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Thyrotropin-Secreting Pituitary Tumors*

PAOLO BECK-PECCOZ, FRANÇOISE BRUCKER-DAVIS, LUCA PERSANI, ROBERT C. SMALLRIDGE, AND BRUCE D. WEINTRAUB

Institute of Endocrine Sciences, University of Milan, Ospedale Maggiore IRCCS (P.B.-P.) and Centro Auxologico Italiano IRCCS (L.P.), Milan, Italy; Molecular and Cellular Endocrinology Branch (F.B-D., B.D.W.), NIDDK, NIH, Bethesda, Maryland 20892; and Endocrinology Division (R.C.S.), Mayo Clinic Jacksonville, Jacksonville, Florida 32224

I. Introduction

The term "TSH-secreting pituitary tumors" includes two opposite clinical conditions: true thyrotroph neoplasia that results in secondary hyperthyroidism, also called "central hyperthyroidism," and pituitary hyperplasia resulting from longstanding primary hypothyroidism. The latter condition was first recognized 145 yr ago (1), while the former was not clearly identified until the RIA era (2–8). However, in the 1950s and 1960s, while it became clear that Graves' disease was not caused by hyperpituitarism (9, 10), scattered reports suggested a possible association between pituitary tumors and hyperthyroidism (11–15), although no measurement of TSH levels was available during this time. The first case of TSH-secreting pituitary adenoma (TSH-oma) was documented in 1960 by measuring serum TSH levels with a bioassay (16). In 1970, Hamilton *et al.* (17) reported the first case of TSH-oma proved by a RIA that was much more sensitive and specific than the previously used bioassays. Classically, TSH-omas were diagnosed at the stage of invasive macroadenoma and had the reputation of being difficult to cure. However, with the introduction of ultrasensitive immunometric assays, routinely performed as a first-line thyroid function test, patients with TSH-oma are more often recognized earlier, before the stage of macroadenoma.

TSH-secreting pituitary adenomas are part of the syndromes of "inappropriate secretion of TSH" (IST). Indeed, the hormonal profile is characterized by a nonsuppressed TSH in the presence of high levels of free thyroid hormones (FT4 and FT3), reflecting an abnormal feedback (2). TSH-omas are also called neoplastic IST (4), to differentiate them from the syndrome of resistance to thyroid hormone (RTH), a nonneoplastic form of IST (2, 18–21). The etiology of these tumors is currently unknown. In contrast, the etiology of pituitary hyperplasia is better understood, with the thyrotroph cells becoming enlarged by lack of negative feedback; indeed, the hormonal profile is usually straightforward, displaying unambiguous marked primary hypothyroidism with low circulating thyroid hormones and elevated TSH, easily reversible upon thyroid replacement.

Failure to recognize these two different entities may result in dramatic consequences, such as unnecessary pituitary surgery in hypothyroid patients or improper thyroid ablation in patients with central hyperthyroidism. In contrast, early diagnosis and correct treatment of pituitary tumors prevent the occurrence of complications (visual defects by compression

Address reprint requests to: Paolo Beck-Peccoz, M.D., Istituto Clinico Humanitas, Via Manzoni 56, 20089-Rozzano (MI)-Italy.

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of the optic chiasm, hypopituitarism) and should improve the rate of cure.

In the present paper, we will successively review all the reported cases of TSH-oma and pituitary hyperplasia, discuss the main diagnostic and therapeutic approaches, and propose diagnostic algorithm and prognostic criteria. We will also review the most recent studies on the pathogenesis of thyrotroph neoplasia and discuss future directions in which to expand their understanding.

II. TSH-Secreting Pituitary Adenomas as Cause of Central Hyperthyroidism

A. Classification

Using the classification of IST by Brenner-Gati and Gershengorn (3) and Faglia *et al.* (4), based on hormone secretion and not immunostaining, TSH-secreting pituitary adenomas belong to class IA. To date, 280 different cases have been published (Table 1) (2, 4, 16, 17, 22–186). Microadenomas (diameter < 1 cm) were recorded in 28 cases (10%). The majority of TSH-secreting adenomas (72%) were secreting TSH alone, often accompanied by unbalanced hypersecretion of its α-subunit (see below). In 28% of the cases, mixed adenomas were found with the concomitant hypersecretion of other anterior pituitary hormones, mainly GH and/or PRL, which are known to share a common transcription factor (Pit-1) with TSH. TSH and GH hypersecretion (16%) is the most frequent association. In four of these patients, PRL was also cosecreted (33, 78, 174), while in another case both PRL and FSH were hypersecreted along with TSH and GH (54). Mixed TSH and PRL adenomas were seen in 30 patients (11%). Occasionally, another type of hormone is cosecreted: in four cases, gonadotropin hypersecretion was observed, FSH alone being hypersecreted in three (39, 79, 102) and FSH/LH in one (165). No association with ACTH hypersecretion has been documented to date, although positive immunostaining with anti-ACTH antibodies was seen in seven adenomas (61, 116, 129, 176). Positive immunostaining with anti-gonadotropin antibodies was also frequently found without evidence of hypersecretion (56, 61, 82, 103, 138, 147, 162). In addition, one must be aware of the possibility of "trapped" normal cells responsible for faint false positive staining.

By using double gold particle immunostaining, we have recently documented the existence of TSH-omas composed of two different cell types, one secreting α-subunit alone and another cosecreting α-subunit and TSH (169). The latter type contributed to a minority (<5%) of all adenomatous cells. Therefore, mixed TSH/α-subunit adenomas should be included in the classification of central hyperthyroidism. Taking into account only the adenomas not associated with hypersecretion of other pituitary hormones (GH-, PRL-, FSH/LH-secreting adenomas are, in fact, frequently associated with α-subunit hypersecretion), this tumor type may actually be present in certain TSH-omas, particularly in those presenting with an extremely high (>30) α-subunit/TSH molar ratio (23, 35, 40, 54, 79, 83, 90, 120, 157, 171) or showing clear discrepancies between TSH and α-subunit responses to TRH (reported in 13/62 cases) (33, 35, 40, 41, 45, 104, 107, 120, 156).

Finally, Cooper and Wenig (186a) have recently described the first case of hyperthyroidism caused by an ectopic (nasopharynx) TSH-secreting pituitary tumor.

TABLE 1. Recorded cases of TSH-secreting pituitary adenoma (updated to January 1996)

	Class[a]	Number	% of total
Total TSH-secreting pituitary adenomas	IA	280	
Not associated with hypersecretion of other anterior pituitary hormones[b]	IA1	202	(72.1%)
Associated with hypersecretion of other anterior pituitary hormones	IA2	78	(27.9%)
With GH hypersecretion[c]	IA2a	44	(15.7%)
With PRL hypersecretion	IA2b	30	(10.7%)
With FSH/LH hypersecretion	IA2c	4	(1.4%)
With ACTH hypersecretion	IA2d	0	(0.0%)

[a] Modified from the classification of the syndromes of IST based on hormone secretion and not immunostaining, according to Brenner-Gati and Gershengorn (3) and Faglia *et al.* (4).

[b] This includes one tumor composed of two different cell types, one secreting α-subunit alone and another cosecreting α-subunit and TSH (169).

[c] Three patients had mixed GH/PRL and one mixed GH/PRL/FSH hypersecretion.

B. Occurrence

Central hyperthyroidism due to TSH-secreting pituitary adenoma is a rare disorder accounting for about 0.5% of all pituitary adenomas in both clinical (187) and surgical or pathological series (120, 144, 188). Since the prevalence of clinically manifest pituitary tumors in the general population is about 0.02%, the prevalence of TSH-omas accounts for about one per million. It is noteworthy that the number of reported cases tripled in the last 9 yr (Fig. 1) in connection with the introduction of the ultrasensitive immunometric TSH assays. This trend is corroborated by the recent findings from a large surgical series of pituitary adenomas, in which the occurrence of TSH-omas increased from less than 1% to

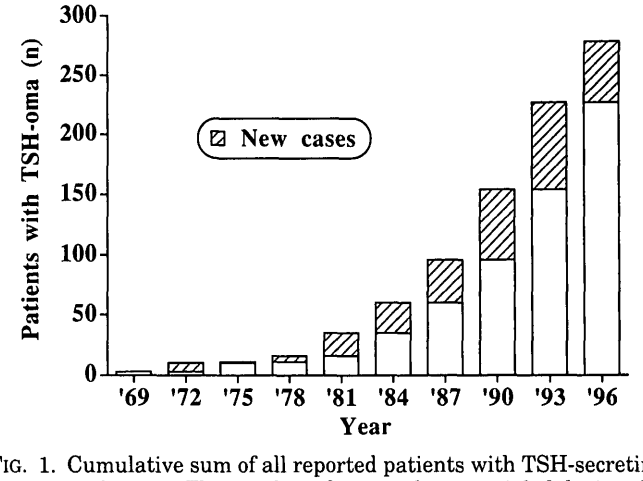

FIG. 1. Cumulative sum of all reported patients with TSH-secreting pituitary adenoma. The number of reported cases tripled during the last 9 yr, as a result of the introduction of TSH-ultrasensitive immunometric assays as the first line test for the evaluation of thyroid function.

2.8% in the period 1989–1991 (129). Contrary to previous RIAs, ultrasensitive TSH assays allow a clear distinction between patients with primary hyperthyroidism (in whom TSH secretion is suppressed) and euthyroid subjects (in whom TSH secretion is not suppressed); therefore, they are now used as a first line test for the evaluation of thyroid function. Based on the finding of measurable serum TSH levels in the presence of elevated free thyroid hormone concentrations, many patients previously thought to be affected with Graves' disease can be correctly diagnosed as TSH-secreting pituitary adenoma or, alternatively, RTH.

C. Clinical findings

Table 2 summarizes the main clinical findings in the 280 reported cases, including signs related to the cosecretion of other pituitary hormones, as well as tumoral features.

TSH-omas may occur at any age (range 11–84 yr) and, in contrast with the common thyroid disorders, there is no preferential incidence in females. Most patients presented with a long history of thyroid dysfunction, often mistakenly diagnosed as Graves' disease, and about one third had inappropriate thyroidectomy and/or radioiodine thyroid ablation. Clinical features of hyperthyroidism were usually present, often progressive in their installation, and sometimes milder than expected given the level of thyroid hormones; in some acromegalics, hyperthyroid features were clinically overlooked, as they were overshadowed by those of acromegaly (35, 120), and three other untreated patients with TSH-oma were also clinically euthyroid (69, 102, 153). This emphasizes the importance of systematic measurement of TSH and FT4 (and other anterior pituitary hormones) in all patients with pituitary tumor. In contrast, cardiotoxicosis with atrial fibrillation and/or cardiac failure was present in 19 cases, and typical episodes of periodic paralysis have been reported in one Japanese patient (100).

The presence of a goiter was the rule (94%), even in patients with previous partial thyroidectomy. Multinodular goiter was observed in few TSH-omas and in one was associated with thyroid follicular carcinoma (44), suggesting a potential role of longstanding TSH hypersecretion in nodule formation and tumorigenesis. Nodular progression toward functional autonomy and hyperthyroidism was reported in one patient (22). In contrast with Graves' disease, the occurrence of circulating antithyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) was rare (8%), similar to that found in the general population, while specific anti-TSH receptor autoantibodies were detectable in only three of 74 patients (4%), who in fact had or developed Graves' disease after pituitary surgery (29, 97, 148).

Graves-associated bilateral exophthalmos was reported in five patients (29, 84, 149, 183), while unilateral exophthalmos due to orbital invasion by pituitary tumor was seen in three additional patients (16, 164, 186). Dermopathy and acropachy were never observed.

In addition, dysfunction of the gonadal axis was not rare, with menstrual disorders present in one third of the reported cases; central hypogonadism (32, 79), delayed puberty (166), and decreased libido (165) were also found in a number of males with TSH-omas and/or mixed TSH/FSH adenomas. In mixed tumors, clinical findings were dependent on the nature of the hormone cosecreted: when hypersecretion of GH was concomitant (n = 44), typical acromegalic features were present in all but two patients (40, 74), including gigantism in a young male (162); when PRL was cosecreted (n = 30), amenorrhea and/or galactorrhea was the usual presentation.

As a consequence of tumor suprasellar extension or invasiveness, signs and symptoms of expanding tumor mass prevailed over those of thyroid hyperfunction in many patients. Visual field defects were reported in about one half of patients and headache in one sixth.

Last, four patients with TSH-oma also had hyperparathyroidism and multiple endocrine neoplasia type I (43, 108, 185). Only one TSH-oma occurred in a familial setting of

TABLE 2. Clinical characteristics of patients with TSH-secreting pituitary adenoma reported in the literature (updated to January 1996)

	No thyroid ablation % (n)[a]	Previous thyroid ablation % (n)	All patients % (n)
Age (years)[b]	41 ± 15 (156)	42 ± 13 (80)	41 ± 14 (236)
Sex (Female %)	52 (168)	62 (87)	55 (255)
Goiter	92 (114)	97 (63)	94 (177)
Tg-Ab and/or TPO-Ab	11 (63)	2 (43)	8 (106)
Anti-thyrotropin receptor autoantibodies	5 (40)	3 (33)	4 (73)
Exophthalmos	8 (79)	4 (49)	6 (128)
Menstrual disorders[c]	40 (30)	23 (40)	30 (70)
Galactorrhea[c]	50 (12)	17 (18)	30 (30)
Visual field defects	40 (73)	45 (53)	42 (126)
Headache	23 (44)	13 (61)	17 (105)
Tumor size			
Microadenomas and intrasellar macroadenomas	34 (155)[d,e]	19 (88)[d,e]	29 (243)
Macroadenoma with extrasellar extension	39 (155)[f]	32 (88)[f]	36 (243)
Invasive macroadenoma	27 (155)	49 (88)	35 (243)

[a] n refers to the number of patients for whom the information was available.
[b] Mean ± SD.
[c] Data include women with or without associated PRL hypersecretion.
[d] P = NS *vs.* macroadenoma with extrasellar extension (by Fisher's exact test).
[e] $P < 0.0006$ *vs.* invasive macroadenoma (by Fisher's exact test).
[f] $P < 0.006$ *vs.* invasive macroadenoma (by Fisher's exact test).

pituitary tumors (117), and one was found in an atypical McCune-Albright's syndrome with functionally normal Gsα protein (78). Hyperthyroidism due to TSH-oma was also recorded in two pregnant women (46, 74).

D. Baseline laboratory findings

1. TSH, thyroid hormones, and α-subunit. High concentrations of circulating thyroid hormones in the presence of detectable TSH levels characterize the hyperthyroidism secondary to TSH-secreting pituitary adenomas. In the case of prior thyroidectomy or thyroid ablation, it is crucial to assess patients in steady-state, as TSH levels need 4 to 6 weeks to adjust to a change in L-T_4 dose. Many different clinical conditions may present with hyperthyroxinemia and detectable serum TSH levels and should be distinguished from TSH-omas. As shown in Table 3, most of them may be recognized on the basis of either a patient's clinical history or by measuring the concentrations of FT_4 and FT_3 with direct "two-step" methods, *i.e.* methods able to avoid contact between serum proteins and tracer at the time of the assay, such as equilibrium dialysis + RIA, adsorption chromatography + RIA, and back-titration (189, 190). In addition, total and FT_3 levels are usually normal in patients with familial dysalbuminemia and in the neonatal period and may be low in systemic illnesses and as a result of some drug treatments. In clinically ambiguous situations, the differential diagnosis rests on the recognition of the underlying disorder, as well as documenting normalization of thyroid function tests at a later stage or after recovery of drug withdrawal. Indeed, if patients with one of the listed conditions had Graves' disease or other forms of primary hyperthyroidism, serum TSH levels should be undetectable. Furthermore, some factors may interfere with the measurement of either thyroid hormones or TSH (Table 4). The presence of anti-iodothyronine autoantibodies (anti-T_4 and/or anti-T_3) or abnormal albumin/transthyretin forms, such as those circulating in familial dysalbuminemic hyperthyroxinemia, may cause FT_4 and/or FT_3 to be overestimated, particularly when "one-step" analog methods are employed (190, 191). The more common factors interfering in TSH measurement and giving spuriously high levels of TSH are the circulating heterophilic antibodies, *i.e.* antibodies directed against mouse γ-globulins (192), or anti-TSH antibodies (193). Anti-TSH antibodies, however, usually lead to an underestimation of the actual levels of TSH and very rarely to overestimation, since they frequently prevent the formation of the "sandwich" between the two monoclonal anti-TSH antibodies used in the noncompetitive immunometric assays and the circulating TSH molecules (193). It is necessary to measure with direct methods other than those based on the analog technique, the free moiety of circulating thyroid hormones instead of the total one, to prevent possible misinterpretation due to variation of thyroid hormone transport proteins (189–191). In fact, normal levels of total T_4 (range 53–143 nmol/liter, n = 12) were recorded in several patients with TSH-oma (51, 54, 64, 79, 105, 122, 145, 146), and only the measurement of FT_4 allowed the correct diagnosis of IST. Also, patients may have T_3-toxicosis as in other forms of hyperthyroidism; thus, there is a need to measure T_3 and, in particular, FT_3 when T_4 levels are normal.

In TSH-omas, serum TSH levels, as well as thyroid hormone concentrations, showed a very broad range of values (TSH: <1.0-568 mU/liter; total T_4, 150–678 nmol/liter; total T_3, 3.0–21.0 nmol/liter; FT_4, 20 – >100 pmol/liter; FT_3, 8.0–40.2 pmol/liter). About one third of untreated and only one tenth of treated patients with TSH-oma showed TSH levels within the normal range (Table 5), and no correlation between free thyroid hormone and TSH levels was found. As detailed below in *Section II.H.4.*, variations in the biological activity of secreted TSH molecules most likely account for such findings. Interestingly, TSH levels in patients previously treated with thyroid ablation were 6-fold higher than in untreated patients, although free thyroid hormone levels were still in the hyperthyroid range, and the reduction of total thyroid hormone levels was minimal (Fig. 2). This finding suggests that tumoral thyrotroph cells may increase their TSH secretion and, as documented by the higher number of invasive macroadenomas found in previously treated patients, may undergo more active cellular proliferation in response to even a small reduction in circulating thyroid hormone levels.

In the majority of patients with TSH-oma, and independently of previous thyroid ablation, circulating free α-subunit levels, as well as α-subunit/TSH molar ratio, were clearly elevated (Table 5 and Fig. 3).[1] Either unbalanced

TABLE 3. Conditions associated with hyperthyroxinemia and a detectable serum TSH concentration

Increased circulating transport proteins (thyroxine-binding globulin, albumin, transthyretin)
Familial dysalbuminemia
Abnormal transthyretin forms
Circulating anti-T_4 autoantibodies
Neonatal period
Systemic illness
Acute psychiatric illness
Drugs (Amiodarone, amphetamine, oral contrast agents)
Replacement therapy with L-T_4
TSH-secreting pituitary adenomas
Resistance to thyroid hormones

TABLE 4. Circulating factors that may interfere with the measurement of total and free thyroid hormones or TSH, thus simulating a syndrome of IST, *i.e.* TSH-secreting pituitary adenomas or resistance to thyroid hormones

Circulating antiiodothyronine autoantibodies (anti-T_4 and/or anti-T_3)[a]
Circulating abnormal forms of albumin or transthyretin (familial dysalbuminemic hyperthyroxinemia)[a]
Circulating heterophilic antibodies (directed against mouse γ-globulins leading to interference with monoclonal antibodies used in the immunometric assay)
Circulating anti-TSH antibodies or antibodies cross-reacting with TSH

[a] To prevent misdiagnosis, measure free T_4 and free T_3 by direct two-step methods (189, 190). Avoid the use of the analog technique, since the analog binds to the antiiodothyronine autoantibodies or to the abnormal forms of albumin or transthyretin, thus giving spuriously high free thyroid hormone values.

[1] A rule of thumb to calculate α-subunit/TSH molar ratio is to divide α-subunit (μg/liter) by TSH (mU/liter) and multiply by 10, provided that TSH IRP 80/558 is used in the immunometric assay.

TABLE 5. Laboratory characteristics of patients with TSH-secreting pituitary adenoma

Parameter	No thyroid ablation % (n)[a]	Previous thyroid ablation[b] % (n)	All patients % (n)
Normal TSH levels	33 (154)	11 (80)	26 (234)
High α-subunit levels[c]	64 (94)	69 (48)	66 (142)
High α-subunit/TSH molar ratio[d]	81 (88)	79 (47)	80 (135)
High SHBG levels[e]	94 (30)	53 (15)	80 (45)

[a] n refers to the number of patients for whom the information was available.
[b] With thyroid hormone circulating levels into the hyperthyroid range.
[c] The highest values of α-subunit recorded in normal controls matched for TSH, LH, and FSH levels are as follows (194) 1) in controls with normal TSH, LH, and FSH levels, 1.1 μg/liter; 2) in controls with normal TSH but high LH and FSH levels, 4.2 μg/liter; 3) in controls with high TSH but normal LH and FSH levels, 5.0 μg/liter; 4) in controls with high TSH, LH, and FSH levels, 6.2 μg/liter.
[d] The highest values of α-subunit/TSH molar ratio recorded in normal controls matched for TSH, LH, and FSH levels are as follows (194) 1) in controls with normal TSH, LH and FSH levels, 5.7; 2) in controls with normal TSH but high LH and FSH levels, 29.1; 3) in controls with high TSH but normal LH and FSH levels, 0.7; 4) in controls with high TSH, LH, and FSH levels, 1.0.
[e] The highest values of SHBG recorded in normal controls matched for age and sex are as follows: 1) prepubertal boys and girls, 150 nmol/liter; 2) premenopausal women, 120 nmol/liter; 3) postmenopausal women, 60 nmol/liter; 4) men, 50 nmol/liter.

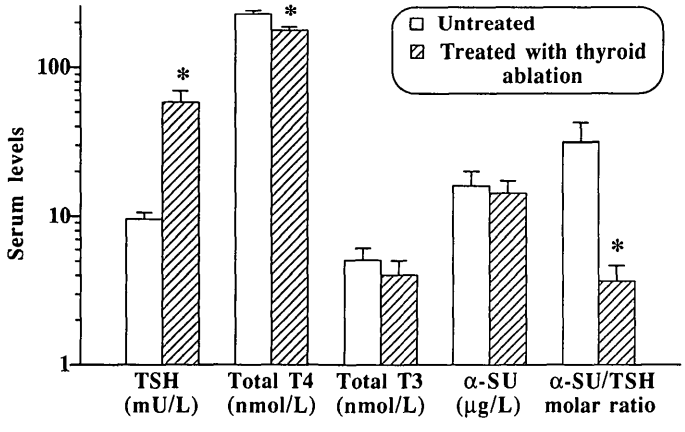

FIG. 2. Circulating levels of TSH, total T_4 and T_3, α-subunit, and α-subunit/TSH molar ratio in patients with TSH-secreting pituitary adenomas divided in two groups according to previous thyroid ablation. * Indicates significant differences ($P < 0.05$) between the two groups. Note the remarkable increase in TSH levels in patients who underwent thyroid ablation, which is accompanied by a small decrease in the concentrations of total T_4 but not total T_3. Interestingly, α-subunit levels were similar in the two groups of patients, while α-subunit/TSH molar ratio is lower in treated patients as a consequence of TSH increment.

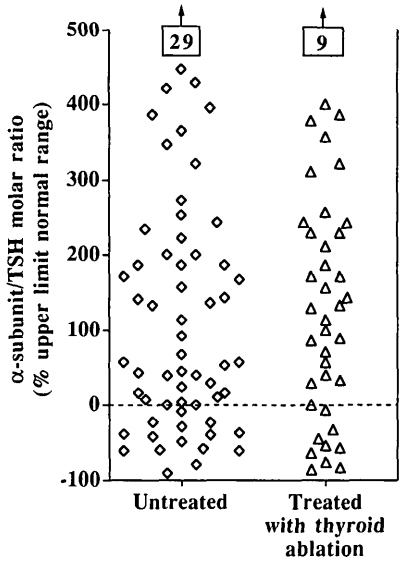

FIG. 3. α-Subunit/TSH molar ratio in 135 patients with TSH-oma untreated (n = 88) or treated with thyroid ablation (n = 47). Values are expressed as a percentage of the upper limit of normal range seen in subjects matched for TSH and gonadotropin circulating levels (*dashed line*) (see legend of Table 5). Normal molar ratios were found in about 20% of patients in both groups.

secretion of the subunit or the presence of a mixed TSH/α-subunit adenoma (see *Section II.A*) may explain this high α-subunit/TSH ratio. Although previous studies have suggested that an α-subunit/TSH molar ratio above 1.0 is indicative of the presence of TSH-secreting pituitary adenoma (2, 5, 104), the finding of α-subunit/TSH molar ratios as high as 5.7 in controls with normal levels of TSH and gonadotropins, and 29.1 in euthyroid postmenopausal women, indicates the need to compare the individual values with those of control groups matched for TSH and gonadotropin levels before drawing any diagnostic conclusions (Table 5) (8, 194). Interestingly, α-subunit levels were within the normal range in 10 of 15 patients with microadenoma (33, 66, 77, 103, 113, 120, 146, 179), but in four of them α-subunit/TSH molar ratio was high.

2. *Parameters of peripheral thyroid hormone action.* The measurements of several parameters of peripheral thyroid hormone action both *in vivo* (basal metabolic rate, cardiac systolic time intervals, Achilles' reflex time) and *in vitro* [sex hormone-binding globulin (SHBG), cholesterol, angiotensin converting enzyme, osteocalcin, blood red cell Na^+ content, etc.] (195), may help in quantifying the degree of peripheral hyperthyroidism, particularly in patients with mild clinical signs and symptoms (4, 5). In our experience (196), SHBG was in the hyperthyroid range in more than 80% of patients with TSH-oma (see also Table 5), a finding that led us to propose this test to help differentiate hyperthyroid patients with TSH-oma from those with thyroid hormone resistance (Fig. 4). In keeping with this, recent personal data suggest that there is no component of peripheral thyroid hormone resistance in TSH-omas (197). Similar results were obtained by measuring the carboxy-terminal cross-linked telopeptide of type I collagen (ICTP), a specific marker of bone resorption and osteoclastic function (198) that could be a good alternative to SHBG measurement in certain situations.

3. *Other measurements.* Serum β-subunit concentrations paralleled those of TSH complete molecule in 26 patients in

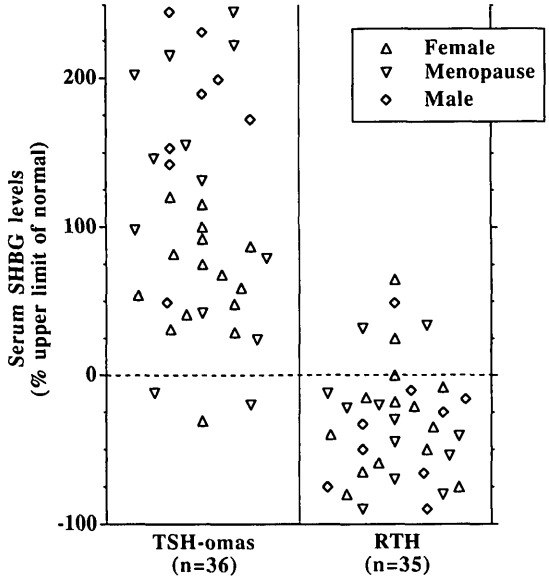

FIG. 4. SHBG levels in 36 patients with TSH-secreting pituitary adenoma (TSH-omas) and 35 patients with RTH. Values are expressed as a percentage of the upper limit of normal range seen in subjects matched for age and sex (*dashed line*) (see legend of Table 5). Among patients with TSH-oma, normal SHBG levels were found in three acromegalics, while among those with RTH high levels of SHBG were seen in four females treated with estrogens and in one male with profound hypogonadism.

whom it was measured. Finally, although the measurement of TRH in the circulation has several well known limitations, the tripeptide was found undetectable after pituitary surgery in one patient (156), while high levels were detected in another case (97), a finding that might suggest a possible etiological role of TRH in tumor formation.

E. Dynamic testing

Several stimulatory and inhibitory tests have been employed to evaluate TSH secretory dynamics in patients with TSH-oma.

1. TSH stimulatory tests. TRH injection (200–500 μg, iv) failed to stimulate TSH secretion in 92% of patients. No significant difference in the TSH responses between untreated patients and those previously treated with thyroid ablation was found (Fig. 5). In both groups, a normal response to TRH was seen only in one tenth of cases. Dopamine antagonists, such as domperidone or sulpiride (10 mg, im), stimulated TSH secretion in only two of 27 TSH-omas tested (35, 81). Chronic treatment with antithyroid drugs was followed by a clear increase in TSH levels in about 60% of patients (8, 143). In most of them, a possible reduction of FT_4 and FT_3 into the hypothyroid range may have caused additional TSH secretion from the normal thyrotrophs surrounding the pituitary tumor. However, the adenoma appears very sensitive to even a small reduction in circulating levels of FT_4 and FT_3, as observed during a close follow-up of two patients in whom TSH increase was manifest when both FT_4 and FT_3 were still in the upper limit of the normal range (120). These data are in contrast with the failure of TSH to decrease during T_3 suppression and suggest that feedback of thyroid hormone,

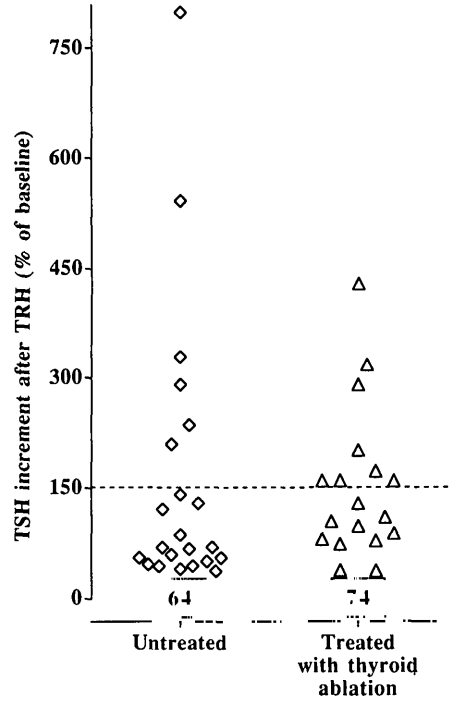

FIG. 5. Serum TSH response to TRH in 86 untreated and 92 thyroid-ablated patients with TSH-oma. The *horizontal dashed line* indicates the minimal increment seen in controls matched for baseline TSH levels. No significant difference between the two groups of patients was observed. Normal TSH responses were found only in about 8% of cases.

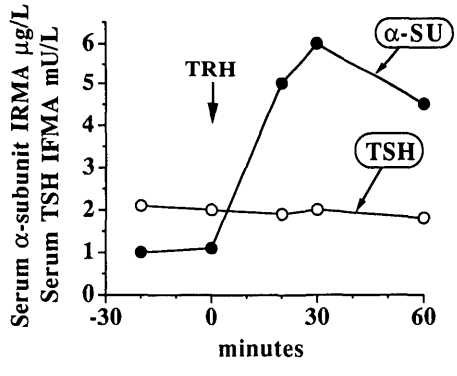

FIG. 6. Representative case of dissociated response between TSH and α-subunit to TRH test (200 μg, iv), which suggests that the two hormones may be secreted from distinct adenomatous cells with different receptor expression (169).

although impaired at high levels, remains partially operative at lower levels. In keeping with this are the observations of significantly higher TSH levels in thyroid-ablated patients than in untreated patients (Fig. 2), as well as the more active proliferation of tumoral cells in treated patients (Table 2).

Although the α-subunit response to the above stimulatory agents usually paralleled that of TSH, in some cases discrepancy between α-subunit and TSH response to TRH has been recorded (Fig. 6) (33, 35, 40, 41, 45, 104, 107, 120, 156). As already stated (see *Section II.A*), such a discrepancy may be due to mixed TSH/α-subunit-secreting adenomas composed of distinct cell types that possess different receptor expression (169).

2. TSH inhibitory tests. A normal response to long T_3 suppression tests (80–100 μg orally for 8–10 days), *i.e.* complete inhibition of both basal and TRH-stimulated TSH secretion, has never been recorded in TSH-omas, although a slight reduction of TSH levels was demonstrated in 13 of 78 tested patients (17%) (Fig. 7). Preliminary data using a short T_3 suppression test (199) confirmed these findings, indicating the autonomy of TSH secretion by the adenoma. In addition, in the case of previous thyroid ablation, a T_3 suppression test seems to be the most sensitive and specific test in documenting the possible presence of a TSH-oma. However, this test is contraindicated in elderly patients or those with coronary heart disease.

Infusion of dopamine (1–4 μg/kg body weight/min) or administration of dopamine agonists, such as bromocriptine (2.5 mg orally), failed to inhibit TSH secretion in about 80% of patients, independently of the presence of a mixed TSH/PRL adenoma. In one case (47), an exaggerated response to dopamine, which disappeared after tumor removal, was observed. On the contrary, corticosteroid administration was accompanied by reduction of circulating TSH in about 80% of patients. Finally, acute injection of native somatostatin (SRIH) or its analogs caused TSH secretion to be inhibited in the majority of cases and may be predictive of the efficacy of long-term treatment in about 94% of patients (200).

Serum α-subunit response to the above inhibitory agents usually paralleled that of TSH.

3. Other studies. The usual absence of circadian TSH rhythmicity confirmed the autonomy of TSH secretion from tumoral thyrotrophs (23, 33, 38, 60, 123, 125, 146, 147, 169). However, the rhythm was normal in two patients (29, 115) and inverted, with acrophase at midday in another patient (33). In addition, TSH pulsatility was preserved in two cases (23, 147) and lost in another (33).

Abnormal or paradoxical TSH responses to nonspecific hypothalamic releasing hormones were scarcely investigated. Interestingly, GnRH injection caused TSH to increase in some patients (33, 107), but not in others (33, 102, 182).

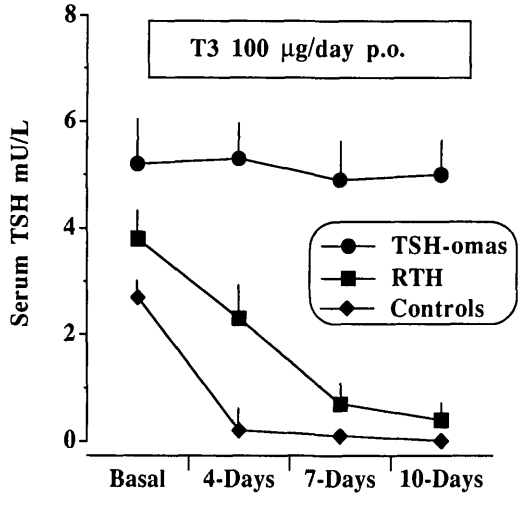

FIG. 7. Results of T_3 suppression test (Werner's test, T_3 being administered orally at the dose of 100 μg/day for 10 days) in 14 patients with TSH-oma, in 16 with RTH, and in 13 normal controls. This test is very accurate in documenting the autonomy (TSH-omas) or the refractoriness (RTH) of pituitary thyrotrophs to thyroid hormone feedback mechanism. Note that the TSH inhibition in RTH patients is qualitatively, but not quantitatively normal.

F. Pituitary imaging

Alterations of the sella profile on plain radiograms were present in almost all patients with macroadenomas. Curiously, in two patients, pituitary stones have been described (180). Indeed, the recognition of pituitary adenomas is now facilitated by the use of high resolution computed tomography (CT) and nuclear magnetic resonance imaging (MRI). This review found that 90% of the TSH-omas were macroadenomas (Table 2), with a suprasellar extension or invasiveness in two thirds of the cases. Previous thyroid ablation by surgery or radioiodine appeared to have deleterious effects on the size of the tumor. In fact, microadenomas (diameter <1 cm) and intrasellar macroadenomas were found in 34% of untreated patients *versus* 19% in those with thyroid ablation, while a reversed figure was seen in patients with invasive macroadenomas. Therefore, previous thyroid ablation may induce an aggressive transformation of the tumor (181), as observed in Nelson's syndrome after adrenalectomy for Cushing's disease. With the most recent imaging techniques, pituitary tumors as small as 3 mm could be detected (161). TSH-secreting pituitary microadenomas are now reported with increasing frequency, accounting for 10% of all recorded cases. In contrast with other secreting pituitary tumors (201), no correlation between circulating TSH levels and tumor size was found in untreated patients with TSH-oma (Fig. 8).

Recently, pituitary scintigraphy with radiolabeled Tyr^3-substituted octreotide has been shown to successfully image TSH-omas (202). Moreover, *in vivo* evidence for both SRIH and dopamine D2 receptors was obtained by Verhoeff *et al.* (175) by using single photon emission tomography with ^{111}In-octreotide and [^{123}I]iodobenzamide. The absence of clear correlation with the tumor size reduction on octreotide and bromocriptine treatment suggests that this technique may not predict the successful outcome of medical treatment. Last, bilateral petrosal sinus sampling has been used in difficult cases, allowing the identification and the lateralization of a microadenoma not seen on radiographic scans (76).

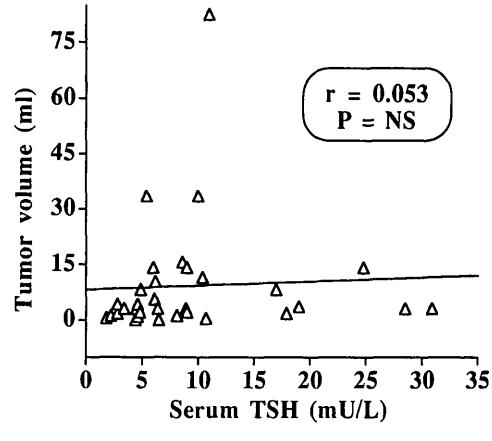

FIG. 8. Lack of correlation between serum TSH levels and the volume of TSH-secreting pituitary adenomas. These data refer to tumors not associated with hypersecretion of other anterior pituitary hormones and never treated.

However, one should expect a certain number of false lateralization, as already observed for other pituitary tumors.

G. Differential diagnosis

The presence of detectable TSH levels in a hyperthyroid patient rules out primary hyperthyroidism, while in patients on L-T_4 replacement for primary hypothyroidism, poor compliance is by far the most common cause of apparent IST (TSH still too high for the levels of the thyroid hormones). This underscores the importance of studying patients in steady state. The T_3 suppression test is helpful in difficult cases, if the repeat of baseline thyroid function tests is not conclusive.

Figure 9 proposes an algorithm in the case of hyperthyroxinemia and detectable TSH. The first step is to measure free thyroid hormone levels and repeat TSH measurement by ultrasensitive assays. The finding of normal TSH, FT_4, and FT_3 levels suggests euthyroid hyperthyroxinemia, while high FT_4 and FT_3 concentrations and suppressed TSH definitively indicate the presence of primary hyperthyroidism due to Graves' disease and other forms of thyrotoxicosis. If FT_4 and FT_3 concentrations are elevated in the presence of measurable TSH levels, it is important to exclude methodological interference, as already discussed in *Section II.D.1*. When the existence of IST is eventually confirmed, several diagnostic steps must be carried out to differentiate a TSH-oma from RTH. This is particularly true for the variant of RTH with predominant pituitary resistance in which there are clear clinical signs of hyperthyroidism (18–21). Indeed, alterations of pituitary content at CT scan or MRI, as well as the possible presence of neurological signs and symptoms (visual defects, headache), or clinical features of concomitant hypersecretion of other pituitary hormones (acromegaly, galactorrhea, amenorrhea) definitely point to the presence of a TSH-oma. Nevertheless, the differential diagnosis may be difficult when the pituitary adenoma is undetectable by CT scan or MRI or in the case of confusing (empty sella) or incidental pituitary lesions (203, 204). No significant differences in age, sex, previous thyroid ablation, TSH levels, or free thyroid hormone concentrations were recorded between patients with TSH-oma and those with RTH (Table 6) (19–21). However, in contrast with RTH patients, familial cases of TSH-oma have never been documented. Serum TSH levels within the normal range are more frequently found in RTH, where an increased bioactivity of the secreted molecules is constantly found (205). Moreover, the findings of elevated

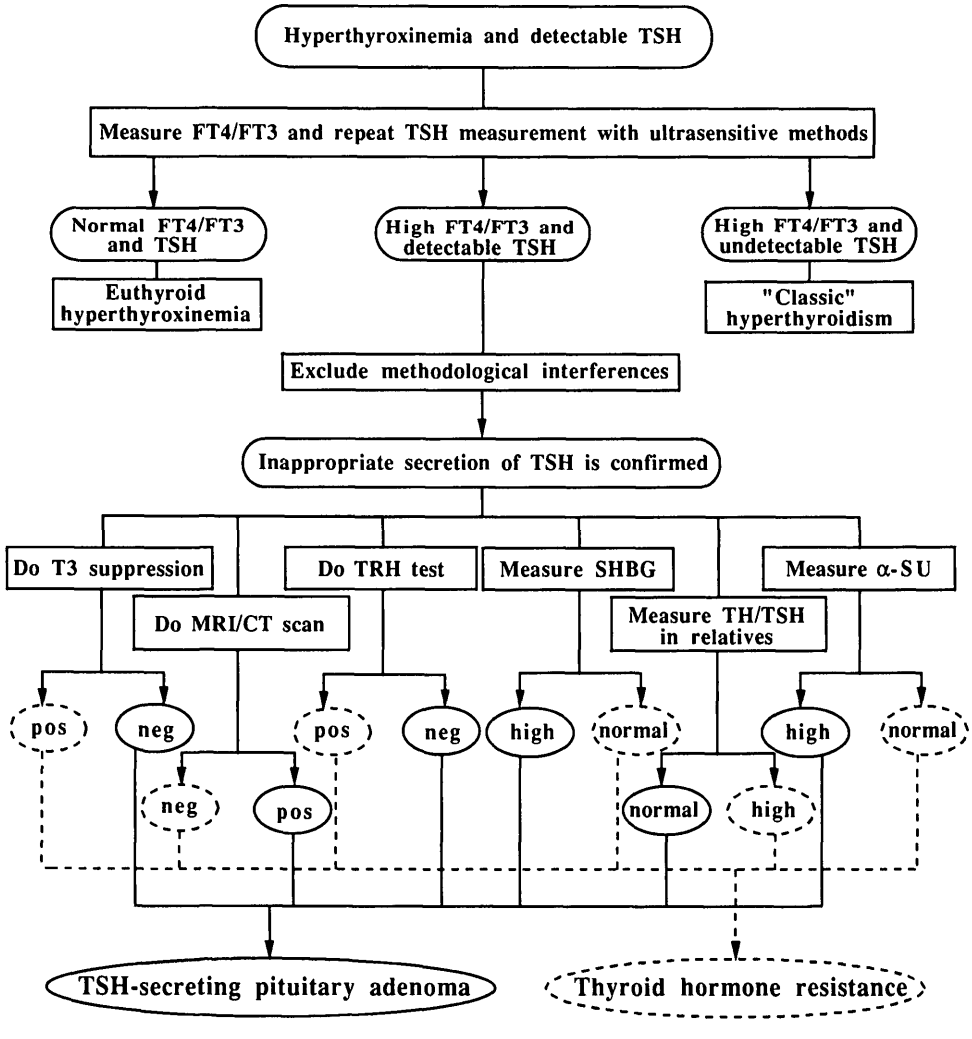

FIG. 9. Diagnostic algorithm for the management of patients presenting with hyperthyroxinemia and detectable TSH levels.

TABLE 6. Differential diagnosis between TSH-secreting pituitary adenomas (TSH-omas) and resistance to thyroid hormones (RTH) (data from the literature, updated to January 1996)

Feature	TSH-omas	RTH	*P* values
Age (years)	11–84	0.1–80	NS
Sex (F/M ratio)	1.26	1.17	NS
Familial cases	0%	82%	<0.001
Previous thyroid ablation	31%	45%	NS
CT scan or MRI lesions	98%	2%	<0.001
Serum TSH levels in the normal range[a]	33%	64%	<0.05
High serum α-subunit levels[a]	64%	2%	<0.001
High α-subunit/TSH molar ratio[a]	81%	2%	<0.001
Elevated SHBG levels[a]	94%	2%	<0.001
Normal or exaggerated TSH response to TRH[a]	8%	96%	<0.001
Qualitatively normal TSH response to T_3[b]	12%	100%	<0.001

[a] Untreated patients.

[b] Werner's test (80–100 μg T_3 for 8–10 days). Quantitatively normal responses to T_3, *i.e.* complete inhibition of both basal and TRH-stimulated TSH levels, have never been recorded in either group of patients.

α-subunit concentrations and/or high α-subunit/TSH molar ratio, absent/impaired TSH responses to TRH administration and to T_3 suppression test (Fig. 7), and values of circulating SHBG in the hyperthyroid range (Fig. 4) favor the presence of a TSH-oma; the few TSH-omas with low SHBG concentrations were those with concomitant hypersecretion of GH, which potently inhibits SHBG secretion, and the few patients with thyroid hormone resistance with high SHBG levels were those treated with estrogens or showing profound hypogonadism. In addition, a 3- to 5-day octreotide test has been proposed to differentiate TSH-omas from RTH; indeed, a strong suppression is usual in TSH-omas, while mild or no response is observed in RTH (36, 197).

Table 7 summarizes the major findings for the differential diagnosis of TSH-oma and RTH. In difficult cases, particularly after thyroidectomy, genetic investigations may be the only diagnostic test but require a specialized laboratory.

Last, an apparent association between TSH-oma and RTH has been recently reported in a young Japanese woman (179). Although genetic studies on T_3 receptor-β_1 mutations and familial investigations were not carried out in this case, the occurrence of TSH-omas in RTH patients is theoretically possible and, therefore, should be carefully considered.

H. Pathology

1. Morphology and histopathology. As discussed above (*Section II.F*), most TSH-omas are diagnosed at the stage of macroadenomas; they are often highly invasive (79) with very fibrous consistency. By light microscopy, adenoma cells usually have chromophobic appearance, although they occasionally stain with either basic or acid dyes. Cells are often arranged in cords, they frequently appear polymorphous and are characterized by large nuclei and prominent nucleoli. Ultrastructurally, the well differentiated adenomatous thyrotrophs resemble the normal ones, while the poorly differentiated adenomas are characterized by the presence of fusiform cells with long cytoplasmic processes, scanty rough endoplasmic reticulum, poorly developed Golgi apparatus, and sparse, small secretory granules (80–200 nm) mainly aligned under the plasma membrane. Occasionally, cells with abnormal morphology or mitoses (82, 172), which may be mistaken for a pituitary malignancy or metastases from distant carcinomas, are found. Indeed, there are no clear criteria of malignancy for TSH-omas except for the presence of metastases. In fact, the transformation of a TSH-oma into a pituitary TSH-secreting carcinoma with multiple metastases has been reported only once (130).

Immunostaining studies showed the presence of TSHβ, either free or combined, in all adenomatous cells from every type of TSH-oma, with only five exceptions out of 135 reported cases (43, 58, 87, 116, 185). Furthermore, the case reported by Mixson *et al.* (130) suggested that the finding of very high circulating concentrations of free α-subunit might portend future malignant behavior and that a concomitant, spontaneous, and marked decrease of both TSH and α-subunit concentrations might indicate that the tumor is becoming less differentiated and correlate with invasive and metastatic behavior.

Although cells from mixed adenomas generally appear monomorphous by electron microscopy, colocalization of TSH and other pituitary tropins in the same cell (96) or even in the same secretory granule has been documented by using particular techniques, such as double gold immunolabeling (35, 69, 107, 123, 169) (Fig. 10). Nonetheless, a positive immunohistochemistry for one or more pituitary hormones does not necessarily correlate with its or their hypersecretion *in vivo* (149). The production and/or the secretion of two or more biochemically unrelated hormones by the same adenomatous cell strongly suggests that mixed TSH-secreting pituitary tumors may develop from a common multipotential progenitor cell.

2. Molecular studies. In recent years, molecular biological techniques have provided several important insights into the pathogenesis of pituitary adenomas. As in the majority of the other pituitary adenomas, three of three TSH-omas were found to be monoclonal in origin (206). Although most information available so far concerns other more frequent functioning and nonfunctioning tumors, these new frontiers are now extending to TSH-omas (Table 8).

Structural genetic abnormalities, such as mutations result-

TABLE 7. Major findings that differentiate patients with TSH-secreting pituitary adenoma from those with resistance to thyroid hormone

1. Presence of specific lesions at the sella turcica imaging (MRI, CT scan).
2. High values of α-subunit and α-subunit/TSH molar ratio.
3. High values of indices evaluating TH effects on peripheral tissues (SHBG, ICTP, osteocalcin, cardiac systolic time intervals, etc.).[a]
4. Absent/impaired TSH responses to both stimulatory and inhibitory tests.
5. Absence of relatives with identical biochemical features (high free TH levels, measurable TSH).

[a] SHBG, Sex hormone-binding globulin; ICTP, carboxy-terminal cross-linked telopeptide of type I collagen.

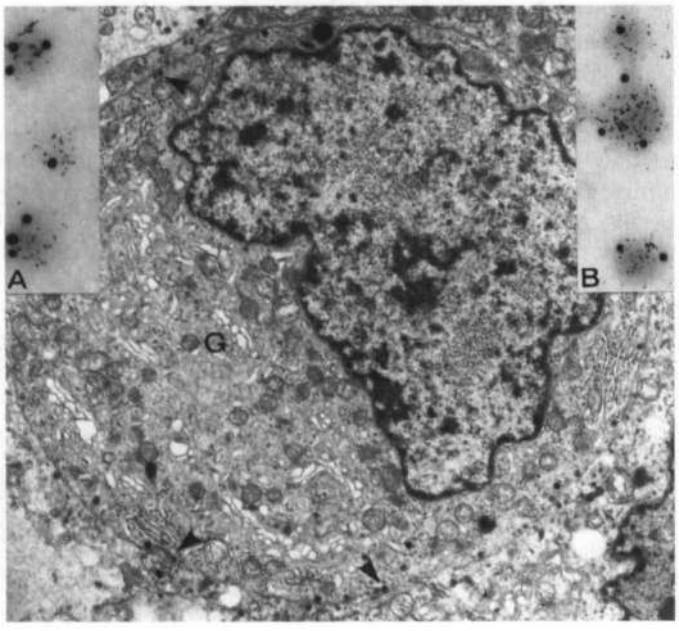

FIG. 10. Electron micrograph of a cell from a monomorphous pituitary adenoma secreting TSH, GH, and α-subunit. A few secretory granules are located at the periphery of the cell (*arrows*). Rough endoplasmic reticulum and Golgi apparatus (G) are well developed (×8,500). Double immunolocalization of GH/α-subunit and GH/TSHβ in secretory granules was performed by using specific antisera and protein A-gold particles of different sizes. A, Immunolocalization of GH (small gold particles) and α-subunit (large gold particles) (×70,000); B, Immunolocalization of GH (small gold particles) and TSHβ (large gold particles) (×60,000). (Courtesy of Dr. M. Bassetti, Department of Pharmacology, University of Milan).

ing in transcriptional activation, have been investigated in few TSH-omas. In contrast with GH-secreting adenomas, in which the expression of *gsp* oncogene is detected in about 40% of the cases (207), none of the 11 TSH-omas screened has been shown to express known activating mutations in the genes coding for the G protein αq-, α11-, αs-, or αi2-subunits (61, 208, 209). Although activating mutations might exist elsewhere in the coding sequences of G proteins or downstream components, these data indicate that impairment in GTPase activity is unlikely to be involved in the pathogenesis of TSH-secreting pituitary adenomas. In support of this view is the lack of reported TSH-omas in patients with McCune-Albright syndrome, where Gαs mutation is present in a mosaic pattern (210), as well as the recent report of a mixed GH/PRL/TSH-secreting pituitary adenoma, in a patient with atypical McCune-Albright syndrome in whom no evidence of *gsp* oncogene was found (78).

In a recent study on c-*myc*, c-*fos*, and c-*myb* gene expression in pituitary adenomas, c-*myc* overexpression was identified in a subgroup of tumors, but again the two TSH-omas studied were both negative for overexpression of these oncogenes (211). *Ras* oncogene has been found in highly invasive prolactinoma and adenocarcinomas (212–214), and protein kinase C mutations have been demonstrated in invasive pituitary tumors (215), but no TSH-omas were tested in these series. Similarly, TSH-omas were not screened for loss of antioncogenes such as retinoblastoma (Rb) gene which was, however, unaltered in other pituitary tumors (211, 216, 217). Moreover, no loss of tumor suppressor gene p53 was found

TABLE 8. Results of *in vitro* studies on oncogenes and protooncogenes in TSH-secreting pituitary adenomas

Study	% (n)[a]	Reference nos
Quantitative alterations		
Pit-1 overexpression	93 (14)	139, 149, 150, 219
p53 overexpression	0 (1)	218
c-*myc*, c-*fos*, and c-*myb* overexpression	0 (2)	211
Absent TRβ1 and TRα1 expression	100 (1)	177
Mutations		
Gαs (gsp)	0 (12)	61, 208, 209
Gαq, Gα11, Gαi2	0 (10)	61, 209
Pit-1	0 (1)	219
P21ras	?[b]	212–214
Protein kinase C	?[b]	215
TRH receptor (activating)	0 (9)	61
Dopamine receptor (D2) (inactivating)	0 (3)	220
TRβ1 (inactivating)	0 (6)	Unpublished
TRα1 (inactivating)	0 (6)	Unpublished
Deletions		
11q13 deletions	0 (1)	209
Rb gene	?[c]	211, 216, 217

[a] n refers to the number of patients for whom the information was available.

[b] Alterations reported in other types of pituitary adenomas, but not in TSH-omas.

[c] No alterations reported in other types of pituitary adenomas, but no data are available in TSH-omas.

in one case studied (218). One TSH-oma was studied for deletions at chromosome 11q13, which are present in about 20% of sporadic pituitary tumors, and found to be negative (209). Nonetheless, hyperthyroidism due to TSH-omas has been reported in four cases within the setting of multiple endocrine neoplasia type 1 syndrome (MEN-1), a dominant autosomal inherited predisposition to neoplastic transformation of parathyroids, endocrine pancreas, and pituitary that is linked to deletions at locus 11q13 (43, 108, 185).

In the search of candidate oncogenes that may be involved in the pathogenesis of TSH-omas, interest has been focused on pituitary-specific Pit-1/GHF-1, a nuclear transcription factor that regulates cell differentiation and expression of PRL, GH, and TSH genes. In fact, overexpression of Pit-1 may be associated with pituitary tumors. However, among 14 TSH-omas studied no detectable mutations in Pit-1 gene were found, although overexpression of Pit-1 was present in almost all cases (139, 149, 150, 219). However, the pathogenetic role of such overexpression remains to be demonstrated. In addition, no mutations of TRH receptor gene, which might result in functional and/or proliferative activation, were found in nine TSH-omas screened by Dong *et al.* (61). Similarly, no inactivating mutations in dopamine D2 receptor gene were found in a series of 79 pituitary tumors, including three TSH-omas (220).

Other potential candidate oncogenes are mutant forms of thyroid hormone receptors (TR). However, after amplifying the DNA encoding for TRβ1 and TRα1 from six different TSH-omas and sequencing all their exons, we found no evidence of gene mutations (P. Beck-Peccoz and V. K. K. Chatterjee, unpublished data). Absence of TRα1, TRα2, and TRβ1 expression was reported in one TSH-oma (177). Although additional studies are required to rule out an oncogenic role

of abnormal thyroid receptors (particularly on the TRβ2 isoform which is highly expressed in pituitary tissue), this appears unlikely since patients with known mutations of TRβ1 do not appear to have an increased risk for developing pituitary adenomas.

Using oligonucleotide probes for specific pituitary hormone mRNAs, TSH α- and β-subunit mRNAs have been detected in tumor tissues. Such mRNAs were of a size similar to that found in normal pituitary, and the TSH gene transcription site was normal (146, 156, 221). Moreover, Sanno *et al.* (150) recently screened five TSH-omas with or without associated GH or PRL hypersecretion and found the mRNAs encoding for all three hormones, strengthening the concept that both pure and mixed TSH-omas originate from a multipotential cell. However, the limited data are too preliminary to draw definite conclusions on transcriptional events in TSH-omas.

Finally, few studies investigated the expression of substances that, released locally within pituitary tissue, may act on hormone secretion and cell growth. In particular, no detectable SRIH mRNA was detected in one case, in contrast with its constant presence in almost all GH-secreting adenomas (222). Evidence for production of interleukin-6, a putative autocrine growth factor, was provided in one TSH-oma (223). Recently, Ezzat *et al.* (67) found increased basic fibroblast growth factor (bFGF) levels in blood from two patients with invasive mixed PRL/TSH-secreting adenomas characterized by marked fibrosis. Interestingly, bFGF levels decreased after adenomectomy in both cases, while elevated concentrations were found in culture media. The tumoral origin of bFGF was confirmed by the finding of specific mRNA in the tissues removed at surgery, suggesting a possible autocrine role for this growth factor in tumor development. Further studies are needed to determine its potential correlation with tumor invasiveness and fibrosis.

3. In vitro secretion and receptor studies. The secretion of TSH from tumoral thyrotrophs in primary culture has been investigated in small series. The amounts of TSH and its subunits present in media samples were generally high, although extremely variable. Similarly, the α-subunit/TSH molar ratio was elevated and in general correlated with the values observed in serum. In mixed adenomas, *in vitro* TSH secretion was frequently associated with hypersecretion of other hormones, particularly GH, as expected on the basis of *in vivo* data.

The effects on TSH secretion of different releasing and inhibiting hormones have been investigated in short-term cultures of TSH-omas. The pharmacological manipulations suggested that a large number of functioning receptors are expressed by TSH-omas. Although the majority of responses would be predicted from *in vivo* data (96, 160), discrepancies between the *in vivo* and *in vitro* responsiveness were frequently observed. If *in vivo* TSH response to TRH was usually absent, several *in vitro* studies showed either the presence (26, 41, 63, 70, 110, 111, 123) or the absence (69, 96, 186) of TSH response. These data suggest that the majority of tumors possesses TRH receptor, whereas lack of TRH-binding sites was documented in only a few cases (48, 141).

Receptors for inhibitory neurohormones, such as SRIH and dopamine, have been found with variable frequency. SRIH binding experiments indicate that almost all TSH-omas express a variable number of SRIH receptors, generally lower than those found in GH-secreting tumors (26, 40, 115, 141, 167), but higher than in normal thyrotroph cells. Even though no data have been so far reported in TSH-omas, it is worth noting that, among the five SRIH receptor subtypes recently cloned, molecular studies showed heterogeneous expression of all types of SRIH receptor, except for SSTR4, in different types of pituitary tumors (224–226). Although one study dealing with basal and TRH-stimulated TSH secretion failed to show any effect of SRIH (26), recent studies showed that SRIH induces TSH-oma cell membrane hyperpolarization, which is responsible for the decrease in intracellular Ca^{2+} concentrations ($[Ca^{2+}]i$) and inhibition of TSH secretion (167). In addition, SRIH inhibited the sustained increase of $[Ca^{2+}]i$ and the decrease in membrane conductance induced by TRH. It is worth noting that in a series of 10 TSH-omas the highest SRIH-binding site densities were found in two mixed GH/TSH adenomas (40). Since SRIH analogs are highly effective in reducing TSH secretion by neoplastic thyrotrophs, the inhibitory pathway mediated by SRIH receptors appears to be intact in such adenomas (26, 69, 110, 123, 160, 167, 182). The existence of normally functioning SRIH receptors in TSH-omas is further supported by the good correlation between SRIH-binding capacity and maximal biological response, as quantified by inhibition of TSH secretion and *in vivo* restoration of euthyroid state (40).

The presence of dopamine receptors in TSH-omas was the rationale for therapeutic trials with dopaminergic agonists, such as bromocriptine (227). However, binding studies have shown variable expression of dopamine receptors (41, 47). In addition, both positive (69, 96) and negative (41, 70, 110) TSH responses to dopamine were seen in primary cultures. Moreover, abnormal coupling of dopamine receptors with adenylate cyclase, resulting in a paradoxical enzyme stimulation, has been reported in one case (160). This finding may account for the *in vivo* paradoxical TSH increase observed after L-dopa administration in one woman with a TSH-secreting macroadenoma (47).

Due to the infrequent occurrence of TSH-omas, the presence or absence of receptors for other hypothalamic neurohormones has not been studied so far. In particular, no data are available on the responsiveness of these tumors to agents that are able to stimulate almost all pituitary tumors independently of their secretory capacity, such as pituitary adenylate cyclase-activating peptide and vasoactive intestinal peptide (228).

In agreement with the marked insensitivity of neoplastic thyrotrophs to thyroid hormone feedback, the addition of T_3 to primary cultures had no effects on TSH secretion in two cases (70, 96). However, T_3 was able to reduce TSH secretion in one (110) and to inhibit TSH response to TRH in two additional cases (111). In addition, type II 5′-deiodinase, the enzyme that converts T_4 to T_3 in the pituitary gland, was unaltered in one TSH-oma (93).

Several *in vivo* and *in vitro* studies suggest that TSH-omas are sensitive to corticosteroid action. Dexamethasone was effective in suppressing basal and TRH-stimulated *in vitro* TSH secretion in one case, but no effect was observed in

another, showing a good correlation with *in vivo* results (26). Finally, estrogen receptors were recently demonstrated by *in situ* hybridization in two TSH-omas, further supporting the idea that thyrotrophs may be a significant target of estrogen action (229). However, results are too sketchy to draw meaningful conclusions on the potential deleterious *in vivo* impact of estrogen (therapy or pregnancy) on tumor growth.

4. *Posttranslational processing.* TSH belongs to the glycoprotein hormone family, and both intrapituitary and circulating TSH exist as multiple isoforms characterized by heterogeneity of oligosaccharide chains (230–232). Tumoral thyrotrophs produce a wide spectrum of TSH molecules with different isoelectric points, bioactivities, and MCRs due to differences in their oligosaccharide residues. Bioactivity of TSH from patients with TSH-oma was initially measured on material separated by isoelectrofocusing from tumor extracts (176) or obtained from primary tumor cell cultures (70). Both studies showed that adenomas produce various TSH isoforms and that TSH molecules may have an enhanced bioactivity. Sergi *et al.* (154) confirmed such results and showed that intratumoral isoforms resemble those of the normal pituitary content and that the loss of regulation in neoplastic TSH secretion may lead to the preferential release of more neutral and acidic forms. Thus, the altered ratio between active and inactive isoforms may be responsible for the variable stimulation of the thyroid gland in patients with TSH-oma.

The first demonstration that circulating TSH in patients with TSH-oma may possess an enhanced bioactivity was given in one patient with a mixed GH/TSH-secreting pituitary adenoma (35). Serum TSH levels were within the normal range with high free thyroid hormone, and the ratio between biological and immunological activities (B/I) of TSH was significantly higher than that of controls (TSH B/I: 6.9 ± 0.2 *vs.* 4.4 ± 1.1). Gel filtration revealed a molecular weight slightly lower than that of normal TSH, suggesting possible alterations in glycosylated chains. More recent studies, using modern and more sensitive techniques, indicate that the circulating TSH B/I ratio may be either normal, reduced, or increased in patients with TSH-oma (41, 79, 232). Furthermore, studies dealing with lectin affinity chromatography revealed an altered glycosylation of circulating TSH from several patients with TSH-oma, with marked differences in sialic acid and fucose content or with a prevalence of immature forms (*i.e.* those with high-mannose carbohydrate chains) that firmly bind to concanavalin A (121, 233). Together these findings further stress the fact that an impaired control of TSH synthesis and autonomous secretion may be associated with alterations of the posttranslational processing of the molecule resulting in the release of TSH forms with altered glycosylation and variable bioactivity.

The possible role of hypothalamic agents on the abnormally glycosylated forms of TSH has been scarcely investigated. In particular, TRH injection had no effects on TSH bioactivity (234) and TSH binding to lentil lectin (122). Conversely, *in vivo* octreotide treatment was able to affect TSH glycoisomer distribution pattern on lectin chromatography in one patient (74). It is conceivable that the restoration of euthyroidism in some patients showing no definite variation in immunoreactive levels of TSH during octreotide (87, 200) or bromocriptine (83) administration may be due to a reduction of the bioactivity of secreted molecules.

I. Treatment and outcome

1. Pituitary surgery and radiation therapy. The primary goal of treatment of TSH-omas is to remove the pituitary tumor or, alternatively, to block TSH secretion and cell replication and restore euthyroidism. Therefore, the first therapeutic approach to TSH-secreting pituitary adenomas should be to surgically remove or debulk the tumor by transsphenoidal or subfrontal adenomectomy, the choice of the route depending on the tumor volume and its suprasellar extension (235). This may be particularly difficult because of the marked fibrosis of these tumors, which is possibly related to high expression of a form of fibroblast growth factor, as cited in *Section II.H.2.* In addition, such tumors may be locally invasive involving the cavernous sinus, internal carotid artery, or optic chiasm, thus rendering complete resection of the tumor either dangerous or impractical. Antithyroid drugs (methimazole or propylthiouracil, 20–30 and 200–300 mg/day, respectively) or octreotide (100 μg sc, twice or three times daily) along with propranolol (80–120 mg/day orally) can be administered to restore euthyroidism before surgery. However, they may obscure the immediate postoperative course of TSH secretion, which may be a useful criterion to assess potential cure (see below). If surgery is contraindicated or declined, pituitary radiotherapy (no less than 45 Gy fractionated at 2 Gy per day or 10–25 Gy in a single dose if a stereotactic Gamma Unit is available) and subsequent SRIH analog administration should be considered.

TABLE 9. Results of pituitary surgery and/or irradiation in the treatment of TSH-secreting pituitary adenomas

Treatment	n	Apparently cured[a] %	Improved[b] %	Unchanged %
Pituitary surgery alone	120	33	33	34
Pituitary irradiation alone	6	33	50	17
Pituitary surgery, immediately followed by pituitary irradiation	21	14	48	38
Pituitary surgery and/or irradiation in two or more successive stages	30	40	37	23
Total	177	32	36	32

[a] Normalization of thyroid hormone circulating levels with complete removal of tumor mass.
[b] Normalization of thyroid hormone circulating levels without complete removal of tumor mass.

Table 9 shows the general outcome after surgery alone or combined with radiotherapy (in one or more successive stages): normalization of thyroid hormone circulating levels and apparent complete removal of tumor mass was observed in 32% of patients who may therefore be considered apparently cured (follow-up ranged from 2 to 55 months). An additional 36% of patients were judged improved, as normalization of thyroid hormone circulating levels was achieved in all, though there was no complete removal of the adenoma. Together these findings indicate that about two thirds of TSH-omas are under control with surgery and/or irradiation. In the remaining patients, TSH hypersecretion was unchanged after the above treatments, a fact that undoubtedly reflects the large size and the invasiveness of the tumor. In contrast to what was observed in a series of TSH-omas (79, 181), the analysis of data from 147 patients does not suggest that a marked elevation of α-subunit or cosecretion of other pituitary hormones are unfavorable prognostic factors. Previous thyroid ablation or antithyroid drug treatments did not significantly affect the results of surgery and/or radiotherapy. Postsurgical deaths were reported in five cases (28, 53, 79, 128, 181). Because of the possible iatrogenic hypopituitarism, evaluation of other pituitary functions, particularly ACTH secretion, should be carefully undertaken soon after surgery and checked again every year, especially in patients treated by radiotherapy. In addition, in the case of surgical cure, postoperative TSH is undetectable and may remain low for many weeks or months, causing central hypothyroidism. The time necessary for the recovery of normal thyrotrophs is variable, and occasionally permanent central hypothyroidism may occur because of damage to the normal thyrotroph by the tumor or during surgery. Thus, transient or permanent L-T_4 replacement therapy may be necessary. Finally, in six cases total thyroidectomy was performed after pituitary surgery failure, as the patients were at risk of thyroid storm (4, 59, 107, 157, 183, 186). It is noteworthy that a transient, often asymptomatic, syndrome of inappropriate ADH secretion is not uncommon, occurring about 1 week postoperatively, as observed after surgery for other pituitary tumors (236).

2. *Medical treatment.* The medical treatment of TSH-omas depends on SRIH analog octreotide (36, 54, 200) or, as recently suggested, lanreotide (77) administration. In fact, previous experience with administration of dopamine agonists, such as bromocriptine (20–60 mg/day orally), showed that this drug failed to persistently block TSH secretion in the majority of patients and caused tumor shrinkage in only one (184). On the contrary, in 73 TSH-omas, octreotide (50–750 μg sc twice or three times daily) was effective in reducing TSH and α-subunit secretion in 92% and 93% of cases, respectively, with normalization of TSH in 79% and restoration of the euthyroid state in the majority of them (Table 10). In 52% of patients, a clear shrinkage of tumor mass could be demonstrated, and vision improvement was observed in 75%. Tachyphylaxis occurred in 22% of patients and responded to increasing octreotide doses, whereas long term studies demonstrated true escape from the inhibitory effects in 10% of cases. In only 4% of cases has a true resistance to octreotide treatment been documented (23, 54, 90, 115). In almost all patients with mixed TSH/GH hypersecretion, signs and symptoms of acromegaly concomitantly disappeared. Of interest is the recent report on octreotide treatment that was effective in restoring euthyroidism in a pregnant woman and had no side effects on fetal development and thyroid function (145). Patients on octreotide must be carefully monitored, as untoward side effects, such as cholelithiasis and carbohydrate intolerance, may become manifest. The dose administered should be tailored for each patient, depending on therapeutic response and tolerance (including gastrointestinal side effects). The marked octreotide-induced suppression of TSH secretion and consequent biochemical hypothyroidism seen in some patients may require L-T_4 substitution. Whether SRIH analog treatment may be an alternative to surgery and irradiation in patients with TSH-oma remains to be established. However, the recent slow-release preparation of SRIH analogs, lanreotide-SR and octreotide-LAR, may represent a useful tool for long-term treatment of such rare pituitary tumors (77).

J. Criteria for cure and follow-up

Due to the rarity of the disease and the great heterogeneity of the methods used, the criteria of apparent cure of patients operated or irradiated for TSH-omas have not been clearly established. The most common among them are summarized in Table 11. It is obvious that previous thyroid ablation makes some of these criteria not applicable. In untreated hyperthyroid patients, it is reasonable to assume that cured patients have clinical and biochemical reversal of thyroid hyperfunction. However, the finding of normal free thyroid hormone concentrations or of indices of peripheral thyroid hormone action (SHBG, ICTP, etc.) is not synonymous with complete removal or destruction of tumoral cells, since transient clinical remission accompanied by normalization of thyroid function is possible (120). Disappearance of neurological signs and symptoms is a good prognostic event but lacks both sensitivity and specificity, as even an incomplete debulking of the tumor may cause visual field defects and headache to vanish. The resolution of specific neuroradiological alterations is also affected by low predictivity, since the pituitary imaging performed after surgery is often char-

TABLE 10. Results of the treatment with octreotide (50–750 μg twice or three times daily, sc) in 73 patients with TSH-secreting pituitary adenoma recorded in the literature as of January, 1996

TSH reduction (>50% *vs.* basal)	92%	Vision improvement	75%
TSH normalization	79%	Tumor mass shrinkage	52%
α-Subunit reduction	93%	Tachyphylaxis	22%
Thyroid hormone normalization:		True escape (long-term studies)	10%
Short-term studies	72%	Resistance (long-term studies)	4%
Long-term studies	95%	Discontinuation of therapy due to side effects	7%
Goiter size reduction	18%		

TABLE 11. General criteria for the evaluation of the efficacy of pituitary surgery or radiotherapy in patients with TSH-oma

Criteria	Comments
Clinical remission of hyperthyroidism.	Not applicable in the case of thyroid ablation.
Disappearance of neurological symptoms.	Nonspecific.
Normalization of serum thyroid hormone levels and indices of peripheral thyroid hormone action.	Not applicable in the case of thyroid ablation.
Normalization of serum TSH levels.	They are frequently (33%) normal in untreated patients. Not applicable in the case of thyroid ablation.
Normalization of α-subunit and α-subunit/TSH molar ratio.	Generally good, but sensitivity is low.
Resolution of neuroradiological alterations.	Generally good, but sensitivity is low.
Complete suppression of TSH secretion during T_3 administration (Werner's test).	Unequivocally good. However, may be contraindicated in certain patients.

acterized by false negative imaging. The criteria of normalization of circulating TSH is not applicable to previously thyroidectomized patients or to the 26% of patients with normal basal values of TSH. In our experience, undetectable TSH levels 1 week after surgery are likely to indicate complete adenomectomy, provided that the patient was hyperthyroid and presurgical treatments were stopped at least 10 days before surgery (120). Normalization of α-subunit and/or α-subunit/TSH molar ratio is in general a good index for the evaluation of therapy efficacy (3–5, 34, 79). However, both parameters are characterized by less than optimal sensitivity, as they are normal in about 25% of patients with TSH-oma. The most sensitive and specific test to document the complete removal of the adenoma remains the T_3 suppression test (in the absence of contraindication) (120). In fact, only patients in whom T_3 administration completely inhibits basal and TRH-stimulated TSH secretion appear to be truly cured (Fig. 11).

No data on the recurrence rates of TSH-oma in patients judged cured after surgery or radiotherapy have been reported. However, the recurrence of the adenoma does not appear to be frequent, at least in the first years after successful surgery (120). In general, the patient should be evaluated clinically and biochemically 2 or 3 times the first year postoperatively and then every year. Pituitary imaging should be performed every 2 or 3 yr but should be promptly

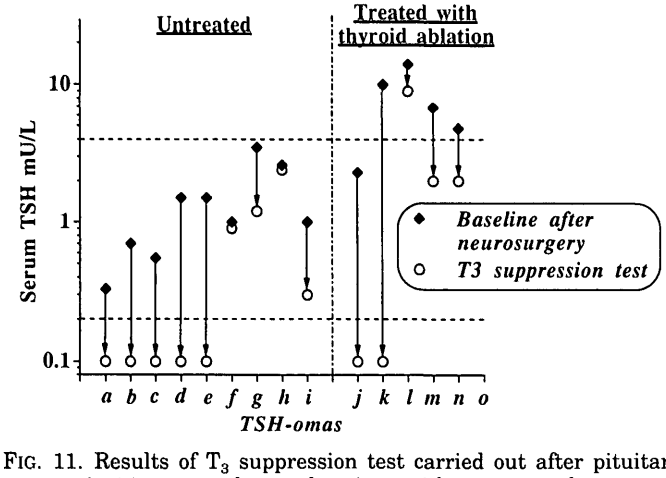

FIG. 11. Results of T_3 suppression test carried out after pituitary surgery in 14 apparently cured patients either untreated or treated with thyroid ablation before neurosurgery. *Horizontal dashed lines* indicate the upper and the lower limits of TSH normal range. Note that only five of nine untreated patients and two of five previously thyroid-ablated patients could be judged truly cured, as their serum TSH levels were completely suppressed.

done whenever an increase in TSH and thyroid hormone levels or clinical symptoms occur. In the case of persistent macroadenoma, a close visual fields follow-up is required because vision is threatened. Emergency surgical decompression is not always able to reverse even a recent deficit.

III. Pituitary Hyperplasia and Primary Hypothyroidism

Primary hypothyroidism is a common disorder, particularly in women and the elderly (237). Occasionally, patients present with atypical clinical features, such as precocious puberty, amenorrhea-galactorrhea, or visual fields defects, which draw attention to the pituitary gland. The possibility of increased size of the pituitary in primary hypothyroidism was recognized for the first time by Niepce (1) in 1851 at the autopsy of a cretin. Pituitary hyperplasia is usually asymptomatic but complications are possible, particularly in long-standing untreated hypothyroidism. Consequently it is imperative that the entity of reactive pituitary hyperplasia be identified; it should not be mistaken for a primary pituitary process, which could lead to unwarranted pituitary surgery. Indeed, pituitary hyperplasia, reversible on thyroid hormone replacement, is the main etiological diagnosis of a pituitary mass occurring in the context of untreated primary hypothyroidism. However, nodular hyperplasia or occasionally a TSH-secreting pituitary tumor can arise in a hyperplastic gland, even though its autonomy remains unclear in humans. In addition, an incidental pituitary tumor not related to the hypothyroidism is also possible. These latter diagnoses should be considered in the case of inadequate resolution of the pituitary mass on thyroid hormone replacement.

A. Animal models

Pituitary hyperplasia secondary to primary hypothyroidism was well established after experimental studies were performed in rats and mice (238–255). Knowing that thyrotroph cells represent only 10% of all pituitary cells in euthyroid rats (238), it is remarkable that primary hypothyroidism can result in significant hyperplasia. Nevertheless, as Surks and De Fesi (238) have shown, the percentage of thyrotrophs increases to 34% in hypothyroidism. Induction of pituitary hyperplasia and then adenoma is easily obtained in mice, and to a lesser degree in rats, after thyroidectomy (240, 242), ^{131}I therapy (249), propylthiouracil treatment (252), or even chronic iodine deficiency (239). Females in general are more

prone to tumorigenesis, and the degree of hypothyroidism correlates positively with pituitary tumor development and negatively with tumor induction time (240). By transplantation, pituitary tumors are transferable to isologous hypothyroid mice; here again, the latency period of tumor growth and the rate of proliferation are inversely correlated to the degree of thyroid hypofunction of the host (245); in addition, administration of thyroid hormone to the host prevents or slows the development of tumor (248). The behavior of a thyrotroph tumor in the host varies, remaining partially thyroid hormone dependent or becoming thyroid hormone independent (autonomous), particularly after several passages in the hypothyroid host. In an euthyroid host, a thyrotroph tumor graft is unlikely to develop, and then, only after several passages in hypothyroid hosts (244). Interestingly, the graft of an autonomous thyrotroph tumor induces thyroid hyperplasia and numerous thyroid adenomas in a host with an intact thyroid (246); furthermore, a marked stimulation of the gonads has been noted in athyreotic hosts of both genders. A case of a tumor paradoxically stimulated by thyroid hormone has even been reported, after multiple passages in normal hosts, but the tumor had lost its thyrotropic activity (254).

B. Pathogenesis

1. Anatomic pathology

Animals. The natural history of pituitary changes in animals with induced primary hypothyroidism is the rapid occurrence of thyrotroph cell hyperplasia, followed usually by specific tumorigenesis.

Histologically, the thyrotroph cells of hypothyroid animals undergo characteristic transformation; the first step is described as "thyroidectomy cells" or "thyroid deficiency cells" (250, 255): "thyroidectomy cells" appear about 2 weeks after induction of hypothyroidism. They are mildly basophilic (periodic acid Schiff-positive) or even chromophobic with a large cytoplasm; the chromophobe aspect is due to the fact that the granules, also called T granules (255), are only barely visible, at the limit of resolution of light microscopy. After 6 months, a focal adenoma consisting of "thyroidectomy cells" appears, and after 10 months, a gross adenoma develops with less differentiated cells (250). Electron microscopic studies allow one to follow the progressive changes from normal to autonomous cells (243): cells from "dependent" thyrotroph tumors (responsive to thyroid hormone) resemble "thyroidectomy cells," with large cytoplasm, large Golgi apparatus, numerous vesicles, but few secretory granules; cells from "autonomous" tumors have more complicated nuclear infolding and a progressive decrease in cell size and number of granules. More recently, studies of congenitally hypothyroid mice (mutant *hyt* mice) have shown hyperplastic and hypertrophied thyrotrophs (251, 253) with dilated rough endoplasmic reticulum ("confronting cisternae"); these abnormalities are reversible on L-T_4 replacement.

Humans. A systematic autopsy study of 64 patients with primary hypothyroidism (256) showed diffuse and nodular thyrotroph hyperplasia in, respectively, 69% and 25% of cases; in 12%, an entity called "tumorlet formation" (incomplete monomorphism, lack of destruction of reticulin network) was described as an intermediate stage between nodular hyperplasia and adenoma; true adenomas were present in 12 patients (older on average), with five of them staining for TSH. In reviewing the literature, we found other pathological reports, including autopsies (257–262) and surgical cases (263–269). Since the 1950s, much progress has been made in defining the different types of pituitary cells, with the introduction of electron microscopy, specific staining (for thyrotrophs: alcian blue, aldehyde-thionin), and immunostaining (immunoperoxidase). The equivalent of "thyroidectomy cells" is found in humans; cells are often described as chromophobes or mildly periodic acid Schiff-positive, the granules are small and confined to the peripheral cytoplasm near the membrane, the Golgi apparatus is hypertrophic, and there is abundant rough endoplasmic reticulum and free ribosomes, as well as microfilaments. Adenomatous cells are monomorphous and smaller with fewer granules and numerous microtubules. Immunostaining is not always positive for TSH; its absence does not rule out TSH production, particularly in the case of rapid turnover or prior thyroid treatment (264, 270).

2. Mechanisms.

Thyrotroph hyperplasia could be explained by the classic negative feedback loop in which reduced circulating levels of thyroid hormone result in overstimulation of thyrotrophs by TRH; other hypothalamic factors may be involved, as well as a direct T_3 feedback at the level of the pituitary. However, nothing is known of what causes the transformation of "thyroidectomy cells" into adenomatous cells, with a monomorph population of tumoral cells and changes in the reticulin architecture. As discussed in *Section II.H.2*, it is tempting to speculate that an oncogenic "hit" would be necessary for the transformation of thyrotroph cells, but to date no mutations have been found. In humans, the duration and/or severity of hypothyroidism necessary for development of thyrotroph adenoma is unknown. Inference from animals to humans suggests that thyroid hormone replacement could be efficient in reversing both pituitary hyperplasia and nonautonomous adenoma; however, in humans, it is unclear whether complete resolution can always be obtained on thyroid hormone replacement, particularly beyond the stage of hyperplasia.

Finally, lactotroph hyperplasia (diffuse or nodular), found in about 20% of autopsy cases (256), may result from excess TRH or from reduced hypothalamic dopamine content (256, 271).

C. Clinical features

Since the first observation of pituitary enlargement in primary hypothyroidism (1), many cases have been published. Review of the literature illustrates the different stages in the history of endocrinology, with the introduction of hormonal assays, sophisticated imaging by CT and MRI, and progress in pathological analysis. Since the review article written by one of us (158), the reports have been enriched by better imaging and hormonal studies, including dynamic tests. For this article, we reviewed 210 published cases (83% females, 76% adults), very uneven in the depth of the analysis and the

focus, depending on the year of publication and the specialty of the authors (257, 259, 260, 263–269, 272–358).

1. Presentation. The different types of presentation bringing the patient to seek medical attention (hypothyroidism, tumoral signs, amenorrhea-galactorrhea suggestive of prolactinoma or puberty abnormality) are indicated in Table 12. Results are presented separately in children and adults. In children, there was an equal frequency of a pubertal abnormality or hypothyroidism as the main finding at presentation (45% and 42%, respectively); in adults, hypothyroidism was the main reason for seeking medical attention (38%), while suspicion of prolactinoma or tumoral signs were present in one-third and one-fourth of the cases, respectively.

2. Signs and symptoms. Table 13 shows the frequency of symptoms in general and according to the type of presentation. Although patients presented often with other dominant complaints, symptoms and/or signs of hypothyroidism were almost always present (96%), but were very mild in 7% of the cases. The time of evolution since the first symptom was on average about 9 yr (n = 126). A goiter was present in 16% of adults and 13% of children. Hypothyroidism had a childhood onset (juvenile or congenital hypothyroidism) in 38% of the cases and an adulthood onset in 62%. The relative overrepresentation of juvenile hypothyroidism may be biased because children often present with precocious puberty, where pituitary imaging is part of the workup; alternatively, the pituitary in juvenile un- or mistreated hypothyroidism may be more prone to thyrotroph hyperplasia; interestingly, we found that TSH was higher in juvenile than in adult-onset hypothyroidism (n = 40, 551 ± 89 mU/liter, range 34.7 to 2000 *vs.* n = 98, 292 ± 38 mU/liter, range 9.6 to 2500; $P < 0.005$). The causes of primary juvenile hypothyroidism, reported in 49 cases, were congenital (cretinism or ectopic gland, 47%), autoimmune (29%), or unknown (24%); it has occurred in the neonatal period (300, 328) or in the context of Down's (297, 299, 329) or Turner's (286) syndromes. In adult-onset hypothyroidism, the main causes (reported in 88 cases) were autoimmune disease (59%), including postpartum thyroiditis (4%), and surgical thyroidectomy or ^{131}I therapy (13%), but the cause was unknown in 28%. Of special interest is the diagnosis of pituitary mass in patients who underwent thyroidectomy for hyperthyroidism. Indeed, in the absence of specific signs of Graves' disease and/or a suppressed TSH reading at the time of the diagnosis of hyperthyroidism, one should consider the possibility of a primary TSH-secreting pituitary adenoma responsible for the initial hyperthyroidism, rather than a pituitary enlargement resulting from induced hypothyroidism. In these cases, an elevated α-subunit/TSH molar ratio may be useful (8, 104). In addition, patients with RTH who have undergone inappropriate thyroidectomy for an erroneous diagnosis of hyperthyroidism should be considered good candidates for pituitary hyperplasia; to date the association of RTH with TSH-secreting pituitary adenoma has been reported only once (179), and the diagnosis of RTH was only putative because it was not genetically established. Last, the possibility of hypophysitis should also be considered, particularly in the postpartum period or in the context of hypopituitarism; indeed, hypophysitis is part of the etiological diagnosis of a pituitary mass (359, 360). The association of hypophysitis and autoimmune thyroiditis could result in less elevated TSH than expected, because of the central component.

Headaches were present in 60% and visual problems in 28%, obviously more frequent when tumoral signs were dominant at presentation.

In premenopausal women, menstrual irregularity was the rule, with amenorrhea present in 53% of the cases; galactorrhea, noted in 79% of the cases, was often misleading for a prolactinoma.

Bone age was generally delayed (86%), with short stature present in 90% of juvenile-onset cases, and GH secretion was impaired in 57% of children tested.

Of special interest, an abnormality of puberty was observed in 77% of children, including precocious puberty (275, 279, 285, 300, 310, 329, 345, 352) in 37% of the cases (n = 14, including 11 females), dissociation between adrenarche and gonadarche in pubertal age children (279, 310, 326, 334, 351, 352) in 23% of the cases (n = 8, including six females), or delayed puberty (274, 281, 293, 297, 320) in 17% of the cases (n = 6 females). Precocious puberty in primary hypothyroidism has been recognized since 1905 (361), and several cases have been reported since then, sometimes without clear information on pituitary size (362–367). The main characteristic in girls is primarily early menses and breast development in the absence of axillary or pubic hair; ovarian cysts are common (315, 334, 352, 363–365, 367). In boys, macroorchidism without a growth spurt is typical. Precocious puberty in girls is reversible on thyroid hormone replacement (17 of 17 in our series), with marked resolution or disappearance of the ovarian cysts; in boys, macroorchidism can regress (four of five cases in our series), but there is less follow-up than for the girls in the literature. As previously discussed, in animals, there is a stimulation of the gonads in athyreotic and, to a lesser degree, in euthyroid hosts with transplanted TSH pituitary tumors, suggesting that high TSH levels may be involved (247). In hypothyroid children, the mechanisms of precocious puberty are now better understood and could involve cross-reaction of TSH with the FSH receptor (368) and/or TRH-mediated stimulation of the gonadal axis (369). Indeed, high FSH levels have been reported in these children (here 75% of the cases *vs.* 17% of children with normal or delayed puberty, $P < 0.01$). The use

TABLE 12. Chief complaints at presentation in patients with pituitary hyperplasia and primary hypothyroidism[a]

	Adults (n = 152)	Children (n = 48)
Hypothyroidism (%)	38	42
Tumoral signs (%)[b]	25	3
Prolactinoma (%)[c]	36	2
Abnormal puberty (%)	0	45
Other complaints (%)[d]	6	4

[a] Data are given for 200 of 210 patients. In 10 cases, the age of the patient was not available. This table summarizes the group of symptoms bringing the patient to medical attention.

[b] Tumoral signs include headaches and/or visual defect.

[c] Prolactinoma includes amenorrhea and/or galactorrhea.

[d] Other complaints included Addison's disease, hypoglycemia, heart disease, delusions, death (autopsy) and none (incidental blood tests).

TABLE 13. Symptoms according to type of presentation in patients with pituitary hyperplasia and primary hypothyroidism

Group	Hypothyroid at presentation	Tumoral signs	Hyperprolactinemia	Abnormal puberty	Total[a]
	% (n)	% (n)	% (n)	% (n)	% (n)
Hypothyroidism	100 (62)	86 (22)	94 (34)	100 (16)	96 (134)
Headaches	44 (16)	88 (17)	70 (10)	0 (0)	60 (50)
Visual defect	8 (25)	94 (17)	6 (17)	0 (0)	28 (71)
Amenorrhea[b]	43 (7)	29 (7)	65 (23)		53 (38)
Galactorrhea[b]	43 (7)	75 (4)	95 (21)		79 (33)
Delayed bone age[c]	100 (13)	50 (2)	100 (1)	82 (11)	86 (28)
Short stature[d]	95 (23)	66 (6)	100 (2)	86 (7)	90 (40)
Abnormal puberty[c]	54 (11)	33 (3)		100 (20)	77 (35)
Precocious	9	0		60	37
Delayed	27	33		10	17
Asynchrone[e]	18	0		30	23

[a] Total refers to all patients for whom data were available; this includes some patients who had another type of presentation. n refers to the number of patients for whom the information was available.
[b] Amenorrhea and galactorrhea percentages are given for premenopausal women.
[c] Bone age and abnormal puberty results are given for children.
[d] Short stature data are given for patients with juvenile onset of hypothyroidism.
[e] Asynchrone puberty is defined by the dissociation between adrenarche and gonadarche.

of an analog of GnRH demonstrated that macroorchidism was not GnRH dependent (369); TRH was able to induce a response of FSH, suggesting the possibility of a direct response of the gonadal axis to TRH stimulation or a falsely high FSH assay in the presence of very high levels of TSH. Interestingly, as shown in Fig. 12, among the patients reported here, the ones with precocious puberty tended to have higher levels of TSH (n = 6, 970 ± 286 mU/liter, range 44–1797) than their counterparts (n = 12, 459 ± 84 mU/liter, range 21–1995, $P < 0.05$), stressing the possible critical level of TSH necessary to act through the FSH receptor. However, lack of thyroid hormones could act directly at the level of the testes, as suggested by Jannini *et al.* (370); this hypothesis is supported by experimental studies in rats (371), as well as by the ontogenic distribution of T_3 receptor in the testes. The absence of T_3 in prepuberal rats could be a signal that triggers the full differentiation and proliferation of the Sertoli cells (372).

In addition, a few cases of hirsutism have been reported, reversible on L-T_4 therapy (327). The mechanism is considered to be hyperkeratosis.

D. Laboratory findings and pituitary imaging

1. Hormonal studies. Hormonal assessment of these patients has been very heterogeneous and is reported in Table 14.

Thyroid function. In early cases, protein-bound iodine in baseline or after TSH injection was used to confirm the diagnosis of hypothyroidism but was abandoned in the 1970s with the development of RIAs for TSH and thyroid hormones. We report here results of TSH levels in baseline and after TRH stimulation. While the size of the pituitary appears to be directly linked to the degree of hypothyroidism (280, 354), it is noteworthy that 11% of the adults had only moderately elevated basal TSH levels (<500% of the upper limit of normal for the assay). Thirty percent of the adults who underwent a TRH test had a flat or diminished response (<150% of the baseline value). Figure 12 shows that TSH levels were lower in adults than in children and were higher in children with precocious puberty. Antithyroid antibodies,

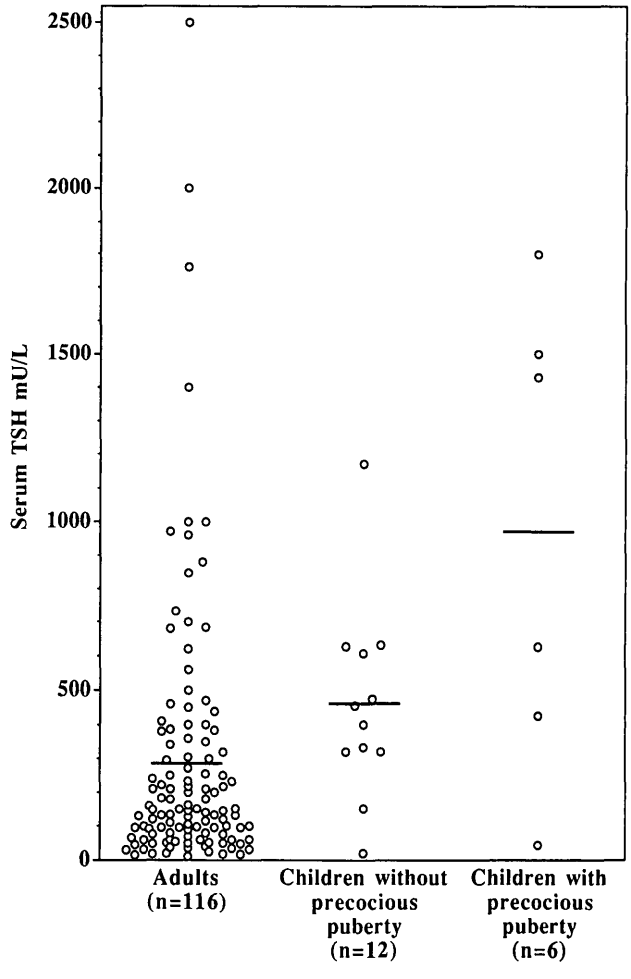

FIG. 12. Scattergram of TSH values in adults, children without precocious puberty, and children with precocious puberty. Data are given as individual *dots*, with the mean value illustrated by a *horizontal line*.

when measured, were positive in more than 75% of the cases (n = 76).

PRL. Hyperprolactinemia, usually moderate, was present in about three quarters of the patients. The cause of hyper-

TABLE 14. Hormonal assessment in patients with pituitary hyperplasia and primary hypothyroidism

	Adults[a]	Children[a]
	Mean or % (n)	Mean or % (n)
TSH mU/liter	289 ± 37 (116)[b]	612 ± 102 (29)
Subnormal TSH (%)[c]	11 (116)	3 (29)
Stim TSH (% of baseline)[d]	300 ± 37 (20)	420 ± 220 (2)
Nonresponsive TRH test (%)[e]	30 (20)	0 (2)
Antithyroid antibodies (%)	75 (78)	81 (20)
PRL μg/liter	62 ± 7 (41)	39 ± 6 (15)
High PRL (%)[f]	73 (72)	76 (15)
Stim PRL (% of baseline)[g]	482 (123)	203 (1)
Other abnormal endocrine tests (%)[h]		
Low GH	43 (23)	57 (7)
High LH	7 (55)	36 (11)
High FSH	10 (51)	31 (13)
Low LH	29 (55)	18 (11)
Low FSH	22 (51)	23 (13)
Low cortisol	23 (51)	8 (13)
Hypopituitarism[i]	12 (33)	0 (8)

[a] Results are expressed as mean ± SE or percentage; n refers to the total number of patients for whom the data were available. Adults include patients with juvenile-onset hypothyroidism diagnosed in adulthood.

[b] $P = 0.0004$ *vs.* children.

[c] Subnormal TSH is defined by a baseline TSH below 500% of the upper limit of normal for the assay.

[d] Stim TSH is the TRH-stimulated TSH expressed as percentage of baseline TSH.

[e] A nonresponsive TRH test is defined by a TRH-stimulated TSH below 150% of baseline TSH.

[f] High PRL is defined as a PRL above the upper limit of normal for the assay.

[g] Stim PRL is the TRH-stimulated PRL expressed as percentage of baseline PRL.

[h] Abnormal endocrine tests include abnormally low or elevated hormonal levels, in baseline or after specific stimulatory test if available.

[i] Hypopituitarism is defined by at least two low pituitary hormones.

prolactinemia in primary hypothyroidism is often attributed to the stimulatory effect of TRH on lactotropic cells; a decrease in hypothalamic stores of dopamine could also be contributory (271). The incidence of hyperprolactinemia in primary hypothyroidism varies from one third (373) to two thirds (346); this was associated with a higher incidence of pituitary size increase (373). Both TRH- and metoclopramide-stimulated PRL levels were less responsive in the group with hyperprolactinemia (373). Seventy five percent were not completely normalized on thyroid hormone replacement (346), but this did not correlate with the persistence of pituitary microadenoma on CT scan.

Others. GH testing was abnormal in about half of the patients: GH secretion was impaired in 14 of 30 patients (45%), contributing to the short stature in juvenile hypothyroidism, while paradoxical GH stimulation during TRH (282) and oral glucose tolerance test and arginine and exercise tests (311, 356) was observed in a few cases.

Elevated LH and FSH concentrations were observed in 13% of the patients, and particularly in children (one third of the cases tested), where it can result in precocious puberty. In contrast, low LH and low FSH were found in 18 of 66 (27%) and 14 of 64 (22%) patients, respectively, while cortisol was decreased in 13 of 64 patients (20%). However, hypopituitarism involving at least two axes was rare, observed only in four older adults out of 33 who had full hormonal assessment (12%, mean age 64 yr); one underwent surgery that revealed a macroadenoma with a negative immunostaining for TSH, two had abnormal visual fields that improved on thyroid hormone replacement, and one was stable on medical treatment.

2. *Radiology.* Several studies looked systematically at the incidence of x-ray pituitary abnormalities in primary hypothyroidism (280, 282, 304, 346, 354, 373). Up to 81% of patients with primary hypothyroidism had increased volume of the sella on skull x-ray above 800 mm^3 (354). Sella volume was positively correlated with the severity of chemical hypothyroidism (280, 354); however, there was no correlation with the duration of symptoms.

CT and MR imaging were introduced more recently to study pituitary abnormalities in primary hypothyroidism. The published series display some heterogeneity both in the groups studied and in the results. Boyages *et al.* (282) found five enlarged pituitaries in 20 untreated adult cretins (25%) and eight had a partially empty sella (40%). Thomas *et al.* (346) described abnormal findings in 15 of 19 patients with hypothyroidism (79%): enlarged pituitaries in 11 cases (58%), with possible adenoma in nine, empty sella in two, and normal size pituitary with a suspicion of microadenoma in two cases. On the other hand, Tchernova and colleagues (373), who studied 30 women with primary hypothyroidism, found 12 (40%) with abnormal pituitary CT scans; they were able to demonstrate that CT pituitary abnormalities were much more frequent in patients with concomitant hyperprolactinemia (90%) than in patients without hyperprolactinemia (15%). This suggests that hyperplasia of lactotroph cells could contribute to pituitary hyperplasia in primary hypothyroidism; however, this hypothesis is not supported by the fact that, after normalization of TSH, there was no clear correlation between residual hyperprolactinemia and persistent pituitary changes (346), and that lactotroph abnormalities were not dominant on pathological analysis of pituitaries from hypothyroid patients who underwent surgery or autopsy (256). Last, Katevuo *et al.* (304) found that eight of 12 hypothyroid patients had an enhanced density of the pituitary gland after intravenous injection of contrast as observed in pituitary adenoma; this was reversible in seven cases after thyroid hormone replacement and TSH normalization. This enhancement could reflect an increased pituitary circulation associated with augmented function of the thyrotroph cells.

Table 15 summarizes the results of baseline pituitary CT and/or MRI performed in 100 patients with primary hypothyroidism (267, 274, 275, 281, 282, 287, 288, 290–294, 298, 301, 304, 307–309, 312, 314, 318, 320, 322, 327, 328, 331–333, 337, 339, 345, 346, 350, 353, 356). A mass with suprasellar extension was the most frequent finding (59%). Despite recent progress in imaging, it is still difficult to distinguish between mere pituitary hyperplasia and adenoma, even when high resolution CT with contrast injection or MRI with gadolinium injection is used. This probably reflects the different stages of pathological entities (hyperplasia, nodular hyper-

TABLE 15. CT and MRI imaging before and after thyroid hormone replacement in patients with pituitary hyperplasia and primary hypothyroidism

Before treatment (n = 100)[a]	
59	Mass with suprasellar extension
18	Enlarged pituitary
12	Intrasellar mass
3	Empty sella
8	Density enhancement
After treatment (n = 80)	
50	Normalization (62%)
23	Decrease (29%)
3	Stable (4%)
3	Empty sella (4%)[b]
1	Increase (1%)

[a] Thirteen patients had an imaging compatible with microadenoma.

[b] Including two already seen on the scan before treatment.

plasia, and adenoma) observed in this condition and their degree of autonomy. Ahmed *et al.* (274) proposed the "nipple sign" as suggestive of hyperplasia (midline prominence with smooth contours). The best approach, however, is probably to rescan patients on thyroid hormone replacement, with normalization of pituitary size strongly suggesting hyperplasia. However, it is noteworthy that pituitary abnormalities suggestive of adenoma are found in about 10% of normal controls on MRI scan (204); furthermore, asymptomatic pituitary adenomas (particularly microprolactinomas) are found in 2–27% at autopsy (374, 375). Therefore, in the case of marked improvement without complete normalization, the meaning of persistent minimal abnormality is unclear.

E. Treatment

The treatment of pituitary enlargement due to primary hypothyroidism is medical, with adequate replacement dose of thyroid hormones. Follow-up information (complete or not) was available on 140 patients, with an average duration of 1 yr.

Clinically, regression of symptomatology was observed in 91 of 106 cases (86%); as discussed above, regression of precocious puberty was the rule in children. Initial worsening of tumor-like symptoms was possible on thyroid hormone replacement (pseudotumor cerebri in children), with the appearance or progression of a visual field defect and/or papilledema in eight cases; four had decompressive surgery, which discovered two adenomas that did not stain for TSH (266, 294), one hyperplasia (269), and one nodular hyperplasia (267); four were treated medically only, with complete resolution of the symptoms (292, 320, 352, 355). The objective increase in pituitary volume was explained by a dissociation between a decrease of secretion and an increase of synthesis and storage of TSH, induced by the restoration of euthyroidism. This justifies a close clinical follow-up at the beginning of treatment when pituitary enlargement is known.

Radiologically, CT or MRI follow-up was performed in 80% of the patients who had undergone an initial scan. Table 15 gives a summary of the literature. There was no correlation of the radiological outcome with the initial TSH levels or with the length of follow-up. Total or partial regression was observed in 62% and 29%, respectively, of the cases. These dramatic changes can occur in 1 or 2 months, or even within a week in the case of acute thyroid hormone therapy (376). Figure 13 shows complete resolution of a pituitary mass with suprasellar extension after 1 month of thyroid hormone therapy, as demonstrated by MRI (376). The mechanisms responsible for such a shrinkage could involve a decrease in volume of rough endoplasmic reticulum and Golgi complexes, resulting in reduced volume of thyrotroph cells, as observed in adenomatous lactotrophs after bromocriptine therapy (377).

Persistence of the mass in 4% of the cases suggested a

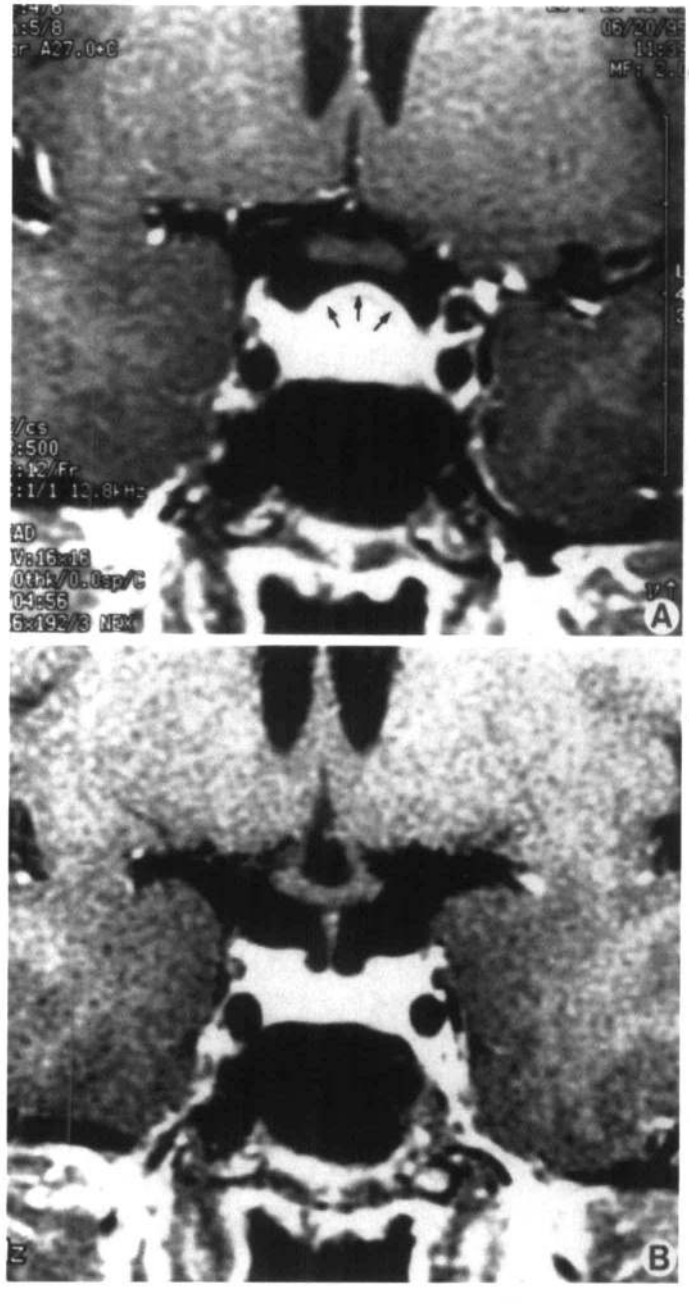

FIG. 13. MRI of the pituitary in a patient with ^{131}I-induced hypothyroidism. A, Initial MRI after gadolinium demonstrates a large pituitary "tumor" with suprasellar extension and a rim of enhancing pituitary tissue that could be easily mistaken for normal pituitary gland (*arrows*). B, Follow-up MRI after gadolinium obtained 1 month later, after high doses of thyroid hormone therapy, shows complete resolution of suprasellar mass.

possible incidental pituitary tumor or a secondary autonomous microadenoma (304, 317, 346). In 1% of the cases the pituitary increased in size: this could reflect increased TSH production and storage but also the progression of an incidental tumor. Last, an empty sella was found in three patients (4%) (316, 346); interestingly, it was already present in two of the three patients at the initial assessment, even when TSH was high, implying the coexistence of pituitary hyperplasia and "empty sella."

Biologically, in six of 110 patients (5%), TSH was apparently not normalized as a result of thyroid hormone replacement (275, 292, 301, 317, 320, 337); there was no difference in duration of follow-up or initial TSH levels in these patients, and they did not have a history of prior thyroidectomy or ^{131}I treatment. However, the follow-up pituitary scans in these six patients showed a normalization in three patients, an improvement in one (337), an empty sella in one (320), and no change in one patient with poor compliance (317). Thus, there is currently no good evidence that such patients develop autonomous "tertiary" hyperthyrotropinemia.

Twenty four patients underwent surgery (263–269, 283–289, 294, 306, 308, 314, 338, 342, 344, 358), including 19 whose surgery preceded any thyroid hormone replacement and five in whom surgery was required because of worsening or absence of improvement on thyroid hormone replacement. Of the 19 patients who had initial surgery, eight presented with tumoral signs, six with symptoms suggesting prolactinoma, and four with hypothyroidism; in one case the type of presentation was unknown. Pathological analysis was available in 16 of these patients, showing hyperplasia in four cases, nodular hyperplasia in two cases, and adenoma in 10 cases; immunostaining was available in seven cases: five adenomas stained for TSH and two did not. Retrospectively, initial surgery could have been avoided in many of these cases.

Surgery should be reserved for decompression of the optic chiasm or to obtain a pathological diagnosis in the case of a pituitary mass not responding or worsening on thyroid hormone replacement.

IV. Conclusions and Future Directions

TSH-secreting pituitary tumors are associated with both central hyperthyroidism and primary hypothyroidism. TSH-secreting pituitary adenomas are a rare cause of hyperthyroidism characterized by IST. Their diagnosis is now facilitated by the recent introduction of ultrasensitive TSH immunoassays as well as free thyroid hormone assays that are not obscured by abnormal serum transport proteins. Increased awareness and early recognition of these tumors will prevent mistreatment, such as thyroid ablation or long-term antithyroid drug administration, which undoubtedly increases TSH secretion, tumor size, and invasiveness. Although no single diagnostic test is pathognomonic in establishing the diagnosis, the elevation of α-subunit levels and serum SHBG concentrations, as well as the frequently absent or impaired TSH responses to TRH and T_3 suppression tests, are the most useful markers to distinguish patients with TSH-omas from those with thyroid hormone resistance. Furthermore, high resolution CT scan and MRI may help in detecting tumors as small as 3 mm. Surgery still remains the first therapeutic approach to the disease, followed by radiotherapy in the case of surgical failure. The finding of measurable TSH levels after a simple T_3 suppression test definitely indicates that the removal of the tumor cells was incomplete, thus requiring a closer follow-up of the patient and/or additional therapies. If needed, treatment with SRIH analogs, which allows restoration of euthyroidism and even tumor shrinkage in many cases, is worthwhile.

In contrast, hyperplasia of the pituitary as a result of long-standing hypothyroidism is common but is rarely symptomatic. However, when symptoms are present, tumoral signs, amenorrhea-galactorrhea, or even postpartum thyroiditis are frequent presentations in adults, while precocious puberty is classic in children. Medical treatment is the rule because of the almost certain regression of pituitary abnormalities on proper thyroid hormone replacement. The evolution should be monitored closely, given the possibility of initial worsening (pseudotumor cerebri) or the possibility of an incidental nonthyrotrophic pituitary tumor that will not regress on thyroid hormone replacement. The association of moderate hyperprolactinemia is common; however, if amenorrhea-galactorrhea or hyperprolactinemia do not resolve on thyroid hormone replacement, a prolactinoma should be suspected.

Finally, the etiology of TSH-omas remains unknown, although efforts have been made to exclude certain candidate oncogenes, using cellular, biochemical, and molecular biological techniques. Future diagnosis and treatment of this rare disorder depend on the recognition of the genetic basis leading to tumor development. This will open the way to etiological therapeutic approaches such as gene therapy.

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