Pituitary Tumors

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Pituitary tumors are the most commonly occurring intracranial neoplasms. They are found in 8% to 24% of autopsied people, most of whom in life harbored small asymptomatic tumors that did not cause hormonal disturbance (Kovacs et al., 1980; Parent et al., 1981; Teramoto et al., 1994; Tomita and Gates, 1999). Pituitary tumors can, however, produce profound physiologic upset by secreting supraphysiologic amounts of hormones or, when large, by compressing critical neural structures adjacent to their typical location in the sella turcica.

The treatment of pituitary tumors has undergone a renaissance since the revival of transsphenoidal techniques by Guiot and Hardy 35 years ago. This process has been aided by the development of hormonal assaying techniques and radiographic imaging during the last three decades. Today, small pituitary tumors can be detected more easily and their hormonal activity can be assessed more accurately than has previously been possible. Medical therapy, particularly for prolactin-secreting adenomas, but also for acromegaly, has developed sufficiently so that surgery can be avoided in some patients who can be managed with drugs alone.

In general, pituitary tumors are diagnosed earlier and treated more effectively now than at any previous time. Nevertheless, a significant number of pituitary tumors deviate from the typical pattern of benign histology and slow growth.

Pituitary adenomas can be invasive and penetrate adjacent dura to enter the sphenoid sinus, cavernous sinuses, or other parts of the skull base. These tumors can grow to a significant size and cause neurologic damage by provoking cranial neuropathies or optic nerve dysfunction; engulfing the carotid arteries and their tributaries; or impinging on the brain. Such aggressive variants behave as malignant tumors of the skull base. Even small, benign tumors may produce a chronic, uncontrolled hypersecretion of pituitary hormone that causes profound physiologic changes over time. By any of these means, pituitary adenomas continue to pose an oncologic threat that warrants their inclusion in any list of clinically significant tumors of the central nervous system (CNS).

PATHOLOGY

Most pituitary gland tumors arise from the anterior portion of the gland known as the adenohypophysis. They are adenomas, tumors of the secretory elements, which in many cases produce and release one or more of the pituitary hormones produced by the anterior lobe. A pseudocapsule, sharply demarcating them from the adjacent normal gland, which may be compressed by tumor, usually encloses these lesions. Although preferred locations for each of the different secretory types have been described within the anterior lobe, in actual fact any of the different subtypes can arise anywhere within the anterior lobe. Rare cases have been reported of adenomas arising in the pars tuberalis, a small extension of the anterior lobe along the distal anterior portion of the stalk (Rothman et al., 1976), or of tumors arising within the sphenoid sinus, nasopharynx, or clivus from embryonic rests of the pharyngeal pituitary (Hori et al.,
When less than 10 mm in diameter, these tumors are called microadenomas; when larger, they are called macroadenomas. A typical adenoma histologically shows loss of the normal acinar pattern and its intervening reticulin network. The cells are fairly uniform in appearance, with small nuclei and a small amount of cytoplasm (Fig. 8-1).

Older schemes of classification, which have relied on standard hematoxylin and eosin staining to produce an appearance of basophilic, acidophilic, or chromophobe staining, have little functional significance and are now obsolete. Current pathologic analysis of pituitary adenomas relies heavily on immunohistochemistry (Asa, 1998). The six major hormones of the anterior lobe (prolactin, growth hormone, thyrotropin [TSH], luteinizing hormone [LH], follicle-stimulating hormone [FSH], and adrenocorticotropic [ACTH]) can be detected by applying a polyclonal or monoclonal antiserum to tumor sections and then exposing the sections to a secondary antibody linked to reagents that give a colorizing reaction. The demonstration of hormonal production does not necessarily correlate with hormone secretion, and a number of clinically nonfunctional tumors, which produce no detectable rise in serum hormone levels, have been found to contain hormone, usually FSH or LH, that has been synthesized in small amounts but not secreted or secreted inefficiently (Black et al., 1987; Daneshdoost et al., 1993; Sano and Yamada, 1994). In addition, pituitary tumors in many cases produce hormones in a disorderly fashion, with an imbalance in the production of the α- and β-subunits, which (in the case of TSH, LH, and FSH) must link covalently to produce a bioactive molecule. Some tumors produce hormone that is detectable through conventional techniques but is biologically inactive (Katznelson et al., 1992; Trouillas et al., 1991) or hyperactive (Gesundheit et al., 1989). In most patients, however, a reasonable correlation exists between the clinical endocrine status of the patient, serum hormone levels, and the hormones demonstrated within the tumor through immunohistochemistry.

The spectrum of tumors that are truly inactive has narrowed greatly with the development of more sensitive hormone detection techniques. Such tumors are called null-cell adenomas (Kovacs et al., 1980). These tumors stain negatively for all hormones and contain none of the granules detected by electron microscopy in typical secretory tumors. It has been suggested that they arise from cells of gonadotrophic lineage, although their origin remains controversial. A subset of these tumors contains large numbers of mitochondria visible by electron microscopy, which are called oncocytomas (Bauserman et al., 1978). Oncocytomas are typically large when diagnosed and affect males more frequently than females (Silbergeld et al., 1993).

It is now apparent that many of the tumors traditionally called nonsecreting actually do secrete hormone in amounts too small to be of clinical significance (Asa et al., 1992; Greenman et al., 1998), or they may produce the α-subunit or chromogranin (Nobels et al., 1993). These two secreted products, neither of which has hormonal activity, can be detected in the blood of some patients with clinically nonfunctional adenomas. The α-subunit is one of the

Figure 8-1. Hematoxylin and eosin stained (A) prolactinoma demonstrating monomorphic population of cells with spherical nuclei and delicate rims of cytoplasm. The same tumor stained with prolactin (B) shows immunoreactivity in the paranuclear location corresponding to the Golgi apparatus.
two subunits necessary for hormonal activity in glycoprotein hormones; alone, however, the α-subunit has no hormonal function. Chromogranin is produced by a variety of neuroendocrine tumors, including most pituitary tumors. These two products may be the only molecular species available for surveillance after surgery or other types of therapy in patients with hormonally inactive adenomas. The most common nonfunctional adenomas in patients under 40 years of age are silent corticotropin and gonadotropic adenomas, and their oncocyctic variants typically occur in patients over age 40 years.

**NATURAL HISTORY**

Although pituitary adenomas are rare in children and fairly common in elderly patients at autopsy, the true prevalence of pituitary tumors in the different decades of life is not known. One preliminary study found focal abnormality of the pituitary suggestive of tumor in 10% of asymptomatic adults undergoing high-resolution scans (Hall et al., 1994). The expected rate of change in small or large adenomas is also not known. Although one study of patients with prolactin-secreting microadenomas found that many do not change in size over time (March et al., 1981), its authors used now-outdated techniques for radiologic surveillance. Another survey that examined untreated hyperprolactinemia found a gradual increase in tumor size in only 20% of patients, but did not address the question of the rate of tumor growth (Schlechte et al., 1989). In patients with clinically nonfunctional tumors in whom a partial surgical removal has been achieved, careful radiographic surveillance of the tumor remnant has shown regrowth in one-third, with a mean time to detection of 5.4 years (Turner et al., 1999). However, another study showed only 6% of endocrine-inactive tumor remnants recurring within 5 years (Lillehei et al., 1998). As the odds of tumor progression weigh heavily on decisions to use (or withhold) postoperative radiotherapy, such information has great practical value. However, these determinations have never been addressed adequately for patients with other forms of pituitary tumor. Most therapeutic decisions in pituitary tumor algorithms are based on logical, although not clearly proven, assumptions that the tumor will enlarge over time and that present hormone levels predict future hormone levels in the untreated state.

**CLINICAL PRESENTATION**

Pituitary tumors cause a panoply of signs and symptoms that can be grouped into four categories: (1) compression of adjacent normal gland, (2) hormonal hypersecretion, (3) visual disturbance, and (4) headache.

**Compression of Adjacent Normal Gland**

Patients may present with hypopituitarism, that is, impairment of the normal function of the various hormonal axes subserved by the anterior pituitary. Particularly vulnerable is the pituitary-gonadal axis, in which minor disturbances of the cycling of FSH or LH can affect libido and fertility in both sexes and the menstrual cycle of women. Also vulnerable to local pressure effects are the pituitary-thyroid and pituitary-adrenal axes. Patients may therefore present with secondary hypothyroidism or a relative hypocortisolism predisposing them to addisonian crisis.

In adults, low levels of prolactin are not thought to be significant. Traditionally, the same assumption has been held regarding growth hormone. During the past decade, however, the clinical effects of growth hormone deficiency on body composition and bone metabolism—and the benefits of treating such deficiency—have become widely accepted. Diabetes insipidus caused by insufficient production of antidiuretic hormone rarely occurs, but, when it does, it heralds granulomatous involvement of the skull base (or a metastasis to the pituitary from a systemic cancer) rather than a pituitary adenoma in most patients who present with the disorder.

**Hormonal Hypersecretion**

Pituitary tumors may produce excess amounts of one or more pituitary hormones, which can induce symptoms relative to the specific hormone present in excess. Growth hormone–secreting tumors produce the syndrome of acromegaly, which is characterized by enlargement of the distal extremities and a coarsening of facial features from bony overgrowth in the
skull. Patients with these tumors are prone to cardiac disease and diabetes mellitus and if untreated (or unsuccessfully treated) have a significantly shortened life expectancy, with an observed-to-expected mortality ratio of 1.6 to 3.3 (Wright et al., 1970; Holdaway and Rajasoorya, 1999).

Adrenocorticotropin-secreting tumors produce hypercortisolism and present with the findings of Cushing’s disease. The protean nature of this disease reflects the importance of cortisol in many organ systems. Patients with Cushing’s disease show changes in body habitus caused by excess fat deposits, giving them the classic “buffalo hump” and moon facies. Patients also tend to have abdominal striae, osteoporosis, and diabetes mellitus; show muscle weakness, particularly in the proximal distribution; and may exhibit psychiatric disturbances (McCutcheon and Oldfield, 1992).

The effects of ACTH-secreting tumors can be subtle in some patients and may present only as a tendency to arterial hypertension or as a very slow change in skin texture and facial contour. Patients with thyrotropin-secreting tumors have typical sequelae of the hyperthyroid state, including heat intolerance, nervousness, and cardiac dysrhythmias.

Prolactinomas cause galactorrhea in men and women and menstrual irregularity in women, which in many cases leads to infertility. A chronic, indirect suppression of estrogen caused by excess prolactin also predisposes the patient to osteoporosis. Men with prolactinomas may show a decreased sex drive and are prone to infertility. Gonadotropin-secreting tumors producing FSH, LH, or both, have a similar effect on the menstrual cycle, fertility, potency, and sex drive as do prolactinomas, but do not cause galactorrhea.

Visual Disturbance

Patients with suprasellar extension of a clinically nonfunctional tumor usually come to medical attention because of visual loss. Any pituitary tumor can cause decreasing vision if it grows large enough to compress the visual pathways. Typically a macroadenoma extending above the sella to the optic chiasm causes a defect in the bitemporal fields that begins in the upper quadrants and can progress to complete bitemporal hemianopia. Because of the anatomic variability in the placement of the chiasm relative to the pituitary stalk, a variety of presentations have been noted. Von Willebrandt’s knee (where nerve tracts from the contralateral retina occupy part of the proximal optic nerve anterior to the chiasm) allows patients occasionally to present with a junctional scotoma, and some tumors are more eccentric to the right or left, thus causing a diversity of nonhomonymous field cuts. Long-standing compression of the optic nerves or chiasm can produce optic atrophy, with a resulting permanent loss of visual acuity. In addition, a tumor that extends into the cavernous sinus may, in its later phases of growth, cause disturbances of third, fourth, or sixth cranial nerve function, resulting in diplopia and ptosis.

Headache

Many patients with pituitary tumors present with headache. These patients often have chronic, refractory headaches that lead a physician to request a brain scan, which may disclose an unsuspected lesion in the pituitary fossa. Although headache is logical in patients with large tumors spilling out of the sella turcica and invading or compressing the pain-sensitive dura, its presence in patients with small, noninvasive tumors must be regarded as coincidental in the absence of any other logical explanation. Suggestions that such tumors cause headache by raising intrasellar pressure are intriguing but have not been proven sufficiently to gain general acceptance (Arafah et al., 2000). Occasionally, pituitary adenomas are found in patients who present with persistent headache after a minor head injury and in whom imaging performed once the headache begins reveals a small pituitary tumor that had been previously undetected.

In a few patients, headache indicates sudden changes in the size and structural integrity of the pituitary tumor. A small percentage of pituitary adenomas hemorrhage and produce an apoplectic syndrome of acute headache and sudden neurologic deterioration caused either by direct compression of the hypothalamus or its vascular supply or by diffuse effects of bleeding across the diaphragma sellae into the subarachnoid space (Randeva et al., 1999). In addition, such patients may show sudden hypopituitarism from acute compression of the normal gland. Occasionally, a patient with a clinically nonfunctional, previously unsuspected adenoma will present in this fashion and will experience diplopia, headache, and
a sudden decrease in vision. Such patients require urgent surgical decompression if vision is to be recovered or preserved.

**LABORATORY INVESTIGATIONS**

The standard laboratory work-up for a patient suspected of having a pituitary tumor involves measurement of an array of hormones that provide direct and indirect indices of pituitary and tumor function (Table 8–1). The typical biochemical survey includes serum levels of prolactin, TSH, LH, and FSH. Growth hormone may also be measured, but this is only necessary if there is clinical evidence of acromegaly. If it is measured, then somatomedin-C (insulin-like growth factor-I) should also be determined because it provides a better picture of growth hormone secretion over time. Some endocrinologists have advocated measuring insulin-like growth factor binding proteins (most specifically IGFBP-3) as a measure of disease activity in acromegaly, but this remains controversial and has not gained widespread acceptance as a replacement for insulin-like growth factor-I surveillance (DeHerder et al., 1995; Paramo et al., 1997; Halperin et al., 1999). Normal levels of LH and FSH differ in men and women, and also differ in women during the various phases of the menstrual cycle. Measurement of thyrotropin levels should be accompanied by measurement of triiodothyronine and L-thyroxine so that elevations in TSH caused by primary pituitary hypersecretion can be distinguished from elevations caused by primary thyroid insufficiency.

Adrenocorticotropic hormone is not generally measured directly; rather, the activity of the pituitary-adrenal axis is determined by measurement of cortisol, one of the main adrenal hormones produced in response to adrenocorticotropic stimulation. Both cortisol and ACTH are heavily subject to diurnal rhythms, and it is generally considered best for coherent and consistent interpretation of serum cortisol levels to collect them at 8 am, when they are relatively high. For women, estradiol levels are checked. These are fairly sensitive indices of gonadal failure but must be interpreted in conjunction with levels of FSH and LH.

Prolactin is measured for all patients. Elevations of prolactin may occur because of hypersecretion by tumor cells but can also be caused by anatomic distortion of the pituitary stalk by the tumor mass. This distortion results in inadequate flow through the portal-hypophyseal system of those dopaminergic factors that exert a tonic inhibition on prolactin production. When the stalk is compressed, this inhibition is released, and prolactin levels rise. Because the elevation caused by a prolactin-secreting tumor is usually significantly higher than that caused by a nonfunctional tumor disturbing the stalk, it is usually possible to distinguish between the two by a careful analysis of prolactin levels over time.

Other important information on the hormonal condition of the patient can be obtained by the use of provocative hormonal tests. In these tests, a synthetic stimulatory factor (such as the corticotrophin-releasing factor) is administered intravenously to the patient, and the hormonal response is evaluated over time. Such tests provide a dynamic indication of the ability of the gland to push hormone levels above baseline values. In subtle cases of hormone dysfunction, and particularly in patients with Cushing’s syndrome where these tests can help with the differential diagnosis and localization of the hypersecretory source, the use of provocative tests may be considered. They also have value for the assessment of normal pituitary function in patients recovering from sur-

**Table 8–1. Laboratory Work-Up for Patients Suspected of Having a Pituitary Tumor**

<table>
<thead>
<tr>
<th>Hormone</th>
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<tbody>
<tr>
<td>Prolactin</td>
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<tr>
<td>Thyrotropin</td>
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<tr>
<td>Triiodothyronine</td>
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<tr>
<td>L-thyroxine</td>
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<tr>
<td>Luteinizing hormone</td>
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<tr>
<td>Follicle-stimulating hormone</td>
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<td>Growth hormone, if clinical evidence of acromegaly</td>
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<tr>
<td>Somatomedin-C (insulin-like growth factor-I)</td>
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<tr>
<td>Cortisol</td>
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<tr>
<td>Estradiol levels in women</td>
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<tr>
<td>Prolactin</td>
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<tr>
<td>Provocative hormonal tests (tailor to clinical situation: critical in Cushing’s disease)</td>
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<tr>
<td>Serum electrolytes (serum and urine osmolality, fluid intake and output, urine specific gravity when diabetes is suspected)</td>
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<td>Measurement of α-subunit for patients with clinically nonfunctional adenomas or those with a thyrotropin-secreting adenoma</td>
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Halperin et al., 1999). Normal levels of LH and FSH differ in men and women, and also differ in women during the various phases of the menstrual cycle. Measurement of thyrotropin levels should be accompanied by measurement of triiodothyronine and L-thyroxine so that elevations in TSH caused by primary pituitary hypersecretion can be distinguished from elevations caused by primary thyroid insufficiency.
surgery for a pituitary tumor. In the postoperative setting, basal hormone values are remeasured after a suitable interval. This helps both to establish the presence or absence of continuing hypersecretion by residual tumor and to assess the adequacy of normal gland function, because such function may be damaged by the gentle manipulation required to separate a tumor from the adjacent normal gland. After surgery pre-existing hormone deficits will be restored in approximately 50% of patients, and 20% develop new deficits of anterior pituitary function (Webb et al., 1999).

The function of the posterior lobe is assessed by measurement of serum electrolytes and, in cases where there is a high suspicion of diabetes insipidus, by checking serum and urine osmolality and by recording fluid intake and output and urine specific gravity. It is exceedingly rare for a patient with a pituitary tumor to present with diabetes insipidus. If a sellar mass is seen on a scan and diabetes insipidus forms part of the clinical presentation, it is highly possible that the tumor is not a pituitary adenoma, but rather a metastatic tumor arising in the lung, breast, prostate, or another organ system. Diabetes insipidus occurs much more often in the postoperative period, when about 15% of patients show this phenomenon either transiently or permanently. The production of vasopressin by the pituitary is more sensitive than other hormonal axes to the trauma of surgery. Special vigilance is necessary during the first week after surgery, because patients with partial diabetes insipidus can become dehydrated and hypernatremic if the condition goes unrecognized and if no hormone supplementation is given. Surveillance for hyponatremia is also required during the first 2 weeks after surgery, as 2% (Hensen et al., 1999) to 21% (Olson et al., 1997) of patients develop a transient dysregulation of vasopressin release that can be clinically significant.

Measurement of the α-subunit has been considered experimental but is gaining acceptance. It is now recognized that some tumors are pure α-subunit–secreting adenomas (Ridgway et al., 1981). As a rule, this measurement should be taken for all patients with clinically nonfunctional adenomas (Warnet et al., 1994). The other group in whom the α-subunit has particular relevance is the occasional patient who presents with a TSH-secreting adenoma. Measurement of the α-subunit/TSH molar ratio in this instance is valuable in sorting out those patients with a “syndrome of inappropriate TSH secretion” who have a pituitary tumor from those who have pituitary resistance to the effects of TSH (Gesundheit et al., 1989; McCutcheon et al., 1990).

**RADIOLOGIC EVALUATION**

The preferred radiologic technique for pituitary tumor detection and follow up is magnetic resonance imaging (MRI). Magnetic resonance imaging has now supplanted previous methods of sellar tomography and computed tomography (CT), which are less sensitive and should only be used when MRI is unavailable (Webb et al., 1992). An occasional patient is still brought to medical attention by the incidental finding of erosion or enlargement of the sellar boundaries on a skull radiograph. Such patients generally have large nonfunctional tumors, and the most accurate way of defining the anatomic boundaries of the tumor is with a MRI scan. In years past, concerns about carotid artery aneurysms that masquerade as pituitary tumors led to the occasional use of angiograms for such patients. This too is now unnecessary, as standard MRI shows nicely the distinction between the flow void of the carotid artery within the cavernous sinus and the tumor within the sella and adjacent areas.

Tumors as small as 3 mm in diameter now represent the limits of detection of MRI scans enhanced by gadolinium (Lundin and Bergstrom, 1992). Pituitary tumors are generally seen on contrast scans as hypointense to isointense areas against a slightly hyperintense area of normal gland (Fig. 8–1). This situation is the reverse of that seen with glial tumors of the cerebral parenchyma, where enhancement is seen within the tumor and within adjacent areas of edematous brain with an impaired blood–brain barrier. There is no blood–brain barrier in the pituitary gland, and by virtue of this pattern of enhancement the vessels within the tumor would seem to be less immediately leaky to contrast than those of the normal gland. The best delineation is therefore seen in scans done early (i.e., from 2 to 5 minutes after gadolinium injection) (Hayashi et al., 1995).

There are still a number of patients in whom no distinct adenoma is seen but in whom biochemical tests suggest the presence of such a lesion. This circumstance is particularly relevant in Cushing’s disease, where tumors may be very small, yet produce
a profound physiologic upset because of the primacy of ACTH in a number of the physiologic processes relevant to homeostasis. Other secretory tumors tend to come to attention only when they are larger. Patients with Cushing’s disease frequently have obvious hypercortisolism on biochemical and clinical examination, but can have a normal MRI of the sella turcica. Although a few such occult tumors become visible when dynamic scanning is performed during contrast infusion, this technique is not widely available (Bartynski and Lin, 1997). The possibility of misdiagnosis of ectopic secretion of ACTH for pituitary hypersecretion emphasizes the importance of rigorous biochemical testing, which should be able to distinguish between these two etiologies. In addition, even tumors larger than 3 mm in diameter can escape detection by scans if their signal characteristics are isointense to those of normal gland. The selection of patients for surgery who have been shown to secrete hormone in excess should be on the basis of biochemical evidence first and, second, on radiologic evidence.

**TREATMENT**

**Rationale for Treatment**

Determining the best way to treat pituitary adenomas depends on the predicted nature of the pathology. Hormonally active tumors usually require suppression by surgery, medical means, and/or radiation therapy to prevent the long-term sequelae of hypersecretion. In particular, patients with Cushing’s disease or acromegaly rarely reach a normal life expectancy because of the deleterious effects that excess ACTH and growth hormone exert on a variety of organ systems, particularly the cardiovascular system. Patients with prolactinomas may require therapy to reverse the infertility imposed by such tumors and to prevent the accelerated osteoporosis that occurs in patients with chronically elevated prolactin levels (Klibanski et al., 1988). Those with TSH-secreting adenomas suffer an intractable form of hyperthyroidism with attendant cardiac irritability and also require definitive treatment. Clinically nonfunctional tumors often present because of chiasmal compression causing visual field defects. The presence of an increasing field cut is a strong indication for surgical decompression, a statement that applies equally to patients with secretory tumors of whatever type. For pituitary tumors as a group, statistics show a twofold excess mortality relative to the population at large, but the reason for this difference is unclear (Nilsson et al., 2000).

The goals of therapy for pituitary tumor include:

- Elimination of hormonal excess by tumor section
- Prevention of optic nerve dysfunction caused by suprasellar extension of tumor
- Restoration or preservation of normal pituitary function
- Avoidance of therapeutic complications
- Long-term remission without biochemical or radiographic evidence for regrowth of tumor

Any treatment that is chosen must be judged by these standards in assessing its efficacy and suitability for a given patient.

**Surgical Approaches**

Entry to the sella turcica is achieved most safely by the transsphenoidal approach in patients with small tumors without extrasellar extension. This method allows the surgeon to avoid entering the intracranial compartment and has the advantage of midline trajectory that circumvents critical structures on either side of the gland (Hardy, 1969, 1991). The incision in such an operation can be made in the sublabial (below the lip) area over the maxilla just beneath the inferior extent of the pyriform apertures, a route that allows direct exposure of the virtual space between the cartilaginous nasal septum and the medial nasal mucosa (mucoperichondrium). A tunnel created within this virtual space leads directly to the vomer, sphenoid sinus, and sella. Alternatively, an endonasal route that avoids an external incision can be chosen, but this requires either a wide nasal cavity or incision of the nasal ala to allow room for a speculum within the nose (Griffith and Veerapen, 1987). In the endonasal approach, the incision is made in the nasal mucosa at the posterior edge of the cartilaginous nasal septum where it meets the bony septum. Transsphenoidal approaches should be chosen for tumors confined to the sella, those with relatively minor suprasellar extension, or those that extend into the sphenoid sinus. Tumors with cavernous sinus extension are frequently excised by the transsphenoidal route, but complete resection should not be expected as the contents of the cavernous sinus usually elude full inspection.
The transtemporal approach is reserved for patients with larger tumors that elevate the diaphragma sellae more than 2 cm above its normal level or that extend laterally from their intrasellar origin. Often, a pterional or combined pterional/subfrontal craniotomy is used, and a bone flap is fashioned that extends as close as possible to the floor of the anterior cranial fossa (Tindall and Tindall, 1987). The sylvian fissure is then split medially, the frontal lobe is elevated, the temporal lobe is slightly depressed with malleable retractors, and the suprasellar and sellar areas are visualized. The operating microscope is an essential tool in this small and anatomically complex region when transcranial and transsphenoidal procedures are performed. Intraoperative fluoroscopy is vital as well in transsphenoidal procedures and allows localization of the position of instruments relative to the bony landmarks of the skull base.

If cavernous sinus exploration or exenteration is desired, a fronto-orbito-zygomatic craniotomy can be performed. This procedure involves a more extensive bony removal that includes the orbital rim and roof, anterior clinoid, and malar eminence (Al-Mefty and Smith, 1990). The zygoma is usually cut free and allowed to fall down with the temporalis muscle, a tactic that grants the surgeon additional exposure over a fairly wide field of view. If carotid resection is planned, we prefer to expose the internal carotid artery in the neck in case a sudden rupture occurs requiring arterial tamponade; others unroof the petrous segment of the carotid instead. Before any cavernous sinus exploration is done, a preoperative carotid balloon occlusion test must be performed, which predicts the ability of the patient to tolerate carotid resection. This clinically qualitative test may be enhanced by the performance of single-photon emission CT or xenon-CT scans that measure cerebral blood flow in the ipsilateral and contralateral cerebral hemispheres (Origitano et al., 1994). These techniques continue to evolve and may offer hope for those patients with extensive disease in the cavernous sinus or skull base who, until recently, were offered radiation therapy as palliative treatment but for whom little other therapy was available (MacKay and Hosobuchi, 1978).

Other variations on these themes have been used over the years. The transtemporal approach has had some proponents but is generally not used because it requires a facial incision and provides an angled, imperfect view that makes anatomic landmarks more difficult to identify than does the midline transsphenoidal approach (Kirchner, 1984). Endoscopic excision of pituitary tumors has been reported and is gaining increasing popularity as part of the trend in all surgical disciplines toward reducing incision size and the “invasiveness” of any given procedure. Although improvement in the quality of endoscopic instrumentation has fostered its use in pituitary surgery, and several medical centers have been enthusiastic in reporting its advantages (Jho, 1999; Sheehan et al., 1999; Jarrahy et al., 2000), no prospective comparison of its efficacy in achieving complete resection of adenomas, large or small, has yet been undertaken. Even though less disruption of the nasal septum occurs during endoscopic transsphenoidal surgery, patients are still subject to the risks of cerebrospinal fluid rhinorrhea and endocrine disturbance, so it is not clear why use of the endoscope should lead to shorter stays in hospital after operation, as some authors have proposed (Jho, 1999). It seems appropriate to use endoscopy as a tool for examining areas within the sella turcica that currently elude direct inspection by the surgeon. In particular, in many patients, the medial wall of the cavernous sinus is poorly seen or not seen at all, and adherent tumor can be left there after an otherwise successful operation. It is likely that endoscopy will become an additional, quite valuable tool for maximizing tumor resection, but that open procedures using the operative microscope will continue to be used for many patients (Jankowski et al., 1992).

Computer-assisted navigation has also been applied to pituitary surgery during the past 5 years. Such devices provide the surgeon with a pointer (typically tracked optically), the location of which is determined by a workstation and displayed on a screen showing the operative field on relevant multiplanar MRI slices. This technology is still evolving and is not yet ready to replace fluoroscopy as the standard localizing tool in transsphenoidal surgery (McCutcheon et al., 2001). However, it is quite useful in locating such surgically relevant structures as the carotid arteries and sphenoid septations, in planning the surgical trajectory, and in locating lateral or inferior extensions of pituitary tumors invading the skull base (Sandeman and Moufid, 1998). Such tools, together with endoscopy, will become important aids to safer and more complete removal of pituitary tumors during the next decade.
SPECIFIC TUMOR TYPES

Table 8–2 summarizes specific types of pituitary tumors.

Prolactin-Secreting Adenomas

Approximately 40% of pituitary adenomas secrete prolactin, and such tumors are more common than any other type of pituitary neoplasm. In contrast to the reliance on surgery as the primary treatment for other forms of pituitary tumor, these tumors are usually treated medically before surgery is considered.

Drug Therapy

Various dopamine analogues that inhibit prolactin release are available, the most common being bromocriptine (Parlodel). About 70% to 80% of patients respond to this drug, but significant side effects occur in 20% to 30% of patients, which limits its use (Molitch et al., 1985). Side effects associated with bromocriptine include nausea, vomiting, orthostatic hypotension, and, in some patients, psychotic reactions. The drug may be stopped, therefore, because of a failure to arrest tumor growth and bring prolactin levels to normal or because the patient cannot tolerate the drug. An alternative long-acting dopamine agonist called quinagolide (or CV 205-502) has been developed. This agent has a higher affinity than bromocriptine for dopamine receptors. Approximately one-half of adenomas that resist bromocriptine therapy respond to quinagolide (Brue et al., 1992b). Quinagolide also invokes side effects and has caused weight loss and psychiatric breakdown in some patients, but has fewer side effects than bromocriptine (Glaser et al., 1994; Merola et al., 1994). Other long-acting bromocriptine analogues have also been studied that may lower the incidence of side effects (Brue et al., 1992a; Maraschini et al., 1991; Jamrozik et al., 1996); however, their role and that of quinagolide, in the clinical management of these patients has been eclipsed by cabergoline, another long-acting dopaminergic agent released for use in the United States in 1998.

Cabergoline (Dostinex) was developed as a D2-receptor–specific agonist, by virtue of which it has less of a tendency to provoke side effects (operating through the D1 as well as the D2 receptor) than either bromocriptine or quinagolide. Because of this and because it is given once or twice weekly, patients are more likely to be compliant in taking the drug. It normalizes prolactin levels in 80% to 90% of patients and causes tumor shrinkage in two-thirds (Verhelst et al., 1999). In a series of patients resistant to bromocriptine, prolactin became normal in 70% of patients taking cabergoline; and, of patients intolerant of bromocriptine’s side effects, 84% tolerated cabergoline and normalized their prolactin levels. Dose escalation improves these numbers even further (Colao et al., 2000). Comparison of cabergoline with quinagolide shows that the two drugs normalize prolactin in an equal proportion of patients, but that a greater chance of tumor shrinkage occurs with cabergoline (Di Sarno et al., 2000). Because of such results, cabergoline is now the drug of choice for medical treatment of prolactinomas, although bromocriptine remains a well-established (and significantly less expensive) alternative.

The response of patients with prolactinomas to medical therapy depends on tumor size and prolactin level. Patients with smaller tumors and lower prolactin levels respond best. If the prolactin level before treatment is greater than 1000 ng/ml, the levels usually fall with dopamine agonist therapy, but do not normalize (Hardy, 1984). Most tumors cause prolactin levels between 50 and 250 ng/ml. From 65% to 80% of patients taking bromocriptine in this range will normalize their prolactin levels, and over time tumor reduction occurs in 76% (Brue et al., 1992a; Maraschini et al., 1991). Cabergoline’s statistics, alluded to above, are comparable or better.

The general assumption is that patients treated medically require life-long therapy to avoid regrowth of suppressed tumor; however, in some patients, the tumor disappears completely and does not recur when bromocriptine is stopped. After withdrawal of cabergoline, approximately 10% of patients exhibit this phenomenon, which appears to be confined to those with microadenomas (Di Sarno et al., 2000). Unfortunately, it is only possible to identify these pa-

Table 8–2. Specific Pituitary Tumor Types

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<td>Clinically nonfunctional adenomas (incidentalomas)</td>
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<td>Gonadotropin-secreting adenomas</td>
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<td>Growth hormone–secreting adenomas</td>
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<td>Thyrotropin-secreting adenomas</td>
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tients after the fact. This dilemma cannot be resolved fully at this time, but does suggest a clinical approach of stopping the drug at intervals and following hormone levels and scans for any sign of regrowth or return of hypersecretion. It is likely that the tumor will regain its activity in the majority of patients who are evaluated long enough and, in those patients, treatment must begin anew.

**Surgery**

Surgery is used only if medical treatment fails or if the patient cannot tolerate the side effects of the treatment. There has been some evidence to support the idea that pretreatment with bromocriptine enhances surgical results (Hubbard et al., 1987) and opposing evidence that it makes tumor excision more difficult by inducing fibrosis within the tumor (Bevan et al., 1987). Although patients may wish to temporize and avoid surgery, it is best not to continue trials of medical therapy for more than 1 year without declaring success or failure and deciding whether surgery will or will not be indicated.

The success of surgical treatment depends on tumor size and preoperative hormone level, both of which predict the invasiveness of the tumor in question. Microadenomas are more readily excised and generally show prolactin levels of 50 ng/ml to 100 ng/ml. In the series of Randall et al. (1983), prolactin levels normalized after surgery in 88% of those with preoperative levels less than 100 ng/ml, but in only 43% of those with levels greater than 100 ng/ml. Patients with prolactin levels greater than 350 ng/ml should be considered to have an invasive tumor, and all will harbor macroadenomas. In the very extensive series of Hardy (1984), the immediate remission rate was 86% for patients with levels less than 250 ng/ml but only 6% for those with levels greater than 1000 ng/ml.

Given the predominant role of medical therapy for prolactinomas, it is now uncommon to operate on patients with small tumors who have not received prior dopamine agonist therapy. It has been suggested that such pre-treatment compromises the success rate of surgical removal. In one surgical series in which all patients had been previously given bromocriptine, only 45% of patients with microadenomas and only 17% of those with macroadenomas had normal levels of prolactin postoperatively (Soule et al., 1996). Such results may reflect bromocriptine-induced fibrosis within the tumor, as well as a selection bias such that more difficult cases were more likely to be referred for surgery.

Despite initial success in most surgical series, a significant number of patients relapse when studied long-term after surgery (Hardy, 1984). Hardy’s recurrence rate was 22% during the first 5 years after surgery. Others have shown recurrence rates of 17% to 50% during the first 2 years after surgery for microadenomas and 20% to 80% for macroadenomas during the same time period (Rodman et al., 1983; Serri et al., 1983). In Wilson’s modern series, more than 90% of patients with microadenomas (and more than 80% of those with small macroadenomas) showed initial remission, as did 40% of those with prolactin levels above 200 ng/ml or with large, invasive tumors (Tyrrell et al., 1999). During 15 years of follow up, about 15% of those in remission relapsed to hyperprolactinemia.

In Adams’ surgical series of microprolactinomas with a mean follow-up period of 70 months, only 1 of 32 patients recurred. It is certainly possible to normalize prolactin in most patients with a small, encapsulated tumor and to expect a sustained remission, but the persistence of remission has not been sufficiently studied for periods longer than 5 years. Because many patients in surgical series are between 25 and 40 years old and may be expected to live for several decades, more data on long-term rates of recurrence are needed. Tumor reactivation may occur for several reasons, including the regrowth of residual microscopic clusters of tumor cells, the presence of an underlying genetic mutation predisposing to tumor growth, or the presence of a mechanism of hypothalamic overdrive that continues unabated after tumor excision.

**Radiation Therapy**

Radiation therapy is useful for patients in whom such regrowth recurs and who wish to avoid further surgery. It is also a valuable adjunct for patients in whom a complete excision cannot be achieved because tumor has infiltrated adjacent dura, neural structures, or the cavernous sinus. Usually a fractionated dose of 45 to 50 Gy is given over 4 to 5 weeks by a limited-field technique that excludes structures outside a 4 cm window centered on the sella turcica. The drawbacks of radiotherapy are its gradual effect and its ability to damage parapituitary structures contained...
within the field as well as late effects that can occur. Several years usually pass before maximum tumor regression occurs, and 2 to 10 years may be required for normalization of prolactin levels. The success rate of sellar irradiation within this time frame has been reported to be as low as 30% (Sheline et al., 1984; Williams et al., 1994), although others have reported an 83% rate of local control over 10 years (Sasaki et al., 2000). Larger prolactinomas (i.e., with volume >30 cm³), however, show particularly poor local control rates and may require specialized techniques or repeat surgery (Izobe et al., 2000).

New methods of irradiation include one that links beam delivery with stereotactic localization, allowing delivery of a highly concentrated, accurately focused dose of radiation to an intracranial target. Although the name "radiosurgery" has been applied to this method, no surgical incision is involved. Rather, this method involves attachment of a stereotactic ring to the patient's head by a neurosurgeon who assists a radiotherapist in planning the isodose contours, a complicated process that requires specialized computers and precise three-dimensional representation of the target. Either a standard radiotherapy gantry with a stationary target (LINAC) or multiple stationary sources of irradiation all focused simultaneously on the target (gamma knife) may be used. In theory, this method reduces the risk of radiation damage to adjacent structures, particularly the medial temporal lobes and the optic chiasm, while maximizing radiation dose. The pituitary gland is still included in the radiation field because of its intimate relation with any intrasellar tumor. In addition, if the cavernous sinus is included within the radiation field, 10% to 15% of patients will develop a cranial neuropathy within 3 years of radiosurgical treatment (Tishler et al., 1993).

The function of the normal gland is at risk with both stereotactic and conventional radiation techniques, and as many as 100% of patients treated conventionally show pituitary insufficiency when studied for 10 years (Littley et al., 1989). The administration of a stereotactic dose of 40 to 70 Gy by charged particle beam (no longer much used since the advent of the gamma knife) yielded a 10% to 30% incidence of post-treatment hypopituitarism, and 60% of patients with prolactin-secreting tumors had normalized prolactin levels within 1 year after treatment (Levy et al., 1991). Although such techniques have been available for a number of years in Europe and North America and were widely used during the 1990s, good long-term statistics are still unavailable. Most treatment centers that perform radiosurgery for pituitary tumors use the gamma knife system in which the target (i.e., the tumor) is placed at the center of a fixed, spherical array of radiation sources. LINAC-based systems, which utilize a roving gantry arm to deliver the radiation beam, can also be employed. However, the gamma knife has a dosimetric advantage in treating pituitary adenomas, as it can achieve a greater conformity index than the LINAC in this anatomic region (Plowman and Dougherty, 1999).

In one small series of patients with microprolactinomas, radiosurgery caused normalization of prolactin levels in 23%, and a decrease (but not normalization) in 62%, during 1 year of follow up (Kim et al., 1999). In a larger series, similar results were achieved but correction of endocrinopathy occurred more frequently in patients with acromegaly or Cush- ing's disease than in those with prolactin-secreting tumors (Pan et al., 1998). As radiosurgery can only be done in patients with microadenomas or tumors with lateral (rather than superior) extension, many patients do not qualify for it and must be treated surgically and/or with more conventional radiotherapeutic techniques. For some, fractionated conformal irradiation may offer increased accuracy of targeting, with reduction in the volume of normal tissue exposed to irradiation. However, only preliminary experience has been reported with its use for pituitary tumors, so it is impossible to conclude whether it will prove safer or more effective than conventional limited-field techniques (Jalali et al., 2000; Perks et al., 1999).

**Summary of Therapeutic Approach**

In our current practice, we treat patients with prolactinomas first with cabergoline, unless a trial of the drug shows side effects the patient cannot tolerate. In years past, such patients were offered quinagolide as an alternative or they chose surgery. Quinagolide has been withdrawn from use in clinical trials in the United States despite its published clinical utility; it remains available in Europe and in Canada. Patients with progressive visual loss are also treated with surgery, but those with a macroadenoma and visual field cut can sometimes be controlled with dopamine agonists, and surgery can thereby be avoided. Radiotherapy is reserved for the relatively few patients whose tumors regrow after surgery or whose tumors cannot be completely excised, as proven by persis-
tent elevation of prolactin despite maximal removal of tumor.

**No Treatment**

Prolactinomas, gonadotropin-secreting adenomas, and clinically nonfunctional adenomas comprise the majority of pituitary tumors and do not generally provoke hormonal derangements affecting long-term survival. What are the chances that a small tumor in this group that does not affect chiasmal function will grow at all if simply left untreated? Patients with macroadenomas often require treatment to preserve or improve vision and to control (in prolactinomas) high levels of hormone secretion that impair fertility and menstruation. These conditions must be corrected in those patients who wish to conceive.

Microadenomas, however, have been shown in some instances not to change for as long as 20 years, and their ability to secrete excess hormone may fade or actually increase over time. Spontaneous involution of such tumors, sometimes as a result of an apoplectic event, may occasionally occur. In a study of 30 patients with small tumors in whom no treatment was given, 14 showed no change in prolactin levels over time; 6 showed a gradual increase; and 10 showed a decrease (Schlechte et al., 1989). For patients with prolactin-secreting microadenomas and for those with small nonfunctional tumors, it is reasonable to follow those in whom some menstruation is present and child-bearing is not desired, with intervention reserved for those in whom tumor growth or increased secretory activity occurs.

**Clinically Nonfunctional Adenomas**

The category of clinically nonfunctional adenomas has been redefined in recent years as techniques in pathologic analysis have become more powerful. It now includes patients with true null cell adenomas that secrete no hormone of any kind; those with α-subunit–secreting adenomas that produce no active hormone; and those with tumors that, although secretory, produce quantities of hormone too small to effect clinical change in endocrine function. Many of the patients in the last category have tumors that, by immunohistochemical analysis, produce FSH or LH (Asa et al., 1992; Young et al., 1996). These gonadotropin-secreting adenomas were previously thought to be quite rare. It is now recognized that a spectrum exists, that at its lower end, includes patients previously classified as nonsecreting and at its high end includes those with detectable elevations of FSH and/or LH in peripheral blood. Each category is addressed here.

About 25% to 33% of pituitary adenomas are clinically nonfunctional and produce symptoms only by compressing the pituitary and parasellar structures and, eventually, causing frank hypopituitarism. This condition often goes unrecognized, except in retrospect, until compression of the visual pathways leads to the diagnosis of a sellar lesion. Approximately one-half of all pituitary adenomas stain on immunocytochemistry for one or more of the glycoprotein hormones or their subunits (α or β) (Black et al., 1987; Daneshdoost et al., 1993; Sano and Yamada, 1994). They are not clinically active because of inefficient hormone release or because they produce hormonal species of low bioactivity. Between 20% and 30% of patients with endocrine-silent pituitary adenomas do have increased levels of serum α-subunit, which may be useful in some cases as a marker of tumor activity (Oppenheim et al., 1990; Nobels et al., 1993). Such hypersecretion of α-subunit is most common in larger tumors (Warnet et al., 1994).

As for any large pituitary tumor, treatment includes hormone replacement to correct deficiency of normal pituitary function. There is no available medical treatment that effectively suppresses the growth of these tumors. However, octreotide has been shown to cause improvement in visual field deficits in clinically nonfunctional macroadenomas, although it has no effect in 50% of such tumors (Warnet et al., 1997). Although nonfunctional tumors are quite common, only a few large surgical series have been published, and all such series include both null cell adenomas and weakly gonadotropin-secreting tumors under the “nonsecreting” or “nonfunctional” heading. Ebersold et al. (1986) reported results from the excision of 100 nonfunctioning adenomas, of which 82 were greater than 2 cm in diameter. Most of these patients had preoperative visual impairment that generally improved after surgery. Because of the high prevalence of invasive features in such tumors, 50% were incompletely resected and required postoperative radiotherapy. Regrowth occurred in 18% of those who received radiation after surgery and in 12% of those (presumably smaller tumors) treated with surgery alone. In Hardy’s series of 126 patients treated over 25 years, vision improved in 75% of those who had
visual impairment before surgery, and 21% regrew during a mean follow-up period of 6.4 years (Comtois et al., 1991). In addition, preoperative hypopituitarism (present in >75% overall) improved in 41% of those with deficits in the pituitary-adrenal axis and in 14% of those with hypogonadism.

As with prolactinomas, radiotherapy is generally recommended when obvious residual tumor remains after surgery or when regrowth occurs and such treatment has not previously been given. Halberg and Shele (1987) administered radiotherapy to 140 patients with clinically nonfunctional tumors. Of these, 23 were poor surgical candidates who received irradiation alone, 37 were treated by surgery only, and 80 underwent combined treatment. A long follow-up period (up to 20 years) was achieved. All patients treated with irradiation alone showed arrested growth of tumor; tumor recurred in 75% of those treated with surgery and radiotherapy and in 100% of patients treated with surgery alone. Such results suggest that many tumors in this category are invasive and are incompletely resected.

An opposing school of more conservative bent has arisen during the past 10 years. The volume of residual tumor in patients undergoing incomplete resection may be small and sit well away from the optic nerves or chiasm and may be followed up accurately with MRI. One group evaluated such non-irradiated patients with serial imaging and found that tumor in only 6% regrew after 5 years (Lillehei et al., 1998). A second report by others showing a recurrence rate of 18% at 5 years and 44% at 10 years is more pessimistic even than their own earlier report, which had suggested a much lower incidence of recurrence (Bradley et al., 1994; Turner et al., 1999). We do a full endocrine screen on such patients and scan them yearly for several years, partly in response to the need to alleviate the patient’s anxiety and partly to identify the minority with endocrine deficits and/or active tumors. Any patient with a tumor causing an asymptomatic visual field loss, however, is offered surgery.

Gonadotropin-Secreting Adenomas

Gonadotropin-secreting adenomas produce no specific clinical syndrome and are treated much like other clinically nonfunctional adenomas (Snyder, 1997). When large, they more often present because of visual impairment and hypopituitarism than endocrine excess. Hypogonadism in such patients may reflect impairment of normal pituitary function through mass effect or may relate to the elevation of FSH or, less commonly, LH produced by the tumor itself. Some tumors secrete gonadotropins in vitro but produce no detectable change in hormone levels in vivo except an occasional elevation of the α-subunit (Asa et al., 1992; Snyder et al., 1984). Others produce small but measurable increases in serum levels of LH, but not consistently enough to allow its use as a tumor marker (Greenman et al., 1998). In addition, tumor immunostaining does not correlate well with serum gonadotropin levels, which further weakens the utility of studying those levels for any clinical purpose (Ho et al., 1997).
The main reason for distinguishing this group from other nonfunctional tumors lies in the potential that medical therapy may prove effective against them. Because dopamine suppresses gonadotropin secretion in the normal gland, bromocriptine has been used with occasional success for patients who have gonadotropin-secreting adenomas (Lamberts et al., 1987). In addition, innovative therapy using LH-releasing hormone and its antagonists has been used for a few patients. LH-releasing hormone increases secretion in most patients, but inhibits it in a few, perhaps by desensitizing the tumor (Klibanski et al., 1989). Antagonists to LH-releasing hormone have yielded mixed results but may eliminate the presumptive hypothalamic stimulus to tumor growth. As mentioned above for clinically nonfunctional tumors, somatostatin analogues have also been used in this subset of patients to obtain clinical improvement, and less often tumor shrinkage. In general, most patients with gonadotropin-secreting tumors are treated like those with other clinically nonfunctional tumors.

**Growth Hormone–Secreting Adenomas**

**Medical Treatment**

The results of drug therapy in treating growth hormone–secreting adenomas are less predictable than those achieved in treating prolactinomas. Bromocriptine, cabergoline, short-acting somatostatin analogues (SMS 201-995, octreotide acetate), or long-acting analogues (lanreotide) have been used. Bromocriptine normalizes growth hormone levels in 20% of patients, but doses at the higher end of the accepted range (20 mg/day) are often necessary, producing a greater incidence of side effects (Wass et al., 1977). Most such tumors will not shrink with bromocriptine, although octreotide has been reported to induce tumor regression in 50% of patients and reduces growth hormone levels in a majority of cases (Barkan et al., 1988; Arosio et al., 1995; Newman et al., 1998). Because some patients achieve persistent biochemical and clinical improvement over long periods of time with chronic somatostatin therapy, this drug can be used as a medical alternative to surgery. Somatostatin has the disadvantages of a subcutaneous route of administration and causes gallstones and gastrointestinal upset in some patients.

We use octreotide occasionally as a preoperative adjunct because it will shrink tumor in 50% of patients to whom it is given, which may make complete surgical excision more feasible. Unlike bromocriptine for prolactinomas, octreotide does not cause histologic changes that impede tumor removal. Shrinkage occurs during the first 2 weeks of treatment, if it is to occur at all, so prolonged courses give no added benefit (Lucas-Morante et al., 1994). Pre-surgical treatment with octreotide does make more complete removal possible in some cases, but the data are not conclusive and studies have been published that both confirm (Steenstra and Beckers, 1993; Lucas-Morante et al., 1994) and deny (Kristof et al., 1999) its utility before surgery for macroadenomas. We have not been impressed with the degree of shrinkage, however, and have become less inclined to pretreat patients unless lateral extension of tumor is present. Somatostatin may also be used to suppress growth hormone production in patients with residual tumor after surgery, a setting in which we are much more likely to apply it. The chance of biochemical normalization does not, however, depend on the dose chosen (Ezzat et al., 1995). These results can be improved by continuous infusion, but this is expensive and rarely used in most medical centers (Tamura et al., 1998).

If medical therapy is chosen, several alternatives to octreotide are available. Long-acting analogues of octreotide (lanreotide, somatostatin-LAR) are similarly efficacious, but may be better tolerated as they are given much less frequently (two to four times per month) (Verhelst et al., 2000). Although bromocriptine has limited utility, cabergoline is more effective and induces a degree of biochemical normalization and tumor shrinkage comparable with that achieved by the somatostatin analogues (Gozzi et al., 1998; Abs et al., 1998). As cabergoline is given orally, it may very well become more popular than octreotide or lanreotide. Data have not yet been accumulated on its use in the preoperative setting.

The newest drug applied to acromegaly is pegvisomant, a growth hormone analogue that binds to and blocks the action of the growth hormone receptor. In a major prospective randomized trial involving in-patients given pegvisomant for 12 weeks, IGF-I normalized in 89% of patients receiving the highest dose tested (20 mg/day subcutaneously) (Trainer et al., 2000). Although side effects seem minimal and these data are promising, it is not known whether it will be effective in long-term use or whether loss of negative feedback due to lower circulating levels of IGF-I will
promote growth of the (otherwise untreated) adenoma responsible for the ongoing growth hormone excess. This drug will be further studied and is expected to join cabergoline and lanreotide as the medical therapies of choice in the future.

Surgery

Surgery is the primary mode of treatment for most patients with pituitary acromegaly. Success rates vary widely among series, and when examining their rates of induced remission, it is important to consider which biochemical criteria the authors used. The largest surgical series reported so far involved 254 patients treated at the University of California, San Francisco as described by Abosch et al. (1998). In that series, growth hormone levels less than 5 ng/ml were achieved in 76% of patients; 29% of patients required postoperative radiotherapy for residual tumor. In a previous paper, these authors compared their own statistics with those of 30 other surgical series involving a total of 1360 patients (Ross and Wilson, 1988). Overall growth hormone levels of less than 5 ng/ml were achieved in 60% of patients. Other series have based successful outcome on achieving growth hormone levels of less than 10 ng/ml (Laws et al., 1987), but the most vigorous modern definition of “cure” requires a level of ≤2.3 ng/ml (Melmed et al., 1998; Levitt et al., 1995). Only a few have followed up somatomedin-C levels, and none has applied provocative testing as a criterion for cure (Kao et al., 1992; Tindall et al., 1993; Abosch et al., 1998). In the series by Tindall et al. (1993), sustained postoperative levels less than 5 ng/ml were achieved in 88% of patients and in 82% when somatomedin-C levels were included in the analysis.

Other series have comparable results, particularly if a single, experienced surgeon has performed all included operations (Ahmed et al., 1999). About 90% of patients with microadenomas, and 40% to 50% of those with macroadenomas, achieve a postsurgical remission.

Sustained remission after surgery should be expected in 60% to 80% of patients overall. The size and location of the tumor affects the ease with which tumor excision is achieved. Fortunately, most of these tumors present as microadenomas and can be identified at surgery and selectively excised. Tumors with suprasellar extension can still be cured, but the chance for leaving residual tumor is greater in such cases. In patients with cavernous sinus tumor, residual tumor almost always remains, even when a transcranial approach is used together with skull-base techniques for cavernous sinus entry that have evolved over the past 10 years (Al-Mefty and Smith, 1990; Origitano et al., 1994). We currently enter the cavernous sinus rarely, with trepidation, and only if tumor mass within it must be debulked to decompress the optic nerve; the risk of cranial neuropathy is high, radiosurgery is available to control focal areas of tumor, and pituitary tumor within the cavernous sinus often goes for years without clinically significant alteration in carotid diameter or cranial nerve function.

Treatment failures should lead to the consideration of several possibilities. Some patients will, of course, have residual tumor. If a complete excision of a microadenoma has been done, however, the possibility of primary hypothalamic gangliocytoma secreting growth hormone–releasing hormone should be considered, as should the possibility that growth hormone or growth hormone–releasing hormone secretion is ectopic (usually from the pancreas) (Asa et al., 1987; Melmed et al., 1985). Although the great majority of patients with acromegaly have pituitary pathology, those who do not can be identified by measuring the plasma level of growth hormone–releasing hormone. If the level is greater than 300 ng/ml, an ectopic source of secretion is likely. In such patients, evidence of pituitary enlargement may appear on MRI scans, and the patient may undergo inappropriate transsphenoidal surgery. Patients in whom a somatotroph hyperplasia is found but no adenoma should have growth hormone–releasing hormone levels measured and, if elevated, the source should be identified by radiologic studies of the chest and abdomen.

Radiation Therapy

Radiation therapy has been used in the past for many patients as a primary treatment for acromegaly. The dose given is similar to that used for other forms of pituitary tumor, and the incidences of hypopituitarism, optic nerve damage, and cerebral radionecrosis are similar as well. Both conventional irradiation and proton-beam bombardment have been used and produce comparable results, although morbidity may be somewhat higher with the latter (Eastman et al., 1979; Kliman et al., 1987; Liidecke et al., 1989). As with other tumors, the main drawback is the gradual effect of such therapy. In most patients,
growth hormone levels decline slowly over the first year and may continue to do so for as long as 10 years after treatment. In 70% of irradiated patients, growth hormone levels less than 10 ng/ml are eventually reached in 5 years, although the response slips to 40% at 10 years (Clarke et al., 1993; Plataniotis et al., 1998; Kokubo et al., 2000). In normal individuals, growth hormone levels range from 0.25 to 0.7 ng/ml, and most authors now consider a level of 2.3 ng/ml or less as remission. A truly rigorous biochemical definition would include normalization of growth hormone and somatomedin-C levels as well as a normal oral glucose tolerance test and thyrotropin-releasing hormone stimulation test (Melmed, 1990; Melmed et al., 1998). These data are generally absent in reported series. Even these criteria are imperfect, as 40% of patients with persistently abnormal dynamic responses show no radiographic regrowth of tumor during the decade after surgery (Ross and Wilson, 1988).

Radiosurgery must also be considered in the array of options available for treating acromegaly. Data on its efficacy in this specific disease are buried within general series of pituitary tumors treated with this modality and are scanty. Two studies have been published that focus on its role in acromegaly. In one, 96% of 79 patients treated achieved normal growth hormone levels over 3 years after treatment (Zhang et al., 2000). Increasing tumor shrinkage was seen over the same time period. Follow up was insufficient in this study to allow conclusions about long-term control. In another study of 16 patients with recurrent acromegaly, growth hormone and IGF-I normalized after 1.4 years, on average; in a comparison group who received conventional fractionated irradiation, the mean time to normalization was 7.1 years (Landolt et al., 1998). Thus, radiosurgery may act more quickly, but the relative risks (over time) for radiosurgery versus fractionated radiation are not well understood. In addition, the interesting observation has been made that acromegalic patients taking octreotide during radiosurgery show a slower, less complete response to irradiation. Thus, octreotide may act as a radioprotectant (Landolt et al., 2000).

Preferred Treatment

At our institution, the general treatment schema for acromegaly includes the preoperative and postoperative measurement of growth hormone and somatomedin-C levels. We use provocative testing only in borderline cases. For a few patients (usually with tumors extending laterally or with large suprasellar components) a trial of somatostatin analogue therapy is given for up to 3 months, and the scans are repeated to check for tumor shrinkage. Half of those so treated show partial regression of the tumor and an unpredictable degree of correction in biochemical abnormalities. Only those in whom somatomedin-C and growth hormone levels normalize (or nearly so, as long as clinical symptoms substantially regress) are offered continuing medical therapy. The majority of patients undergo surgery at this point, and then radiotherapy is used with conventional limited-field techniques for any residual active tumor. Octreotide-LAR is used to control continuing hypersecretion while the patient waits for the irradiation to take effect.

Adrenocorticotropic-Secreting Adenomas

Approximately 4% to 10% of pituitary tumors secrete adrenocorticotropic, and another 5% produce the hormone but do not secrete it in significant amounts. Those in the former category develop Cushing’s disease, the name for a hypercortisolism (Cushing’s syndrome) of pituitary source. About 70% of adults with true hypercortisolism have such a pituitary tumor.

Much endocrinologic effort has been expended inventing and validating tests that identify hypercortisolism as present and identify its ultimate source as the pituitary gland, the adrenals, or an ectopic tumor secreting adrenocorticotropic, such as in the lung. A diagnosis of Cushing’s disease is sometimes difficult to make, because MRI scans fail to show a tumor in 20% to 30% of patients who have an ACTH-secreting adenoma in the pituitary. In years past, as many as 10% of patients with Cushing’s disease were treated with bilateral adrenalectomy as a measure of some desperation to eliminate the target organ on which ACTH acts and thereby eliminate the clinical effects of hypercortisolism. In this circumstance, the naturally occurring negative feedback exerted by cortisol on the normal gland (and on the pituitary tumor) is eliminated, and hypersecretion of ACTH increases dramatically. In the 15% to 25% of adrenalectomized patients in whom Nelson’s syndrome develops, a dramatic growth of pituitary adenoma occurs, although
it may be delayed for a number of years (Nelson et al., 1960; Moore et al., 1976; Nagesser et al., 2000). At least one case has now been reported in which this syndrome was successfully treated with cabergoline, suggesting that it may be as useful in a subset of patients with hypercortisolism as it is in those with prolactin-secreting tumors (Pivonello et al., 1999).

The biochemical assessment of patients with Cushing’s disease must take into account the diurnal variation in levels both of ACTH and cortisol normally released by the pituitary gland. Although this episodic secretion still occurs when a pituitary adenoma is present, neoplastic corticotrophs are relatively insensitive to negative feedback from any glucocorticoid, whether endogenous or exogenous. Within the spectrum of tumor autonomy, only 33% have any real measure of hypothalamic control exerted on them (Van Cauter and Refetoff, 1985).

The bewildering array of diagnostic tests used to establish the presence and source of hypercortisolism in a patient suspected of having Cushing’s syndrome is beyond the scope of this chapter. Several excellent reviews cover the diagnostic approach in detail and explain how to interpret test results (Kaye and Crapo, 1990; McCutcheon and Oldfield, 1992). In general, one recognizes cortisol excess by determining blood levels in relation to time of day or by collecting urine over 24 hours to eliminate diurnal variations. Even salivary sampling may be done when multiple measurements of cortisol are required (Mosnier-Pudar et al., 1995). If confusion persists (as it often does) even after several assays of blood and urine have been performed, provocative tests are used to clarify the presence of a true hypercortisolism; they also give clues to the etiology of the excess. The most popular of these is the dexamethasone suppression test, which has several variations and is accurate about 90% of the time (Liddle, 1960; Nieman et al., 1986). Stimulation tests using corticotrophin-releasing factor are frequently used and show a normal or excessive rise in ACTH in patients with Cushing’s disease, but little response in patients with tumor of the adrenal gland or other sites. This test, like the dexamethasone suppression test, is misleading approximately 10% of the time (Nieman et al., 1986).

In the past 10 years, a great deal of attention has been given to bilateral sampling of the inferior petrosal sinus. In theory, this technique can detect central/peripheral gradients that confirm the presence of pituitary tumor and also can be used to lateralize the tumor within the gland to the right or left half. In practice, the test is useful for confirming the presence of a tumor within the pituitary gland, but intermixing between the two cavernous sinuses leads to numerous cases of inappropriate lateralization (Mamelak et al., 1996). It is now apparent that the rate of false lateralization approaches 40%. The use of corticotrophin-releasing factor stimulation with this test increases its diagnostic accuracy to nearly 100% when a central-to-peripheral ACTH gradient >3.0 is used as the criterion for diagnosis (Oldfield et al., 1991; Kalsas et al., 1999). Direct sampling of hormone levels in cavernous sinus blood performed during surgery may also be used to localize occult microadenomas, but has practical limitations given the time required to perform the analyses; false negatives may still occur, especially in the absence of corticotrophin-releasing hormone stimulation (Doppman et al., 1995; Graham et al., 1999).

Surgery

Surgical excision is the most popular method of eradicating these tumors. Because many are microadenomas, transsphenoidal techniques have proven useful and can achieve a cure rate of 88%, as reported by Mampalam et al. (1988) from a series of 221 such patients. About 5% of these patients showed eventual recurrence of hypersecretion, with a mean time to recurrence of almost 4 years. Those in whom an intrasellar exploration showed no tumor were cured using biochemical criteria a little less than 50% of the time. Some of these patients had hemihypophysectomy based on petrosal sinus sampling, which as mentioned above is an imperfect method of determining tumor location within the gland. Others had complete hypophysectomy, which remains a valid treatment for patients with this ultimately life-threatening disease. The morbidity among all patients in this series was 9% with a mortality of 1%. Such statistics are fairly representative of those reported from other surgical series of ACTH-secreting pituitary tumors (Burke et al., 1990; Chandler et al., 1987; Bochicchio et al., 1995). Only two-thirds of patients with macroadenomas achieve remission after surgery, and they also tend to relapse sooner than those with smaller tumors (Blevins et al., 1998a).

Some patients in whom Cushing’s disease is biochemically identified but in whom surgery fails to effect remission have been misdiagnosed and actually harbor other lesions causing cortisol excess. It is therefore important to review rigorously the evidence from
which the diagnosis was made before performing surgery to re-explore the sella and perhaps to perform a complete hypophysectomy. Reoperation certainly has its place in the treatment of Cushing’s disease and can raise the rate of remission by 20% or more (Ram et al., 1994). If surgery is redone in this setting and an adenoma is found that had previously been overlooked, it is still better to excise it selectively, together with a margin of adjacent normal pituitary, than to extirpate the entire gland. This approach results in remission of hypercortisolism in about half of these patients with much less risk of hypopituitarism.

**Radiation and Other Therapy**

Radiotherapy is not often used as the primary treatment as this tumor, like others, is slow to respond to it. This group of patients, however, needs a fairly quick and definitive elimination of the hormonal excess to correct physiologic derangement in multiple organ systems. Adrenal ablation is now reserved for patients for whom other attempts to ablate the source of adrenocorticotropic, either surgically or medically, have failed. When radiotherapy is used after incomplete surgical resection, 80% of patients achieve remission, most within 2 years (Estrada et al., 1997).

**Preferred Treatment**

Currently, we approach patients suspected of having Cushing’s disease with a rigorous and lengthy endocrine evaluation before any treatment is considered. The work-up includes repeated sampling of blood and collection of 24 hour urine volumes to prove hypersecretion. Even if the first one or two samples fail to show any abnormality, patients with appropriate symptoms should be repeatedly studied because some will harbor a tumor that secretes cortisol episodically, which is easy to miss with a less than strenuous diagnostic work-up (Loh, 1999). Most patients have dexamethasone suppression testing and then petrosal sinus sampling before and after stimulation by corticotrophin-releasing factor. Only then is surgery considered.

In the great majority of patients, a transsphenoidal approach is used and the sella is explored vigorously. For patients with Cushing’s disease, the frequency of cerebrospinal fluid leak and of intraoperative bleeding from the cavernous sinus should be higher than for other patients because a more aggressive exploration is often necessary to find and completely remove small tumors (or areas of corticotroph hyperplasia) that may lurk unseen in the far lateral areas of a normal-appearing gland. The concept that such tumors occur in the “central median wedge” of the gland and that a search for occult tumor should be directed first to the area of the middle third of the gland is somewhat erroneous. These tumors can occur in any part of the anterior lobe and have even been found in the posterior lobe or outside the gland (Pluta et al., 1999), and the stakes for the patient are high enough to make a higher incidence of (treatable) cerebrospinal fluid leakage acceptable. Patients who remain hypercortisolemic even after such a vigorous exploration and perhaps after excision of histologically confirmed tumor should be reviewed assiduously. If any doubt exists about the diagnosis, appropriate tests should be redone. If, despite these precautions, the pituitary is still thought to be the source of ACTH excess, reoperation may be needed with the intent to perform a hemihypophysectomy or more complete removal of the anterior lobe (Friedman et al., 1989). Only after two surgical procedures should radiotherapy, adrenalectomy, or medical suppression of the adrenals with ketoconazole or mitotane be entertained.

**Thyroid-Stimulating Hormone Secreting Adenomas**

Tumors that secrete TSH are rare and represent less than 1% of large series of pituitary tumors. Their rarity is probably exaggerated somewhat by the tendency of physicians to misdiagnose as primary hyperthyroidism, which is much more common, the hyperthyroid syndrome they typically produce. Patients with TSH-secreting adenomas are usually falsely diagnosed with primary thyroid disease for years and are often treated with thyroid ablation without success. This delay frequently allows TSH-secreting tumors to enlarge and makes surgical removal more difficult. In theory, the loss of negative homeostatic feedback caused by thyroid ablation in patients with such tumors might be expected to make the tumor more aggressive, as happens in the occasional case of Nelson’s syndrome that develops after adrenal ablation in patients with Cushing’s disease. Only small series of these patients have been reported, supporting the idea that these tumors are aggressive and that surgery for TSH-secreting adenomas carries a higher risk of perioperative death and/or neurologic morbidity than occurs with other tumor types (McCUTCHEON et al., 1990). The largest series currently on record are composed of 24 patients treated in Europe (Losa et al., 1999) and...
25 patients followed up at the National Institutes of Health (Brucker-Davis et al., 1999). In these series, long-term remission was achieved by a combination of surgical and other therapy in 60% of patients, and only those with undetectable levels of TSH in the early postoperative period demonstrated remission after surgery alone.

If found when small, these tumors are as amenable to surgical cure as are other pituitary adenomas. When the tumor is large, incomplete resection is the rule, and radiotherapy is usually applied as it is with other forms of invasive pituitary adenoma. Although bromocriptine is of little value in controlling this kind of tumor, a somatostatin analogue (e.g., octreotide) can control excess secretion of TSH. In some patients, gross tumor shrinkage occurs after medical therapy begins, and visual field defects have improved in others who are treated medically (Comi et al., 1987; Warnet et al., 1989). Lanreotide, a somatostatin analogue with a longer duration of action than octreotide, also has been effective in normalizing TSH and α-subunit, but does not generally cause tumor shrinkage (Kuhn et al., 2000). The same drawbacks are associated with the use of somatostatin against TSH-secreting adenomas, but it is occasionally helpful for patients with unresectable tumors that do not respond well to radiotherapy.

Patients with these tumors who have been treated inappropriately with chemical or radiotherapeutic ablation of the thyroid gland may be hypothyroid rather than hyperthyroid, so obtaining a careful endocrine history is mandatory if TSH-secreting adenoma is suspected. Also, primary hypothyroidism may itself cause pituitary thyrotroph hyperplasia and adenohypophysereal enlargement that mimics an adenoma. Such patients respond to exogenous thyroid and should not undergo transsphenoidal surgery, as they have no pituitary disease and pituitary enlargement disappears as a euthyroid state is restored (Young et al., 1999).

MALIGNANCY IN PITUITARY ADENOMAS

Pituitary tumors exhibit malignant behavior through a tendency toward invasion, proliferation, or metastasis. Invasive behavior, in particular dural invasion, which allows extension of tumor into the suprasellar areas, sphenoid sinus, or cavernous sinuses, is more common than generally believed. The true incidence of dural invasion in pituitary tumors has not been studied to a great extent, but Selman et al. (1986) reported a rate of 40% in patients from the Mayo Clinic. This figure describes patients with gross evidence of invasion; when microscopic verification is added, the incidence climbs to 85%. Because pituitary tumors are traditionally considered to be benign and well-circumscribed lesions with a plane dividing them from normal gland, and because most are slow growing, the high incidence of a phenomenon that indicates malignancy is surprising. In this sense, pituitary tumors behave most like meningiomas, which are able to invade dura and adjacent bone much more easily than brain.

This phenomenon is not confined to the tumor–dura interface, as microinvasion of normal gland by tumor also occurs frequently along the tumor’s pseudocapsule (Shaft and Wrightson, 1975). In pituitary adenomas, invasive features leading to incomplete surgical resection are commonly associated with TSH-secreting tumors, large prolactin-secreting tumors associated with very high serum prolactin levels, and acromegaly. In patients with growth hormone excess, invasive features are most often associated with an acidophilic stem cell adenoma, a relatively undifferentiated form of somatotrophic tumor comprised from stem cells that can give rise either to prolactin-secreting or growth hormone–secreting cells (Horvath et al., 1981).

The most common form of invasion affects the floor of the sella turcica. As the tumor enlarges, the bony confines of the sella are eroded and appear thinned on lateral skull radiographs or MRI scans. Disappearance of the clinoid processes and a “double floor” sign are considered pathognomonic for an intrasellar tumor. As the tumor enlarges and extends into the suprasellar cistern, the diaphragma bulges upward and stretches, and in some patients allows a dumbbell-like extension through the fenestration provided for the pituitary stalk. Most suprasellar extensions occur in the midline and in severe cases fill the third ventricle and produce hydrocephalus. The adjacent optic chiasm and nerves are thus at high risk for compression in tumors that expand in this direction. Less frequently, lateral extension into one or both cavernous sinuses occurs (Fig. 8–2). In these

Figure 8–2. MRI of pituitary adenomas. (A) T2-weighted coronal MRI, post-gadolinium contrast, with arrow pointing to an occult microadenoma in a patient with Cushing’s disease shows an apparent signal abnormality in an otherwise normal gland (optic chiasm = C). (B) Another coronal image of the microadenoma on the right side of the gland’s superior surface with associated stalk (S) deviation (carotid artery in cavernous sinus = C).
patients, the dura is physically breached by tumor, which gradually fills the venous sinus spaces and encases the carotid artery and cranial nerves. In some patients, tumor also breaches the lateral wall of the cavernous sinus and encroaches directly on the medial temporal lobe. Usually, it simply expands the cavernous sinus, and cranial nerve dysfunction occurs only in later stages of the disease. Narrowing of the carotid artery is seen as tumor progression occurs and can be devastating to patients with poor collateral flow through an anatomically incomplete circle of Willis. Such invasion, whether superiorly, inferiorly, or laterally directed, usually occurs in the absence of the cytologic hallmarks of malignancy. It may, however, correlate with alterations in p53 status, epidermal growth factor receptor activity, or protein kinase C activity; and proliferation indices (such as the MIB-1 labeling index) correlate well with the degree of invasiveness and are highest in frankly metastatic pituitary tumors (Blevins et al., 1998b).

A much smaller proportion of tumors represents the very rare phenomenon of metastasis, and these are considered true pituitary carcinomas. Such metastases have been reported in both cerebrospinal and extraneural sites. Approximately 120 cases have been described, which represent an infinitesimal fraction of all pituitary tumors. In about 50% of patients, tumors disseminate within the neural axis and on histologic examination generally exhibit the cytologic features of malignancy, including pleomorphism, nuclear atypia, and mitotic figures. Some patients demonstrate true leptomeningeal spread of tumor and have positive cytology on examination of cerebrospinal fluid (Ogilvy and Jakubowski, 1973). Most such patients have clinically nonfunctional tumors, although acromegaly, hypoprolactinemia, and Cushing’s disease have all been reported in this setting (Ogilvy and Jakubowski, 1973; Pettersson et al., 1992; Pernicone et al., 1997).

Figure 8–2, (continued) (C) T1-weighted coronal MRI, post-gadolinium contrast, showing macroadenoma (T) extending into the sphenoid sinus and obscuring normal pituitary gland (optic nerves = O, stalk = S, cavernous sinus = C). (D) T1-weighted sagittal MRI, post-gadolinium contrast, showing an invasive macroadenoma (T) filling the sphenoid sinus and destroying the skull base and projecting into the nasopharynx (optic chiasm = C).

Overall, pituitary carcinomas are nonfunctional about half the time and secrete ACTH in 22% of patients, growth hormone in 13%, and prolactin in 11% (Mountcastle et al., 1989). Nonfunctional and ACTH-secreting adenomas are thus overrepresented. Although TSH-secreting tumors are known for their clinical tenacity, only one has been reported with frank metastasis (McCutcheon et al., 1990). Because some patients were reported before the advent of prolactin assays or routine immunocytochemical staining, it is possible that nonfunctional cases have been overestimated and that some were actually prolactinomas or gonadotropin-secreting tumors (McCutcheon et al., 2000).

Many cases of pituitary carcinoma begin as histologically benign, slow-growing adenomas, then progress over a number of years to a more aggressive state. A few are diagnosed de novo as carcinomas. In Nelson’s syndrome and in patients who have TSH-secreting tumors and have undergone thyroid ablation, pituitary carcinomas actually occur quite infrequently. This fact argues against the importance of release of feedback inhibition as a factor promoting malignancy in pituitary tumors. Although radiotherapy causes sarcomatious change in some patients with benign adenomas (Waltz and Brownell, 1966), more than 50% of patients with carcinomas have not had sellar exposure to irradiation, and its role as a transforming agent remains unclear.

Even with aggressive treatment, survival is short in these patients. Kaiser et al. (1983) reviewed 15 patients and found a mean survival time of 1.4 years after the discovery of metastasis; the longest survival time was 4.8 years. One reason these statistics are so dismal is that a true oncologic approach to these neoplasms has not been applied in most patients. By definition, such an approach would include radical resection of the primary site and of any surgically accessible metastatic sites followed by a combination of radiotherapy and cytotoxic chemotherapy. Because...
such patients are rare, chemotherapy protocols have not been developed for them. Isolated, temporary success has been reported in one patient who received 5-fluorouracil, adriamycin, and cyclophosphamide over two courses before tumor relapse occurred (Mixson et al., 1993). A patient with a prolactin-secreting pituitary carcinoma has also been reported in whom improvement of vision occurred with radiographic arrest of tumor growth during four cycles of combined lomustine, procarbazine, and etoposide (Petterson et al., 1992).

A combination of lomustine and 5-fluorouracil has been given to seven patients with aggressive pituitary tumors, four of whom had frank carcinoma (Kaltsas et al., 1998). Some temporary success was obtained in stabilizing symptoms or shrinking tumors, but all died of their disease from 3 to 65 months after starting treatment. Based on chromogranin positivity and a histologic similarity with paraganglioma, we have used a sarcoma regimen for such lesions with limited success (McCutcheon et al., 2000).

The development of skull-base approaches now makes resection of cavernous sinus disease feasible, and this approach might be used for young patients who can tolerate a radical cavernous sinus exenteration. If cavernous sinus exploration is done without carotid and cranial nerve excision, residual tumor is bound to remain, and regrowth will ineluctably occur. Given the dismal natural history of the disease, whenever possible patients with pituitary carcinoma should undergo as aggressive an operation as neurosurgical technical constraints permit.

**PITUITARY APOPLEXY**

Pituitary tumors can also do significant harm to patients when sudden expansion occurs because of intratumoral hemorrhage. This phenomenon, known as pituitary apoplexy, probably represents infarction and subsequent bleeding within a tumor whose angiogenic capacity is insufficient to keep pace with its proliferative capacity. Hemorrhage into the infarcted areas therefore occurs within tumor, not in the adjacent gland, and the gland may recover lost function due to this sudden compression if the tumor and clot are surgically excised without delay (Arafah et al., 1990). Patients who are not operatively treated usually fail to recover from hypopituitarism induced by acute compression, and their pituitary function may actually worsen with time. Some patients present with hemorrhage into a previously undiagnosed, clinically nonfunctional adenoma. In severe cases, bleeding breaks through into the subarachnoid space and produces a typical syndrome of subarachnoid hemorrhage. In that circumstance, the risk of vasospasm depends on the amount of blood in the basal cisterns, just as in patients with aneurysmal rupture that has caused a subarachnoid hemorrhage. These patients can be left with subtle neurophysiologic impairment from cerebral microinfarcts caused by vasospasm in small perforating vessels and should be treated prospectively with hyperdynamic therapy during the recovery phase after transsphenoidal decompression of the sellar contents.

For patients who have macroadenomas, pituitary apoplexy usually presents with the sudden onset of headache, nausea, visual loss, or diplopia. Some patients do not lose pituitary function, but in most patients two or more hormonal axes are impaired. One series reported 9 of 13 patients with hypopituitarism before surgery (Arafah et al., 1990). Surgery may correct endocrine and visual abnormalities in a significant percentage of patients. Long-term hormone replacement with corticosteroids (58%), thyroxine (45%), and testosterone (43% of males) was necessary in one recent series (Randeva et al., 1999). In most of these patients, decreasing vision demands relatively urgent surgical decompression (certainly, within a week of the ictus) in which the goal is to decompress parasellar structures, remove tumor, and restore pituitary function.

**CONCLUSION**

Pituitary tumors act malignantly if they produce a hormonal excess that promotes premature death in afflicted patients; if they invade or compress parasellar structures, particularly the visual pathways; or if they bleed or metastasize. Many are now detected, however, by MRI and by sensitive biochemical tests before they achieve symptomatic size. Although a general reclassification of these tumors according to hormonal production has been ongoing for the past 15 years, a true understanding of their pathogenesis has not been achieved. Medical, surgical, and radio-biologic approaches to treating these lesions have been greatly refined, but a significant number of them cannot be cured by currently available means. Al-
though more aggressive surgery is now possible, it sometimes achieves its success at the expense of neurologic or pituitary function, and the real hope for future therapeutic advances lies in a better understanding of the molecular mechanisms that subserve the proliferative and invasive nature of these diverse neoplasms.

REFERENCES


Pituitary Tumors


