Pituitary tumors: pathophysiology, clinical manifestations and management

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Abstract

Pituitary tumors are frequently encountered intracranial neoplasms. They present with a variety of clinical manifestations that include symptoms and signs of excessive hormone secretion by the tumor, signs of hormone deficits by the normal pituitary gland and others related to expansion of the tumor mass and the resulting compression of surrounding structures such as the optic chiasm and cranial nerves. Advances in molecular biology, immunocytochemical staining and imaging, and the introduction of new treatment options have improved our understanding of the natural history of these adenomas and their management. Available treatments include surgical, medical and radiation therapy. Although the primary treatment for each tumor type may vary, it is important to consider all available options and select the most applicable for that patient. The interaction of all members of management team, including the primary care provider, the endocrinologist and the neurosurgeon in selecting the treatment course can only improve therapeutic outcome. Regardless of the initial choice of treatment, follow-up of all patients should be maintained indefinitely. The managing physician should be familiar with the natural history and long-term complications of pituitary adenomas, and with the side effects of treatments given over the years.

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Introduction

Pituitary tumors are the most commonly encountered intracranial neoplasms. The prevalence of these tumors in autopsy series is reported to be 5–20%, with most series estimating the prevalence to be approximately 10% (Burrows *et al*. 1981, Molitch & Russell 1990). It is interesting to note the vast majority of these tumors discovered at autopsy are small (<10 mm) or microadenomas. The use of magnetic resonance imaging (MRI), in otherwise healthy individuals revealed a similar prevalence of incidentally discovered pituitary adenomas (Hall *et al*. 1994). Although the frequency or prevalence of clinically recognized tumors are not clearly established, they are estimated to be lower than those reported in autopsy studies. Advances in biochemical testing and neuroimaging techniques over the past two decades have facilitated early recognition of pituitary tumors and revolutionized their management. The introduction of immunocytochemical methods and more recently the refinements in techniques in molecular biology, have led to changes in the classification and better appreciation of the pathogenesis of these tumors. In this article, we will review the current classification, pathogenesis and biologic behavior

of pituitary tumors. We will also consider the clinical manifestations and management of pituitary tumors in general and review available therapeutic options for each tumor type.

Classification of pituitary tumors

The older classification of pituitary tumors was based on cellular characteristics using hematoxylin and eosin stains on resected tissue. Tumors were accordingly classified as eosinophilic, basophilic or chromophobic adenomas. The third classification did not take into account clinical symptoms or hormone production by the adenoma. With the advent of immunocytochemical staining, tumors are now classified according to the characteristic hormone staining and electron microscopic changes (Table 1). This classification is in general agreement with the reported clinical signs and symptoms. There are, however, many exceptions where the immunocytochemical staining is not concordant with the clinical or biochemical features. A classical example is that of silent corticotroph adenomas, in which tumor cells stain positively for adrenocorticotrophic hormone (ACTH), and yet

Table 1 Classification of pituitary tumors

Name	Prevalence (% of all tumors)	Hormone staining	Clinical manifestations
Prolactinomas (PRL-secreting)	40–45	Prolactin	Signs of hyperprolactinemia
Somatotroph adenomas (GH-secreting)	20	GH ± prolactin	Acromegaly
Corticotroph adenomas (ACTH-secreting)	10–12	ACTH ± others	Hypercortisolism
Gonadotroph adenomas	15	FSH, LH, aSU, bSU	Mechanical symptoms, hypopituitarism
Null-cell adenomas	5–10	None	Mechanical symptoms, hypopituitarism
Thyrotroph adenomas (TSH-secreting)	1–2	TSH, aSU ± GH	Mild hyperthyroidism, hypopituitarism

PRL, prolactin

patients have no clinical or biochemical features of excessive ACTH secretion. It is postulated that in these instances, adenomatous cells can synthesize the hormone (ACTH) but have impaired secretory ability.

Traditionally, microadenomas refer to tumors that are <10 mm in size and are located totally within the sella turcica. Macroadenomas are large tumors (>10 mm) that can be totally intrasellar but are often associated with extrasellar extension. Such tumors can extend inferiorly into the sphenoid sinus, but more frequently superiorly into the suprasellar space (due to lower resistance), compressing the optic apparatus, or laterally into the cavernous sinuses on either side (Gsponer *et al.* 1999). Although some adenomas are invasive and have pleomorphic nuclei, the vast majority are considered benign. There are only a few documented cases of primary pituitary cancer (Lubke & Saeger 1995). Metastatic spread of other malignant tumors to the pituitary is often seen in patients with extensive spread of cancer to other areas (Aaberg *et al.* 1995).

Pathogenesis and genetics of pituitary tumors

Up until the last decade, there were two prevailing theories for the origin of pituitary tumors. The most commonly accepted theory was that these tumors represent intrinsic abnormalities within the gland itself. The other theory favored a hypothalamic cause for most, if not all, pituitary tumors – that is, according to the latter hypothesis, pituitary tumors originate as a result of continued stimulation by a hypothalamic hormone or factor. Most authorities favored the former hypothesis, advocating that pituitary tumors are primary or arise as a result of intrinsic abnormalities within the gland.

The recent advances in molecular biology have facilitated more definitive studies on these tumors. Using X-allele inactivation methods, studies have demonstrated that pituitary tumors are monoclonal in origin (Alexander *et al.* 1990). Thus tumors arise from a single cell mutation followed by clonal expansion. Pituitary neoplasia is a multi-step process that involves dysregulation of cell growth

or proliferation, differentiation, and hormone production. It may be initiated as a result of activation of oncogene function or after inactivation of a tumor suppressor gene, or both. The former process (activation of oncogene function) is a dominant event and therefore a single allele alteration will lead to a change in cellular function. An example of such an oncogene is present in about 40% of pituitary somatotropinomas. In such tumors, a point mutation in the Gs-α gene leads to a defective G-protein subunit and GTPase activity. This will lead to persistent cAMP concentrations and consequently excessive growth hormone (GH) secretion that bypasses GH releasing hormone (GHRH) (Farfel *et al.* 1999, Adams *et al.* 2000). A similar mechanism is postulated for the development of acromegaly in patients with McCune-Albright syndrome (Lacroix *et al.* 1992, Farfel *et al.* 1999).

In contrast, tumor suppressor inactivation is recessive in nature and therefore both alleles of the gene must be affected to influence cellular events or function. The heterogeneity of genetic defects found in pituitary adenomas is consistent with the multi-step neoplastic process. For example, inactivation of a tumor suppressor gene (either through DNA methylation or through the loss of heterozygosity by point mutation or deletion) is found in different loci in various tumors. In multiple endocrine neoplasia type 1, the gene has been localized to chromosome 11, whereas in sporadic tumors different areas of chromosomes 11, 9, or 13 have been isolated. The role of hypothalamic and other growth factors in modulating these events is under investigation (Farrell *et al.* 1999, Melmed 1999).

The clinical implication once the molecular pathogenesis is further established is for targeted gene therapy. For example, inactivated viruses such as herpes simplex virus-1 and adenovirus are currently used in animal studies to deliver cell-targeted cytotoxic therapy (Windeatt *et al.* 2000). *In vitro*, the antiangiogenesis factors angiostatin and endostatin are being incorporated into these vectors. The process of deactivation of known promoter sequences, as in prolactinoma, and transgene incorporation in the case of mutation, would constitute the heart of gene therapy (Castro *et al.* 1999).

Although not immediately relevant, the above prospect clearly has the potential for human therapy. The ethical beliefs of physicians and patients would need to be addressed. The current ethical/legal consensus allows somatic gene therapy, with therapeutic intent only, and excludes germ line (reproductive) manipulation (Castro *et al*. 1999).

Pathophysiology of clinical manifestations

Patients with pituitary tumors present with a variety of signs and symptoms that can be divided into any of the following categories:

1) Signs and symptoms related to, or caused by, excessive hormone production: e.g., symptoms and signs of hypercortisolism in patients with ACTH-secreting adenomas or signs of acromegaly in patients with GH-secreting adenomas.

2) Signs and symptoms related to the mechanical effects of an expanding tumor within the sella turcica. Such symptoms include headaches, visual disturbances and cranial nerve palsies.

3) Signs and symptoms of impaired normal pituitary function (i.e., partial or panhypopituitarism). This is almost always seen in patients with macroadenomas, the main exception to this being when the impairment in pituitary function is functional in nature, resulting from the effects of excess hormone secretion. A common example of the latter is the finding of hypogonadism in patients with prolactin-secreting adenomas.

Management of pituitary tumors: an overview

Treatment of pituitary tumors should be not only comprehensive, but also individualized. Regardless of the therapeutic option chosen, physicians managing patients with pituitary tumors should address treatment goals and attempt to achieve these objectives in all patients. They include:

1) Controlling clinical and biochemical signs of excessive hormone secretion.

2) Preserving normal pituitary function whenever possible.

3) Reversing or treating impaired pituitary function.

4) Controlling tumor growth and its mechanical effects on surrounding structures.

In experienced medical centers, these objectives can be achieved in most patients with pituitary microadenomas through medical or surgical treatments of the tumors. Several modalities may be necessary in many patients, particularly in those with large, invasive adenomas. Success of treatment in the latter instances depends to a large degree on the type, size and extent of tumor invasion, in addition to the expertise available to the managing team. Available options are discussed below.

Surgical treatment

The primary approach, transsphenoidal surgical adenomectomy, is very effective, with low morbidity and mortality. Normal pituitary function is most often preserved (Hout *et al*. 1988) and recovery of lost function is common (Arafah *et al*. 1994). Despite the enormous size of some tumors, the transsphenoidal approach is preferred by most neurosurgeons. A subsequent craniotomy may be necessary in some patients with residual, suprasellar tumor that did not descend during the transsphenoidal approach. Surgical treatment results in improvement of visual symptoms in at least 70–80% of patients with preoperative chiasmal compression (Young *et al*. 1996).

Complete tumor removal can be achieved in most, but not all patients. The outcome of surgery is determined by the surgeon's experience, the size of the adenoma and the degree of its extension beyond the sella turcica (Freda & Wardlaw 1999, Shimon & Melmed 1998). Extension of the tumor into the cavernous sinus is almost always associated with incomplete removal. Recurrence of pituitary adenoma after apparent complete surgical resection is reported to occur in 10–25% of patients, usually within the first 4 years. However, recurrences and continued tumor growth have been seen after long-term follow-up. Therefore, periodic hormonal testing and repeat imaging studies are recommended annually. The initial MRI follow-up after surgery is usually done 3–4 months later, to allow time for healing and removal of post-operative debris. Transsphenoidal surgery is generally well tolerated with minimal morbidity and mortality. The complication rate is usually low, in experienced hands, and is influenced by size and location of the adenoma, in addition to the patient's medical condition. Commonly encountered side-effects or complications include diabetes insipidus in 5–15% of patients, which is often transient, and, less commonly, infection and leakage of cerebrospinal fluid.

The hypopituitarism found in the majority of patients at presentation can very often be reversible. Recovery of pituitary function can be documented to occur immediately after operation (Arafah *et al*. 1994). This is even true in patients with pituitary tumor apoplexy, in whom recovery of pituitary function has also been demonstrated immediately after operation (Arafah *et al*. 1997). It is, therefore, important to monitor pituitary function after surgery and assess the potential for recovery, and to document persistence of previous function.

Radiation therapy

Radiation therapy has been advocated as a treatment option, for different reasons. In earlier studies preceding recent advances in neurosurgical techniques, radiation therapy was recommended as a primary treatment for all types of pituitary

tumors, particularly in patients who were poor surgical risks. The use of radiation therapy has since diminished, because of the noted advances in neurosurgical techniques and the availability of additional forms of medical treatments for most types of adenomas.

At the present time, radiation therapy is rarely recommended as a primary form of therapy for pituitary tumors in general. It is, however, used as an adjunctive therapy in patients with either functioning or non-functioning adenomas. Every attempt should be made to exclude the optic chiasm from the field of irradiation, even if an additional surgical decompression procedure becomes necessary. Although the standard fractionated delivery using the linear accelerator is still commonly utilized (Plowman 1995), other approaches are now available. These include heavy particle irradiation and stereotactic delivery (Ganz 1995). A promising approach that is being currently tested in a few centers is the fractionated stereotactic method.

Complications caused by radiation therapy itself are many, and some are serious. One of the serious complications seen in some patients, within a short period of time, is worsening visual symptoms secondary to edema, tumor hemorrhage and optic nerve necrosis. Other complications include increased risk of developing malignant brain tumors, brain necrosis and dementia (Plowman 1995). Progressive loss of pituitary function is a frequent chronic complication of radiation therapy. It is estimated that, after 10 years of follow-up, more than 90% of patients have at least two or more deficient hormones. Even though pituitary radiation is associated with a substantial number of side effects, it is fairly effective in controlling pituitary adenoma growth, preventing regrowth after surgery and causing tumor shrinkage in most patients (Plowman 1995). However, the beneficial effects of radiation are often delayed for years.

Medical treatment

Primary medical treatment is available for most pituitary tumors. It is well tolerated in general, but usually entails several years of therapy at least. There are various medications available depending on the different hormones secreted and on the specific level of action of the drug along the hypothalamic–pituitary–end-organ axis. The specific therapies will be discussed under each tumor type.

Management of specific types of pituitary tumors

Prolactin-secreting adenomas

Clinical manifestations and diagnosis of prolactinomas

These tumors represent the majority of clinically recognized pituitary adenomas, accounting for approximately 40–45% of

all. They are reported to occur more frequently in women than in men, particularly between the second and third decades of life, when the ratio is estimated to be 10:1. After the fifth decade of life, the frequency of prolactinomas is similar in both sexes (Mindermann & Wilson 1994). Prolactinomas vary in size at presentation with most women presenting with microadenomas, whereas men tend to have macroadenomas at diagnosis. Although the biology of the tumor may differ, it is likely that a contributing factor for the variance in size at diagnosis includes differences in the clinical symptoms of hyperprolactinemia. In women, hyperprolactinemia causes oligomenorrhea or amenorrhea in addition to galactorrhea. In men, however, the main presenting symptom is impotence and diminished libido, which can often be overlooked and attributed to other causes. In addition to the symptoms of excessive hormone secretion, the clinical manifestations include symptoms caused by mechanical effects of the tumor (headaches and visual symptoms) and variable degrees of hypopituitarism. The latter set of symptoms are seen in patients with macroadenomas and not in those with microadenomas. It is important to point out that persistence of the state of hyperprolactinemia, regardless of its cause, will lead to a prolonged period of hypogonadism that, by itself, will cause decreased bone mineral density and osteoporosis in both men and women.

Very often the diagnosis of prolactinoma is very simple and is suggested by extreme increase in serum prolactin concentrations (Ciccarelli & Camanni 1996). However, the use of immunoradiometric assay in the measurement of serum prolactin concentrations might result in falsely low values because of the 'hook' effect (St-Jean *et al*. 1996). This phenomenon is reported primarily in patients with giant prolactinomas where initial measurements of serum prolactin concentration were reported to be only mildly increased (50–150 µg/l). However, on serial dilutions, the actual concentrations are often reported to be in the several thousands range. Thus serum prolactin concentration should be measured after dilutions in patients with very large tumors (>3cm) in whom the initial concentrations were mildly increased. Because of its therapeutic implications, the latter process is clinically important, as it helps differentiate patients with prolactinomas from others. With rare exceptions, serum prolactin concentrations greater than 200 µg/l are diagnostic of prolactinomas and should be easy to document further with imaging studies. Serum prolactin concentrations between 100 and 200 µg/l are usually, but not always, caused by prolactin-secreting adenomas. When such concentrations are seen in patients with giant tumors, the possibility of the 'hook' effect should be considered and repeat measurements with serial dilutions should be undertaken. In patients with modest increases, one needs to consider the differential diagnosis of hyperprolactinemia (Table 2). If the hyperprolactinemia cannot be readily

Table 2 Causes of hyperprolactinemia

Pituitary diseases	Drugs
Functioning adenomas	Dopamine receptor antagonists
Non-functioning adenomas	Inhibitors of dopamine synthesis and release
Stalk section	Estrogens
Hypothalmic disease	**Neurogenic**
Tumors	Chest wall/spinal cord lesions/injury
Irradiation	Breast stimulation
Infilitrative disease	Suckling
Inflammation	
Granulomas	**Others**
	Primary hypothyroidism
	Renal failure
	Idiopathic

explained or reversed, it is important to undertake an MRI of the sella, because most patients with macroadenomas, regardless of their cell type, have mild to moderately increased prolactin concentrations (20–200 μg/l) as a result of compression of the pituitary stalk and portal vessels (Arafah *et al*. 1994, Gsponer *et al*. 1999). The latter group of patients will often have variable degrees of hypo-pituitarism.

Once the clinical and biochemical diagnosis is made, remaining pituitary function should be assessed, particularly in patients with macroadenomas. The preferred imaging study is MRI of the sella, which can provide details of the tumor location, size, extent and relation to surrounding structures such as the optic chiasm and cavernous sinuses.

Indications for treatment

Treatment is indicated for all patients with symptoms, particularly those with hypogonadism. Patients with no signs or symptoms related to the tumor or hyperprolactinemia may not require treatment unless their adenoma is large. They should be followed carefully as they are likely to present with symptoms at some point in the future.

Treatment options

Specific treatment depends to a large degree on the size of the tumor, its extent, the patient's preference and the available expertise for the managing physician (Besser 1993, Molitch *et al*. 1997). Generally, the two main therapeutic options include surgical and medical treatments, as will be detailed here. Both options should be presented and discussed with the patient before a decision is made. Although radiation therapy is still an option, it is rarely used in patients with prolactinomas, particularly those with microadenomas. The availability of effective surgical and medical treatments have limited the need for using radiation to patients with large tumors that are resistant to standard treatment.

Treatment of patients with microprolactinomas: surgery versus medical therapy

Most authorities favor medical therapy as the primary treatment of patients with this disorder. Some believe, however, that patients with microadenomas can be successfully treated medically or surgically (Turner *et al*. 1999). It is crucial not to offer surgery as a first-line option except in centers where there has been an established high success rate, given the variability of outcomes reported in the literature (Tyrrell *et al*. 1999). Some experienced centers report an 85–90% cure rate, with less than 10% incidence of post-operative complications, and virtually no hypopituitarism (Arafah *et al*. 1986, Molitch *et al*. 1997). Both surgical and medical options are equally effective in such cases, and the choice between them depends largely on the patient's desire and their tolerance of medications (Besser 1993, Molitch *et al*. 1997). At our institution, we offer both options and favor initial medical therapy. The options are readdressed after 2–3 months of medical therapy to assess compliance, tolerance, and clinical response. The majority of patients choose to continue on medical therapy, but some elect to try the surgical option.

Transsphenoidal resection of the tumor can achieve all the therapeutic goals addressed earlier in the majority of patients, within hours or days (Arafah *et al*. 1986, Feigenbaum *et al*. 1995). In experienced hands, almost 85–90% of patients have immediate normalization of serum prolactin concentrations, followed several weeks later by clinical improvement. The long-term benefit in most such patients with microadenomas is favorable, as recurrences are reported in fewer than 10% at 10 years (Arafah *et al*. 1986). The risk for serious side effects, including that of hypopituitarism, is very small – less than 1% in most experienced centers. In patients with successful outcome, serum prolactin concentrations decrease to very low values immediately after surgery and gradually to low-normal range over weeks. One can use data obtained immediately

post-operatively to predict long-term benefit from surgery, as recurrences are very unlikely in patients who have very low serum prolactin concentrations after surgery (Arafah *et al*. 1986). Historically, surgery was the first choice in late 1970s and early 1980s, until bromocriptine became widely available and was shown to be equally effective in controlling tumor growth in the majority of patients.

As stated earlier, most authorities in the field believe that medical therapy is the primary treatment of choice for patients with newly diagnosed prolactinomas. Thus the vast majority of these patients are now being treated medically using one of three currently available dopamine agonists: bromocriptine, pergolide or cabergoline. These agents are equally effective in their ability to decrease serum prolactin concentrations and shrink tumor sizes although, theoretically, cabergoline is believed to be more effective because it has more D2-receptor specificity and a longer half-life (Abs *et al*. 1998). The three dopamine agonists have different half-lives and, consequently, the frequency of their administration is different: bromocriptine has to be used three to four times daily (5–30 mg/day; average dose 7.5 mg), pergolide can be used once or twice daily (0.05–0.25 mg/day; average dose 0.1 mg), and cabergoline is prescribed twice weekly (0.5–2.0 mg/week). Approximately 80–90% of patients given any of the three dopamine agonists will normalize their serum prolactin concentration over several weeks (Molitch *et al*. 1985, 1997); among these patients, shrinkage of tumor can be noted in about 70% within 3–6 months. The initial rapid shrinkage is attributed to loss of the cells' protein secretory apparatus such as Golgi and vesicles (Webster 1999). In 30–40% of patients, the adenoma can no longer be visualized on imaging studies. Patients with persistent hyperprolactinemia should be given the highest tolerable dose recommended.

Common side effects from all dopamine agonists include: nausea, vomiting, constipation, dizziness, postural hypotension and nasal congestion. These side effects can be minimized by introducing the drug very slowly and mixing it with food.

Duration of treatment in patients with prolactin-secreting pituitary microadenomas is still not clear. We recommend at least 5–6 years of continuous treatment before the therapy can be slowly tapered and discontinued. If, during that period of time, an increase in serum prolactin concentration is observed, the dose can be increased and treatment prolonged.

Treatment of patients with macroprolactinomas

These patients are managed in a manner similar to that of patients with microadenomas. The main difference is that surgery is not as successful in patients with macroadenoma. Even in patients with suprasellar extension and chiasmal compression, dopamine agonist therapy is the primary treatment of choice. Patients should be monitored carefully to ensure tumor regression with medical therapy. Patients

who do not respond within the first 3–4 months should have a surgical procedure to debulk the tumor and alleviate pressure from the optic chiasm. Once there is extension of tumor beyond the confines of the sella, surgical success is less likely and is usually less than 50% (Feigenbaum *et al*. 1995). In experienced hands, complete or near complete adenomectomy, with normalization of the serum prolactin concentration can be achieved in up to 60–70% of patients with intrasellar macroadenoma. Recurrences of 20–50% are likely in this group of patients over a 10-year period (Feigenbaum *et al*. 1995).

With the lower chance for surgical cure, it is not surprising that most authorities utilize dopamine agonist as first-line treatment in patients with prolactin-secreting macroadenomas (Klibanski & Zervas 1991, Molitch *et al*. 1997). Such treatment is effective in normalizing the serum prolactin concentration in approximately 85% of patients, and in shrinking the size of the tumor in approximately 70% of patients. A recent study suggested that of the three dopamine agonists, cabergoline was the most effective in reducing tumor size (Colao *et al*. 2000). Although cabergoline was effective in all patients, it appears to be most effective in those who never received dopamine agonists previously (Colao *et al*. 2000). In most patients, tumor shrinkage occurs over several months, although rapid changes were reported in occasional patients. Duration of treatment with any dopamine agonist remains controversial, but should be at least 5–6 years. Tolerance to dopamine agonists in these patients is similar to that of patients with microadenomas.

Although radiation therapy was commonly used in the past as an alternative treatment, it is now reserved for patients with tumors that cannot be controlled medically or surgically. Only a small number of patients require such treatment. Regardless of the therapeutic choice, patients need to be followed up regularly and for indefinite periods of time. Occasional patients whose tumors are resistant to dopamine agonist and radiation may require several surgical procedures, including transfrontal craniotomy.

It is worth mentioning that tumor growth also occurs in men with prolactinomas after testosterone replacement. The postulated mechanism seems to be via conversion of testosterone to estradiol. This effect is enhanced in the presence of hyperprolactinemia, as prolactin seems to inhibit conversion of testosterone into dihydrotestosterone. In addition, symptoms of hypogonadism are expected to improve in the majority of men with prolactinomas, with therapy. It is therefore recommended to withhold testosterone replacement in men with prolactinomas and hypogonadism until prolactin levels are normalized (Prior *et al*. 1987).

Prolactinoma and pregnancy

A potential area of concern in patients with prolactinoma is pregnancy. It is commonly known that, once serum prolactin

decreases, fertility is restored in men and women within a few weeks. It is important for women to use contraception to avoid pregnancy. Patients interested in becoming pregnant are asked to use mechanical contraception for several months until two or three menstrual cycles are reported. This will help patients recognize the possibility of potential pregnancy once mechanical contraception is discontinued. The rationale for this approach is to minimize the use of dopamine agonists during pregnancy. In addition, it is advisable to switch to bromocriptine from the newer, longer-acting agents during the period of time when mechanical contraception is discontinued until pregnancy. Although not approved by the US Food and Drug Administration for this use, bromocriptine has been used during all stages of pregnancy to suppress compressive symptoms. Bromocriptine crosses the placenta and suppresses pituitary prolactin secretion, but has not been associated with increased fetal abnormalities (Molitch *et al*. 1997). Although other agents such as pergolide and cabergoline have occasionally been used during pregnancy without side effects, the experience with bromocriptine is more extensive, and thus it would be the preferred drug during pregnancy if treatment with dopamine agonists becomes necessary. In the absence of any form of contraception, patients will often become pregnant before menses are resumed.

Because estrogens normally stimulate lactotrophs, it was initially presumed that a prolactinoma might increase in size during pregnancy. This, however, was not found to be a clinically relevant issue in most patients. It is estimated that fewer than 5% of microadenomas might slightly increase in size during pregnancy. The risk is somewhat greater in patients with macroadenomas, especially with suprasellar extension, and is estimated to be 15% (Molitch 1985). Measurement of serum prolactin during pregnancy in these patients is not helpful in identifying those with potential tumor growth. In women who experienced a minimal to moderate decrease in tumor size with initial medical therapy, some authorities utilize a surgical debulking procedure before pregnancy, in order to decrease the chance of tumor expansion during pregnancy. If compressive symptoms develop during pregnancy, and surgery is not recommended, bromocriptine would be an effective agent in such instances (Molitch *et al*. 1997).

GH-secreting adenomas

Clinical manifestations and diagnosis

These tumors account for approximately 20% of all pituitary tumors and present with the clinical syndrome of acromegaly in adults and gigantism in children. The incidence of acromegaly is 3–4 cases per million, with a prevalence of 40–60 cases per million (Lissett *et al*. 1998). There are no known sex, ethnic or racial differences. The peak incidence

is in the fourth or fifth decade of life. The disease is associated with increased mortality and morbidity, and premature death, if left untreated. Patients with acromegaly have increased prevalence of diabetes mellitus, hypertension, cardiovascular and respiratory disorders (Melmed *et al*. 1986, Melmed 1990, Klibanski & Zervas 1991, Teramoto & Ouchi 1997). For these reasons, patients with acromegaly need to be treated effectively once the diagnosis is confirmed.

Although excessive secretion of GH itself can cause significant morbidity, most of the complications and symptoms seen in patients with acromegaly are due to increased production of a GH-dependent factor, known as somatomedin-C or insulin-like growth factor-I (IGF-I). This growth factor (IGF-I) is synthesized in almost all body tissues, but liver secretion accounts for most of its circulating concentration.

The vast majority (>98%) of patients with acromegaly have GH-secreting pituitary adenomas (Melmed 1990). Other rare causes of acromegaly include tumors secreting the hypothalamic releasing factor (GHRH) ectopically (e.g, pancreatic cancer, carcinoid) or eutopically (e.g., hypothalamic hamartoma, pituitary gangliocytoma). Ectopic secretion of GH itself is extremely rare, but has been documented. Tumors secreting GHRH cause diffuse somatotroph hyperplasia and increased release of GH from the pituitary (Sano *et al*. 1988). Regardless of the cause of GH excess, its secretion continues to be episodic, although the amplitude and frequency of pulses are greater than normal. Furthermore, GH responses to stimulation and suppression are altered in patients with acromegaly.

Chronic effects of excessive GH secretion are not only disabling but also disfiguring. Most patients present with 5–10 years history of changes in features, bony overgrowth, soft tissue swelling, skin changes, diabetes mellitus, hypertension and other cardiovascular symptoms. In addition to signs and symptoms of GH excess, some patients present with signs of disordered sleep and hypopituitarism, in addition to headaches and visual symptoms (Furman & Ezzat 1998). Excessive linear growth is the predominant symptom/ sign in prepubertal patients with GH-secreting adenomas. About 30% of patients with such adenomas have hyperprolactinemia as a result of co-secretion of GH and prolactin by the tumor or secondary to compression of the portal vessels. Galactorrhea is seen in many patients with acromegaly, even in those with normal serum prolactin concentrations. In the latter group of patients, galactorrhea is explained by the lactogenic properties of GH. In addition to progressive cosmetic deformities, and disabling degenerative arthritis, patients with acromegaly are at a greater risk for colonic polyps and cancer, particularly colon cancer.

Diagnosis of acromegaly is relatively simple and depends on clinical recognition of patients with signs and symptoms. In these patients, measurement of GH response to a glucose load had been the standard diagnostic test (Arafah

et al. 1987, Klibanski & Zervas 1991, Melmed *et al.* 1998; Giustina *et al.* 2000). Perhaps the simplest, most practical and yet reliable test is the determination of plasma IGF-I concentration. With only few exceptions, increased plasma IGF-I concentrations are biochemically diagnostic of acromegaly. One can use measurement of GH responses to various agents (e.g., thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH)), as supportive evidence for the diagnosis. Even though the latter tests are not necessary for making the diagnosis, responses to these agents are helpful in determining whether surgical treatment was curative (Arafah *et al.* 1987): after complete tumor resection, GH responses to a glucose load, TRH, GnRH and insulin-hypoglycemia become normal (Arafah *et al.* 1987). The production of IGF-I binding protein 3 (IGFBP-3), the main carrier of IGF-I in plasma, is stimulated by GH, and its concentrations are currently being evaluated as an additional parameter in the follow-up of patients with acromegaly. Currently available data indicate that the levels of IGFBP-3 do not correlate well with those of high GH concentrations and, so far, do not appear to provide additional diagnostic or prognostic value (Charalampaki *et al.* 1998, Wass 1997).

Treatment of GH-secreting adenomas

In view of the known complications of GH excess and their adverse influence on cardiovascular morbidity and mortality, treatment of all patients with acromegaly is indicated. The consensus opinion of practically all authorities in the field is that transsphenoidal adenomectomy is the treatment of choice for GH-secreting adenomas. The goals of treatment should be those set earlier for all patients with pituitary tumor, including: normalizing GH-secretion, preserving normal pituitary function and reversing the mechanical effects of the tumor on surrounding structures. These goals can be achieved in approximately 50% of patients with acromegaly after adenomectomy. The main predictors of outcome after surgery include tumor size and location, preoperative GH concentrations, and the expertise of the surgeon (Lissett *et al.* 1998, Melmed *et al.* 1998, Swearingen *et al.* 1998). After complete surgical removal of the tumor, plasma IGF-I and both basal GH concentrations and its responses to dynamic stimulation become normal. Recurrences in these patients are rare with prolonged follow-up (Arafah *et al.* 1987). The most sensitive predictor of outcome after surgery remains a GH concentration within the first week after operation, that is less than 2 μg/l (Valdemarsson *et al.* 2000).

However, normal basal postoperative serum GH and IGF-I are not sufficient criteria for complete resection of the adenoma, as the responses to stimulation and suppression tests have also to be normal. Even though some patients might have normal basal serum GH and IGF-I concentrations post-operatively, those who have persistent abnormalities to

dynamic testing (e.g., oral glucose tolerance test) are at high risk for recurrence within 2–10 years (Arafah *et al.* 1987).

Patients with residual tumor activity post-operatively and those who are poor surgical candidates require additional treatments to control excessive GH secretion. Options include external irradiation and medical treatment. Radiation can be given through the traditional linear accelerator, which has been used over the past two decades (Plowman 1995). Alternatively, radiation can be given stereotactically (Ganz 1995) as one dose (gamma knife) or, more recently, in small fractions (fractional stereotactic irradiation). Traditional external irradiation has been used for decades as a primary form of treatment for acromegaly. In fact, it was only after the safety of transsphenoidal surgery was appreciated that adenomectomy rather than irradiation became the primary form of treatment for acromegaly. Radiation therapy is effective in controlling tumor growth in 70–80% of patients. It is estimated that basal serum GH concentrations decrease to less than 5 μg/l in 75% of patients, 10 years after the traditional irradiation. This assessment took a serum GH concentration of 5 μg/l as being the upper limit of normal; however, it is now well established that such a value is too high and inaccurate, particularly when drawn at random. In fact, most patients whose serum GH concentrations were less than 5 μg/l after irradiation continue to have active acromegaly as indicated by increased plasma IGF-I concentrations (Barkan *et al.* 1988). When one uses 2 μg/l as a cutoff, the success rate after irradiation is 45–65% (Biermasz *et al.* 2000, Powell *et al.* 2000). Currently, most authorities believe that measurements of plasma IGF-I are the best method to assess treatment outcome, including that of irradiation. Recent preliminary data suggest that stereotactic surgery may induce remission in a shorter period of time and might be associated with lower incidence of side effects; however, long-term studies with this new modality are lacking (Powell *et al.* 2000). Hypopituitarism is one of the main long-term complications of radiation therapy. Radiation-induced loss of normal pituitary function usually becomes symptomatic 2–25 years after irradiation. Its onset is very insidious, over months or years. For these reasons, patients should be kept under surveillance indefinitely.

Before the introduction of the somatostatin analogue, octreotide, medical treatment was primarily limited to the use of dopamine agonists such as bromocriptine, pergolide and, more recently, cabergoline. Initial experience using primarily bromocriptine indicated that this drug suppresses GH secretion in 10–15% of patients, and only in a few patients does the level reach normal (Melmed 1990). Recent data using pergolide, however, showed improved efficacy such that plasma IGF-I concentrations are normalized in 20–30% of patients. More impressive results were obtained using the longer-acting dopamine agonist, cabergoline. With this drug, 30–45% of treated patients will have a normal plasma IGF-I concentration and a similar proportion will show a decrease

in tumor size (Abs *et al*. 1998). The dose required to achieve these effects is usually much greater than those required for effective treatment of prolactin-secreting adenomas. Patients whose tumors co-secrete prolactin and those with relatively mild disease are the ones most likely to respond to dopamine agonist therapy.

The introduction of octreotide provided a major advance in the medical treatment of GH-secreting adenomas. Octreotide has a relatively long half-life such that it can be used three to four times daily and, unlike the natural peptide, does not cause rebound hypersecretion when therapy is interrupted (Stewart & James 1999). Effective doses range from 300 to 2000 µg per day, given in three or four divided doses administered subcutaneously. This regimen is associated with a decrease in both serum GH and plasma IGF-I concentrations in 80–90% of treated patients (Barkan *et al*. 1988, Melmed 1990). However, these values become normal in only 50–60% of treated patients. Octreotide therapy is associated with not only a reduction in plasma GH and IGF-I concentrations, but also moderate decreases in tumor size in 30–40% of patients. Most patients tolerate this treatment well, with minimal side effects that include abdominal pain and diarrhea. Chronic therapy is associated with increased prevalence of cholelithiasis, particularly in patients with prior gallbladder disease. Discontinuing therapy is associated with recurrence of excess GH and IGF-I concentrations. For that reason, medical treatment with octreotide should be part of a comprehensive treatment program. Octreotide therapy is often used in conjunction with other forms of treatment for acromegaly, such as irradiation with which the beneficial effects may take several years to show. Although some reports advocate the use of octreotide before operation (Barkan *et al*. 1988), it is not clear whether such treatment affects the outcome.

Long-acting preparations of somatostatin analogues have been introduced over the past few years. These include the long-acting forms of octreotide and lanreotide (Sandostatin-LAR and lanreotide-SR respectively). After repeated intramuscular injection of Sandostatin-LAR, octreotide concentrations remain at therapeutic values for 4–6 weeks (Cozzi *et al*. 1999). A typical dose ranges from 20 to 40 mg every 30 days (equivalent to 750–1250 µg/day of octreotide). Lanreotide-SR is very similar in structure and differs in that the injection dose is fixed (30 mg), but the dosing frequency varies from 7 to 21 days. The efficacy of both seems equivalent, and also comparable to that of octreotide. The side effects of diarrhea and abdominal pain are described less frequently, but the incidence of asymptomatic cholelithiasis appears to be similar, at 20% (Cozzi *et al*. 1999, Davies *et al*. 1998).

Because there are failures of treatment with somatostatin analogues, there is a surge of interest in alternate therapies such as GH receptor antagonism. The available agent under study is pegvisomant, which is a 191 aa recombinant protein with two binding sites. The first binding site is identical to GH, ensuring receptor competitive (reversible) binding. The second site differs from GH, therefore not allowing the formation of an active receptor–dimer complex with GH, which is essential for signal transduction in forming IGF-I (Parkinson & Trainer 1999).

Preliminary data provided in a randomized double-blind multicenter trial comparing pegvisomant with placebo among 112 patients with acromegaly was recently reported by Trainer *et al*. (2000). Pegvisomant was administered at 10 mg, 15 mg or 20 mg, per day in patients with active acromegaly and a plasma IGF-I concentration more than 1.3 times normal. At the end of a 12–week trial period, there was normalization of IGF-I in 89% of the 20 mg treatment group, compared with 10% in the placebo group. GH concentrations increased from a mean of 8.1 to 21.7 µg/l in the 20 mg group, whereas it remained at the same baseline in the placebo group. There were no reports of tumor expansion. There was one incident of asymptomatic increase in transaminases. These results appear promising, and may stimulate phase 4 and long-term trials in which the chronic efficacy of pegvisomant could be compared with that of somatostatin analogues, and in which the effect on tumor size is further assessed.

To summarize, acromegaly is not only a disfiguring disease, but is also associated with increased morbidity and mortality if left untreated. Every attempt should be made to normalize serum GH and IGF-I concentrations. Surgical adenomectomy is the best primary treatment for patients with GH-secreting adenomas. Such treatment is likely to be curative in only 50% of the patients. Those with residual tumors and others who are poor surgical candidates should be treated medically, with or without radiation therapy. Medical therapy could include a dopamine agonist, an octreotide derivative, or both. The introduction of the GH-receptor antagonist, pegvisomant, has introduced a new dimension to the management of such patients. The goal with all of the above-mentioned therapies should be to normalize plasma IGF-I concentrations.

Corticotropin-secreting pituitary adenomas

Clinical manifestations and diagnosis

These tumors represent approximately 10–12% of all pituitary adenomas and are seen predominantly in women, with a female to male ratio of 8:1 and a peak incidence in the third to fourth decades of life (Mindermann & Wilson. 1994, Tsigos *et al*. 1995). ACTH-secreting pituitary adenomas represent the most common cause of endogenous hypercortisolism, accounting for approximately 65–70% of all cases of Cushing's syndrome. Although such tumors are generally benign, they are more invasive than most other pituitary adenomas. Cushing's syndrome refers to a state of

hypercortisolism (endogenous or exogenous) regardless of its etiology. However, Cushing's disease is a state of hypercortisolism caused by excess pituitary secretion of ACTH. Virtually, and only with an occasional exception, all patients with Cushing's disease have an associated ACTH-secreting adenoma. An occasional patient may have corticotroph cell hyperplasia as a result of ectopic secretion of corticotropin-releasing hormone (CRH) from a carcinoid or a malignant tumor.

The clinical manifestations of ACTH-secreting adenomas include predominantly symptoms and signs caused by excess ACTH secretions and the resulting increased glucocorticoid production. Although most of these tumors are small at diagnosis, some are invasive and others are large, so that patients may present with headaches and visual disturbances. Occasionally, pituitary tumor apoplexy might be the first manifestation of the disease in patients with large adenomas. Symptoms and signs of hypercortisolism include central obesity, easy bruisability, proximal myopathy, striae, hypertension, hirsutism, menstrual irregularity, mood changes, increased supraclavicular and dorso–cervical fat pads, poor wound healing, osteoporosis and hyperglycemia. Hypokalemia is seen in 20–25% of patients with Cushing's disease.

Diagnosis of Cushing's disease is often relatively easy, once the clinical picture is suspected. However, on many occasions, and despite many recent advances, difficulties in the diagnosis of Cushing's disease still exist. Initial screening of suspected patients can be achieved by either the overnight 1-mg dexamethasone suppression test or a 24-h urinary free cortisol measurement. Pitfalls in initial screening tests remain in distinguishing Cushing's from pseudoCushing's states. Entities such as major depression, alcohol withdrawal, and uncontrolled diabetes mellitus are associated with high cortisol levels, which limits the diagnostic accuracy of the above tests to about 70% (Papanicolaou *et al*. 1998). Although somewhat impractical to perform routinely, a midnight serum or salivary cortisol level greater than 7.5 µg/dl was reported to have improved the specificity and the sensitivity of the test, as the circadian rhythm of cortisol secretion is maintained in pseudoCushing's (Papanicolaou *et al*. 1998, Raff *et al*. 1998). The best additional test to confirm the diagnosis of true hypercortisolism and to differentiate patients with Cushing's syndrome from those with pseudoCushing's disease, is the combined CRH-dexamethasone test (Yanovski *et al*. 1993). Patients are given dexamethasone (0.5 mg orally every 6 h) for 24 h followed by CRH administered as an intravenous bolus. A serum cortisol concentration greater than 1.4 µg/dl obtained 15 min after CRH is diagnostic of Cushing's syndrome. The rationale behind this test is that the hypercortisolism in pseudoCushing's is due to increased stimulation of CRH-secreting neurons. As the hypothalamo–pituitary–

adrenal axis is otherwise 'normal' in patients with pseudoCushing's, and unlike that in patients with true Cushing's syndrome, CRH stimulation cannot overcome the suppressive effects of large doses of dexamethasone (Yanovski *et al*. 1993). To determine the etiology of hypercortisolism, one will need to measure plasma ACTH and perform a high-dose dexamethasone suppression test (Orth 1995). A plasma ACTH concentration greater than 10 ng/l indicates an ACTH-dependent process and eliminates primary adrenal disease. Differentiating an ACTH-secreting pituitary adenoma from ectopic ACTH secretion can be very difficult and relies on the data obtained from the dexamethasone suppression test and the degree of increase in plasma ACTH concentrations, in addition to the response to other agents such as CRH and metyrapone (Orth 1995). It is important to emphasize that none of these tests provides 100% specificity or sensitivity.

Imaging studies of the pituitary (MRI) have a sensitivity of 60–70% in detecting abnormalities and may yield false-positive results. In most patients, the diagnosis can be made once data from clinical, biochemical and imaging studies are analyzed collectively. Some centers with experience in petrosal sinus catheterization use that approach for confirmation of diagnosis. The latter is an invasive procedure with potentially significant risk of complications (bleed, thrombosis). As the diagnostic yield increases significantly to nearly 100% at experienced centers, this approach remains useful in patients with negative imaging studies, when performed by an experienced radiologist (Findling & Raff 1999). Additional imaging studies such as a computed tomography scan of the chest and octreotide scan can be done to look for ectopic ACTH secretion when this is suspected.

Primary treatment of ACTH-secreting adenomas

One of the initial requirements for optimal therapy is making the correct diagnosis (Arafah & Pearson 1985, Tyrrell & Wilson 1994). The presence of a pituitary adenoma in a patient with hypercortisolism does not necessarily indicate that the tumor is the source of Cushing's syndrome. Confirming the diagnosis will require analyzing the clinical, biochemical and imaging studies, and histopathologic documentation of ACTH secretion by the tumor. Patients with Cushing's syndrome require particular attention to details at all times.

Transsphenoidal adenomectomy is the treatment of choice for patients with ACTH-secreting pituitary adenoma (Arafah & Pearson 1985, Klibanski & Zervas 1991, Tyrrell & Wilson 1994, Tsigos *et al*. 1995). It is a very effective and safe approach that results in rapid biochemical and, subsequently, clinical responses. Selective removal of the adenoma results in immediate development of ACTH deficiency that lasts 6–24 months. At surgery, most centers

treat patients with exogenous steroids during and continuously after operation and assess the response to surgery a few days to weeks later. At our institution, patients undergoing transsphenoidal surgical removal of ACTH-secreting adenomas are not given steroids during or immediately after surgery (Arafah & Pearson 1985). Instead, they are monitored carefully with measurements of plasma ACTH and cortisol concentrations twice daily. Once patients show symptoms of adrenal insufficiency (usually 24–48 h) or have documentation of low serum cortisol concentrations (<3 µg/dl; 85 nmol/l), exogenous steroids are administered. We use hydrocortisone in three divided doses totaling 60 mg/day during the first 2 weeks, 40 mg during the second 2 weeks and 25–40 mg during the next 4–6 months (Arafah & Pearson 1985). The dose can then be tapered as clinically tolerated. Measurement of plasma cortisol concentrations after 24 h of withholding therapy can be very helpful in guiding steroid taper. Cortisol responses to tetracosactrin and insulin-hypoglycemia can also be used to document recovery of adrenal responsiveness.

Most patients (80–85%) with pituitary-dependent Cushing's disease have microadenomas that can be selectively removed. In some, the adenoma might not be apparent at the time of surgery. In such patients, and depending on the surgical findings and preoperative studies, one may have to perform a hemihypophysectomy, particularly in patients who exhibited lateralization on inferior petrosal sinus sampling. With the morbidity and mortality associated with Cushing's disease, every attempt should be made to control this illness. Therefore, one needs to balance the known morbidity from this disease with the potential risk from the treatment chosen. In approximately 15–20% of patients with Cushing's disease, the tumor is large and extends beyond the sella turcica. This will limit the chance for complete resection and will often indicate need for additional treatments to control hypercortisolism and tumor growth.

Radiation therapy is a second form of treatment for ACTH-secreting adenomas (Arafah & Pearson 1985, Tsigos *et al*. 1995, Plowman 1995). Before the refinement of transsphenoidal adenomectomy, radiation was the only treatment offered to control tumor growth. In those instances, patients were given radiation to control the tumor and had bilateral adrenalectomies to eliminate the state of hypercortisolism. Currently, radiation therapy is reserved for patients with persistent ACTH hypersecretion after pituitary surgery. The response to treatment is often delayed for months or years. Such treatment is associated with the known side effects of irradiation, including the development of hypopituitarism. As discussed earlier, stereotactic radiosurgery is being used more frequently than the traditional irradiation. Since the effects of radiation are delayed, other treatments should be offered to control the

state of hypercortisolism. In the past, surgical adrenalectomy was the main treatment in such patients. However, with the introduction of newer pharmacologic agents, medical therapy became the main treatment in such patients.

Medical therapy

Several pharmacologic approaches are used in the adjunctive therapy of patients with hypercortisolism (Arafah & Pearson 1985, Tsigos *et al*. 1995). Drugs that inhibit adrenal cortisol secretion include ketoconazole, which is known to inhibit cytochrome P450 enzymes involved in steroid synthesis. In doses of 600–1200 mg/day, ketoconazole is relatively effective in controlling hypercortisolism. Its effects are reversible once the drug is discontinued. Hence, medical therapy is provided to supplement other forms of treatments such as irradiation.

Other drugs used to control hypercortisolism include aminoglutathemide and metyrapone. Both agents are also used as adjunctive treatments and are more expensive, less effective and have more side effects than ketoconazole. Another agent used occasionally in patients with Cushing's disease is mitotane (Lysodren or *o,p*-DDD). This agent results in adrenal atrophy and is used predominantly in patients with adrenal carcinoma. It has significant side effects that would limit its routine use in patients with Cushing's disease. Despite initial favorable reports, medical treatment of excessive secretion of ACTH with cyproheptadine, a serotonin and histamine antagonist, or with the dopamine agonist, bromocriptine, have been disappointing and rarely, if ever, effective.

Octreotide is not effective in the medical management of Cushing's disease caused by ACTH-secreting pituitary adenomas. However, it is reported to be very effective in the treatment of ectopic ACTH secretion by carcinoid tumors and in patients with food-dependent or gastric inhibitory peptide-mediated hypercortisolism (Lacroix *et al*. 1992, Herder & Lamberts 1999).

Nelson's syndrome

This syndrome is seen in patients with Cushing's disease who were previously treated with bilateral adrenalectomies to control the state of hypercortisolism. Removal of the source of hypercortisolism leads to further increases in plasma ACTH concentrations from previously known, or at times unrecognized, ACTH-secreting pituitary adenomas. Studies showed that pituitary irradiation after bilateral adrenalectomies does not necessarily prevent the development of Nelson's syndrome. The clinical manifestations of Nelson's syndrome include hyperpigmentation, in addition to signs and symptoms related to the growth of the tumor (i.e. headaches and visual symptoms). Such tumors can be very invasive, extending into surrounding structures such as

cavernous sinuses. Apoplexy can also be one of the presentations of such tumors.

Gonadotroph pituitary adenomas

Only a few years ago, approximately 20–25% of all pituitary adenomas were considered non-functioning or non-secreting. However, recent studies using more sensitive techniques showed that the majority of these tumors, previously labeled as non-functional, were indeed secreting follicle-stimulating hormone (FSH) or luteinizing hormone (LH), or both, or their respective alpha and beta subunits. However, hormone secretion by these tumors is minimal or inefficient and the clinical behavior is that of an inactive tumor (Samuels & Ridgway 1995, Snyder 1995). Gonadotroph adenomas account for 10–15% of all pituitary adenomas, whereas 5–10% of all tumors are truly non-functional and are referred to as null-cell adenomas (Table 1).

Gonadotroph adenomas encompass broad clinical and pathologic features that depend on the investigational techniques used. When studied *in vivo*, these adenomas are identified on the basis of hypersecretion of FSH, LH, the alpha subunit (aSU) or the beta subunit (bSU), in the basal state or after dynamic stimulation with TRH. *In vitro* studies performed on surgically resected tumor tissue (immunocytochemistry, cell culture or northern blot analysis) have allowed the broader characterization of these adenomas such that some tumors had positive staining but no measurable hormone secretion. From a practical standpoint, we feel that the most reasonable criterion for defining gonadotroph adenomas would be one that is based on immunocytochemical studies performed on resected tumor tissues. Such a criterion will therefore include tumors that are silent, in addition to those secreting gonadotropins.

Clinical and biochemical characteristics and diagnosis

By the time most of these tumors are clinically recognized, they are large (>10 mm) and often have extension beyond the sella tursica. Only an occasional patient can be diagnosed with a small (<10 mm) gonadotroph adenoma. The most common clinical presentation has been related to the mechanical effects of the expanding macroadenoma. These manifestations include visual complaints (diminished vision, visual field deficits and alterations in eye motility), headaches and hypopituitarism. As these tumors are very inefficient in hormone secretion, symptoms of excessive hormone secretion are rare and are seen in occasional patients with increased LH production. Male patients with these features present with increased serum testosterone concentrations and increased libido. Similarly, the occasional woman with LH hypersecretion can present with ovarian hyperstimulation syndrome, including supranormal estradiol concentrations, multiple ovarian cysts and endometrial hyperplasia.

However, as a result of the large size of these tumors, most patients present with various signs and symptoms of hypopituitarism.

As stated earlier, and for unknown reasons, gonadotroph adenomas are generally inefficient in hormone secretion. Furthermore, their secretory characteristics vary from one tumor to another. Recent studies suggest that only 30–40% of patients with gonadotroph adenomas, as documented on immunocytochemical staining of resected tissue, have increased serum concentrations of the common aSU or either of the pituitary gonadotropins. In addition to direct measurements of serum aSU concentrations, determination of the molar ratio of aSU to FSH and LH has been recommended as an additional marker in the diagnosis of gonadotroph adenomas. This would be particularly valuable in postmenopausal women who normally have a ratio that ranges from 1.4 to 3.3. Secretion of FSH, LH, or both, is also increased in such tumors. On the basis of these findings, it was advocated that FSH might be a more specific, though less sensitive, marker of gonadotroph adenomas. Additional studies have shown that the increase in aSU of LH after TRH stimulation was a specific and a frequent finding in men and women with gonadotroph adenoma. Published reports indicate that the increase in aSU concentration can be used as a diagnostic tool with which to identify patients with gonadotroph adenomas with normal basal hormone concentrations (Daneshdoost *et al.* 1991, Snyder 1995).

Given the limitations of available *in vivo* and *in vitro* testing, and the discrepancies seen in the results from different studies, it is recommended that the basal serum hormone concentrations of intact FSH, intact LH and aSU be measured. If specific assays are available for the aSU, then FSH and LH should be determined before operation in any patient with clinically non-functioning pituitary adenoma. More than 10% of the cells of resected adenoma tissue should stain positively for intact FSH, LH or the aSU, or combinations thereof. Tumors that demonstrate isolated aSU immunostaining would be classified as gonadotroph adenomas when appropriate morphologic characteristics are demonstrated at the ultrastructural level. The accurate classification of non-functioning adenomas as gonadotroph tumors is necessary, as this might affect future medical treatments of recurrent or residual tumors.

Treatment of gonadotroph adenomas

Surgical adenomectomy

The primary treatment for gonadotroph adenomas is transsphenoidal surgical adenomectomy. The effectiveness of this approach has been discussed in a previous section (see Management of pituitary tumors: an overview).

Radiation therapy

In patients with gonadotroph tumors, radiation therapy can be used in patients whose adenomas could not be removed

completely at surgery, or those with recurrent tumors that are not compressing the optic chiasm. It is not common practice to use adjuvant irradiation in completely resected tumors. The rationale for the latter is that recurrence from these tumors is infrequent (5–25%), indolent, and can be controlled with irradiation at the time of recurrence (Lillehei *et al*. 1998). The effectiveness and the side effects of radiation therapy are the same in gonadotroph adenomas as those discussed previously (see Management of pituitary tumors: an overview).

Medical therapy of gonadotroph adenomas

Currently, there is no standard medical therapy for gonadotroph adenomas. Most published data are based on case reports and anecdotal experiences. Dopamine agonists can suppress the release of gonadotropins and their subunits from the majority of gonadotroph tumors, both *in vivo* and *in vitro*. Suppression of the secretory activity of the adenoma is, occasionally, accompanied by improvement in visual field defects or tumor shrinkage. Dopamine agonist therapy should be attempted when surgical resection is incomplete. The optimal dose of dopamine agonist (e.g. bromocriptine), is unknown but 10–15 mg/day bromocriptine seems reasonable. Treatment should continue as long as it is shown to be effective or until the benefits of other therapeutic modalities used simultaneously (e.g. radiation therapy) are appreciated.

Therapy with GnRH agonists has, in general, been disappointing. The GnRH antagonist (Nal-Glu) was effective in normalizing FSH levels, but not in reducing tumor size when tried over a 3–12 month period. The discordant effects of the drug on tumor growth and serum hormone concentrations were postulated to be caused by the presence of factors other than GnRH controlling tumor growth (McGrath *et al*. 1993).

Another potential approach in the medical treatment of these patients is the use of octreotide, which has been demonstrated to inhibit gonadotropin or aSU secretion both *in vivo* and *in vitro*. Its influence on tumor growth appears to be less predictable and less common as minimal reductions in size were reported in fewer than 10–15% of treated patients. Until more experience is acquired using large numbers of patients, octreotide cannot be recommended for routine use (Shomali & Katznelson 1999).

In summary, at present, there is no effective medical treatment for gonadotroph-secreting tumors, and thus the management does not differ from null-cell adenomas.

Thyrotropin (TSH)-secreting pituitary adenomas

Clinical and biochemical characteristics

These tumors are not common, accounting for approximately 1% of all pituitary adenomas. Although their clinical manifestations have probably not changed over the years, TSH-secreting tumors have become recognized more frequently over the past decade. The prevalence is slightly more in females than in males, with a relative ratio of 1.7:1. Despite the absence of any clinical signs or symptoms of excessive GH secretion, some of these tumors stain positively for GH, in addition to TSH. More than 80% of these tumors secrete aSU in excessive amounts (Oppenheim *et al*. 1990), thus giving an aSU/TSH molar ratio greater than 1; this can be used in confirming the diagnosis and in follow-up evaluation after surgery. The concentrations of TSH are often 'normal', although they are inappropriately high for the circulating concentrations of thyroid hormones (Gesundheit *et al*. 1989). Stimulation with TRH can be used also for confirming the diagnosis and for follow-up studies after surgery. Patients with TSH-secreting adenomas fail to increase their TSH concentrations after TRH administration.

The main disease to be considered in the differential diagnosis of TSH-secreting adenomas is thyroid hormone resistance. Patients with the latter disorder are clinically euthyroid or mildly hypothyroid and have high normal or clearly high thyroid hormone concentrations associated with 'normal' or mildly increased TSH concentrations. In contrast, patients with TSH-secreting adenomas often have a goiter and mild evidence of hyperthyroidism, without other clinical signs of Graves' disease. By the time these tumors are diagnosed, they are often large, and many have extrasellar extension. Such patients have variable signs of hypopituitarism and often present with symptoms of mechanical compression such as headaches and visual field compromise. Imaging studies such as MRI scan can define the anatomic changes and relationship to surrounding structures.

Treatment of TSH-secreting adenomas

The best treatment for these tumors is surgical resection, preferably through the transsphenoidal approach. Complete removal of such adenomas results in rapid improvement of all symptoms and reversal of the biochemical features and maintenance of normal pituitary function. Although these objectives can be achieved in some patients, many will continue to have persistent disease after operation, as most TSH-secreting adenomas are large at the time of diagnosis. In such cases, additional forms of treatment should be offered, some of which can be targeted towards the tumor itself (radiation or medical therapy, or both), whereas others are used to treat the state of hyperthyroidism. The latter can include either radioactive iodine therapy or antithyroid drugs; they can provide symptomatic relief from hyperthyroidism, but they do not suppress, and can in fact result in further increase in, tumor activity.

Treatment of persistent TSH hypersecretion is primarily medical or using irradiation. As discussed earlier, radiation therapy takes many years to achieve benefit and is associated

with side effects, particularly hypopituitarism. Octreotide treatment, whether a short-acting or long-acting preparation, is very effective in controlling excessive secretion of TSH in 80–90% of patients (Comi *et al.* 1989, Chanson *et al.* 1993, Caron *et al.* 2001). Such treatment has modest effects on tumor growth, in approximately 30% of patients. Octreotide treatment decreases TSH concentrations and consequently results in decreasing thyroid hormone concentrations to normal. Treatment can be used as long as it is effective, and should be part of an overall management plan. In that respect, octreotide therapy can, at times, be used to prepare patients before surgery and, on other occasions, treat others who were given irradiation after unsuccessful surgery. Dopamine agonists can also be effective in treating patients with persistent excessive TSH secretion (Sriwatanakul *et al.* 1984). The doses required are high and the response rate to such treatment is less than that of octreotide.

Null-cell adenomas and tumors discovered incidentally

These tumors often present with mechanical effects of the adenoma (e.g. headaches, visual symptoms) and variable degrees of hypopituitarism. The treatment for all these tumors is surgical resection. In patients in whom surgery is not possible, or not complete, radiation therapy is recommended. There is no role for medical therapy (Freda & Wardlaw 1999).

Intrasellar masses that are discovered on imaging for other causes are not infrequent, as microadenomas are found in 10% of autopsies (Nishizawa *et al.* 1998). The differential diagnosis for a non-pituitary mass includes cysts, craniopharyngioma, hypothalamic glioma, parasellar meningioma, and metastatic disease, usually from the breast, prostate, gastrointestinal tract, kidney, lung or melanoma. The differential can be narrowed in most cases, on the basis of clinical and radiological findings. Expansion on this topic is beyond the scope of this paper and the only additional point to make is that diabetes insipidus is an unusual presentation for an adenoma, and should prompt a search for another etiology (Freda & Post 1999). Once a pituitary tumor is suspected, one should evaluate for hormonal hypersecretion with a screening for prolactin and for any hormone suspected on clinical examination (King *et al.* 1997). LH, FSH, and aSU may be measured, but the menopausal status in women should be kept in mind. If there were evidence of hypersecretion, management would be according to that of the specific tumor type. Otherwise, no further evaluation needs be done for microadenomas, and the tumor may be followed by yearly MRI.

Patients with a newly discovered macroadenoma need assessment of visual fields and evaluation of normal pituitary function. We recommend tests that include serum concentrations of prolactin, cortisol, dihydroepiandrosterone

sulphate, free thyroxine, FSH, LH, total and free testosterone (for men) and estradiol (for women). Screening for growth hormone deficiency using insulin-induced hypoglycemia has not been routinely implemented, although it should be considered in symptomatic patients.

In the absence of mechanical compression or hypopituitarism, the management of such tumors should be individualized, as there is no consensus on this issue. Recent data demonstrating that approximately 20% of these tumors followed prospectively either progress or have other complications such as apoplexy, would favor surgical resection as the initial management (Nishizawa *et al.* 1998, Gsponer *et al.* 1999). An alternative approach would be observation with periodic MRI scans. Once growth is documented, surgery should be considered, depending on the patient's general health status and anxiety level, and the extent to which the managing team are comfortable with such a strategy.

Hypopituitarism in patients with pituitary tumors

Pathogenesis and clinical characteristics

Hypopituitarism is a clinical disorder characterized by diminished secretion of some (partial hypopituitarism) or all of the hormones secreted by the anterior pituitary (panhypopituitarism). In most instances, loss of pituitary hormone secretion is a slow and progressive process, occurring over months or years and involving more than one axis (Arafah *et al.* 1995, Vance 1994). Initial clinical manifestations are often vague and non-specific, leading to further delay in diagnosis.

It is important to point out that hypopituitarism is not an all-or-none phenomenon, but represents a continuous spectrum ranging from a mild deficiency of one hormone to a total loss of secretion of all hormones (panhypopituitarism). The severity of the symptoms often depends upon the hormone deficit involved, in addition to the degree and duration of the impairment. Occasionally, hypopituitarism develops acutely, leading to rapid onset of symptoms as is often seen in patients with pituitary tumor apoplexy (Arafah *et al.* 1997).

Considering the physiology of the normal secretion of pituitary hormones and their dependence on hypothalamic regulation, at least three different mechanisms can lead to the development of hypopituitarism. The mechanisms include:

1) Diminished release or secretion (or both) of hypothalamic hormone(s).

2) Interruption of the delivery of hypothalamic hormones to the pituitary.

3) Loss or destruction of pituitary cells as a result of ischemia or necrosis.

Although there are specific examples that apply to each

of these three mechanisms, it is important to point out that, in most patients, more than one mechanism contributes to the development of hypopituitarism. In each instance, there is often a predominant mechanism that dictates not only the degree of impairment but also whether the process is potentially reversible.

The reported improvement in pituitary function in patients with hypopituitarism after selective adenomectomy has provided an insight into the pathophysiology of impaired function in these patients (Arafah *et al.* 1994). On the basis of detailed dynamic testing data in patients with hypopituitarism, we postulated that the hypopituitarism associated with large pituitary tumors was primarily caused by interruption and compression of the portal vessels and the pituitary stalk by the expanding adenoma. Recent studies demonstrate that tumor growth within the sella resulted in increased tissue pressure that can reach levels as high as 60 mmHg (Arafah *et al*. 2000). Furthermore, studies have demonstrated that the increased intrasellar pressure correlated positively with the increase in serum prolactin concentrations. The findings of increased intrasellar pressure in patients with hypopituitarism and the positive correlation with serum prolactin concentrations in these patients suggested that increased intrasellar pressure has a predominant role in the pathogenesis of hypopituitarism in patients with pituitary adenomas (Arafah *et al*. 2000). An additional factor contributing to pituitary failure in this setting, could be the development of ischemia, necrosis, or both, in the normal gland. As the pituitary gland cannot regenerate, recovery of pituitary function would not be expected in the latter instance, even though the pressure on the portal vessels was relieved. Thus, depending on the presence of viable pituitary tissue, recovery of pituitary function might occur after selective adenomectomy.

Management

Patients' education about their disease is an important aspect in the management of hypopituitarism that is often overlooked. Patients should understand the impact of hormone deficit on their daily lives and activities, and to be fully aware that treatment may need to be modified in the event of intercurrent illnesses, accidents or surgical procedures. A medic-alert bracelet or necklace, identifying the patient as hypopituitary and receiving glucocorticoids, should be always worn.

Treatment of hypopituitarism should not be rigid but, instead, always individualized. Management should take into consideration the patient's age, sex, work schedule, education, original disease process and clinical history. Either hydrocortisone (cortisol) or cortisone acetate in two or, preferably, three divided doses totaling 15–25 mg of the former steroid, represent the usual glucocorticoid replacement therapy. The goal is to provide the least amount of glucocorticoid necessary to control symptoms. Although prednisone (at 4–7.5 mg/day in two divided doses) can also be used as a form of replacement therapy, dose titration is easier with hydrocortisone. The dose is titrated individually using primarily clinical symptoms as a guide. Although hyponatremia is seen at times in patients with ACTH deficiency, mineralocorticoid replacement is rarely, if ever, necessary in patients with hypopituitarism, as the function of adrenal zona glomerulosa is almost always maintained. L-Thyroxine treatment is the preferred replacement therapy in patients with TSH deficiency. Measurement of thyroid hormone concentrations is helpful in determining the optimal dose of L-thyroxine, but physicians should rely primarily on clinical symptoms to determine the optimal dose.

Treatment of hypogonadism in postpubertal adults can be achieved by giving gonadal steroid replacement in the form of oral or transdermal estrogen/progestin to women and parenteral or transdermal testosterone to men. Parenteral testosterone treatment in men is often supraphysiologic when given in the currently used doses of 200–300 mg every 2–3 weeks. Frequently overlooked complications of testosterone treatment include hyperlipidemia, fluid retention, excessive snoring, polycythemia, prostatism and progression of previously unrecognized prostate cancer. Every effort should therefore be made to provide the lowest possible dose. In our experience, in most men replacement therapy with 100–175 mg testosterone enanthate or cypionate intramuscularly every 2 weeks is adequate. Newly introduced testosterone skin patches have been reported to provide a stable and physiologic serum concentration throughout the day. This approach in testosterone replacement has fewer reported side effects (Behre *et al*. 1999). The use of a skin patch is limited by local irritation, which can be clinically significant in 10–15% of patients. A newly introduced form of androgen replacement, the testosterone gel, is absorbed more rapidly into the skin (stratum corneum), which serves as a reservoir. When 50–100 mg are used daily, concentrations reach steady state in the mid to upper range of normal (Swerdloff *et al*. 2000). Long-term studies of this form of replacement are lacking. Fertility can be restored, at least transiently, in many patients with hypothalamic hormone deficiency using exogenous gonadotropin injections or the pulsatile administration of GnRH through a portable pump.

Treatment of GH deficiency is essential in children with documented deficiency. There is extensive experience in treating children with GH deficiency, but data on the benefits of such therapy in adults are becoming available now. In a recent review, patients with GH deficiency had increased body fat, decreased skeletal and cardiac muscle mass and strength, lower bone density, decreased energy and feelings of social isolation (Shahi *et al*. 1992, Vance & Mauras 1999). Treatment with GH at a dose of 6–26 µg /kg per day resulted, within 1 year, in an increase in lean body mass, a decrease in fat and an increase in basal metabolic rate. Interestingly,

an improved sense of well-being was observed among adults with adult-onset GH deficiency, but not in those in whom onset was in childhood (DeBoer *et al*. 1995, Vance & Mauras 1999).

Long-term effects on bone density and cardiovascular morbidity and mortality continue to be evaluated. Associated side-effects are dose-related and include glucose intolerance and arthralgia. There is a theoretical risk for tumor recurrence with GH treatment, this however, has not been observed in the studies to date. Although there is no general consensus on the necessity of GH administration in adults, most pituitary endocrinologists are in favor of replacement. The latter should include careful monitoring of side-effects, at a starting dose of 3–4 µg/kg per day with monthly adjustments, for a target IGF-I concentration within the mid-normal range.

Central diabetes insipidus, caused by partial or complete anti-diuretic hormone deficiency, is uncommon in patients with pituitary adenomas. It is most often a complication of surgery and occurs in about 5–15% of patients after operation (Gsponer *et al*. 1999). It is most often transient, but becomes permanent in about 1% of subjects. In either case, the goal of treatment for diabetes insipidus is to correct the free water deficit and to reduce the urinary water loss (Singer *et al*. 1997). In patients with partial diabetes insipidus who have an intact thirst mechanism, free access to water may be the only treatment needed. However, when the polyuria is disruptive to daily life, or when the ability to drink freely is interrupted somehow, pharmacologic therapy is an available option. Although several antidiuretic hormone analogues have been developed over the past few years 1-deamino-8-D-arginine-vasopressin (DDAVP) is the principal agent used, because of its longer half-life and reliable bioavailability (Singer *et al*. 1997). It is administered intranasally, orally, or parenterally. The aqueous intranasal solution and the oral form are most often used chronically. A typical intranasal dose is 10 µg, delivered in a 0.1 ml solution, once or twice daily. Oral doses are 20- to 40-fold higher. Post-operatively, because of the presence of intranasal packs, subcutaneous or intravenous DDAVP is administered, at a dose of 2 µg. The effect is seen within 1 h usually, and this dose can be repeated as needed (Singer *et al*. 1997). Untreated patients with hypopituitarism can survive for many years with their disease. Survival of untreated patients will depend to a large degree on the severity of the hormonal deficit, the axis involved, the etiology of the hypopituitarism, and other concurrent illnesses. Untreated patients with hypopituitarism have increased morbidity and mortality. Such patients may remain compensated until some stress, trauma, prolonged cold exposure, infection or medications precipitate an acute life-threatening decompensation.

Even with treatment, hypopituitarism can be a major health problem. Patients with this disorder require indefinite and often close medical attention. This is especially true for patients with ACTH deficiency, who require monitoring and adjustment of glucocorticoid doses with any intercurrent illnesses, stresses, surgical procedures and trauma. Despite clinically adequate gonadal, thyroid and glucocorticoid replacement therapy, several studies have suggested that hypopituitary patients have increased cardiovascular morbidity and mortality. A recent report implicated myocardial dysfunction in treated adult hypopituitary patients as a possible explanation for increased cardiovascular mortality (Shahi *et al*. 1992). In some studies, the persistence of GH deficiency in hypopituitary patients was suggested as a possible contributing factor for the increased cardiovascular mortality in these patients. There are no additional studies examining the influence of GH deficiency or treatment on cardiovascular morbidity and mortality. Currently available data do not provide adequate explanation for the cause of increased morbidity or mortality in these patients. One should attempt to provide optimal replacement therapy that is as close to being physiologic as humanly possible. It is also important always to think about the potential reversibility of hypopituitarism in many patients, who can be spared life-long replacement therapy.

Summary and conclusions

Pituitary tumors are no longer considered a medical curiosity but, rather, a commonly encountered disease in the population. Many recent advances in biochemical testing, immunocytochemical staining, imaging and treatments have improved our understanding of the natural history of these adenomas and their management. Available treatment options include surgical, medical and radiation therapy. Primary therapy for each tumor type may vary, but it is important to consider all available options and select the most applicable for that patient. The interaction of all members of the management team, including the primary care provider, the endocrinologist and the neurosurgeon, in selecting the treatment course can only improve patients' management. Regardless of the initial choice of therapy, follow-up of all patients should be maintained indefinitely. The managing physician should be familiar with the natural history and long-term complications of pituitary adenomas, and the side effects of treatments given over the years.

Acknowledgements

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