ENDOCRINE DISEASES

1
PITUITARY GLAND

NORMAL PITUITARY GLAND

Embryology

The human pituitary gland consists of the adenohypophysis and neurohypophysis, and can be recognized grossly by the third month of fetal development (1,4,6,10,11,17). The adeno-hypophysis develops from Rathke's pouch, which starts to form around the fourth and fifth fetal weeks from an evagination of the stomateal ectoderm. This ectoderm grows upward, detaches from the buccal cavity, and comes to lie in a de-pression of the sphenoid bone, the anlage of the sella turcica. The neurohypophysis is formed by the merging of the infundibular process of the primitive diencephalon with Rathke's pouch. The three parts of the neurohypophysis include the infundibulum, the infundibular stem, and the posterior lobe. The anterior lobe is formed by the proliferation of cells in the anterior part of Rathke's pouch. Although an intermediate lobe does not develop in humans, the posterior wall of Rathke's pouch forming the neurohypophy-sis gives rise to the pars tuberalis, which is an upward extension around the stalk.

The pharyngeal pituitary is formed by nests of adenohypophyseal cells trapped in the pharyngeal mucosa. The most common location of the pharyngeal pituitary is in the sphenoid bone, although various other loca-tions have been reported (3). Ectopic pituitary adenomas may arise from these pharyngeal pituitary nests (14).

The hormone-producing cells of the anterior pituitary can be recognized fairly early in develop-ment (2,16). Corticotropin (ACTH) cells can be recognized by 5 weeks, growth hormone (GH) cells by 8 weeks, and the alpha subunit of glyco-protein hormone by 9 weeks of gestation. Thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) cells can be detected by 12 weeks of gestation. Prolactin (PRL) cells are detected starting around 12 weeks and increase in number to term.

Recent advances in molecular biology have isolated and characterized various transcription factors, which are proteins that regulate cell differentiation and proliferation by binding to DNA in the cell nucleus (Table 1-1). These transcription factors are important for the nor-mal development and function of the anterior pituitary (18). Molecular and other defects in the expression of transcription factors can lead to specific endocrine disorders.

Gross Anatomy

The pituitary gland in adults weighs be-tween 400 and 600 mg and measures about 13 x 9 x 6 mm. During pregnancy the gland can double in weight, and it is consistently heavier

Table 1-1

TRANSCRIPTION FACTORS IMPORTANT FOR PITUITARY DEVELOPMENT

Factor	Target Cells
Pit-1/GHF1	GH/PRL/TSH
Thyrotroph embryonic factor (TEF)	TSH
Corticotroph upstream transcription element-binding (CUTE) protein	ACTH
Steroidogenic factor Ad4BP/SF-1	LH/FSH
Estrogen receptor	PRL/Gonadotroph
Glucocorticoid receptor	ACTH

Figure 1-1

NORMAL ANATOMY
OF PITUITARY GLAND

Sagittal T1-weighted image of the normal pituitary demonstrating: 1) pituitary gland, 2) infundibular stalk, 3) optic chiasm, 4) optic nerve, 5) third ventricle, and 6) mammillary body.
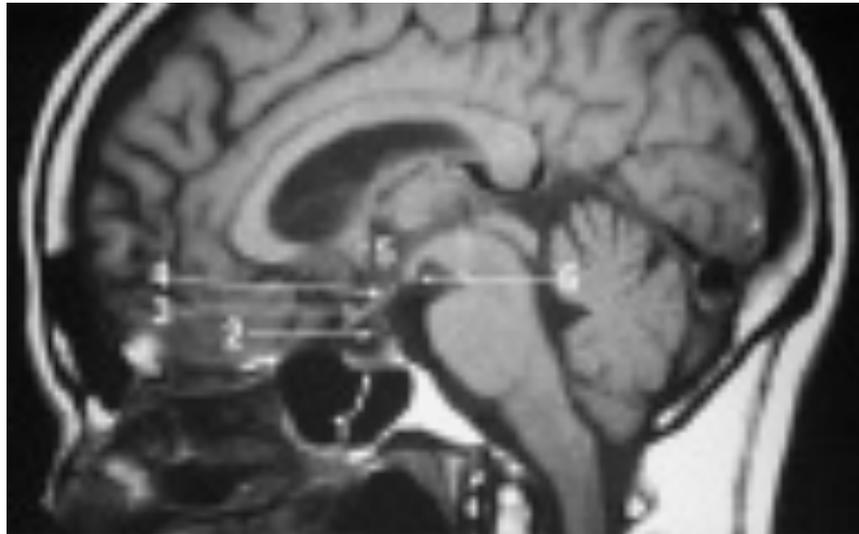

Figure 1-2

GROSS NORMAL ANATOMY
OF PITUITARY GLAND

Gross photograph showing the relationship of the pituitary gland to various structures. The optic chiasm is present on top, the internal carotid arteries laterally, and the sphenoid air sinus. (Courtesy of B. Scheithauer, Rochester, MN.)

in multiparous women (1,11). The pituitary is surrounded by the dura mater which forms the roof of the sella turcica in which the pituitary lies. The pituitary lies adjacent to many important structures including the internal carotid arteries, lateral in the cavernous sinuses, the optic chiasm and optic tracts in front and above, the base of the diencephalon above, and the sphenoid air sinus in front and below (figs. 1-1, 1-2). The sellar diaphragm is also present on the roof of the sella turcica and is made up of a fold of dura mater extending transversely across the sella. Its center is perforated for the passage of the infundibulum.

The adenohypophysis or anterior pituitary constitutes about 70 to 80 percent of the gland. It is composed of: 1) the pars distalis, which contains all of the hormone-producing cells; 2) remnants of the pars intermedia represented by a few colloid-filled cavities lined by epithelial cells; and 3) the pars tuberalis composed of squamous cell nests and a few anterior pituitary cells, especially glycoprotein-producing hormone cells (fig. 1-3).
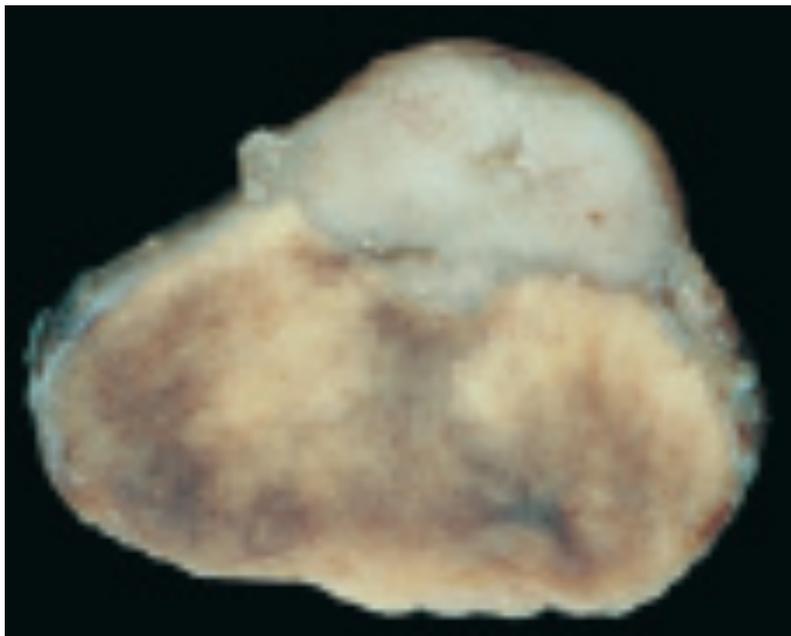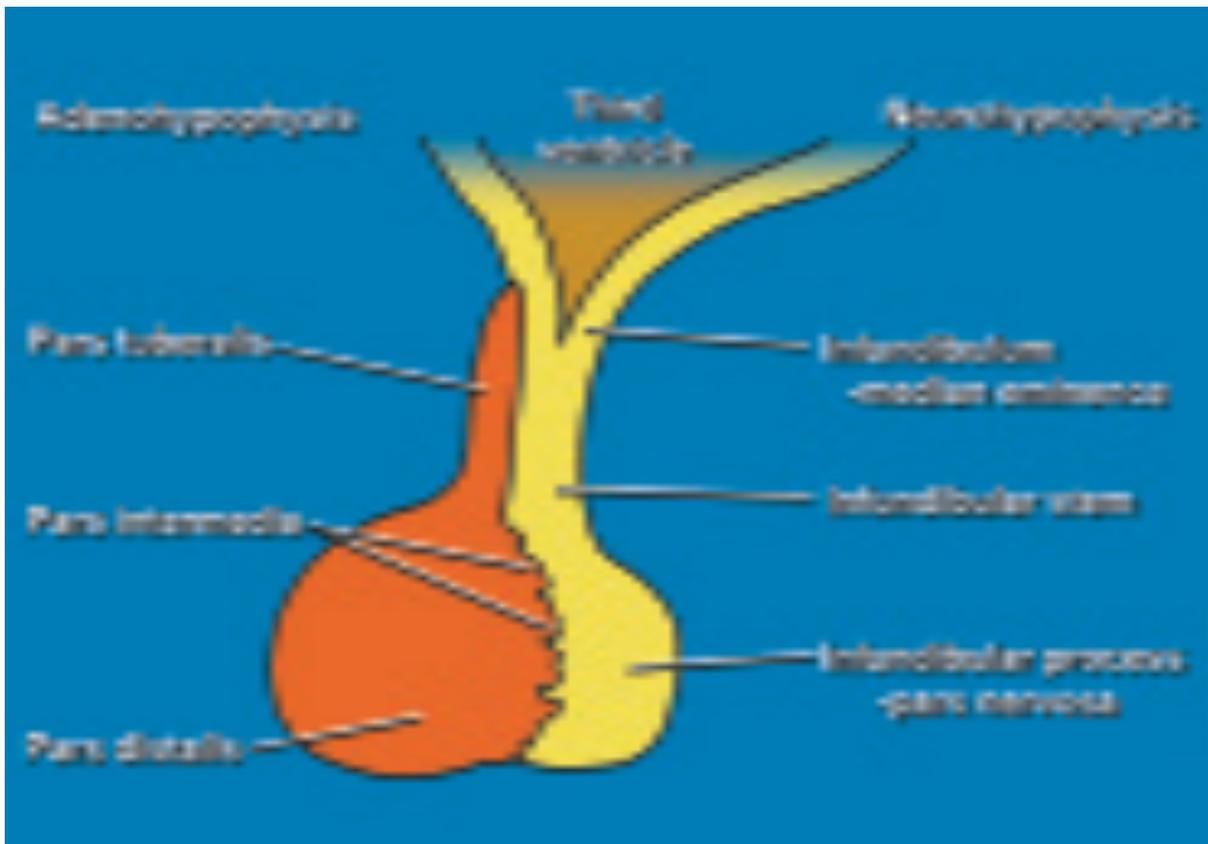
Figure 1-3

NORMAL ANATOMY
OF PITUITARY GLAND

Above: Diagram illustrating the parts of the adenohypophysis and neurohypophysis.

Left: Horizontal cross section showing the anterior (lower) and posterior (upper) lobes. (Figure 1-5 from Fascicle 22, 3rd Series.)

The neurohypophysis or posterior pituitary constitutes the remaining 20 to 30 percent of the gland (fig. 1-3). It is composed of: 1) the infundibulum or median eminence, which is attached to the hypothalamus and receives the hypothalamic peptidergic neurons with releasing and inhibiting hormones that regulate anterior pituitary cell function; 2) the pituitary stalk or infundibular stem composed of unmyelinated nerve fiber tracts which originate in the hypothalamus and portal vessels. These fibers transport hypothalamic peptides to the anterior pituitary; and 3) the posterior lobe, composed of the infundibular process and pars nervosa, which stores vasopressin and oxytocin hormones.

The pituitary gland is located strategically within the sphenoid bone and is adjacent to the internal carotid arteries and lateral to several cranial nerves. The internal carotid arteries give rise to the paired superior, middle, and inferior hypophyseal arteries (7). The external plexus is formed by the superior hypophyseal arteries entering the medial eminence. They terminate in gomitoli or long central arteries with muscle layers and a dense capillary plexus. Parallel veins are formed from the capillaries that travel down the pituitary stalk and end in the fenestrated capillaries of the anterior pituitary lobe. The inferior hypophyseal arteries supply blood to the posterior lobe while the middle hypophyseal arteries enter the anterior lobe and supply some of the adenohypophyseal cells at the periphery of the gland. The short portal vessels which originate in the posterior lobe and distal portions of the stalk supply about 10 to 20 percent of the blood flow to the anterior lobe (7). Venous blood from the pituitary returns via the cavernous sinuses, inferior petrosal sinuses, and internal jugular veins.

The pars distalis has no direct nerve supply, except for a few sympathetic fibers that penetrate the anterior lobe along the capillaries. These pericapillary nerve fibers do not regulate anterior pituitary hormone secretion, but may affect blood flow to the pituitary.

The posterior pituitary lobe is composed of nerve fibers and axon terminals, pituicytes, and dense core granules of stored neurosecretory proteins: oxytocin, vasopressin, and neurophysin. The hypothalamic tracts from the supraoptic and paraventricular nuclei travel from the
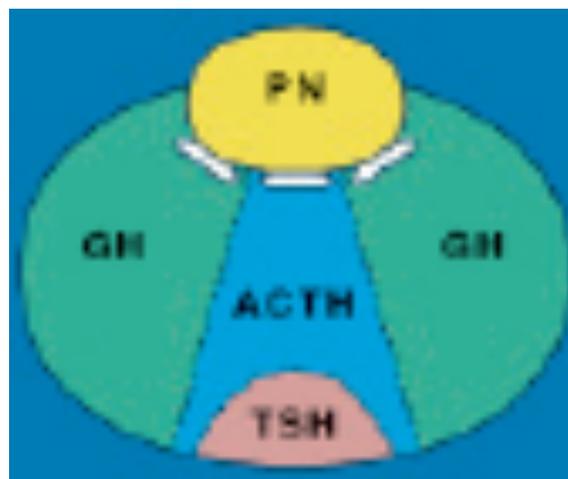

Figure 1-4

NORMAL HISTOLOGY OF PITUITARY GLAND
Diagram illustrating the topographic distribution of various pituitary cell types in the adenohypophysis and the adjacent pars nervosa (PN) of the neurohypophysis.

hypothalamus to the stalk of the posterior lobe as tracts of the supraopticohypophyseal and tuberohypophyseal fibers. Neural connections influence posterior pituitary secretion of oxytocin and vasopressin, as evidenced by the severe atrophy of the neurohypophysis after stalk sectioning or with injury to the axons originating in the supraoptic and paraventricular nuclei.

Microscopic Anatomy and Physiology

A horizontal section across the anterior pituitary reveals fibrous trabeculae in the mid-central portion with lateral wings and a central mucoid wedge (fig. 1-4). Hematoxylin and eosin (H&E)–stained sections show acidophil, basophil, and chromophobe cells. The acidophil cells are present mainly in the lateral wings, the basophil cells are in the mucoid wedge, while the chromophobe cells are widely dispersed (fig. 1-5). Each anterior pituitary cell has a basement membrane, and groups of cells form reticulin-positive clusters with adjacent capillaries (fig. 1-5). Unlike the anterior pituitary which has an indirect arterial blood supply, the posterior pituitary has a direct blood supply from branches of the inferior branches of the internal carotid arteries. Immunohistochemical staining is the method of choice for identifying individual anterior pituitary cells
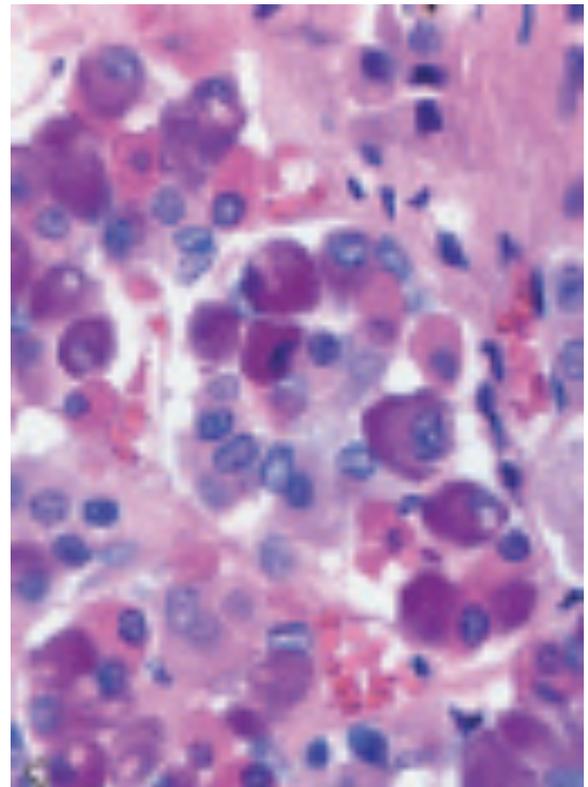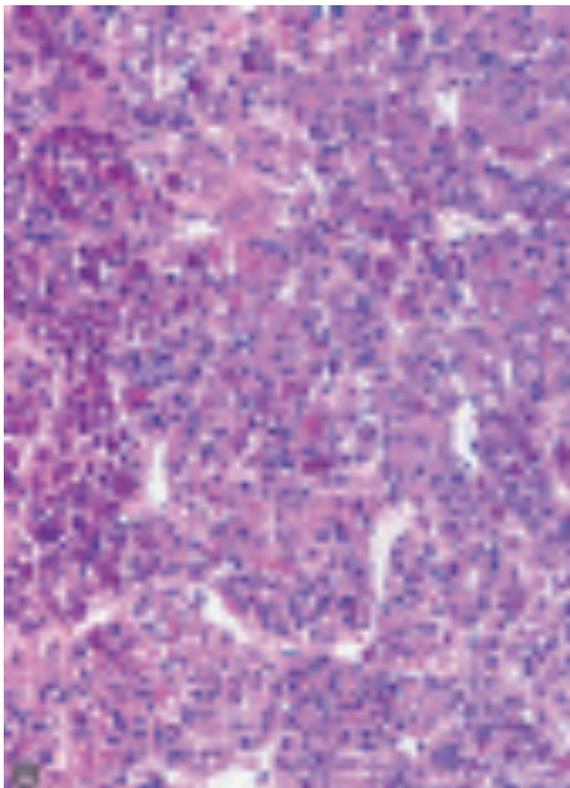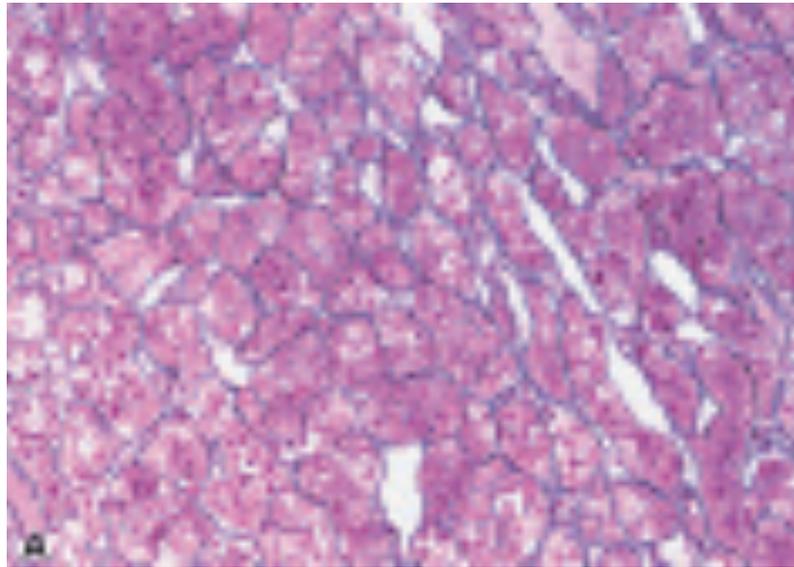
Figure 1-5

NORMAL HISTOLOGY OF ANTERIOR PITUITARY GLAND

Clusters of various cell types are present.
A: Reticulin stain highlights the acinar clusters.
B: The H&E-stained section shows a mixture of various cell types in the acinar clusters.
C: Higher magnification illustrates acidophils with pink cytoplasm, basophils with red cytoplasm, and chromophobes with amphophilic cytoplasm.

Figure 1-6

IMMUNOHISTOCHEMISTRY
OF PITUITARY GLAND

Immunohistochemical staining shows various cell types in the anterior pituitary. The PRL cells stain brown, the GH cells stain blue, and the LH cells stain gray-black. GH cells are the most abundant type in the anterior pituitary (immunohistochemistry chromogens include: diaminobenzidine [brown], NBT-BCIP [blue], and 4-chloro-1-napthol [gray-black]).
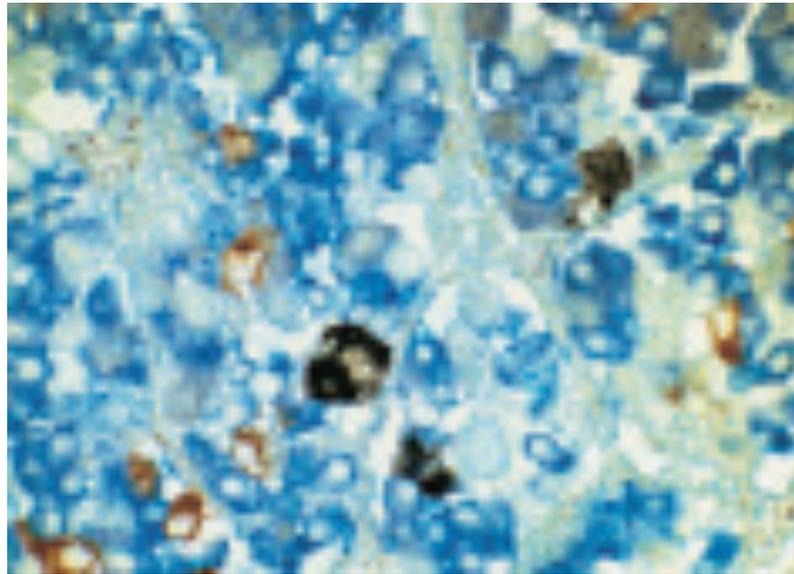

Table 1-2

HYPOTHALAMIC HORMONES REGULATING PITUITARY SECRETION AND TARGET TISSUES

Peptide/Amine	Pituitary Hormone	Target Tissues
Stimulating		
Corticotropin-releasing hormone	ACTH	Adrenal cortex
Gonadotropin-releasing hormone	FSH/LH	Ovaries, testes
Growth hormone–releasing hormone	GH	Many tissues
Thyrotropin-releasing hormone	TSH/PRL	Thyroid, breast, many other tissues
Vasoactive intestinal polypeptide	PRL	Breast, many other tissues
Inhibitory		
Somatostatin	GH	Many tissues
Dopamine	PRL	Breast, many other tissues
Others		
Vasopressin (ADH)	(Posterior pituitary)	Kidney
Oxytocin	(Posterior pituitary)	Uterus, breast

(fig. 1-6). Electron microscopic examination also allows the characterization of unique features of different cell types (fig. 1-7) (9,11).

The hypothalmic-releasing and -inhibiting hormones are important in regulating anterior pituitary function (Table 1-2, fig. 1-8). A negative feedback mechanism operates between specific target organs, the pituitary, and the hypothalamus. For example, thyroid hormone exerts a negative feedback effect on the pituitary and hypothalamus to regulate the secretion of thyrotropin-releasing hormone from hypothalamic neurons and thyroid-stimulating hormone from the pituitary gland.

Somatotroph (GH) Cells

These cells are usually acidophilic on H&E staining. They constitute approximately 40 to 50 percent of the secretory cells in the adult pituitary gland (fig. 1-9). Most GH cells are present in the lateral wings of the anterior pituitary. Ultrastructural analysis show cells with dense secretory granules ranging from 350 to 500 nm in diameter.

The GH gene, located on chromosome 17, is 2.5 kb long and directs the synthesis of a 191 amino acid single-chain peptide with two inter-chain disulfide bands. At the ultrastructural level, GH secretory granules are present throughout
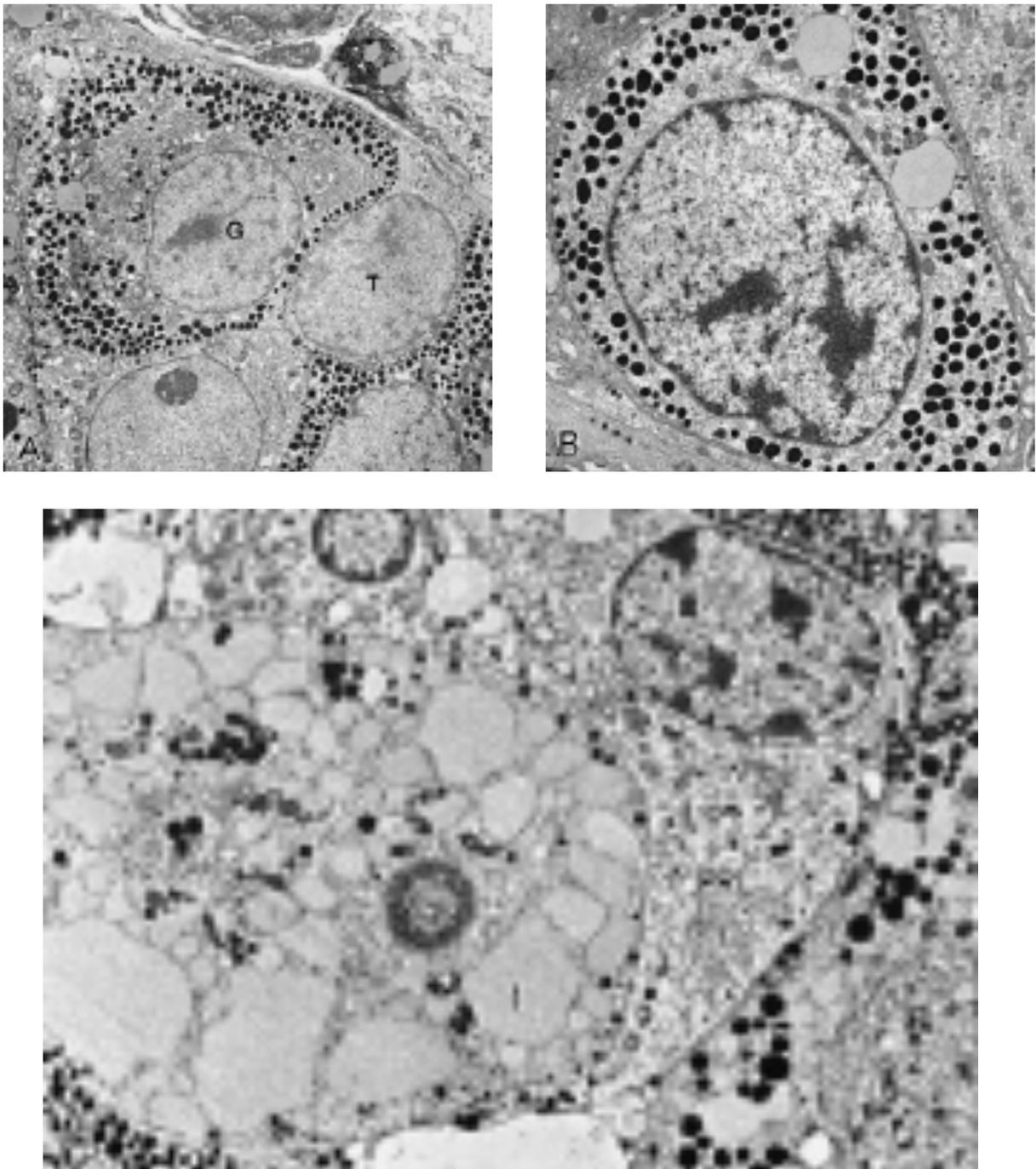
Figure 1-7

ULTRASTRUCTURE OF ANTERIOR PITUITARY GLAND

A: Ultrastructural features of anterior pituitary hormones show a mixture of various cell types with secretory granules of specific size. G, growth hormone cell; T, thyrotroph (X3,000).

B: Higher magnification of a growth hormone cell showing abundant secretory granules 350 to 500 nm in diameter (X7,000).

C: Two stimulated gonadotrophs (1,2) show marked dilation of the rough endoplasmic reticulum and prominent Golgi complex. Secretory granules are sparse and relatively large. A PRL cell (PRL) is between the two gonadectomy cells. (Figure 30 from Fascicle 21, 2nd Series.)
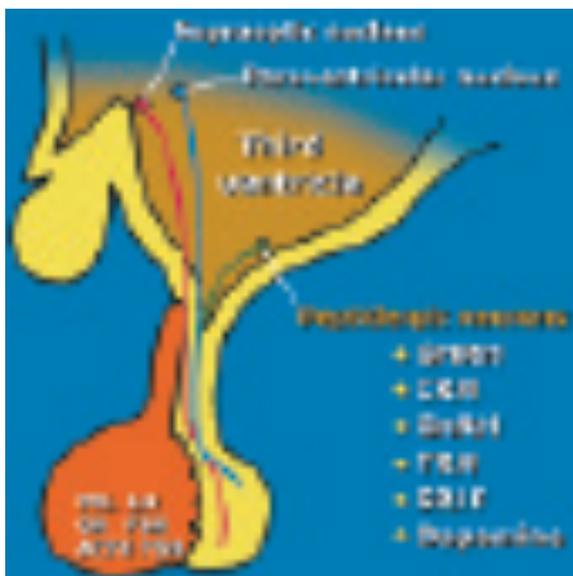
Figure 1-8

HYPOTHALAMIC HORMONES

Schematic diagram showing the hypothalamic neurons producing the various stimulatory and inhibitory substances that regulate anterior pituitary function. The supraoptic and paraventricular nuclei produce oxytocin and vasopressin which are stored in the posterior pituitary. GHRH = growth hormone-releasing hormone; CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone; TRH = thyrotropin-releasing hormone; SRIF = somatostatin. Unlike the other peptides, dopamine is an amine that inhibits PRL secretion.

Table 1-3

ANTERIOR PITUITARY HORMONES: CELL TYPE, DISTRIBUTION, AND FUNCTION

Cell Type	Cell Percentage in Pituitary (Approximately)	Function
GH	40–50	Stimulates linear growth
PRL	10–30 production	Stimulates breast milk
ACTH	10–20	Stimulates cortisol synthesis
FSH/LH	10	Stimulates estrogen and testosterone synthesis
TSH	5	Stimulates thyroid hormone synthesis

the cytoplasm. GH secretion is regulated by growth hormone-releasing hormone (GHRH) and somatostatin release-inhibiting factor (SRIF). The latter peptide inhibits growth hormone secretion. Insulin-like growth factor 1 (IGH-1) or somatonectin C, which is produced by the liver, mediates many of the effects of GH. IGH-1 exerts a negative feedback effect on GH secretion at the hypothalamic and pituitary levels.

Lactotroph (PRL) Cells

Lactotrophs may be acidophilic or chromophobic and are present in the highest density in the posterolateral wings, but are located throughout the anterior pituitary (fig. 1-10). PRL cells account for 10 to 30 percent of anterior pituitary cells (Table 1-3) (1). The exact percentage varies with age, sex, parity, and hormonal status. Electron microscopy shows that PRL cells

are usually sparsely granulated, with secretory granules of up to 650 nm in diameter. The cells usually have well-developed rough endoplasmic reticulum and Golgi complexes.

The PRL gene, located on chromosome 6, is greater than 10 kb long, and the mRNA is about 1 kb long. The protein is a 198 amino acid peptide which has a common evolutionary origin with GH. At the ultrastructural level, PRL cells have secretory granules 200 to 300 nm in diameter. PRL cells have a unique way of extruding granules by "misplaced" exocytosis in which the granule content is secreted into the extracellular space away from the capillaries (fig. 1-11).

One of the functions of PRL hormone is to stimulate lactation. Receptors for PRL are widely distributed in many cells, although the function of the hormone in many tissues remains unknown. Stimulation of pituitary PRL secretion is by thyrotropin-releasing hormone (TRH) and vasoactive intestinal polypeptide (VIP), while dopamine inhibits PRL secretion.

Mammosomatotroph (PRL/GH) Cells

These uncommon cells are present in the normal pituitary gland and increase in number during pregnancy. The regulation of this cell type is unknown, but tumor cells with features of mammosomatotrophs are not uncommon in large series of pituitary adenomas examined ultrastructurally (9,11,12).
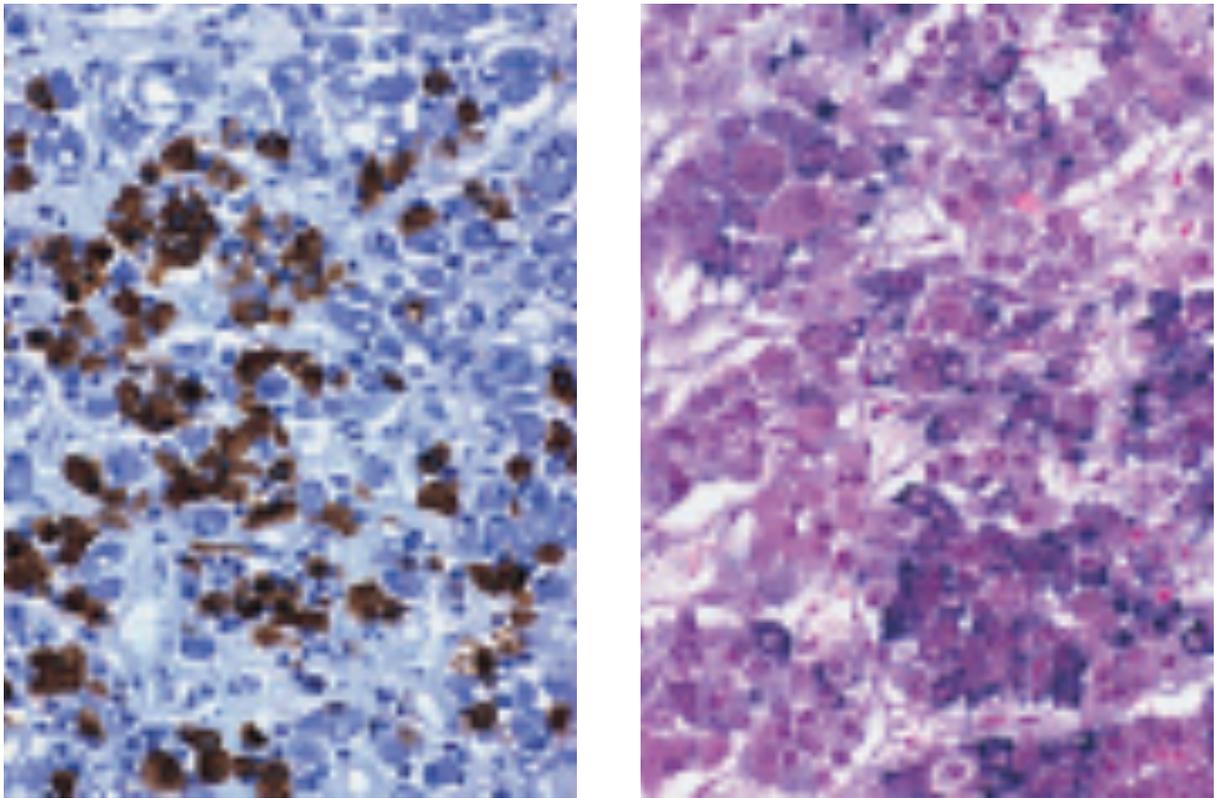
Figure 1-9

IMMUNOHISTOCHEMISTRY OF GH CELLS

Left: Immunohistochemical staining for GH shows many positive cells with brown cytoplasmic staining.

Right: In situ hybridization for GH messenger RNA shows many positive cells with blue cytoplasmic staining using alkaline phosphatase with NBT/BCIF. GH cells constitute about 40 to 50 percent of anterior pituitary cells.
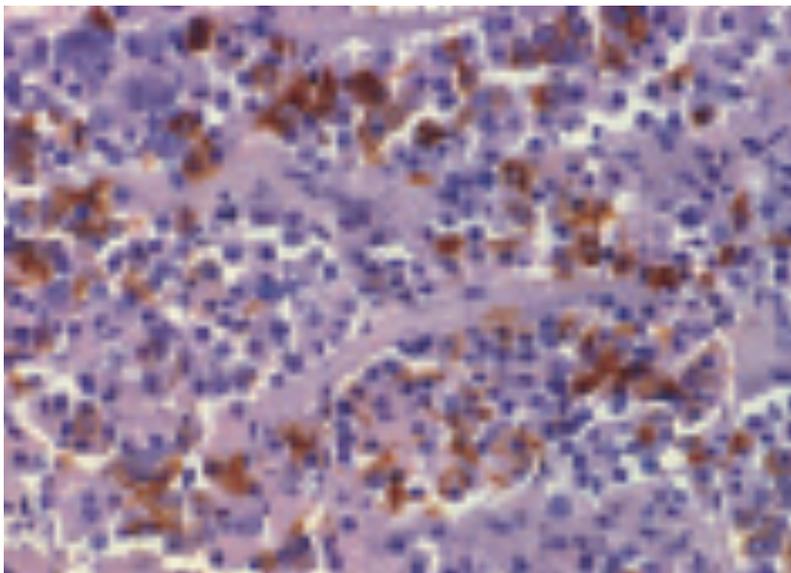

Figure 1-10

IMMUNOHISTOCHEMISTRY
OF PRL CELLS

Immunohistochemical staining for PRL in the anterior pituitary. These cells constitute 10 to 30 percent of anterior pituitary cells.

Figure 1-11

ULTRASTRUCTURE
OF PRL CELLS

Ultrastructural examination shows "misplaced" exocytosis in a prolactinoma (arrows). The secretory granules are secreted into the extracellular space away from the capillary (X14,000) (diaminobenzidine chromogen).

Corticotroph (ACTH) Cells

ACTH cells are basophilic cells representing 10 to 20 percent of anterior pituitary cells (fig. 1-12). They are present mainly in the mucoid wedge, the area that on horizontal cross section is the central portion of the gland that abuts the pars nervosa. Clusters of ACTH cells may be seen in the posterior pituitary, a phenomenon known as basophil invasion (fig. 1-13). The importance of recognizing this condition is to distinguish it from corticotrophic adenomas (11,13). ACTH cells stain for periodic acid–Schiff (PAS). In contrast, the GH and PRL cells are PAS negative. At the ultrastructural level, they contain 300- to 500-nm secretory granules and large perinuclear vacuoles known as enigmatic bodies; the latter are large phagolysosomes.

The pro-opiomelanocortin (POMC) gene is located on chromosome 2 and consists of three exons. ACTH is a 39 amino acid single-chain peptide derived from the 31-kd POMC glycoprotein. Perinuclear clusters of type 1, 6- to 9-nm keratin filaments, which react with antibodies directed against keratins of 54 to 60 kd, are commonly present in the cytoplasm.

ACTH stimulates the adrenal cortex to secrete glucocorticoids, mineralocorticoids, and sex steroids. The hypothalamus produces corticotropin-releasing hormone (CRH) which stimulates ACTH secretion. Glucocorticoids exert a direct negative feedback effect on both hypothalamic CRH and anterior pituitary ACTH secretion. When ACTH cells are suppressed by high levels of glucocorticoids from endogenous or exogenous sources, type 1 intermediate filaments accumulate in the cytoplasm and the secretory granules are pushed to the cell periphery adjacent to the cell membrane (fig. 1-14). These distinctively pathognomonic changes are known as *Crooke's hyalinization* or *Crooke's hyaline changes*.

Thyrotroph (TSH) Cells

TSH cells comprise less than 5 percent of anterior pituitary cells and are located principally in the anteromedial portion of the mucoid wedge (fig. 1-15). TSH cells are angular and contain cytoplasmic PAS-positive droplets. Ultrastructurally, TSH cells have small spherical secretory granules, 100 to 200 nm in diameter, usually located close to the cell membrane.

The TSH beta subunit gene is located on chromosome 1 and consists of three exons. The alpha subunit gene is found on chromosome 6 and is 9.4 kb long with four exons. The alpha subunit protein consists of 92 amino acids. The thyrotropin molecule is a 28-kd glycoprotein and the beta subunit which confers the specificity for TSH action ranges from 18 to 21 kd, depending on whether it contains one or two carbohydrate chains.
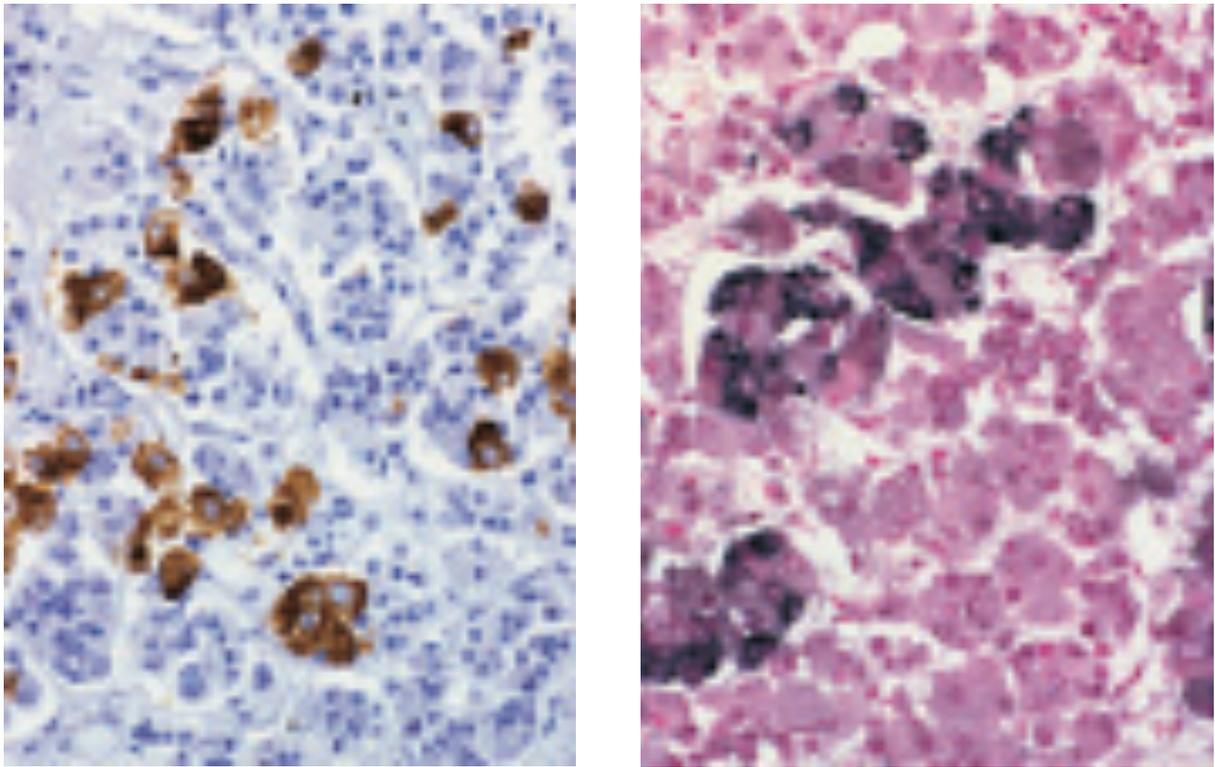
Figure 1-12

IMMUNOHISTOCHEMISTRY OF ACTH CELLS

Left: Immunohistochemical staining for ACTH.

Right: Another area of the anterior pituitary stained for pro-opiomelanocortin (POMC) messenger RNA by in situ hybridization shows a nodular cluster of POMC cells in the mucoid wedge. ACTH cells are present in 10 to 20 percent of anterior pituitary cells (alkaline phosphatase with NBT/BCIP).

The hypothalamic thyrotropin-releasing hormone (TRH) stimulates TSH secretion from the pituitary. Thyroid hormone feeds back on the hypothalamus and pituitary to regulate TSH secretion.

Gonadotroph (FSH/LH) Cells

Most gonadotropic cells produce both FSH and LH (fig. 1-16). FSH/LH cells are basophilic and are evenly distributed in the anterior pituitary. They comprise about 10 percent of anterior pituitary cells. Both FSH and LH share the same alpha subunit as TSH, while the beta subunit is unique for each molecule. The FSH beta gene is located on chromosome 11 and consists of three exons; the protein has 130 amino acids. The LH beta gene is located on chromosome 19 and consists of three exons; the LH beta protein consists of 145 amino acids.

Most gonadotroph cells contain both FSH and LH proteins which are located in small (200 nm) and larger (300 to 600 nm) secretory granules. FSH stimulates spermatogenesis and the growth of ovarian follicles while LH induces ovulation, luteinization of the ovarian follicles, and steroidogenesis. LH also stimulates Leydig cells to produce testosterone and the ovary to elaborate luteal phase hormones. Removal of the gonadal organs results in hypertrophy and hyperplasia of the pituitary gonadotropic cells with formation of "gonadectomy" cells (see fig. 1-7C).

Folliculostellate Cells

These are agranular cells located in the anterior pituitary (fig. 1-17) (5,15). They are irregular and somewhat star-shaped, hence the designation stellate. Folliculostellate cells have long cytoplasmic processes that extend between
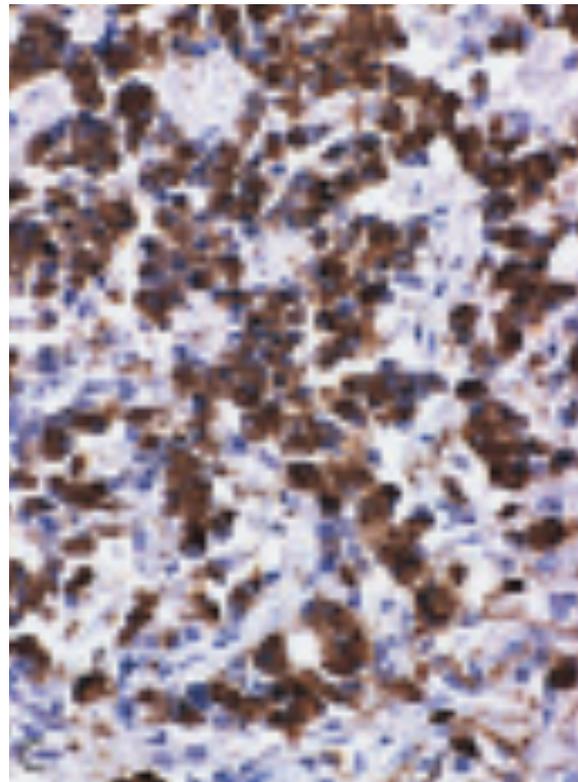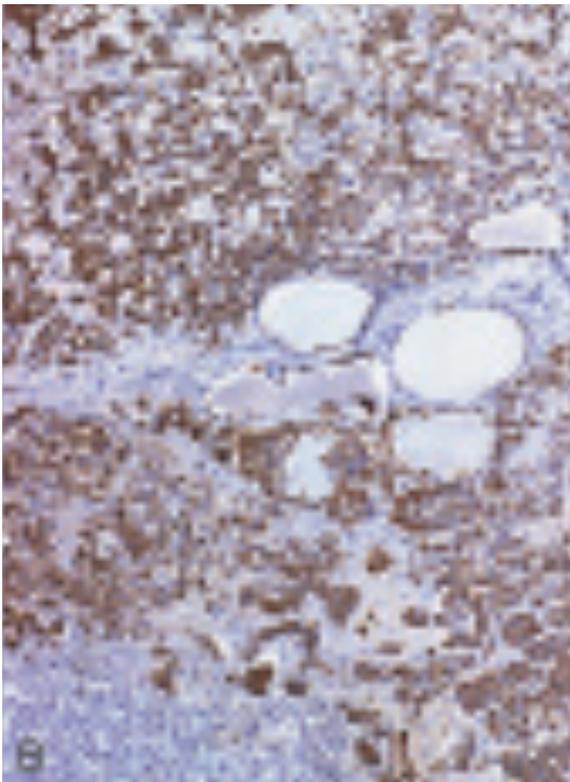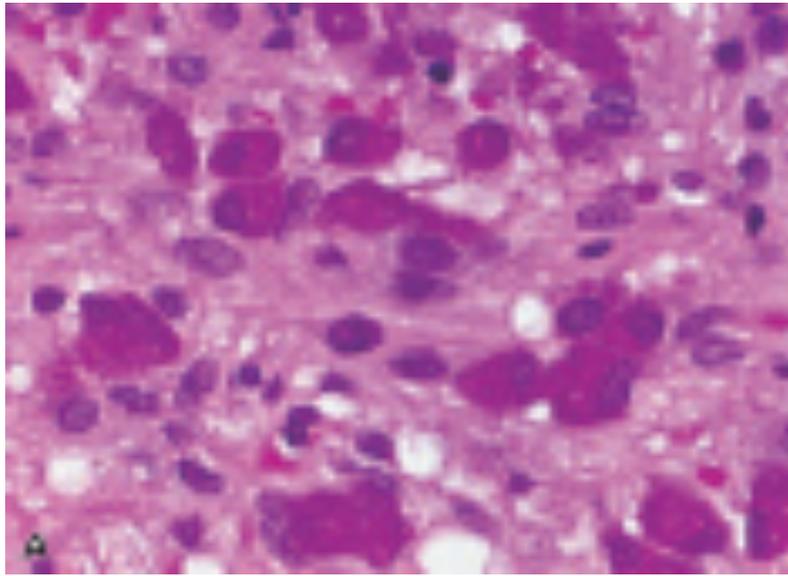
Figure 1-13

BASOPHIL INVASION

Basophil or corticotroph invasion into the pars nervosa. The "invading" cells have basophilic cytoplasm and are located among the processes of the pars nervosa (A). The relationship of the ACTH cells in the anterior pituitary (left) and the "invading" ACTH cells in the pars nervosa is shown in B. The two groups of cells are separated by the cystic spaces of the residual pars intermedia (B). Higher magnification of the ACTH-positive cells in the pars nervosa shows that some cells are in small clusters which could be misdiagnosed as an ACTH adenoma in a small biopsy (C).
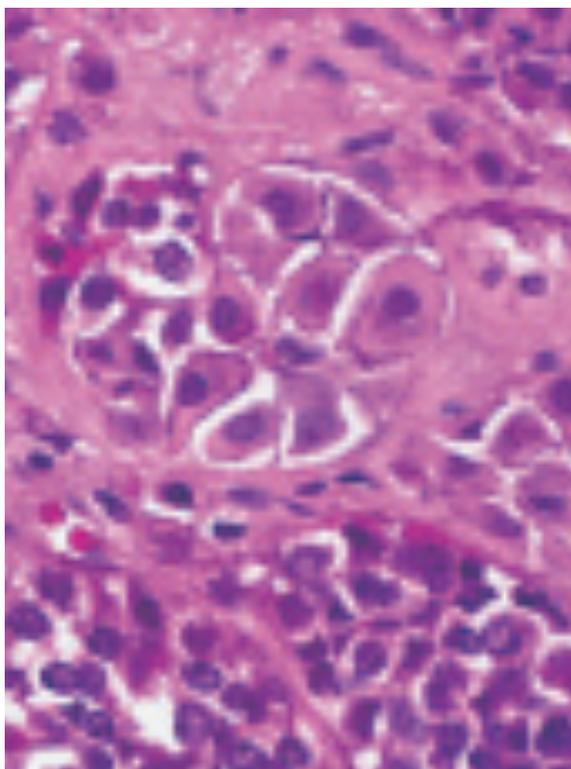
Figure 1-14

CROOKE'S CHANGES

Crooke's hyaline changes secondary to excess glucocorticoids leads to accumulation of type 1 intermediate filaments. The secretory granules are pushed to the periphery of the cells, and the hyaline-appearing keratin filaments are prominent in the cytoplasm.
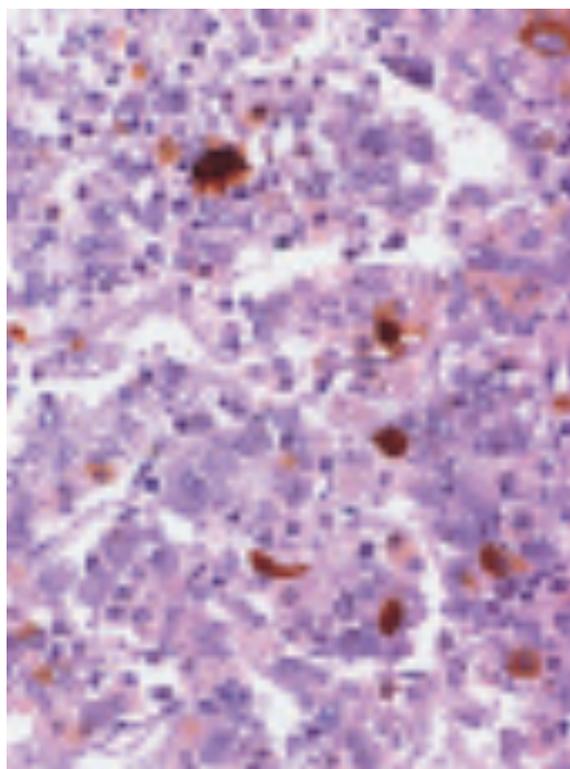

Figure 1-15

IMMUNOHISTOCHEMISTRY OF TSH CELLS

TSH cells in the anterior pituitary shown by immunostaining. These angular cells comprise less than 5 percent of anterior pituitary cells.
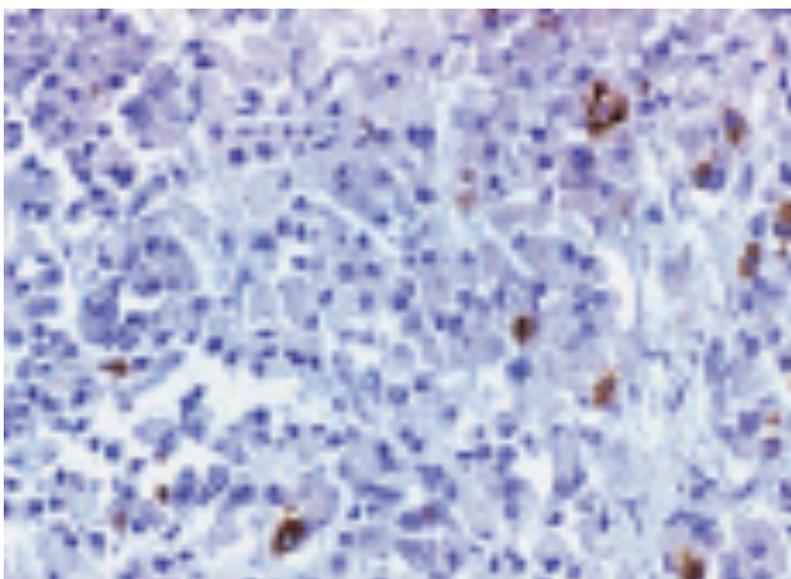

Figure 1-16

IMMUNOHISTOCHEMISTRY
OF LH CELLS

Gonadotroph cells in the anterior pituitary immunostained for LH. These cells make up about 10 percent of anterior pituitary cells. FSH and LH are present in the same pituitary cells (diaminobenzidine chromogen).

Figure 1-17

FOLLICULOSTELLATE CELLS

Folliculostellate cells revealed by immunopositivity for S100 protein. These cells have cytoplasmic processes that extend between the hormone-producing cells (diaminobenzidine chromogen).
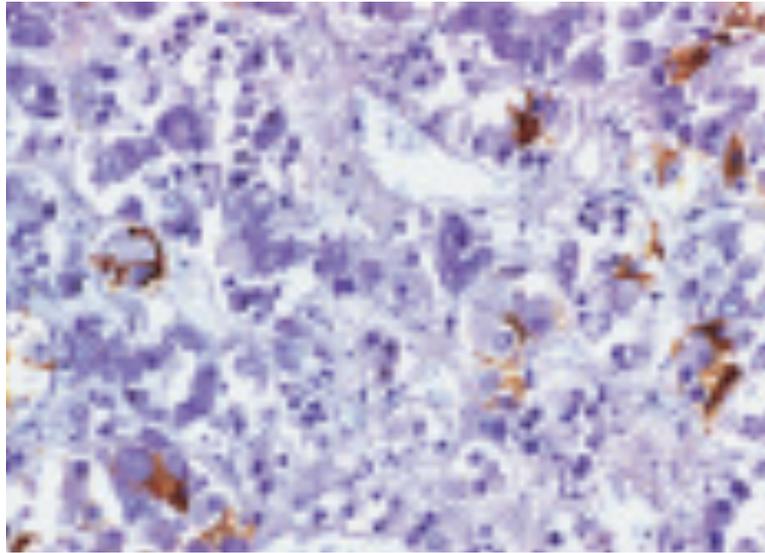
hormone-producing cells. They are positive for S100 protein, glial fibrillary acidic protein (GFAP), and vimentin. Folliculostellate cells have several functions including phagocytosis, production of cytokines, and production of growth factors such as vascular endothelial growth factor and interleukin 6 in different species (8). These cells probably exert paracrine regulatory functions on the hormone-secreting anterior pituitary cells.

Neurohypophysis

The posterior pituitary is made up of pituicytes which are GFAP-positive glial cells, nerve fibers, and capillaries (fig. 1-18). The nerve fibers travel from the hypothalamic neurons which produce oxytocin, vasopressin, and neurophysin, along the axoplasm of unmyelinated nerve fibers, to the posterior lobe where they are stored by focal axonal dilatation in secretory granules (Herring bodies).

REACTIVE CHANGES

Pregnancy

During pregnancy the pituitary gland doubles in weight. This can be visualized by magnetic resonance imaging (MRI) (fig. 1-19). The increase in size is caused mainly by hyperplasia of the PRL cells (figs. 1-20, 1-21). There is an increase in the cells producing both PRL and GH with a concomitant decrease in the GH-producing cells (31,32). Because of the markedly

increased size of the gland, there is an increased risk of pituitary infarcts during pregnancy, especially during delivery, which may be associated with hypotension (*Sheehan's syndrome*). Although the pituitary gland decreases in weight after delivery, it remains larger in multiparous compared to nulliparous women.

Hormonal Syndromes

Hypofunction of endocrine target organs can lead to reactive changes in the pituitary gland, especially pituitary cell hyperplasias such as Addison's disease and Schmidt's syndrome (20,22). This is discussed later in the chapter. Most of the anterior pituitary cells producing trophic hormones directed at specific organs can be affected via a direct feedback effect due to decreased hormonal production.

Hyperfunction of specific endocrine target organs can also lead to reactive changes in the pituitary. Examples include hyperadrenocorticalism and hyperthyroidism.

Hyperadrenocorticalism. Excessive glucocorticoids from endogenous or exogenous sources lead to specific morphologic changes in the anterior pituitary; these are designated as Crooke's hyaline changes (21,23,24,28,29). In this process the cells have a glassy or hyalinized appearance on H&E-stained sections due to the accumulation of cytokeratin filaments in the cytoplasm. The secretory granules are pushed to the cell periphery, close to the cell
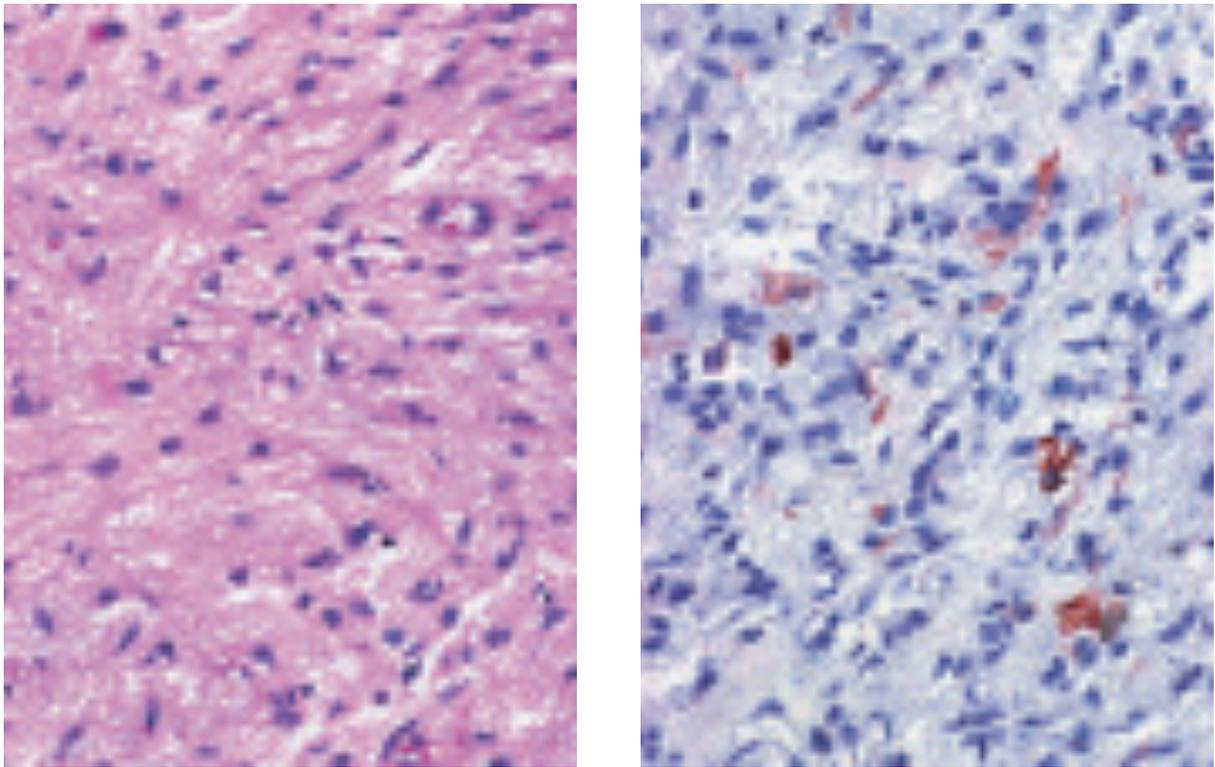
Figure 1-18

POSTERIOR PITUITARY

Left: Posterior pituitary made up of pituicytes, glial cells, and nerve fibers.
Right: The glial cells are positive for glial fibrillary acidic protein.

membrane (see fig. 1-14). Specific conditions leading to Crooke's hyaline changes include: 1) adrenocortical hyperplasias, adenomas, and carcinomas; 2) ectopic production of ACTH or CRH by tumors such as small cell lung carcinomas, bronchial carcinoids, thymomas, pheochromocytomas, and others; 3) treatment with glucocorticoids for autoimmune diseases, organ transplantation, and other conditions; and 4) production of excessive ACTH by a pituitary adenoma. The latter leads to Crooke's change predominantly in the non-neoplastic ACTH cells, although such changes can also occur in adenomas. Crooke's changes are reversible once the stimulus is removed.

Hyperthyroidism. Patients with thyrotoxicosis may appear to have a decrease in the number of TSH cells, as detected by immunostaining (26,30). However, there usually are more TSH-positive cells with less immunoreac-

tive hormone in this condition than previously realized, because the cells with small amounts of stored TSH do not stain with anti-TSH antibodies. The decreased immunostaining is probably related to the negative feedback effects of the increased triiodothyronine (T3) and thyroxine (T4) associated with hyperthyroidism.

Effects of Specific Drugs

Specific drugs used for various medical therapies may lead to reactive changes in the anterior pituitary (27). High dosages of estrogens are associated with PRL cell hyperplasia and hyperprolactinemia (29,34). In patients with PRL adenomas, estrogen may stimulate further growth of the tumor.

Somatostatin analogues such as octreotide are used in the treatment of many neuroendocrine tumors, including GH adenoma. In the normal pituitary, these drugs can inhibit GH