
Surgical treatment of thyrotropin-secreting pituitary adenomas

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Thyrotropin-secreting pituitary adenomas have been diagnosed more frequently as radiographic techniques and biochemical assays have improved; however, they remain uncommon and are unfamiliar to most neurosurgeons. This report concerns eight patients with hyperthyroidism, inappropriately elevated levels of serum thyrotropin and α-subunit, and radiographic evidence of pituitary tumor. All underwent surgery and had pathological confirmation of a thyrotropin-secreting adenoma, and most had been subjected to prior ablation of the thyroid gland. Only one tumor was a microadenoma; the others ranged in size from 1.4 to 12 cm, and invasion of parasellar structures was common. Thyrotropin, triiodothyronine, thyroxine, and α-subunit were measured preoperatively and at intervals postoperatively. Coexistent hormonal abnormalities (which occurred in all patients) included acromegaly and hyperprolactinemia and were also monitored. All four patients who had tumors less than 2 cm in diameter remain alive. Complete extirpation of tumor in these patients produced rapid correction of all hormonal abnormalities and resolution of clinical hyperthyroidism. The other four patients had larger invasive tumors: two died soon after surgery, one died of disseminated tumor 8 years after presentation, and one remains alive with residual tumor.

Tumors secreting thyroid-stimulating hormone are less easily cured by surgery than are other types of pituitary adenoma because of the large size and invasive features that many attain during the delay to diagnosis; medical therapy can subdue the tumor but not cure it. The experience with these patients establishes the importance of early diagnosis and surgical excision for successful treatment, and demonstrates the utility of modern diagnostic techniques for finding these lesions. As occurs in Nelson's syndrome after adrenalectomy for Cushing's disease, ablation of the target organ may allow the tumor to convert to a more clinically malignant form which is resistant to cure.

KEY WORDS • pituitary tumor • adenoma • thyrotropin • hyperthyroidism • transsphenoidal surgery

Pituitary adenomas that secrete thyrotropin (thyroid-stimulating hormone or TSH) are unusual endocrine lesions that comprise less than 1% of most published series of pituitary tumors.32,39,44 Improvements in radiographic imaging of the sella and the development of increasingly sensitive radioimmunoassays (RIA's) for TSH and its subunits have allowed more frequent detection and diagnosis of these tumors than was possible before 1970. Their clinical manifestations are initially those of hyperthyroidism; many patients with TSH-secreting tumors are treated, chronically and unsuccessfully, with biochemical or surgical ablation of the target organ (the thyroid gland), a strategy that produces cycles of temporary clinical and biochemical relief followed by recurrence of hyperthyroidism.

Often the suspicion that the excess TSH reflects neoplastic pituitary hypersecretion comes only when the tumor reaches a size sufficient to produce signs and symptoms of local compression. Thus, in many patients these tumors are identified only after they have already invaded parasellar structures, although biochemical clues indicating a TSH-secreting pituitary tumor may have been present for years. Furthermore, detectable levels of TSH in the face of elevated levels of triiodothyronine (T3) or thyroxine (T4), which occur with TSH-secreting tumors, can also be caused by resistance to thyroid hormones by the pituitary thyrotrophs or by peripheral tissues. Together, these varieties of hyperthyroidism form the "syndromes of inappropriate secretion of TSH," of which TSH-secreting adenomas are a significant subset.8,42
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In patients with hyperthyroidism and inappropriate secretion of TSH, the presence of a TSH-secreting adenoma can often be confirmed biochemically (and distinguished from central or peripheral resistance) by demonstrating an elevated molar ratio of serum α-subunit to TSH.25,32 Thyrotropin and the other glycoprotein hormones secreted by the pituitary (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) are initially synthesized as individual α- and β-subunits, of which the latter confer hormonal specificity. Hormonal activity requires covalent linkage of the (nonspecific) α-subunit with the (specific) β-subunit, which are coded for by separate genetic loci. Normal production of TSH results in equimolar serum concentrations of α-subunit and TSH. In TSH-secreting adenomas an excess secretion of α-subunit often occurs; an α-subunit/TSH ratio greater than 1.0 suggests secretion by a TSH-secreting tumor.

The biochemical spectrum of TSH-secreting adenomas of the pituitary gland has been well studied.12,37 The anecdotal nature of most published cases has, however, obscured the variety of surgical problems which these tumors present. The only previously reported series have gathered patients from several institutions14,16 or have given scant attention to the surgical aspects of this disease.8,13,32 and case reports have often failed to specify the surgical approach used. We present here the detailed clinical course of eight patients who underwent evaluation and surgery (six) at the National Institutes of Health (NIH) for TSH-secreting pituitary adenomas confirmed as such by endocrine testing and immunohistochemical examination. These patients’ medical management has been presented in detail elsewhere.12

Clinical Material and Methods

All eight patients evaluated at the NIH with a confirmed diagnosis of TSH-secreting pituitary adenoma (a total of eight) and surgically treated for their tumor between 1982 and 1988 (six underwent surgery at the NIH and two had operations at their referring institutions after evaluation at the NIH) are included in this series. All patients met the biochemical criteria for inappropriate secretion of TSH: namely, a detectable serum level of TSH with elevated serum levels of T3 and/or T4, or a high serum content of TSH with normal T3 and T4 values. The T3 and T4 levels were measured before and after operation using commercially available kits. Thyrotropin was measured by either double-antibody RIA or a more sensitive immunoradiometric assay, and α-subunit was determined using an RIA described previously.25 Serum levels of other pituitary hormones including growth hormone (GH), LH, FSH, and prolactin were also measured by specific RIA’s using antisera and standards from the National Pituitary Agency. A molar ratio of α-subunit/TSH greater than unity was considered highly suggestive of neoplastic secretion. This ratio was calculated by assuming molecular weights of 14,700 daltons for the α-subunit and 28,000 daltons for TSH and by assigning to the latter a value of 5 μU/ng.25

Radiographic examinations included plain skull x-ray films, computerized tomography (CT), and magnetic resonance (MR) imaging. In six patients, CT showed the presence of a sellar mass. The adenoma of one patient with an allergy to intravenous iodinated contrast was demonstrated only by MR imaging with gadolinium infusion, although plain CT was suggestive of intrasellar tumor. Collectively, these studies indicated neoplasm in seven of the eight patients studied. In the eighth patient, strong biochemical evidence for tumor was present but radiography was unrevealing. All patients had preoperative evaluation of visual fields by Goldmann perimetry.

All patients underwent surgery, six at the NIH (performed by E.H.O.) and two at their referring institutions. Of the former, tumor was resected by the transsphenoidal approach in five (one of whom later required craniotomy as well) and by transfrontal craniotomy in one. Both patients who received surgery at the referring institution (Cases 2 and 6) underwent transsphenoidal procedures. The total of 13 operations performed included three craniotomies and ten transsphenoidal procedures. Two patients had undergone their first operation at an institution other than the NIH (a craniotomy in one patient and two transsphenoidal explorations in the other). Tissue from seven patients was submitted for pathological examination and stained by immunoperoxidase techniques using anti-hormonal antisera against α-subunit, TSH, and prolactin (and, in cases with clinical features suggesting acromegaly or hypogonadism, GH, FSH, and LH). Biopsy samples stained positive for TSH in all cases but one. External-beam irradiation of the tumor in the postoperative period was given to three patients. One patient had undergone sellar irradiation before referral to the NIH. Clinical and biochemical follow-up evaluation of all patients continued at least annually from the time of surgery through 1989. The mean follow-up period after surgery of the patients still living is 54 months.

Results

The clinical profile of our patients is summarized in Table 1. The mean age at first operation was 37 years. Six of the eight patients were women. All patients had been clinically hyperthyroid and all but one had been subjected to ablation of the thyroid gland an average of 5½ years before operation. Two patients also had acromegalic features. Galactorrhea was present in four patients, headache in three, amenorrhea in two, hypogonadism in one, and visual loss in one. Four patients had visual field defects determined by perimetry. Preoperative therapy included propylthiouracil (PTU) in six,131I in five, thyroidectomy in three, bromocriptine in two, and somatostatin analogue in two. Extrasellar extension of the tumor was present in six patients, of whom all
TABLE 1
Clinical profile of eight patients operated on for thyrotropin-secreting pituitary adenomas*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Time Since Thyroid Ablation</th>
<th>Visual Field Defect</th>
<th>Prior Surgery</th>
<th>Operations</th>
<th>Outcome</th>
<th>Sellar Irradiation (rad)</th>
</tr>
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<tr>
<td>Case 1</td>
<td>51, M</td>
<td>4 yrs</td>
<td>yes</td>
<td>none</td>
<td>TSS, craniotomy</td>
<td>alive with tumor died</td>
<td>5200</td>
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<tr>
<td>Case 2</td>
<td>45, F</td>
<td>no ablation</td>
<td>yes</td>
<td>craniotomy</td>
<td>TSS ×2 craniotomy, TSS</td>
<td>died</td>
<td>3000</td>
</tr>
<tr>
<td>Case 3</td>
<td>32, F</td>
<td>chemical ablation 5 yrs after 1st op</td>
<td>no</td>
<td>TSS</td>
<td>died</td>
<td>4860</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>38, F</td>
<td>3 yrs</td>
<td>suprasellar region</td>
<td>yes</td>
<td>none</td>
<td>TSS</td>
<td>died</td>
</tr>
<tr>
<td>Case 5</td>
<td>24, F</td>
<td>5 yrs</td>
<td>none</td>
<td>no</td>
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<td>35, F</td>
<td>8 yrs</td>
<td>sphenoid sinus</td>
<td>no</td>
<td>none</td>
<td>TSS, cured</td>
<td>none</td>
</tr>
<tr>
<td>Case 7</td>
<td>31, F</td>
<td>8 yrs</td>
<td>sphenoid sinus, suprasellar region</td>
<td>yes</td>
<td>none</td>
<td>TSS, cured</td>
<td>none</td>
</tr>
<tr>
<td>Case 8</td>
<td>40, M</td>
<td>5 yrs</td>
<td>none</td>
<td>no</td>
<td>none</td>
<td>TSS, cured</td>
<td>none</td>
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* Age is given at first operation. TSS = transsphenoidal surgery.

had suprasellar tumor, five had tumor in the sphenoid sinus, two had erosion of the clivus, and one each had cavernous sinus tumor and tumor in the orbit and ethmoid sinuses. In two patients, invasive tumor had destroyed a major portion of the medial third of the skull base, including the clivus and medial segments of the petrous portions of the temporal bones.

Pre- and postoperative hormone measurements are shown in Table 2. Serum TSH and α-subunit content was elevated preoperatively in all patients. Serum T₃ level was elevated in two patients and normal in six. Serum T₄ value was low in one case, normal in two, and elevated in five. One month after the operation, the serum TSH level had fallen to normal in two of the four patients for whom such data are available. Serum T₃ and serum T₄ levels were both normal in three of these four and remained elevated in one. At the most recent follow-up examination for the six living patients, the serum TSH value remained high in one patient and the serum T₄ level remained high in two; the serum T₃ content was low in one and normal in five; the α-subunit level was normal in four patients and elevated in two. The preoperative molar ratio of α-subunit/TSH was high in seven patients and normal in one. It was still elevated in the three patients for whom such data were available at 1 month postoperatively, and in all four for whom data were available at the most recent follow-up examination.

Cure was achieved in all four patients with smaller tumors (< 2 cm in maximum diameter). Cure was defined as disappearance of clinical hyperthyroidism, absence of tumor on follow-up radiographic studies, persistence postoperatively of normal serum TSH and α-subunit levels, and normalization of any associated abnormalities of GH, FSH, LH, or prolactin. Normalization of the α-subunit/TSH molar ratio either did not occur or was not calculable because of a vanishingly small denominator. Of the four patients with larger, more invasive tumors, two died in the early postoperative period and one remains alive with clinical and biochemical evidence of continuing inappropriate secretion of TSH by tumor. The last of these four died after a prolonged course that culminated in distant metastases. One patient who died was treated initially by craniotomy and another by transsphenoidal surgery. Postoperative complications also included leakage of cerebrospinal fluid (CSF) in two, epidural hematoma in one, seizures in one, and pulmonary embolism in one. Pathological examination of tumor revealed immunoreactive β-subunit of TSH in six of seven cases so studied. Two tumors also showed positive staining for prolactin.

Case Reports

Large Invasive Tumors

Four patients had invasive pituitary macroadenomas with suprasellar extension and extensive destruction of the skull base. These tumors were as large as 12 cm in maximum diameter.

Case 1. This 47-year-old Puerto Rican man was found to be hyperthyroid. Medical therapy, which included thyroid ablation with PTU and ¹³¹I, did not give sustained relief. At the age of 51 years he was noted to have a bitemporal defect in his visual fields. This finding prompted measurement of his TSH level, which was 47 μU/ml (normal < 5 μU/ml), with normal T₃ and T₄ levels. A CT scan showed mild hydrocephalus with tumor present in the sella and suprasellar region. The lesion extended into the sphenoid and posterior ethmoid sinuses and prepontine cistern, and also encroached on the left orbit where it produced widening of the optic canal. The medial aspect of the petrous temporal bone, the dorsum sellae, and the clivus were all invaded by tumor.

At transsphenoidal surgery, subtotal removal of a 4
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A sellar and suprasellar mass, 10 to 12 cm across, which contained the sella turcica, optic chiasm, and optic nerves. The T3 and T4 values were both elevated. ACT scan showed a large tumor invading the sphenoid sinus and the interpeduncular cistern, and a subunit/TSH Case TSH (μU/ml) T3 (ng/dl) T4 (μg/dl) a-Subunit (ng/ml) Ratio a-Subunit/TSH Other Hormones

<table>
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<th>Case No.</th>
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<th>Postop</th>
<th>Preop</th>
<th>Postop</th>
<th>Preop</th>
<th>Postop</th>
<th>Preop</th>
<th>Postop</th>
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<td>8</td>
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<td>13.5</td>
<td>13.1</td>
<td>4.2</td>
<td>2</td>
<td>5.2</td>
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<td>1.5</td>
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<tr>
<td>5†</td>
<td>42</td>
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<td>446</td>
<td>194</td>
<td>15.4</td>
<td>16.7</td>
<td>14.1</td>
<td>0.6</td>
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<td>6‡‡</td>
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<td>10.7</td>
<td>15</td>
<td>2.6</td>
<td>1.4</td>
<td>20</td>
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<tr>
<td>7‡‡‡</td>
<td>516</td>
<td>2.6</td>
<td>157</td>
<td>59</td>
<td>21</td>
<td>9.6</td>
<td>43</td>
<td>0.9</td>
<td>0.8</td>
<td>3.5</td>
</tr>
<tr>
<td>8‡‡‡‡</td>
<td>40.3</td>
<td>&lt;0.1</td>
<td>178</td>
<td>106</td>
<td>2</td>
<td>10</td>
<td>7.8</td>
<td>0.5</td>
<td>19.4</td>
<td>—</td>
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</table>

* Preoperative values represent the last hormonal measurement made before surgery was performed; postoperative values represent those measured at the most recent follow-up visit. TSH = thyroid-stimulating hormone (normal < 5 μU/ml); T3 = triiodothyronine (normal 75–195 ng/dl); T4 = thyroxine (normal 4–12 μg/dl); a-subunit (normal < 3 ng/ml); a-subunit/TSH ratio (normal < 1) calculated as: 10 (a/TSH), after Kourides, et al. 20 (no value given when TSH < 0.1 μU/ml); LH = luteinizing hormone (normal 6–26 mIU/ml); FSH = follicle-stimulating hormone 5–25 mIU/ml; GH = growth hormone (normal < 5 μg/ml); prolactin (normal < 20 ng/ml); — = not calculated.

† Postoperative values measured while patients were on replacement doses of l-thyroxine.
‡ Preoperative values measured while patients were on replacement doses of l-thyroxine.
‡ Patients who died within 11 days after surgery.

A 6-cm invasive TSH-secreting adenoma was achieved. After postoperative CT showed residual tumor he received 5200 rad to sellar, infrasellar, and suprasellar portals in fractionated doses. Ten months after initial surgery, the patient returned, complaining of decreasing vision in the superior nasal quadrant of his left visual field. The T3 level was 6.8 μU/ml with normal T4 and T3 values. ACT scan showed an additional extension of the tumor to the sella anteriorly, inferiorly, posteriorly, and to both optic foramina. A left frontotemporal craniotomy was performed which revealed tumor beneath both optic nerves. The right optic nerve was drawn inferiorly into the sella by adhesions. The patient has undergone intermittent treatment with a somatostatin analogue during the 5½ years since his discharge and continues to have elevated TSH with normal T3 and T4 levels. He remains in atrial fibrillation and is blind in the left eye with a stable temporal visual field defect in the right eye.

Case 2. This 45-year-old woman had undergone a craniotomy for suprasellar tumor described as an ependymoma of the third ventricle at 18 years old. Excision was subtotal and she received 3000 rad of postoperative irradiation to that region. Her presenting symptoms (visual blurring and loss of the left temporal field) cleared and she had no further complaints until the age of 43 years, when typical signs and symptoms of hyperthyroidism began along with gradual binocular visual loss, coarsening of facial features, and increasing hand and foot size. Two years later, when she was admitted to the NIH, she had a nodular goiter, acromegalic appearance, and bitemporal hemianopsia. Her serum TSH level was 8 μU/ml, GH level was 12 ng/ml, and T3 and T4 values were both elevated. A CT scan showed a sellar and suprasellar mass, 10 to 12 cm across, which had destroyed the clivus and the medial segments of the petrous portions of the temporal bones, filled the sphenoid sinus and interpeduncular cistern, and encroached on the third and lateral ventricles. At transsphenoidal surgery, after tumor was removed from the sphenoid sinus and from the area in front of the brain stem (the clivus having been almost wholly destroyed by the lesion), the suprasellar portion of the tumor was resected. The patient did not wake from anesthesia and died 48 hours after the operation. Autopsy findings were compatible with intraoperative hypothalamic injury.

Case 3. This 32-year-old woman had onset of headache, hirsutism, and amenorrhea without galactorrhea. Her serum prolactin level was elevated. After CT revealed an intrasellar tumor, she underwent transsphenoidal resection of a pituitary tumor but no immunohistochemical studies of the tumor were performed. The tumor was assumed to be a prolactinoma. At 34 years old, she developed hyperthyroid symptoms. A CT scan at that time showed extension of the tumor into the sphenoid sinus. At 37 years of age she underwent repeat transsphenoidal surgery at the same institution but an incomplete excision was achieved. Postoperatively, she continued to be hyperthyroid and was treated with PTU, propranolol, and bromocriptine. She was then referred to the NIH for further evaluation and treatment. Serum TSH level was 16 μU/ml with normal T3 and T4 values. A CT scan showed a large tumor invading the sphenoid sinus, clivus, and left temporal lobe. At the age of 38 years, the patient underwent a left temporal craniotomy and partial excision of her tumor. Invasion of the left cavernous sinus was evident at surgery and biopsy specimens stained positively for TSH and prolactin. She received external-beam irradiation postoperatively but, during radiotherapy, she de-
developed CSF rhinorrhea, which continued intermittently. She was also treated with somatostatin analogue in an attempt to arrest further tumor growth. Eight years after her first operation, tumor extension into both cavernous sinuses (as well as both ethmoid sinuses and the posterior nasopharynx) produced facial numbness and an abducens palsy (Fig. 1). Further transphenoidal debulking of tumor was performed uneventfully. A month after surgery, the patient developed bilateral abducens palsy, Vernet’s syndrome, and recurrent nosebleeds, and suddenly lost all vision in her right eye. Magnetic resonance imaging with gadolinium infusion revealed impressive growth of tumor into the orbits, preopontine area, oropharynx, and soft palate, and showed distortion of the optic nerve by tumor (Fig. 1). She was given additional radiotherapy and high doses of somatostatin analogue which caused her to regain some vision and the ability to swallow. She subsequently developed spread of TSH-immunopositive tumor to her pelvis, spinal column, and lungs, and died from widespread metastasis 8 years after the onset of hyperthyroidism.

Case 4. This 35-year-old woman presented with palpitations and hypertension and was diagnosed as hyperthyroid. She was given $^{131}$I and PTU and then placed on thyroid replacement therapy. She underwent subtotal thyroidectomy for continuing hyperthyroidism 2 years later, after which she began having right-sided headaches, then visual loss in the right eye and galactorrhea. Examination revealed a bitemporal visual field cut, which gradually improved. A CT scan was unremarkable except for the presence of subarachnoid hemorrhage. On the 6th postoperative day she became obtunded and developed hemiparesis which evolved over the course of a week. Magnetic resonance imaging with gadolinium injection revealed normal visual fields and expressible contents above the superior limits of the sella. Examination revealed a sellar tumor; she began a course of bromocriptine and her TSH value fell but did not normalize. A CT scan showed sellar and suprasellar mass extending to the floor of the third ventricle, but no hydrocephalus. Her serum TSH level at that time was 113 μU/ml, with normal T₄ and elevated T₃ values. She began treatment with somatostatin analogue but this drug was discontinued after it induced intractable nausea and vomiting. She then returned to her referring institution, where a transphenoidal operation was performed with complete excision of a tumor 3 cm in maximum diameter. On the day after surgery she had sudden loss of vision in the left eye and worsening of the preexisting right temporal field cut, which gradually improved. A CT scan was unremarkable except for the presence of subarachnoid blood. On the 6th postoperative day she became obtunded and developed hemiparesis which evolved over 2 days to decerebrate coma; CT showed ventricular enlargement and infarction in the territories of the right anterior and middle cerebral arteries. Treatment of intracranial hypertension failed to arrest her clinical decline, and death followed on the 11th postoperative day.

Tumors Less Than 2 cm in Maximum Diameter

Four patients had smaller tumors confined to the general region of the sella, or had tumors which invaded only the sellar floor. One was a microadenoma (8 mm in diameter) and the others ranged in diameter from 1.4 to less than 2 cm.

Case 5. This 19-year-old woman presented with hyperthyroidism and was begun on a course of PTU and propranolol. Her symptoms continued and she was given $^{131}$I 3 years later. She then developed galactorrhea and left-sided headaches. The refractory nature of her symptoms caused her referral to the NIH, where hormonal testing revealed elevation of prolactin, TSH, T₃, and T₄ levels. An elevated α-subunit value and α-subunit/TSH molar ratio both indicated a pituitary etiology for the hyperthyroidism, although CT and MR imaging each showed an enlarged pituitary gland and a sella without other evidence of tumor. During transphenoidal surgery an 8-mm microadenoma was removed from the left side of the gland. In the 4 years since her operation, α-subunit/TSH molar ratios have been less than 1.0 and clinical hyperthyroidism has not recurred. She has been maintained on exogenous T₄ to suppress secretion of TSH. Follow-up MR imaging has shown no recurrence of tumor.

Case 6. This 21-year-old woman began to have intermittent breast tenderness and galactorrhea after a spontaneous abortion. Four years later she noted dry skin and hair and a hand tremor, but was not diagnosed as hyperthyroid until 2 years after that. She received $^{131}$I with resolution of her hyperthyroidism, but galactorrhea persisted and she developed right orbital headaches. Both TSH (169 μU/ml) and prolactin (although not GH) levels remained high. A CT scan revealed a sellar mass with infundibular shift to the right, focal erosion of the sellar floor, and bulging of the sellar contents above the superior limits of the sella. Examination revealed normal visual fields and expressible galactorrhea. During transphenoidal surgery at her referring institution, an 8 x 14-mm adenoma was selectively excised without complication. No immunoreactive TSH was found in the tumor on pathological examination. The galactorrhea resolved and serum TSH levels returned to normal. The patient has continued to take exogenous T₄, and CT has revealed no evidence of residual or recurrent tumor.

Case 7. This 23-year-old woman developed hyperthyroidism during pregnancy. She was given PTU and remained hyperthyroid but stable for 2 years, at which time a goiter appeared. At the age of 25 years, she underwent subtotal thyroidectomy but remained hyperthyroid postoperatively. Two years later, she developed amenorrhea and galactorrhea. Prolactin, TSH, T₃, and T₄ levels were elevated. A CT scan failed to demonstrate a sellar tumor; she began a course of bromocriptine and her TSH value fell but did not normalize. At 29 years of age, she was still clinically hyperthyroid and was given $^{131}$I, after which her TSH level became elevated to over 60 μU/ml. Two years later, another CT scan showed sellar and suprasellar pituitary tumor. Although she had no subjective complaints relating to vision, visual field testing revealed a right temporal field defect in the central isopter (an early sign of chiasmal compression). An area of soft-tissue density consistent with inferior extension of tumor was visible in the...
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**FIG. 1.** Magnetic resonance (T2-weighted) images after intravenous infusion of gadolinium in Case 3. **Upper Pair:** Images obtained before the patient's fourth operation. **Lower Pair:** Images obtained 1 month later after progressive cranial nerve deficits and recurrent epistaxis culminated in sudden and complete loss of vision in the right eye. The tumor has extended from the sella into the clivus, sphenoid sinus, nasopharynx, and soft palate and compresses the right optic nerve, both temporal lobes, and the inferior surface of the right frontal lobe.

sphenoid sinus on a skull x-ray film. At that time, her TSH content was 516 μU/ml. She was referred to the NIH for further treatment. The tumor, which measured 2 x 1.5 x 1.5 cm, was removed by transsphenoidal surgery. Her visual field defect cleared and menses resumed. She has since been maintained on l-thyroxine for hypothyroidism.

**Case 8.** This 31-year-old man was diagnosed as hyperthyroid and placed on increasing doses of PTU without effect. Five years later he underwent subtotal thyroidectomy, after which his symptoms improved but did not disappear. At the age of 40 years, his TSH level was found to be elevated and he was referred to the NIH for further treatment. Somatostatin analogue was administered but he did not tolerate its gastrointestinal side effects. Computerized tomography, performed without administration of contrast material because of allergy, showed thinning of the right sellar floor; MR imaging with gadolinium enhancement showed unequivocally an area of low signal intensity (consistent with tumor) in the right lateral pituitary gland, with stalk deviation to the left. The patient's visual fields and general neurological examination were normal. Transsphenoidal excision of a 14 x 10 x 8-mm adenoma was performed without complication. Postoperatively, TSH has been completely suppressed by exogenous T4. There has been no clinical or radiographic evidence of tumor regrowth in the 3 years since surgery.

**Discussion**

The patients presented here show both the diversity inherent in TSH-secreting adenomas of the pituitary gland and the difficulties these tumors present to the surgeon. It was the aim of this study to gather a significant series of patients from a single institution and to compare the preoperative clinical features and the re-
sults obtained by surgical treatment with those seen in surgically treated patients previously reported in the literature. Certain aspects of these patients' clinical course also provide clues about the biological behavior of such tumors.

**Diagnosis**

Early diagnosis depends on adequate biochemical and radiographic screening and a high degree of clinical suspicion in any patient with inappropriate secretion of TSH. Patients can present at any point on the spectrum of thyroid function and still have a pituitary tumor that produces TSH. Most commonly these patients are hyperthyroid by history and examination, as were all of our cases. Some patients with a TSH-secreting tumor are hypothyroid by biochemical criteria and have never been hyperthyroid,\(^{7,9,40}\) while others have no clinical evidence of thyroid dysfunction.\(^{13,24,32,34}\) Therefore, the absence of hyperthyroidism from a patient's history or clinical presentation does not exclude pituitary neoplasm as a cause of inappropriately elevated TSH levels. Disordered cellular synthesis of polypeptides by some tumors produces TSH with increased bioactivity,\(^{3}\) while others produce TSH in a biologically inactive form.\(^{1,7}\)

The pitfalls of operating on a patient with a pituitary mass and high serum levels of TSH must not be overlooked. In the presence of hypothyroidism the negative feedback of thyroid hormones on the pituitary gland and hypothalamus is absent, serum levels of TSH rise, and the pituitary thyrotrophs undergo hyperplasia and hypertrophy. The pituitary gland (and occasionally the sella turcica) in such patients is larger than normal.\(^{45}\) Although the pituitary in this setting of hypothyroidism and excess secretion of TSH returns to normal when exogenous T\(_2\) is given, these patients have occasionally received surgery for decompression of the visual pathways.\(^{15,30,33,38}\)

Other endocrine dysfunction (apart from thyroid hormone abnormalities) may also be associated with these lesions, either from tumoral secretion of other pituitary hormones or from the pressure that the tumor applies to the adjacent pituitary gland and stalk.\(^{5,37}\) The most common of these is prolactin. Clinical and biochemical features of acromegaly occurred in two of our eight patients. Immunohistochemical examination of tumors showed that most stained positively for TSH, and two also contained prolactin; none stained positively for GH, which suggests that it too may be secreted in a superactive form by some tumors. These figures are consistent with the contention of Scheithauer, et al.,\(^{35}\) that 10% to 15% of all pituitary adenomas are plurihormonal. Amenorrhea and, to a lesser extent, galactorrhea were also commonly found, presumably because of disturbances in the secretion of prolactin. Its low occurrence, established by histochemistry, implies that the hyperprolactinemia in many cases reflects release from inhibition consequent to stalk compression. Tumor compression of the optic chiasm produced visual field defects (mainly bitemporal hemianopsia) in five of our patients. Most patients with field cuts did not, however, complain of visual loss. The only other commonly reported neurological complaint was headache, seen in three patients in our series.

Biochemical diagnosis of a TSH-secreting tumor depends heavily on measurements of the serum level of \(\alpha\)-subunit and the \(\alpha\)-subunit/TSH molar ratio, which suggests neoplastic secretion when greater than unity.\(^{25,42}\) Neither predicted clinical outcome. The finding of \(\alpha\)-subunit/TSH ratios less than 1.0 in Cases 3, 4, and 6 shows that absolute reliance on these biochemical values is an unsound practice. Modern techniques for diagnosing pituitary adenomas include high-resolution CT with contrast enhancement and gadolinium-enhanced MR imaging of the sella, and consistent and accurate preoperative diagnosis of TSH-secreting tumors may require that each be available. It is possible that MR imaging with gadolinium would have shown the tumor in Case 5, but this contrast agent was unavailable at the time of that patient's hospitalization.

**Thyroid Ablation and Tumor Growth**

Factors promoting the growth of TSH-secreting pituitary tumors are poorly understood. In about 70% of patients the antithyroid drugs used to treat hyperthyroidism cause a rise in serum TSH that could represent a release of either normal thyrotrophs or thyrotrophic tumor cells from suppression by circulating thyroid hormone (T\(_3\) and T\(_4\)).\(^{37}\) Although no clear-cut proof of the induction of TSH-secreting adenomas by antithyroid drugs or thyroid irradiation exists in man, experimental models of such tumors use surgical, radiological, and chemical techniques of thyroid ablation very similar to those used on all but one of our patients before the existence of a sellar lesion was suspected.\(^{10,11,17}\) In mice subjected to thyroid ablation, a clear progression from thyrotrophic hyperplasia to adenoma formation can be seen histologically in the pituitary gland.\(^{10}\)

The ability of thyroid ablation to induce TSH-secreting tumors in rodents and the finding that these tumors ultimately grow less readily in normal mice than in athyroid mice suggest that similar events may occur in man.\(^{11}\) In mice, thyroid ablation initiates the development of hyperplasia and hypertrophy of the pituitary basophils; by 6 months focal thyrotrophic adenomas are seen, and tumors are grossly visible by 10 months. These tumors are transplantable in syngeneic, athyroid mice and at first require an athyroid host for survival. After many passages, however, variants arise that are capable of growing in allogeneic, euthyroid mice as well. The speed with which this transformation occurs is highly variable. Ultimately a pituitary carcinoma capable of metastasis may arise from some cell lines.\(^{10,11}\)

The effects of adrenalectomy on adrenocorticotropic tumor growth in patients with Cushing's disease are well known.\(^{26}\) It is possible that the large size and invasive nature of the TSH-secreting tumors we encountered stem from the transformation of these lesions to a more aggressive state after removal of the suppres-
Thyrotropin-secreting pituitary adenomas

The goals of therapy are the removal of neoplastic tissue and restoration of the euthyroid state with normal serum levels of TSH and preservation of global pituitary function. Surgery is the only effective way to accomplish these goals. Successful resection is followed by a rapid fall in serum TSH, T3, T4, and α-subunit to normal levels as soon as 11 hours after surgery.20 Secretion of other hormones including GH and prolactin should also return to normal if the patient has been cured. By these criteria, all four patients with smaller, less invasive tumors achieved a cure. All those with giant tumors either died or remain hyperthyroid with residual tumor. This dichotomy strongly suggests that earlier diagnosis would make these tumors easier to treat and cure. However, the several failures seen in the literature after excision of TSH-secreting microadenomas are evidence that, even when detected early, thyrotrophic tumors have not always been cured. Of the seven reported cases of microadenomas (including our own), four (57%) were cured (one after two operations).21,23,25 two remain hyperthyroid,1,26 and one had an unknown postoperative course.13 Other large series of pituitary microadenomas without TSH-secreting tumors report higher overall rates of cure,39,44 a disparity that suggests an intrinsic tenacity of these tumors not present in other pituitary neoplasms.

Medical therapy for these tumors, notably bromocriptine, has been unsuccessful. The somatostatin analogue SMS 201-995 given subcutaneously has been found effective in controlling neoplastic hypersecretion of TSH46,45 and has produced improvement of visual deficits in patients with a TSH-secreting tumor and visual compromise.49 However, its use is limited by the severe gastrointestinal upset it causes in some patients, and the benefits of therapy stop when the drug is discontinued. This drug was tried in one patient before surgery but was withdrawn after she developed intractable nausea and vomiting. It has been helpful postoperatively in controlling TSH secretion by residual tumor in two patients with large invasive tumors.

Radiotherapy is of unproven benefit in treating TSH-secreting tumors incompletely removed at operation. In both of our patients who received sellar irradiation after transsphenoidal surgery (Cases 1 and 3), subsequent progression of tumor led to new neurological deficits and reoperation was required. Although biochemical improvement occurred after radiotherapy in Case 1 and vision returned in Case 3, these patients were also treated with somatostatin analogue and the clinical changes cannot be unequivocally ascribed to radiotherapy alone. Sellar irradiation controls tumor growth in patients with acromegaly and Cushing’s disease, but can damage the normal gland and optic pathways.16 The low incidence of TSH-secreting tumors makes a prospective clinical trial unlikely. Postoperative irradiation of residual tumor should continue to be given until other effective methods of treatment are found.

Surgery is and will probably remain the mainstay of treatment for these tumors in the near future. As awareness among physicians and diagnostic techniques improve, they will come to neurosurgical attention earlier and more frequently. It is possible that some of the pituitary adenomas previously classified as nonsecreting or “silent” will be found to be TSH-secreting when subjected to modern immunohistochemical staining. A significant proportion of tumor cells stain positively for α-TSH in 8% to 32% of such tumors.5,18 Successful surgical treatment demands diagnosis when the tumor is small and before it invades adjacent bone and brain. As in other types of pituitary tumors, those patients whose tumor is confined to the sella have a better chance for a cure and a lower risk of morbidity. The short follow-up period given for many patients reported by others as “cured” of their TSH-secreting tumors by surgery may give a falsely high impression of the true incidence of surgical cure. Case reports already in the literature may also overemphasize the prevalence of extrasellar extension; many of these patients were reported before the introduction of more sensitive immunoradiometric assays for TSH which allow earlier detection of these tumors and which may allow better surgical results.8,12,37

In many patients the surgical difficulties presented by these tumors reflect growth during a delay from clinical onset to diagnosis. The frequent use of thyroid ablation before the pituitary tumor is recognized may permit its transformation into a more aggressive lesion in a manner analogous to the transformation that occurs in Nelson’s syndrome.79
We recommend attempting complete, curative excision of smaller noninvasive TSH-secreting tumors and suggest debulking for larger invasive lesions where cure is not possible and radical attempts at complete removal carry a high degree of risk. Residual tumor can sometimes be controlled by somatostatin; radiotherapy may be useful in controlling tumor growth after incomplete surgical excision. These unusual lesions demand the full range of skill both of the endocrinologist and of the pituitary surgeon.

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