Partial Target Organ Resistance to Thyroid Hormone

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ABSTRACT An 8-year old boy with a small goiter, normal basal metabolic rate (BMR), and elevated serum thyroid hormone levels (thyroxine [T_4] 19.5 μg per 100 ml, free T_4 4 ng per 100 ml, triiodothyronine [T_3] 505 ng per 100 ml) was studied. He had measurable serum thyroid-stimulating hormone (TSH) levels (average 5.5 μU per ml), and the thyroxine-binding proteins, hearing, and epiphyseal structures were normal. There was no parental consanguinity nor were there thyroid abnormalities either in the parents or six siblings.

Methimazole, 50 mg daily, depressed thyroxine synthesis (T_4 10.5, free T_4 2.5) and caused a rise in TSH to 11 μU per ml. After discontinuation of treatment, TSH declined to 4.2 μU per ml and chemical hyperthyroidism returned (T_4 21.0 μg per 100 ml, free T_4 4.2, and total T_3 475 ng per 100 ml, radioactive iodine [RAI] uptake 68%), but studies of BMR and insensible water loss showed the patient to be clinically euthyroid. Thyrotropin-releasing hormone (TRH), 200 μg i.v., caused a brisk rise in TSH to 28 μU per ml, with T_4 rising to 28 μg per 100 ml, free T_4 to 5.6, and T_3 to 730 ng per 100 ml, thus indicating that the pituitary-thyroid system was intact and that the patient's TSH was biologically active. The unusual sensitivity of the pituitary cells to TRH in spite of the markedly elevated serum thyroid hormone levels also suggested that the pituitary was insensitive to suppression by T_3 or T_4. Serum dilution studies gave immunochemical evidence that this patient's TSH was normal. Neither propranolol, 60 mg, chlorpromazine, 30 mg, nor prednisone, 15 mg daily, influenced thyroid indices. Steroid treatment, however, suppressed the pituitary response to TRH. T_3 in doses increased over a period of 12 days to as much as 150 μg daily caused a rise in serum T_3 to above 800 ng per 100 ml, a decline of T_4 to euthyroid levels (T_4 9.5 μg per 100 ml, free T_4 1.6 ng per 100 ml), suppression of the RAI uptake from 68% to 35%, and marked blunting of the responses to TRH, but the BMR and insensible water loss remained normal. The data suggest that the patient's disorder is due to partial resistance to thyroid hormone.

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INTRODUCTION

The concept of target organ unresponsiveness to hormone stimulation as first introduced to medicine by Albright, Burnett, Smith, and Parson (1) has now been extended to almost every endocrine system. A selective tissue resistance to thyroxine was postulated by Refetoff, DeWind, and DeGroot (2) to account for elevated protein-bound iodine (PBI)[1] levels, deaf mutism, stippled epiphyses, and goiter in three clinically euthyroid siblings. These patients have subsequently been reevaluated (3–5) and were found to be resistant to treatment with both thyroxine and triiodothyronine in high doses.

The subject of this report is an 8-year old boy who demonstrates partial peripheral resistance to thyroid hormone, but the disorder in this case is not accompanied by auditory or skeletal anomalies.

METHODS

Stimulation tests with synthetic thyrotropin-releasing hormone (TRH)[2] were performed with the patient fasting and at rest. TRH, 200 μg, was injected rapidly through an indwelling venous catheter kept in place for collection of blood samples for determination of serum thyrotropin (TSH) at -6, 0, 5, 10, 15, 20, 30, 45, 60, 120, and 180 min, and serum thyroxine (T_4), free T_4, and total triiodothyronine (T_3) at -6, $+60$, and $+180$ min. The

[1] *Abbreviations used in this paper:* BMR, basal metabolic rate; LATS, long-acting thyroid stimulator; PBI, protein-bound iodine; RAI, radioactive iodine; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TRIAC, triiodothyroacetic acid; TSH, thyroid-stimulating hormone (thyrotropin).

[2] Provided by M. S. Anderson, M.D., Department of Clinical Research, Abbott Laboratories, Chicago, Ill. 60064.

patient complained of slight nausea within 15 sec after infusion of TRH, and this symptom subsided spontaneously in less than 1 min. He also had enuresis during the first infusion. The TSH radioimmunoassay was a modification of the method of Odell, Wilber, and Utiger (6). TSH[3] was labeled with ^{125}I (specific activity 50–100 μCi per μg) by the method of Hunter and Greenwood (7), and the [^{125}I] TSH was purified by gel chromatography on Sephadex G-100. Duplicate serum samples or TSH standards[4] containing an equivalent amount of hypopituitary serum were preincubated with the antihuman TSH (anti-hTSH) for 24 h to 48 h at 4°C before the addition of approximately 0.05 ng [^{125}I]TSH. After a further 72 h incubation, antibody-bound TSH was precipitated within 24 h by the addition of appropriate amounts of goat antirabbit gamma globulin. The tubes were centrifuged, the supernates decanted, and the precipitates counted in a standard auto gamma spectrometer. Less than 2% of the radioactivity was nonspecifically precipitated in tubes without anti-TSH, and greater than 80% was precipitated with excess anti-TSH. The sensitivity of the method was less than 0.5 μU per ml serum, and the range of values found in serum of normal individuals was 0.5–6 μU per ml with a mean of 1.8 μU per ml.

Serum T_4 was measured by the method of Cassidy, Benotti, and Pino (8) and free T_4 by a modification of the method of Sterling and Brenner (9). The assay for total T_3 was accomplished by the method of Sterling, Di Bellabara, Newman, and Brenner (10) as modified by Benotti, Grimaldi, Pino, and Maloof (11).[5] Long-acting thyroid stimulator (LATS) assay was performed by the mouse bioassay procedure (12), and the thyronine-binding proteins were determined by a modification of the technique of Elzinga, Carr, and Beierwaltes (13).

CASE REPORT

E. M. (Massachusetts General Hospital (MGH) Unit no. 165-87-67), an 8-year old white male, was referred to the Pediatric Clinic of the Massachusetts General Hospital for evaluation of his learning disability. His developmental milestones had been normal during early childhood. He entered kindergarten at age 6, was not promoted, and after 2 yr was transferred to special classes. He was described as hyperactive, had temper tantrums, and suffered from enuresis. He had been born after a full-term, uneventful pregnancy, the fourth of six children of a 40-year old father of Irish-Scottish descent and an unrelated 30-year old Portuguese mother. Neither the parents nor the siblings had physical or laboratory evidence of thyroid dysfunction. Sensory neural deafness was present on the maternal side of the family (Fig. 1), but there was no evidence by history of goiter, thyroid dysfunction, or nystagmus. On physical examination, the patient was a well-developed, well-nourished boy at the 50th percentile in height (131.6 cm) and the 25th percentile in weight; he had a normal head circumference, normal body proportions with a upper/lower body segment ratio of 1.02 and an arm span of 130 cm. The blood pressure was 110/70, pulse 88 per min, and the oral temperature was 36.8°C. The thyroid was diffusely enlarged, estimated at twice normal size, soft, and without nodules. A small pyramidal lobe was palpable. There was no bruit. There was no exophthalmos, lid lag, muscle weakness, tremor, or other obvious signs of hyperthyroidism. His skin was not abnormally smooth or warm. There was no erythema or onycholysis. The neurological and audiometric examinations were normal. Cortical function tests showed mild retardation with an IQ of 78. A skeletal survey disclosed a bone age of 8 yr and no evidence of epiphyseal abnormalities.

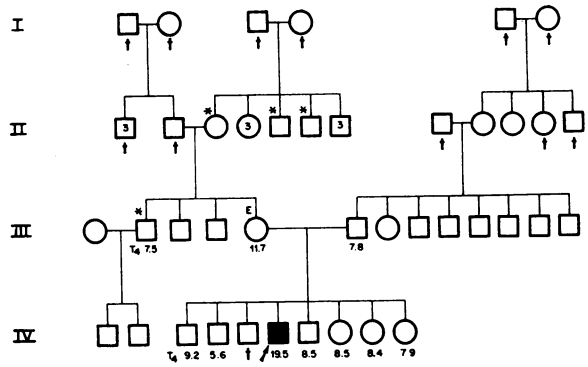

FIGURE 1 Pedigree of patient E. M. The data appear to exclude a dominantly inherited anomaly save for the possibility of a new mutation. T_4 levels are given by the numbers adjacent to the symbols for the family members available for study. There was no clinical or laboratory evidence of thyroid disease in the proband's siblings, parents, or one maternal uncle. His mother was on estrogen therapy (E) and had an elevated level of TBG (35 μg per 100 ml). One older brother had died from a brain tumor. In generations II and III, four members (indicated by asterisks) developed progressive sensory neural deafness in the fourth decades of their lives.

[3] Purified hTSH for labeling and rabbit anti-hTSH were supplied by the National Pituitary Agency.

[4] Human thyrotropin research standard B was supplied by the Medical Research Council, Mill Hill, England.

[5] Determinations of T_4 and T_3 by radioimmunoassay (14) were carried out on two blood samples collected from the patient, the first before and the second shortly after beginning treatment with methimazole. The results were as follows:

Sample	Method...	T_4 RIA(14)	T_4 Chrom.(8)	T_3 RIA(14)	T_3 CPB(11)
		μg per 100 ml		*ng per 100 ml*	
1		20.0	19.6	252	415
2		16.8	15.8	220	330

The T_4 values are in close agreement; the T_3 values show the discrepancy expected from the fact that in normal controls, T_3 by radioimmunoassay (RIA) averages 65% of the values found by competitive protein binding (CPB). (11, 14).

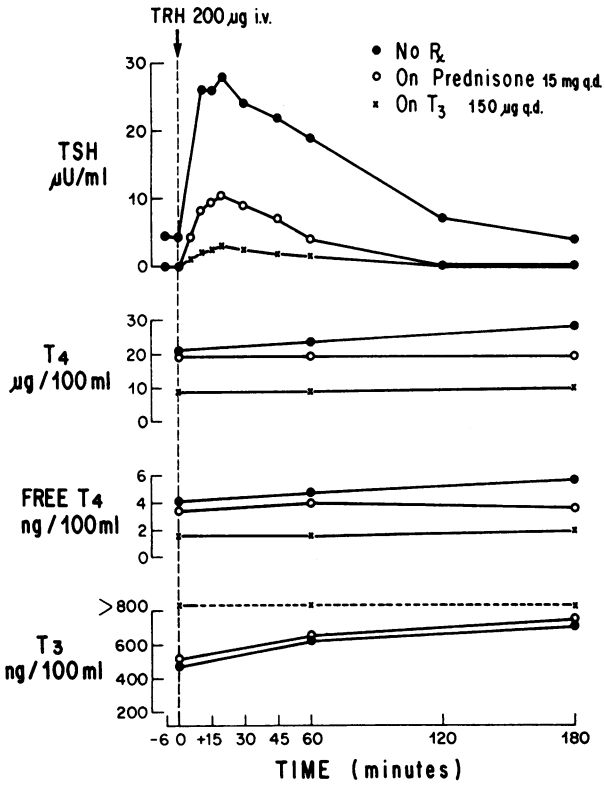

FIGURE 2 Suppression by prednisone and T_3 of TSH responses to TRH infusion. In each circumstance the peak TSH response is seen at the normal time at 20 min in contrast to the delayed response observed in patients with hypothalamic disease (17). Note the high normal TSH levels before and at the end of the infusion test during the control period. The rises in T_4, free T_4, and T_3 are abnormally great during the control study. Prednisone did not alter the concentration of T_3. The minimal rise of TSH during treatment with high doses of T_3 suggests that the patient has partial target organ resistance to thyroid hormone.

RESULTS

Initial studies of thyroid function showed: T_4 19.5 μg per 100 ml (normal 4–11); free T_4 4.0 ng per 100 ml (normal 0.8–2.4); TSH readily measurable at 4.8 μU per ml; the serum contained no LATS activity or antibodies against thyroglobulin, thyroid microsomal or cytoplasmic antigens; the thyroxine-binding proteins were normal (T_4-binding globulin [TBG] 15 μg per 100 ml; T_4-binding prealbumin [TBPA] 201 μg per 100 ml) and the serum cholesterol was 200 mg per 100 ml. On reevaluation 1 mo after the first visit, signs of hyperthyroidism were again absent. At this time in response to leading questions the patient's mother gave the additional history of polyphagia, frequent bowel movements, and episodic hyperhidrosis. This plus the persistently elevated serum thyroxine concentration led to a diagnosis of thyrotoxicosis and initiation of treatment with methimazole, 50 mg, given in a single daily dose. After 1 mo of therapy, the serum thyroxine concentration fell to levels in the high normal range (T_4 10.5 μg, free T_4 2.5 ng per 100 ml); TSH rose to 11.0 μU per ml.

Because of a skin rash, the daily methimazole dose was reduced to 30 mg whereupon there was a prompt return of the thyroid indices to thyrotoxic levels (T_4 18.0 μg, free T_4 3.4 ng per 100 ml). The patient's circulating serum TSH averaged 5.5 μU per ml, a level significantly higher than we or others (15–18) have observed in the usual patients with thyrotoxicosis assayed against standards diluted in serum from patients with hypopituitarism (< 0.5–1.5 μU per ml).

In order to study this boy's pituitary TSH secretion, he received an i.v. injection of TRH, 200 μg. Because TRH has been found to be ineffective in stimulating TSH secretion in patients with hyperthyroidism or during treatment with full doses of T_4, it was felt that this test would be helpful in discriminating between hyperkinesis on the basis of minimal brain dysfunction and clinically subtle Graves' disease. The patient responded with a substantial rise in serum TSH. Furthermore, there was a brisk secondary burst in the secretion of T_4, free T_4, and T_3, serum concentrations of the latter increasing more than is expected in the normal individual (Fig. 2) and proving the biological activity of the released TSH. In addition, dilutions of serum drawn at the peak of the TSH rise showed its behavior in the radioimmunoassay system to be similar to that of the reference standard, thus suggesting immunochemical identity of the two TSHs.

In order to rule out intracranial pathology, other studies of anterior pituitary function, radiographs of the skull, and an assessment of the visual fields were obtained and found to be normal. Treatment with T_3 in an oral dose of 12.5 μg given every 8 h caused a rapid fall of T_4 from 21.0 to 14.0 μg per 100 ml within 3 days but did not cause a significant further decline when this therapy was extended over a period of 7 days (T_4 13.5 μg per 100 ml). The TSH level during this suppression test decreased from 4.2 μU per ml to below 1.0 at 3 days and was 1.4 μU per ml on the 7th day. Inasmuch as the boy's mother volunteered that his symptoms worsened during the treatment with T_3 he was discharged on propranolol, 60 mg daily, in three divided doses. This did not interfere with the return of his thyroid indices to presuppression levels. Because of its TSH-inhibiting effect on the thyroid in vitro (19) and because of its inhibition of fright-induced thyrotoxicosis in animals (20, 21), chlorpromazine, 30 mg daily in three divided doses, was next added to his medication. This program likewise failed to alter the thyroid indices or to suppress the thyroidal uptake of ^{99m}Tc, the uptake at 1 h being 16% (normal control 4%). While on the com-

bined treatment with propranolol and chlorpromazine, however, the patient's enuresis disappeared. His mother reported him less hyperactive but still not as well "controlled" as during treatment with methimazole.

A second hospitalization was arranged to carry out further investigations of the paradox of persistent chemical hyperthyroidism with measurable circulating TSH but apparent euthyroidism. Studies were designed to evaluate critically his metabolic state, to assess the influence of glucocorticoids on his hypothalamic-pituitary axis and to document more thoroughly the suppressive effect of exogenous T_3 in various doses. Daily BMR patient was cooperative and highly reproducible measurements of overnight insensible water loss (22). The measurements were obtained and complemented by measurements of BMR were obtained varying only between + 5 and + 12% even during T_3 treatment (Fig. 3). Insensible water losses were measured overnight on a Brookhaven metabolic scale and also showed normal values ranging between 21 and 25 g/m² per h in a room temperature of 23°C. No polyphagia, increased perspiration, or bowel frequency of hyperactivity was evident despite careful observation. No emotional instability or hyperkinetic behavior was observed in the hospital pediatric ward environment.

Prednisone, 5 mg given every 8 h for 7 days, failed to alter thyroid indices but was associated with a diminished TSH response to TRH (Fig. 2). During prednisone treatment, TRH provoked no change in T_4; the rise in T_3, however, paralleled that of the first test. The patient was then placed on increasing doses of T_3 beginning with 12.5 μg every 8 h and culminating with 50 μg every 8 h on the 10th day. Just before this therapy his radioactive iodine (RAI) uptake was 68%. During the period of T_3 treatment TSH was suppressed and serum T_4 and free T_4 gradually declined with concomitant rises in serum T_3 (Fig. 3). On the 10th day of T_3 administration, repetition of the 24 h RAI uptake gave a value of 35%. The patient did not become clinically hyperthyroid and maintained a stable weight, his self-selected caloric intake underwent no change, averaging 1100 cal/m² per day, and he showed no significant elevations in BMR or insensible water loss. However, the T_3 dose of 50 μg every 8 h was sufficient to suppress the response to TRH (Fig. 2). 2 wk after discontinuation of the T_3 treatment, his thyroid indices had returned to pretreatment levels.

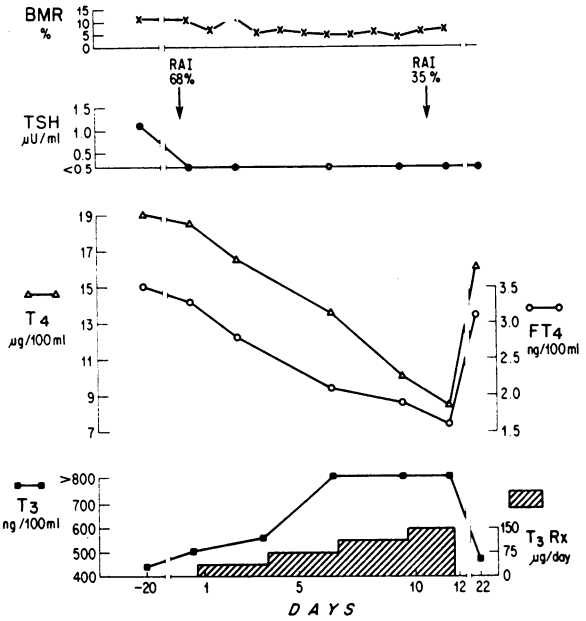

FIGURE 3 Effects of increasing doses of T_3 on thyroid parameters. Before treatment with T_3, the elevated values for RAI uptake, serum T_4, free T_4, and T_3 suggested hyperthyroidism; the BMR, however, was normal. The serum contained TSH in normal measurable amounts when sampled 20 days before treatment, although it was not measurable on the day of initiation of T_3. With gradually increasing doses of T_3 to 150 μg daily, serum T_3 levels rose above 800 ng per 100 ml. The serum T_4 and free T_4 concentrations showed reciprocal falls reaching euthyroid levels. TSH and the RAI uptake declined. The BMR remained normal throughout. The TRH infusion test of Fig. 1 was done on the 10th day of this suppression test.

DISCUSSION

This boy with goiter, mild mental retardation, and elevated circulating levels of bound and free thyroid hormone was judged initially to have thyrotoxicosis. The presenting complaints of poor school performance and hyperactivity were consistent but nonspecific; it was not until after discovery of the elevated thyroid indices that his mother gave the additional history of polyphagia, loose stools, and excessive sweating, and these symptoms were acknowledged only in response to leading questions. Clinical signs of hyperthyroidism were absent and none of the alleged symptoms could be substantiated during two periods of careful observation in the hospital. Measurements of BMR and insensible water loss indicated that the patient was in a normal metabolic state. We believe, therefore, that his behavioral abnormalities were independent of the thyroid anomaly and attributable to minimal brain dysfunction.

The usual biochemical parameters of thyroid status suggested that he was hyperthyroid. He had elevated serum levels of total and free T_4 and total T_3 in the absence of abnormally elevated binding proteins. The absence of LATS and thyroidal antibodies could not be taken to exclude this diagnosis. Inconsistent with the usual findings in patients with Grave's disease, however, were the persistently measurable serum levels of TSH which responded as in normal subjects to administered TRH. Although thyrotoxicosis due to excessive TSH secretion by a pituitary tumor has been observed

in a few patients (23), the presence of pituitary tumor in this boy was highly unlikely considering the normality of the studies of nonthyroidal pituitary function, skull films, visual fields, and electroencephalograms. Stimulation of the pituitary from higher brain centers was still a possibility, especially in view of the patient's alleged behavioral abnormalities. While such a disorder has not been reported in humans, there is a model in the fright-induced thyrotoxicosis of wild hares observed by Kracht and Kracht (20) and by Milin and Stern (21). These investigators showed that captive wild hares stressed by intermittent exposure to dogs rapidly developed symptoms of thyrotoxicosis with elevated uptakes of RAI. The animals succumbed within 3 wk unless treated with propylthiouracil or chlorpromazine. Consideration of a similar type of central hyperthyroidism in this boy led to the therapeutic trial of chlorpromazine. While this was said to be effective in correcting his hyperkinetic behavior and enuresis at home, it failed to change the thyroid indices and thus could not be considered to have been exerting an effect similar to that exhibited in the hares.

Hyperthyroidism due to an unusual thyroid stimulator such as described in molar pregnancies (24) was ruled out by the fact that in the mouse bioassay the patient's serum caused stimulation of ^{131}I release only at 2 h as is typical of pituitary TSH. A TSH-producing tumor was incompatible with the patient's clinical course and the integrity of the pituitary feedback mechanism as shown by suppression of serum TSH and T_4 concentrations during treatment with T_3 and the elevation of TSH during treatment with methimazole.

The results of the studies carried out in this boy provide strong evidence that his basic endocrine defect is decreased responsiveness to circulating thyroid hormone. Subnormal target organ responsiveness included the pituitary, for the negative feedback effect of his high circulating thyroid hormone levels was usually weak. Nonetheless, despite the upward displacement of his euthyroid "set point," the boy responded in a qualitatively normal fashion to all of the pharmacological manipulations employed. When his thyroid hormone synthesis was blocked by methimazole, his circulating thyroxine fell and there was an increased secretion of TSH reflecting a compensatory response of the pituitary. By history, his hyperkinesis improved despite our inability to obtain objective clinical or laboratory measures to support the assumption that he had become mildly hypothyroid. During T_3 treatment, his own hormone production lessened and the stability of intrathyroidal ^{131}I content and decline of radioactivity in urine indicated that iodine turnover was decreased. Furthermore, thyroidal iodine uptake in the tracer study done at the end of T_3 treatment was diminished, TSH was undetectable in serum, and the pituitary became less sensitive to TRH stimulation.

One of the studies conducted in this patient relative to the control of TSH secretion, namely that concerning the effect of prednisone on the response to TRH, yielded information which may be of general clinical importance. The patient responded to exogenous prednisone with a blunting of his response to TRH but no change in the levels of circulating thyroid hormone. This suggested a direct effect of the glucocorticoid on his pituitary. Hitherto, the effect of prednisone to suppress TSH secretion and thyroidal iodine release has usually been interpreted as due to the drug's interference with secretion of TRH (25, 26). This assumption is based on the observation that in rats treated with glucocorticoid, responsiveness to administered TRH is retained. In the human being, however, there may be a direct effect of prednisone on the pituitary. The data obtained in this patient suggest that prednisone is capable of decreasing the sensitivity of the pituitary to TRH, but inasmuch as there was no change in the concentration of circulating thyroid hormone, that this is accomplished by means other than by potentiating the direct negative feedback action of T_4.

The present case shares certain similarities with the patients of Refetoff et al. (2, 5) but differs from them in several other aspects (Table I). The circulating thyroid hormone levels of their three siblings were elevated in a fashion similar to those of the present case and small goiters were present. Short-term glucocorticoid treatment decreased the sensitivity to TRH stimulation in our patient while their cases showed a decrease in thyroidal iodine secretion (4). On the other hand, our patient was euthyroid by objective metabolic parameters whereas those of Refetoff et al. (2, 5) had a number of signs of hypothyroidism. Deaf mutism, congenital nystagmus, epiphyseal dysplasia, and delayed bone age were all absent in our patient and we found no evidence of a familial defect. Our patient showed qualitatively normal endocrine responses to methimazole and T_3 administration. By contrast, in their patients the TSH levels were little affected and BMR, caloric intake, and weight gains were uninfluenced by exogenous T_3, T_4, and antithyroid drugs in doses much higher than were needed to bring about readily documented chemical effects in our patient. Thyroid hormone administration to their patients did, nonetheless, correct a few laboratory parameters suggestive of hypothyroidism such as the decreased urinary excretion of creatinine, creatine, and hydroxyproline. On the other hand, it caused weakness, tremor, and cardiac gallop, suggesting to the authors variation in the response to thyroid hormone of different organ systems.

In both their cases and ours, orally administered T_3 caused a decline in T_4 and in the elevated RAI uptakes.

TABLE I

Comparison of the Prominent Features of the Cases with Target Organ Resistance to Thyroid Hormone

	Refetoff et al. (5)	E. M., MGH no. 158-87-67
Physical findings		
Goiter	Present	Present
Tachycardia	Present	Absent
Deaf mutism, nystagmus	Present	Absent
Stippled epiphyses and delayed bone age	Present	Absent
Genetics	? Autosomal recessive	Unknown
Thyroid studies		
PBI, T_4, free T_4, T_3	Elevated	Elevated
TSH	Detectable	Detectable
RAI uptake	Elevated	Elevated
TBG, TBPA	Normal	Normal
LATS, antibodies	Negative	Negative
BMR	Normal	Normal
T_3 (T_4) suppression test	Decreased RAI uptake and T_4	Decreased RAI uptake, serum TSH, and T_4
Response to antithyroid drugs	None	Fall of serum T_4 and T_3, rise of TSH
Response to KI or TRIAC	Decreased RAI uptake	Not tested
Response to prednisone	Decreased thyroidal iodine secretion (4)	Decreased sensitivity to TRH
Response to TRH	Not tested	Diagnostic for T_3 and T_4 resistance

Refetoff et al. (5) also succeeded in suppressing thyroidal uptake to hypothyroid levels using KI and triiodothyroacetic acid (TRIAC), a metabolic product of T_3 which is less potent than the hormone (*27*). They suggest that possibly these effects of TRIAC and KI in reducing the thyroidal RAI uptake were artifactual, being simply due to an increase in the quanitity of iodide in which the isotope was diluted. In as much as the iodine content of these compounds in the doses used equalled that of the thyroid hormone given during the suppression tests, they also considered that the decline in radioiodine uptake in the latter could have been attributable to dilution rather than to hormonal feedback inhibition of the pituitary. The decline in serum TSH levels and the blunted response to TRH during T_3 treatment makes a similar mechanism unlikely in our patient. Because the methods employed by Refetoff et al. (5) differ significantly from those used in our study, a strict comparison is precluded. Therefore, at the present time, it is impossible to determine if the present patient represents a variant of the syndrome reported by Refetoff et al. (5), characterized by a lesser degree of resistance to thyroid hormone, or a wholly different entity.

Demonstration of pituitary insensitivity to the negative feedback action of thyroid hormones would appear to be a prerequisite for postulation of a syndrome of target organ resistance presenting with goiter and high levels of circulating thyroid hormones. The reduction of the TSH secretory response to TRH by administration of T_3 provides a sensitive in vivo assay for such hormone resistance. The results shown in Fig. 2 appear to justify the conclusion that the basic disorder of the present patient is one of subnormal responsiveness to thyroid hormone.

"Pseudohyperthyroidism" such as appeared to be present in our patient might be explained in at least three ways: defective conversion of T_4 to T_3 in the pituitary and the periphery; secretion of a chemically abnormal thyroid hormone, e.g., the D-isomer of thyroxine; or by target organ resistance to biologically normal hormone. A tissue defect in converting T_4 to T_3 seemed not to be present in view of the patient's high serum content of T_3 in the absence of treatment. This and the second possibility are rendered even more unlikely because in such circumstances exogenous T_3 sufficient to raise levels well into the range of T_3 thyrotoxicosis (28) would have been expected to increase the patient's metabolic rate and completely to suppress his pituitary TSH secretions and thyroid hormone synthesis. In this boy, however, we found no change in metabolic rate, only partial suppression of serum T_4 and incomplete inhibition of the pituitary response to TRH. Furthermore, the RAI uptake fell only from hyperthyroid to euthyroid values. Thus, partial tissue resistance to biologically normal hormone is the most likely explanation of the patient's condition.

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