Conferences and Reviews

Pituitary Tumors
Current Concepts in Diagnosis and Management

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Diagnostic advances have resulted in earlier and more frequent recognition of pituitary tumors. Pituitary tumors cause problems owing to the hormones they secrete or the effects of an expanding sellar mass—hypopituitarism, visual field abnormalities, and neurologic deficits. Prolactin-secreting tumors (prolactinomas), which cause amenorrhea, galactorrhea, and hypogonadism, constitute the most common type of primary pituitary tumors, followed by growth hormone-secreting tumors, which cause acromegaly, and corticotropin-secreting tumors, which cause Cushing's syndrome. Hypersecretion of thyroid-stimulating hormone, the gonadotropins, or α-subunits is unusual. Nonfunctional tumors currently represent only 10% of all clinically diagnosed pituitary adenomas, and some of these are α-subunit–secreting adenomas. Insights into the pathogenesis and biologic behavior of these usually benign tumors have been gained from genetic studies. We review some of the recent advances and salient features of the diagnosis and management of pituitary tumors, including biochemical and radiologic diagnosis, transsphenoidal surgery, radiation therapy, and medical therapy. Each type of lesion requires a comprehensive but individualized treatment approach, and regardless of the mode of therapy, careful follow-up is essential.

(Aron DC, Tyrrell JB, Wilson CB: Pituitary tumors—Current concepts in diagnosis and management. West J Med 1995; 162:340-352)

The prevalence of pituitary tumors, estimated at 10% to 20% in autopsy series, greatly exceeds the frequency of clinically recognized tumors.[1,2] Advances in biochemical and neuroradiologic diagnosis, however, and improvements in surgical technology have revolutionized the diagnosis and treatment of patients with pituitary tumors.* For example, between 1970 and 1977 a tenfold increase in the incidence of prolactin-secreting tumors coincided with the availability of prolactin radioimmunoassays.[3]

Pituitary tumors are no longer designated as chromophobic, eosinophilic, or basophilic on the basis of histologic appearance. They are now classified according to the hormone(s) they secrete, using immunohistochemical and electron-microscopy techniques (Table 1).

Microadenomas are defined as intrasellar adenomas up to 1 cm in diameter without sellar enlargement or extrasellar extension; macroadenomas are larger than 1 cm in diameter and cause focal or generalized sellar enlargement. The diagnosis of a microadenoma is usually made when there are symptoms or signs of hormonal excess; hypopituitarism is rare, except when caused indirectly, as in decreased growth hormone secretion due to glucocorticoid excess in Cushing's disease. Microadenomas may be incidental findings discovered when a computed tomographic (CT) scan or magnetic resonance (MR) image is obtained for another reason.[1,4] Macroadenomas may also cause manifestations of hormonal excess, but hypopituitarism is common.

Pituitary hormone deficiency tends to begin with growth hormone, followed by the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), and later by thyroid-stimulating hormone (thyrotropin) and corticotropin (adrenocorticotropic hormone). Relatively few patients with macroadenomas have panhypopituitarism at diagnosis, and these patients are not necessarily the ones with the largest tumors. This observation may be accounted for by the fact that hypopituitarism may be produced by interference with the flow of hypothalamic-releasing factors to the pituitary or by destruction of the normal pituitary cells.

The problems caused by pituitary tumors are related to either the hormones they secrete or the effects of an expanding sellar mass. The vast majority are benign; pituitary carcinomas are so rare that they appear only in isolated case reports.[5,6] But pituitary tumors may be invasive without being malignant.[7-9]

*See also the editorial by M. H. Samuels, MD, "Advances in Diagnosing and Managing Pituitary Adenomas," on pages 371-373 of this issue.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
FSH = follicle-stimulating hormone
GH-RH = growth hormone-releasing hormone
Gn-RH = gonadotropin-releasing hormone
IGF = insulin-like growth factor
LH = luteinizing hormone
MR = magnetic resonance
T_4 = thyroxine
TRH = thyrotropin-releasing hormone

Therapy, whether it is surgical resection, irradiation, or drugs, aims to correct the hypersecretion of anterior pituitary hormones, preserve the normal pituitary tissue that secretes other anterior pituitary hormones, and remove or shrink the adenoma itself. In referral centers with the greatest experience, especially surgical experience, these objectives are currently achievable in most patients with microadenomas; however, multiple therapies are frequently required for larger tumors and may be less successful.

Prolactinomas

Prolactin-secreting pituitary adenomas, or prolactinomas, formerly included in the category of chromophobic adenomas, account for about 60% of primary pituitary tumors. Although estrogen has been implicated in the increased frequency of prolactinomas, studies of women taking oral contraceptives have failed to establish such an association.[10,11] Most chromophobic adenomas previously classified as "nonfunctional" actually contain prolactin.[12-14] Prolactinomas vary in size from microadenomas, which most commonly arise from the lateral wings of the anterior pituitary gland, to large invasive tumors with extrasellar extension.[13-17]

Clinical Manifestations

Prolactinomas have different manifestations in men and women. Women commonly present with galactorrhea, amenorrhea, oligomenorrhea with anovulation, or infertility. The amenorrhea is usually secondary and may follow pregnancy or the use of oral contraceptives. The prevalence of hyperprolactinemia is as high as 20% in women with unexplained primary or secondary amenorrhea, even when galactorrhea or other symptoms of pituitary dysfunction are not present. Some of these patients are found to have prolactinomas. In men, excess prolactin secretion produces hypogonadism, but only occasionally causes galactorrhea. Many men experience decreased libido or impotence because serum gonadotropin and testosterone levels are low. Infertility due to a reduced sperm count is a less common initial symptom. Impotence that occurs in patients with hyperprolactinemia may not be reversed by testosterone replacement if hyperprolactinemia is not corrected. Prolactin-secreting microadenomas generally grow slowly, and many show no evidence of progression during years of follow-up.[16,18-20] Among men, prolactinomas frequently go undetected during the initial phase of hyperprolactinemia; therefore, large tumors are more common in men than in women.

A macroadenoma of any type may produce hypogonadism by mechanical damage to the gonadotropin-secreting cells or by interference with the delivery of gonadotropin-releasing hormone (Gn-RH) by the hypophysial-portal system. Hyperprolactinemia itself interferes with the hypothalamic-pituitary-gonadal axis. Prolactin inhibits both the normal pulsatile secretion of LH and FSH and the midcycle LH surge, resulting in anovulation; basal gonadotropin levels are within the "normal" range despite reduced sex steroid levels. The positive feedback effect of estrogen on gonadotropin secretion is also inhibited. Prolactin also affects the ovaries directly. Biochemical estrogen deficiency may be accompanied by symptoms such as decreased vaginal lubrication and osteopenia, as assessed by bone densitometry. Estrogen deficiency also increases the synthesis of adrenal androgens (such as dehydroepiandrosterone sulfate) and may cause hirsutism.

Differential Diagnosis

The extensive differential diagnosis of hyperprolactinemia is shown in Table 2. Pregnancy is one cause. Prolactin secretion increases in pregnancy and may result in serum levels of 200 μg per liter (200 ng per ml) during the third trimester. Hyperprolactinemia persisting for 6 to 12 months or longer after delivery warrants an evaluation

TABLE 1.—*Major Anterior Pituitary Hormones and Their Hypothalamic Regulation*

Pituitary Hormone	*Hypothalamic Factor*	*Effect*
Growth hormone	Growth hormone-releasing factor	+
	Somatostatin	−
Prolactin	Dopamine	−
	Thyrotropin-releasing hormone	+
	Prolactin-inhibitory factor (postulated)	−
	Prolactin-stimulatory factor (postulated)	+
Corticotropin (ACTH)	Corticotropin-releasing factor	+
	Vasoactive intestinal peptide	+
Thyrotropin (TSH)	Thyrotropin-releasing hormone	+
	Somatostatin	−
LH, FSH	Gonadotropin-releasing hormone	+

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone, TSH = thyroid-stimulating hormone, + = stimulatory, − = inhibitory

TABLE 2.—*Differential Diagnosis of Hyperprolactinemia*

Physiologic
Pregnancy, lactation
Nonphysiologic
Prolactin-secreting tumors
Prolactinomas—unihormonal
Tumors secreting multiple hormones
Drugs
Dopamine synthesis inhibitors, depletors, and receptor blockers—α-methyldopa, reserpine, verapamil, phenothiazines, thiothixenes, and butyrophenones
Others—estrogen, narcotics
Central nervous system disorders that lead to pituitary disinhibition
Hypothalamic lesions—tumor, sarcoid, histiocytosis X, and other infiltrative diseases
Pituitary stalk lesions—trauma (stalk section) and compression by tumor or other mass lesions
Miscellaneous
Systemic illnesses—cirrhosis, renal failure
Primary hypothyroidism
Chest wall and spinal cord lesions—postsurgical, herpes zoster, burns
Polycystic ovarian disease
Macroprolactinemia
Idiopathic

for prolactinoma. Another cause of hyperprolactinemia is primary hypothyroidism, which may also produce substantial anterior pituitary enlargement, a combination that mimics a prolactin-secreting pituitary tumor.[21] The prolactin response to thyrotropin-releasing hormone (TRH) is usually exaggerated in these patients. A third cause is the ingestion of dopamine depletors or dopamine-receptor blockers such as phenothiazines. Drug ingestion usually results in prolactin levels of less than 100 μg per liter (<100 ng per ml). Other causes include hypothalamic disorders, liver disease, chronic renal failure, polycystic ovarian disease, previous cranial irradiation, breast and chest wall disorders, and spinal cord lesions. Mild to moderate hyperprolactinemia, galactorrhea, and amenorrhea may occur after estrogen therapy or oral contraceptive use, but their persistence is suggestive of prolactinoma. Finally, macroprolactinemia, a disorder characterized by circulating high-molecular-weight forms of prolactin that may be biologically inactive,[22-24] must also be ruled out. When all of these conditions have been excluded, the most likely cause of persisting hyperprolactinemia is prolactinoma, especially if there is associated hypogonadism.[13,14]

The diagnosis of prolactinoma is primarily based on basal prolactin levels and neuroradiologic studies. Although others may disagree, we think that the assessment of the prolactin response to stimulation with TRH or other currently available dynamic tests is not sufficiently sensitive or specific for routine clinical use in distinguishing prolactin-secreting tumors from other causes of hyperprolactinemia.[25-27] Elevated prolactin levels are correlated with tumor size. With few exceptions, basal prolactin levels of greater than 200 μg per liter (>200 ng per ml) are virtually diagnostic of prolactinoma; levels between 100 and 200 μg per liter are usually caused by prolactinoma, usually identifiable on high-resolution MR images as a microadenoma. Diagnosis is much more difficult if the prolactin level is between 20 and 100 μg per liter because this mild to moderate hyperprolactinemia is found in patients with prolactin-secreting microadenomas and many other conditions. Magnetic resonance imaging should

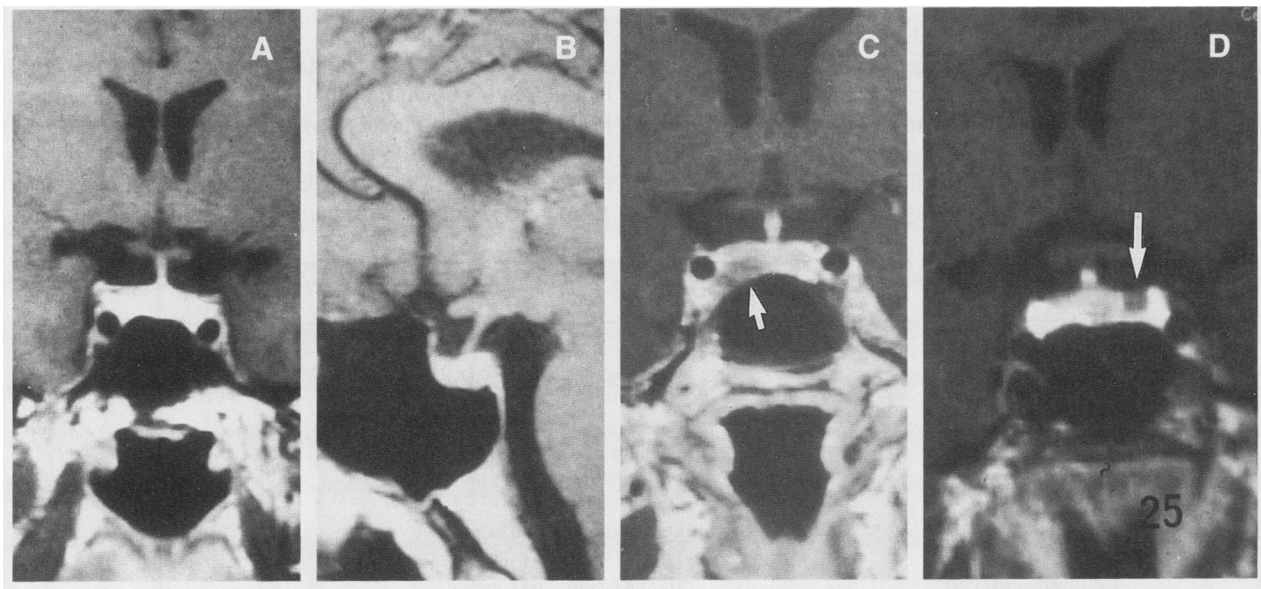

Figure 1.—Gadolinium-enhanced magnetic resonance images are shown of the pituitary gland. **A** and **B**, Coronal and sagittal images show the normal, uniformly enhancing pituitary stalk and pituitary gland. **C**, A pituitary microadenoma appears as a low-intensity lesion in the inferior aspect of the right lobe of the gland (**arrow**). **D**, The pituitary microadenoma appears as a low-intensity lesion between the left lobe of the pituitary and the left cavernous sinus (**arrow**). (Photographs courtesy of David Norman, MD.)

therefore be done in these patients; high-resolution images often show a definite pituitary microadenoma (Figure 1). Computed tomographic scanning is indicated only when MR imaging is not available or its use is contraindicated.[14,28-30] Computed tomographic scans or MR images showing only minor or equivocal abnormalities must be interpreted cautiously because of the high incidence of false-positive results in the normal population.[1] Further evaluation, including serial assessment of prolactin levels, is required to diagnose a prolactinoma. It is important to recognize that hyperprolactinemia associated with pituitary disinhibition related to non–prolactin-secreting sellar and parasellar lesions may mimic a prolactinoma.[31]

Treatment of Microadenomas

The following recommendations apply for patients whose clinical presentation, laboratory data, and MR images have ruled out any reasonable doubt that a prolactinoma exists.

Treatment is recommended to prevent early osteoporosis due to persistent hypogonadism and to restore fertility in all patients with microadenomas.[32-35] Treatment is also recommended for patients in whom neuroradiologic studies show no abnormalities, but who have persistent hyperprolactinemia and hypogonadism, especially if the hypogonadism is of long duration. Prolactin hypersecretion, galactorrhea, and abnormal gonadal function can be satisfactorily controlled in most patients with prolactin-secreting microadenomas. Whether the primary therapy should be medical or surgical is more controversial.[13,36-38]

Surgery. Transsphenoidal microsurgical resection returns prolactin levels to normal, restores normal menses, and stops galactorrhea in 85% to 90% of patients with microadenomas. Success rates are highest in patients with basal prolactin levels of less than 200 μg per liter (<200 ng per ml) and a duration of amenorrhea of less than five years. In these patients, the risk of serious complications is less than 1%, and surgically induced hypopituitarism is rare. Recurrence rates vary considerably in reported series.[38,39] In our experience, more than 72% of patients have had long-term remissions, and 25% have had recurrences five to ten years after surgical therapy.[40]

Pharmacologic agents. Many clinicians would recommend the use of the potent dopamine agonist bromocriptine hydrochloride instead of surgical treatment. It has been used extensively and has effects at both the hypothalamic and pituitary levels.[41,42] The dose is 2.5 to 10 mg per day orally in divided doses. Side effects (dizziness, postural hypotension, and nausea), common early in the course of therapy, usually can be avoided by starting with a low dose and may resolve with continued treatment. Bromocriptine directly inhibits prolactin secretion by the tumor, thereby successfully reducing levels to normal in more than 90% of cases. This allows normal gonadal function to recover and ovulation and fertility to be restored. Hyperprolactinemia usually returns when treatment is discontinued, even after several years, although remissions may occur. Questions remain about possible long-term risks and the indicated duration of therapy for patients with microadenomas.

Bromocriptine restores fertility in most female patients; therefore, mechanical contraception should be advised if pregnancy is not desired. Ovulation should not be induced in patients with hyperprolactinemia without careful assessment of pituitary anatomy and sella turcica size, because pregnancy may cause further expansion of these tumors, although this has been seen in less than 5% of patients.[43] Current data do not indicate an increased risk of multiple pregnancy, abortion, or fetal malformations in pregnancies that occur during bromocriptine therapy; however, it should be discontinued at the first missed menstrual period and a pregnancy test obtained.

Treatment of Macroadenomas

All patients with prolactin-secreting macroadenomas should be treated because of the risks of further tumor expansion, hypopituitarism, and visual impairment. The treatment of women who wish to become pregnant is controversial. Treatment with surgical or radiation therapy before the restoration of ovulation with bromocriptine or gonadotropin therapy will decrease the risk of tumor expansion and visual deficits in the latter part of pregnancy, complications seen in about 15% to 25% in patients with macroadenomas. Therapy with bromocriptine alone may be sufficient, however.[43]

Surgery versus pharmacologic agents. Transsphenoidal microsurgical therapy for macroadenomas is considerably less successful in restoring normal prolactin secretion than it is for microadenomas. If a tumor is 1 to 2 cm in diameter with no extrasellar extension, and basal prolactin levels are under 200 μg per liter, transsphenoidal surgery results in complete tumor resection and restoration of normal basal prolactin secretion in about 80% of cases. In patients with higher basal prolactin levels and larger tumors, the success rate is about 25% to 65%. Although the likelihood of surgical cure is much lower in this group, many centers recommend surgical therapy to decompress vital structures such as the optic chiasm and to reduce tumor bulk and prolactin hypersecretion. Initial treatment with bromocriptine may reduce the tumor size and increase the likelihood of a surgical cure. If surgical therapy is not curative, bromocriptine may be used to control residual hyperprolactinemia. Reported results in general come from centers with the most experience, and it cannot be assumed that these results are easily duplicated.

Many clinicians recommend treatment with bromocriptine instead of transsphenoidal resection[36,37] because it controls hyperprolactinemia in many patients with prolactin-secreting macroadenomas, even when basal prolactin levels are markedly elevated,[36,44] and reduces tumor size within days or weeks in about 70% to 80% of patients (Figure 2). It also has been used to restore vision in patients with major suprasellar extension and chiasmal compression. Questions remain about the appropriate duration of therapy for patients with macroadenomas.[45,46]

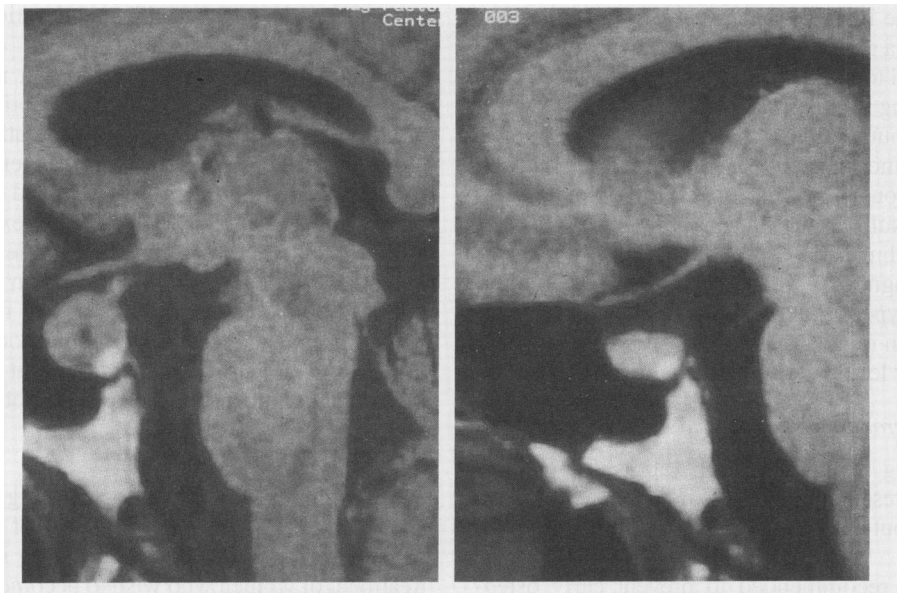

Figure 2.—Sagittal magnetic resonance images were taken of a patient with a prolactinoma treated with bromocriptine hydrochloride. **Left,** The pretreatment image shows a 15-mm adenoma with expansion of the sella turcica and suprasellar extension. **Right,** The post-treatment image after three months of bromocriptine therapy shows pronounced reduction in the size of the adenoma. (Photographs courtesy of David Norman, MD.)

Pergolide mesylate, a newer and more potent agent than bromocriptine, is a long-acting ergot derivative with dopaminergic properties; its use reduces hypersecretion and shrinks most prolactin-secreting macroadenomas.[47] Although this drug has been released, it is not approved for the treatment of hyperprolactinemia. Doses of 25 to 300 μg per day are required to treat hyperprolactinemia. In addition to side effects similar to those of bromocriptine, hepatic and cardiac toxicities have been reported. Other agents are under investigation, including non–ergot-derived compounds.[48]

Radiation therapy. Conventional radiation therapy is reserved for patients with prolactin-secreting macroadenomas who have persisting hyperprolactinemia after surgical treatment and who cannot tolerate bromocriptine. Conventional irradiation to 4,500 cGy prevents further tumor expansion, although prolactin levels rarely fall into the normal range.[44,49] Impairment of anterior pituitary function, a side effect of irradiation, occurs in approximately 30% to 50% of patients.

Treatment of suprasellar extension. A transfrontal craniotomy is required for the 1% to 2% of patients with major suprasellar extension of a macroadenoma requiring decompression of vital structures not accessible by the transsphenoidal route. Bromocriptine or radiation therapy should be given postoperatively because residual tumor is virtually always present.

Growth Hormone-Secreting Pituitary Tumors—Acromegaly and Gigantism

Growth hormone-secreting pituitary adenomas account for about 20% of all primary pituitary tumors.[13] Long-term growth hormone excess has deleterious effects on many systems and results in serious morbidity and a shortened life expectancy, although deaths are rarely due to the space-occupying or destructive effects of the pituitary tumor per se.[50-55]

Growth hormone-secreting pituitary adenomas are responsible for the vast majority of cases of acromegaly,[56,57] the incidence and prevalence of which are estimated to be 50 to 60 cases per million and 3 to 4 cases per million per year, respectively.[50,58] Rates are the same in both sexes.

Pathogenesis

The classic clinical syndromes of acromegaly and gigantism result from chronic growth hormone hypersecretion, which in turn leads to excessive generation of the somatomedins (insulin-like growth factors [IGFs]), the mediators of most of the effects of growth hormone.[59-61] In rare cases, carcinoid or islet cell tumors ectopically secrete growth hormone-releasing hormone (GH-RH), causing acromegaly. More commonly, such tumors express the GH-RH messenger RNA, but do not secrete the hormone itself and, therefore, do not cause the clinical syndrome.[62] Excess levels of ectopic GH-RH due to hypothalamic or pituitary gangliocytomas or hypothalamic hamartoma are extremely rare, and ectopic secretion of growth hormone itself is rarer still.[62]

Growth hormone-secreting pituitary adenomas usually arise from the lateral wings. Because of the slow progression of the clinical manifestations, these tumors are usually greater than 1 cm in diameter when diagnosed; fewer than 10% are diagnosed as microadenomas. Excessive pituitary secretion of growth hormone is a primary pituitary disorder in almost all cases.[56] In acromegaly,

growth hormone is secreted episodically, but the number, duration, and amplitude of secretory episodes are increased, and there is a loss of the characteristic nocturnal surge. Growth hormone dynamics are abnormal, as manifested by a loss of the physiologic suppression of growth hormone levels by glucose. The stimulation of growth hormone secretion by hypoglycemia is absent. Hypothalamic-releasing factors that normally do not stimulate growth hormone secretion (TRH and Gn-RH) may cause its release. Paradoxically, dopamine agonists, which normally stimulate growth hormone secretion, suppress it in about 70% to 80% of cases.[63]

Clinical Manifestations

The clinical features of acromegaly are shown in Table 3. In adults, chronic hypersecretion of growth hormone leads to acromegaly, which is characterized by a local overgrowth of bone, particularly of the skull and mandible. Previous fusion of the long bone epiphyses prevents linear growth. In children and adolescents, chronic growth hormone hypersecretion leads to gigantism[61] because the associated secondary hypogonadism delays epiphysial closure, which allows continued acceleration of linear growth. If growth hormone hypersecretion persists through adolescence and into adulthood, features of acromegaly are superimposed.

Acromegaly is a slowly progressing disorder that is chronically disabling and disfiguring; symptoms usually occur five to ten years before diagnosis. In addition to the classic physical appearance, glucose intolerance and hyperinsulinism resulting from growth hormone-induced insulin resistance are common, occurring in 50% and 70% of patients, respectively. Overt clinical diabetes mellitus is much less common, and diabetic ketoacidosis is rare. Hypogonadism, which is multifactorial in origin, occurs in 60% of female and 46% of male patients; compression of the normal pituitary gland or the pituitary stalk by the tumor may impair gonadotropin secretion directly or by interfering with the delivery of Gn-RH through hypophysial-portal vessels. Associated hyperprolactinemia or the prolactinlike effect of excessive growth hormone secretion may decrease gonadotropin secretion and impair gonadal function. In men, low total plasma testosterone levels may be due to suppression of sex hormone-binding globulin levels by growth hormone; in these cases, plasma free testosterone levels and gonadal function may be normal. Because the diagnosis of growth hormone-secreting adenomas is being made earlier, hypothyroidism and adrenal insufficiency due to destruction of the normal anterior pituitary are unusual, occurring in 13% and 4% of patients, respectively. Galactorrhea occurs in about 15% of patients and is usually caused by hyperprolactinemia resulting from a mixed somatotroph-cell and lactotroph-cell pituitary adenoma. Hyperprolactinemia may also result from lactotroph-cell disinhibition due to stalk compression. Although acromegaly may be a component of multiple endocrine neoplasia type I syndrome, this is seldom the case. For this reason, concomitant parathyroid hyperfunction or pancreatic islet cell tumors are rare.

TABLE 3.—*Clinical Features of Acromegaly*

Disorder	*Signs and Symptoms*
Bony overgrowth	Coarsening of features, frontal bossing, prognathism, malocclusion, barrel chest
Soft tissue swelling	Enlarged hands, feet, and tongue; carpal tunnel syndrome
Skin changes	Increased thickness, skin tags, seborrhea, sweating, hypertrichosis
Degenerative joint disease	
Hyperglycemia	
Hypertension	
Cardiomyopathy	
Fatigue	
Kidney stones	
Manifestations of a pituitary tumor	Headache, visual field defects, hypopituitarism

Complications of chronic hypersecretion of growth hormone include progressive cosmetic deformity and disabling degenerative arthritis and an increased incidence of cancer, especially colonic polyps and colon cancer.[51-57] It has been recommended that patients with acromegaly undergo colonoscopic screening using guidelines similar to those for other high-risk patients such as first-degree relatives of patients with colon cancer.[54] In addition, acromegaly is associated with increased mortality[50,52,58]; the death rate from cardiovascular and cerebrovascular atherosclerosis and respiratory diseases after age 45 in patients with acromegaly is twice that of the healthy population. Death rates are highest in patients with hypertension or clinical diabetes mellitus.

Diagnosis

Acromegaly and gigantism are usually clinically obvious and can be readily confirmed by assessing growth hormone secretion.[63] Basal fasting growth hormone levels (normal, 1 to 5 μg per liter [1 to 5 ng per ml]) are greater than 10 μg per liter in more than 90% of patients and range from 5 to more than 500 μg per liter, with a mean of about 50 μg per liter. Single measurements are not entirely reliable, however, because growth hormone secretion is episodic in acromegaly and because other conditions may increase its secretion, such as anxiety, exercise, acute illness, chronic renal failure, cirrhosis, starvation, protein-calorie malnutrition, anorexia nervosa, and type I (insulin-dependent) diabetes mellitus.

Failure to suppress growth hormone secretion with oral glucose is the simplest and most specific dynamic test for acromegaly. In healthy subjects, the oral administration of 100 grams of glucose suppresses the growth hormone level to less than 5 μg per liter at 60 minutes (<2 μg per liter in most). In patients with acromegaly, growth hormone levels fail to decrease to less than 5 μg per liter,

and this lack of response is diagnostic. Other tests that help establish or confirm the diagnosis are growth hormone stimulation with TRH, the absence of a nocturnal growth hormone surge, and the paradoxical suppression of growth hormone by levodopa, dopamine, bromocriptine, or apomorphine. These tests are usually unnecessary except in patients with mild acromegaly who may have normal or only mildly elevated growth hormone levels and equivocal responses to glucose suppression. Estrogen therapy may increase growth hormone responsiveness to various stimuli, but manifestations of excess should be recognizable. The measurement of somatomedin-C (IGF-I) levels, which are elevated in patients with acromegaly, is another useful diagnostic test for growth hormone hypersecretion and has excellent test characteristics. It is especially useful in differentiating patients with acromegaly from those with diabetes mellitus. Patients with diabetes may have elevated growth hormone levels that are not suppressible with glucose; their somatomedin-C levels are normal or low, however.[63]

Treatment

All patients with acromegaly or gigantism should undergo therapy to halt progression of the disorder and to prevent later complications. The objectives of therapy are to remove or destroy the pituitary tumor, reverse growth hormone hypersecretion, and maintain normal anterior and posterior pituitary functions. These objectives are currently attainable in most patients, especially those with smaller tumors and only moderate growth hormone hypersecretion. In patients with large tumors and pronounced growth hormone hypersecretion, several therapies are usually required to achieve normal secretion. A basal value of less than 5 μg per liter is considered normal by most; more rigorous criteria would be a growth hormone level of less than 2 μg per liter after oral glucose administration and a return to normal of IGF-I levels. Many patients whose basal values fall in that range, however, do not have normal growth hormone secretion and dynamics.

Surgery. Selective removal of the adenoma by transsphenoidal resection is the therapy of choice. In our experience, transsphenoidal surgical resection successfully reduces growth hormone levels in about 85% of patients and in more than 90% of patients with tumors less than 2 cm in diameter.[64] In patients with larger tumors and basal growth hormone levels greater than 50 μg per liter, particularly those with major extrasellar extension of the adenoma, resection of the adenoma is more difficult, and growth hormone levels are successfully reduced in only 60% to 70%. The recurrence rate after a successful initial response was 5% at our institution.[64] Serious surgical complications or damage to the normal pituitary gland occur in 1% to 2% of patients. Craniotomy is indicated for the rare cases in which major suprasellar extension precludes the transsphenoidal approach.[64,65]

Radiation therapy. Conventional radiation therapy in doses of 4,500 to 5,000 cGy prevents tumor progression and successfully reduces growth hormone hypersecretion in 60% to 80% of patients, although these levels may not return to normal until several years after therapy.[66] In a recent series, growth hormone levels were less than 10 μg per liter in 40% of patients two years after treatment, but were lower than these levels in 60% of patients at five years and in 75% at ten years.[66] Irradiation-induced hypopituitarism is common. Hypothyroidism occurred in 19% of the patients in this series, hypoadrenalism in 38%, and hypogonadism in about 50% to 60%. Because it reduces growth hormone levels so slowly, conventional radiation therapy is reserved for patients whose growth hormone hypersecretion persists after pituitary microsurgery.

Pharmacologic agents. The administration of bromocriptine reduces growth hormone levels in 60% to 80% of patients[67]; however, levels of 10 μg per liter or less are reached by only a few patients. In addition, bromocriptine therapy seldom reduces tumor size and is only suppressive; growth hormone hypersecretion rapidly recurs when treatment is discontinued. Therefore, bromocriptine is used as adjunctive therapy in patients with acromegaly whose growth hormone levels have not been adequately reduced by surgical or radiation therapy.

Octreotide acetate, a long-acting analogue of somatostatin, has been effective in the management of acromegaly.[68-71] Its use reduces growth hormone and IGF-I levels to normal in most patients and, in some, causes notable tumor shrinkage. Effective doses appear to be in the range of 100 to 500 μg, administered subcutaneously three times a day. The need for subcutaneous administration is a major disadvantage because long-term therapy is required. Side effects include abdominal pain, steatorrhea, and cholelithiasis.

Corticotropin-Secreting Pituitary Adenomas—Cushing's Disease

Pathogenesis

Corticotropin hypersecretion by a pituitary adenoma (Cushing's disease) is now recognized as the most common cause of spontaneous hypercortisolism (Cushing's syndrome). It is much more common in women; the ratio of females to males is about 8:1.[72-74] Cushing's disease must be distinguished from the other kinds of adrenocorticosteroid excess, namely, syndromes of ectopic secretion of corticotropin and of corticotropin-releasing hormone, adrenal adenomas, and adrenal carcinomas. Corticotropin-secreting pituitary tumors, which are found to be either basophilic or chromophobic adenomas by routine staining, are almost always benign microadenomas. More than 50% are 5 mm or less in diameter, but they cannot always be histologically confirmed.[75] Corticotropin-secreting tumors are rarely large and invasive.

Diffuse hyperplasia of anterior pituitary corticotroph cells or adenomatous nodular hyperplasia, presumed to result from the hypersecretion of corticotropin-releasing hormone, occurs rarely.

Cushing's disease is considered to be a primary pituitary disorder.[74-76] Virtually all patients with Cushing's dis-

TABLE 4.—*Clinical Features of Cushing's Disease*

Obesity, especially truncal
Facial plethora
Hirsutism, acne, and menstrual disorders
Hypertension
Striae
Bruising
Proximal muscle weakness
Hyperglycemia
Psychiatric symptoms, especially depression
Osteoporosis
Susceptibility to infection
Decreased wound healing
Hyperpigmentation
Edema

ease have corticotropin-secreting pituitary tumors. In addition, selective complete removal of pituitary microadenomas by transsphenoidal microsurgical resection corrects corticotropin hypersecretion and hypercortisolism. After the operation, these patients have temporary but often prolonged corticotropin deficiency with secondary hypoadrenalism. Normal circadian rhythmicity of corticotropin and cortisol, responsiveness of the hypothalamic-pituitary axis to hypoglycemic stress, and low-dose dexamethasone suppressibility of cortisol secretion eventually return. There is, therefore, no evidence for a persisting hypothalamic abnormality in these patients.

Clinical Manifestations

The clinical features of Cushing's disease are shown in Table 4. Cushing's disease causes signs and symptoms of hypercortisolism and adrenal androgen excess that develop over months or years. The weight gain is characterized by a peculiar fat distribution with truncal obesity, round facies (moon face), dorsocervical fat accumulation (buffalo hump), supraclavicular fat pads, and a relative sparing of the extremities. Excessive glucocorticoid action also results in a catabolic state with thin skin, easy bruising, and osteoporosis. Hyperglycemia is common. Adrenal androgen excess produces hirsutism and acne and contributes to amenorrhea. Hypokalemia, edema, and hyperpigmentation are less common in Cushing's disease than in the ectopic corticotropin syndrome.

There are several endocrine abnormalities in Cushing's disease: hypersecretion of corticotropin, with bilateral adrenocortical hyperplasia and hypercortisolism; absent circadian periodicity of corticotropin and cortisol secretion; absent responsiveness of corticotropin and cortisol to stress (hypoglycemia or surgical procedures); abnormal negative feedback of corticotropin secretion by glucocorticoids; and subnormal responsiveness of growth hormone, thyrotropin, and gonadotropins to stimulation.

Diagnosis

The initial step in the diagnosis of a corticotropin-secreting pituitary adenoma is the documentation of endogenous hypercortisolism. This is confirmed by demonstrating the presence of abnormal cortisol suppressibility with low-dose dexamethasone and an increased level of urinary cortisol excretion in a 24-hour urine collection.[77]

A corticotropin-secreting pituitary tumor can be differentiated from other causes of hypercortisolism by measuring basal levels of corticotropin in plasma and by the response to suppression testing with high-dose dexamethasone. Patients with Cushing's disease have normal or slightly elevated corticotropin levels ranging from 9 to 44 pmol per liter (40 to 200 pg per ml; normal, 2 to 11 pmol per liter [10 to 50 pg per ml] by sensitive immunoradiometric assays). Low levels (<2 pmol per liter [<10 pg per ml]) usually indicate an autonomously secreting adrenal tumor, and levels greater than 44 pmol per liter (>200 pg per ml) suggest an ectopic corticotropin-secreting neoplasm. Patients with Cushing's disease are occasionally seen who have similar levels; several corticotropin levels using the highly sensitive immunoradiometric assays and corticotropin-releasing hormone testing may be necessary for an accurate diagnosis. The plasma corticotropin levels associated with pituitary tumors, however, overlap those associated with the ectopic corticotropin syndrome. Administration of low-dose dexamethasone fails to suppress corticotropin secretion and, therefore, glucocorticoid secretion in nearly all patients with Cushing's syndrome, but in some patients, the negative glucocorticoid feedback effect is maintained by corticotropin-secreting pituitary tumors. Thus, administering high-dose dexamethasone will suppress plasma or urinary corticosteroids in most, but not all, patients with Cushing's disease.[77,78]

The rapid, overnight high-dose dexamethasone test is a more reliable and simple way to distinguish corticotropin-secreting pituitary tumors from other forms of endogenous hypercortisolism than is the standard two-day suppression test of Liddle. The Liddle test requires administering 2 mg of dexamethasone every six hours for two days.[79] In the rapid overnight test, 8 mg of dexamethasone is given at 11 PM. The next morning at 8 AM, the plasma cortisol level will be less than 50% of baseline in patients with typical Cushing's disease. The failure of the plasma cortisol level to be suppressed indicates the presence of either the ectopic corticotropin syndrome or an adrenal tumor.

Problems in diagnosis are common, especially in distinguishing Cushing's disease from corticotropin secretion from an occult ectopic source.[72,80,81] Ectopic corticotropin from an occult tumor may be indistinguishable clinically from that due to Cushing's disease. The results of high-dose dexamethasone suppression tests should be cautiously interpreted because they are not entirely specific. Neuroradiologic techniques may not show the microadenomas.[77] High-resolution MR imaging of the sella turcica at best has a sensitivity of 60% and may yield false-positive results. Computed tomographic scanning of the adrenal glands may also be misleading. For example, nodular adrenal hyperplasia due to a corticotropin-secreting pituitary tumor may appear as a solitary adrenal mass

and mimic an adrenal neoplasm.[82,83] Although combining information from all of these laboratory tests and MR images often establishes the diagnosis of Cushing's disease, doing so with certainty requires techniques with better sensitivity and specificity. A few centers have experience with taking blood specimens from the inferior petrosal sinuses and a peripheral vein to document a cephalic gradient of corticotropin. Values from the inferior petrosal sinus should be at least two times the simultaneously determined peripheral value. Bilateral simultaneous petrosal sinus sampling with corticotropin-releasing hormone stimulation of corticotropin release has been reported to have 100% sensitivity and specificity.[84,85] When it can be done with such accuracy, it becomes the diagnostic procedure of choice for most patients.[86] It must be performed by a radiologist skilled in catheterization techniques, and even then, serious complications have occurred.[87] Sampling corticotropin from the petrosal sinus occasionally lateralizes the lesion accurately, thereby assisting a surgeon in locating the tumor. Other tests have been proposed, such as assessing the peripheral blood corticotropin response to corticotropin-releasing hormone, but their role has yet to be established.[77]

Treatment

Surgery. Selective transsphenoidal resection of corticotropin-secreting pituitary adenomas is the treatment of choice because of its efficacy, the rapid clinical response, and low complication rate.[88-92] The tumor, which is characteristically found in the anterior lobe tissue, is removed selectively, leaving the normal gland intact. If the tumor is too small to locate during the operation, total hypophysectomy may be performed in adult patients who are past reproductive age and whose biochemical diagnosis has been confirmed with inferior petrosal sinus sampling of plasma corticotropin levels.

Selective microsurgical therapy successfully corrects hypercortisolism in about 85% to 90% of patients with microadenomas.[88-92] Most patients have transient secondary adrenocortical insufficiency requiring postoperative glucocorticoid support until the hypothalamic-pituitary-adrenal axis recovers, which usually takes 6 to 18 months. Total hypophysectomy is necessary to correct hypercortisolism in about 10% of patients with pituitary adenomas; selective tumor removal is unsuccessful in the remaining 5%. Approximately 10% to 15% of patients with Cushing's disease have pituitary macroadenomas or extrasellar extension of tumor. Transsphenoidal surgical therapy is successful in only about 25% of these patients. Surgical results vary widely among centers.

Before pituitary microsurgery was introduced, bilateral total adrenalectomy was the preferred treatment for Cushing's disease, and it may still be used when other therapies are unsuccessful. Bilateral adrenalectomy, however, has a high complication rate, and patients require lifelong hormone replacement. In addition, the preexisting corticotropin-secreting pituitary adenoma persists and may progress, causing hyperpigmentation and invasive complications (Nelson's syndrome).[72]

Radiation therapy. Conventional irradiation in doses of 4,500 to 5,000 cGy leads to biochemical and clinical improvement in as many as 70% of patients with Cushing's disease, but the response to treatment is delayed, and only about 40% of patients are cured.[93] Adjunctive antiadrenal drug therapy has been used with some success, but the ultimate response to radiation therapy is often unsatisfactory, and prolonged drug therapy is therefore required.

Pharmacologic agents. Drugs that inhibit adrenal cortisol secretion are useful in treating Cushing's disease, often as adjunctive therapy.[94] Ketoconazole, an imidazole derivative used as a broad-spectrum antimycotic agent, inhibits the cytochrome P450 enzymes involved in adrenal steroid biosynthesis. In daily doses of 600 to 1,200 mg, the administration of ketoconazole has been effective in managing mild to moderate Cushing's disease. It is also less expensive than other antiadrenal medications. Hepatotoxicity is common, but may be transient.

Metyrapone, an 11β-hydroxylase inhibitor, and aminoglutethimide, which inhibits the conversion of cholesterol to pregnenolone, are expensive drugs that have both been used to reduce cortisol hypersecretion. Their use results in increased corticotropin levels that may overcome the enzyme inhibition; gastrointestinal side effects may limit their effectiveness, however. Hypercortisolism can be controlled more effectively and with fewer side effects by the combined use of metyrapone and aminoglutethimide. They are usually used while awaiting a response to therapy or when preparing patients for surgical treatment.

The use of the adrenolytic drug mitotane (Lysodren [formerly *o, p'*-DDD]) results in adrenal atrophy predominantly of the zonae fasciculata and reticularis and produces the remission of hypercortisolism in about 80% of patients. Mitotane therapy is limited by the delayed response, which may take weeks or months, and by the frequent side effects, including severe nausea, vomiting, diarrhea, somnolence, and skin rash. Moreover, relapse after therapy is stopped is common.

Pharmacologic inhibition of corticotropin secretion with the use of cyproheptadine, a drug with antiserotonin, antihistamine, and anticholinergic effects, has had limited success. The use of bromocriptine has been reported to be effective in rare cases and should probably be reserved for those few patients who have hyperprolactinemia associated with Cushing's disease.

Nelson's syndrome. Nelson's syndrome, the clinical manifestation of a corticotropin-secreting pituitary adenoma after bilateral adrenalectomy in patients with Cushing's disease, is caused by progression of a preexisting adenoma after the restraint of hypercortisolism on corticotropin secretion and tumor growth has been removed.[72,74] The incidence of Nelson's syndrome after adrenalectomy in patients with Cushing's disease ranges from 10% to 78%, depending on the diagnostic criteria used. Pituitary irradiation before or after adrenalectomy does not prevent the development of this syndrome. Classic Nelson's syndrome with progressive hyperpigmentation and an obvious corticotropin-secreting tumor

develops in about 30% of patients undergoing adrenalectomy for Cushing's disease; about 50% have evidence of a microadenoma without marked progression, and in about 20%, progressive tumor never develops. These tumors are among the most aggressive and rapidly growing of all pituitary tumors.

Patients with Nelson's syndrome present with hyperpigmentation, greatly elevated plasma corticotropin levels (usually greater than 220 pmol per liter [>1,000 pg per ml]) and manifestations of an expanding intrasellar mass lesion. Visual field defects, headache, cavernous sinus invasion with extraocular muscle palsies, and even malignant changes with local or distant metastases may occur. Pituitary apoplexy is a relatively frequent complication.

Pituitary surgery, usually by the transsphenoidal approach, is the initial treatment of Nelson's syndrome, but complete resection of the larger tumors is usually not possible. Conventional radiation therapy alone is satisfactory in a few patients, but it is often given after surgical therapy in patients with extrasellar extension.

Thyrotropin-Secreting Pituitary Adenomas

Although rare, thyrotropin-secreting pituitary adenomas are being diagnosed with increasing frequency.[95-98] In our recent experience, thyrotropin-secreting tumors accounted for 2.8% of pituitary adenomas.[95] There is a modest female predominance; the female to male ratio was 1.7:1 in our series. Moreover, there are sex-dependent differences in the tumor biology; men tend to have larger, more invasive, and more rapidly growing tumors that present later in life. The tumors are found to be chromophobe adenomas by routine staining.

Clinical Manifestations

Patients usually present with thyrotoxicosis, goiter, and elevated serum levels of both thyroid hormones (thyroxine [T_4] and triiodothyronine) and elevated or at least inappropriately nonsuppressed thyrotropin, as measured by highly sensitive assays. The diagnosis may be made based on visual impairment caused by the large size of these tumors, rather than on their endocrine activity. Pituitary thyrotropin hypersecretion that occurs when there is no demonstrable pituitary tumor and that may be due to central thyroid hormone resistance has also been reported to cause hyperthyroidism in a few patients.

Patients with thyrotropin-secreting tumors are often resistant to routine ablative thyroid therapy and require large, often multiple doses of radioactive iodine and several operations to control thyrotoxicosis.

Diagnosis

The routine use of highly sensitive thyrotropin assays to evaluate the presence of thyrotoxicosis is likely to detect more cases of thyrotropin-secreting pituitary adenoma. In patients with thyrotropin-secreting tumors (thyrotroph-cell adenomas), thyrotropin levels have ranged from 1 to more than 400 mU per liter (1 to > 400 μU per ml). The ratio of biologically active to immunologically active thyrotropin may be increased. Thyrotropin responses to dynamic testing are variable.[96,99] The administration of TRH (protirelin) rarely stimulates thyrotropin secretion from these tumors, nor does administering T_4, levodopa, or bromocriptine suppress thyrotropin as it does the thyrotropin hypersecretion caused by primary hypothyroidism. The thyrotropin-secreting pituitary adenomas occasionally co-secrete growth hormone and prolactin; hyperprolactinemia may also result from pituitary disinhibition. More than 80% of thyrotroph-cell adenomas secrete free α-subunit; the ratio of the α-subunit to thyrotropin is usually greater than 1. This helps distinguish thyrotropin-secreting tumors from the syndrome of central resistance to thyroid hormone, in which the ratio of the α-subunit to thyrotropin is less than 1[100] and the sella is normal. The differential diagnosis of a thyrotropin-secreting pituitary adenoma also includes rare cases of primary hypothyroidism in which major reactive thyrotroph-cell hyperplasia, sellar enlargement, and, occasionally, suprasellar extension develop.

Treatment

Transsphenoidal surgical resection of the adenoma is the best initial treatment. If thyrotropin hypersecretion persists, ablative treatment of the thyroid with either radioactive iodide (iodine 131) or surgical intervention is necessary to achieve clinical remission of the thyrotoxic state. Treatment directed at the thyroid gland alone may accelerate growth of the pituitary tumor. The administration of octreotide acetate, a long-acting somatostatin analogue, has been effective in decreasing thyrotropin secretion from these tumors when the drug is given in subcutaneous doses similar to those used for the treatment of acromegaly; it has also been shown to shrink the tumors.[101,102]

Clinically Endocrine-Inactive Pituitary Adenomas

Sensitive techniques for detecting pituitary hormone synthesis and secretion have documented that most pituitary tumors thought to be nonfunctional are, in fact, functional. The term "endocrine-inactive" refers to their clinical behavior and not their capacity for hormone synthesis. These tumors can be classified into several types: null cell, oncocytoma, gonadotropin-secreting, glycopeptide-secreting, and silent corticotropin-secreting.[103] Most of these "nonfunctional" tumors synthesize gonadotropins or their subunits.[104-107] Even null-cell tumors can be induced to produce glycopeptide subunits in vitro. Some adenomas contain secretory granules that show immunohistochemical or electron-microscopic characteristics of corticotropin granules when there is no evidence of Cushing's disease (silent corticotroph-cell adenomas) or of other hormones causing no clinical disorders.

Clinical Manifestations and Diagnosis

Endocrine-inactive tumors are usually large at the time of diagnosis and are therefore associated with neurologic manifestations, typically bitemporal hemianopia and hypopituitarism. The endocrine manifestations usually de-

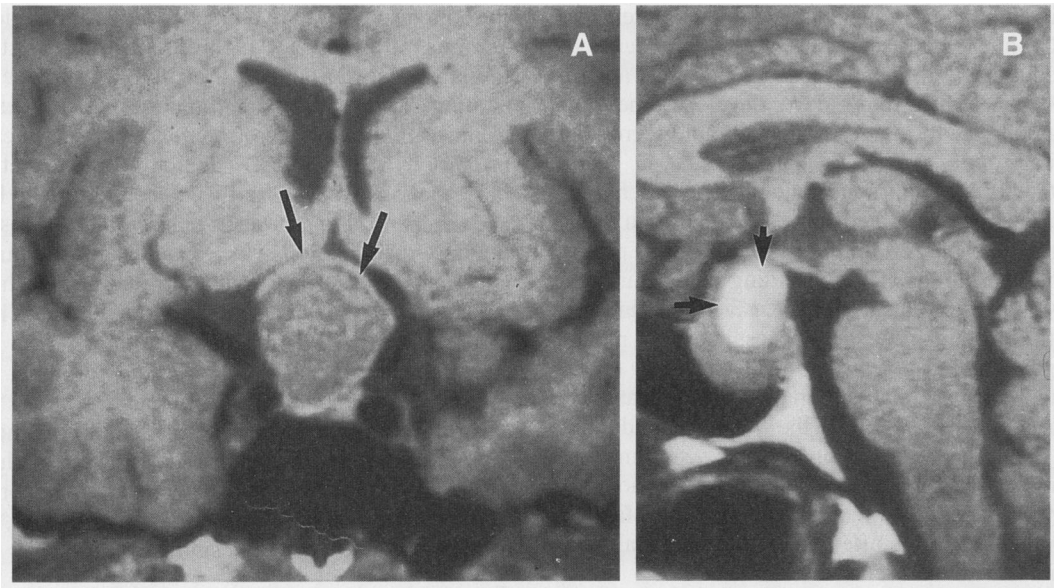

Figure 3.—A, The coronal magnetic resonance (MR) image shows a large nonfunctioning pituitary adenoma (**arrows**) with pronounced suprasellar extension and chiasmal compression. **B,** A sagittal MR image of another large pituitary adenoma shows spontaneous hemorrhage within the suprasellar portion of the adenoma (**arrows**). (Photographs courtesy of David Norman, MD.)

velop over a period of years. In rare cases, these tumors secrete sufficient amounts of gonadotropins to produce clinical manifestations.[108,109] Until recently, almost all such cases were diagnosed in men. Hypogonadism may be apparent in men or premenopausal women. Some men have testicular enlargement induced by the hypersecretion of FSH, but this is extremely rare. Long-standing primary hypogonadism—such as Klinefelter's syndrome—may cause hyperplasia of gonadotropin cells and pituitary enlargement. This diagnosis must be excluded in any patient with elevated levels of gonadotropins and enlargement of the sella turcica. Serum levels of intact gonadotropins may be normal or slightly elevated. Both α- and β-subunits of the glycoprotein hormones may also be secreted in excess. Pure α-subunit hypersecretion has also been identified. Secretory dynamics of FSH and LH are abnormal, and responses to Gn-RH are variable. The secretion of FSH, LH, and LH-β-subunit, however, is often provoked by TRH; such stimulation is not observed in healthy persons.

Magnetic resonance imaging readily localizes these large tumors (Figure 3). Visual field testing should always be done. Assessing pituitary and end-organ function will determine the presence of hypopituitarism and hypersecretion. Hypersecretion is useful as a tumor marker even if its effects are subclinical. Nonsecreting tumors must be differentiated from nonneoplastic mass lesions.

Treatment

Surgical removal is the initial treatment of choice for endocrine-inactive adenomas. Complete surgical removal is possible in no more than 40% of patients. Postoperative irradiation (4,500 cGy) will obliterate residual cells in almost all incompletely removed tumors and is indicated in most patients when removal is known to be incomplete. There is virtually no role for medical therapy at this time.

Hypopituitarism due to these endocrine-inactive pituitary adenomas, as well as to other macroadenomas, may be reversible if the tumor is surgically removed.[110] In the absence of an endocrine marker of tumor hypersecretion, serial CT scans or MR images and visual field examinations at yearly intervals are required to assess the response to therapy and to detect possible recurrences.

Follow-up After Treatment

Regardless of the mode of therapy, careful follow-up of all patients with pituitary tumors is essential. Patients undergoing transsphenoidal microsurgical resection should be reexamined four to six weeks after the operation to document that the adenoma has been completely removed and that the endocrine hypersecretion has been corrected. Those with successful responses should be examined yearly to look for any recurrence; late hypopituitarism does not occur after the microsurgical procedure. Follow up of patients treated by pituitary irradiation is equally important because the response to therapy may be delayed, and the incidence of hypopituitarism increases with time. At least yearly endocrinologic assessment of both the hypersecreted hormone and the other pituitary hormones is recommended.

Future Research

Research on the pituitary gland continues to yield interesting findings. For example, rare cases have been described of pituitary tumors secreting other hormones such as β-endorphin and cholecystokinin.[111] With the identification of novel hormones in the anterior and posterior pituitary glands and the application of new imaging techniques such as positron-emission tomographic scanning, it is likely that new syndromes will be described in the future.

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