowing the physician to make a clinical diagnosis. Such patients lack the infiltrative ophthalmopathy and thyroid dermopathy associated with Graves' disease. For the purpose of classifying patients as having either GRTH or PRTH it is essential to note what the original criteria for ablative thyroid therapy were, since most reported patients with either condition have received some form of thyroid ablative therapy before a correct diagnosis is made. In some such reports it is difficult to be certain of the proper classification.

PRTH was first recognized in 1975 in a patient reported by Gershengorn and Weintraub (60). There are now at least 30 patients with PRTH reported in the literature (61-74, only more complete and more recent reports listed). It is interesting that 9 reports encompassing 14 patients (or almost half of all reported patients) have appeared in the last three years (66-74). This may reflect availability of sensitive TSH assays mentioned above and the impact that they have had on assessing thyroid status. In other words, patients are being recognized as having inappropriately normal TSH in the setting of clinical thyrotoxicosis. In contrast to GRTH in which most affected individuals have other affected family members, the opposite is true for PRTH in which there appear to be only three clear instances of familial occurrence (63,68,74). In these three families the pattern of inheritance is most consistent with an autosomal dominant mechanism of transmissions of the disorder. In one instance of a detailed family report the youngest of six family members in three generations had a small goiter and elevated thyroid hormone levels at age 12 but did not have signs and symptoms of thyrotoxicosis (63). The mother and daughter with PRTH followed by me for the last several months are illustrative of the clinical picture:

> J.H. at age 31 in 1978 presented to a physician in another state complaining of fatigue, insomnia with palpitations, heat intolerance, hyperdefecation, and tremor. Serum T_4 was 16.4 µg/dl and RAIU at 24h was 40%. She was treated with 10mCi ^{131}I. She was given only propranolol after her radioiodine therapy and gradually improved and was tapered off the propranolol. Her serum T_4 was normal in 1980 and 1982.
>
> In 1983 at age 36 she had return of nervousness, sweating, and hyperdefecation. Her pulse was recorded at 95, and serum T_4 was 13.4 µg/dl

with total T_3 of 213 ng/dl. She was given methimazole 5 mg b.i.d. until 1986 when her serum T_4 was 7.3 µg/dl and TSH was >45µU/ml, and methimazole was discontinued.

I first saw her in early 1989 at age 42 at which time she was taking levothyroxine 0.025 mg/day. She indicated that her mother was currently being treated for hyperthyroidism with methimazole. A brother was also thought to have a "thyroid problem". She was taking a β-blocker at the time for hypertension in addition to conjugated estrogens for replacement in light of prior hysterectomy and oophorectomy for menorrhagia and ovarian cysts. She complained of gradual weight gain and fatigue. She had a pulse of 66 and blood pressure of 120/88, no eyes signs, some palpable thyroid tissue near the isthmus, missing middle phalanges of first digits of both hands and feet. I assumed that she had mild hypothyroidism and advised her to increase the dose of levothyroxine to 0.1 mg/day. However, her free T_4 index returned at a high normal value of 12.5 (nl 4.5-12.5) and the TSH was 11 µU/ml (nl 0.4-4.5).

She did not return to see me for more than 20 months calling on a couple of occasions to report that her TSH measured in the physician's office where she worked was still slightly elevated in the 7µU/ml range. I suggested 25 µg increments in levothyroxine reaching a dose of 0.15 mg daily in 10/90. I did not receive reports of serum thyroxine at the time the TSH values were reported. Several weeks after reaching 0.15 mg/day she phoned to reports problems with heat intolerance and palpitations. She was next seen in 12/90 while receiving 0.125 mg/day of levothyroxine with a T_4 and free T_4 index of 22.0 µg/dl and TSH of 3.5 µU/ml. She thus had barely normalized her TSH at the expense of a serum T_4 level causing symptomatic thyroid hormone excess. The diagnosis of PRTH was finally suspected several weeks later after seeing her daughter (described below).

A.H., 20 years old, the daughter of J.H. was seen on 12/90 for evaluation of increased TFTs and goiter noted by her gynecologist. She had a three month history of emotional lability, tremor, seven pound weight loss, fatigue, nausea without vomiting, and menstrual irregularity. On exam she had a pulse of 90/min, fine hair, no eye signs, a small 1.5 times normal symmetrical goiter, and a fine tremor. She was felt to be hyperthyroid and started on methimazole 10 mg t.i.d. and propranolol 20 mg as neded for tremor. Her free T_4 index returned elevated at 14.7, however, total T_3 was normal at 109 ng/dl (nl 80-169) as was TSH at 0.8µU/nl (nl 0.4-4.5). I tried to somehow convince myself that she was being seen very early in course of hyperthyroidism so that T_3 was not elevated as in typical Graves' disease and TSH had not become fully suppressed. When she returned three weeks later with the free T_4 index elevated further at 21.6 and the TSH measured 1.0 µU/ml, it was clear that this was not typical hyperthyroidism.

Both J.H. and A.H. had their medication discontinued and returned after several weeks for baseline measurements and TRH tests.

Table 3. Thyroid tests on J.H. and A.H.

	Total T_4 µg/dl (nl 4.5-12.5)	Total T_3 ng/dl (nl 80-169)	free T_4 ng/dl (nl 0.9-2.5)	TSH µU/ml baseline	after TRH
J.H.	14.8	158	1.8	16.0	142
A.H.	17.5	203	2.6	1.4	14.9

Thus J.H. had a normal free T_4 at the expense of an elevated TSH with an appropriately exagerrated response to TRH reflecting her prior partial thyroid ablation. A.H. had elevated thyroid hormone levels with inappropriately normal basal and post-TRH TSH values. And, moreover, at the time of the above study, A.H. had recurrence of her symptoms of thyrotoxicosis and had a pulse of 102/min.

The observations of PRTH in these patients is unusual in that familial occurrence of PRTH is uncommon and that most prior reports only included studies after some form of thyroid ablative therapy. Speculation about the pathogenesis in this family and description of the treatment of these two patients will be given below.

60. Gershengorn MC, Weintraub BD. Thyrotropin-induced hyperthyroidism caused by selective pituitary resistance to thyroid hormone. J Clin Invest 56:633-642, 1975

61. Kourides IA, Ridgway EC, Weintraub BD, Bigos ST, Gershengorn C, Maloof F. Thyrotropin-induced hyperthyroidism: use of alpha and beta subunit levels to identify patients with pituitary tumors. J Clin Endocrinol Metab 45:534-542, 1977

62. Spanheimer RG, Bar RS, Hayford JC. Hyperthyroidism caused by inappropriate thyrotropin hypersecretion. Arch Intern Med 142:1283-1286, 1982

63. Rösler A, Litvin Y, Hage C, Gross J, Cerasi E. Familial hyperthyroidism due to inappropriate thyrotropin secretion successfully treated with triiodothyronine. J Clin Endocrinol Metab 54:76-82, 1982

64. Gharib H, Carpenter PC, Scheithauer BW, Service FJ. The spectrum of inappropriate pituitary thyrotropin secretion associated with hyperthyroidism. Mayo Clin Proc 57:556-563, 1982

65. Williams G, Kraenzlin M, Sandler L, Burrin J, Law A, Bloom S, Joplin GF. Hyperthyroidism due to non-tumoural inappropriate TSH secretion. Effect of a long-acting somatostatin analogue (SMS 201-995). Acta Endocrinol (Copenh) 113:42-46, 1986

66. Isales CM, Tamborlane W, Gertner JM, Genel M, Insogna KL. Effect of short-term somatostatin and long-term triiodothyronine administration in a child with nontumorous inappropriate thyrotropin secretion. J Pediatr 112:51-55, 1988

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68. Salmela PI, Wide L, Juustila H, Ruokonen A. Effects of thyroid hormones (T_4,T_3), bromocriptine and TRIAC on inappropriate TSH hypersecretion. Clin Endocrinol 28:497-507, 1988

69. Hamon P, Bovier-Lapierre M, Robert M, Peynaud D, Pugeat M, Orgiazzi J. Hyperthyroidism due to selective pituitary resistance to thyroid hormones in a 15-month-old boy: efficacy of D-thyroxine therapy. J Clin Endocrinol Metab 67:1089-1093, 1988

70. Sato M, Otokida K, Kato M. A case of hyperthyroidism caused by the syndrome of inappropriate secretion of thyroid stimulating hormone: association of primary hypergonadotropic hypogonadism. Jpn J Med 28:223-227, 1989

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72. Kunitake JM, Hartman N, Henson LC, Lieberman J, Williams DE, Wong M, Hershman JM. 3,5,3'-triiodothyroacetic acid therapy for thyroid hormone resistance. J Clin Endocrinol Metab 69:461-466, 1989

73. Chan AW, MacFarlane IA, van Heyningen C, Foy PM. Clinical hyperthyroidism due to non-neoplastic inappropriate thyrotrophin secretion. Postgrad Med J 66:743-746, 1990

74. Dorey F, Strauch G, Gayno JP. Thyrotoxicosis due to pituitary resistance to thyroid hormones. Successful control with D thyroxine: a study in three patients. Clin Endocrinol 32:221-228, 1990

B. Differential Diagnosis

In contrast to GRTH in which the differential diagnosis is primarily one of non-diseases such as an abnormality of thyroid hormone hormone binding to a variant albumin or an artifact of a circulating antibody or nonthyroidal illness, the differential diagnosis of PRTH includes usual hyperthyroidism and a TSH-secreting pituitary adenoma, two serious alternative diagnoses. As indicated in the above section, patients with PRTH lack the infiltrative ophthalmopathy and thyroid dermopathy typical of the most common form of hyperthyroidism, Graves' disease. In keeping with an entirely different pathogenesis of PRTH is the absence of thyroid-stimulating immunoglobulin in the serum of patients with PRTH (75). However, not all "usual" hyperthyroidism is Graves' disease (e.g. 10-15% toxic multinodular goiter or thyroiditis), not all patients with Graves' disease have ophthalmopathy, and thyroid-stimulating immunoglobulin is rarely measured in clinical practice. In ruling out the usual form of hyperthyroidism as the explanation for the patients elevated T_4 and T_3, the clinician is thus left with the serum TSH measurement.

Only in the last five or six years has the measurement of serum TSH been useful in the evaluation of suspected hyperthyroidism. The change was the

result of development of the immunoradiometric TSH assay which, unlike the old radioimmunoassay, is sensitive enough to detect TSH in normal subjects and to confirm that patients with usual hyperthyroidism have lower than normal levels. Most patients with usual hyperthyroidism in fact have undetectable serum TSH levels. However, it is important to know the quality of the TSH immunometric assay (IMA) available in your lab. Nicoloff and Spencer have stressed that functional sensitivity, defined as the concentration at which the interassay coefficient of variation is 20%, more accurately reflects the ability of a particular assay to distinguish the suppressed values of hyperthyroidism from the euthyroid levels than does the analytical sensitivity determined by intraassay replicate measurements of a blank (Fig. 10) (76). As shown in Fig. 10, some supposedly "sensitive" IMAs for TSH do not reliably distinguish usual hyperthyroid patients from normals (e.g. assays 10,11, and 12).

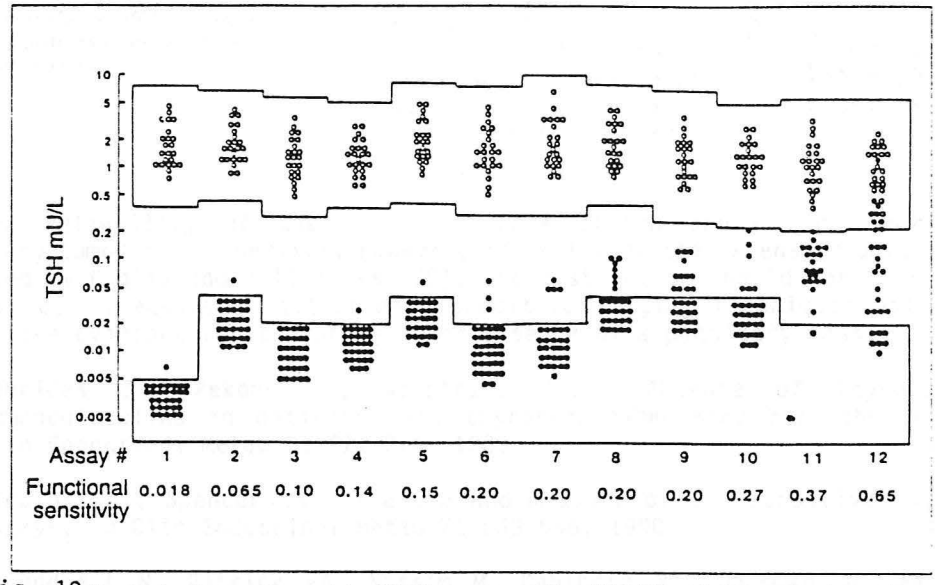

Fig. 10 Functional performance characteristics of 12 different commercially available IMAs with respect to their functional sensitivity[a] and their ability to differentiate between the same euthyroid (open circles) and clinically hyperthyroid (closed circles) sera. The open columns represent the mean ±3 SD for the euthyroid sera, while the upper margin of the shaded area represents the analytical sensitivity limit,[a] cited by the manufacturer. The assays are ordered (left to right) according to decreasing functional sensitivity (20% interassay CV) established from the interassay precision profiles constructed for each IMA from seven separate runs. (Reprinted from Nicoloff JT, Spencer CA,[34] with permission.)

Figure 10

The inability to confirm an "appropriately" low TSH in a patient with usual hyperthyroidism due to a poor quality assay could, of course, result in the incorrect conclusion that the patient's TSH was inappropriately normal and thus suggestive of PRTH.

The other condition of importance to exclude in the differential diagnosis is a TSH-secreting pituitary adenoma (77). Dr. Weintraub has been instrumental in the studies to clarify the distinction between these two causes of inappropriate TSH secretion and summarized the major criteria in an early review

(78). In essence, patients with a TSH-producing pituitary adenoma have: 1) failure of serum TSH to appropriately increase in response to TRH, 2) failure of serum TSH to decrease in response to suppressive doses of administered thyroid hormone, and 3) increased levels of the α-subunit of TSH with an α-to-TSH molar ratio greater than 1.0. The TSH, α, and TSHβ response to TRH in three patients with each disorder is shown in Fig. 11 (61).

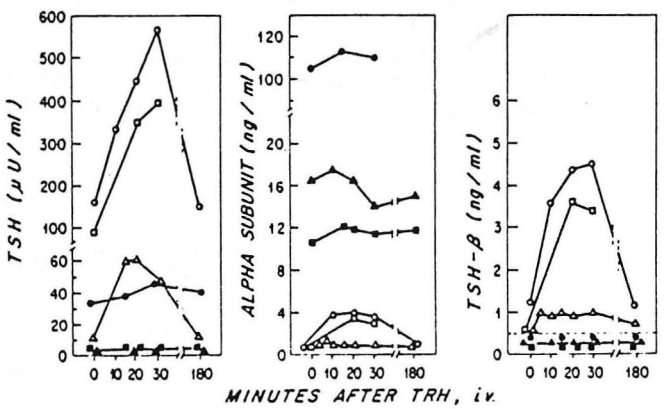

FIG. 11 Response of serum TSH, alpha subunit, and TSH-β to iv administered TRH in the three patients with a pituitary tumor (A ●, B ▲, C ■) and the three patients without a pituitary tumor (D ○, E △, F □). Five patients received 500 μg TRH; patient D received 200 μg TRH. Patient C was studied in 1971 after an inadequate hypophysectomy and radiotherapy.

Figure 11

The reliability of the three criteria stated above for identifying a pituitary tumor is not perfect. However, in reviewing the extensive data in tables computed by Faglia and colleagues (20), the distinction should not be a problem. Of course, in equivocal situations, sensitive imaging techniques will provide supportive evidence for the presence or absence of a pituitary mass.

75. Kourides IA, Pekonen F, Weintraub BD. Absence of thyroid-binding immunoglobulins in patients with thyrotropin-mediated hyperthyroidism. J Clin Endocrinol Metab 51:271-274, 1980

76. Nicoloff JT, Spencer CA. The use and measure of the sensitive thyrotropin assays. J Clin Endocrinol Metab 71:553-558, 1990

77. Gesundheit N, Petrick PA, Nissim M, Dahlberg PA, Doppman JL, Emrson CH, Braverman LE, Oldfield EH, Weintraub BD. Thyrotropin-secreting pituitary adenomas: clinical and biochemical heterogeneity. Ann Intern Med 111:827-835, 1989

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C. The Etiology of PRTH

There have been no reports of abnormal TRs in tissues or cells from patients with PRTH either in regard to hormone binding or DNA sequence. If one were to postulate which of the three TRs would be the likely candidate for a mutation causing PRTH, TRβ2 would seem to be the likely candidate since this TR appears to be limited to the pituitary. Thus an abnormal TRβ2 in the pituitary could either compete for TREs in the pituitary or form less than normally active

heterodimers with normal TR with defective transactivation as diagrammed in Fig. 9 with peripheral (i.e. non-pituitary) tissues responding normally to thyroid hormones.

An alternative etiology for PRTH has been suggested by observations in a few patients. Whereas most patients with PRTH respond to exogenous thyroid hormone, usually T_3, with only a partial lowering of basal or stimulated TSH levels, in one family replacement doses of T_3, i.e. 25µg t.i.d., resulted in normalization of T_4 and TSH within one week (Fig. 12) (63). Moreover, following the initial suppression, long-term treatment with a single morning dose of 37.5-50 µg T_3 resulted in normalization of both T_4 and T_3 in addition to TSH and resolution of any metabolic abnormality.

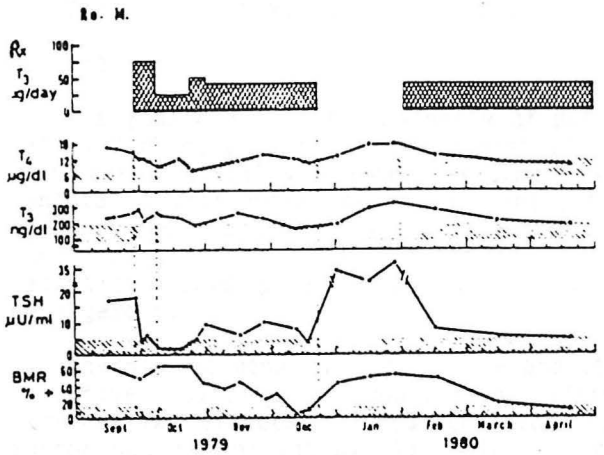

FIG. 12 T_4 suppression test (75 µg/day, in three divided doses) and effects of long term therapy with T_4 (37.5 µg/day, in one morning dose) in Ro.M. See Fig. 2 for more details.

Figure 12

Recall that T_3 formed from T_4 within the pituitary by 5'-deiodinase II is the more important source of T_3 to occupy nuclear TR in that tissue rather than T_3 in the circulation which is formed primarily in liver and kidney (8). Thus one could postulate that these patients had an impairment in the 5'-deiodinase that is specific to pituitary, brain and a few other tissues resulting in impaired negative feedback of the thyroid hormone and resultant inappropriate TSH secretion. Presumably, temporarily elevated serum T_3 levels following oral ingestion allow sufficient intrapituitary T_3 to saturate receptors in these patients.

There is another family reported to have suspected GRTH rather than PRTH who seemed to respond to 75 µg/day of T_3 but not 200 µg/day of T_4 with normalization of TSH (79). The index patient was evaluated only after three subtotal thyroidectomies, the first of which was done as an adolescent. She was described as developing symptoms of thyroid hormone excess on a combination of 100 µg T_4 and 20 µg T_3 daily in her 30s. This seems inconsistent with GRTH. The only other family members available to the authors were children with elevated thyroid hormones who were not clinically thyrotoxic. This may be similar to the youngest child in the just mentioned family with PRTH (63) who did not have symptoms of thyroid hormone excess (see above).

In light of the possibility of a pituitary 5'-deiodinase defect in my two patients, J.H. and A.H., I prescribed T_3 25 µg t.i.d. for each patient. After a little over three weeks on this regimen, in J.H. T_4 was 3.6 µg/dl and TSH 1.0 µU/ml and in A.H. T_4 was 6.6 µg/dl and TSH 0.1 µU/ml. The total T_3 was slightly above normal in J.H. and clearly elevated in A.H. (in keeping with her suppressed TSH). I thus changed the dose of T_3 to 50 µg/d in J.H. and 37.5 µg/d in A.H. and will assess long term response. When the gene for the 5'-deiodinase II is cloned it will be interesting to determine whether they have an abnormality.

79. Vandalem JL, Pirens G, Hennen G. Familial inappropriate TSH secretion: evidence suggesting a sisociated pituitary resistance to T_3 and T_4. J Endocrinol Invest 4:413-422, 1981

D. Therapy

The management of the majority of patients with PRTH (who do not respond to T_3) is difficult (80). Although most of the patients reported in the literature have been initially treated by some form of ablative thyroid therapy (i.e. subtotal thyroidectomy or radioiodine), this is not recommended because of the tendency for the continual TSH stimulation to result in regrowth of any residual functioning tissue. Moreover, if thyroid ablation were actually successful, TSH secretion would presumably increase to a level that might risk pituitary enlargement.

Thyroid hormone analogs or metabolites have been used with the hope of selective pituitary suppression without excessive peripheral thyroid hormone-like effects. 3,5,3'-triiodothyroacetic acid (TRIAC) has been used in Europe but is not yet available in this country (2,68,72). In the more recent report, although TRIAC reduced TSH and T_4, careful measurement of metabolic parameters indicated that no reduction in peripheral action of thyroid hormone could be demonstrated, i.e. the intrinsic peripheral action of TRIAC offset whatever decrease in thyroid hormone it produced (72).

D-thyroxine has been used in two reports (69,74). A 15 month old boy had an excellent response with relief of symptoms of thyrotoxicosis and normalization of T_4 and TSH. He was managed long term with 5 mg/day of D-T_4 (69). In three adults with PRTH, a dose of 2 mg/day of D-T_4 resulted in a sustained response for more than two years of therapy with normalization of TSH and a number of markers for peripheral thyroid hormone effects (74). The TSH levels in one of these patients on various regimens is shown in Fig. 13 (74).

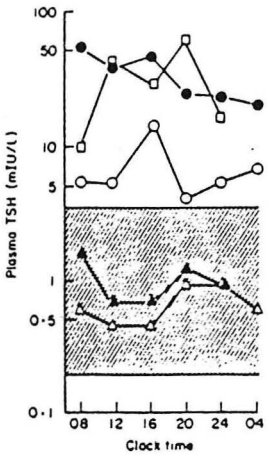

Fig. 13 Longitudinal measurements of TSH plasma levels over 24 h under medication in patient I □, ATD at the time of diagnosis; ●, ATD + bromocriptine for 6 months; ○, ATD + DT4 (1 mg t.i.d.) for 5 months; ▲, after DT4 alone (1 mg b.i.d.) for 5 months and △, for 15 months. The shaded area represents the normal range.

Figure 13

Dopamine agonists such as bromocriptine or pergolide have been used with variable success (68, 80). Short term success was followed by return of TSH elevations during prolonged bromocriptine therapy in one report (68). Somatostatin given by continuous intravenous infusion is successful in lowering TSH in PRTH (66). The use of the longer acting somatostatin analog, octreotide, has had little or no success in this form of inappropriate TSH secretion (71, 73). However, it has been very useful in TSH-secreting pituitary tumors (71,80).

80. Petrick PA, Weintraub BD. Inappropriate secretion of thyroid-stimulating hormone. In: Current Therapy in Endocrinology and Metabolism 4th Ed, C. Wayne Bardin ed, B.C. Decker Inc., Philadelphia, 1991 pp 44-49