designated *Cushing disease*. Large destructive pituitary adenomas can develop in patients after surgical removal of the adrenal glands for treatment of Cushing syndrome. This condition, known as *Nelson syndrome*, occurs most often because of a loss of the inhibitory effect of adrenal corticosteroids on a preexisting corticotroph microadenoma. Because the adrenals are absent in persons with this disorder, hypercortisolism does not develop, and patients present with mass effects due to the pituitary tumor, and there can be hyperpigmentation because of the stimulatory effect of other products of the ACTH precursor molecule on melanocytes.

Other Anterior Pituitary Adenomas

Pituitary adenomas may elaborate more than one hormone (e.g., mammosomatotroph adenomas). Other unusual "plurihormonal" adenomas secrete multiple hormones; these tumors are usually aggressive. A few comments are made about several of the less frequent functioning tumors.

- *Gonadotroph (LH-producing and FSH-producing) adenomas* can be difficult to recognize because they secrete hormones inefficiently and variably, and the secretory products usually do not cause a recognizable clinical syndrome (*nonfunctioning adenomas*, see later). Gonadotroph adenomas are most frequently found in middle-aged men and women when they become large enough to cause neurologic symptoms, such as impaired vision, headaches, diplopia, or pituitary apoplexy. Pituitary hormone deficiencies can also be found, most commonly impaired secretion of LH. This causes decreased energy and libido in men (due to reduced testosterone) and amenorrhea in premenopausal women. The neoplastic cells usually demonstrate immunoreactivity for the common gonadotropin α-subunit and the specific β-FSH and β-LH subunits; FSH is usually the predominant secreted hormone. Gonadotroph adenomas usually express steroidogenic factor-1 (SF-1) and GATA-2, transcription factors associated with normal gonadotroph differentiation.
- *Thyrotroph (TSH-producing)* adenomas are uncommon, accounting for approximately 1% of all pituitary adenomas. Thyrotroph adenomas are a rare cause of *hyperthyroidism*.
- *Nonfunctioning pituitary adenomas* are a heterogeneous group that constitutes approximately 25% to 30% of all pituitary tumors. Their lineage can be established by immunohistochemical staining for hormones or by biochemical demonstration of cell type-specific transcription factors. In the past, many such tumors have been called *silent variants* or *null-cell adenomas*. Not surprisingly, nonfunctioning adenomas typically present with symptoms stemming from mass effects. These lesions may also compromise the residual anterior pituitary sufficiently to cause hypopituitarism, which may appear slowly due to gradual enlargement of the adenoma or abruptly because of acute intratumoral hemorrhage (pituitary apoplexy).

Pituitary carcinoma is rare, accounting for less than 1% of pituitary tumors. The presence of craniospinal or systemic metastases is a sine qua non of a pituitary carcinoma. Most pituitary carcinomas are functional, with prolactin and ACTH being the most common secreted products. Metastases usually appear late in the course, following multiple local recurrences.

KEY CONCEPTS

Hyperpituitarism

- The most common cause of hyperpituitarism is an anterior lobe pituitary adenoma.
- Pituitary adenomas can be *macroadenomas* (greater than 1 cm in diameter) or *microadenomas*.
- Functioning adenomas are associated with distinct endocrine signs and symptoms, while nonfunctioning (silent) adenomas typically present with mass effects, including visual disturbances.
- Lactotroph adenomas secrete prolactin and can present with amenorrhea, galactorrhea, loss of libido, and infertility
- Somatotroph adenomas secrete GH and present with gigantism in children and acromegaly in adults, impaired glucose tolerance, and diabetes mellitus.
- Corticotroph adenomas secrete ACTH and present with Cushing syndrome and hyperpigmentation.
- The two distinctive morphologic features of most adenomas are their cellular monomorphism and absence of a reticulin network.

Hypopituitarism

***Hypopituitarism* refers to decreased secretion of pituitary hormones, which can result from diseases of the hypothalamus or of the pituitary.** Hypofunction of the anterior pituitary occurs when approximately 75% of the parenchyma is lost or absent. This may be congenital or the result of a variety of acquired abnormalities that are intrinsic to the pituitary. Hypopituitarism accompanied by evidence of posterior pituitary dysfunction in the form of diabetes insipidus (see later) is almost always of hypothalamic origin.

Most cases of hypopituitarism arise from destructive processes directly involving the anterior pituitary. The causes include the following:

- *Tumors and other mass lesions:* Pituitary adenomas, other benign tumors arising within the sella, primary and metastatic malignancies, and cysts can cause hypopituitarism. Any mass lesion in the sella can cause damage by exerting pressure on adjacent pituitary cells.
- *Traumatic brain injury and subarachnoid hemorrhage* are among the most common causes of pituitary hypofunction.
- *Pituitary surgery or radiation:* Surgical excision of a pituitary adenoma may inadvertently extend to the nonadenomatous pituitary. Radiation of the pituitary, used to prevent regrowth of residual tumor after surgery, can damage the nonadenomatous pituitary.
- *Pituitary apoplexy:* As mentioned earlier, this is caused by a sudden hemorrhage into the pituitary gland, often occurring into a pituitary adenoma. In its most dramatic presentation, apoplexy causes the sudden onset of