Thyrotropin-Induced Hyperthyroidism Caused by Selective Pituitary Resistance to Thyroid Hormone

A NEW SYNDROME OF "INAPPROPRIATE SECRETION OF TSH"

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ABSTRACT An 18-yr-old woman with clinical and laboratory features of hyperthyroidism had persistently elevated serum levels of immunoreactive thyrotropin (TSH). During 11 yr of follow-up there had been no evidence of a pituitary tumor. After thyrotropin-releasing hormone (TRH), there was a marked increase in TSH and secondarily in triiodothyronine (T_3), the latter observation confirming the biologic activity of the TSH. Exogenous T_3 raised serum T_3 and several measurements of peripheral thyroid hormone effect, while decreasing serum TSH, thyroxine (T_4), and thyroidal radioiodine uptake. After T_3, the TRH-stimulated TSH response was decreased but was still inappropriate for the elevated serum T_3 levels. Dexamethasone reduced serum TSH but did not inhibit TRH stimulation of TSH. Propylthiouracil reduced serum T_4 and T_3 and raised TSH. This patient represents a new syndrome of TSH-induced hyperthyroidism, differing from previous reports in the absence of an obvious pituitary tumor and in the responsiveness of the TSH to TRH stimulation and thyroid hormone suppression. This syndrome appears to be caused by a selective, partial resistance of the pituitary to the action of thyroid hormone.

This case is also compared with previous reports in the literature of patients with elevated serum levels of immunoreactive TSH in the presence of elevated total and free thyroid hormones. A classification of these cases, termed "inappropriate secretion of TSH," is proposed.

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INTRODUCTION

Serum thyrotropin (TSH)[1] is usually suppressed in clinical disorders associated with the hypersecretion of thyroid hormones, thyroxine (T_4), and triiodothyronine (T_3) (1-4). However, recently the combination of elevated serum TSH and thyroid hormones has been described in a few patients. Even this small group appears heterogeneous, since clinical features of the patients and proposed pathogenesis of the TSH hypersecretion differ. Hamilton, Adams, and Maloof (5), Faglia et al. (6), O'Donnell, Hadden, Weaver, and Montgomery (7), and Mornex et al. (8) studied patients with pituitary tumors, hypersecretion of TSH and hyperthyroidism, while Hamilton and Maloof (9) described a similar patient who also had acromegaly.[2] Refetoff, DeGroot, Benard, and DeWind (10, 11), Bode, Danon, Weintraub, Maloof, and Crawford (12), and Lamberg (13) have described clinically euthyroid patients with elevated serum thyroid hormones and TSH who appear to have varying degrees of tissue resistance to the action of thyroid hormones and elevated serum TSH. More recently, Emerson and Utiger (14) reported a patient with hyperthyroidism and elevated serum TSH but without evidence of a pituitary tumor. In their case

[1] *Abbreviations used in this paper:* PBI, protein-bound iodine; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

[2] In this paper the designation "TSH" is restricted to hormone measured by specific radioimmunoassay. Before the availability of radioimmunoassay, TSH was measured by relatively nonspecific bioassays, which did not always differentiate among various thyroid-stimulating substances. Several older reports that showed an association of pituitary tumor, hyperthyroidism, and increased serum thyroid-stimulating activity are not considered in this paper.

the relatively autonomous TSH hypersecretion was thought to result from excessive pituitary stimulation by an endogenous releasing factor, possibly thyrotropin-releasing hormone (TRH).

In the patient described herein, hyperthyroidism appears to be caused by excessive thyroidal stimulation by TSH, which remains partially responsive to both normal stimulatory and inhibitory factors. The principal abnormality appears to be a selective resistance of the pituitary to suppression by thyroid hormones.

CASE REPORT

S. F. (NIH 053533), a 7-yr-old white girl, was referred to the National Institutes of Health in December 1963, because of hyperkinesia, decreased attention span, and excessive sweating. She was the product of a normal gestation, weighed 5 lbs, 8 oz., and appeared entirely normal at birth, and attained her developmental milestones normally. Upon entering kindergarten she was found to have a learning disability, subsequently diagnosed as a specific dyslexia. Before her initial evaluation at the NIH, her only medical illness had been rubeola. There was no family history of thyroid disease. She was mildly hyperactive with a resting pulse rate of 110/min, and her height was 117 cm (just over the 10th percentile). She weighed 17.6 kg (just below the 3rd percentile). She had widened palpebral fissures but no proptosis or lid lag. Her palms were warm and moist, and the deep tendon reflexes were hyperactive. The thyroid gland was soft, symmetric, nontender, and minimally enlarged. Protein-bound iodine (PBI) was 14.4 μg/dl (normals 4.0-8.0), T_4 was 19.7 μg/dl (normals 4.6-10.7), thyroxine-binding globulin binding capacity was 18.5 μg T_4/dl (normals 15-25), and radioiodine uptake was 55% at 24 h (normals 10-35).

Treatment with methimazole, 60 mg/day, was begun, and the patient became euthyroid within 2 mo. 4 mo later her thyroid gland enlarged, and thyroid studies revealed a PBI of 3.4 μg/dl and a T_4 of 2.6 μg/dl. Methimazole was continued at the same dose, and T_3, 50 μg/day, was added. For the next 3½ yr she was followed regularly in the outpatient department. She was treated with methimazole in doses varying from 40 to 120 mg/day and thyroid hormone with little change in symptoms or thyroid size. In July 1969, she developed pruritus and urticaria. These were thought to be manifestations of an allergic reaction to the medication, and it was discontinued. Therefore, in September, 1969, after preoperative preparation with potassium iodide and propylthiouracil, a near-total thyroidectomy was performed elsewhere. At operation, a 257-g goiter was removed, and a minimal amount of thyroid tissue was left *in situ*. Histologic examination revealed diffuse parenchymatous hyperplasia and two adenomatous nodules.

Postoperatively, while receiving no medication, she appeared euthyroid, her PBI was 8.0 μg/dl, and her T_4 was 8.1 μg/dl. However, within 10 mo, the patient redeveloped mild symptoms of hyperthyroidism, and the thyroid gland enlarged to approximately four times normal. At that time PBI was 13.8 μg/dl, and T_4 was 15.1 μg/dl. Propylthiouracil therapy was reinstituted in July 1970 and continued through September 1971, when she was lost to follow-up. She was next seen in August 1972, and although she volunteered no specific complaints, a goiter was present and her serum hormone levels were in the hyperthyroid range: T_4 was 15.9 μg/dl and free T_4 was 3.5 μg/dl (normal 1.0-2.1). Propylthiouracil, 100 mg/day, was reinstituted, and within 3 mo the serum hormone levels returned to normal (T_4 was 7.0 μg/dl). In January 1974, while taking 50 mg/day propylthiouracil, she was entirely asymptomatic and appeared clinically euthyroid. However, her thyroid gland had enlarged. Serum hormone levels at that time were as follows: T_4 was 10.4 μg/dl, free T_4 was 2.3 ng/dl, T_3 by radioimmunoassay was 275 ng/dl (normals 90-160), and TSH was 26 μU/ml (normals < 0.5-3.5). Because of the enlarging thyroid gland, propylthiouracil was stopped, and 2 mo later serum thyroid hormone levels had increased: T_4 was 19.1, free T_4 was 3.5, T_3 was 355, and TSH had decreased to 9.2.

The patient was admitted to the NIH in August 1974 at age 18 for further study. She volunteered no complaints. She had undergone menarche at age 13 and had normal menstrual cycles. Her weight was 43.4 kg (just below the 3rd percentile), and her height was 150 cm (just below the 3rd percentile). Pulse was 85-95/min. Her skin was warm and dry. There were no signs of Graves' ophthalmopathy, no acropachy, and no pretibial myxedema. The thyroid gland was multinodular and enlarged, the right lobe measuring 4.0 × 4.5 cm and the left lobe measuring 3.0 × 4.0 cm. Her deep tendon reflexes were hyperactive. Routine laboratory studies were within normal limits. Her visual fields were full, and tomographic study of the sella turcica showed no enlargement or asymmetry. Audiogram was normal, and bone radiographs showed no stippled epiphyses. Thyroid scan showed an enlarged, asymmetric gland with nonhomogeneous distribution of radionuclide in both lobes.

METHODS

Serum TSH was measured by a double-antibody radioimmunoassay with a sensitivity of 0.5 μU/ml of serum; the range of normal values was < 0.5–3.5 μU/ml with a mean of 1.7 μU/ml (4). Serum T_4 was measured by competitive protein-binding analysis (15), and serum T_3 (16) and prolactin (17) were measured by radioimmunoassay. A variety of other hormone measurements and endocrine tests were performed by previously published methods (see references, Table II).

TABLE I
Thyroid Studies

Study	July 1969*	March 1974‡	May 1974§	August 1974‖	Normals
T_4, *μg/dl*	17.0	10.4	19.1	12.7	4.6–10.7
Free T_4, *ng/dl*		2.3	3.5	2.7	1.0–2.1
T_3, *ng/dl*		275	355	220	60–190
TSH, *μU/ml*	2.7	26	9.2	9.3	<0.5–3.5
Thyroxine-binding globulin capacity, *μg T_4/dl*				19	10–26
Anti-thyroglobulin antibodies				<1:16	<1:16
Antimicrosomal antibodies				<1:4	<1:4
Long-acting thyroid stimulator¶				neg	neg
Thyroidal ^{131}I uptake 4 h, %				26	5–15
24 h, %				43	10–35
[^{131}I]PB, *% dose/liter*				0.14	0.03–0.13
BMR, %				+20	−10 to +10
Pulse-wave arrival time, *ms***				135	186–235
Red cell sodium content, *mmol/liter cells*‡‡				9.4	6.1–8.4
Cholesterol, *mg/dl*				190	150–250
Urinary creatine, *mg/d*				35	<50

* Before thyroidectomy, 4 wk after stopping methimazole, and before beginning propylthiouracil.
‡ While taking 50 mg/day propylthiouracil.
§ 2 mo after stopping propylthiouracil.
‖ Basal studies just before T_3 suppression test.
¶ Gamma globulin fraction concentrated twofold.
** Performed by Dr. D. Rodbard.
‡‡ Performed by Dr. J. Gardner.

TRH, 500 μg, was injected rapidly i.v., and blood was collected at − 10, 0, 15, 20, 30, 45, 60, 120, and 180 min for measurement of TSH and at 0, 60, and 180 min for T_3. The peak TSH response in normals was 5–30 μU/ml; in hyperthyroid patients with Graves' disease, toxic multinodular goiter, or toxic adenoma, there was no TSH response detected, as previously reported (2–4).

RESULTS

Base-line studies. Basal thyroid function studies are outlined in Table I. All measurements of thyroid hormones were elevated (T_4 was 12.7 μg/dl, free T_4 was 2.7 ng/dl, T_3 was 220 ng/dl), and the binding proteins were normal (thyroxine-binding globulin capacity was 19 μg of T_4/dl). The TSH was not only absolutely elevated (9.3 μU/ml), but was particularly inappropriate relative to the elevated thyroid hormone levels normally associated with suppressed TSH (< 0.5 μU/ml) (1-4). Thyroidal hyperactivity was shown by elevated ^{131}I uptake (4-h was 26%, 24-h was 43%) and [^{131}I] PBI (0.14% of dose/liter at 48 h). Peripheral hyperthyroidism, that is excessive effect of thyroid hormone on peripheral tissues, was documented by elevated BMR of +20% (18), shortened pulse-wave arrival time (QK_4 interval) of 135 ms (19), and elevated red cell sodium content of 9.4 mmol/liter of cells (20).

Stimulation by TRH on day 2 (Fig. 1) resulted in a rise in serum levels of both TSH at 20 min to 62 μU/ml and T_3 to 420 ng/dl at 180 min. The TSH response was twice normal, similar to that usually seen in primary hypothyroidism (21). The rise in serum T_3, secondary to thyroidal stimulation by the TRH-liberated circulating TSH, indicated that the measured TSH was biologically effective and that the patient's thyroid gland was able to respond to it. In addition, the patient's TSH was immunologically identical to a pituitary TSH standard, as demonstrated by parallelism between curves generated with serial dilutions of the patient's serum and standard TSH in the radioimmunoassay.

The integrity of secretion of the other anterior pituitary hormones and their effectiveness at their respective target organs were studied both in the basal state and after provocative stimuli (22-24, Table II). Basal serum prolactin was slightly elevated, and there was an increased response to TRH. Basal serum growth hormone was normal, but the peak of stimulation after arginine and after insulin-induced hypoglycemia were both excessive. Gonadotropin response to luteinizing hormone releasing hormone and adrenocorticotropin response, as measured by the increase in serum cortisol to insulin-induced hypoglycemia, were normal.

Response to antithyroid drugs. The patient had been treated effectively with methimazole from January 1964

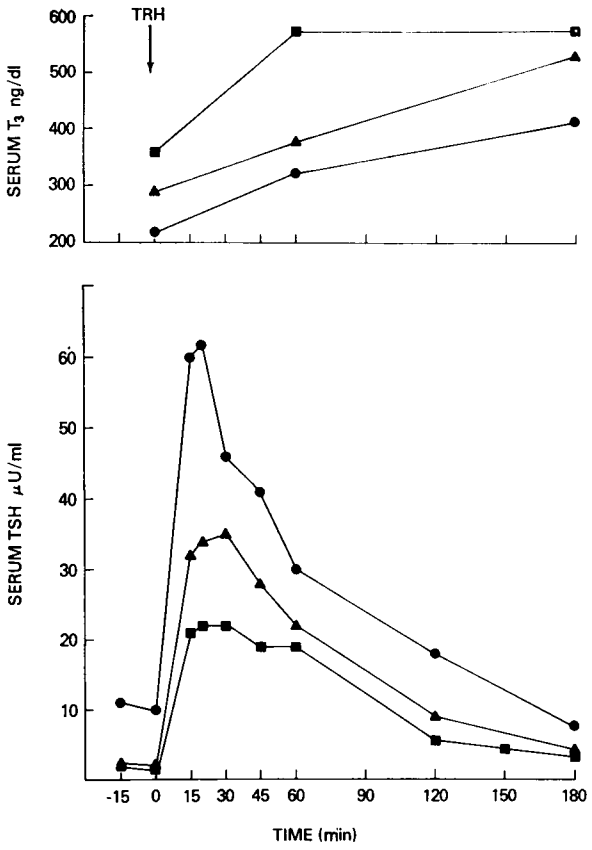

FIGURE 1 Effect of exogenous T_3 (see Fig. 2) on the serum TSH response to TRH stimulation. TRH, 500 μg i.v., was administered before T_3 therapy on day 2 (●), after 1 wk of T_3 on day 8 (▲), and after 2 wk of T_3 on day 15 (■). Basal and peak TSH levels were elevated during the control period and responded appropriately for euthyroid individuals during T_3 therapy. Hyperthyroid patients and normals treated with these doses of T_3 usually have undetectable basal TSH (< 0.5 μU/ml) and do not respond to TRH (see text). There was a significant TSH-induced release of endogenous T_3 in each test.

until the development of an allergic reaction in July 1969. After thyroidectomy drug therapy was reinstituted with propylthiouracil. In March 1974, while the patient was receiving 50 mg of propylthiouracil/day, her serum T_4 was 10.4 μg/dl, free T_4 was 2.3 ng/dl, T_3 was 275 ng/dl, and TSH was 26 μU/ml (Table I). 2 mo after propylthiouracil was stopped in May 1974, her serum T_4 had increased to 19.1 μg/dl, free T_4 to 3.5 ng/dl, and T_3 to 355 ng/dl, while the TSH decreased to 9.2 μU/ml. It is evident that when serum thyroid hormones were maintained at minimally elevated levels by antithyroid drug, serum TSH was markedly elevated and that only after discontinuing the medication when thyroid hormones had risen further, did the TSH level fall.

T_3 suppression. T_3 in increasing doses was administered to study the ability of exogenous thyroid hormone to suppress the pituitary (and secondarily the thyroid) and to stimulate peripheral tissue metabolism. During the 18-day period of T_3 administration, in doses of 25-100 μg/day, the patient experienced no aggravation of hyperthyroid symptoms. Serum T_3 measured in the morning 12 h after the previous dose of exogenous T_3 rose steadily from 220 to 390 ng/dl, while TSH declined from 9.3 to 2.0 μU/ml (Fig. 2). The serum T_3 was probably much higher than this minimal level through most of the day (25). The thyroidal response to the lowered circulating TSH concentration was manifested by a decline in the uptake of radioiodine at 4 h from 26 to 8% and at 24 h from 43 to 9% and as a progressive fall in the serum T_4 level from 12.7 to 6.6 μg/dl. However, the patient's overall metabolism appeared accelerated. BMR increased from +20 to +60%, and urinary creatine excretion increased from 35 to 340 mg/day. Other indices of peripheral tissue effects of thyroid hormone, including sleeping pulse rate, serum cholesterol, transaminase, and creatine phosphokinase, QK_d interval, red cell sodium content, and urinary excretion of hydroxyproline, were unchanged.

The degree of pituitary suppression achieved by the various T_3 dosages was further evaluated by repeated stimulation with TRH (Fig. 1). In an individual with a normal pituitary-thyroid axis, these levels of circulating T_3 would have completely inhibited both basal and stimulated pituitary TSH secretion (2–4). Although the patient's TSH response to TRH was partially blunted by the increasing level of circulating T_3, even at the highest T_3 level there was still a marked TSH response to TRH, a response appropriate for a euthyroid individual. Again, the immunoreactive TSH was bioactive, as shown by the further elevation of the T_3 60 min after i.v. administration of TRH. The serum prolactin level, by contrast, was not lowered basally, nor was there suppression of the prolactin response to TRH by exogenous T_3.

Dexamethasone administration. Dexamethasone, 2 mg every 6 h, was given for four doses to study the suppressive effect of glucocorticoids on TSH secretion. Although basal serum TSH fell from 12.4 to 4.5 μU/ml, the response to TRH was not suppressed. In fact, the peak TSH level of 68 μU/ml at 20 min was slightly higher than that achieved in the base-line study, even though the unstimulated level was lower (9.3 vs. 4.5 μU/ml). This response is similar to that reported in certain patients with primary hypothyroidism (21), although others have reported inhibition of both basal and peak TSH after dexamethasone (26).

TABLE II

Studies of the Secretion of Other Anterior Pituitary Hormones

Serum hormone	Basal value	Normals	Peak of stimulation	Normals
Prolactin, *ng/ml*	24	3.5–21	140*	14–70 (22)
Luteinizing hormone, *mIU/ml*	7.7	6–26‡	33§	32–190‖
Follicle-stimulating hormone, *mIU/ml*	2.7	2–16‡	9.7§	10–24‖
Estradiol, *pg/ml*	75	10–100‡		
Growth hormone, *ng/ml*	10	<1–10	210¶	18–27 (23)
			140**	10–77 (24)
Cortisol, *μg/dl*	17	6.9–19	23**	21–29 (24)

* TRH, 500 μg i.v.
‡ Follicular phase.
§ Luteinizing hormone releasing hormone, 100 μg subcutaneously.
‖ Rogol, A. D., and S. W. Rosen, unpublished data.
¶ Arginine 0.5 g/kg i.v. over 30 min.
** Insulin 0.1 U/kg i.v.

DISCUSSION

The patient described herein presents a new syndrome of hyperthyroidism secondary to chronic thyroidal overstimulation by TSH from a pituitary that retains responsiveness to thyroid hormone suppression and TRH stimulation. The patient's thyrotoxic state was first documented in December 1963, when she was only 7 yr old. Throughout the 11 yr of follow-up her condition responded to antithyroid chemotherapy and even remitted transiently in 1969 after surgical removal of over 98% of the thyroid gland, only to recur several months later with regrowth of the goiter. Recently, as during most of her course, the patient demonstrated only mild symptoms and signs of hyperthyroidism. Therefore, although this patient did not have deaf-mutism, delayed bone maturation, or stippled epiphyses, as

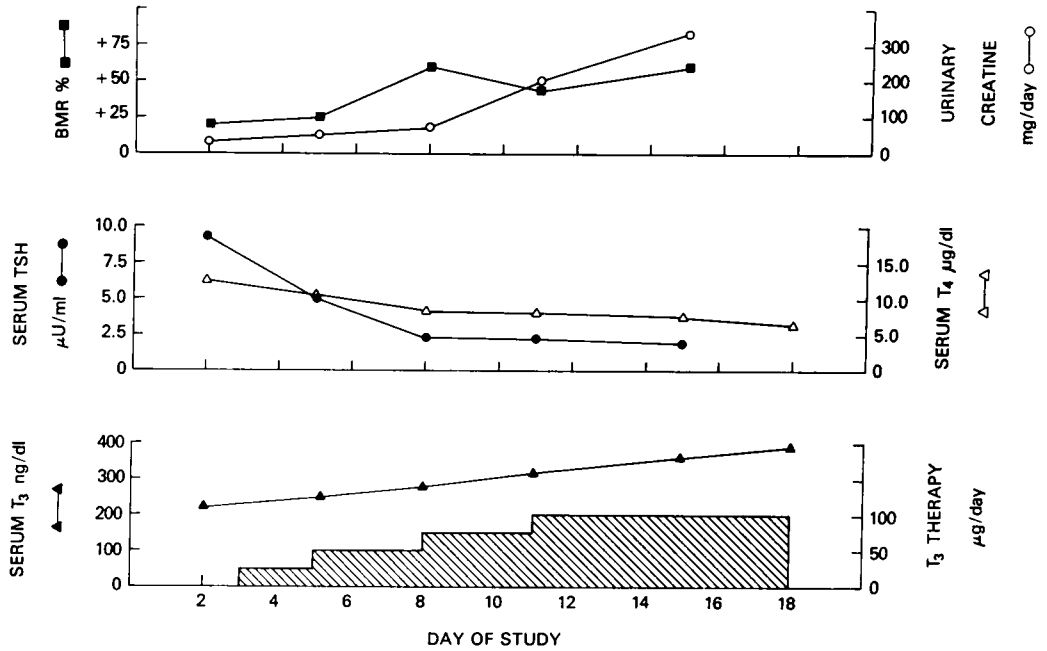

FIGURE 2 Response of serum T_3, T_4, and TSH, BMR, and urinary excretion of creatinine to increasing doses of exogenous T_3. Serum T_3 was measured in the morning, 12 h after the previous dose, and was probably higher than this minimal level through most of the day (25).

TABLE III

*[Proposed Classification of Inappropriate Secretion of TSH**

I. Neoplastic production of TSH
A. Pituitary tumors
1. Not associated with acromegaly
2. Associated with acromegaly
B. Nonpituitary tumors (ectopic production)
II. Nonneoplastic pituitary hypersecretion of TSH
A. Target organ resistance to thyroid hormone
1. General—peripheral tissues and pituitary
2. Pituitary
B. Abnormal stimulation of TSH secretion
1. By TRH
2. By other stimulators

* Elevated serum levels of immunoreactive TSH in the presence of elevated total and free serum thyroid hormones.

seen in the patients described by Refetoff et al. (10, 11), consideration was given to a state of target organ resistance to the action of thyroid hormone, as described by Bode et al. (12) and Lamberg (13). The elevated base-line values of tests that measure peripheral effects of thyroid hormone, including BMR, pulse-wave arrival time, and red cell sodium content, and the progressive increase of the BMR and urinary creatine excretion during exogenous T_3 administration strongly favored normal peripheral tissue responsiveness to thyroid hormone. We, therefore, concluded that this patient was both chemically and clinically hyperthyroid.

The elevated levels of immunoreactive TSH could have been explained if this molecule were not biologically active or if the patient's thyroid gland were unable to respond to it. These possibilities were excluded in two separate studies. First, during the course of each TRH stimulation test, there was an appropriate increase in the circulating T_3 level. Since TRH has not been shown to stimulate thyroidal secretion of thyroid hormones directly, nor to alter their metabolism, the rise in T_3 must have been secondary to TSH-stimulated thyroidal secretion of T_3. Secondly, during the T_3 suppression study as the circulating TSH level decreased there was a simultaneous decrease in the thyroidal uptake of radioiodine and in the secretion of T_4. Moreover, recent experiments involving continued administration of T_3 (100 μg/day) have revealed a dramatic decrease in thyroid gland size as measured by palpation and ultrasound (27).

Although the elevated circulating TSH level appeared to be responsible for the thyroid hyperactivity, the much more common cause of toxic diffuse goiter, Graves' disease, might have been the initiating etiology and/or have been present concurrently. It was important, therefore, that at no time during this patient's course were signs or symptoms of ophthalmopathy present, nor was long-acting thyroid stimulator detectable in the serum. Moreover, in July 1969 before subtotal thyroidectomy and while she received no antithyroid medication the serum TSH was 2.7 μU/ml when the thyroid hormone levels were clearly elevated: T_4, 17.0 μg/dl and PBI, 14.4 μg/dl. Therefore, there was no evidence of Graves' disease at any time, and the serum TSH was inappropriately elevated whenever it was measured.

The combination of elevated serum levels of thyroid hormones and TSH may be seen in several different clinical situations. A proposed classification of this differential diagnosis, herein defined as inappropriate secretion of TSH, is presented in Table III. Of these, some are well-documented clinical entities while others are only postulated. Pituitary tumors associated with hypersecretion of TSH and hyperthyroidism have been described. Hamilton et al. (5) described a patient with a chromophobe adenoma, persistently elevated levels of TSH, and hyperthyroidism, whose thyrotoxicosis remitted and TSH levels returned to normal after surgical and irradiation therapy directed at the pituitary adenoma. Faglia et al. (6), O'Donnell et al. (7), and Mornex et al. (8) also reported patients with pituitary tumors, hyperthyroidism, and elevated levels of TSH. Hamilton and Maloof (9) described a patient with acromegaly and hyperthyroidism secondary to pituitary hypersecretion of TSH, who demonstrated remission of both pathologic processes after therapy directed at the pituitary tumor. Lastly, an animal model for this clinical syndrome has been described by Furth, Moy, Hershman, and Ueda (28). Sustained deficiencies of thyroid hormones, produced by radiothyroidectomy, caused hypertrophy and hyperplasia of the pituitary thyrotrophs, which led eventually to autonomous thyrotropic tumors. These tumors secreted large amounts of TSH in addition to several other trophic hormones.

Ectopic production of pituitary TSH has not yet been demonstrated. However, hyperthyroidism has been associated with several tumors of trophoblastic origin (29–31), which produced substances with bioassayable thyroid-stimulating activity but no immunologic relation to pituitary TSH.

Elevated serum thyroid hormone and TSH levels have been found in several patients who demonstrated resistance to the action of thyroid hormone. Refetoff et al. (10, 11) described a familial syndrome of deaf-mutism, stippled epiphyses, goiter, elevated thyroid hormone levels, detectable circulating TSH, and a euthyroid clinical state in three of six siblings. In these studies certain tests of the peripheral action of thyroid hormones yielded results compatible with hypothyroidism, while others suggested euthyroidism. More re-

TABLE IV

*Case Reports of Inappropriate Secretion of TSH**

Authors	TSH response				Peripheral hypermetabolism‡	Proposed classification*
	Thyroid hormone	Glucocorticoid	TRH	Antithyroid drug		
Refetoff et al. (10, 11)	ND§	ND	ND	ND	Absent	IIA_1
Hamilton et al. (5)	ND	ND	ND	0	Present	IA_1
Hamilton and Maloof (9)	ND	ND	ND	↑	Present	IA_2
Faglia et al. (6)	↑↓	ND	ND	↑	Present	IA_1
O'Donnell et al. (7)	0	ND	ND	ND	Present	IA_1
Mornex et al. (8)	↓	ND	↑	ND	Present	IA_1
Bode et al. (12)	↓	↓	↑	↑	Absent	IIA_1
Lamberg (13)	↓	ND	↑	ND	Absent	IIA_1
Emerson and Utiger (14)	↓‖	↓	0	↑	Present	IIB_2 or IIA_2 + IIB
Present case	↓	↓¶	↑	↑	Present	IIA_2

* See Table III.

‡ Defined by clinical and laboratory studies as described in text.

§ ND, not done; 0, no response; ↑, rise in TSH; ↓, fall in TSH; ↑↓, equivocal response.

‖ Small, but significant, fall.

¶ Basal TSH decreased; TSH response to TRH unchanged.

cently, Bode et al. (12) and Lamberg (13) have described two very similar patients, euthyroid clinically and by peripheral tests of thyroid function but with elevated serum thyroid hormones and inappropriately high TSH levels. Various studies, most notably altering their circulating thyroid hormone levels with exogenous T_4 (13), T_3 (12), or antithyroid drugs (12), showed at least partial pituitary TSH responsiveness. Moreover, these cases, like those reported by Refetoff et al. (10, 11), showed no clinical or chemical peripheral target organ response to large doses of thyroid hormone. It was concluded that these patients demonstrated partial resistance of the peripheral tissues as well as the pituitary to the action of thyroid hormone.

Selective resistance of the pituitary[3] to thyroid hormone action and abnormal stimulation of the pituitary by TRH or other as yet unidentified stimulators could produce a syndrome of hyperthyroidism unrelated to a neoplasm and caused by thyroidal overstimulation by TSH. Although inadequate methodology precludes definite etiologic classification of patients with this clinical complex at the present time, our patient and the one reported by Emerson and Utiger (14) appear to fit this syndrome. Table IV compares these patients with other patients with the syndrome of elevated serum levels of thyroid hormone and TSH. In our patient, a pituitary tumor is a very unlikely etiology, in view of the prolonged clinical course and apparently normal pituitary size, as documented by careful tomography of the sella turcica and full visual fields. However, although to our knowledge a microadenoma of the pituitary associated with high serum TSH has never been described, we cannot definitely exclude this possibility. This is especially true since the natural history of clinically undetectable pituitary microadenomas, for example, those associated with hyperprolactinemia and surgically proved (33), is unknown. A nonpituitary tumor producing TSH ectopically is also unlikely; the prolonged clinical course in this young woman is against neoplasia. Moreover, TSH responsiveness to both stimulation and suppression argues for a pituitary rather than an ectopic origin. General target organ resistance to the action of thyroid hormone is ruled out by the demonstrated increase in peripheral tissue effects of thyroid hormone in the base-line state. Our patient like the patient reported by Emerson and Utiger, therefore, is an example of the syndrome of nonneoplastic hypersecretion of TSH and hyperthyroidism.

Our patient and the one reported by Emerson and Utiger, although apparently presenting similar clinical syndromes, demonstrate several important differences. Their patient had originally presented a more usual picture of toxic diffuse goiter with suppressed pituitary TSH, and only after a period of radioiodine-induced hypothyroidism did the serum TSH concentration become inappropriate for the level of circulating thyroid hormones. In our patient, the TSH level was inappropriately high even before subtotal thyroidectomy in 1969. However, we cannot prove that thyroidal overstimula-

[3] Although thyroid hormones clearly inhibit pituitary TSH secretion, recent evidence suggests that they may stimulate hypothalamic secretion of TRH (32). Therefore, in contrast to pituitary resistance to the action of thyroid hormone, hypothalamic resistance should not produce TSH hypersecretion.

tion by TSH was the initial cause of our patient's hyperthyroidism. At the time of study, the patient reported by Emerson and Utiger exhibited only mild symptoms of hyperthyroidism, but clinical signs and laboratory tests of peripheral thyroid hormone effects were normal. Our patient was also only mildly symptomatic and demonstrated few clinical signs of excessive thyroid hormone action. However, several laboratory tests, including BMR, pulse-wave arrival time, and red cell sodium content, documented excessive tissue effects of thyroid hormone. Moreover, during the T_3 suppression test our patient showed modest clinical and dramatic laboratory evidence of increasing thyroid hormone peripheral effects, while theirs showed none. Both patients exhibited excessive secretion of TSH in the basal state, similar reductions in serum TSH after dexamethasone administration, and a similar, qualitatively appropriate rise in TSH after the circulating thyroid hormone levels were lowered by antithyroid drugs. However, the responses of the pituitary thyrotrophs to T_3 suppression and TRH stimulation were different. Their patient showed slight suppression of serum TSH (from 13.8 to 9.0 μU/ml) by large doses (200 μg/day) of T_3 given for 7 days. Ours, on the other hand, showed significant suppression by as little as 25 μg T_3/day for 2 days and a marked lowering of the serum TSH level after 100 μg T_3/day for 7 days. Emerson and Utiger attempted stimulation with TRH on two occasions in their patient. Even though the serum thyroid hormones had been significantly reduced by methimazole therapy before the second attempt, there was no change in serum TSH levels after TRH administration in their patient. In contrast, our patient showed a markedly increased response to TRH in the base-line study, similar to that observed in patients with primary hypothyroidism. Moreover, even when circulating thyroid hormone levels were raised by exogenous administration of T_3, a significant although attenuated response was found after TRH administration. Therefore, although both Emerson and Utiger's patient and our patient had hyperthyroidism that appeared to be secondary to nonneoplastic pituitary hypersecretion of TSH and although definition of an underlying etiology is not possible with present methodology they appear to represent distinct variants and probably have different etiologies.

Emerson and Utiger hypothesized that because of the lack of TSH response to exogenous TRH in their patient her illness might have been caused solely by hypersecretion of endogenous TRH. However, their patient's TSH secretion was not completely inhibited by serum levels of thyroid hormones that would normally totally inhibit the TSH response to large doses of exogenous TRH (2-4, 34). Therefore, unless there are major differences in the TSH response to endogenous as compared to exogenous TRH, their patient must have had partial resistance of the pituitary to thyroid hormone in addition to hypersecretion of TRH. Alternatively, pituitary TSH secretion might have been stimulated by an as yet unidentified substance capable of overcoming thyroid hormone suppression. Reliable methods to measure endogenous TRH will be necessary to clarify this problem.

In our case the cause of the TSH hypersecretion appears to be a selective resistance of the pituitary to the action of thyroid hormone. Interestingly, this resistance may not be confined to thyrotrophs but may also be shared by somatotrophs and lactotrophs. Although the patient's serum growth hormone and prolactin were normal in the basal state, both hormones showed increased responses to provocative stimuli. These increased responses were particularly striking in view of the elevated serum thyroid hormones, shown in certain instances to blunt the growth hormone response to hypoglycemia (35) as well as the prolactin response to TRH (22) in humans. Moreover, neoplastic rat pituitary cell lines that secrete both prolactin and growth hormone in vitro have been shown to have high-affinity nuclear receptors for thyroid hormone (36).

The pituitary resistance to thyroid hormone in this patient was only partial, since the TSH responded to both stimulatory and suppressive factors as in patients with primary hypothyroidism. Specifically, there was an exaggerated TSH response to exogenous TRH stimulation, blunting of the TSH response to TRH by thyroid hormone, and blunting of basal TSH but not of TRH-stimulated TSH secretion by dexamethasone. However, unlike patients with primary hypothyroidism (or normals) our patient achieved a normal basal TSH and response to TRH only with markedly elevated serum T_3 levels. In fact, we have not yet determined what dose of thyroid hormone would be required to suppress both basal and TRH-responsive TSH totally. As described above, these data are not compatible solely with hypersecretion of endogenous TRH. This syndrome is, therefore, functionally analogous to Cushing's disease, in which there is a qualitatively normal but quantitatively abnormal response of ACTH to glucocorticoid suppression. However, the histopathology of the pituitary as well as the biochemical basis for resistance to thyroid hormone in this disorder remain to be elucidated.

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