Clinical Course. Increased serum levels of prolactin, or *prolactinemia*, cause amenorrhea, galactorrhea, loss of libido, and infertility. The diagnosis of an adenoma is made more readily in women than in men, especially between the ages of 20 and 40 years, presumably because of the sensitivity of menses to disruption by hyperprolactinemia. Lactotroph adenoma underlies almost a quarter of cases of amenorrhea. In contrast, in men and older women, the hormonal manifestations may be subtle, allowing the tumors to reach considerable size (macroadenomas) before being detected clinically.

Hyperprolactinemia may result from causes other than prolactin-secreting pituitary adenomas. Physiologic hyperprolactinemia occurs in pregnancy. Prolactin levels are also elevated by nipple stimulation, as occurs during suckling in lactating women, and as a response to many types of stress. Pathologic hyperprolactinemia can also result from *lactotroph hyperplasia* caused by loss of dopamine-mediated inhibition of prolactin secretion. This may occur with damage of the dopaminergic neurons of the hypothalamus, damage of the pituitary stalk (e.g., due to head trauma), or exposure to drugs that block dopamine receptors on lactotroph cells. Any mass in the suprasellar compartment (e.g., a pituitary adenoma) may disturb the normal inhibitory influence of the hypothalamus on prolactin secretion, resulting in hyperprolactinemia. Therefore, a mild elevation in serum prolactin in a person with a pituitary adenoma does not necessarily indicate a prolactin-secreting tumor. Other causes of hyperprolactinemia include renal failure and hypothyroidism. Lactotroph adenomas are treated by surgery or, more commonly, with bromocriptine, a dopamine receptor agonist that causes the lesions to diminish in size.

Somatotroph Adenomas

Growth hormone (GH)-secreting somatotroph adenomas are the second most common type of functioning pituitary adenoma, and cause gigantism in children and acromegaly in adults. Somatotroph adenomas may be quite large by the time they come to clinical attention because the manifestations of excessive GH may be subtle.

MORPHOLOGY

Histologically, pure somatotroph adenomas are also classified into **densely granulated** and **sparsely granulated subtypes**. Densely granulated adenomas are composed of monomorphic, acidophilic cells that have strong cytoplasmic GH reactivity on immunohistochemistry. In contrast, the sparsely granulated variants are composed of chromophobe cells with considerable nuclear and cytologic pleomorphism and focal, weak staining for GH. Bihormonal **mammosomatotroph** adenomas that synthesize both GH and prolactin are being increasingly recognized; morphologically, most bihormonal adenomas resemble the densely granulated pure somatotroph adenomas, but are distinguished by having immunohistochemical reactivity for prolactin as well as GH.

Clinical Course. Persistently elevated levels of GH stimulate the hepatic secretion of insulin-like growth factor 1 (IGF-1), which causes many of the clinical manifestations.

- If a somatotroph adenoma appears in children before the epiphyses have closed, the elevated levels of GH (and IGF-1) result in *gigantism*. This is characterized by a generalized increase in body size with disproportionately long arms and legs.
- If the increased levels of GH are present after closure of the epiphyses, *acromegaly* develops. In this condition, growth is most conspicuous in skin and soft tissues, viscera (thyroid, heart, liver, and adrenals), and the bones of the face, hands, and feet. Bone density may increase (hyperostosis) in both the spine and the hips. Enlargement of the jaw results in its protrusion (prognathism), and broadening of the lower face. The feet and hands are enlarged, and the fingers become thickened and sausage-like. In most instances gigantism is also accompanied by evidence of acromegaly. These changes may develop slowly over decades before being recognized, hence the opportunity for the adenomas to reach substantial size.
- GH excess can also be associated with a variety of other disturbances, including gonadal dysfunction, diabetes mellitus, generalized muscle weakness, hypertension, arthritis, congestive heart failure, and an increased risk of gastrointestinal cancers.

The diagnosis of pituitary GH excess relies on documentation of elevated serum GH and IGF-1 levels. In addition, failure to suppress GH production in response to an oral load of glucose is one of the most sensitive tests for acromegaly. The underlying pituitary adenoma can be either removed surgically or treated via pharmacologic means. The latter includes somatostatin analogs (recall that somatostatin inhibits pituitary GH secretion) or the use of GH receptor antagonists, which prevent hormone binding to target organs such as the liver. When effective control of high GH levels is achieved, the characteristic tissue overgrowth and related symptoms gradually recede, and the metabolic abnormalities improve.

Corticotroph Adenomas

Excess production of ACTH by functioning corticotroph adenomas leads to adrenal hypersecretion of cortisol and the development of *hypercortisolism* (also known as *Cushing syndrome*).

MORPHOLOGY

Corticotroph adenomas are usually microadenomas at the time of diagnosis. These tumors are most often basophilic **(densely granulated)** and occasionally chromophobic **(sparsely granulated)**. Both variants stain positively with periodic acid-Schiff (PAS) because of the presence of carbohydrate in proopiomelanocortin (POMC), the ACTH precursor molecule; in addition, they demonstrate variable immunoreactivity for POMC and its derivatives, including ACTH and β-endorphin.

Clinical Course. The clinical manifestations of Cushing syndrome are discussed in more detail later with the diseases of the adrenal gland. The syndrome can be caused by a wide variety of conditions in addition to ACTH-producing pituitary tumors. When the hypercortisolism is due to excessive production of ACTH by the pituitary, it is