Hyperthyroidism due to inappropriate TSH secretion with associated hyperprolactinaemia—a case report and review of the literature

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Summary

A patient with inappropriate thyrotrophin (TSH) secretion is described. She initially presented with classical hyperthyroidism during pregnancy, responded to propylthiouracil and, subsequently, had a normal delivery. Hyperthyroidism persisted and 7.5 months later a subtotal thyroidectomy was performed. After a further 16 months, mild symptoms of hyperthyroidism recurred. She again responded to propylthiouracil, but developed galactorrhoea. At that stage, it was noted that she had persistently elevated circulating TSH in the presence of elevated T_4 and T_3 levels. Her symptomatology was mild, although objective indices of thyroid activity, including pulse rate, BMR, sex hormone binding globulin and cholesterol, were indicative of hyperthyroidism. CT scan and tomography of the sella were normal.

She had a markedly exaggerated TSH response to thyrotrophin releasing hormone (TRH). Basal TSH and responsiveness to TRH was suppressed by high dose dexamethasone. The TSH response to TRH was partially suppressed by exogenous T_3 , but there was no effect on basal TSH levels. TSH also decreased slightly with L-dopa and bromocriptine. Circulating TSH rose markedly during methimazole administration. TSH α and β subunits were elevated and appropriate for the high TSH. In addition, both subunits increased following TRH. The patient had basal hyperprolactinaemia with an impaired prolactin (PRL) response to TRH and metoclopramide. PRL suppressed with L-dopa and bromocriptine. The remaining anterior pituitary function was intact. Most of the laboratory findings argue against the presence of a TSH producing pituitary tumour and

the most likely cause for inappropriate TSH secretion in this patient is selective resistance of the thyrotroph to thyroid hormones. A mild element of peripheral resistance might also be present. The hyperprolactinaemia could be related to lactotroph resistance to thyroid hormone.

The complexities of treatment in this patient are stressed. Therapy was initially attempted with low dose dexamethasone, but this had no effect. Low dose treatment produced an exacerbation of her symptomatology and did not influence basal TSH, thyroid hormones, or ^{131}I uptake. Bromocriptine administration for 11 months partially suppressed basal TSH without influencing T_3 and there was an increase in T_4 . Methimazole did decrease her T_4 and T_3 , but TSH and PRL rose to even greater levels. Her hyperthyroidism was eventually controlled with an ablative dose of ^{131}I . Thyroid hormone will be given in an attempt to suppress her TSH.

KEY WORDS: pregnancy, thyroidectomy, galactorrhoea.

Introduction

In the classical forms of hyperthyroidism due to Graves' disease, toxic adenoma or toxic multinodular goitre, thyrotrophin (TSH) levels are suppressed and there is no increase in TSH following the administration of thyrotrophin-releasing hormone (TRH) (Condliffe and Weintraub, 1979; Gershengorn, 1981; Shenkman, Mitsuma and Hollander, 1973). In some instances, hyperthyroidism may be associated with inappropriate secretion of TSH. This occurs in a patient whose basal or TRH-stimulated serum concentration of immunoreactive TSH is inappropriately elevated in the presence of elevated, free serum thyroid hormones (Gershengorn, 1981). Many of

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these patients have an associated pituitary tumour (Condliffe and Weintraub, 1979). We now present a patient with hyperthyroidism and inappropriate TSH secretion who also had mild basal hyperprolactinaemia without any evidence of a pituitary tumour. The complexity of therapy in this syndrome in general and in this patient in particular is emphasized.

Methods

Serum TSH, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), and growth hormone (GH) were determined by previously described methods (LeRoith *et al.*, 1981; Spitz, Gonen and Rabinowitz, 1979; Spitz *et al.*, 1980). The normal range for basal TSH in our female controls is 1.8–6.0 μ U/ml. Following 200 μ g TRH intravenously (i.v.), the peak TSH response ranges from 12–38.7 μ U/ml. TSH α and β subunits were measured according to Kourides *et al.* (1975, 1977). Total thyroxine (T_4), total tri-iodothyronine (T_3) and T_3 resin uptake (T_3 RU) were measured using test kits supplied by Dr S. Zierling, Diagnostic Products Corporation, Los Angeles, California. In our laboratory, the normal range for T_4 is 60–155 nmol/l, for T_3 from 1.15–3.38 nmol/l and for T_3 RU from 25–37%, respectively. The T_3 RU gives an assessment of the concentration of unsaturated binding sites on thyroid binding globulin (Ingbar and Woeber, 1974). Free T_4 levels were measured by a kit supplied by the Radiochemical Centre, Amersham, England. The normal range is from 0.92–1.96 ng/100 ml. Sex hormone binding globulin was estimated by the method of Mickelson and Petra (1974).

Case report

In March 1977, at the age of 22 years, during pregnancy, the patient developed severe palpitations together with syncope. On examination she had tachycardia, a slight tremor, and a smooth uniformly enlarged thyroid gland. Her T_4 was 245 nmol/l and her T_3 6.39 nmol/l. She was treated with propylthiouracil 400 mg daily (Fig. 1). The tachycardia and other symptomatology subsided and she had an uncomplicated pregnancy with a normal delivery. Propylthiouracil was continued for a further 5 months. By then, the patient was clinically and biochemically euthyroid. Three weeks after withdrawing propylthiouracil, a tracer dose of 131 I was given and thyroid uptake was measured at 2 hr (35%) and 24 hr (70%). Propylthiouracil was recommenced and 2.5 months later, in February 1978, the patient underwent a subtotal thyroidectomy, preceded by a short course of Lugol's iodine. A total of 68 g of thyroid tissue was removed and a minimal amount

was left *in situ*. Histological examination showed large, irregular acini of different sizes, some of which were distended. The epithelial cells lining the acini showed supranuclear vacuolization, indicative of hyperactivity.

The patient remained asymptomatic for 16 months with no medication. In January 1979, 131 I uptake was 27% at 2 hr and 47% at 24 hr. 99 Tc scan showed diffuse regeneration of both lobes of the thyroid. Thereafter, T_4 levels gradually increased and by July 1979, she was complaining of palpitations and moist hands. There was no exophthalmos or tremor. Propylthiouracil was recommenced with amelioration of her symptomatology and reduction in T_4 levels. However, her white count decreased to 3,300/cm³ and treatment was withheld. T_4 levels again increased, PRL and TSH levels were found to be elevated, and tachycardia returned. Galactorrhoea was noted for the first time and she was referred to Jerusalem for further evaluation in January 1980.

At that stage, the patient's complaints were palpitations and heat intolerance. She also had mild nervousness and generalized weakness. There was no excess sweating. Appetite was normal and there was no weight loss. On physical examination she had persistent tachycardia which ranged from 96–120/min. Her blood pressure was 150/80 mmHg. She had a thyroidectomy scar with a diffusely enlarged symmetrical nodular non-tender thyroid gland. There was mild sweatiness of her palms with no tremor. Galactorrhoea was present in both breasts. There were no signs of ophthalmopathy, nor pretibial oedema. Visual fields were full.

Results

Thyroid hormone concentrations

In 17 samples, basal T_4 levels ranged from 190–329.5 nmol/l and T_3 total from 4.61–10.55 nmol/l. Serial dilution of the patient's serum gave results parallel to the standard curves in the T_4 and T_3 immunoassays. T_4 and T_3 levels were also measured in four additional radioimmunoassay test systems utilizing different antisera and various methods of separation. A competitive protein binding technique was also used to measure T_4 . All these tests gave values exceeding the controls. Thus the high levels of thyroid hormones did not represent iodoproteins other than T_4 or T_3 . Free T_4 levels were 3.8, 4.6, and 6.0 μ g/100 ml, which is also greater than the controls. T_3 RU levels in six samples ranged from 35–44.2% ($P < 0.001$ compared to the controls).

No antibodies were detected against thyroglobulin, thyroid microsomal or cytoplasmic agents. The 131 I uptake was 54% at 2 hr and 63% at 24 hr. The scan showed regeneration of both lobes. Basal metabolic rate (BMR) measured +15%, +19%, +24% (normal

FIG. 1. Profile of TSH (upper panel), T_3 (middle panel), and T_4 (lower panel) in the patient over the course of the study. PTU=propylthiouracil, T_3 =tri-iodothyronine, DXM=dexamethasone, METH=methimazole. For propylthiouracil, methimazole and bromocriptine scale indicates dosage in mg/day. At A, patient had normal full-term delivery. At B, patient had subtotal thyroidectomy.

range -5 to $+15\%$). Serum cholesterol ranged from 3.3 – 3.8 mmol/l (normal range 3.8 – 6.5 mmol/l) and sex hormone binding globulin from 84 – 134.6 pg/ml (upper normal limit being 50 pg/ml).

TSH levels

Mean $\pm$ s.d. basal TSH levels determined in 25 samples in the untreated state in the patient were 22.7 ± 8.1 μ U/ml (range 11.3 – 40.5 μ U/ml). This was significantly greater than the female controls ($P < 0.001$). The patient was challenged with TRH (200 μ g) on six occasions in the basal state (Fig. 2). In all instances, the peak response was much greater ($P < 0.001$) than the normal females. The patient's TSH was immunologically identical to the pituitary TSH standard (68/38) as demonstrated by parallelism between curves generated with serial dilutions of the patient's serum and the TSH standard in the assay. Sephadryl G200 gel chromatography on the patient's serum showed that the TSH immunoreactivity eluted in a position corresponding to the TSH standard.

Subunit studies (Table 1)

Mean TSH α and β subunit levels were greater in

the patient than in female controls, and were similar to patients with primary hypothyroidism. Following TRH administration there was a definite increase in both TSH α and β subunits. The values attained were greater than the controls and similar to female patients with primary hypothyroidism.

Further studies (Table 1, Fig. 3)

Basal LH and FSH levels, as well as their responses to LHRH (100 μ g) were normal. GH levels increased after both L-dopa and bromocriptine administration (Fig. 3). Basal PRL levels were elevated and the mean in 26 samples was 30.6 ± 14.5 ng/ml. This was greater than the female controls ($P < 0.001$) where the mean is 9.5 ± 3.3 ng/ml. PRL suppressed after L-dopa and bromocriptine (Fig. 3). There was, however, an attenuated PRL response to TRH (Fig. 2) and metoclopramide (Table 1). X-ray skull with polytomograms of the pituitary fossa, as well as computerized tomography of the brain, including coronal sections with contrast enhancement, were normal.

Dexamethasone administration

The patient was given 2 mg dexamethasone every hr for a total of four doses. When challenged 2 hr

FIG. 2. TSH (●—●) and PRL (○---○) responses to TRH (200 µg) in patient throughout period of observation. Responses in normal female controls (mean ± s.e.m.) are shown in the first panel. noRx indicates no treatment. T₃(a) = test after T₃ (50 µg daily) for 1 week; T₃(b) = test after T₃ (100 µg daily) for 2 weeks; METH = test during methimazole; DXM(a) = test after 8 mg dexamethasone; DXM(b) = test after 1 mg dexamethasone daily for 1 month; bromocriptine = test after 2 weeks and 23 weeks of treatment with bromocriptine. Scale of PRL has been changed for the test during methimazole administration.

TABLE 1. Basal and peak hormonal values

Stimulus	Hormone		Basal	Peak
LHRH (100 µg)	LH (miu/ml)	P*	30.1	53.6
		C†	20.4 ± 10.2	67.8 ± 28.7
LHRH	FSH (miu/ml)	P	11.2	17.8
		C	7.6 ± 2.1	13.8 ± 3.4
Metoclopramide (10 mg)	TSH (µu/ml)	P	30.1	32.5
		C	2.1 ± 0.9	2.6 ± 0.6
Metoclopramide	PRL (ng/ml)	P	34.8	82.7
		C	8.5 ± 1.4	194.8 ± 40.3
TRH (200 µg)	TSHα (ng/ml)	P	4.8	15.0
		C	0.5–2.0	0.5–2.0
		h‡	0.7–7.3	2.5–11.7
TRH	TSHβ (ng/ml)	P	1.0	1.5
		C	0.5	0.5
		h	0.5–9.3	2.6–15.5

*P = patient; †C = normal females; ‡h = hypothyroid females. For LH, FSH, TSH and PRL values for controls are mean ± s.d. For TSHα and TSHβ ranges are shown for both control groups. The subunit data has been obtained from Kourides *et al.*, 1975.

after the last dose of dexamethasone, T₃ levels had decreased to 1.84 nmol/l and basal TSH levels to 2.1 µu/ml. There was no change in T₄. The peak TSH response to TRH was now within the normal range (Fig. 2). Basal PRL and the peak response to TRH was also normal (Fig. 2). In view of this dramatic response, the patient was subsequently given a trial of dexamethasone 0.5 mg every 12 hr for 1 month. During this period, tachycardia persisted and there was no change in thyroid hormone levels; in contrast to the response to high dose dexamethasone, there was also no effect on TSH, PRL, T₄ and T₃ concentrations. After 1 month, the patient developed severe epigastric pain and the trial was terminated.

FIG. 3. GH, TSH, and PRL responses to L-dopa in the left hand panel and bromocriptine in the right hand panel.

T₃ suppression test

Tri-iodothyronine (T₃) was initially administered in a daily dose of 50 µg for 1 week. This was later increased to 100 µg daily for 2 weeks. During this period T₃ levels increased to 9.22 nmol/l but there was no alteration in T₄, PRL or basal TSH. There was however a reduction in the TSH response to TRH (Fig. 2). Nevertheless, considering the high dose of administered T₃ and the elevated levels of endogenous hormone, these responses were still inappropriately high (Shenkman *et al.*, 1973). During T₃ therapy, the patient complained of a marked increase in the severity of her palpitations, as well as

excessive sweating. Her pulse was consistently over 120/min and her BMR was +28%. Because of the exacerbation of her symptomatology, the therapeutic trial was disbanded. On the last day of her T_3 administration, a repeat ^{131}I uptake was 42% at 2 hr and 71% at 24 hr.

Treatment with methimazole

This was given on two occasions. The first trial consisted of a 3-week course. Ten milligrams were given daily for 1 week and subsequently 20 mg daily. There was a slight decrease in T_4 although levels were still above the normal range. No changes were observed in T_3 . There was a marked increase in basal and TRH-induced TSH and PRL levels (Figs. 1, 2).

On a subsequent occasion, methimazole was given in a daily dose of 30–40 mg a day for 11 weeks. This produced an amelioration of her symptomatology with a reduction of T_4 and T_3 but increase in TSH levels. The administration of T_3 during methimazole administration was effective in reducing TSH levels to the pre-methimazole level (Fig. 1).

Response to bromocriptine

L-dopa and bromocriptine administered on a one-time basis produced a slight decrease in TSH (Fig. 3). An 11-month trial of bromocriptine was attempted together with propranolol (80 mg daily). The dose of bromocriptine was gradually increased from 7.5 mg daily to 30 mg daily. Twenty to 30 mg per day was given for 24 weeks. Galactorrhoea disappeared and there was also a marked decrease in basal and TRH induced PRL levels (Fig. 2). TSH levels also decreased during bromocriptine. The mean of 17 samples was $13.1 \pm 3.7 \mu\text{U/ml}$ and less ($P < 0.001$) than values prior to bromocriptine. Nevertheless, these levels were still greater than in normals ($P < 0.001$). There was no change in the TSH response to TRH (Fig. 2). T_3 levels fluctuated markedly and only one level was below 3.07 nmol/l . The mean of 19 samples during bromocriptine was $5.78 \pm 1.25 \text{ nmol/l}$ and not significantly different from pretreatment values. T_4 levels increased during bromocriptine. Mean of 27 samples was $286 \pm 32.2 \text{ nmol/l}$ as compared to $234 \pm 45.0 \text{ nmol/l}$ in the untreated period ($P < 0.001$). Withholding propranolol for a few days was associated with return of tachycardia. After 11 months of therapy, the ^{131}I uptake was 39% at 2 hr and 57% at 24 hr. In view of this lack of response, the therapeutic trial with bromocriptine was abandoned.

Family studies

Since inappropriate TSH secretion is frequently familial (Elewaut, Mussche and Vermeulen, 1976;

Refetoff, Dewind and DeGroot, 1967; Rosler *et al.*, 1982; Brooks *et al.*, 1981), we examined the patient's mother and her six sisters. Her mother was asymptomatic, but had slight thyromegaly with a T_4 of 22.5 nmol/l and T_3 of 4.61 nmol/l . TSH levels were less than $1 \mu\text{U/ml}$ and there was an absent TSH response to TRH. She thus had the biochemical picture of classical hyperthyroidism. None of the patient's six sisters had any thyromegaly. All had normal thyroid hormone levels and a normal TSH response to TRH.

Discussion

This patient had elevated serum TSH in the presence of high circulating levels of thyroid hormones and thus has inappropriate TSH secretion (Condliffe and Weintraub, 1979; Gershengorn, 1981). Since the advent of the TSH radioimmunoassay, an increasing number of these patients have been recognized. The clinical and laboratory presentation of inappropriate TSH secretion is diverse. A classification of the potential causes of this syndrome has been proposed by Gershengorn and Weintraub (1975). Many of these subjects harbour a pituitary tumour (Baylis, 1976; Duello and Halmi, 1977; Waldhausl *et al.*, 1979; Horn *et al.*, 1976; Tolis *et al.*, 1978; Smallridge, Wartofsky and Dimond, 1979). Their clinical and laboratory presentation has recently been reviewed (Gershengorn, 1981).

In our patient, there was no evidence of a tumour and polytomography of the sella and computerized tomography were normal. In a tumour, hyperthyroidism occurs in association with autonomous TSH secretion. In our patient, TSH rose predictably with TRH and methimazole, was partially suppressed by exogenous T_3 , L-dopa and bromocriptine and fully suppressed by high dose dexamethasone. The high TSH thus responded qualitatively in a normal manner. In contrast, only one out of 19 cases with a TSH producing tumour showed an increase in TSH with TRH and one out of 10 a reduction with exogenous T_3 (Gershengorn, 1981). TSH suppression with dexamethasone as well as L-dopa and bromocriptine, however, has been documented in patients with TSH-producing tumour (Gershengorn, 1981; Horn *et al.*, 1976; Smallridge *et al.*, 1979).

The data on TSH subunits is also against the diagnosis of a tumour. In our patient, both TSH α and β subunits increased following TRH administration, as has been described in other non-tumour cases (Kourides, 1981; Tamagna *et al.*, 1979). There is only one exception to this (Emerson and Utiger, 1972; Mihailovic *et al.*, 1980). Tumours characteristically show no subunit response to TRH (Kourides *et al.*, 1977; Smallridge *et al.*, 1979; Kourides, 1981). In our patient, basal TSH α and β subunit levels were elevated, and equivalent to what is expected in

primary hypothyroidism (Kourides *et al.*, 1975; Kourides *et al.*, 1977). In 10 out of 12 patients with a tumour, TSH α subunit was markedly elevated as compared to that of TSH, whereas TSH β was suppressed (Kourides, 1981). The appropriately elevated TSH α and β subunits which respond qualitatively to stimulation is evidence against a tumour.

Non-tumoural patients with inappropriate TSH secretion form a very heterogeneous group with different clinical features encompassing the whole spectrum of thyroid disease. The variable clinical presentation may be related to the fact that the pathophysiological mechanisms causing the syndrome in non-tumour cases are diverse. In several cases, especially those with mild symptomatology, it has been suggested that the cause of the inappropriate TSH secretion is selective resistance to the action of thyroid hormones at the pituitary thyrotroph (Gershengorn, 1981; Kourides *et al.*, 1977; Elewaut *et al.*, 1976; Gershengorn and Weintraub, 1975; Novogroder *et al.*, 1977; Sato *et al.*, 1979).

In our patient, indices of peripheral tissue effects of thyroid hormones were increased. This included elevation of resting pulse and BMR. Sex hormone binding globulin, which is also an index of hyperthyroidism, was also increased (Staub, Conti and Huber, 1978). Serum cholesterol levels were reduced. Nevertheless, considering the markedly elevated levels of thyroid hormones, there was a discrepancy between the clinical and laboratory findings. This raised the question of thyroid hormone resistance at target organs. Indeed, patients with elevated TSH levels have been described who are clinically euthyroid or even hypothyroid, confirming the presence of pituitary as well as peripheral resistance (Refetoff *et al.*, 1967; Brooks *et al.*, 1981; Bode *et al.*, 1973; Lamberg, 1973; Cooper *et al.*, 1982; Linde *et al.*, 1982; Kaplan *et al.*, 1981).

Recently, a kindred has been described (Rosler *et al.*, 1982) in which amelioration of both clinical and biochemical hyperthyroidism occurred on administration of T_3 . In these patients, it was postulated that there was pituitary resistance to T_3 or, alternatively, that there was a defect in intracellular monodeiodination of T_4 to T_3 . In these patients after 1 week of 75 μ g T_3 , TSH levels were suppressed as was the TSH response to TRH; T_4 , T_3 , and 131 I uptake also reverted to normal. In contrast, after 3 weeks of T_3 treatment in our patient, no change in these parameters occurred except for the partial suppression of the TSH response to TRH.

In the majority of the cases of pituitary resistance to thyroid hormones, as well as in the kindred described above, TRH and antithyroid agents stimulate and T_3 suppresses TSH (Kourides *et al.*, 1977; Elewaut *et al.*, 1976; Rosler *et al.*, 1982; Gershengorn and Weintraub, 1975; Novogroder *et al.*, 1977; Sato *et*

al., 1979). In one patient (Emerson and Utiger, 1972; Mihailovic *et al.*, 1980) without demonstrable tumour, there was only slight suppression of TSH by thyroid hormone and no stimulation with TRH.

Other mechanisms for non-tumour inappropriate TSH secretion which have been proposed, but not proven, include ectopic production of TSH, or defects in TSH suppression secondary to abnormalities of dopamine or somatostatin (Gershengorn, 1981). Considering all the possible mechanisms of non-tumoural inappropriate TSH secretion, the most likely one operating in this subject is thyrotroph resistance to thyroid hormones.

Of interest in this patient was the presence of mild basal hyperprolactinaemia. Several patients with inappropriate TSH secretion have been described with hyperprolactinaemia, galactorrhoea and even amenorrhoea (Rosler *et al.*, 1982; Gershengorn and Weintraub, 1975; Baylis, 1976; Duello and Halmi, 1977; Horn *et al.*, 1976; Benoit *et al.*, 1980; Werner, 1979). Usually, these patients have an associated pituitary tumour, which often hypersecretes TSH, as well as PRL (Baylis, 1976; Duello and Halmi, 1977; Horn *et al.*, 1976; Benoit *et al.*, 1980; Werner, 1979). However, in some patients, no tumour has been evident (Rosler *et al.*, 1982; Gershengorn and Weintraub, 1975). Basal hyperprolactinaemia, as in the present case, is usually mild and decreases with bromocriptine and L-dopa (Horn *et al.*, 1976; Werner, 1979). In our patient, PRL increased only minimally with TRH or metoclopramide. This has been observed previously in tumour cases (Baylis, 1976; Horn *et al.*, 1976; Werner, 1979), although in situations without a tumour, exaggerated responses to TRH have been described (Rosler *et al.*, 1982; Gershengorn and Weintraub, 1975; Sato *et al.*, 1979).

Although thyroid hormones can inhibit PRL (Snyder *et al.*, 1973), we and others observed no change in basal PRL levels nor PRL responses to TRH during T_3 therapy (Rosler *et al.*, 1982; Gershengorn and Weintraub, 1975). On the other hand, high dose dexamethasone, L-dopa and bromocriptine did decrease PRL levels; and bromocriptine also blocked the PRL response to TRH. Thus, although the picture of basal hyperprolactinaemia with impaired response of PRL to TRH and metoclopramide is typical of a tumour, none could be demonstrated. It is conceivable that the thyroid hormone resistance operating at the thyrotroph in this patient also extends to the lactotroph (Gershengorn and Weintraub, 1975).

In view of the heterogeneity of the presentation of inappropriate TSH secretion, therapy can be complex. In cases with a tumour, primary therapy is directed at the pituitary. In euthyroid cases without a tumour, no treatment may be required. Indeed, antithyroid agents are contra-indicated. The judi-

ous use of thyroid hormones may be justified, especially when peripheral resistance is accompanied by signs of hypothyroidism (Gershengorn, 1981).

The main therapeutic difficulty is with non-tumour patients with peripheral manifestations of hyperthyroidism, such as in the present case. In this regard, it should be emphasized that there are no long-term follow-up studies and no controlled trials of different therapeutic approaches. In the present case, several treatment modalities are explored based on the neuroendocrine control of TSH secretion.

High-dose glucocorticoids are known to suppress basal and TRH-induced TSH secretion, as well as T_3 , but do not produce changes in T_4 (Re *et al.*, 1976). This was observed when 8 mg dexamethasone was given over 24 hr to our patient. However, on a maintenance dose of dexamethasone for 1 month, there was no clinical or laboratory effect. Because of the development of severe abdominal pain, the trial was abandoned.

TSH secretion is under dopamine control and dopamine, as well as bromocriptine, inhibits TSH secretion (Scanlon *et al.*, 1980). In a patient with a TSH-producing tumour, L-dopa and bromocriptine-decreased TSH secretion in an acute experiment on a one time basis (Horn *et al.*, 1976), although others have failed to confirm this (Waldhausl *et al.*, 1979; Tolis *et al.*, 1978; Benoit *et al.*, 1980; Werner, 1979). Since these agents produced marginal TSH suppression in this patient, we carried out a long-term trial with bromocriptine. There was a dramatic effect on PRL suppression. Although TSH values decreased slightly, levels were still considerably greater than normal. There was, moreover, no effect on T_3 and T_4 increased. No change in ^{131}I uptake occurred and after 11 months, the trial was terminated.

Mention has been made of the kindred who responded to T_3 administration (Rosler *et al.*, 1982). When our patient received T_3 , clinical symptomatology exacerbated. Somatostatin has been reported to decrease TSH levels in acute experiments in these patients (Reschini *et al.*, 1976), but we did not use this agent.

Clinical improvement with reduction in thyroid hormone levels, occurred during propylthiouracil and methimazole therapy. However, this was accompanied by marked elevation of both TSH and PRL. After prolonged periods of thyroid deficiency, the pituitary of the mouse undergoes a progressive sequence of TSH cell hyperplasia, nodularity and then neoplastic change (Furth *et al.*, 1973). This can be prevented by administration of thyroid hormones (Furth *et al.*, 1955). The danger of propylthiouracil and methimazole in this patient is the potential for thyrotroph hyperplasia and hypertrophy, when there is prolonged inadequate thyroid hormone effect. Indeed, progression to neoplasm with pituitary en-

largement has been seen in chronic primary hypothyroidism (Vagenakis, Dole and Braverman, 1976; Samaan *et al.*, 1977). In this patient, the hyperthyroidism was finally controlled with an ablative dose of ^{131}I . It is planned to add T_3 to the regimen in an attempt to decrease TSH and prevent thyrotroph stimulation.

In summary, this patient presented with decreased sensitivity of the thyrotrophs and lactotrophs to thyroid hormones. No pituitary tumour could be demonstrated. Since she had signs of hyperthyroidism, resistance at the peripheral tissues was only partial. Even at the thyrotroph, resistance was incomplete since T_3 effected qualitatively normal, but quantitatively abnormal TSH inhibition.

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