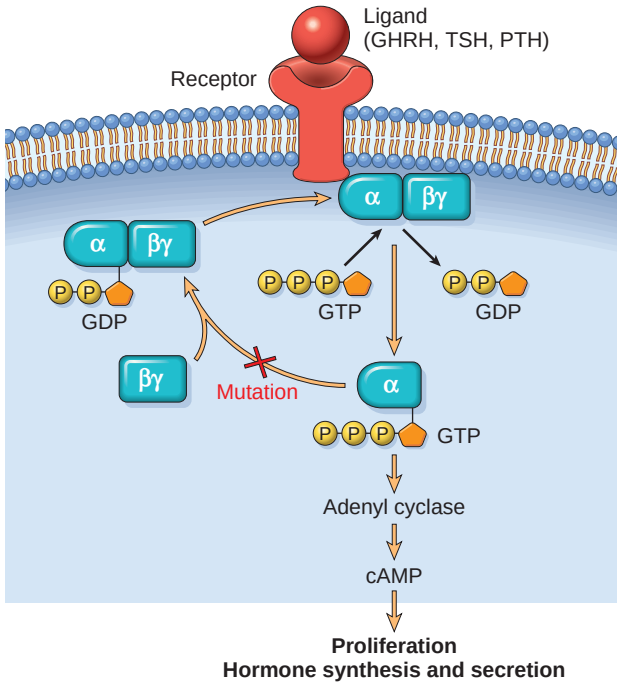

Figure 24-3 G-protein signaling in endocrine neoplasia. Mutations that lead to G-protein hyperactivity are seen in a variety of endocrine neoplasms, including pituitary, thyroid, and parathyroid adenomas. G proteins (composed of α and βγ subunits) play a critical role in signal transduction, transmitting signals from cell surface receptors (GHRH, TSH, or PTH receptor) to intracellular effectors (e.g., adenyl cyclase), which then generate second messengers (cAMP, cyclic adenosine monophosphate) that stimulate cellular responses. GDP, guanosine diphosphate; GTP, guanosine triphosphate; P_i, inorganic phosphate. See Figure 24-1 for other abbreviations.

critical role in signal transduction, transmitting signals from particular *cell surface receptors* (e.g., GHRH receptor) to *intracellular effectors* (e.g., adenyl cyclase), which then generate *second messengers* (e.g., cyclic adenosine monophosphate, cAMP). These are heterotrimeric proteins, composed of a specific α-subunit that binds guanine nucleotide and interacts with both cell surface receptors and intracellular effectors (Fig. 24-3); the β- and γ-subunits are noncovalently bound to the specific α-subunit. G_s is a stimulatory G protein that has a pivotal role in signal transduction in several endocrine organs, including the pituitary. The α-subunit of G_s ($G_s\alpha$) is encoded by the *GNAS* gene, located on chromosome 20q13.

In the basal state, G_s exists in an inactive state, with guanosine diphosphate (GDP) bound to the guanine nucleotide-binding site of $G_s\alpha$. On interaction with the ligand-bound cell surface receptor, GDP dissociates, and guanosine triphosphate (GTP) binds to $G_s\alpha$, activating the G protein. The activation of $G_s\alpha$ results in the generation of cAMP, which is a potent mitogen for a variety of endocrine cell types (e.g., pituitary somatotrophs and corticotrophs, thyroid follicular cells, parathyroid cells), promoting cellular proliferation and hormone synthesis and secretion. Normally, $G_s\alpha$ activation is *transient* because of an intrinsic GTPase activity in the α-subunit, which hydrolyzes GTP into GDP.

Approximately 40% of somatotroph cell adenomas bear GNAS mutations that abrogate the GTPase activity of Gsα, leading to constitutive activation of Gsα, persistent generation of cAMP, and unchecked cellular proliferation (Table 24-2). *GNAS* mutations have also been described in a minority of corticotroph adenomas; in contrast, *GNAS* mutations are absent in thyrotroph, lactotroph, and gonadotroph adenomas, because their respective hypothalamic release hormones do not act via cAMP-dependent pathways.

- The overwhelming majority of pituitary adenomas are sporadic in nature, but approximately 5% of cases arise as a result of an inherited genetic defect. Four causative genes have been identified thus far: *MEN1*, *CDKN1B*, *PRKAR1A*, and *AIP* (see Table 24-2 for a summary of these aberrrations and most commonly associated pituitary tumor subtypes). Of note, somatic mutations of these four genes are rarely encountered in sporadic pituitary adenomas.
- Molecular abnormalities associated with aggressive behavior include aberrations in cell cycle checkpoint proteins, such as overexpression of cyclin D1, mutations of *TP53*, and epigenetic silencing of the retinoblastoma gene (*RB*). In addition, activating mutations of the *HRAS* oncogene are observed in rare *pituitary carcinomas* (Table 24-2).

MORPHOLOGY

The **typical pituitary adenoma** is soft and well-circumscribed. Small adenomas may be confined to the sella turcica, but with expansion they frequently erode the sella turcica and anterior clinoid processes. Larger lesions usually extend superiorly through the diaphragm sella into the suprasellar region, where they often compress the optic chiasm and adjacent structures, such as some of the cranial nerves (Fig. 24-4). In as many as 30% of cases, the adenomas are not grossly encapsulated and infiltrate neighboring tissues such as the cavernous and sphenoid sinuses, dura, and on occasion, the brain itself. Such lesions are termed **invasive adenomas**. Not unexpectedly, macroadenomas are invasive more frequently than smaller tumors. Foci of hemorrhage and necrosis are also more common in these larger adenomas.

Histologically, typical pituitary adenomas are composed of uniform, polygonal cells arrayed in sheets or cords. Supporting connective tissue, or reticulin, is sparse, accounting for the soft, gelatinous consistency of many of these tumors. Mitotic activity is usually sparse. The cytoplasm of the tumor cells may be acidophilic, basophilic, or chromophobic, depending on the type and amount of secretory product within the cells, but it is generally uniform throughout the tumor. **This cellular monomorphism and the absence of a significant reticulin network distinguish pituitary adenomas from nonneoplastic anterior pituitary parenchyma** (Fig. 24-5). The biologic behavior of the adenoma cannot always be reliably predicted from its histologic appearance. A subset of pituitary adenomas demonstrates elevated mitotic activity and nuclear p53 expression, a feature that correlates with the presence of *TP53* mutations. These tumors have a higher propensity for aggressive behavior, including invasion and recurrence, and are termed **atypical adenomas**.

Clinical Course. The signs and symptoms of pituitary adenomas are related to endocrine abnormalities and mass effects. The effects of excessive secretion of anterior