Pituitary Tumors

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Pituitary tumors comprise approximately 10 percent of all intracranial tumors. They may cause a remarkable variety of symptoms due either to hormone secretion by the tumor itself, or to compression and compromise of the adjacent normal pituitary and neural tissues. In this review, we will consider the clinical problems caused by pituitary tumors and their treatment. The various consequences of these neoplasms can best be understood in the context of the normal anatomy and physiology of the pituitary gland.

NORMAL PITUITARY STRUCTURE AND FUNCTION

Normal Anatomy
In man, the pituitary gland is essentially composed of two lobes, anterior and posterior, and a stalk composed of neural and vascular elements, which connect the gland with the hypothalamus. The anterior lobe arises in embryonic life as an evagination from ectodermal tissue in the roof of the oral cavity, known as Rathke’s pouch.1,2 These cells migrate upward and surround the anterolateral surfaces of the posterior lobe and the stalk, which have arisen as a down-pocketing from the floor of the third ventricle. The anterior lobe contains cells involved in the synthesis and secretion of a variety of polypeptide and glycoprotein hormones. The posterior lobe and stalk contain terminal axons arising from neurons in hypothalamic nuclei. These axons contain secretory granules and release posterior pituitary hormones synthesized in the hypothalamic nuclei and transported down the stalk to the posterior lobe.

The pituitary gland rests in a cavity of the sphenoid bone, referred to as the sella turcica. (Fig. 1.) Important contiguous anatomical landmarks include the sphenoid sinuses inferiorly, and the diaphragm sella superiorly; the latter, an extension of the dura mater, serves as a roof for the sella and separates the gland from neural structures (including the optic chiasm) that lie above. The posterior boundary of the sella is formed by the dorsum sellae, a thin sheet of bone with two prominences, the posterior clinoids, at its superior lateral margins. The anterior wall of the sella contains a superior prominence, the tuberculum sellae, that contains two projections on its lateral margins, the anterior clinoids. Lateral to the sella are the cavernous si-
Lateral view of the normal sella turcica. The sella is of normal dimensions and configuration. The walls of the sella, including the dorsum sellae, are well defined and intact.

nuses, which are traversed by portions of the internal carotid arteries and by the second, third, fourth and sixth cranial nerves. Tumors of the pituitary may not only expand and erode the walls of the sella, but they may also expand beyond the sella inferiorly into the sphenoid sinus, laterally into the cavernous sinuses with their contained vascular and neural elements, and superiorly to affect the optic chiasm and the hypothalamus. Normally the maximal anteroposterior diameter of the adult sella is about 15 mm., and the maximal vertical dimension is about 12 mm., not exceeding 1092 mm. in volume.\textsuperscript{1,3}

The vascular supply of the gland is of great physiological importance. The superior hypophyial arteries, derived from each internal carotid, send branches to the median eminence, a prominence in the superior portion of the neural stalk at its connection to the floor of the third ventricle. These arterial branches form a capillary network in the median eminence and upper portions of the stalk; a system of portal veins emerges from this capillary network to conduct blood to the anterior lobe. Hypothalamic neurohormones, which regulate the release of anterior pituitary hormones, are transported down these portal vessels of the stalk to their target cells in the anterior pituitary. The posterior pituitary gland is nourished by branches of the inferior hypophyial arteries, which are in turn derived from the internal carotids.

Anterior Pituitary Cell Types and Hormones

Attempts to classify anterior pituitary cells on the basis of their morphological appearance have focused on the pres-
ence of secretory granules and their staining characteristics. Early light microscopic studies classified the cells into chromophobes, which lacked apparent granules, and acidophils or basophils, which possessed granules reacting with either acidic or basic dyes.\textsuperscript{1,2} Further histochemical, immunohistochemical and electron microscopic studies have revealed a greater level of complexity. For example, many cells classified as chromophobes by light microscopy reveal some degree of granulation under the electron microscope. In addition, basophils and acidophils are not homogeneous cell populations, but are composed of subgroups, each believed to be involved in the elaboration of specific hormones. Thus, employing a combination of electron microscopic and immunohistochemical techniques, specific cell types can be linked to the secretion of particular hormones. Table 1 lists the anterior pituitary hormones, the cell types from which the hormones originate, based on the classical tinctorial

| Hormone                        | Pituitary Cell | Hormone Structure | Some Biological Actions                                                                 |
|-------------------------------|----------------|-------------------|-----------------------------------------------------------------------------------------|
| Growth hormone (GH)           | Acidophil      | Peptide           | Growth of bone, cartilage, muscle, connective tissue, viscera Elevates blood sugar      |
| Prolactin (Prl)               | Acidophil      | Peptide           | Promotes lactation                                                                     |
| Follicle stimulating hormone (FSH) | Basophil    | Glycoprotein      | Female: Promotes maturation of ovarian follicles and formation of ovarian steroids Male: Promotes spermatogenesis |
| Luteinizing hormone (LH)      | Basophil       | Glycoprotein      | Female: Promotes formation of corpus luteum and ovarian steroids Male: Stimulates testosterone formation by interstitial cells of testis |
| Thyroid stimulating hormone (TSH) | Basophil   | Glycoprotein      | Increases thyroid growth and synthesis of thyroid hormones                               |
| Adrenocorticotropic hormone (ACTH) | Basophil  | Peptide           | Promotes adrenocortical growth and steroidogenesis                                       |
| Melanocyte stimulating hormones (β-MSH, etc.) | Basophil | Peptide           | Skin darkening                                                                        |
characteristics of the secretory granules and, in very abbreviated form, some of the biological actions of the hormones.

It is worth noting that while growth hormone hypersecretion may be associated with adenomas of the acidophilic type, and ACTH hypersecretion resulting in Cushing's disease may be associated with basophilic adenomas, hormonally active tumors (producing, for example, growth hormone, prolactin or ACTH) may appear to be chromophobes under the light microscope. More careful examination of such adenomas using the electron microscope, however, frequently reveals secretory granules, albeit sparse in quantity. Furthermore, clinical syndromes resulting from pituitary hormone hypersecretion are not invariably accompanied by the presence of an adenoma, either as evidenced by examination of the sella turcica radiologically or by examination of the pituitary histologically.

**Regulation of Anterior Pituitary Function**

The secretion of a particular anterior pituitary hormone is usually the net result of several stimulatory or inhibitory influences. Humoral substances that either stimulate or inhibit release of the pitu-

| Hypothalamic Hormone                      | Structure | Pituitary Hormone |
|------------------------------------------|-----------|-------------------|
| TSH releasing hormone (TRH)              | Peptide   | TSH (1)           |
|                                          |           | Prolactin (1)     |
| LH releasing hormone (LHRH)              | Peptide   | LH (1)            |
|                                          |           | FSH (1)           |
| GH releasing factor (GHRF)               | ?         | GH (1)            |
| GH inhibiting factor (GHIF, somatostatin)| Peptide   | GH (1)            |
|                                          |           | TSH (1)           |
| Prolactin inhibiting factor (PIF)        | ?         | Prolactin (1)     |
| Corticotropin releasing factor (CRF)     | ?         | ACTH (1)          |

Note: Stimulatory or inhibitory effects on release of particular pituitary hormones are indicated by the arrows in parentheses.
It is known that pituitary hormones originate in the hypothalamus and are transported to anterior pituitary cells via the portal vessels of the pituitary stalk. Some of the metabolic, hormonal or neural signals known to influence anterior pituitary hormone secretion do so through the mediation of these hypothalamic factors, while others act directly on the anterior pituitary cells themselves. Some of the hypothalamic releasing factors (hormones) are listed in Table 2, along with the pituitary hormones whose release they either promote or inhibit. These factors are synthesized in neurosecretory cells in various loci in the hypothalamus; in some cases, they are found also in other regions of the central nervous system (TRH) and outside of the central nervous system as well (somatostatin). The neurosecretory cells are subject to regulation by endocrine or metabolic influences, as well as by neural signals feeding in from various regions of the CNS and communicated to the effector neurosecretory cell by

Table 3. Some Stimulatory and Inhibitory Influences on Pituitary Hormone Secretion

| Hormone | Stimulates Secretion | Inhibits Secretion |
|---------|----------------------|--------------------|
| Growth hormone | Hypoglycemia, Amino acids (arginine), Deep sleep, L-dopa, Glucagon, Estrogens | Acute increase in plasma glucose, Increase in plasma free fatty acids, Phenothiazines |
| Prolactin | Pregnancy, Suckling, Deep sleep, Phenothiazines | L-dopa, Ergot alkaloids |
| LH | Female: decreased estrogens, Male: decreased testosterone, Clomiphene | Large doses estrogens or testosterone |
| FSH | Female: decreased estrogens, Clomiphene | Large doses estrogens |
| TSH | Decreased thyroid hormones | Increased thyroid hormones |
| ACTH/β-MSH | Stress, Hypocortisolism, Hypoglycemia, Vasopressin | Hypercortisolism |
neurotransmitters, such as norepinephrine, dopamine and serotonin. Various drugs that influence anterior pituitary hormone secretion, either in experimental animals or in man, may do so through actions on the neurotransmitter systems of the hypothalamus.

Some of the influences either stimulating or inhibiting anterior pituitary hormone secretion are listed in Table 3. In several cases, the secretion of a specific anterior pituitary hormone is inhibited by the hormone product of the specific target gland. Sometimes the negative feedback effect is exerted directly on the anterior pituitary; for example, thyroid hormones render the anterior pituitary cells less responsive to the stimulatory effect of TRH. In other cases, negative feedback is exerted at least in part at the hypothalamic level. This appears to be true for the inhibition of gonadotropin secretion by large doses of estrogens and for the inhibition of ACTH secretion by cortisol.

### TYPES OF PITUITARY TUMORS

**Pituitary Adenomas**

Adenomas arise within the sella turcica from pituitary cells.⁵ According to common usage, such tumors are referred to as acidophilic, basophilic or chromophobe, according to the presence and staining quality of secretory granules. (Table 4.) As noted above, most chromophobes, when examined carefully under the electron microscope, exhibit sparse secretory granules. Acidophilic adenomas may be associated with hypersecretion of growth hormone or prolactin, while basophilic adenomas are associated with hypersecretion of ACTH and β-MSH. Tumors classified as chromophobes may be associated with hormone secretory patterns that also characterize the acidophilic or basophilic adenomas. Furthermore, some "non-functioning" tumors, which have not appeared to be hormonally active in vivo, have been studied in vitro and found to produce small quantities of hormone, prolactin, for example. Thus, some tumors may produce hormones but not enough to elevate blood levels and induce endocrinological effects.

Pituitary adenomas are quite uncommon in children before adolescence. However, the occurrence of a growth hormone secreting adenoma prior to adolescence may produce the dramatic clinical phenomenon of pituitary gigantism. Adenomas usually exhibit a slow

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**Table 4.** Intracellular and Suprasellar Tumors

| Intracellular Tumors | Suprasellar Tumors |
|----------------------|--------------------|
| Acidophilic adenomas (GH, Prl) | Craniopharyngiomas |
| Basophilic adenomas (ACTH, β-MSH) | Meningiomas |
| Chromophobe adenomas (GH, Prl, ACTH, β-MSH) | Ependymomas |
| Craniopharyngiomas | Gliomas |
| | Pinealomas |
| | Teratomas |
| | Metastatic tumors; breast |

**Note:** Hormones produced are shown in parentheses.
growth rate. In the functioning adenoma, active hormone secretion often produces metabolic and clinical abnormalities early, signalling the presence of the tumor before it reaches a large size. Conversely, tumors that produce little or no hormone may not be appreciated until they reach a larger size and induce substantial anatomical derangements.

The factors leading to the development of pituitary adenomas remain unknown, but there is speculation that they may develop as a result of chronic hyperstimulation of pituitary cells by releasing factors.\textsuperscript{5,6} This theory would place the primary defect in the hypothalamus. An alternative hypothesis holds that pituitary adenomas arise as autonomous primary neoplasms from cells that have somehow become independent of the factors that normally limit their proliferation.\textsuperscript{7} Since hypothalamic hormones are known to inhibit as well as to stimulate pituitary function, both theories suggest an important role for the hypothalamus in tumor development. Answers to this controversy may have to wait until the secretion of hypothalamic releasing factors can be more reliably measured in man.

**Craniopharyngiomas**

The craniopharyngioma is the most common type of pituitary tumor found in childhood. It is believed that these tumors arise from embryonic nests of cells that have migrated from the roof of the primitive oral cavity during pituitary development in embryonic life. They vary in their histological appearances from cystic structures, lined by epithelial cells and containing cholesterol-rich fluid, to non-cystic solid tumors. They are most often found in a suprasellar location, but they not infrequently occupy the sella as well. These tumors often exhibit calcification which provides a helpful clue on skull X-ray. (Fig. 2.) Craniopharyngiomas tend to grow slowly, and they do not secrete hormones. Therefore, they usually achieve a rather large size by the time of their discovery.

**Other Neoplasms**

Discussions of pituitary tumors commonly include reference to other non-pituitary neoplasms arising in adjacent suprasellar sites, since the anatomical derangements produced by such tumors may overlap those of pituitary adenomas and craniopharyngiomas, and since these tumors may produce endocrine dysfunction. Primary tumors of the brain or meninges may involve the hypothalamus. (Table 4.) Metastatic cancer, particularly cancer of the breast, may also occupy this region.

**CLINICAL DIAGNOSIS OF PITUITARY TUMORS**

The predominant symptoms of pituitary tumor may be either neurological or endocrinological. In general, the child or young adult will more readily demonstrate endocrine abnormalities, while the older patient more often presents with symptoms due to pressure from the expanding mass. Even in patients having predominantly neurological symptoms, some degree of endocrine dysfunction can usually be demonstrated by appropriate testing. It is important that the practicing physician be able to recognize both the neurological and endocrine manifestations of pituitary tumor and be aware of the diagnostic tests that may be used to delineate the anatomical and hormonal abnormalities. The performance of the more specialized diagnostic procedures is usually the responsibility of the neuroradiologist, the neurosurgeon or the endocrinologist. These procedures are critical for accurate diagnosis and appropriate therapy.

**Neurological Derangements**

The "non-functioning" chromophobe adenoma may remain asymptomatic for
several years before the appearance of neurological symptoms. Such symptoms are due to pressure on the optic chiasm and nerves, the hypothalamus, the cranial nerves in the cavernous sinus and the surrounding bony structures. Many of the same symptoms may be caused by non-pituitary tumors, such as craniopharyngiomas or teratomas, which arise within or near the sella turcica. The most serious localized pressure effect is optic nerve compression which may lead to blindness. Classically, but not invariably, vision is lost first in the superior temporal quadrants bilaterally. Approximately 85 percent of patients with chromophobe tumors will have visual impairment at diagnosis and, in most cases, a peripheral temporal field defect will be found. Nasal field defects, probably due to secondary vascular compression of the uncrossed optic tract fibers, occur rarely. The detection of mild to moderate visual field abnormalities depends upon careful tangent screen examination, usually conducted by the ophthalmologist. The most sensitive methods of perimetry utilize a red object, or even light from a red laser beam, to detect the earliest changes. Sequential visual field testing at three to six month intervals can give critical information regarding the growth or regression of a pituitary mass.

Headache may be a symptom in 50 to 70 percent of patients, while confusion and impaired memory are much less common. Pituitary adenomas seldom cause more specific manifestations of increased intracranial pressure such as hydrocephalus or papilledema. In contrast, suprasellar tumors frequently grow into the third ventricle where they may cause obstruction near the foramen of Monro.
The majority of children with craniopharyngioma have definite evidence of increased intracranial pressure (headache, vomiting or papilledema) at the time of diagnosis and in most cases appropriate X-ray studies will demonstrate hydrocephalus and deformity of the third ventricle.\(^\text{11,12}\)

**Procedures for Anatomical Assessment of the Tumor**

Pituitary adenomas greater than 10 mm in diameter usually cause an enlargement in the dimensions of the sella turcica. X-ray enlargement of the sella has been reported in up to 95 percent of "non-functioning" adenomas\(^\text{13}\) and in 90 percent of patients with acromegaly. In contrast to chromophobe or acidophilic adenomas, basophilic tumors seldom present with sellar enlargement. Large tumors may destroy the posterior clinoids and dorsum sella, erode the anterior clinoids, depress the sellar floor and cause the lateral sellar configuration to become more rounded or "balloon-like." (Fig. 3.) Asymmetrical tumor growth often results in a "double-floored sella," seen on lateral view. Small pituitary adenomas between five and 10 mm in size do not cause an appreciable increase in sellar volume, but they may still be diagnosed by careful tomography.\(^\text{14}\) In such cases, the experienced radiologist may detect a lateralized bulging in a limited portion of the sellar wall.

Plain skull films or tomograms are also valuable in demonstrating tumor calcification in the pituitary and hypothalamic areas. The pituitary adenoma seldom contains calcium deposits unless it has previously undergone hemorrhage or necrosis. Craniopharyngiomas, on the other hand, demonstrate either intrasellar or suprasellar calcification in 80 percent of children. In adults, this tumor is much less likely to calcify. This difference, together with certain other histological and clinical differences in typical juvenile and adult craniopharyngiomas, has led some observers to postulate two different tumor types.\(^\text{15}\) Other pituitary and suprasellar lesions that may calcify include granulomas, teratomas, meningiomas, gliomas and vascular aneurysms.

**Special X-ray Procedures**

The clinician must know the extent of tumor growth outside the sella in order to plan an optimum approach to therapy. For this purpose, plain X-rays are seldom sufficient, and more invasive X-ray procedures are necessary. Carotid arteriography is probably the most accurate means of detecting lateral extension of the tumor. Besides differentiating pituitary tumor from aneurysm of the internal carotid artery, this examination can disclose lateral displacement of the internal carotids in the cavernous sinuses or upward displacement of the anterior cerebral arteries by tumor. Vertebroarteriography is more useful than carotid arteriography in detecting posterior suprasellar extension. In this case, bowing of the thalamoperforate arteries is usually seen.\(^\text{15}\) Abnormal tumor vasculature and tumor "blush" may be detected using direct serial magnification with subtraction techniques.\(^\text{16}\)

Pneumoencephalography has been considered the most reliable method for delineating superior tumor extension, which may be limited to a slight bulge in the chiasmal cistern or may deform the floor of the third ventricle and displace it backward. With air in the ventricular system, tomograms will usually allow a reasonably accurate assessment of the size, configuration and location of the mass. The pneumoencephalogram also distinguishes between an intrasellar mass and the empty sella syndrome, where the enlarged sella is occupied by cerebral spinal fluid rather than by tumor tissue. If this syndrome is mistaken for a pituitary tumor, inappropriate ablative therapy may be undertaken. It should be
emphasized, however, that pneumoencephalography may be a dangerous form of stress, particularly in patients with pituitary insufficiency. During the procedure, adequate coverage with parenteral glucocorticoids and continuous attendance by a physician are the minimal requirements for safety when pituitary or hypothalamic lesions are present.

Unfortunately, newer non-invasive procedures, such as isotopic brain scanning and computerized axial tomography, have not replaced the need for angiography or pneumoencephalography. Computerized tomography can detect only relatively large masses in the suprasellar area, although it offers the possibility of detecting hemorrhage into the tumor (due to the increased density of blood) and tumor areas which are cystic (due to the decreased density of cyst fluid). More experience will be needed to fully determine the proper role for such procedures in evaluating suprasellar lesions.

Endocrine Derangements
Endocrine symptoms may result either from a deficiency or an excess of one or more pituitary hormones. With the “non-functioning” pituitary adenoma, hypopituitarism is usually observed only after rather extensive compression and loss of normal anterior pituitary cells. Posterior pituitary insufficiency is uncommon with intrasellar tumors because neurohypophysial hormones are manufactured in the hypothalamus. Cranio-phyaryngiomas or other tumors arising above the sella can cause hypopituitarism by interfering with the hypothalamic control of adeno-hypophysial secre-
tion. With suprasellar tumors, the secretion of neurohypophysial hormones is frequently impaired, and diabetes insipidus may result. Although a differentiation between intrapituitary and hypothalamic lesions is valuable for understanding of the pathogenesis of endocrine abnormalities, many cases will actually be a combination of both types of lesions.

As pituitary function becomes progressively impaired, the symptoms of hypopituitarism that first appear will depend upon the age and sex of the patient. In prepubertal children, the earliest clinical finding is almost always the cessation of linear growth. Normal sexual maturation fails to occur, and puberty may be indefinitely delayed. Skeletal maturation or “bone age” is also retarded, due to secondary lack of gonadal steroids and thyroid hormones. Clinically evident hypothyroidism and hypoadrenalism are seldom early findings, but may occur later in the course of the disease.

In premenopausal adult females, impaired gonadotropin secretion will usually lead to oligomenorrhea or amenorrhea as the earliest endocrine complaint; among adult males, impotence is a common early finding. Both sexes may note a loss of libido. Later, objective changes in secondary sexual characteristics, such as loss of axillary and pubic hair and atrophy of testes or the breasts, may occur. Growth hormone deficiency, which may occur at an early stage, may produce no symptoms or may result in fasting hypoglycemia.

Symptoms of secondary hypothyroidism are usually manifest after symptoms of gonadal insufficiency are well established.

Lack of ACTH may not cause symptoms of hypoadrenalism until late in the course of the disease. Then the patient may exhibit profound weakness and postural hypotension. Stress, in the form of intercurrent illness, or surgery may uncover partial adrenal insufficiency, and shock may appear suddenly and unexpectedly. Unlike patients with primary adrenal failure who have hyperpigmentation, patients with secondary adrenal insufficiency tend to have pale skin due to deficiencies in both ACTH and β-MSH.

Early recognition of pituitary insufficiency is especially difficult in the postmenopausal female or the elderly male. Here, the early endocrine symptoms are usually non-specific ones, such as weakness or fatigue, and there is a tendency to attribute such symptoms to other co-existing diseases.

Hypersecretion by Pituitary Tumors
While hypopituitarism may be the end result of an enlarging pituitary mass, functioning adenomas lead to diseases of hormone excess. Five types of hypersecreting pituitary tumors have been described. Characteristic clinical syndromes may result from the overproduction of prolactin, growth hormone, ACTH, TSH or FSH. Such syndromes may appear with small, hormonally active tumors long before the onset of hypopituitarism, and even before the occurrence of detectable sellar enlargement.

Hyperprolactinemia
Prolactin is the hormone most frequently secreted by pituitary tumors. This hormone may be hypersecreted not only by pituitary tumor cells, but also by the normal pituitary when hypothalamic damage leads to a deficiency of the prolactin inhibitory factor. A number of galactorrheic syndromes have been described in the past, and modern immunoassay methods have shown that hyperprolactinemia is the common feature in all. The Forbes-Albright syndrome is characterized by non-puerperal galactorrhea, amenorrhea and low urinary FSH in women with pituitary tumors. Galactorrhea may also be the presenting
Symptom of pituitary tumors in men. These tumors are usually of the chromophobe type, but they contain immunologically stainable granules of prolactin. Since hyperprolactinemia can be the result of very small tumors or microadenomas, any patient with unexplained galactorrhea should be followed with periodic X-rays of the sella turcica, even when the initial films appear normal.

Not all patients with elevated prolactin levels will show the effects of prolactin excess. It has been estimated that at least 30 percent of all pituitary tumors are associated with hypersecretion of prolactin. Hence, serum prolactin levels can be useful in following the progress of tumor therapy, even in the absence of galactorrhea.20 (Table 5.)

**Growth Hormone Excess**

Gigantism or acromegaly invariably accompanies the growth hormone-secreting pituitary adenoma. The physical appearance of acromegaly is well known, yet the diagnosis is often delayed because the changes are so insidious. The late manifestations of the disease, including hypertension, diabetes mellitus, cardiomyopathy and arthritis cause disability and even death; thus, early diagnosis and therapy are desirable. Immunoassay of serum growth hormone (Table 5) provides the most sensitive indicator

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**Table 5.**

| Hormone | Diagnostic Agent | Site of Action | Normal Response | Response with Tumor |
|---------|------------------|----------------|-----------------|---------------------|
| Prolactin | Chlorpromazine TRH L-dopa | Hypothalamus Pituitary Hypothalamus | ↑ ↑ ↓ | ↓ or ↑ (high basal level) Usually ↑ Usually ↓ |
| Growth hormone | Insulin hypoglycemia (also arginine, L-dopa) Hyperglycemia | Hypothalamus Hypothalamus | ↑ ↓ | ↓ → Usually ↓ |
| LH and FSH | Clomiphene LHRH | Hypothalamus Pituitary | ↑ ↑ | ↑ or → |
| TSH | TRH | Pituitary | ↑ ↑ | ↑ or → (response may be delayed) |
| ACTH | Metyrapone Dexamethasone | Adrenal-hypothalamus Hypothalamus | ↑ ↓ | → in hypopituitarism ↑ in Cushing's disease ↓ (Low dose) Cushing's disease ↓ (High dose) Cushing's disease |

Note: ↑ indicates secretion increased of the hormone in question. ↓ indicates decreased secretion. → indicates no change in secretion.
for the presence of acromegaly, even though the degree of growth hormone elevation does not always correlate with the severity of the disease. The great majority of growth hormone-producing tumors will enlarge the sella, and some will extend upward, causing visual field defects or other neurological symptoms. The tumors of some acromegalic patients also secrete prolactin.

ACTH Excess

Cushing’s disease results from the hypersecretion of pituitary ACTH. Although ACTH-secreting tumors large enough to increase the sella volume are uncommon, microadenomas may be present. Most of the tumors that have been examined contain basophilic granules. The clinical features of Cushing’s disease are due to the hypercortisolism that results from chronic adrenal stimulation. In children, the earliest and most striking symptom is the arrest of linear growth. In adults, symptoms related to the protein catabolic effects of glucocorticoids usually prevail. Easy bruising of the skin, osteoporosis and muscle weakness are common. Body fat, redistributed to the face and trunk, produces a characteristic appearance, and glucose intolerance may be present. Concurrent hypersecretion of adrenal androgens may cause hirsutism, particularly in females. These processes, if untreated, lead to increasing disability and often to death.

Diagnostically, it is essential to distinguish pituitary ACTH hypersecretion from other causes of cortisol excess, including adrenal tumors and ectopic ACTH secretion by non-pituitary tumors. The key to the correct diagnosis lies in the fact that feedback control mechanisms of ACTH and cortisol secretion continue to operate in Cushing’s disease, although larger than usual quantities of glucocorticoid are needed to inhibit ACTH secretion. Endogenous cortisol secretion can be suppressed by giving large doses of an exogenous glucocorticoid, such as dexamethasone, while in the other forms of hypercortisolism, no suppression can be shown. (Table 5.) This observation suggests that the pituitary adenomas of Cushing’s disease are not autonomous, but that they arise as the result of an error in the hypothalamus, where an excess of corticotropin-releasing factor is secreted. This “set point” hypothesis is supported by the observation that following the correction of hypercortisolism by adrenalectomy, ACTH rises to very high levels. A few patients without evidence of sellar changes before adrenalectomy will develop enlarging tumors after surgery.

Thyrotropin Excess

Hyperthyroidism is seldom due to TSH hypersecretion by a pituitary tumor, but a few well-documented cases have been described. It is more common for pituitary enlargement to occur in patients with long-standing hypothyroidism. Most of these cases probably represent pituitary hyperplasia rather than neoplasm since TSH can be normally suppressed by thyroid hormone replacement. In mice, however, sustained deficiency of thyroid hormone initiates first hyperplasia and then true neoplastic disease.

Gonadotropin Excess

Gonadotropin-secreting pituitary tumors are also believed to be rare. However, several patients have been reported in which pituitary tumors followed chronic gonadal failure. In one recent case, a chromophobe adenoma in a eunuchoid male was shown to secrete large amounts of FSH.

Endocrine Function Tests in the Diagnosis of Pituitary Tumors

Appropriate laboratory tests can confirm which hormones are deficient and which hormones are produced in excess by the
tumor. In recent years, accurate methods have been developed for the immunoadsorption of each pituitary hormone in blood, and several of the hypothalamic factors have become available for experimental use as diagnostic drugs. The result has been a rapid proliferation of proposed new pituitary function tests. Several reviews have been written on various aspects of the subject.\textsuperscript{1,2,28} In this article, we will offer a few principles to guide the practicing physician in the selection of tests. For details concerning the execution of the tests and the specific interpretations of results, the references should be consulted.

It is reasonable to divide the tests into those that are designed to show a deficiency of a particular hormone, and those that are designed to show an excess. (Table 5.) In general, one should test for deficiency under conditions that normally stimulate secretion of the hormone in question. Conversely, one tests for excess under conditions that suppress the hormone. In planning a complicated and expensive series of tests, the physician should first ask whether the results will make a real difference in the future management of the patient. Sometimes the laboratory tour-de-force will be inappropriate; for example, in managing a patient with progressive visual loss, where craniotomy and hypophysectomy are being planned, there is usually little reason for a detailed preoperative study of all the pituitary hormones.

\textit{Tests for Detection of Pituitary Hormone Deficiency}

As hypopituitarism develops, certain tests tend to become abnormal earlier than others. There is a considerable overlap in the basal ranges seen for most of the hormones in normal and hypopituitary subjects. To detect early deficiency, one must utilize some of the stimulation tests summarized in Table 5. Abnormalities in growth hormone and gonadotropin secretion are usually detectable at an earlier stage than are measurable deficiencies in TSH or ACTH secretion.\textsuperscript{29}

Insulin-induced hypoglycemia is the most consistently effective stimulus for growth hormone secretion,\textsuperscript{20,21} but L-arginine infusion or L-dopa given orally are also useful. Each of these stimuli requires a responsive hypothalamus, as well as a responsive pituitary. Either intrasellar or suprasellar lesions therefore may cause test abnormalities.

Low baseline serum LH or FSH in the presence of deficient gonadal steroid secretion suggests that hypothalamic or pituitary disease is present. In early pituitary failure, the basal levels of both gonadotropins and gonadal steroids often fall within the lower limits of normal, yet the patient will complain of amenorrhea or decreased libido. Clomiphene has been used as a diagnostic stimulus in such patients.\textsuperscript{28,32} This drug is thought to block the negative hypothalamic feedback of endogenous estrogen on gonadotropin secretion. If clomiphene fails to cause an increase in serum gonadotropin levels, disease of the hypothalamus or the pituitary is implied.

The hypothalamic releasing factor for gonadotropins, LH-RH, should offer additional possibilities as a diagnostic drug, since it acts directly upon the pituitary without requiring hypothalamic mediation. After recent evaluations of LH-RH in many laboratories, it appears that the drug may not be of great help in detecting the early pituitary tumor, nor will it always allow a clear cut distinction between pituitary and hypothalamic disease. Many patients with untreated intrasellar tumors have responded normally to intravenous LH-RH. After transfrontal hypophysectomy or extensive pituitary infarction (Sheehan's syndrome), the response is usually subnormal.\textsuperscript{33,34} Some patients with long-standing hypothalamic dysfunction have failed to show a normal re-
response to LH-RH initially, but with repeated administration, responsiveness usually returns.\textsuperscript{35} In this situation, a form of atrophy of the gonadotropin-producing cells may occur.

Low or normal basal TSH levels, in the presence of low serum thyroid hormone, implies secondary hypothyroidism. However, in euthyroid subjects with early pituitary lesions, basal TSH measurements may be of little value. Synthetic TRH has been used for the testing of both TSH and prolactin reserve in patients suspected of having pituitary or hypothalamic lesions. In many patients with documented pituitary tumors, the TSH response has been delayed or subnormal, but this is not invariably the case, especially with smaller tumors where the response may be normal. Organic lesions of the hypothalamus may also be associated with a delayed response.\textsuperscript{36,37} This is in contrast to idiopathic hypopituitarism, where the TSH response is characteristically normal. Failure of prolactin to respond to TRH implies extensive pituitary destruction, but smaller pituitary tumors do not necessarily ablate the prolactin response.

ACTH immunoassays are technically difficult to perform. Consequently, ACTH deficiency is usually determined indirectly through measurements of the adrenal response to maneuvers such as metyrapone administration, which stimulates ACTH.\textsuperscript{28,38} Valid interpretations of the tests of ACTH reserve can be made only when it is known that the adrenal can respond to exogenous ACTH.

\textit{Tests for Detection of Pituitary Hormone Excess}

The tests that may be useful in confirming excessive secretion of the individual pituitary hormones are also summarized in Table 5. Often the measurement of elevated basal levels by specific radioimmunoassay is sufficient for diagnosis, but when acromegaly or Cushing’s disease are suspected, suppression tests are desirable. There is an overlap between the basal growth hormone levels in normal subjects and in acromegalics. Growth hormone secretion is normally suppressed by hyperglycemia. Patients with acromegaly rarely show full suppression, even though their basal hormone levels may fall within the normal range.

In suspected Cushing’s disease, the dexamethasone suppression test is essential for proper diagnosis. Failure to suppress endogenous cortisol secretion at a low dose of dexamethasone (two mg. per day in adults) confirms that hypercortisolism or Cushing’s syndrome is present. A large dose of dexamethasone (eight mg. per day) will then allow differentiation of pituitary ACTH excess from other causes of hypercortisolism.\textsuperscript{28,39} The metyrapone test may furnish valuable additional diagnostic information. (Table 5.)

\section*{The Treatment of Pituitary Tumors}

Considerable diversity exists in the therapeutic preferences of various centers treating pituitary neoplasms. Continuing controversy about therapy indicates that no one form of treatment is completely satisfactory. Unfortunately, the arguments marshalled in favor of one form of treatment versus another have seldom been based on controlled studies. The therapist who has mastered a given approach may be inclined to apply that approach to every patient he encounters. The authors believe that the choice of therapy should differ with the type of tumor, as well as its size and location. The ideal treatment center should therefore offer expertise in more than one treatment alternative. The two primary methods for tumor ablation are surgery and radiation. Both include several important variants. (Table 6.)
Surgical Therapy

Pituitary tumors may be removed surgically through open craniotomy (usually transfrontal) or through a transsphenoidal approach. Transfrontal craniotomy is most effective in cases where there is extensive suprasellar tumor spread, or where there is rapid visual loss due to optic nerve compression. The surgeon's goal is to decompress the optic nerves and to remove, under direct vision, as much tumor tissue as is practical. Any remaining normal pituitary tissue will usually be removed at the same time, so that permanent hypopituitarism, if it does not already exist, will develop postoperatively. With experienced surgeons, the operative mortality ranges from three to 10 percent and may be due to bleeding or frontal lobe damage incurred while exposing the sella. In a minority of cases, vision actually deteriorates as a result of surgery; infection is an additional source of morbidity.

Transsphenoidal pituitary surgery has undergone a revival in popularity in recent years. It is most useful in cases of sellar or suprasellar tumor extension and when there has been rapid loss of visual function due to optic nerve compression. The transsphenoidal approach is the preferred technique when there is involvement of the anterior pituitary gland or when there has been extensive suprasellar tumor spread. The transsphenoidal approach is also useful when there is a high risk of hypothalamic injury with the transfrontal route. The operative mortality for the transsphenoidal approach ranges from 2 to 3 percent, making it the procedure of choice for many surgeons.

Table 6. Modes of Therapy for Pituitary Tumors

| Therapy          | Principle Indication                          | Contraindications                                      | Undesired Effects                                      |
|------------------|-----------------------------------------------|-------------------------------------------------------|--------------------------------------------------------|
| Transfrontal resection | Parapituitary or marked suprasellar extension; progressive visual loss | Intrasellar tumor without hypopituitarism or visual loss | Permanent hypopituitarism in all; diabetes insipidus; frontal lobe or optic nerve damage; hemorrhage; infection |
| Transsphenoidal resection | Intrasellar tumor; limited suprasellar extension | Parapituitary or extensive suprasellar involvement | Temporary diabetes insipidus; CSF rhinorrhoea; hemorrhage; infection |
| Cryohipophysectomy | Intrasellar tumor                             | Extravascular involvement                              | Reduced pituitary function; temporary diabetes insipidus; cranial nerve dysfunction; CSF rhinorrhoea |
| Supervoltage X-ray | Intrasellar tumor; limited suprasellar extension or visual field loss | Progressive visual loss; extravascular involvement except as adjunct to surgery; cystic tumors | Delayed therapeutic effect; empty sella syndrome |
| Proton beam irradiation | Intrasellar tumor                             | Visual loss; extravascular involvement; previous X-ray therapy | Reduced pituitary function in a few; temporary oculomotor or visual defects |
| Radioimplantation | Intrasellar tumor                             | Visual loss; extravascular involvement                | Reduced pituitary function; CSF rhinorrhoea; meningitis; oculomotor and visual defects |
cent years. Actual approaches vary, but modern techniques utilize a binocular dissecting microscope and televised radiofluoroscopic control. Intrasellar tumors are best suited for removal by this method. Tumors with moderate suprasellar bulging can also be removed, since such tumors usually collapse into the sella when the inferior capsule is opened from below. Small adenomas can be selectively removed by microdissection, so that normal pituitary function may be preserved. This offers a great advantage in patients with hypersecretion syndromes, such as acromegaly or Cushing’s disease, where hypopituitarism is not present. The mortality rate of the procedure is less than three percent, and brain damage is rare. Transient diabetes insipidus is common. Among the less frequent causes of surgical morbidity are CSF rhinorrhea, meningitis or bleeding.

With cryohypophysectomy, a cryoprobe is inserted transnasally into the sella with X-ray monitoring. Cryonecrosis of surrounding tissue is induced by probe temperatures of \(-170^\circ\) to \(-184^\circ\)C. This method is applicable only to intrasellar tumors. Both normal and abnormal intrasellar tissues are killed, so that varying degrees of postoperative hypopituitarism are the rule. Transient diabetes insipidus, cranial nerve dysfunction and CSF rhinorrhea are all relatively common, but they usually resolve spontaneously.

Radiation Therapy

Supervoltage X-irradiation will kill pituitary tumor cells at total dosages of 4000-5000 rads. Today, fractionated dosages through multiple opposing portals are usually given over a period of several weeks. “Non-functioning” or chromophobe adenomas show an arrest in growth and a regression of symptoms in most patients submitted to radiation therapy. When visual field defects have been present, improvement has occurred in over half of the patients. The chief disadvantage of X-ray therapy may be its delay in producing the desired results. Growth hormone secreting tumors show a gradual decline in function after treatment, reaching a plateau only after two to four years. Cystic tumors are less susceptible to radiation, and this may account for the observation that most craniopharyngiomas are resistant. Even in adenomas, cystic elements existing in up to 20 percent of tumors may limit the responsiveness to X-ray. Although X-ray therapy is not usually recommended as the sole treatment for suprasellar tumors, it may be a useful adjunct to surgery in chromophobe adenomas with suprasellar extension, and perhaps in craniopharyngiomas. With the X-ray dosages usually administered today, normal brain and pituitary tissues rarely develop lasting dysfunction. Indeed, X-ray treatment induces fewer complications than any other therapeutic modality. The empty sella syndrome, accompanied by headaches and mild visual disturbances, has occasionally developed after pituitary irradiation. This complication is presumably due to late fibrosis and contraction following necrosis of the tumor.

Proton beam or \(\alpha\) particle irradiation allows somewhat higher energies to be concentrated within the sella, particularly if the Bragg peak is utilized. This form of therapy has been used extensively in a few centers possessing a cyclotron, which must be used to generate the beam. Between 3500 and 10,000 rads may be administered within a few hours. When the Bragg peak is to be focused on the tumor, the patient’s head must be held firmly in a stereotactic device. Proton beam irradiation is quite effective in killing tumor tissue. The decline in growth hormone secretion following treatment for acromegaly is probably more rapid than the decline following conventional irradiation. A favorable clinical response usually occurs...
within three to six months, but serum growth hormone levels continue to fall for up to two years. This type of therapy has also been effective in treating chromophobe adenomas and Cushing's disease. Like conventional X-ray, the proton beam is not well suited for the treatment of tumors with marked extrasellar extension.

Existing pituitary function is maintained in about 85 percent of patients, indicating that normal pituitary tissue is generally more resistant than tumor tissue. Neurologic complications, such as oculomotor palsy or visual field defects, are somewhat more common than with conventional X-ray, but are seldom major or permanent. Proton beam therapy is contraindicated in patients who have already received therapeutic doses of conventional pituitary irradiation because these patients have a higher chance of developing neurological sequelae.52,53

A third form of radiation therapy is administered by implanting radioactive seeds of yttrium or gold within the sella. 90Y is a β emitter with a half-life of 64 hours. It may be introduced transnasally or tranethmoidally under X-ray monitoring. This technique, which is practiced in only a few centers, has been used primarily to treat functioning intrasellar tumors. The occurrence of clinical improvement after the treatment of acromegaly or Cushing's disease with 90Y implantation has been comparable to that obtained with conventional X-ray or proton beam therapy.21,54,55 The morbidity associated with this form of radiation is probably higher, and includes persistent CSF rhinorrhea, meningitis and, more rarely, ocular complications.

Drug Therapy

Hormone Replacement

Drug therapy in patients with pituitary tumors may accomplish two purposes. First, deficient hormones must be replaced. A typical replacement regimen for an average adult with panhypopituitarism is shown in Table 7. Several forms of each type of hormone are available, and dosages must often be adjusted to produce the desired results. This is especially true with the adrenal glucocorticoids, where stress or intercurrent illness may double or triple the daily requirements. It is always wise for the patient to carry identification stating his diagnosis and emphasizing the need for prompt steroid replacement in case of emergency. Even the patient without a requirement for adrenal corticoids, under normal conditions, should receive supplementary glucocorticoids during surgery or other stress, if a pituitary tumor is known to be present. Therapy with mineralocorticoids such as 9 α-fluorocortisol is not usually necessary in hypopituitarism because aldosterone continues to be secreted by the adrenal even when ACTH levels are too low to support adequate cortisol secretion. If an adequate sodium intake is maintained, glucocorticoid replacement alone should suffice.

Growth hormone therapy is indicated in children who would not otherwise be expected to reach a minimum acceptable stature. Since only human growth hormone is effective in promoting growth, supplies are quite limited. Human growth hormone is distributed for approved usage in the United States through the National Pituitary Agency.

Hormone Suppression

Besides replacing the missing hormones, the therapist of the future may hope to suppress the secretion of unwanted hormones by appropriate drug therapy. Basic research has already revealed several pharmacological agents which can inhibit the secretion of one or more pituitary hormones. Some of these agents are normally present in the hypothalamus and may actually perform a physiological inhibitory role. Somatostatin, which can inhibit growth hor-
mone secretion in both normal subjects and acromegalics, may eventually become a valuable therapeutic agent. This peptide acts directly upon the growth hormone-producing pituitary cells.

Other promising drugs appear to act on essential neurotransmitter mechanisms in the hypothalamus to effect pituitary suppression. The ergot alkaloid, bromocryptine, is thought to be a long-acting stimulator of dopamine receptors.
This drug has been found useful in suppressing prolactin secretion in a number of patients with abnormal sellas, galactorrhea and hypogonadotropic hypogonadism. Concurrent with reduction in the serum prolactin levels, normal gonadotropin secretion has sometimes been restored, allowing menstruation and even pregnancy.58 Bromocryptine or L-dopa can also suppress growth hormone secretion in acromegals.59 This is a paradoxical effect, for in normal subjects, the effects of L-dopa on growth hormone secretion are just the opposite.

A final promising example of what may be ahead in drug therapy was reported recently. The serotonin antagonist, cyproheptadine, when given to several patients with Cushing's disease, resulted in amelioration of the systems of hypercortisolism. Cortisol secretion rates returned toward normal, but the abnormal diurnal rhythms of plasma cortisol concentrations persisted. Cyproheptadine probably acts by suppressing the release of pituitary ACTH.60

None of these agents, or others yet to be discovered, is likely to offer definitive therapy for patients with hypersecreting pituitary tumors. Yet, when tumor ablation by surgery is contraindicated, and the effects of external irradiation are uncertain or delayed, the chemical blockade of unwanted tumor secretions may prove to be a very valuable therapeutic option.

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