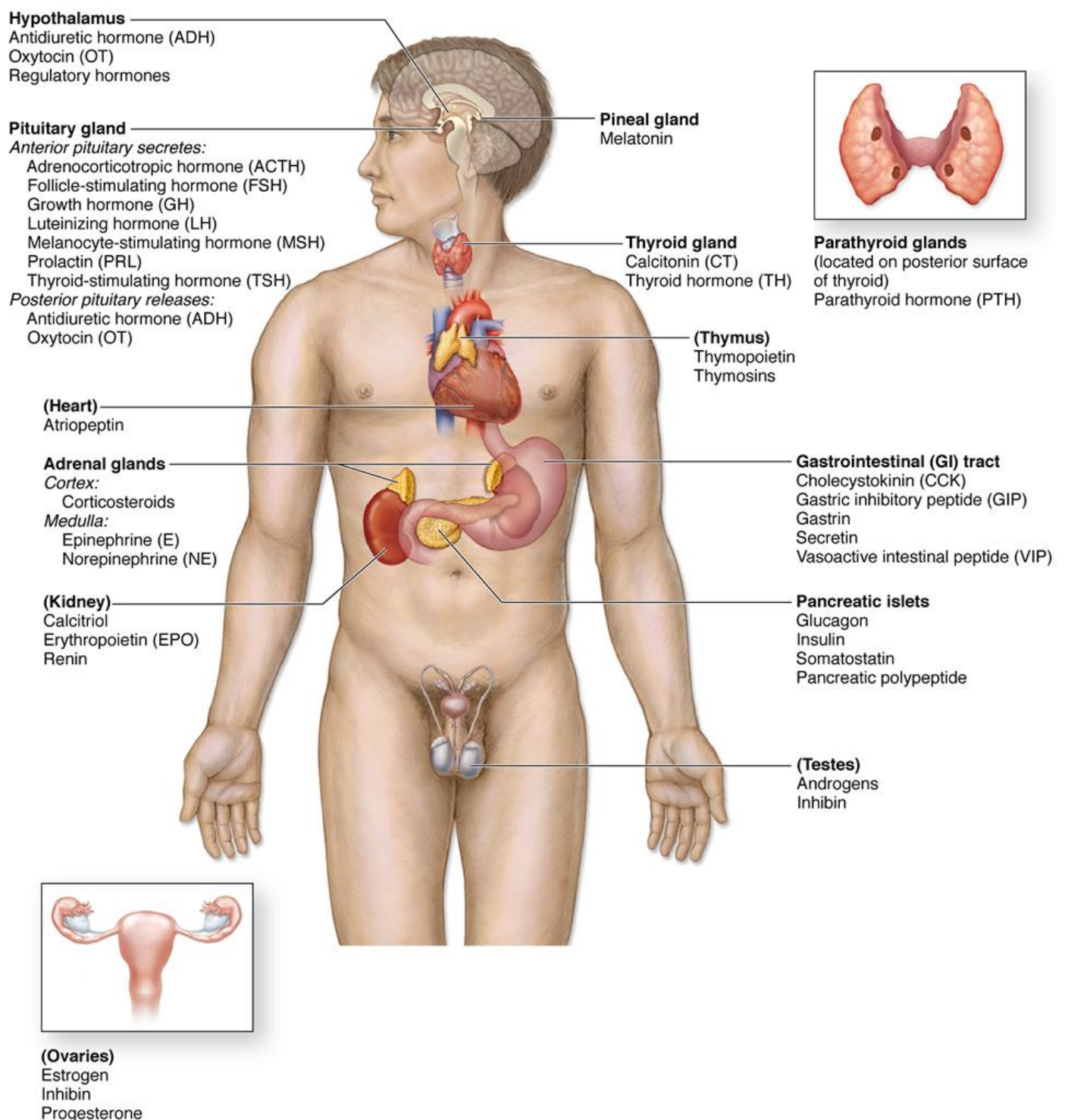


Endocrinology

Hormones are molecules, secreted from special cells (the **endocrine cells**) into the blood stream to act as chemical signals on tissues or organs (the **target tissues**) that lie usually away from the secreting cells. Endocrine cells are found either as aggregations of cell cords or follicles (the **endocrine glands**) or as isolated endocrine cells in organs specialized for other functions, e.g: endocrine cells of the GIT, heart, JG cells of the kidney & cells of the placenta. In addition to endocrine way, signaling molecules may act by the following ways:



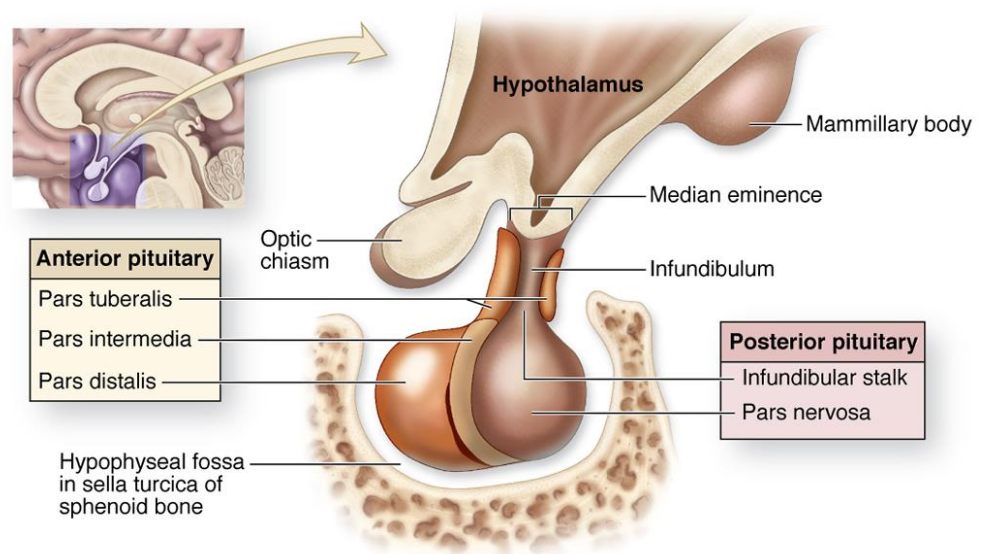
- **Paracrine secretion:** the molecule is secreted into the extracellular matrix & diffuse to the nearby target cells (e.g: somatostatin (from D cells) inhibits insulin secretion (from B cells) in Langerhans' islets of the pancreas), or through short loops of blood vessels (e.g: gastrin from pyloric G-cells reaches target cells in the fundic glands).
- **Juxtacrine secretion:** the molecule remains on the surface of the cell (or the very close extracellular matrix) & affects adjacent cells that have receptors for it.
- **Autocrine secretion:** the molecule is produced & affects its own cell or other cells of the same type, e.g: cells secreting insulin-like growth factors (IGFs).

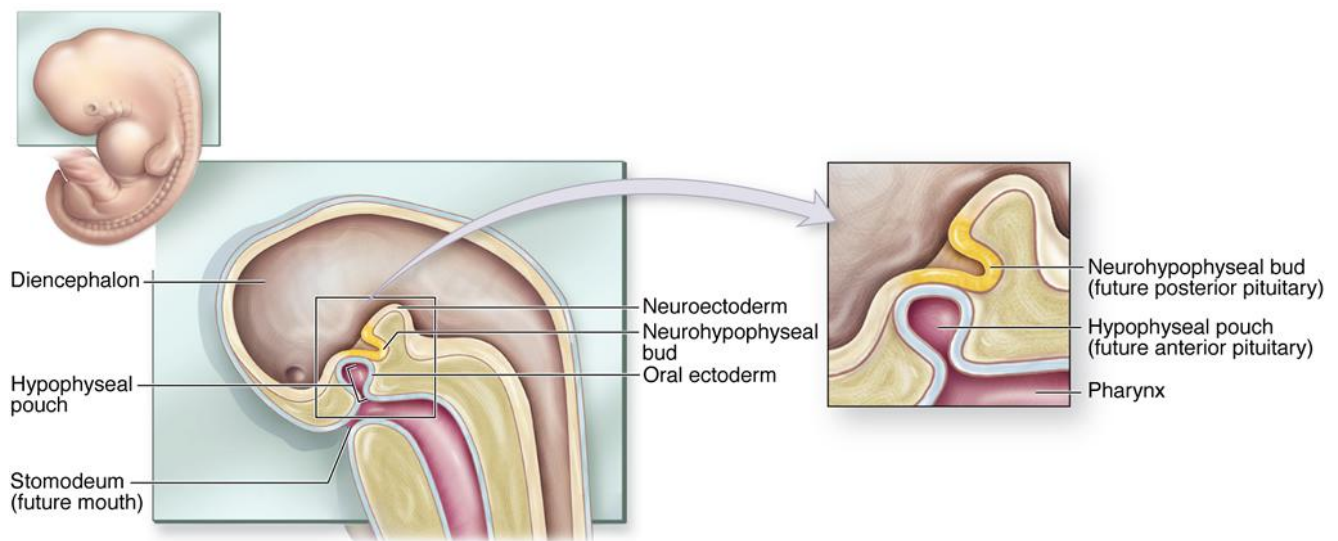
Target tissues react to hormones because their cells have receptors specific to each hormone. Endocrine glands themselves are controlled by the hormones of pituitary gland which are -in turn- controlled by the hypothalamus. Endocrine glands include the pituitary, thyroid, parathyroid, adrenal, pineal glands & the islets of Langerhans in the pancreas. Testes & ovaries also secrete hormones, but they will be considered separately. Biochemically, Hormones are either hydrophilic molecules (proteins, glycoproteins, peptides, or modified amino acids) & their receptors lie on the surface of target cells, or hydrophobic molecules (steroid & thyroid hormones) that need transport plasma protein & diffuse through the membrane of target cells to activate their intracytoplasmic receptors.

The Hypophysis (Pituitary Gland)

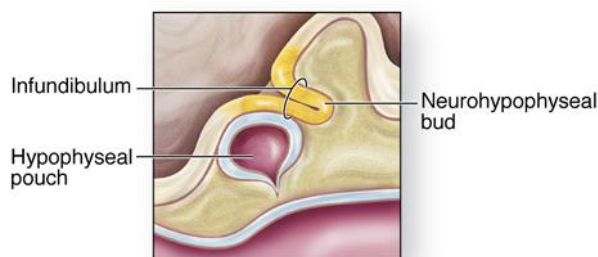
This is the most important endocrine gland because it controls most of the other endocrine glands. The hypophysis is a small gland (0.5gm weight, 10x13x6mm) that lies below the base of the brain in a fossa on the body of sphenoid bone (the hypophyseal fossa in sella turcica) suspended from the ventral surface of the hypothalamus by the **infundibulum**.

Embryologically, the hypophysis develops as follows (see the fig.):

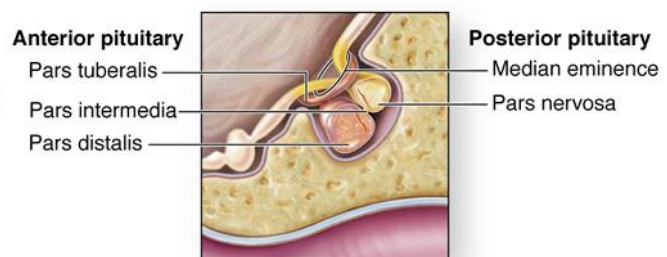




a Week 3: Hypophyseal pouch and neurohypophyseal bud form.



b Late second month: Hypophyseal pouch loses contact with roof of pharynx.



c Fetal period: Anterior and posterior pituitary have formed.

- 2 outgrowths: the larger, anterior upgrowth from the roof of the mouth (ectoderm) & the smaller, posterior downgrowth from the floor of the diencephalon (ectoderm).
- The 2 outgrowths contact each other, the lower one detaches from the roof of the mouth & contains a cavity; **hypophyseal (Rathke) pouch**, & the upper one keeps contact with the floor of the diencephalon & contains no cavity.
- The anterior wall of the oral component grows & forms the **anterior lobe (pars distalis)**. The posterior wall & the remnants of Rathke's pouch form the rudimentary **intermediate lobe (pars intermedia)**. The uppermost part of the oral component grows to surround the narrowing of the neural component forming **pars tuberalis**. All together make the **anterior pituitary gland (adenohypophysis)** which constitutes about 75% of the whole gland.
- The neural component forms the **posterior pituitary gland (neurohypophysis)**, which makes the rest (25%) of the gland & is divided into:
 1. **Pars nervosa:** the dilated inferior part,
 2. **Infundibulum:** the stalk that connects pars nervosa to the hypothalamus at the median eminence (the funnel shaped structure attached to the hypothalamus) , the infundibulum is surrounded by pars tuberalis of the adenohypophysis.

Blood Supply & the Hypophyseal Portal System:

From each internal carotid artery, multiple superior hypophyseal aa. & a single inferior hypophyseal a. arise. **The superior hypophyseal arteries** supply the median eminence, infundibulum & pars tuberalis. **The inferior hypophyseal arteries** supply the pars nervosa & communicate with the superior hypophyseal arteries. In the region of infundibulum, the superior hypophyseal aa. form a plexus of fenestrated capillaries (the **primary capillary plexus**), those unite to form veins that run to the pars distalis & divide again forming the (**secondary capillary plexus**), & this is called the (**hypothalamo-hypophyseal portal system**). Larger veins then drain the secondary plexus & pars nervosa into the cavernous & intercavernous sinuses. There is no blood-brain barrier in the neurohypophysis.

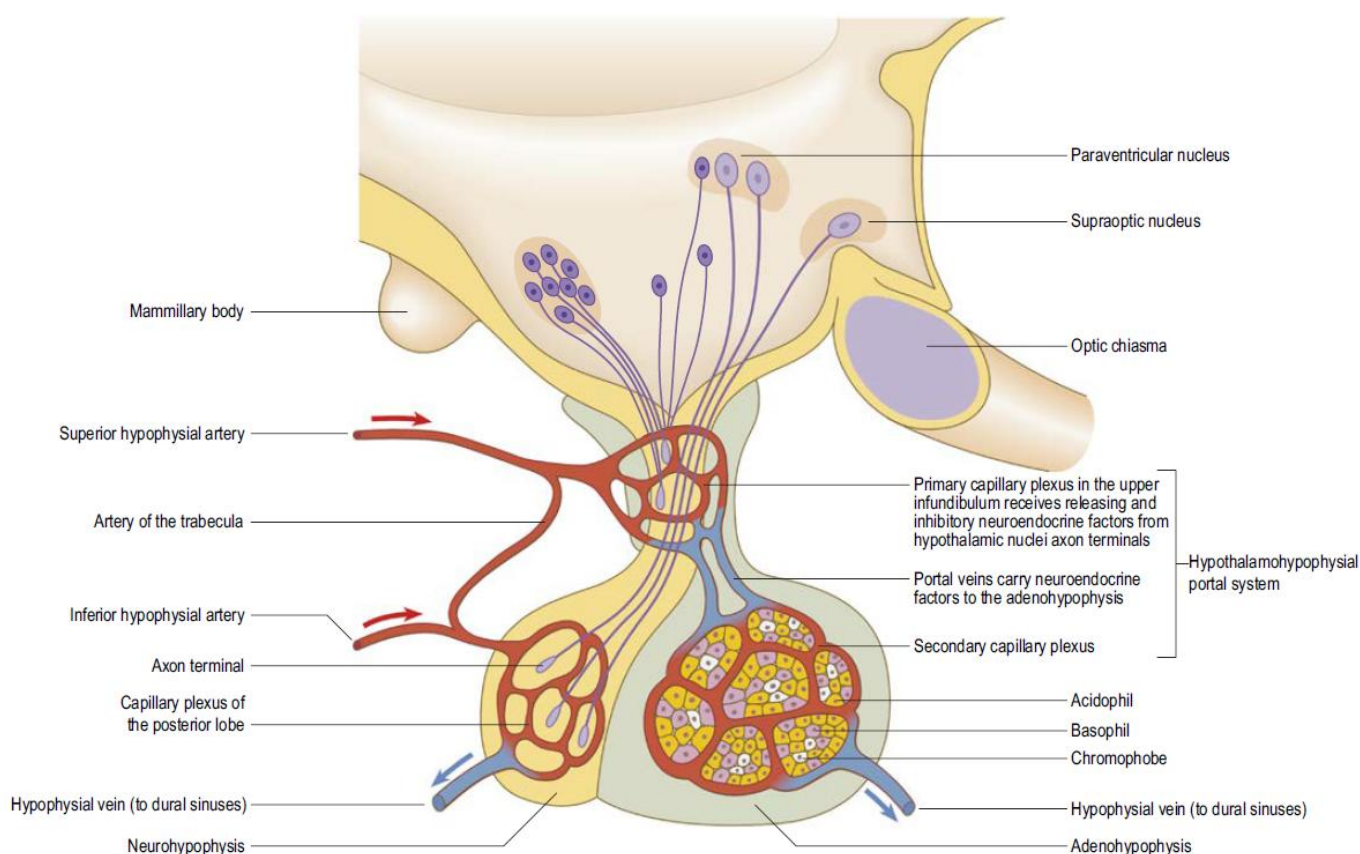


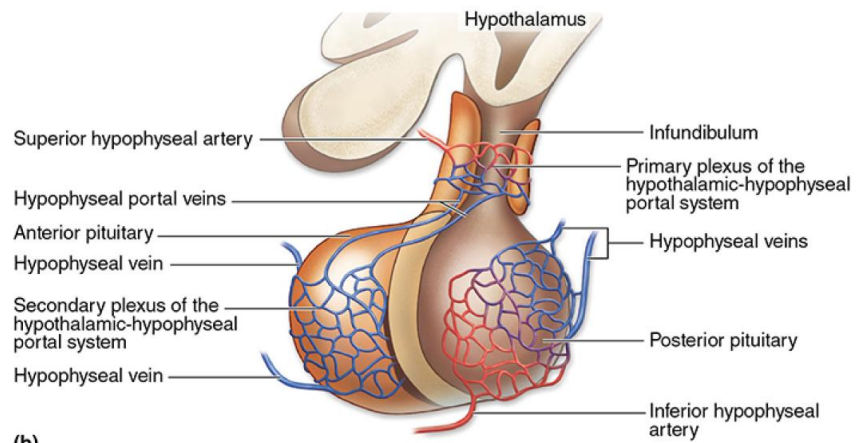
Fig. 30.11 The main systems controlling the endocrine secretory activities of the pituitary gland.

Hypothalamo- Hypophyseal System:

The hypothalamus contains many nuclei, these control the secretion of the pituitary gland in the following 2 ways (see the fig. above):

- 1- For pars nervosa: the **supra-optic & paraventricular nuclei** lie in the anterior part of the hypothalamus, cell bodies secrete 2 hormones: *antidiuretic hormone (ADH)* (from supra-optic nucleus) & *oxytosin* (from paraventricular nuclei). The hormones

then are transported via the axons that pass through the infundibulum to end in the pars nervosa where they are liberated to the blood capillaries.



2- For pars distalis: **dorsomedial, ventromedial, & infundibular** (b)

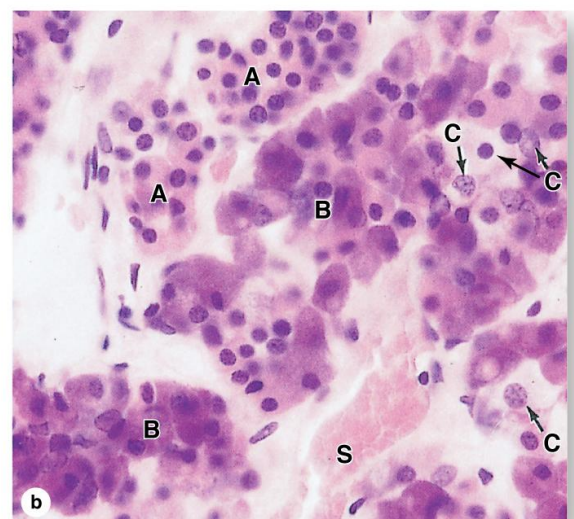
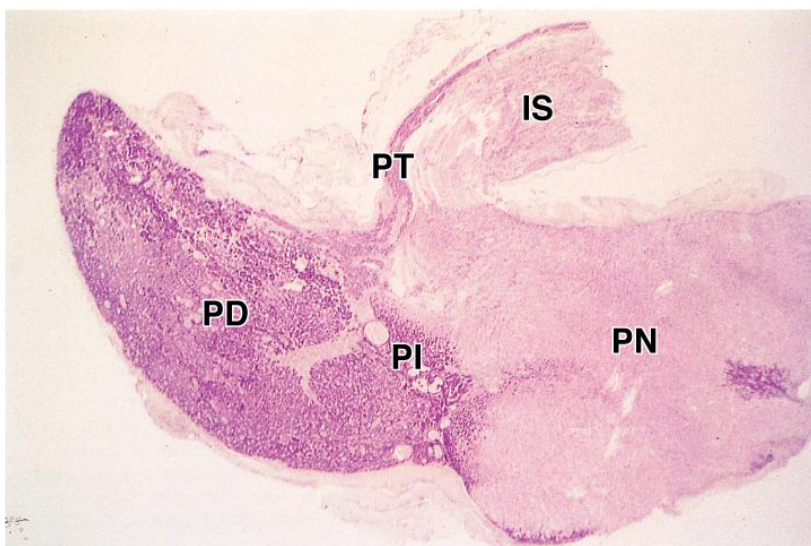
nuclei lie in the posterior part of the hypothalamus, cell bodies secrete peptide hormones (the hypothalamic releasing & inhibiting hormones) that descend down the axons to be stored in the nerve endings in the median eminence (the region of primary capillary plexus). According to the body need, these hormones are liberated into the capillaries & reach the secondary capillary plexus where they control the secretion of the endocrine cells of pars distalis (stimulating or inhibiting the release of pars distalis hormones).

Adenohypophysis Histology

Pars distalis: This is covered by a thin fibrous capsule & consists mainly of cords of epithelial endocrine cells interspersed with fenestrated capillaries, with few fibroblasts that produce reticular fibers that support the endocrine cells. Endocrine cells contain secretory granules & are divided into 3 groups:

1- **Acidophils:** these have secretory granules that take acidic stains, they form about 50% of pars distalis cells & include:

- **Somatotropic cells**, which secrete *growth hormone (GH)* (or *somatotropin*) under stimulation of hypothalamic *growth hormone- releasing hormone (GHRH)*.



- **Mammotropic cells**, (15-20%), which secrete *prolactin (PRL)* under hypothalamic stimulation by (TRH).

2- **Basophils**: these have secretory granules that take basic stains, they include:

- **Thyrotropic cells**, (5%) which secrete *thyrotropin (TSH)* under stimulation of hypothalamic *thyrotropin-releasing hormone (TRH)*.
- **Corticotropic cells**, (15-20%), which secrete *adrenocorticotrophic hormone (ACTH)* under stimulation of hypothalamic *corticotropin releasing hormone (CRH)* & β -*lipotropin (β -LPH)* which regulates lipid metabolism.
- **Gonadotropic cells**, (10%), which secrete *follicular stimulating hormone (FSH)* & *luteinizing hormone (LH)* under stimulation of hypothalamic *gonadotropin-releasing hormone (GnRH)*.

3- **Cromophobes**: these cells do not stain intensely, they contain few or no secretory granules. These cells represent a heterogenous group, including stem cells, undifferentiated progenitor cells, etc.

- Acidophils & basophils are called together **chromophils**.
- Each chromophil cell produces one hormone, except gonadotrops & corticotrops, which produce 2 hormones each.
- Subtypes of chromophils cannot be distinguished by light microscopy, this can only be done by immunohistochemistry or transmission electron microscopy.

Pars tuberalis: histologically this resembles pars distalis, with predominance of gonadotropic cells which are arranged as cords parallel to the blood vessels.

Pars intermedia: this rudimentary part is a thin zone of basophilic cells between pars distalis & pars nervosa, which is often invaded by these cells. Pars intermedia develops from the dorsal wall of the hypophyseal pouch, & usually contains colloid-filled cysts that represent the remnants of the pouch's cavity. These cells produce two types of *melanocyte stimulating hormone (MSH)*, γ -*LPH*, & β -*endorphin*.

Control of Adenohypophysis Secretion:

The activity of adenohypophysis cells is controlled by 3 mechanisms:

1. **Hypothalamic releasing & inhibiting hormones**: The main way, the hypothalamus produces peptide hormones that reach adenohypophysis' cells via

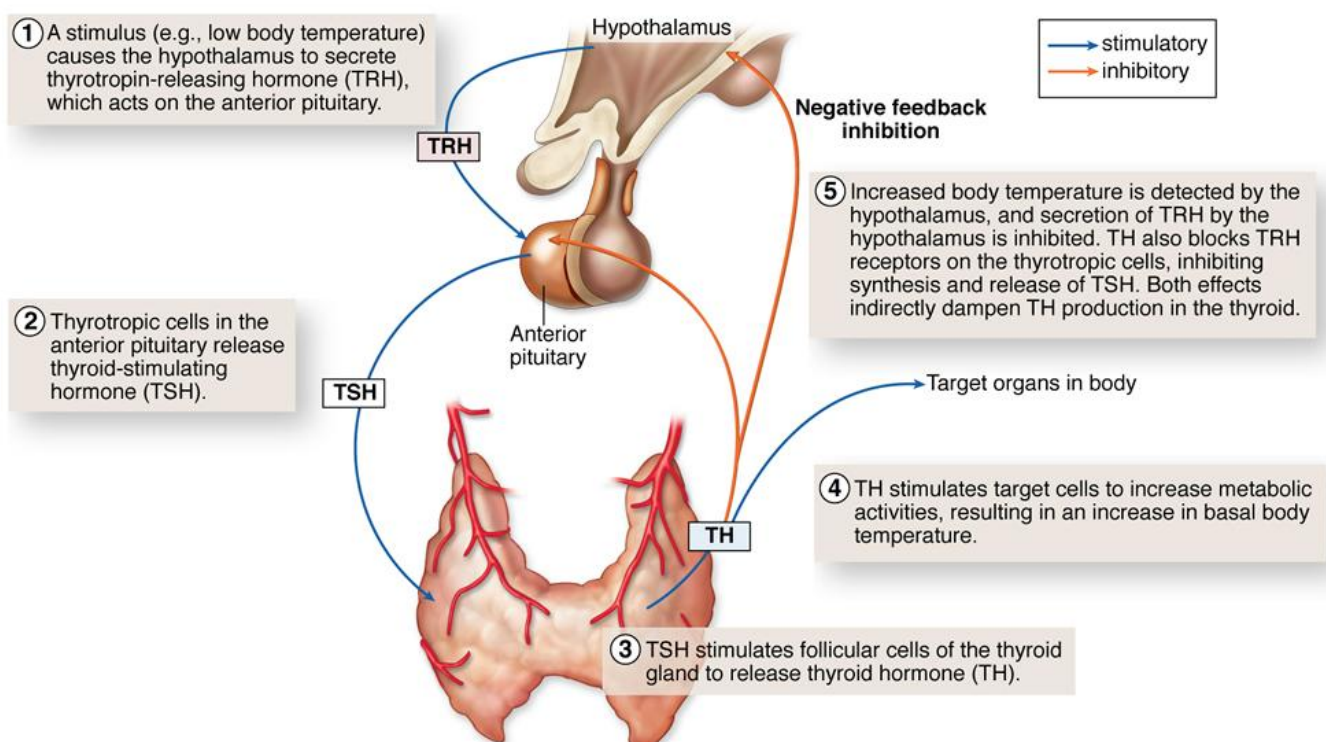
the portal system (see above) to stimulate or inhibit the activity of anterior pituitary cells. See the details in the table below.

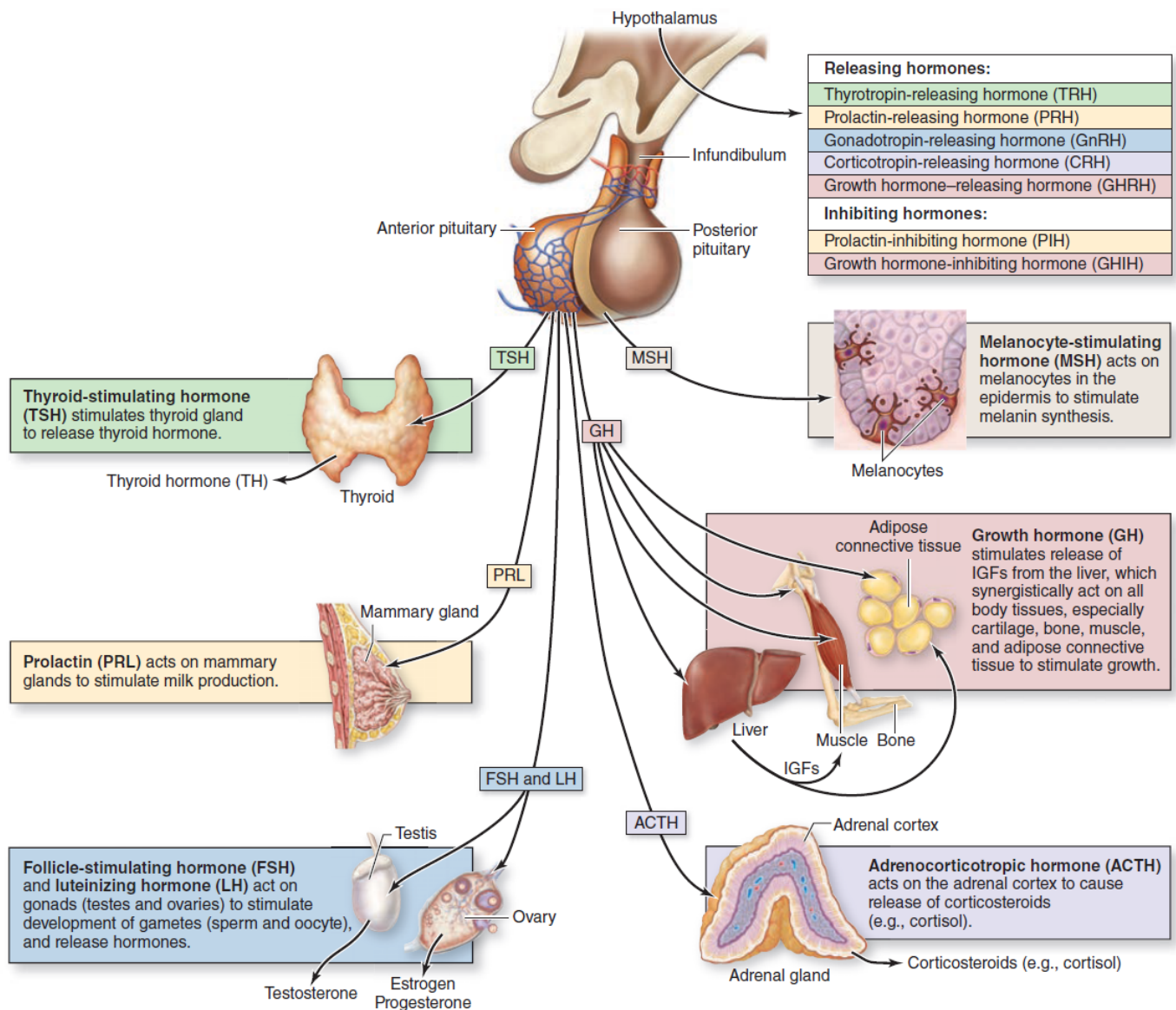
TABLE 20–1
Major cell types of the anterior pituitary and their major functions.

Major cell types of the anterior pituitary and their major functions.

Cell Type	% of Total Cells	Hormone Produced	Major Function
Somatotrophs	50	Somatotropin (growth hormone, GH), a 22-kDa protein	Stimulates growth in epiphyseal plates of long bones via insulin-like growth factors (IGFs) produced in liver
Lactotrophs (or mammotrophs)	15–20	Prolactin (PRL), a 22.5-kDa protein	Promotes milk secretion
Gonadotrophs	10	Follicle-stimulating hormone (FSH) and luteinizing hormone (LH; interstitial cell-stimulating hormone [ICSH] in men), both 28-kDa glycoprotein dimers, secreted from the same cell type	FSH promotes ovarian follicle development and estrogen secretion in women and spermatogenesis in men; LH promotes ovarian follicle maturation and progesterone secretion in women and interstitial cell androgen secretion in men
Thyrotrophs	5	Thyrotropin (TSH), a 28-kDa glycoprotein dimer	Stimulates thyroid hormone synthesis, storage, and liberation
Corticotrophs	15–20	Adrenal corticotropin (ACTH), a 4-kDa polypeptide Lipotropin (LPH)	Stimulates secretion of adrenal cortex hormones Helps regulate lipid metabolism

2. Negative feedback mechanism: Another way to control adenohypophysis' activity. When hormones are secreted from the target glands on which the anterior pituitary hormones act, these hormones – in addition to their main action- inhibit the relevant hypothalamic & pituitary hormones that caused their release. See the below figure that shows this process using the thyroid gland as an example.





Release of the six major tropic hormones from the anterior pituitary (all except MSH) is promoted by specific peptide releasing hormones. Release of PRL and GH is further regulated by specific inhibiting peptide hormones. These regulatory peptides are all secreted by

specific hypothalamic neurons and then carried to the anterior pituitary by the hypothalamic-hypophyseal blood supply shown in the upper diagram. Organs throughout the body targeted specifically by the seven tropic hormones are also shown here.

3. Hormones outside the feedback loop: Anterior pituitary activity is also affected by hormones other than those secreted by the main target tissues. Examples include: **inhibin & activin** are produced in the gonads & control the release of FSH & LH, **gherlin** is produced in the gastric mucosa & stimulates GH secretion, and **oxytocin** liberated in the posterior pituitary during breast-feeding & stimulates prolactin secretion.

TABLE 20–2
anterior pituitary.

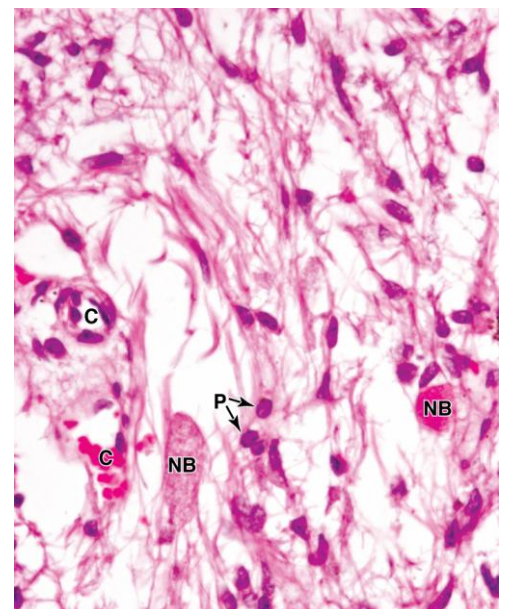
Hypothalamic hormones regulating cells of the

Hormone	Chemical Form	Functions
Thyrotropin-releasing hormone (TRH)	3-amino acid peptide	Stimulates release of thyrotropin (TSH)
Gonadotropin-releasing hormone (GnRH)	10-amino acid peptide	Stimulates the release of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
Somatostatin	14-amino acid peptide	Inhibits release of both somatotropin (GH) and TSH
Growth hormone-releasing hormone (GHRH)	40- or 44-amino acid polypeptides (2 forms)	Stimulates release of GH
Dopamine	Modified amino acid	Inhibits release of prolactin (PRL)
Corticotropin-releasing hormone (CRH)	41-amino acid polypeptide	Stimulates synthesis of pro-opiomelanocortin (POMC) and release of both β -lipotropic hormone (β -LPH) and corticotropin (ACTH)

Neurohypophysis Histology

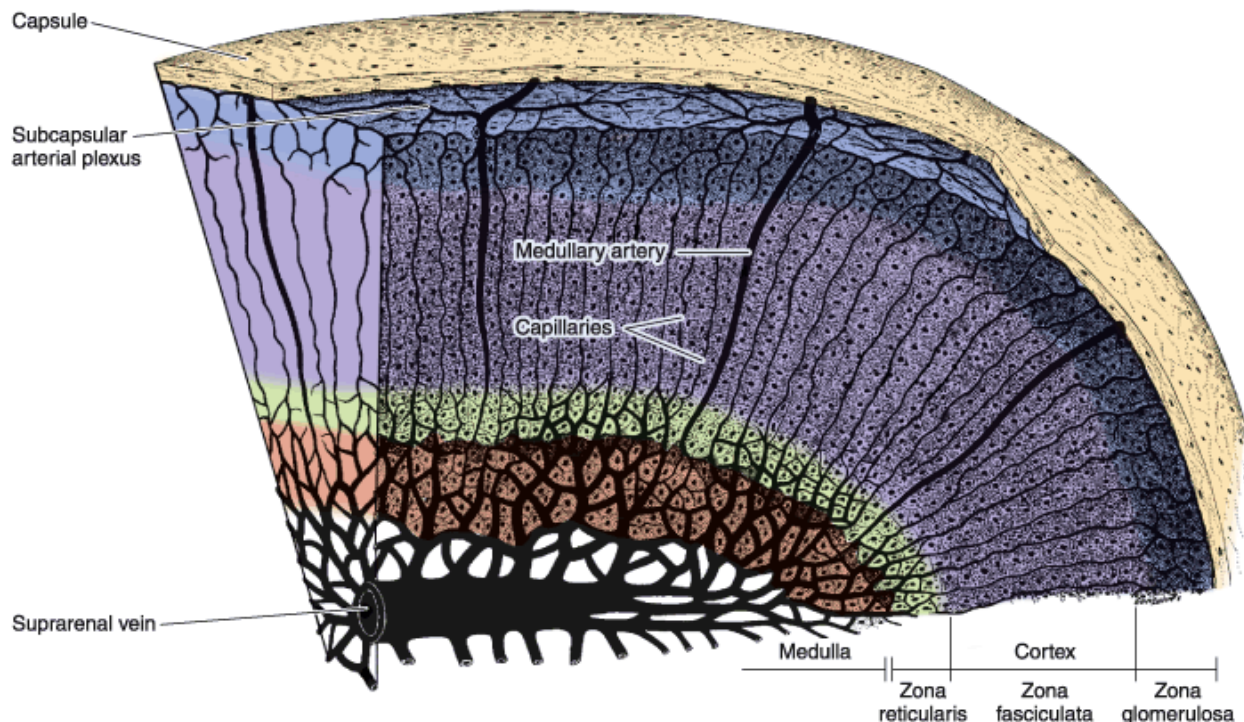
Infundibulum: This consists of unmyelinated axons of the neurons of hypothalamic nuclei that control the function of the pituitary gland, & axons of neurons producing the hormones of pars nervosa, in addition to the primary capillary plexus of the hypothalamo-hypophyseal portal system.

Pars nervosa: Unlike the adenohypophysis, this part contains no secretory cells. It consists of the axons of the above neurons. The secretory neurons have all the characteristics of typical neurons, including conducting action potentials. Their axons are larger in diameter, & have large dilated terminals called **neurosecretory (Herring) bodies**. Those terminals (visible by light microscope as faintly eosinophilic structures) are filled with large membrane-limited granules that contain either oxytocin or antidiuretic hormone (both bound to a carrier protein called **neurophysin**). Nerve impulses along the axons trigger the release of these 2 hormones, oxytocin during breast-feeding & ADH in response to increased blood tonicity recognized by hypothalamic osmoreceptor cells. The neurohypophysis contains also highly branched glial cells called (**pituicytes**).



Adrenal (Suprarenal) Gland

The adrenal glands are paired organs that lie above the kidneys, embedded in the perirenal fatty tissue (see the figure on the previous page). The right gland is pyramidal in shape while the left is half-moon shaped. Histologically, adrenal gland shows the typical endocrine gland appearance (cords of endocrine cells along capillaries). The gland is surrounded by a dense connective tissue **capsule** that sends thin septa that partially divide the cortex. The stroma consists of rich reticular fibers network that supports the secretory cells. The gland consists of an outer yellow **cortex** & an inner reddish-brown **medulla**. The cortex & medulla are united anatomically but separated embryologically & functionally. The adrenal cortex is derived from the *mesodermal* coelomic epithelium & secretes steroid hormones, while adrenal medulla is derived from the *ectodermal* neural crest & secretes catecholamines.



Blood Supply:

Several **adrenal arteries** enter the gland at various points. They form a network beneath the capsule that supplies it & gives off:

- **The cortical arterioles:** run subcapsularly, give the cortical capillaries that run between the cords of cortical cells & join the medullary capillaries.
- **The medullary arterioles:** large branches that traverse the cortex & form an extensive capillary network in the medulla (thus medullary cells receive arterial blood from medullary capillaries & venous blood from cortical capillaries).

Cortical & medullary capillaries (both are fenestrated with diaphragm & continuous basal lamina) unite to form the **medullary veins** that unite to form the **adrenal vein**.

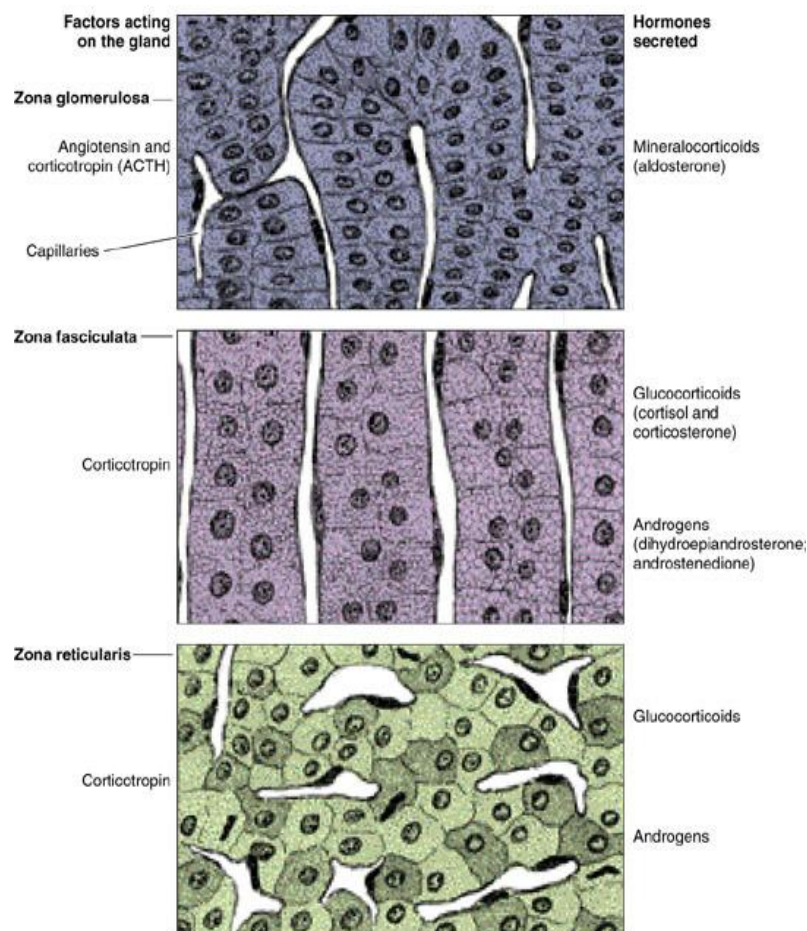
Adrenal Cortex:

The cells of adrenal cortex are steroid-secreting. They have central nuclei & acidophilic cytoplasm, usually rich in lipid droplets. The cytoplasm contains an exceptionally profuse smooth ER of interconnected tubules, which is important for steroid hormones synthesis. The mitochondria are often spherical, with tubular rather than shelf-like cristae. These cells don't store the secretory product in granules, but synthesize & secrete steroid hormones on demand. Steroids are low molecular weight lipid-soluble molecules that are seen in the cytoplasm as many different-sized lipid droplets. Adrenal cortex is subdivided according to the appearance (arrangement) of its cells into:

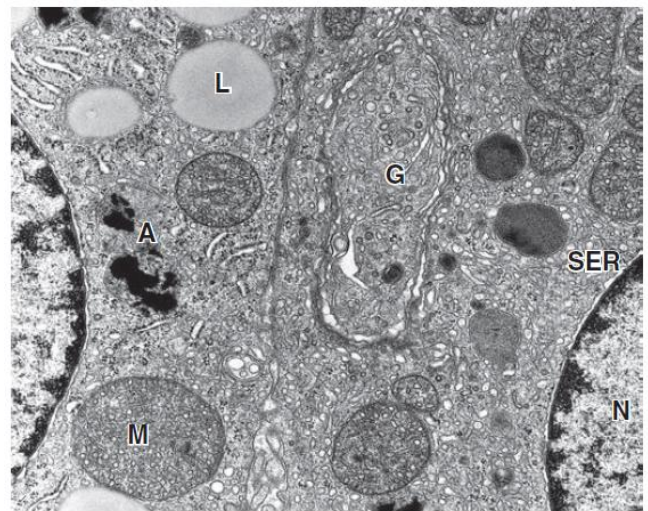
1. **Zona Glomerulosa:** the outermost layer (15% of the gland size) that lie beneath the capsule. The cells are columnar or pyramidal arranged in packed rounded or arched columns, surrounded by capillaries. They secrete *mineralocorticoid hormones*.

2. **Zona Fasciculata:** the second layer (65-80% of the gland size), arranged as parallel columns of large polyhedral cells (1-2 cell thick) that run perpendicular to the gland surface with capillaries between them. The cells are large with great number of lipid droplets that dissolve during histological preparations giving a vacuolated appearance to the cells, which are called *spongiocytes*. Zona fasciculata secretes *glucocorticoid hormones*, (mainly cortisol) and small amounts of androgens.

3. **Zona Reticularis:** the innermost layer (10% of the gland size) that surrounds adrenal medulla. The cells are arranged in irregular cords that form an



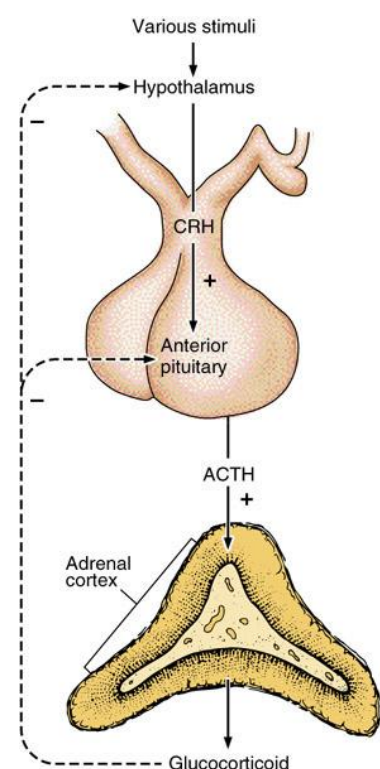
anastomosing network. The cells are smaller than those of z.fasciculata & stain more deeply because they contain less lipid droplets & more lipofuscin pigment. Zona reticularis secretes the weak androgen *dehydroepiandrosterone (DHEA)* which is converted to testosterone in other tissues, in addition to cortisol.



TEM of two adjacent steroid-secreting cells from the zona fasciculata shows features typical of steroid-producing cells: lipid droplets (L) containing cholesterol esters, mitochondria (M) with tubular and vesicular cristae, abundant SER, and autophagosomes (A), which remove mitochondria and SER between periods of active steroid synthesis. Also seen are the euchromatic nuclei (N), a Golgi apparatus (G), RER, and lysosomes. (X25,700)

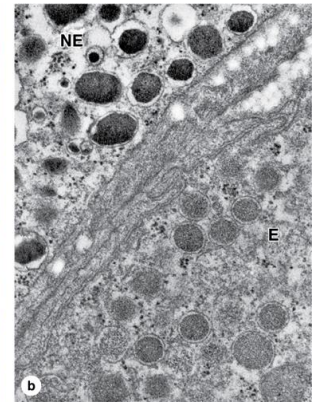
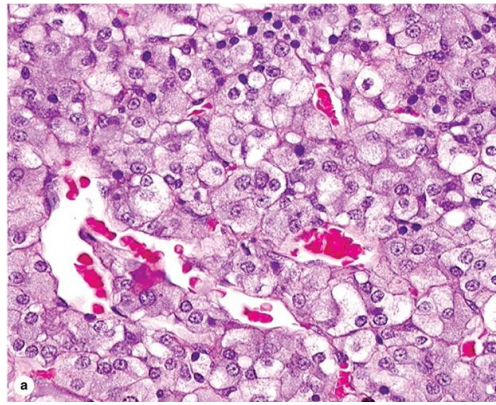
Cortical Hormones: Adrenal steroids are made from cholesterol. **Mineralocorticoid hormones** (the main one is aldosterone) are made by zona glomerulosa (under stimulation of angiotensin-II, high plasma K⁺, but weakly by ACTH) & act to conserve sodium in the body by enhancing Na⁺ reabsorption in the epithelium of renal DCT & GIT. **Glucocorticoid hormones** (the main one is cortisol) are made by zona fasciculata (under stimulation of ACTH) & affect mainly glucose metabolism. They enhance the synthesis of glucose from amino acids & fatty acids (gluconeogenesis) & the conversion of glucose into glycogen & may decrease glucose uptake by the cells, thus, maintaining adequate blood glucose levels during stress & hunger. Glucocorticoids have many other effects, e.g: they suppress growth & immune system when taken for long periods. **Androgen hormones** (the main one is DHEA) are made by zona reticularis in small amounts under control of ACTH. They are sex hormones that act after transformation into testosterone in the tissues (in both males & females).

The secretion of glucocorticoids is controlled by the hypothalamic-hypophyseal-adrenal axis through negative feedback mechanism: when blood level of cortisol is low, the hypothalamus secretes corticotrophin-releasing hormone (CRH) that stimulates the ant. Pituitary to secrete adrenocorticotrophic hormone (ACTH) that stimulates zona fasciculata to produce & secrete glucocorticoids. High blood cortisol suppresses the secretion of (CRH) & (ACTH) from the hypothalamus & pituitary gland respectively.

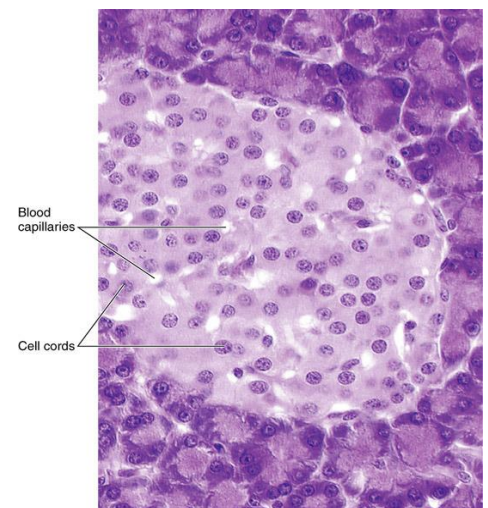


Adrenal Medulla:

This is composed of polyhedral, deeply basophilic cells arranged in cords or clumps & supported by reticular fibers. Medullary (chromaffin) cells receive sympathetic nerve endings that



secrete acetylcholine. An extensive capillary network intervenes between cords, & few parasympathetic ganglion cells also exist. Adrenal medullary cells originate from the neural crest (the origin of autonomic ganglia) & can be considered as modified sympathetic postganglionic neurons that have lost their dendrites & axons (during embryonic life) & became secretory cells. Those cells contain many membrane-limited secretory granules containing catecholamines: adrenaline (80%) or noradrenaline (20%), (= epinephrine or norepinephrine) in addition to other materials like ATP, enkephalin, etc. Catecholamines are synthesized from an amino acid called tyrosine, stored in the granules bound to a protein called chromogranin, & secreted under the stimulation of cholinergic sympathetic preganglionic fibers. Medullary cells that secrete adrenaline differ from those secreting noradrenaline: adrenaline-containing granules are smaller, less electron-dense & filled with adrenaline, while noradrenaline-containing granules are larger, more electron-dense & the secretory material is irregular & separated from the wall of the granule by space. Catecholamines are stored in medullary cells & secreted largely during emotional or stressful condition. Adrenalin cause $\uparrow$ heart rate, dilates bronchioles, & dilates the arteries in the skeletal and cardiac muscles. Noreadrenaline constricts vessels of the digestive system & skin. Both hormones stimulate glycogen breakdown, elevating blood glucose levels and $\uparrow$ B.P. Noradrenalin-secreting cells are also found in paraganglia (collections of catecholamine-secreting cells adjacent to autonomic ganglia) & in various viscera. During normal activity, the adrenal medulla continuously secretes small quantities of these hormones.



Pancreatic Islets (of Langerhans)

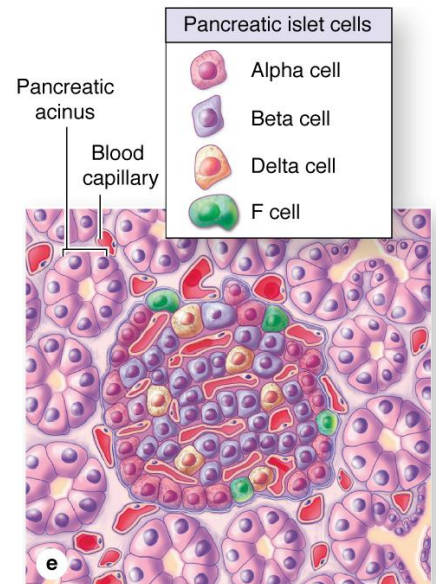
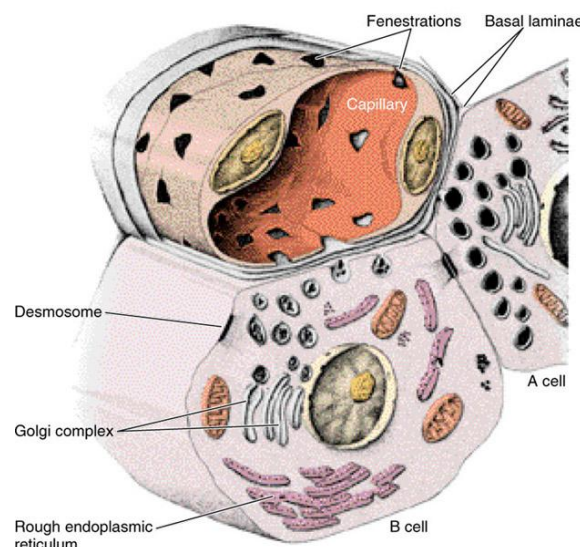
These are rounded or oval clusters of different endocrine cells embedded within the exocrine pancreatic tissue (more towards the tail), surrounded by a very thin capsule of reticular fibers. Each islet is 100-200 μm in diameter & contains several hundreds of cells. There are about 1 million islets in the pancreas, making only 1-2% of its volume. The cells are polygonal, smaller & more lightly stained than acinar cells, arranged in cords separated by capillary network. Autonomic nerve fibers supply some of the endocrine cells & the blood vessels. 4 types of cells have been seen in the islet:

TABLE 20–4

Major cell types and hormones of pancreatic islets.

Cell Type	Quantity (%)	Hormone Produced	Hormone Structure and Size	Hormone Function
α	~30	Glucagon	Polypeptide; 3500 Da	Acts on several tissues to make energy stored in glycogen and fat available through glycogenolysis and lipolysis; increases blood glucose content
β	~60	Insulin	Dimer of α and β chains with S-S bridges; 5700–6000 Da	Acts on several tissues to cause entry of glucose into cells and promotes decrease of blood glucose content
δ or D	5–10	Somatostatin	Polypeptide; 1650 Da	Inhibits release of other islet cell hormones through local paracrine action; inhibits release of GH and TSH in anterior pituitary and HCl secretion by gastric parietal cells
PP	Rare	Pancreatic polypeptide	Polypeptide; 4200 Da	Stimulates activity of gastric chief cells; inhibits bile secretion, pancreatic enzyme and bicarbonate secretion, and intestinal motility

10% of islet cells receive sympathetic & parasympathetic innervation. Gap junctions transfer autonomic stimuli to the other cells. Sympathetic stimulation increases glucagon release & inhibits insulin release, while parasympathetic stimulation increases the secretion of both.



Diffuse Neuroendocrine System (DNES)

The *enterochromaffin* cells scattered in both the islets and small ducts of the pancreas, together with similar cells in the digestive tract and respiratory mucosa (Granule cells), collectively make up the diffuse neuroendocrine system (DNES). Most of these cells are derived from endodermal cells of the embryonic gut or bronchial buds. These secretory cells are considered neuroendocrine because they produce many of the same polypeptides and neurotransmitter-like molecules, such as serotonin, also released by neurosecretory cells in the CNS. Most of these hormones are polypeptides and act in a paracrine manner, affecting primarily the activities of neighboring contractile cells and secretory cells (both exocrine and endocrine).

Many cells of the DNES are stained by solutions of chromium salts and have therefore been called enterochromaffin cells, while those staining with silver nitrate are sometimes called *argentaffin* cells. DNES cells secreting serotonin or certain other amine derivatives demonstrate amine precursor.

TABLE 15-1

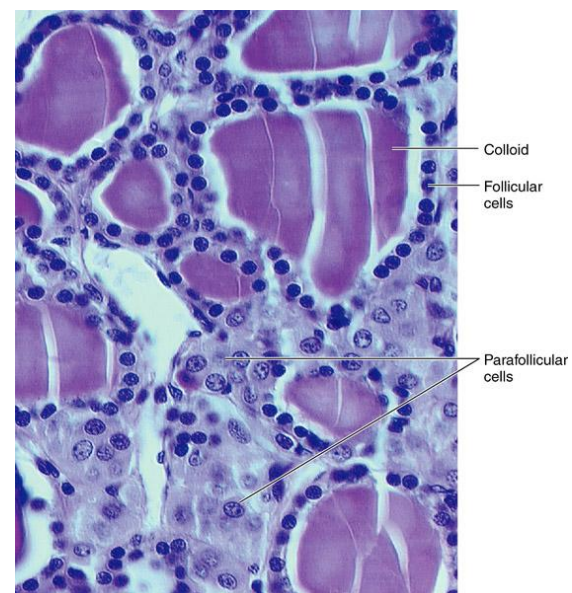
Principal enteroendocrine cells in the gastrointestinal tract.

Cell Type	Major Location	Hormone Produced	Major Action	
			Promotes	Inhibits
D cells	Pylorus, duodenum, and pancreatic islets	Somatostatin		Secretion from other DNES cells nearby
EC cells	Stomach, small and large intestines	Serotonin and substance P	Increased gut motility	
G cells	Pylorus	Gastrin	Gastric acid secretion	
I cells	Small intestine	Cholecystikinin (CCK)	Pancreatic enzyme secretion, gallbladder contraction	Gastric acid secretion
K cells	Duodenum and jejunum	Gastric inhibitory polypeptide (GIP)		Gastric acid secretion
L cells	Ileum and colon	Glucagon-like peptide (GLP-1)	Insulin secretion	Gastric acid secretion Sense of hunger
L cells	Ileum and colon	Peptide YY	H ₂ O and electrolyte absorption in large intestine	Gastric acid secretion
Mo cells	Small intestine	Motilin	Increased gut motility	
N cells	Ileum	Neurotensin		Gastric acid secretion
S cells	Small intestine	Secretin	Pancreatic and biliary bicarbonate and water secretion	Gastric acid secretion Stomach emptying

Thyroid Gland

This gland lies at the base of the neck anterior to the larynx & upper trachea. It consists of 2 lobes united by an isthmus. It originates from the endoderm of the dorsum of the tongue & descends to its cervical position.

Thyroid gland consists of millions of different-sized microscopic spheres (the **thyroid follicles**) that are



lined by simple epithelium & filled with a gelatinous material (the **colloid**) which stores the thyroid hormones & stains variably (usually acidophilic & sometimes basophilic). Thyroid gland is unique in that it stores its products outside the secretory cells, it stores them in very large amounts (that are sufficient for up to 3 months), & it is the only endocrine gland made of follicles.

Follicular cells (that line the follicles) range from squamous to columnar according to the activity of the follicle (the more active the follicle, the higher the follicular cells). Different states of follicular activity may be seen in the same gland. Follicular cells have the ultrastructure of protein-secreting cells, with large amount of rER in the basal part, round central nucleus & well developed Golgi apparatus & colloid-filled secretory granules in the apical part. In addition, large number of phagosomes, lysosomes & mitochondria are found throughout the cytoplasm. The apical surface shows some microvilli, in addition to typical junctional complexes.

The follicles are densely packed together, separated from each other by thin irregular connective tissue made of reticular fibers, derived from the loose capsule that covers the gland. Thyroid gland has a very rich blood supply (2 superior & 2 inferior thyroid arteries) & lymphatic drainage.

The **parafollicular cells (C-cells)** are the 2nd type of cells in the thyroid gland. They are found either as clusters among the thyroid follicles or between follicular cells & their basement membrane. Parafollicular cells are larger & less stained than follicular cells, they have few rER, long mitochondria, large Golgi apparatus, with many small secretory granules containing the hormone **calcitonin**. Calcitonin lowers blood calcium level by inhibiting bone resorption. Its secretion is stimulated by high blood Ca^{++} level.

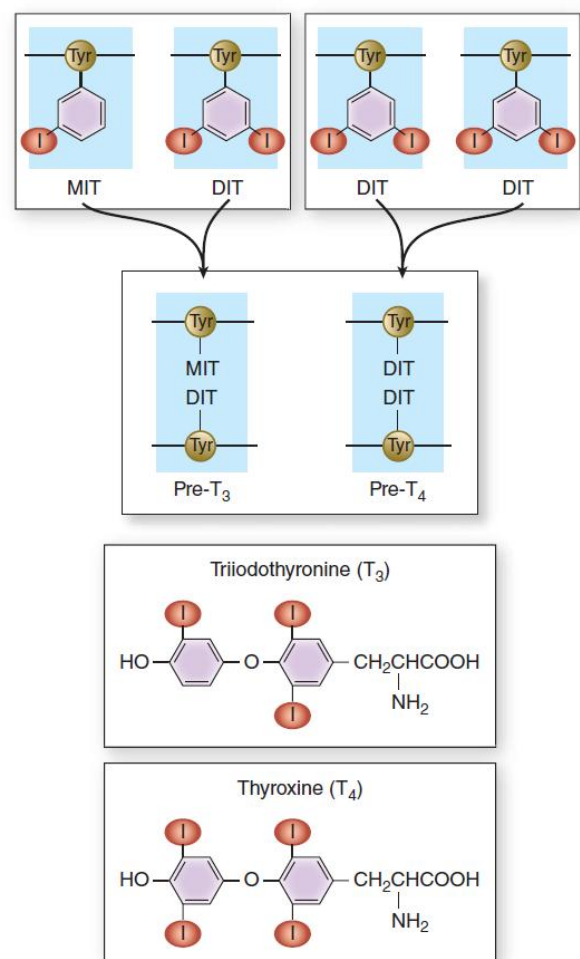
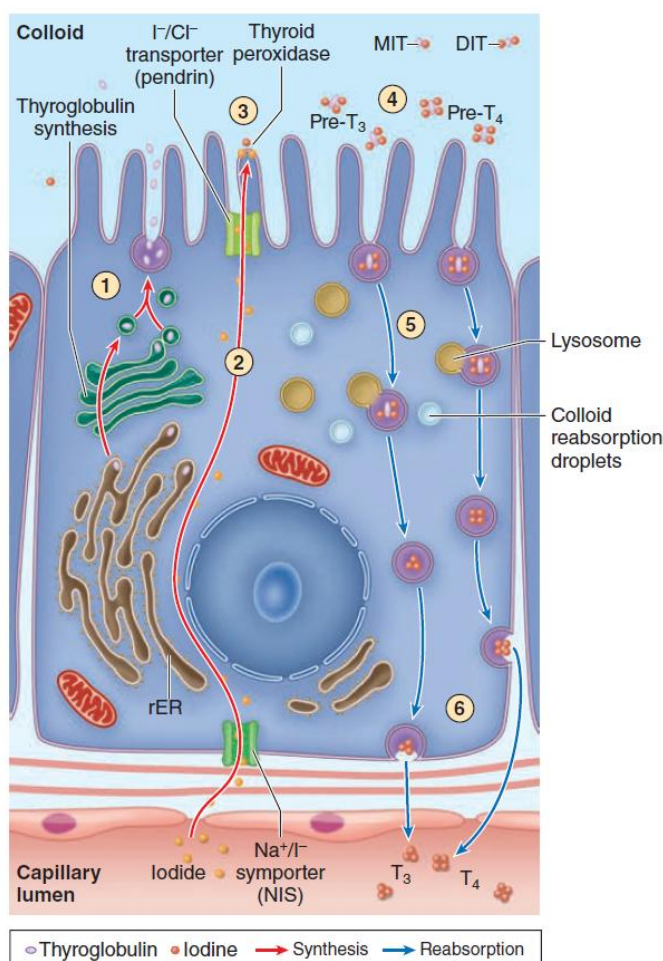
Control of thyroid hormones: Thyroid gland produces 2 thyroid hormones: **thyroxin (tetra-iodothyronine, T4) & tri-iodothyronin (T3)** under stimulation of pituitary thyrotropin (TSH), which is secreted under stimulation of hypothalamic thyrotropin-releasing hormone (TRH). Sufficient levels of T3 & T4 in the blood inhibit the secretion of both (TRH) & (TSH).

Synthesis: Thyroid hormones are synthesized as follows:

1. Thyroglobulin (a giant protein molecule) is made in the rER of follicular cells & sugar is added in the Golgi complex. Thyroglobulin is secreted to the colloid by exocytosis.

- Iodide is taken by follicular cells from the blood by Na/I symporters (NIS) in the thyrocytes' basolateral cell membranes (active transport), oxidized, & transported from thyrocytes into to the colloid by an apical iodide/chloride transporter (called pendrin).
- In the colloid, thyroglobulin is iodinated with iodine atoms forming the precursors of T₃ & T₄.
- Formation of T₃ and T₄ (also called thyroxine) occurs as two iodinated tyrosines, still part of colloidal thyroglobulin, which are covalently conjugated in coupling reactions.
- Follicular cells endocytose thyroglobulin molecules, digest them with lysosomes, freeing active thyroid hormones T₃ & T₄.
- Secretion of T₄ and T₃ at the basolateral aspects of thyrocytes, then both molecules are immediately taken up by capillaries.

Action: Thyroid hormones are important for growth & cell differentiation. They increase the O₂ consumption by the cell & thus elevate the basal metabolic rate (BMR). Thyroid hormones affect the metabolism of proteins, lipids, & carbohydrates.



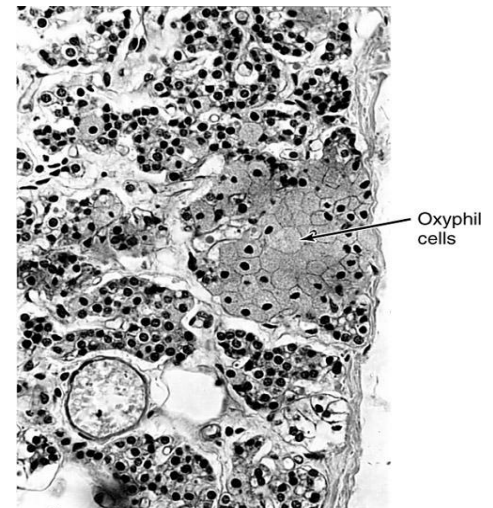
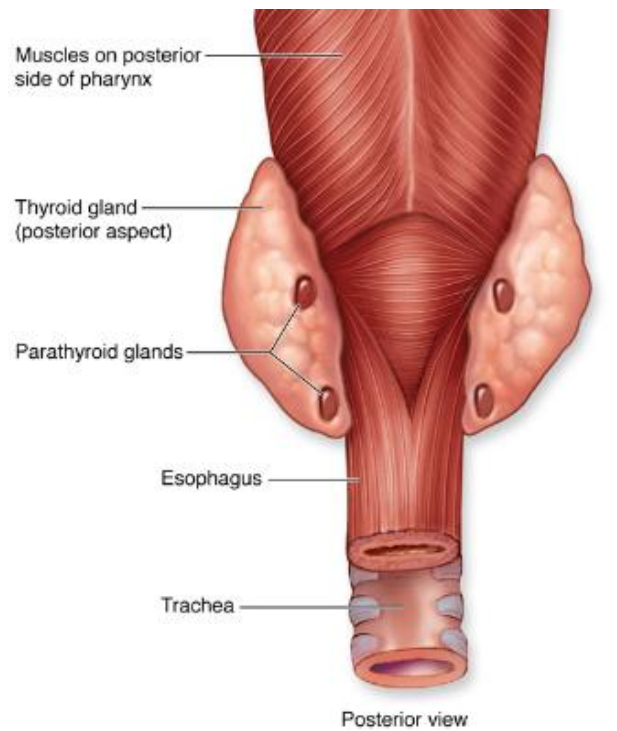
The diagram shows the multistep process by which thyroid hormones are produced via the stored thyroglobulin intermediate. In an exocrine phase of the process, (1) the glycoprotein **thyroglobulin** is made and secreted into the follicular lumen and (2) iodide is pumped across the cells into the lumen. In the lumen (3) iodide is converted to iodine by membrane-bound thyroid peroxidase and added to **tyrosine residues** of thyroglobulin (4) to form

monoiodotyrosine (MIT) or diiodotyrosine (DIT), which are then covalently coupled to form T₃ and T₄ still within the glycoprotein. The iodinated thyroglobulin is then (5) endocytosed by the thyrocytes and degraded by lysosomes, (6) releasing free **active T₃ and T₄** to the adjacent capillaries in an endocrine manner. Detailed steps are given in the text. Both phases are promoted by TSH and may occur simultaneously in the same cell.

Parathyroid Glands

Those are four small (3x6 mm) glands with a total weight of 0.4g. They are found behind the thyroid gland embedded in its covering capsule (or sometimes in the thyroid itself). Parathyroids are derived from the pharyngeal pouches (up to 10% of people have parathyroid tissue attached to the thymus, which has the same embryological origin). They are supplied mainly by the inferior thyroid arteries. Each parathyroid gland is covered by connective tissue capsule that sends septa into the gland, which merge then with the reticular fibers supporting the cords of endocrine cells. With aging, many secretory cells are replaced by adipocytes (which may make >50% of the gland in old people). Endocrine cells are of 2 types:

- **Chief (principal) cells:** the majority, small polygonal cells with a round nucleus & pale, slightly acidophilic cytoplasm. Irregular secretory granules are seen containing the **parathyroid hormone (PTH)**, which acts to increase blood calcium levels.
- **Oxyphil cells:** the minority (more seen in old people), clusters of larger polygonal cells with acidophilic cytoplasm filled with abnormally shaped mitochondria. Some oxyphil cells show low levels of PTH synthesis, suggesting that these cells are transitional derivatives of chief cells.



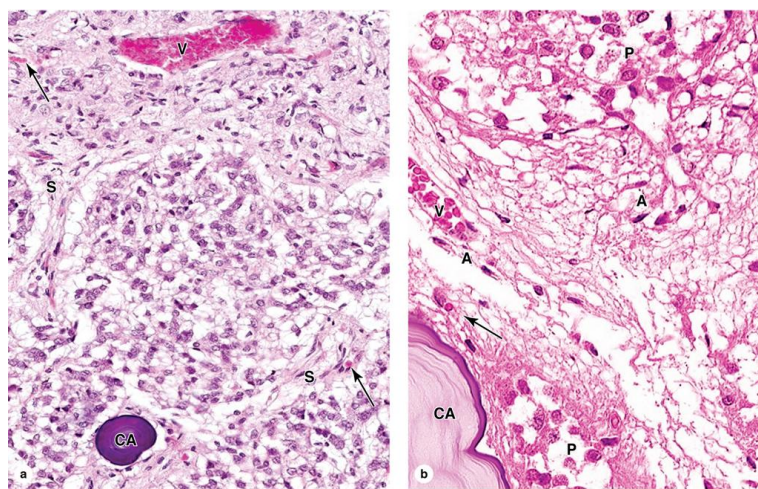
Pineal Gland

The pineal gland (the epiphysis cerebri, the pineal body) is a flattened conical organ situated on the roof of the diencephalon (5-8 mm long, 3-5 mm wide). It is covered by pia mater, from which connective tissue septa penetrate the gland dividing it into irregular lobules & carrying blood vessels & unmyelinated nerves. The lobules consist of cellular cords surrounded by capillaries. Pineal gland consists of 2 main cell types:

- **Pinealocytes:** slightly basophilic cytoplasm & large irregular or lobulated nuclei with sharply defined nucleoli. The cytoplasm contains secretory vesicles & many mitochondria. These cells have long tortuous cytoplasmic processes that end near the capillaries as flattened dilatations (indicating endocrine function). Pinealocytes secrete *melatonin* & other peptides. Melatonin secretion is stimulated by darkness & inhibited by daylight. The resulting fluctuation in blood melatonin level induces rhythmic changes in the hypothalamus, pituitary gland & other endocrine tissues that characterize the circadian rhythm of our physiology & behavior. Light & darkness cycle is detected by the retina & reaches the pineal gland-after a complex pathway-via the sympathetic nerves.
- **Interstitial Glial Cells:** special cells found between the cords of pinealocytes & in the perivascular areas. They resemble astrocytes, having dark elongated nuclei & long cytoplasmic processes that contain large number of intermediate filaments.

Nerve fibers lose myelin sheath when they enter pineal gland. Unmyelinated axons end among pinealocytes forming some synapses, with great number of noradrenaline-containing vesicles seen in these nerve endings. Serotonin is also present.

A characteristic feature of the pineal gland is the presence of variously sized calcium & magnesium salts called **corpora arenacea** or brain sand. These appear during childhood & increase in number & size with age, with no apparent effect on the gland's function.



>> MEDICAL APPLICATION

Graves disease is an autoimmune disorder in which antibodies produce chronic stimulation of the follicular cells and release of thyroid hormones (**hyperthyroidism**), which causes a hypermetabolic state marked by weight loss, nervousness, sweating, heat intolerance, and other features. **Hypothyroidism**, with reduced thyroid hormone levels, can be caused by local inflammation (**thyroiditis**) or inadequate secretion of TSH by the anterior pituitary gland and is often manifested by tiredness, weight gain, intolerance of cold, and decreased ability to concentrate.

>> MEDICAL APPLICATION

Diabetes mellitus is characterized by loss of the insulin effect and a subsequent failure of cells to take up glucose, leading to elevated blood sugar or **hyperglycemia**. **Type 1 diabetes** or **insulin-dependent diabetes mellitus (IDDM)** is caused by loss of the β cells from autoimmune destruction and is treated by regular injections of insulin. In **type 2 diabetes** or **non-insulin-dependent diabetes mellitus (NIDDM)**, β cells are present but fail to produce adequate levels of insulin in response to hyperglycemia, and the peripheral target cells "resist" or no longer respond to the hormone. Type 2 diabetes commonly occurs with obesity, and poorly understood, multifactorial genetic components are also important in this disease's onset.

>> MEDICAL APPLICATION

Benign **pituitary adenomas** often produce excessive numbers of functional acidophils or basophils. Adenomas involving somatotrophic cells can cause **gigantism** if occurring in children before closure of the long bones' epiphyseal plates or **acromegaly** in adults, with musculoskeletal, neurologic, and other medical consequences.

>> MEDICAL APPLICATION

Posterior pituitary function can be adversely affected by heritable mutations in the gene for vasopressin (ADH)-neurophysin, by compression from a tumor in adjacent tissues, and by **head trauma**. By lowering levels of vasopressin, such conditions can produce diabetes insipidus, a disorder characterized by inability to concentrate urine, which leads to frequent urination (**polyuria**) and increased thirst (**polydipsia**).

>> MEDICAL APPLICATION

In the adrenal medulla, benign pheochromocytomas periodically secrete high levels of catecholamines that cause swings in blood pressure between hypertension and hypotension.

>> MEDICAL APPLICATION

Addison disease or **adrenal cortical insufficiency** is a disorder, usually autoimmune in origin, which causes degeneration in any layer of adrenal cortex, with concomitant loss of glucocorticoids, mineralocorticoids, or androgen production.

>> MEDICAL APPLICATION

In **hypoparathyroidism**, diminished secretion of PTH can cause bones to become more mineralized and denser and striated muscle to exhibit abnormal contractions due to inadequate calcium ion concentrations. Excessive **PTH** produced in **hyperparathyroidism** stimulates osteoclast number and activity, leading to increased levels of blood calcium that can be deposited pathologically in cartilage, arteries, or the kidneys.

>> MEDICAL APPLICATION

Chronic dietary iodine deficiencies inhibit thyroid hormone production, causing thyrotrophic cells of the anterior pituitary gland to produce excess TSH. This leads to excessive growth of thyroid follicles and enlargement of the thyroid gland, a condition known as **goiter**.

End