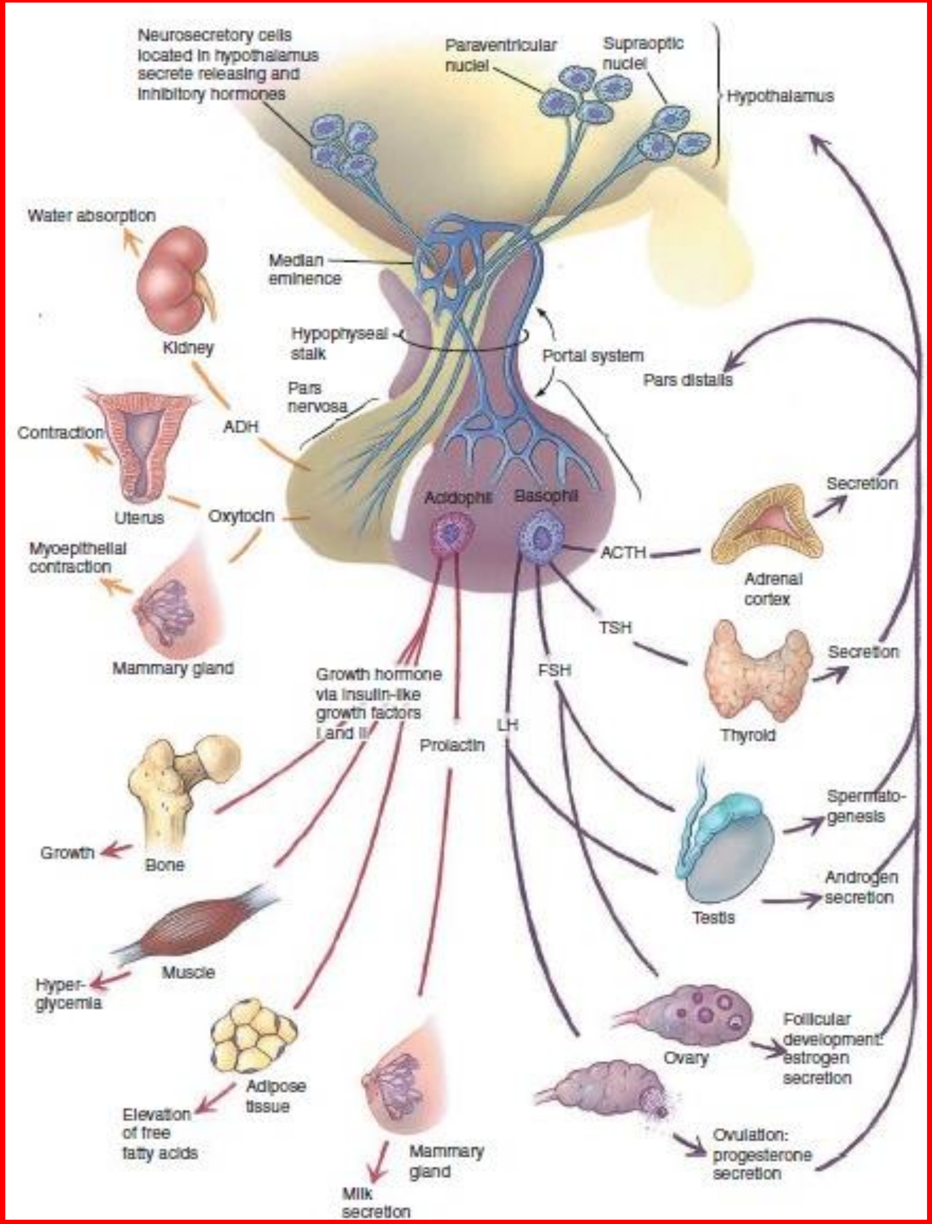
DEPARTMENT OF HISTOLOGY-EMBRYOLOGY

HISTOLOGY II LECTURE

ENDOCRINE SYSTEM



ENDOCRINE SYSTEM

- The endocrine system is a major regulator of homeostasis that modulates many biological functions playing an essential role in the interaction between millions of complex mechanisms that make normal life possible. Thus, longitudinal growth and development, reproduction, regulation of fluid and electrolyte balance, and control of food intake and energy expenditure represent some of the crucial physiological functions played by hormones.

- Endocrine secretions, together with the nervous system, coordinate water and ion balance, metabolism, reproduction, and nutrient absorption. Consequently, most tissues in the body are targets for one or more endocrine hormones.

THE HISTORY OF THE ENDOCRINE SYSTEM

- As endocrinology carved in stone, **a bust of pharaoh Amenhotep (IV)**, aka Akhenaton, bears all the signs of **acromegaly**, which is mostly induced by tumor-secreted growth hormone.
- **Thyroid gland malfunctions** were known long ago and were treated with (iodine-containing) seaweed or dried sponges.
- Since the beginning of animal husbandry, **castration of male cattle** has been known to make them infertile and to **enhance their size and fat content**. Those bullocks are easier to handle than bulls must also have been apparent.

ENDOCRINE SYSTEM

- **Protozoans** sense signals from the environment on their cell surface and adapt to these messages. They **do not require the kinds of messages** which help cells in multicellular organisms to communicate information to one another about their conditions, their requirements, and how they can serve other cells.

- Once multicellular organisms with different organs and their different functions had developed from protozoans, it became **necessary** to develop **message transport** within the organism. Two systems evolved: **the nervous system and the endocrine system**. There is a third system, the **immune system**, which also processes information.

HOW DO WE DEFINE THE ENDOCRINE SYSTEM?

When comparing the endocrine system with the **nervous system or the immune system**, we should recognize that the endocrine system is distinguished by the **following two characteristics**:

1. ***Single organs at defined places:***

- **Very few single organs** are found in the endocrine system, **rather** some of them are doubled and are present on both sides of the body. In contrast, in the immune system, there are some single organs such as the spleen and thymus, many lymph nodes with similar functions are distributed across the whole organism, and Peyer's patches, for example, are present in the gut. In the endocrine system, soluble hormones drift through the organism, whereas in the immune system, cells wander throughout the circulation and the lymphatics as well. A similar migration of endocrine cells occurs only in metastatic tumors.

HOW DO WE DEFINE THE ENDOCRINE SYSTEM?

2. *Soluble mediators with distant effects*

- This contrasts with the nervous system, where information is transferred across the very narrow synaptic cleft. Nerve cells with their axons connect the distant organs and body regions: that is, far-reaching cells and short ways for the mediators (neurotransmitters) in the nervous system, narrowly defined organs, and far-reaching mediators (hormones) in the endocrine system.

- All three systems have in common that the activity of all cells is controlled by either synaptic contacts or soluble mediators. Hormones act on nerve cells, immune cells, and endocrine cells, and nerves reach nerve cells, endocrine cells, and immune cells; the mediators of the immune system, on the other hand, have receptors at nerve cells and endocrine cells.
- The three systems are intimately linked and mutually influence each other.

WHAT IS A HORMONE?

- Hormones are signals. They announce to the **organism the state of the secreting cell as well as the state of the hormone-producing organ**. Thus, the effect of a hormone is solely within the target organ.

- Hormones are transferred from the releasing organ to the target organ **by means of the blood**. Some hormones need a **specific vehicle** for this transport, **however,** most hormones move **without a vehicle through the circulation**.

- During transport, hormones are prone to enzymatic degradation. To reach the target organ in sufficient concentrations, many hormones are released by the coordinated action of many cells.

HORMONE CLASSES

- Hormones, like neurotransmitters, are **frequently hydrophilic molecules** such as proteins, glycoproteins, peptides, or modified amino acids with receptors on the surface of target cells. **Alternatively, hydrophobic steroid and thyroid hormones** must circulate on transport proteins but can diffuse through the cell membranes and activate cytoplasmic receptors in target cells.
- Hormones can be divided into three main groups in terms of their origin;

A) Protein/Peptide Hormones:

- Insulin, glucagon, growth hormone [GH], adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], antidiuretic hormone [ADH], oxytocin, interleukins, and various growth factors).

B) Steroids Hormones:

- Gonadal and adrenocortical steroids.

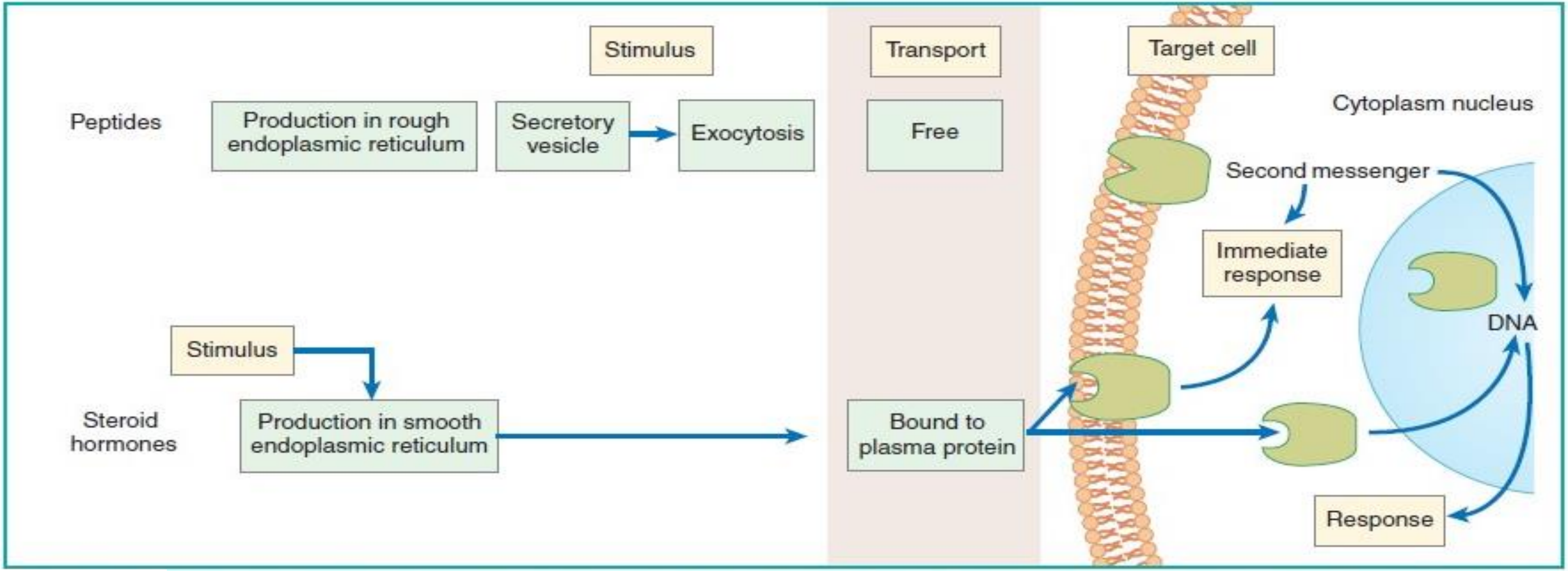
C) Amino Acid Derivatives:

- Catecholamines (norepinephrine and epinephrine-phenylalanine/tyrosine derivatives), prostaglandins, prostacyclins, leukotrienes (arachidonic acid derivatives) and thyroid hormones.

- **Steroid hormones** are derived from cholesterol. Consequently, steroid hormones are generally poorly soluble in water and, following secretion, are transported bound to plasma-binding proteins. Steroids diffuse across the plasma membrane and bind to a cytoplasmic binding protein. The steroid–binding protein complex diffuses to the nucleus and activates a hormone response element, which initiates DNA transcription and translation. The reliance on DNA transcription and translation means that steroid hormones generally have a long lag time between secretion and effect. Some steroids, like aldosterone and estrogen, can produce acute effects independent of any nuclear effects. This allows such hormones to have both acute and chronic actions.

- **Peptide and catecholamine hormones** first bind to cell membrane receptors and consequently have a rapid onset of response. Some second messenger systems do affect transcription and translation, allowing peptide hormones to also have longer term trophic activities.

- **Proteins and polypeptides hormones** are synthesized in the endoplasmic reticulum. Proteins and polypeptide hormones bind to cell membrane receptors on target tissues. Peptide hormones require second messengers for effects and generally have rapid response times.

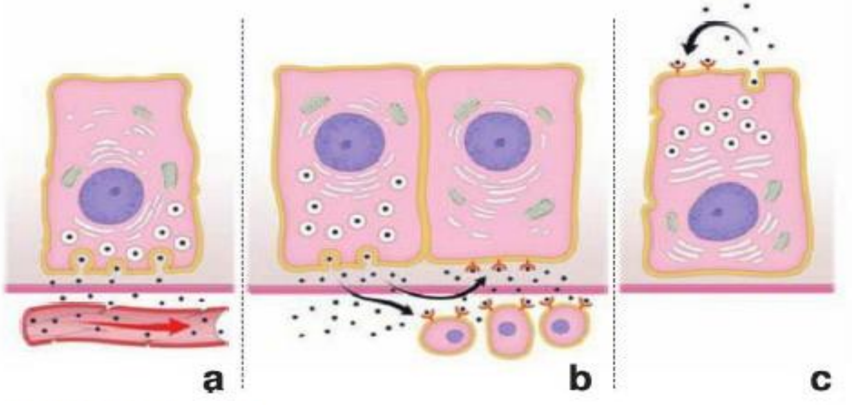


Peptide and steroid endocrine agents exhibit different patterns of action. Peptide hormones are synthesized in advance and released by exocytosis following an appropriate stimulus. Once released, they travel within the plasma until binding with a receptor on the cell surface of the target tissue and quickly activating intracellular second messenger systems. In contrast, steroid hormones are synthesized on demand following an appropriate stimulus. Following release, steroid hormones travel bound to plasma protein, enter the cell by diffusion, and bind an intracellular receptor, ultimately affecting DNA transcription and translation.

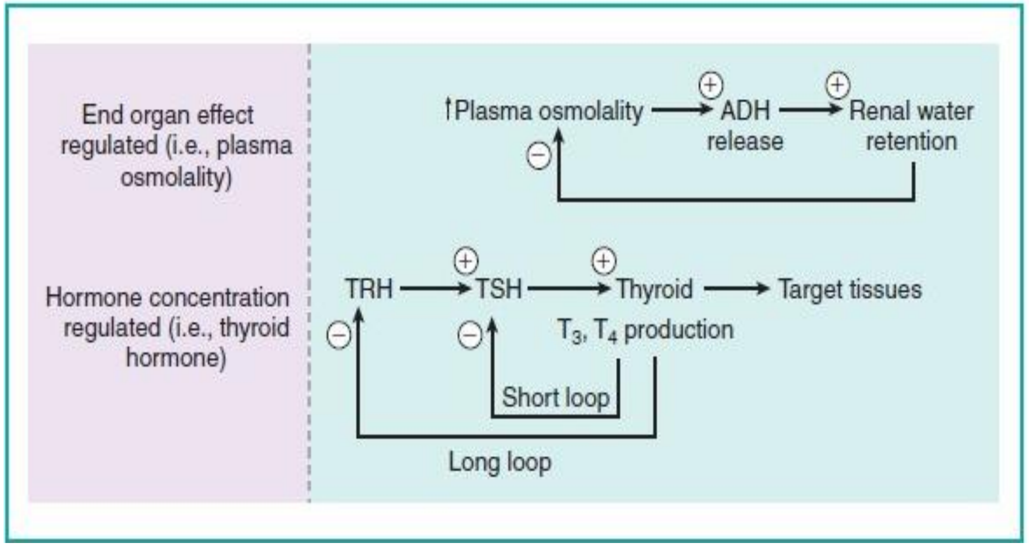
NOTE: Catecholamines and thyroid hormone do not share common mechanism of action, even though they are both derived from amino acid precursors. Catecholamines act on cell membrane receptors and work through second messengers similarly to peptide hormones. Thyroid hormones bind cytoplasmic receptors and alter DNA transcription, similarly to steroid hormones.

ENDOCRINE SYSTEM CONTROL & REGULATION

- Negative feedback loops provide precise control of endocrine secretions. The controlled component of the negative feedback loop can be ion concentrations, physical parameters (e.g., blood pressure), and hormone concentrations. Stimulators of endocrine gland secretion also have important trophic effects. Stimuli that cause hormone release frequently also cause hypertrophy and hyperplasia of the endocrine organ. This increases the quantity of hormone synthesized and released. Endocrine control often is integrated with neural function. Sympathetic nerves innervate some endocrine organs, such as the adrenal medulla and pancreas. Nerves in the hypothalamus release factors controlling anterior pituitary secretions. Nervous system function often complements endocrine actions. Hemorrhagic hypotension causes an increase in angiotensin II production and ADH release, as well as an increase in sympathetic nerve activity. Together, these systems promote the renal retention of sodium and water, which helps restore blood volume and blood pressure toward normal. Specific external controls are discussed later in this chapter with the appropriate endocrine hormone.



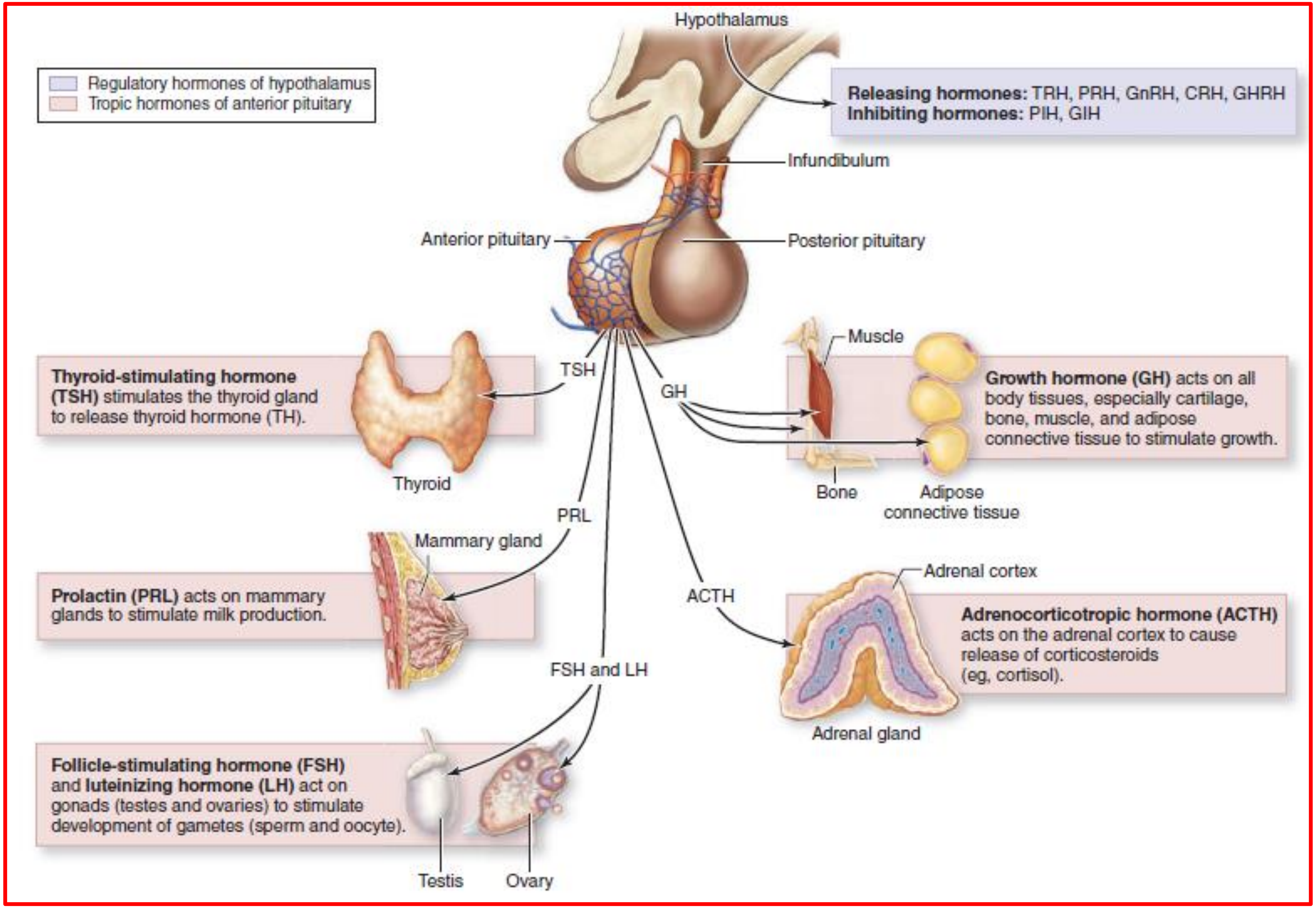
Hormonal control mechanisms. This schematic diagram shows three basic types of control mechanisms. **a.** In endocrine control, the hormone is discharged from a cell into the bloodstream and is transported to the effector cells. **b.** In paracrine control, the hormone is secreted from one cell and acts on adjacent cells that express specific receptors. **c.** In autocrine control, the hormone responds to the receptors located on the cell that produces it.



Hormone release is regulated by negative feedback loops. The negative feedback signal can be provided by an end organ effect, or the circulating hormone levels themselves may provide the negative feedback signal.

ENDOCRINE ORGANS

- HYPOTHALAMUS
- PITUITARY GLAND
- THYROID GLAND
- PARATHYROID GLAND
- PINEAL GLAND
- ADRENAL GLAND



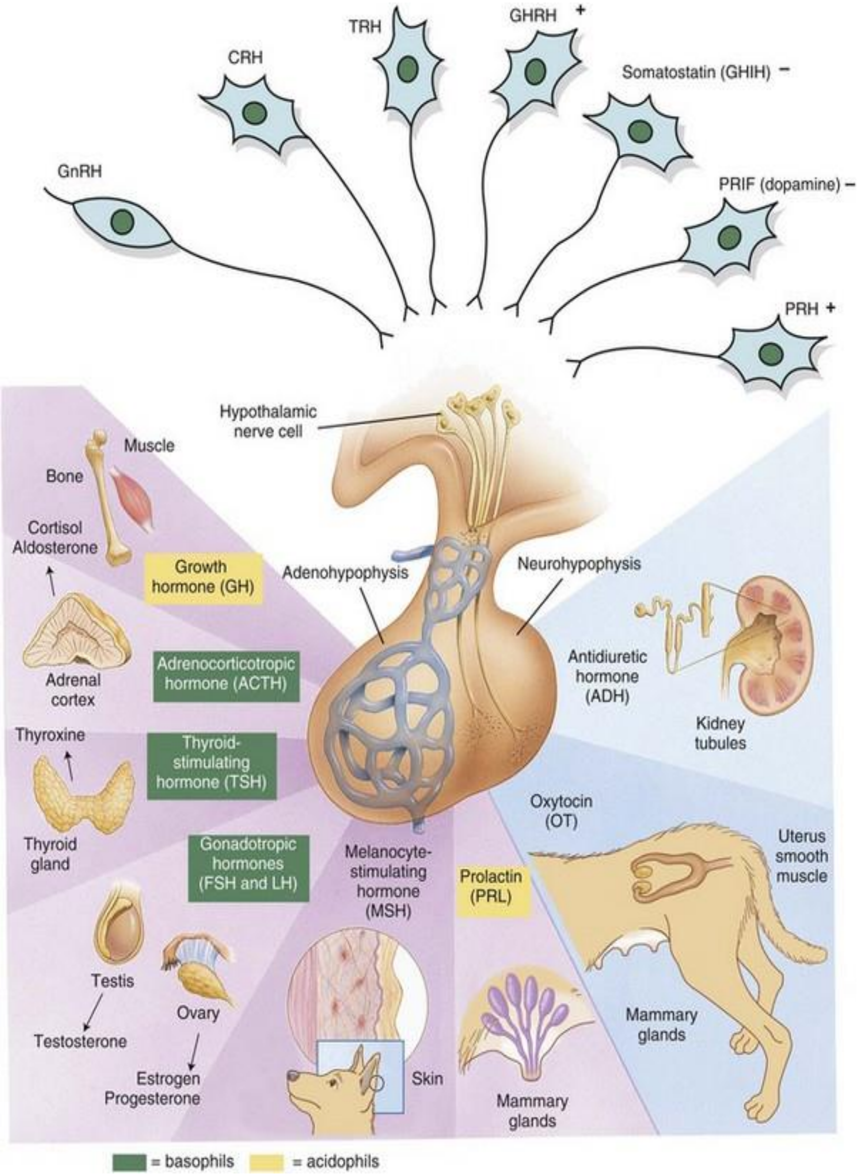
Hypothalamus
Regulatory hormones of hypothalamus
Tropic hormones of anterior pituitary
Releasing hormones: TRH, PRH, GnRH, CRH, GHRH
Inhibiting hormones: PIH, GIH
Infundibulum
Anterior pituitary
Posterior pituitary
TSH
GH
Muscle
Thyroid-stimulating hormone (TSH) stimulates the thyroid gland to release thyroid hormone (TH).
Growth hormone (GH) acts on all body tissues, especially cartilage, bone, muscle, and adipose connective tissue to stimulate growth.
Thyroid
Bone
Adipose connective tissue
PRL
Mammary gland
Adrenal cortex
Prolactin (PRL) acts on mammary glands to stimulate milk production.
ACTH
Adrenocorticotropic hormone (ACTH) acts on the adrenal cortex to cause release of corticosteroids (eg, cortisol).
FSH and LH
Adrenal gland
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) act on gonads (testes and ovaries) to stimulate development of gametes (sperm and oocyte).
Testis
Ovary

1. HYPOTHALAMUS

- The hypothalamus sits dorsal to the pituitary gland and regulates secretion of both anterior and posterior pituitary hormones. Hypothalamic-releasing hormones regulate secretion of five of the six anterior pituitary hormones.

1. Thyroid hormone–releasing hormone (thyroid-releasing hormone, TRH) controls pituitary output of thyroid stimulating hormone (TSH).
2. Corticotropin-releasing hormone (CRH) controls pituitary secretion of adrenocorticotropic hormone (ACTH).
3. Gonadotropin-releasing hormone (GnRH) causes release of both pituitary luteinizing hormone (LH) and pituitary follicle-stimulating hormone (FSH).
4. Growth hormone–releasing hormone (GHRH) regulates pituitary secretion of growth hormone (GH).
5. Two hypothalamic hormones inhibit pituitary secretion. Prolactin inhibitory hormone (dopamine) inhibits pituitary release of prolactin.

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)



2. PITUITARY GLAND (HYPOPHYSIS)

- The **pituitary gland**, or **hypophysis** (Gr. *hypo*, under + *physis*, growth) lies below the brain in a small cavity on the sphenoid bone, the sella turcica. The pituitary is formed in the embryo partly from the developing brain and partly from the developing oral cavity.

- The neural component is the neurohypophyseal bud growing down from the floor of the future diencephalon as a stalk (or infundibulum) that remains attached to the brain.

- The oral component arises as an outpocketing of ectoderm from the roof of the primitive mouth and grows cranially, forming a structure called the **hypophyseal (Rathke) pouch.**

2. PITUITARY GLAND (HYPOPHYSIS)

- Because of its dual origin, the pituitary actually consists of two glands—the posterior **neurohypophysis** and the anterior **adenohypophysis**—united anatomically but with different functions.

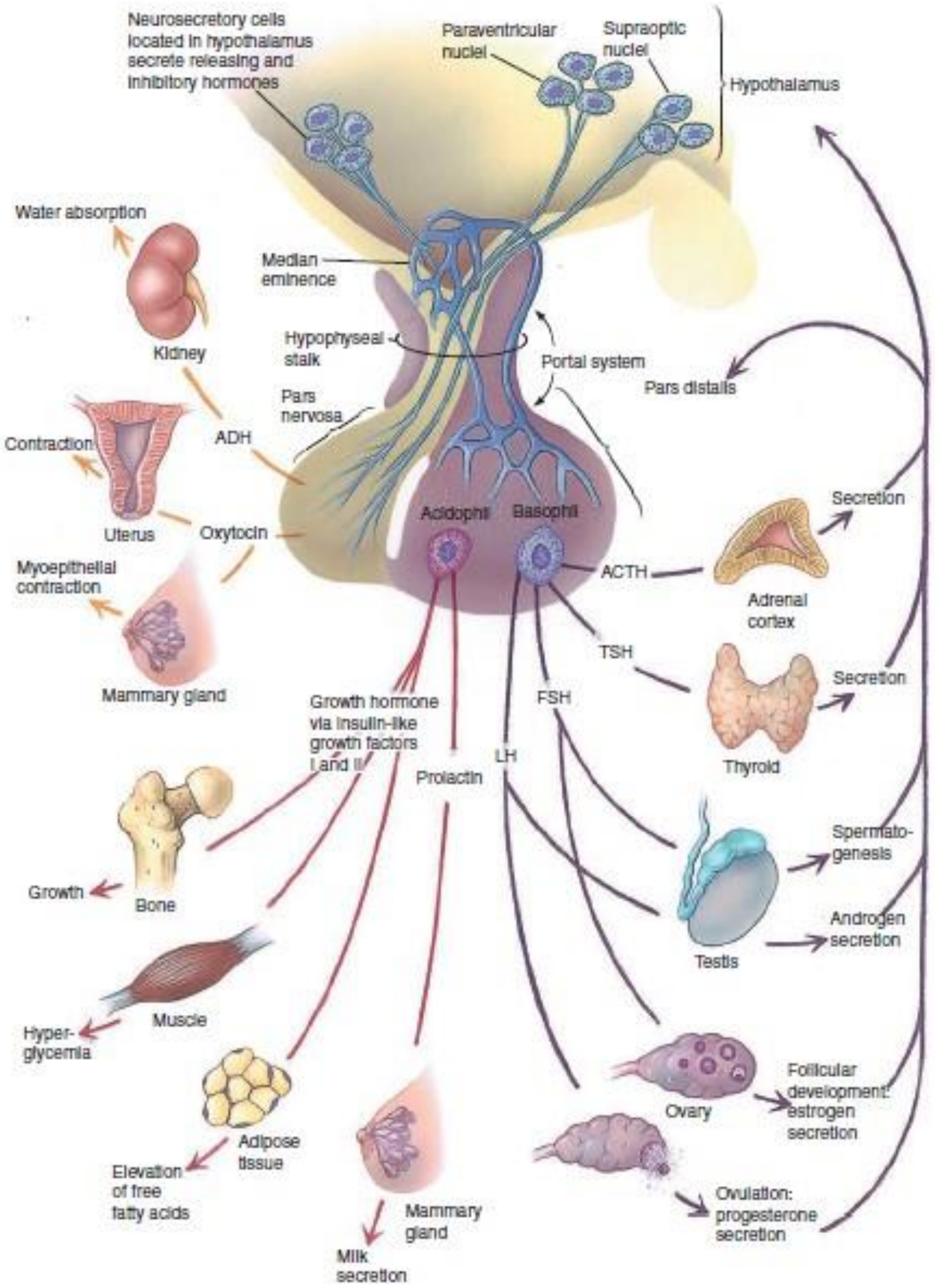
- The neurohypophysis retains many histologic features of brain tissue and consists of a large part, the **pars nervosa**, and the smaller **infundibulum** stalk attached to the hypothalamus at the **median eminence**.

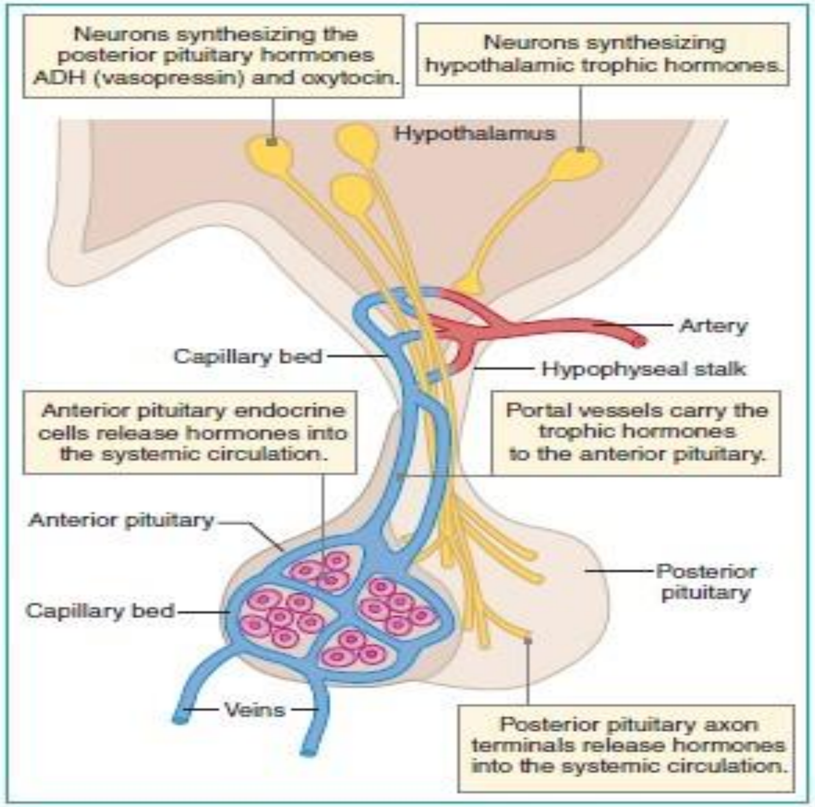
- The **adenohypophysis**, derived from the oral ectoderm, has three parts:

a) a large **pars distalis** or **anterior lobe**;

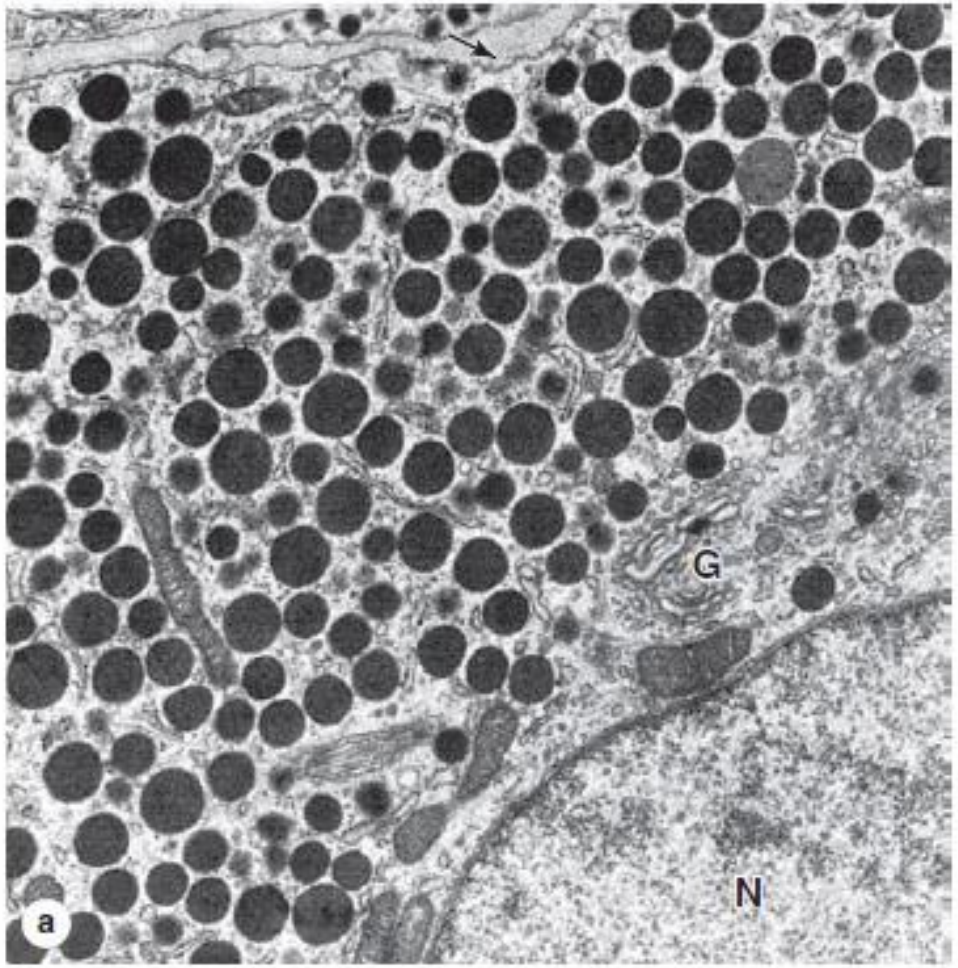
b) the **pars tuberalis**, which wraps around the infundibulum;

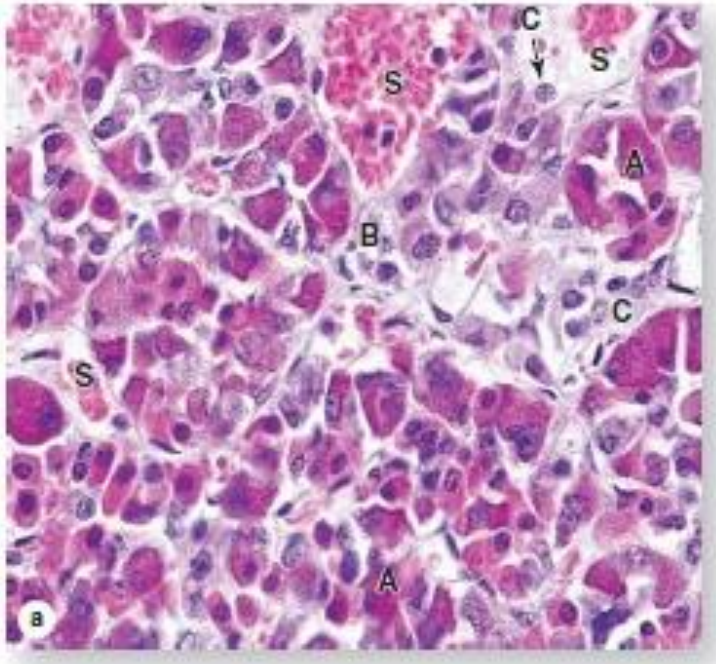
c) and the thin **pars intermedia** adjacent to the posterior pars nervosa.

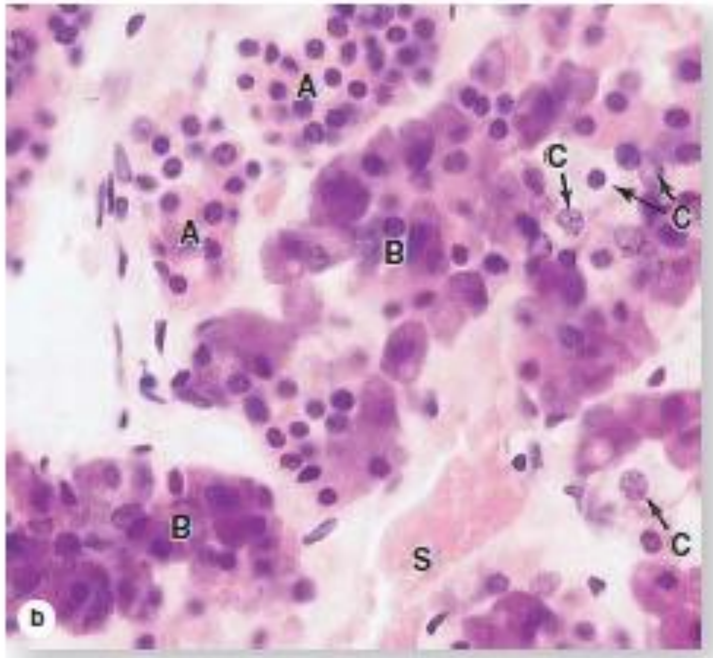


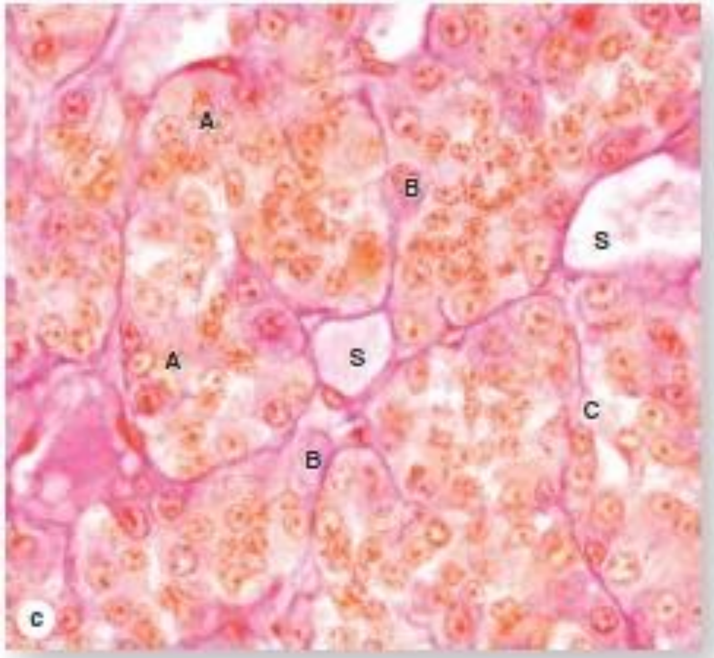


The hypothalamus and pituitary have complex neural and endocrine interactions. Neurons in the hypothalamus synthesize oxytocin and antidiuretic hormone. The hormones are transported within axon terminals to the posterior pituitary for release. In contrast, the anterior pituitary is in endocrine gland. Hormone release is controlled by releasing and inhibitory peptides that pass from the hypothalamus to the anterior pituitary by a vascular hypothalamic-hypophyseal portal system.









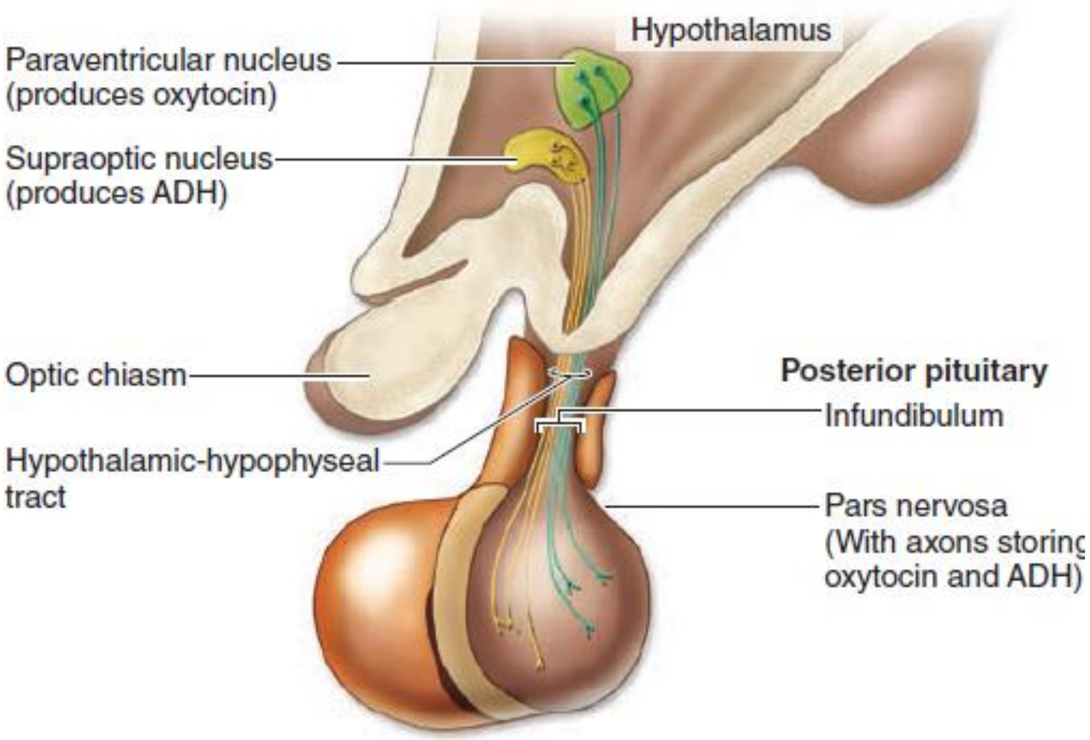
(**a**) Ultrastructurally, cytoplasm of all chromophil cells is shown to have well-developed Golgi complexes (**G**), euchromatic nuclei (**N**), and cytoplasm filled with secretory granules, as seen here in a somatotroph, the most common acidophil. The **arrow** indicates the cell membrane. Specific chromophils are more easily identified

(**a, b**) Most general staining methods simply allow the parenchymal cells of the pars distalis to be subdivided into acidophil cells (**A**), basophils (**B**), and chromophobes (**C**) in which the cytoplasm is poorly stained. Also shown are capillaries and sinusoids (**S**) in the second capillary plexus of the portal system. Cords of acidophils and basophils vary in distribution and number in different regions of the pars distalis, but are always closely associated with microvasculature that carries off secreted hormones into the general circulation. (X400; H&E)

(**c**) The same area is seen after staining with Gomori trichrome. (X400)

The Hypothalamic-Hypophyseal Tract & Blood Supply

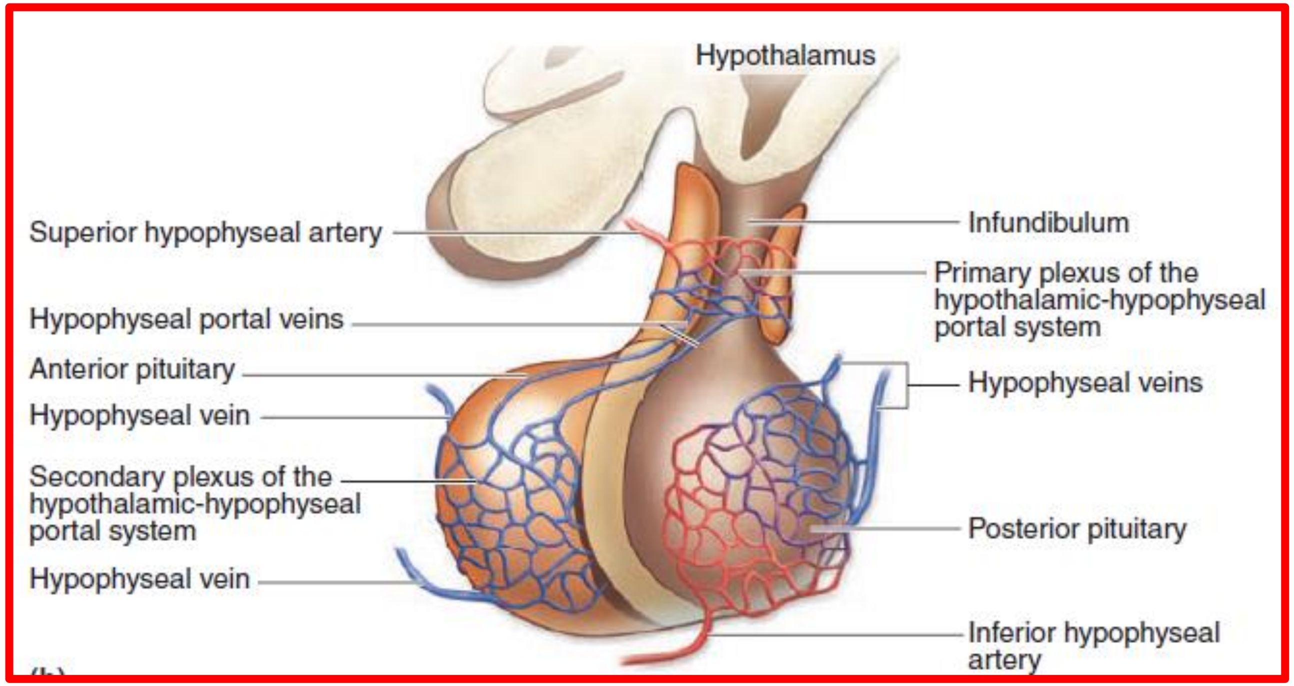
- The pituitary gland's neural connection to the brain and its blood supply are both of key importance for its function. Embryologically, anatomically, and functionally, the pituitary gland is connected to the hypothalamus at the base of the brain.
- In addition to the vascular portal system carrying small regulatory peptides from the hypothalamus to the adenohypophysis, a bundle of axons called the **hypothalamic-hypophyseal tract** courses into the neurohypophysis from two important hypothalamic nuclei.
- The peptide hormones **ADH** (antidiuretic hormone) and **oxytocin** are synthesized by large neurons in the **supraoptic** and the **paraventricular nuclei**, respectively. Both hormones undergo **axonal transport** and accumulate temporarily in the axons of the hypothalamic-hypophyseal tract before their release and uptake by capillaries branching from the inferior arteries.



The Hypothalamic-Hypophyseal Tract & Blood Supply

- The blood supply derives from two groups of vessels coming off the internal carotid artery and drained by the hypophyseal vein. The **superior hypophyseal arteries** supply the median eminence and the infundibular stalk; the **inferior hypophyseal arteries** provide blood mainly for the neurohypophysis. The superior arteries divide into a **primary plexus** of fenestrated capillaries that irrigate the stalk and median eminence. These capillaries then rejoin to form venules that branch again as a larger secondary capillary plexus in the adenohypophysis.

- These vessels make up the **hypothalamic-hypophyseal portal system** that has great importance because it carries neuropeptides from the median eminence the short distance to the adenohypophysis where they either stimulate or inhibit hormone release by the endocrine cells there.

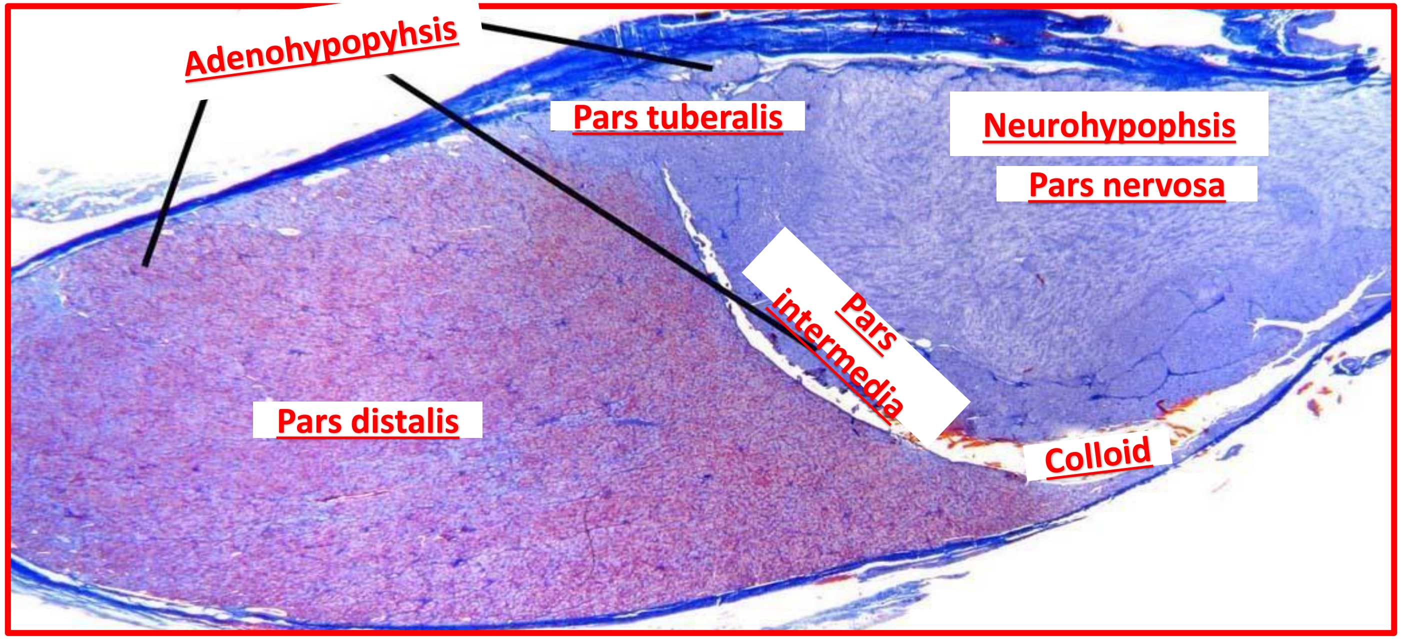


- **Adenohypophysis (Anterior Pituitary)**
- The three parts of the adenohypophysis are derived embryonically from the hypophyseal pouch.

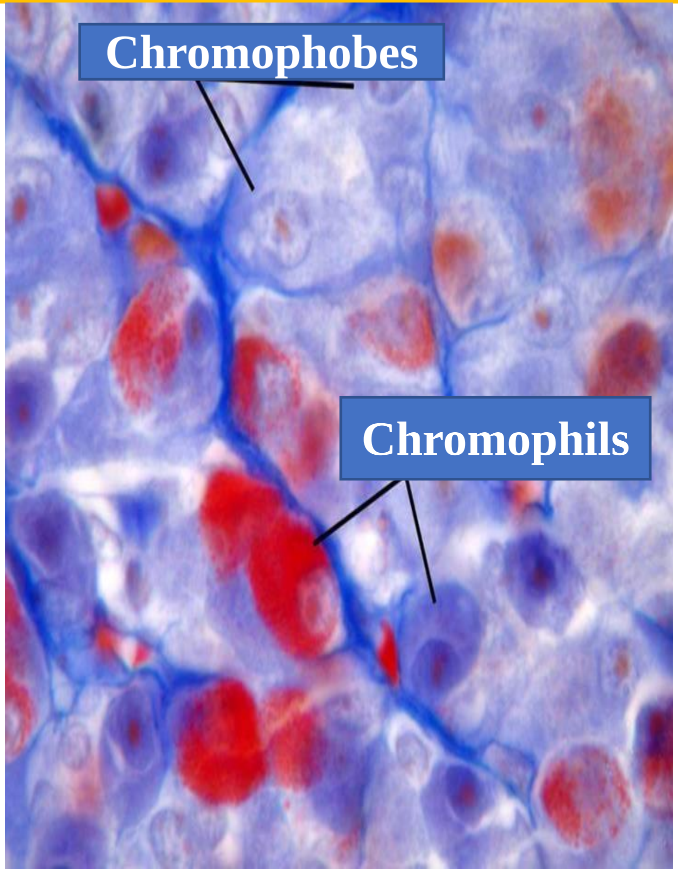
✓**Pars Distalis**

✓**Pars Intermedia**

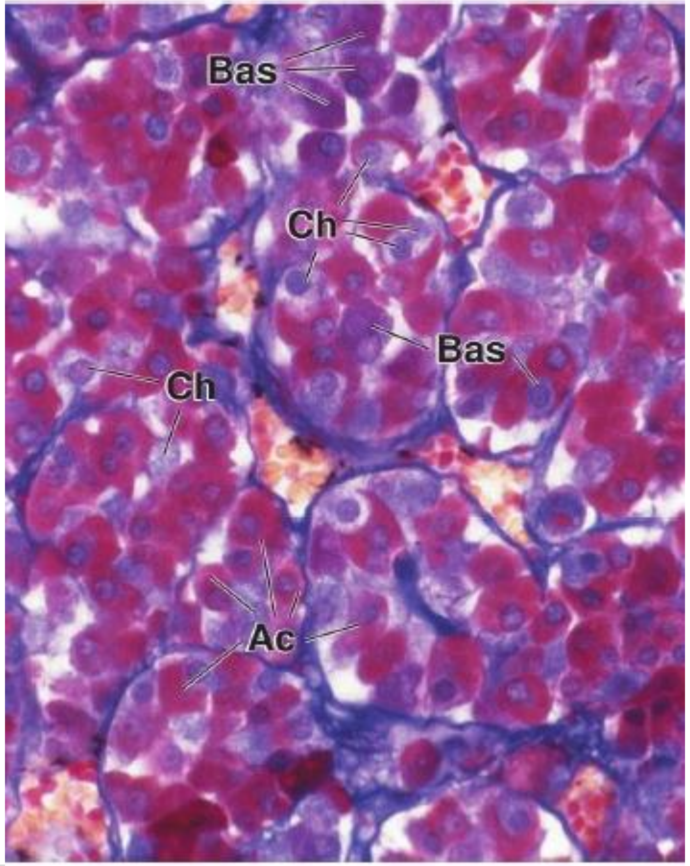
✓**Pars Tuberalis**



Pars Distalis



- The **pars distalis** accounts for 75% of the adenohypophysis and has a thin fibrous capsule. The main components are cords of well-stained endocrine cells interspersed with fenestrated capillaries and supporting reticular connective tissue. Common stains suggest two broad groups of cells in the pars distalis with different staining affinities: **chromophils** and **chromophobes**.
- Chromophils are secretory cells in which hormone is stored in cytoplasmic granules. They are also called **basophils** and **acidophils**, based on their affinities for basic and acidic dyes, respectively.



Pars Distalis

- Subtypes of basophilic and acidophilic cells are identified by their granular morphology in the TEM or more easily by immunohistochemistry. Specific cells are usually named according to their hormone's target cells. Acidophils secrete either growth hormone (somatotropin) or prolactin (PRL) and are called **somatotrophs** and **lactotrophs** (or somatotropic cells and lactotropic cells), respectively.

- The basophilic cells are the **corticotrophs, gonadotrophs, and thyrotrophs**, with target cells in the adrenal cortex, gonads, and thyroid gland, respectively.

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	Stimulates secretion of adrenal cortex hormones
		Lipotropin (LPH)	Helps regulate lipid metabolism

Pars Distalis

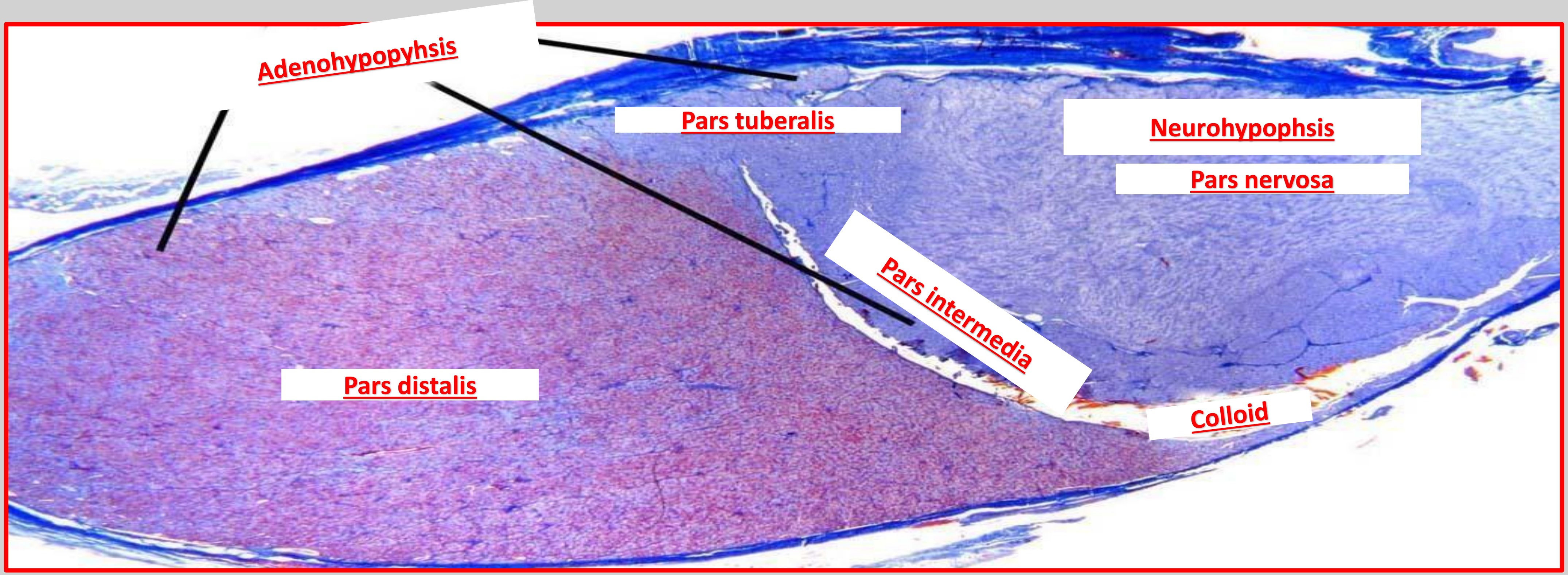
- With two exceptions, each type of anterior pituitary cell makes one kind of hormone. Gonadotrophs secrete two different glycoproteins: **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** (called interstitial cell-stimulating hormone [ICSH]). The main protein synthesized in corticotrophs is pro-opiomelanocortin (POMC), which is cleaved posttranslationally into the polypeptide hormones **adrenocortical trophic hormone (ACTH)** and **β-lipotropin(β-LPH)**. Hormones produced by the pars distalis have widespread functional activities. They regulate almost all other endocrine glands, ovarian function and sperm production, milk production, and the metabolism of muscle, bone, and adipose tissue.
- Chromophobes stain weakly, with few or no secretory granules, and also represent a heterogeneous group, including stem and undifferentiated progenitor cells as well as any degranulated cells present.

Cell Type	Size/Shape	Nucleus/Location	Secretory Vesicle Size/ Characteristics	Other Cytoplasmic Characteristics
Somatotrope	Medium/oval	Round/central, with prominent nucleoli	Dense: 350 nm, closely packed	None
Lactotrope	Large/polygonal	Oval/central	Inactive: 200 nm, sparse Active: dense, pleomorphic, 600 nm, sparse	Lysosomes increase after lactation
Corticotrope	Medium/polygonal	Round/eccentric	100–300 nm	Lipid droplets, large lysosomes, perinuclear bundles of intermediate filaments
Gonadotrope	Small/oval	Round/eccentric	Dense: 200–250 nm	Prominent Golgi apparatus, distended rER cisternae
Thyrotrope	Large/polygonal	Round/eccentric	Dense: <150 nm	Prominent Golgi apparatus with numerous vesicles

rER, rough-surfaced endoplasmic reticulum.

Pars Tuberalis

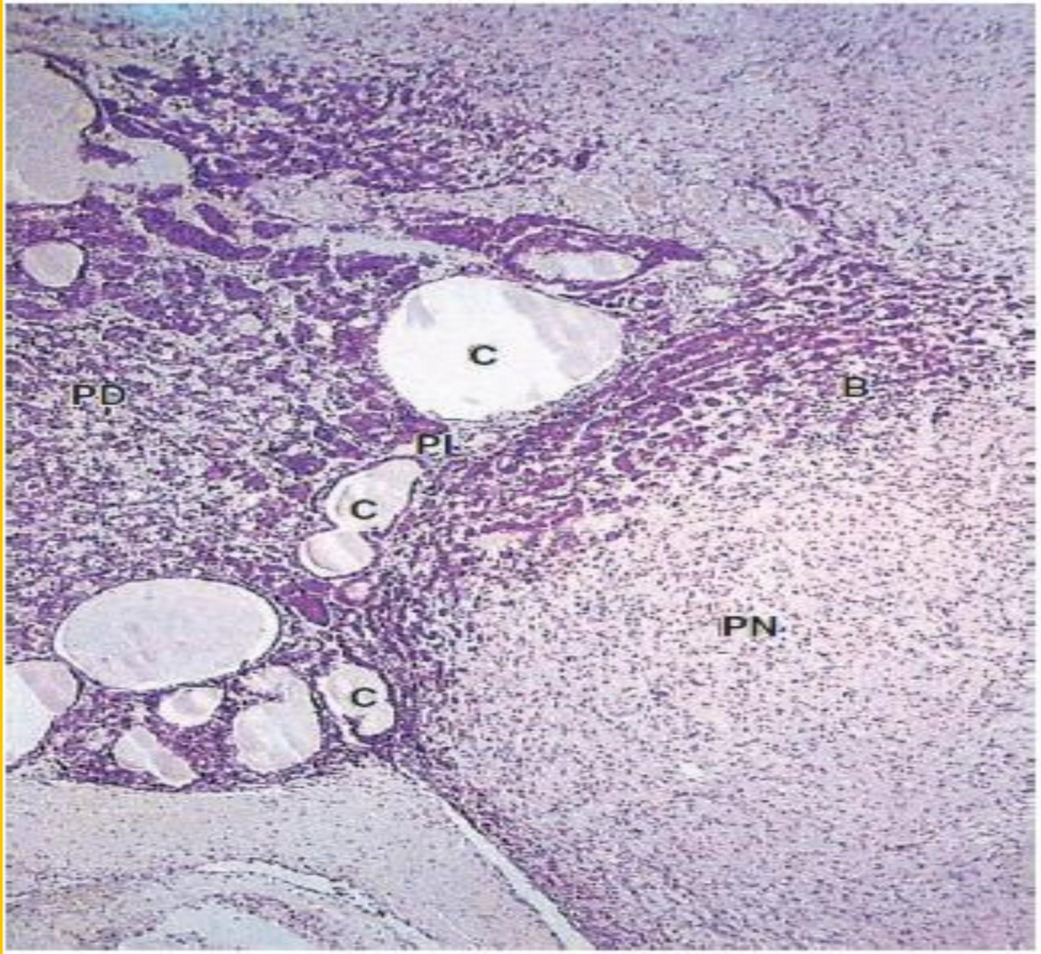
- The **pars tuberalis** is a smaller funnel-shaped region surrounding the infundibulum of the neurohypophysis. Most of the cells of the pars tuberalis are gonadotrophs.



Pars Intermedia

- A narrow zone lying between the pars distalis and the pars nervosa, the **pars intermedia** contains basophils (corticotrophs), chromophobes, and small, colloid-filled cysts derived from the lumen of the embryonic hypophyseal pouch.

- Best-developed and active during fetal life, corticotrophs of the pars intermedia express POMC but cleave it differently from cells in the pars distalis, producing mainly smaller peptide hormones, including two forms of melanocyte-stimulating hormone (MSH), γ-LPH, and β-endorphin. MSH increases melanocyte activity, but the overall functional significance of the pars intermedia remains uncertain.



The pars intermedia (**PI**) is a narrow region lying between the pars distalis (**PD**) and the pars nervosa (**PN**), with many of its basophils (**B**) often invading the latter. Remnants of the embryonic hypophyseal pouch's lumen are usually present in this region as colloid-filled cysts (**C**) of various sizes. Function of this region in humans is not clear. (X56; H&E)

CONTROL OF HORMONE SECRETION IN THE ANTERIOR PITUITARY

- The activities of the cells of the anterior pituitary are controlled primarily by peptide-related **hypothalamic hormones** produced by small neurons near the third ventricle, discharged from axons in the median eminence, and transported by capillaries of the portal system throughout the anterior pituitary. Most of these hormones are **releasing hormones** that stimulate secretion by specific anterior pituitary cells. Two of the hypothalamic factors, however, are **inhibiting hormones**, which block hormone secretion in specific cells of the adenohypophysis. Because of the strategic position of the hypothalamic neurons and the control they exert on the adenohypophysis and therefore on many bodily functions, many sensory stimuli coming to the brain or arising within the central nervous system (CNS) can affect pituitary function and then also quickly affect activities of many other organs and tissues.
- Another mechanism controlling activity of anterior pituitary cells is **negative feedback** by hormones from the target organs on secretion of the relevant hypothalamic factors and on hormone secretion by the relevant pituitary cells.

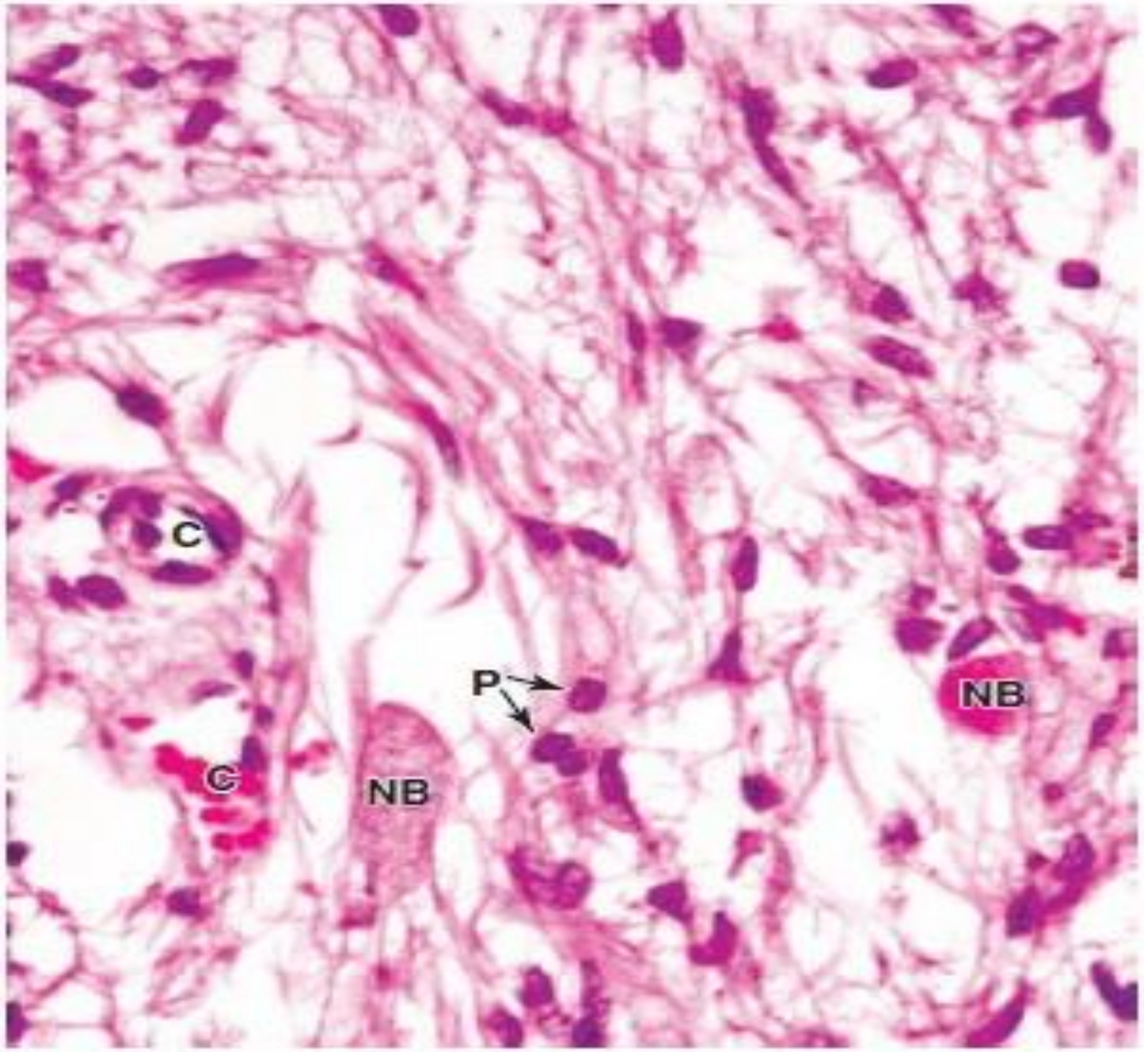
NEUROHYPOPHYSIS (POSTERIOR PITUITARY)

- The neurohypophysis consists of the pars nervosa and the infundibular stalk and, unlike the adenohypophysis, does not contain the cells that synthesize its two hormones. It is composed of neural tissue, containing some 100,000 unmyelinated axons of large secretory neurons with cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. Also present are highly branched glial cells called **pituicytes** that resemble astrocytes and are the most abundant cell type in the posterior pituitary.
- The secretory neurons have all the characteristics of typical neurons, including the ability to conduct an action potential, but have larger-diameter axons and well-developed synthetic components related to the production of the 9-amino acid peptide hormones **antidiuretic hormone (ADH)**—also called arginine vasopressin—and **oxytocin**.

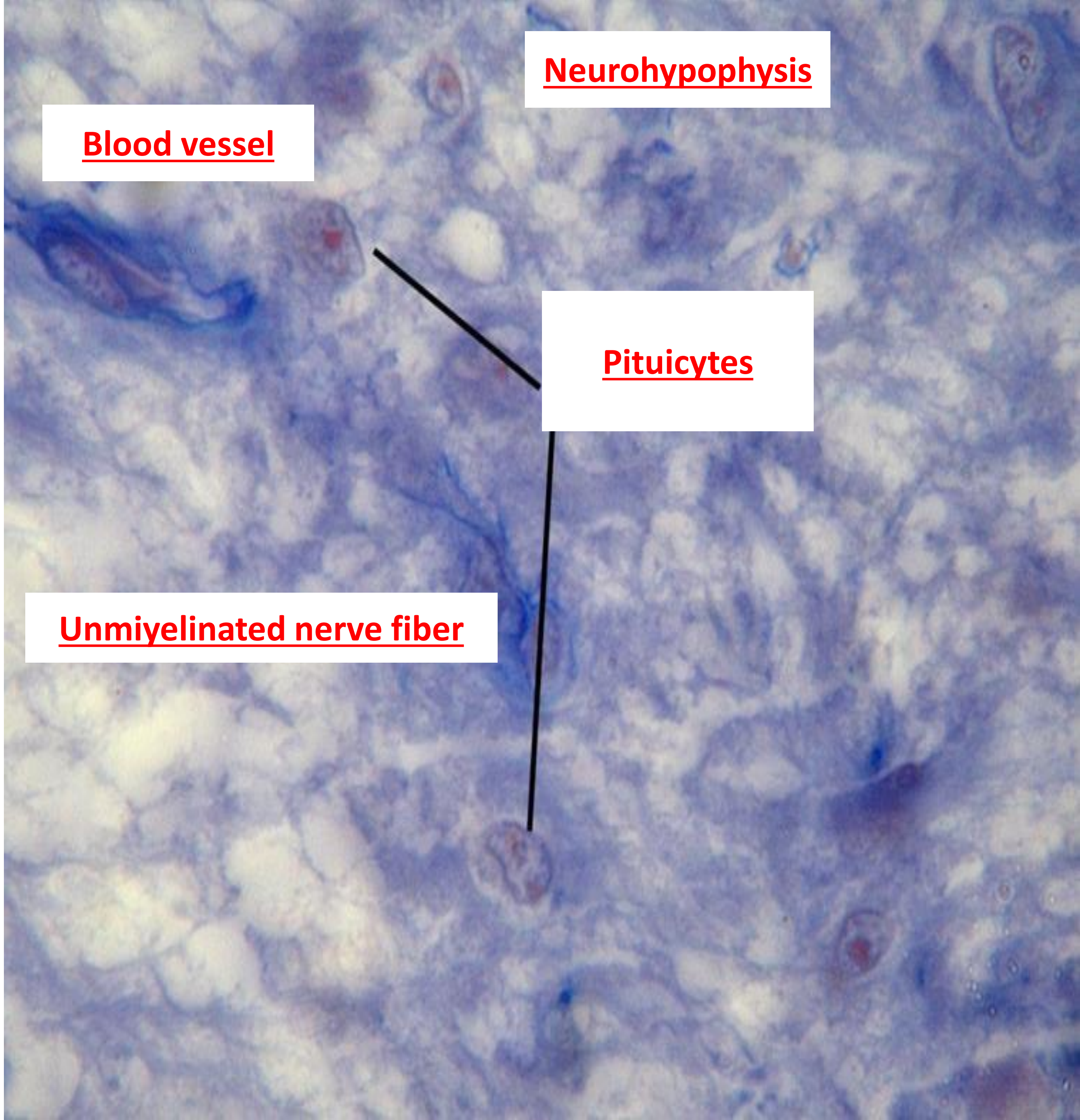
Hormones of the Posterior Lobe of the Pituitary Gland

Hormone	Composition	Source	Major Functions
Oxytocin	Polypeptide containing 9 amino acids	Cell bodies of neurons located in the supraoptic and paraventricular nuclei of the hypothalamus[a]	Stimulates activity of the contractile cells around the ducts of the mammary glands to eject milk from the glands; stimulates contraction of smooth muscle cells in the pregnant uterus
Antidiuretic hormone (ADH; vasopressin)	Polypeptide containing 9 amino acids; two forms: arginine-ADH (most common in humans) and lysine-ADH	Cell bodies of neurons located in the supraoptic and paraventricular nuclei of the hypothalamus[a]	Decreases urine volume by increasing reabsorption of water by collecting ducts of the kidney; decreases the rate of perspiration in response to dehydration; increases blood pressure by stimulating contractions of smooth muscle cells in the wall of arterioles

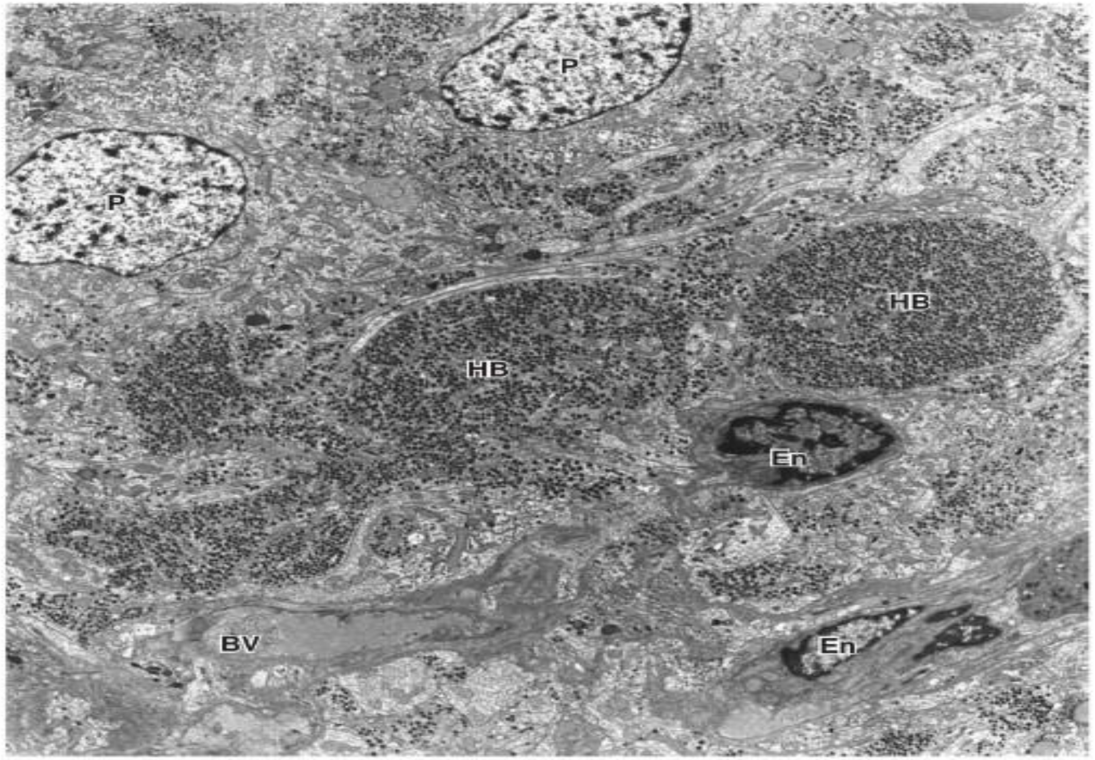
[a]Immunocytochemical studies indicate that oxytocin and ADH are produced by separate sets of neurons within the supraoptic and paraventricular nuclei of the hypothalamus. Biochemical studies have demonstrated that the supraoptic nucleus contains equal amounts of both hormones, whereas the paraventricular nucleus contains more oxytocin than ADH, but less than the amount found in the supraoptic nucleus.



The pars nervosa of the posterior pituitary consists of modified neural tissues containing unmyelinated axons supported and ensheathed by glia cells called **pituicytes** (**P**), the most numerous cell present. The axons run from the supraoptic and paraventricular hypothalamic nuclei, and have swellings called **neurosecretory** (**Herring**) **bodies** (**NB**) from which either oxytocin or vasopressin is released upon neural stimulation. The released hormones are picked up by capillaries (**C**) for distribution. (X400; H&E)

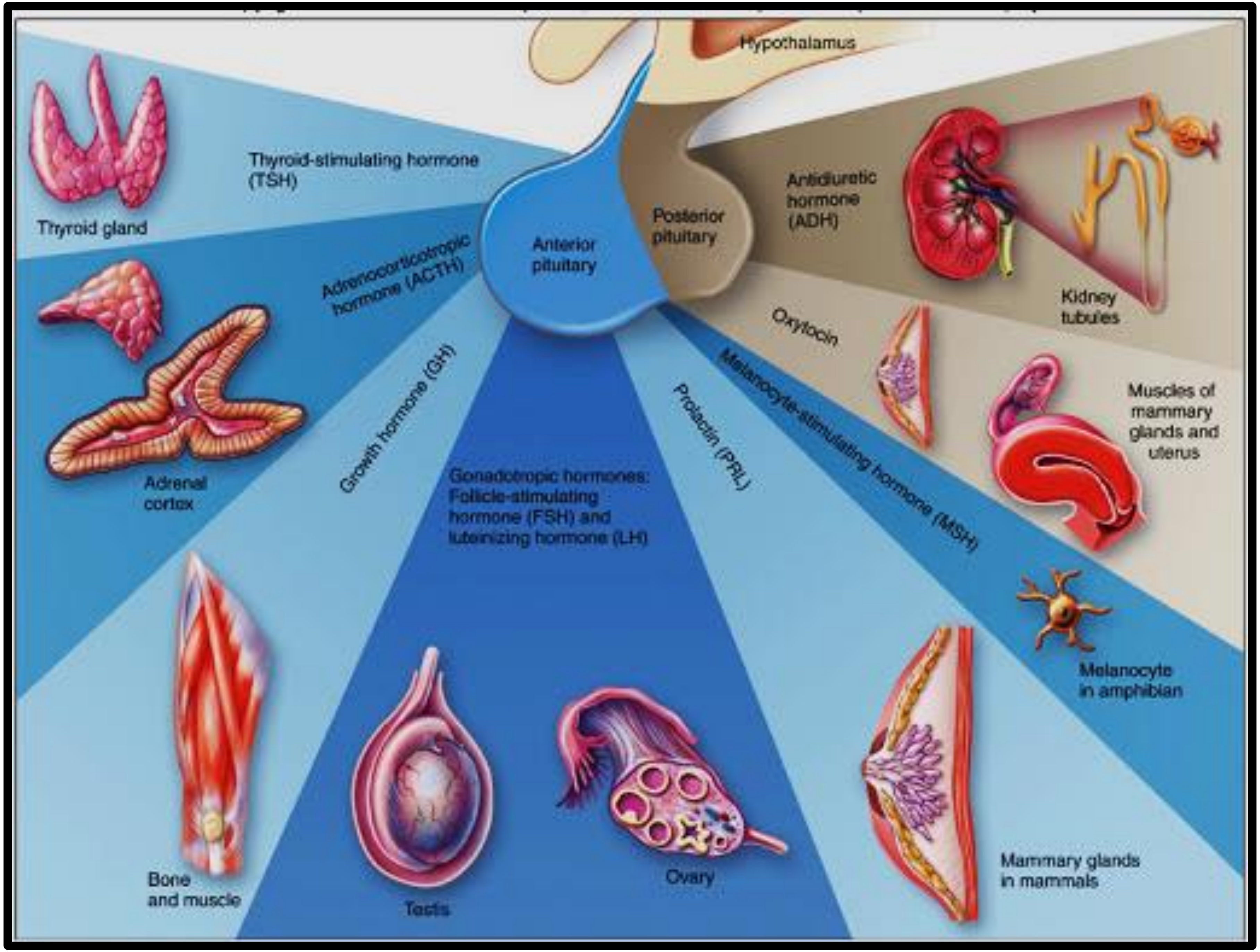


- Transported axonally into the pars nervosa, these hormones accumulate in axonal dilations called **neurosecretory bodies** or **Herring bodies**, visible in the light microscope as faintly eosinophilic structures. The neurosecretory bodies contain membrane-enclosed granules with either oxytocin or ADH bound to 10-kDa carrier proteins called **neurophysin I and II**, respectively.
- Nerve impulses along the axons trigger the release of the peptides from the neurosecretory bodies for uptake by the fenestrated capillaries of the pars nervosa, and the hormones are then distributed to the general circulation. Axons from the supraoptic and paraventricular nuclei mingle in the neurohypophysis but are mainly concerned with ADH and oxytocin secretion, respectively.



▲ **Electron micrograph of Herring bodies of rat posterior lobe.** Dilated portions of axons near their terminals called Herring bodies (*HB*) contain numerous neurosecretory vesicles filled with either oxytocin or ADH. They are surrounded by the specialized glial cells called pituicytes (*P*). Note that Herring bodies reside in a close proximity to blood vessels (*BV*), mainly fenestrated capillaries, lined by endothelial cells (*En*). ×6,000. (Courtesy of Dr. Holger Jastrow.)

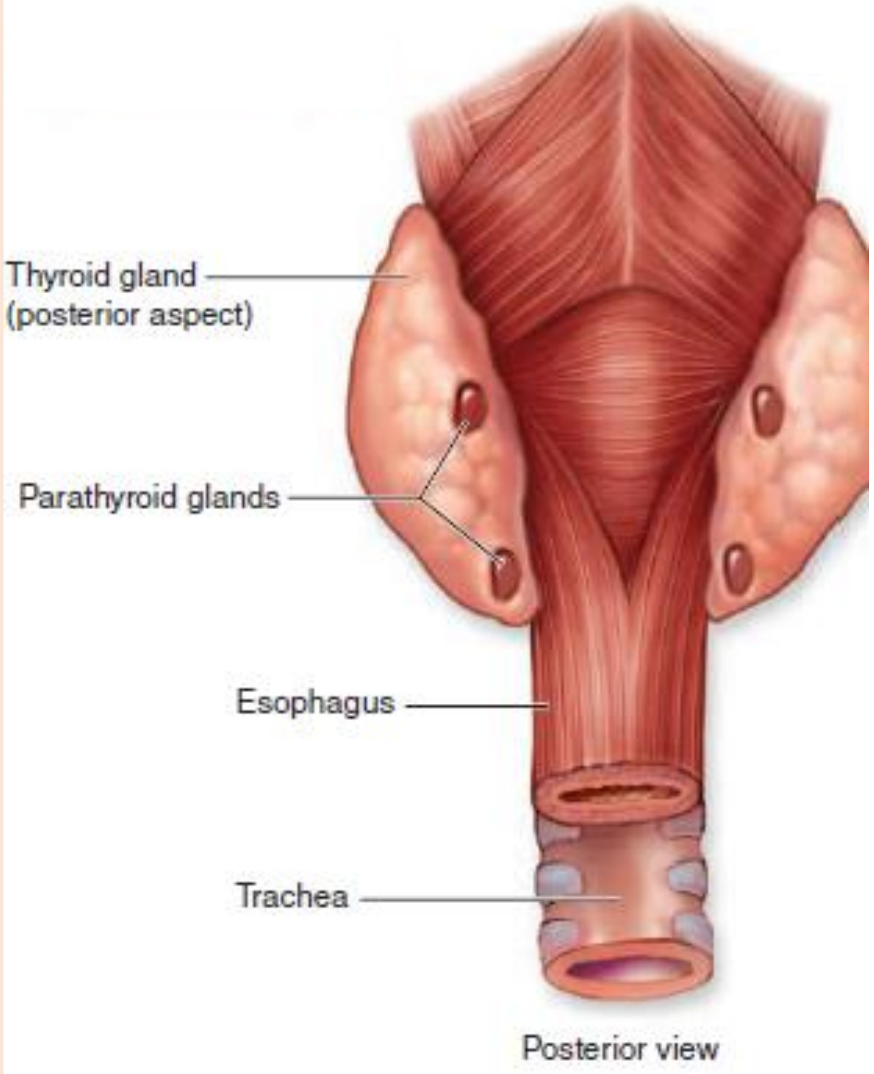
▲ **Electron micrograph of rat posterior lobe.** Neurosecretory granules and small vesicles are present in the terminal portions of the axonal processes of the hypothalamohypophyseal tract fibers. Capillaries with fenestrated endothelium are present in close proximity to the nerve endings. ×20,000. (Courtesy of Drs. Sanford L. Palay and P. Orkland.)



Hypothalamus
Thyroid-stimulating hormone (TSH)
Thyroid gland
Anterior pituitary
Posterior pituitary
Antidiuretic hormone (ADH)
Kidney tubules
Adrenocorticotropic hormone (ACTH)
Adrenal cortex
Oxytocin
Muscles of mammary glands and uterus
Growth hormone (GH)
Gonadotropic hormones: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
Prolactin (PRL)
Melanocyte-stimulating hormone (MSH)
Melanocyte in amphibian
Bone and muscle
Testis
Ovary
Mammary glands in mammals

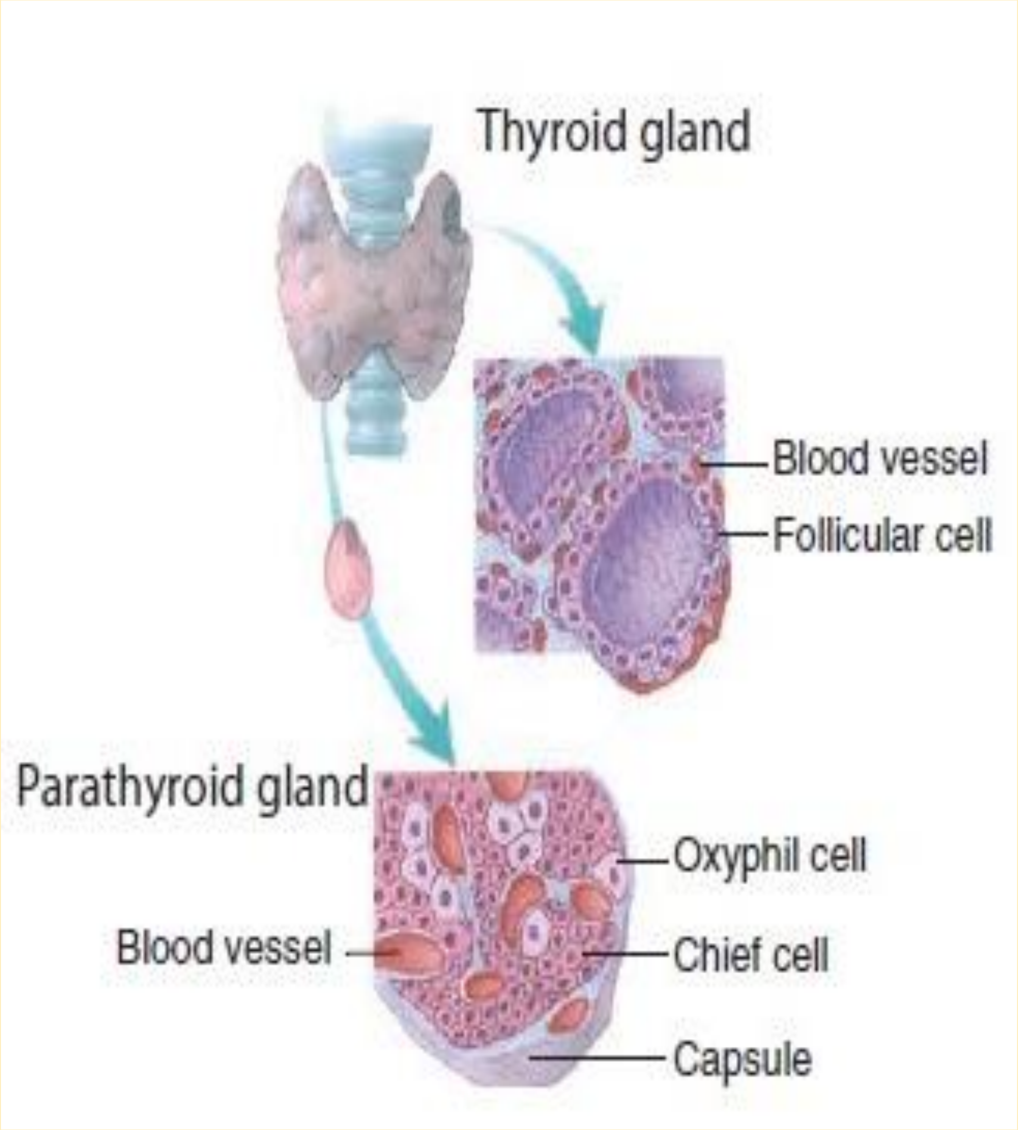
3. THYROID GLAND

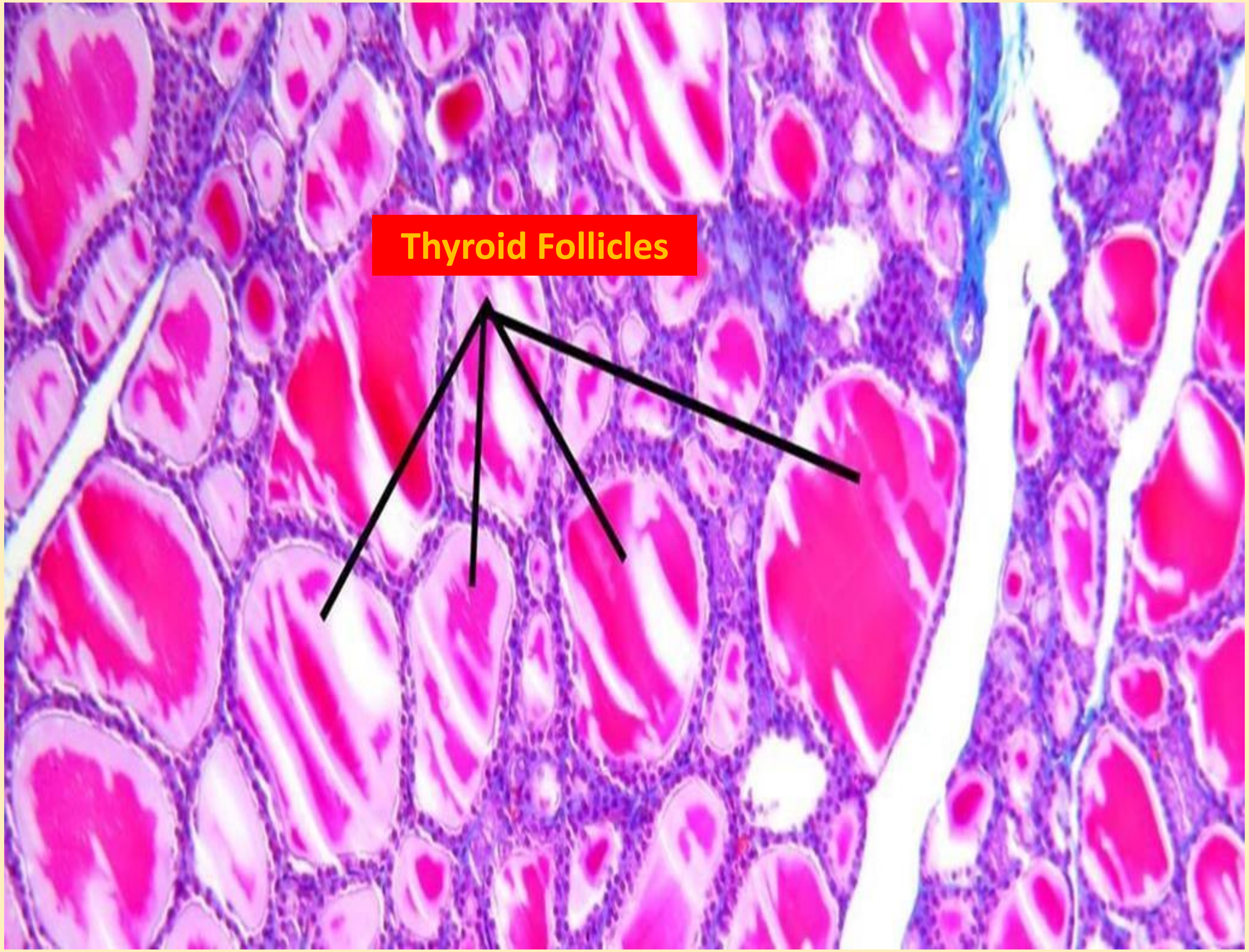
- The thyroid gland, located anterior and inferior to the larynx, consists of two lobes united by an isthmus. It originates in early embryonic life from the foregut endoderm near the base of the developing tongue. It synthesizes the thyroid hormones **thyroxine** (tetra-iodothyronine or **T4**) and **tri-iodothyronine (T3)**, which help control the basal metabolic rate in cells throughout the body, as well as the polypeptide hormone **calcitonin**.
- The parenchyma of the thyroid is composed of millions of rounded epithelial **thyroid follicles** of variable diameter, each with simple epithelium and a central lumen densely filled with gelatinous acidophilic **colloid**. The thyroid is the only endocrine gland in which a large quantity of secretory product is stored. Moreover, storage is outside the cells, in the colloid of the follicle lumen, which is also unusual. Thyroid colloid contains the large glycoprotein **thyroglobulin** (660 kDa), the precursor for the active thyroid hormones.



3. THYROID GLAND

- The thyroid gland is covered by a fibrous capsule from which septa extend into the parenchyma, dividing it into lobules and carrying blood vessels, nerves, and lymphatics. Follicles are densely packed together, separated from one another only by sparse reticular connective tissue, although this stroma is very well vascularized with fenestrated capillaries for transfer of released hormone to the blood.
- The follicular cells, or **thyrocytes**, range in shape from squamous to low columnar, their size and other features varying with their activity, which is controlled by thyroid-stimulating hormone (TSH) from the anterior pituitary. Active glands have more follicles of low columnar epithelium; glands with mostly squamous follicular cells are hypoactive.

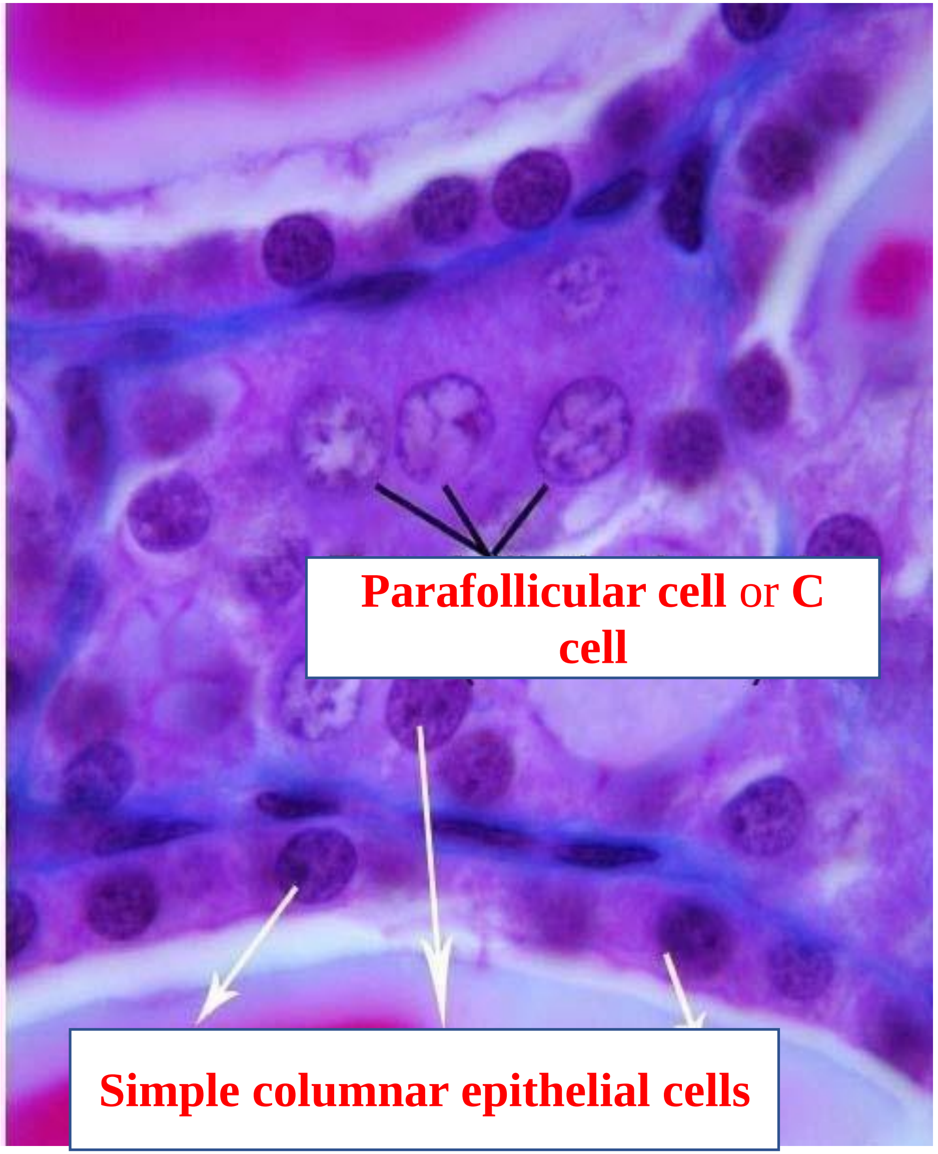

Thyroid gland
Blood vessel
Follicular cell
Parathyroid gland
Oxyphil cell
Blood vessel
Chief cell
Capsule

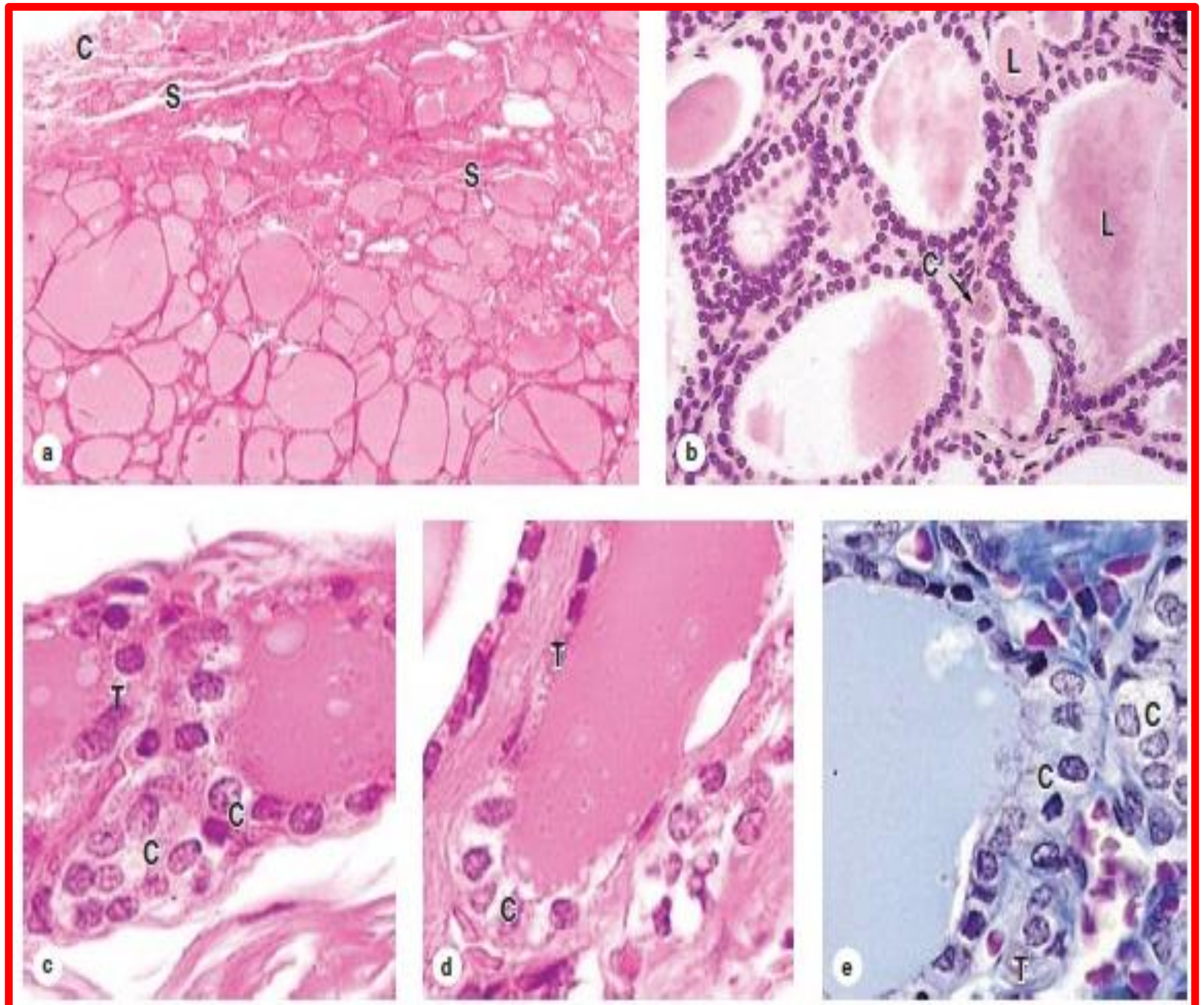

Thyroid Follicles

3. THYROID GLAND

- Thyrocytes have apical junctional complexes and rest on a basal lamina. The cells exhibit organelles indicating active protein synthesis and secretion, as well as phagocytosis and digestion. The nucleus is generally round and central. Basally the cells are rich in rough ER and apically, facing the follicular lumen, are Golgi complexes, secretory granules, numerous phagosomes and lysosomes, and microvilli.

- Another endocrine cell type, the **parafollicular cell**, or **C cell**, is also found inside the basal lamina of the follicular epithelium or as isolated clusters between follicles. Derived from the neural crest, parafollicular cells are usually somewhat larger than follicular cells and stain less intensely. They have a smaller amount of rough ER, large Golgi complexes, and numerous small (100-180 nm in diameter) granules containing calcitonin. Secretion of calcitonin is triggered by elevated blood Ca^{2+} levels, and it inhibits osteoclast activity, but this function in humans is less important than the roles of parathyroid hormone and vitamin D in the regulation of normal calcium homeostasis.

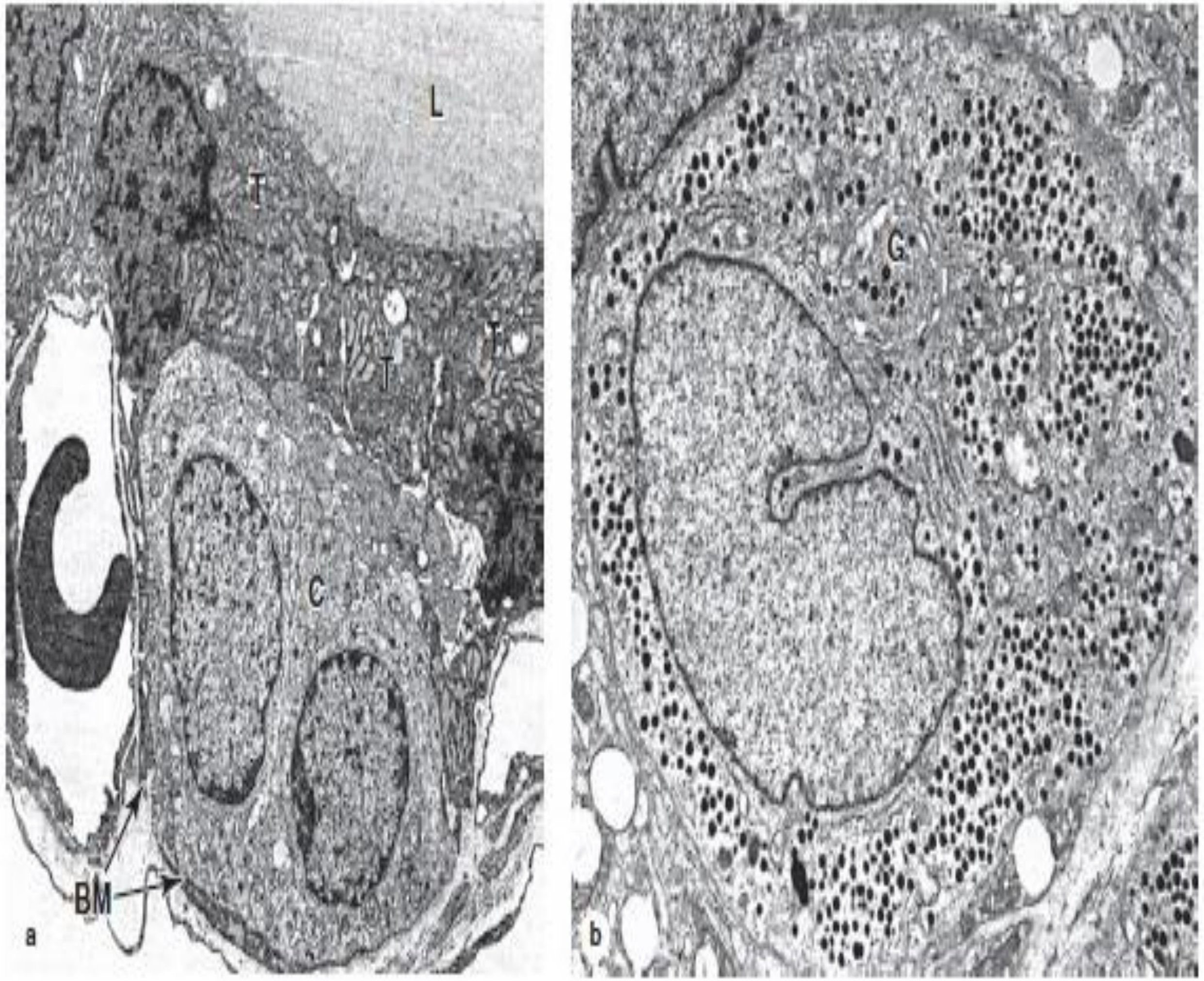




(a) A low-power micrograph of thyroid gland shows the thin capsule (**C**), from which septa (**S**) with the larger blood vessels, lymphatics, and nerves enter the gland. The parenchyma of the organ is distinctive, consisting of colloid-filled epithelial follicles of many sizes. The lumen of each follicle is filled with a lightly staining colloid of a large gelatinous protein called **thyroglobulin**. (X12; H&E)

(b) The lumen (**L**) of each follicle is surrounded by a simple epithelium of thyrocytes in which the cell height ranges from squamous to low columnar. Also present are large pale-staining parafollicular or C cells (**C**) secreting calcitonin, a polypeptide involved with calcium metabolism. (X200; H&E)

(c-e) C cells may be part of the follicular epithelium or present singly or in groups outside of follicles. Thyrocytes (**T**) can usually be distinguished from parafollicular C cells (**C**) by their smaller size and darker staining properties. Unlike thyrocytes, C cells seldom vary in their size or pale staining characteristics. C cells are somewhat easier to locate in or between small follicles. c and d: (X400;H&E); e: (X400; Mallory trichrome)



(a) TEM of the follicular epithelium shows pseudopodia and microvilli extending from the follicular thyrocytes (**T**) into the colloid of the lumen (**L**). The cells have apical junctional complexes, much RER, well-developed Golgi complexes, and many lysosomes. Inside the basement membrane (**BM**) of the follicle, but often not contacting the colloid in the lumen, are occasional C cells (**C**). To the left and right of the two C cells seen here are capillaries intimately associated with the follicular cells, but outside the basement membrane. (X2000)

(b) A TEM of a C cell, with its large Golgi apparatus (**G**), extensive RER, and cytoplasm filled with small secretory granules containing calcitonin. (X5000)

Production of Thyroid Hormone & Its Control

- Production, storage, and release of thyroid hormones involve an unusual, multistage process in the thyrocytes, with both an exocrine phase and an endocrine phase. The major activities of this process include the following six steps:

1. **The production of thyroglobulin**, which is similar to that in other glycoprotein-exporting cells, with synthesis in the rough ER and glycosylation in the Golgi apparatus. Thyroglobulin has no hormonal activity itself but contains 140 tyrosyl residues critical for thyroid hormone synthesis. The glycoprotein is released as an exocrine product from apical vesicles of thyrocytes into the follicular lumen.

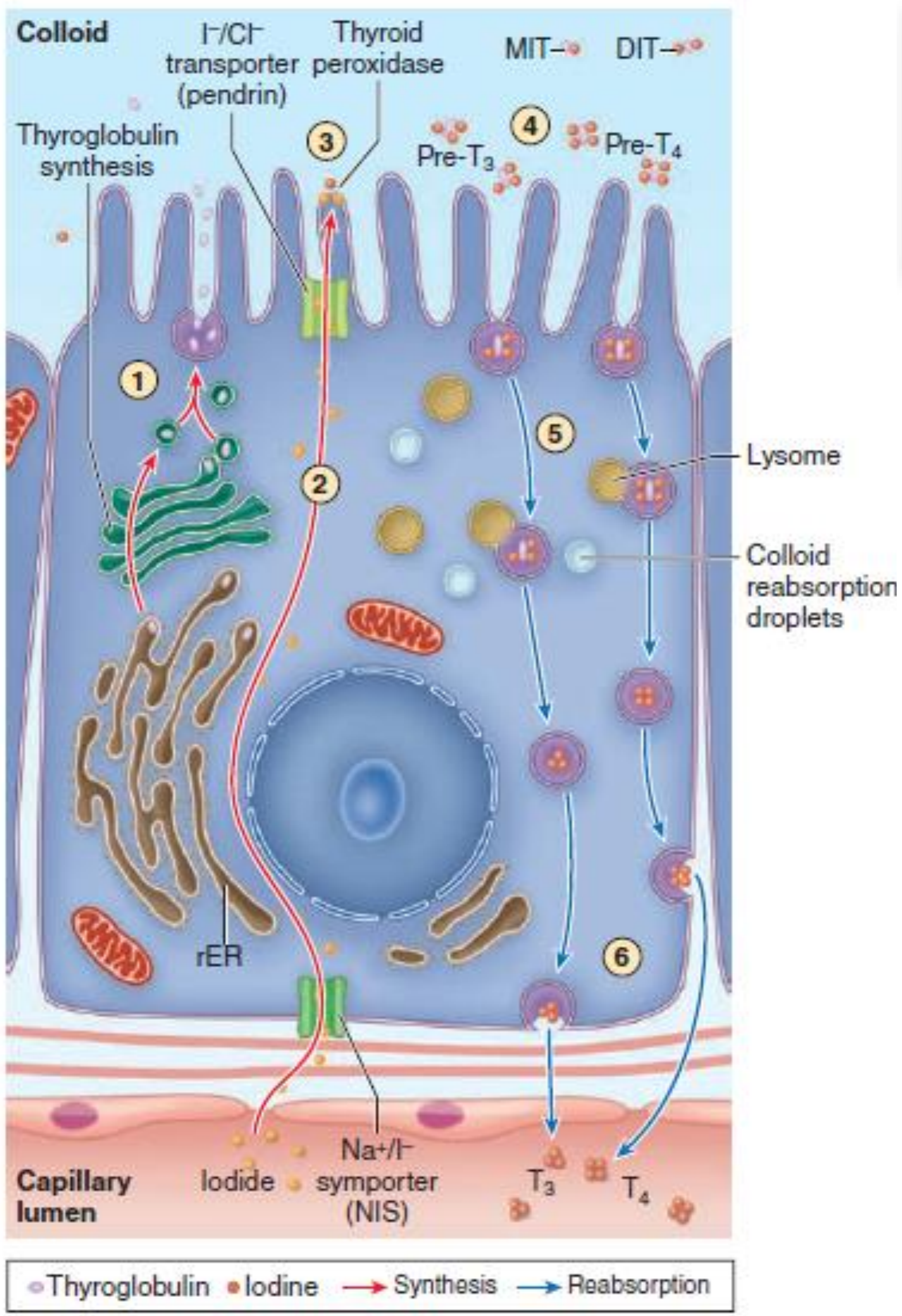
2. **The uptake of iodide** from blood by Na/I symporters (NIS) in the thyrocytes' basolateral cell membranes, which allows for 30-fold concentration of dietary iodide in thyroid tissue relative to plasma. Decreased levels of circulating iodide trigger synthesis of NIS, increasing iodide uptake and compensating for the lower plasma concentration. An apical iodide/chloride transporter (also called **pendrin**) pumps I– from thyrocytes into the colloid.

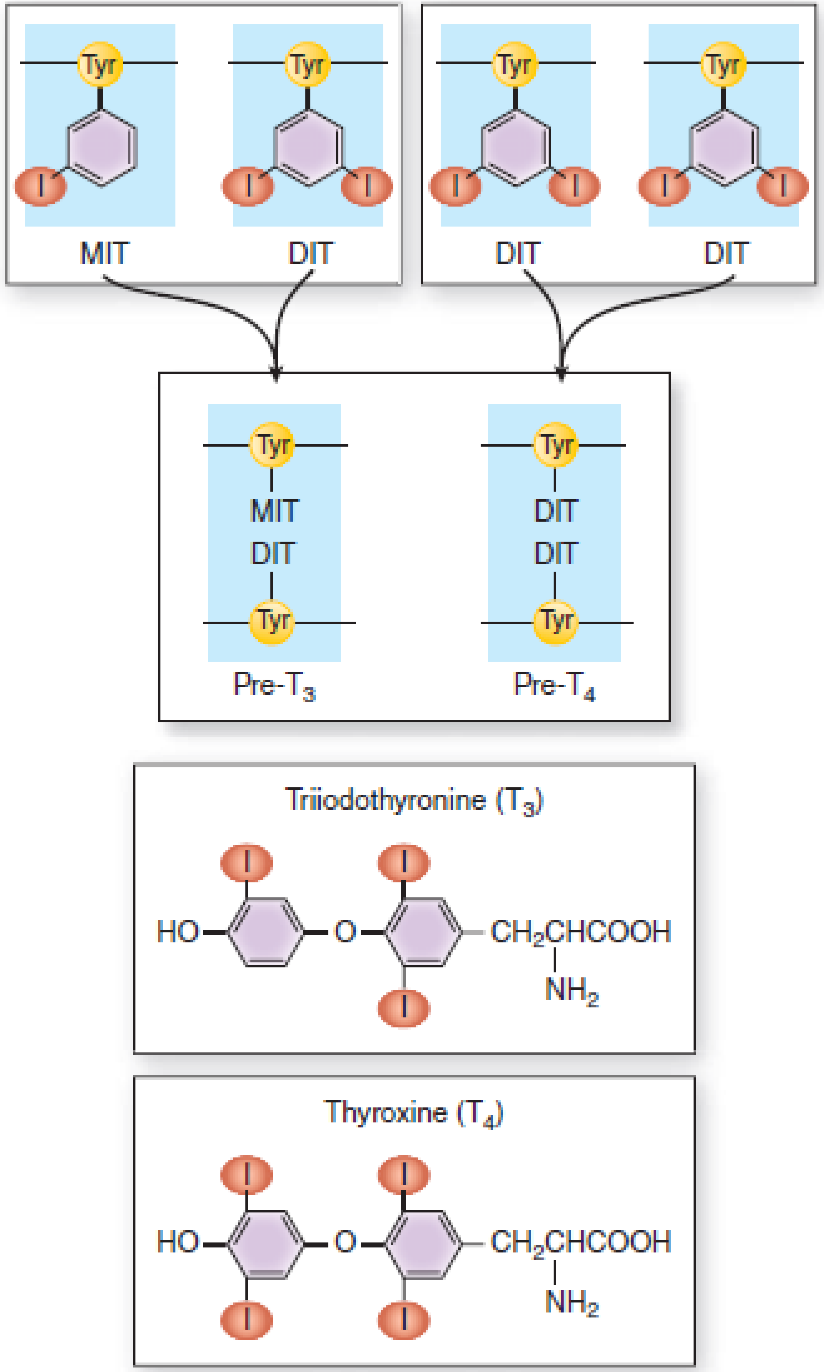
- **3. Iodination of tyrosyl residues** in thyroglobulin with either one or two atoms occurs in the colloid after oxidation of iodide to iodine by membrane-bound thyroid peroxidase on the microvilli surfaces of thyrocytes.

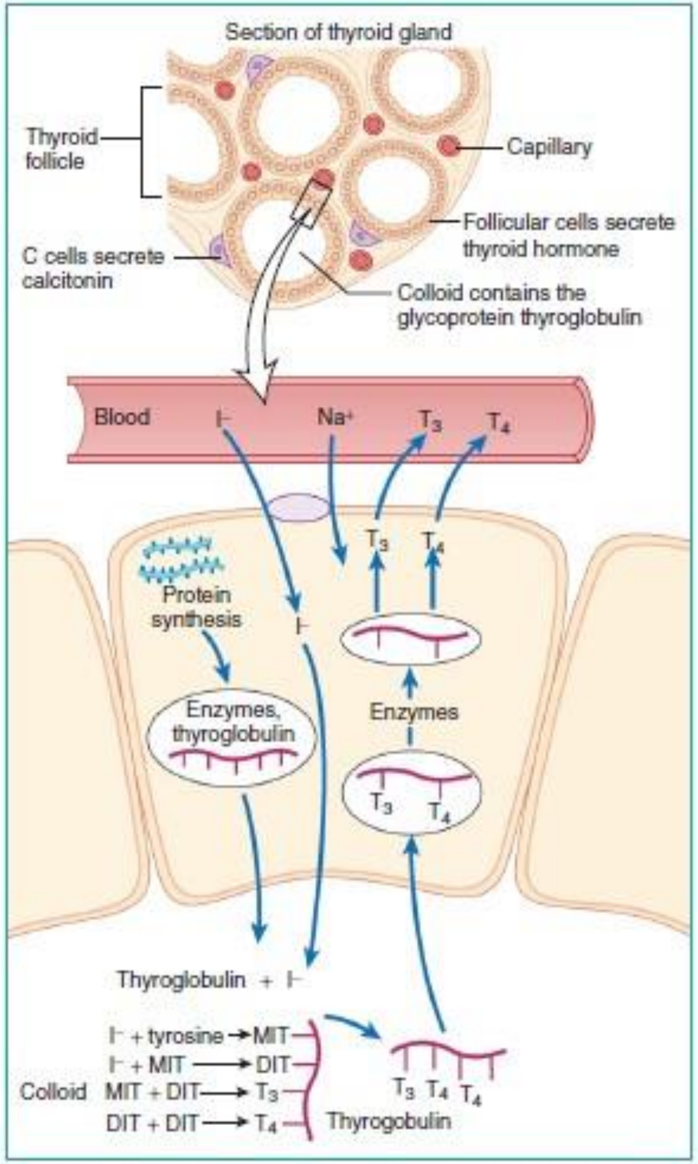
- **4. Formation of T**3 **and T**4 (also called thyroxine) occurs as two iodinated tyrosines, still part of colloidal thyroglobulin, which are covalently conjugated in coupling reactions.

- **5. Endocytosis of iodinated thyroglobulin** by the thyrocytes involves both fluid-phase pinocytosis and receptor-mediated endocytosis. The endocytic vesicles fuse with lysosomes, and the thyroglobulin is thoroughly degraded by lysosomal proteases, freeing active thyroid hormone as both T3 and T4.

- **6. Secretion of T**4 **and T**3 at the basolateral domains of thyrocytes occurs in an endocrine manner: both molecules are immediately taken up by capillaries.





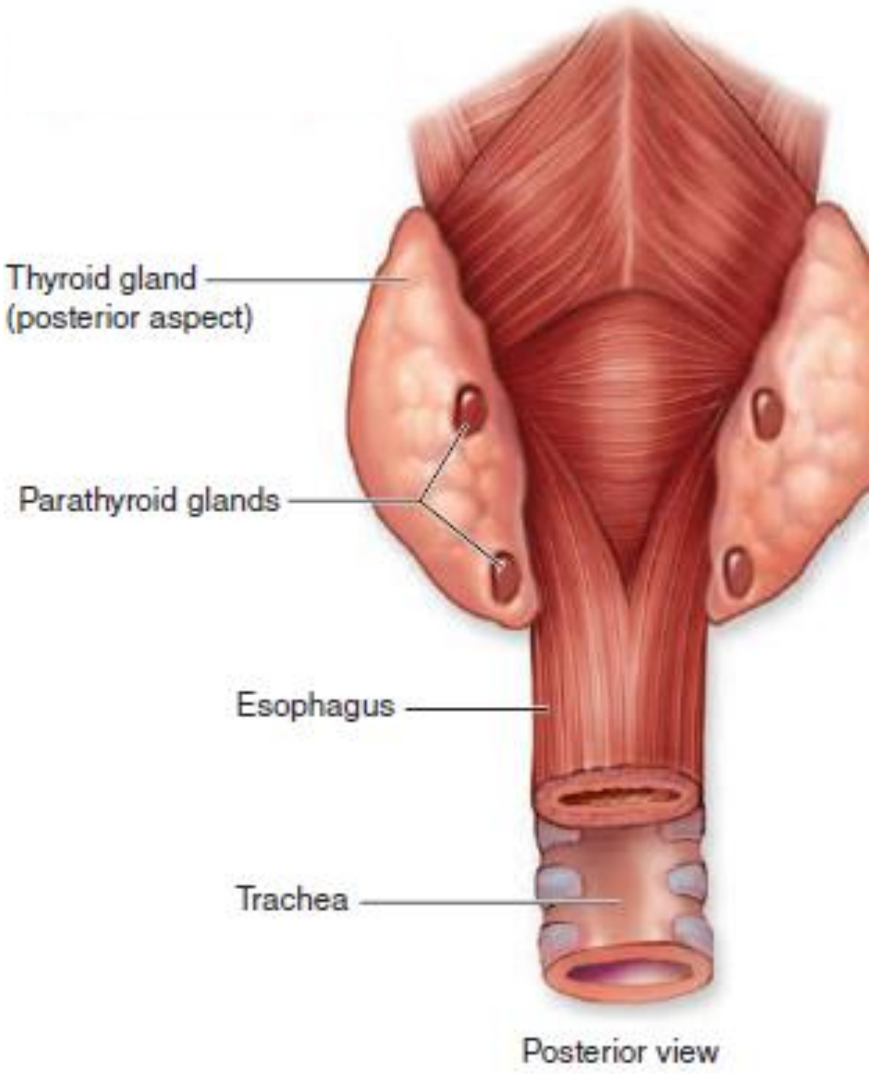


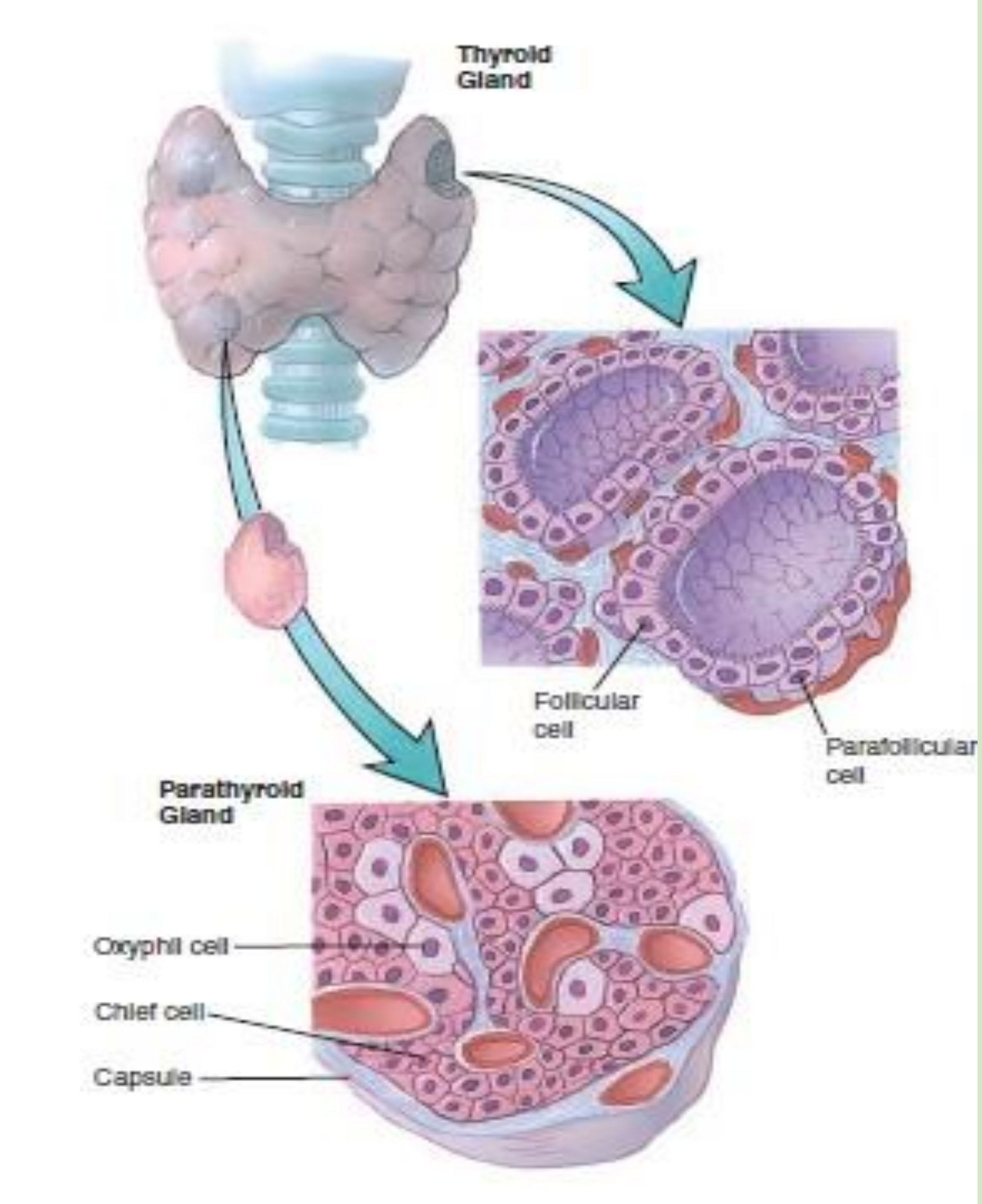
Thyroid hormone is synthesized within the colloid of thyroid follicles. The thyroid follicular cells actively transport iodide (I⁻) into the follicle, where it combines with the tyrosine residues attached to the protein thyroglobulin to make T_3 and T_4. The T_3 and T_4 are separated from the protein and secreted into the blood. MIT, monoiodinated tyrosine; DIT, diiodinated tyrosine.

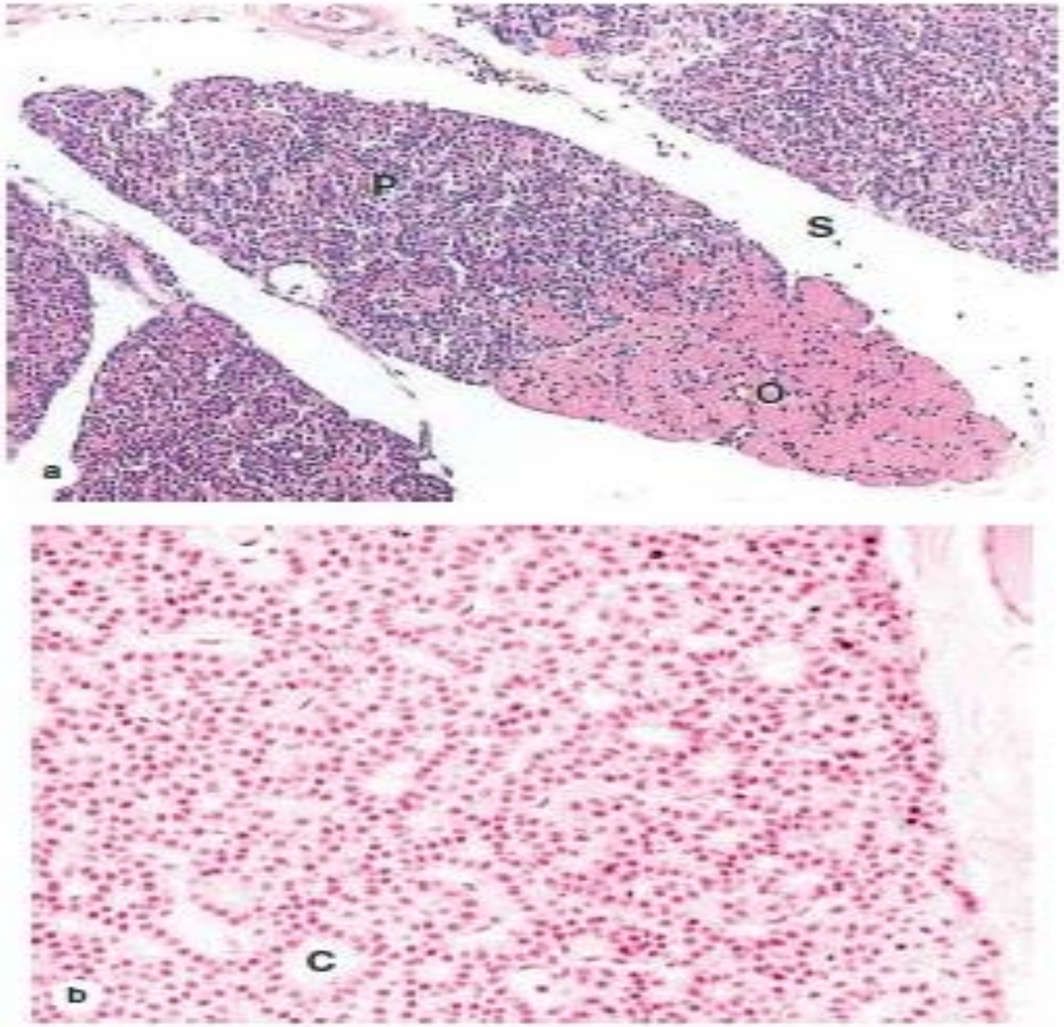
4. **PARATHYROID GLANDS**

- The **parathyroid glands** are four small ovoid masses and located on the back of the thyroid gland, usually embedded in the larger gland's capsule. The microvasculature of each arises from the inferior thyroid arteries. Each parathyroid gland is contained within a thin capsule from which septa extend into the gland. A sparse reticular stroma supports dense elongated clusters of secretory cells.

- The parathyroid glands are derived from the embryonic pharyngeal pouches—the superior glands from the fourth pouch and the inferior glands from the third pouch. Their migration to the developing thyroid gland is sometimes misdirected so that the number and locations of the glands are somewhat variable. Up to 10% of individuals may have parathyroid tissue attached to the thymus, which originates from the same pharyngeal pouches.







(a) A small lobe of parathyroid gland, surrounded by connective tissue septa (**S**), shows mainly densely packed cords of small principal cells (**P**). Older parathyroid glands show increasing numbers of much larger and acidophilic nonfunctional oxyphil cells (**O**) that may occur singly or in clumps of varying sizes. (X60; H&E)

(b) Higher magnification shows that principal cells have round central nuclei and pale-staining cytoplasm. Cords of principal cells secreting PTH surround capillaries (**C**). (X200; H&E)

4. PARATHYROID GLANDS

- The endocrine cells of the parathyroid glands, called **principal (chief) cells**, are small polygonal cells with round nuclei and pale-staining, slightly acidophilic cytoplasm. Irregularly shaped cytoplasmic granules contain the polypeptide **parathyroid hormone (PTH)**, an important regulator of blood calcium levels.

PTH has three major targets:

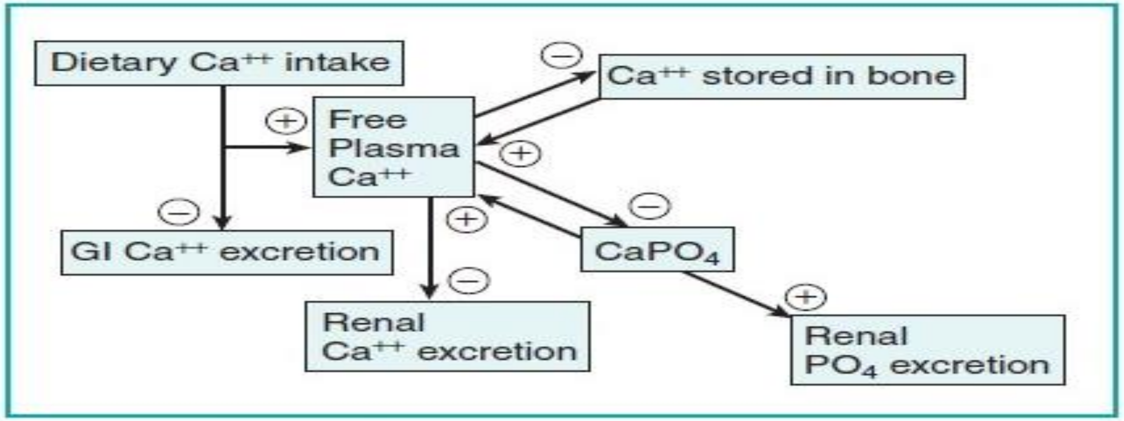
a) Osteoblasts respond to PTH by producing an osteoclast-stimulating factor, which increases the number and activity of osteoclasts. The resulting resorption of the calcified bone matrix and release of Ca^{2+} increase the concentration of circulating Ca^{2+}, which suppresses PTH production. The effect of PTH on blood levels of Ca^{2+} is thus opposite to that of calcitonin.

b) In the distal convoluted tubules of the renal cortex, PTH stimulates Ca^{2+} reabsorption (and inhibits phosphate reabsorption in the proximal tubules).

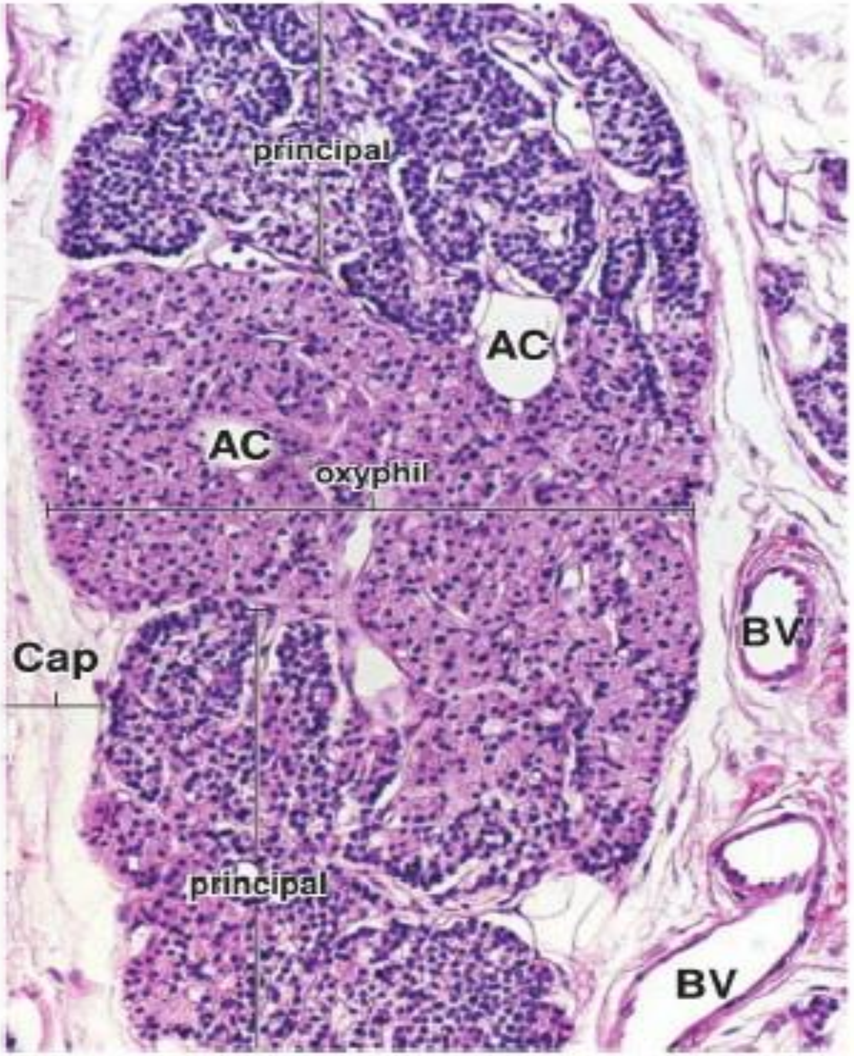
c) PTH also indirectly increases the Ca^{2+} absorption in the small intestine by stimulating vitamin D activation.

- With increasing age, many secretory cells are replaced with adipocytes, which may constitute more than 50% of the gland in older people.

- Much smaller populations of **oxyphil cells**, often clustered, are sometimes also present in parathyroid glands, more commonly in older individuals. These are much larger than the principal cells and are characterized by very acidophilic cytoplasm filled with abnormally shaped mitochondria. Accumulating with age, oxyphil cells are degenerated derivatives of principal cells, with some still exhibiting low levels of PTH synthesis.



Parathyroid hormone increases free plasma Ca^{++}. Free plasma Ca^{++} represents the balance between dietary Ca^{++} uptake, exchange with the bone Ca^{++} storage pool, binding to PO_4, and renal Ca^{++} loss. Parathyroid hormone increases dietary Ca^{++} uptake by increasing vitamin D synthesis, increases osteoclast activity to release Ca^{++} stored in the bone, increases renal PO_4 excretion, and decreases renal Ca^{++} excretion. All these actions increase free plasma Ca^{++} levels.

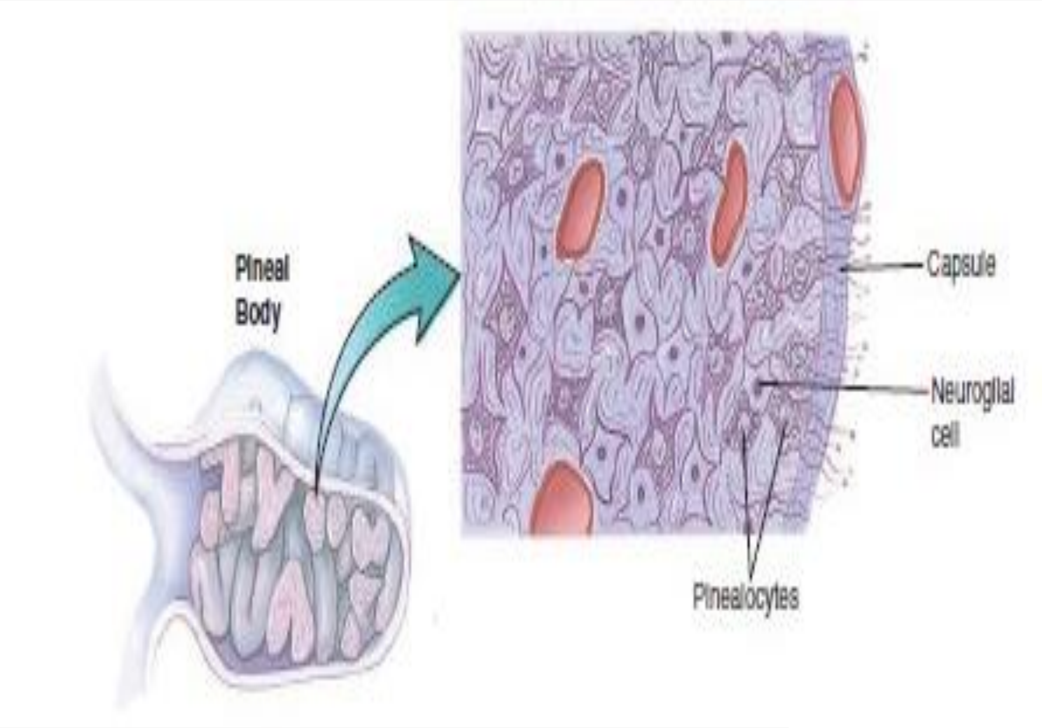


Photomicrograph of human parathyroid gland. This H&E–stained specimen shows the gland with part of its connective tissue capsule (*Cap*). The blood vessels (*BV*) are located in the connective tissue septum between lobes of the gland. The principal cells are arranged in two masses (*top* and *bottom*) and are separated by a large cluster of oxyphil cells (*center*). The oxyphil cells are the larger cell type with prominent eosinophilic cytoplasm. They may occur in small groups or in larger masses, as seen here. The principal cells are more numerous. They are smaller, having less cytoplasm, and consequently exhibit closer proximity of their nuclei. Adipose cells (*AC*) are present in variable, although limited, numbers. ×175.

5. PINEAL GLAND

- The **pineal gland**, also known as the **epiphysis cerebri**, regulates the daily rhythms of bodily activities. A small, pine cone-shaped organ, the pineal gland develops from neuroectoderm in the posterior wall of the third ventricle and remains attached to the brain by a short stalk. The pineal gland is covered by connective tissue of the pia mater, from which septa containing small blood vessels emerge and subdivide variously sized lobules.

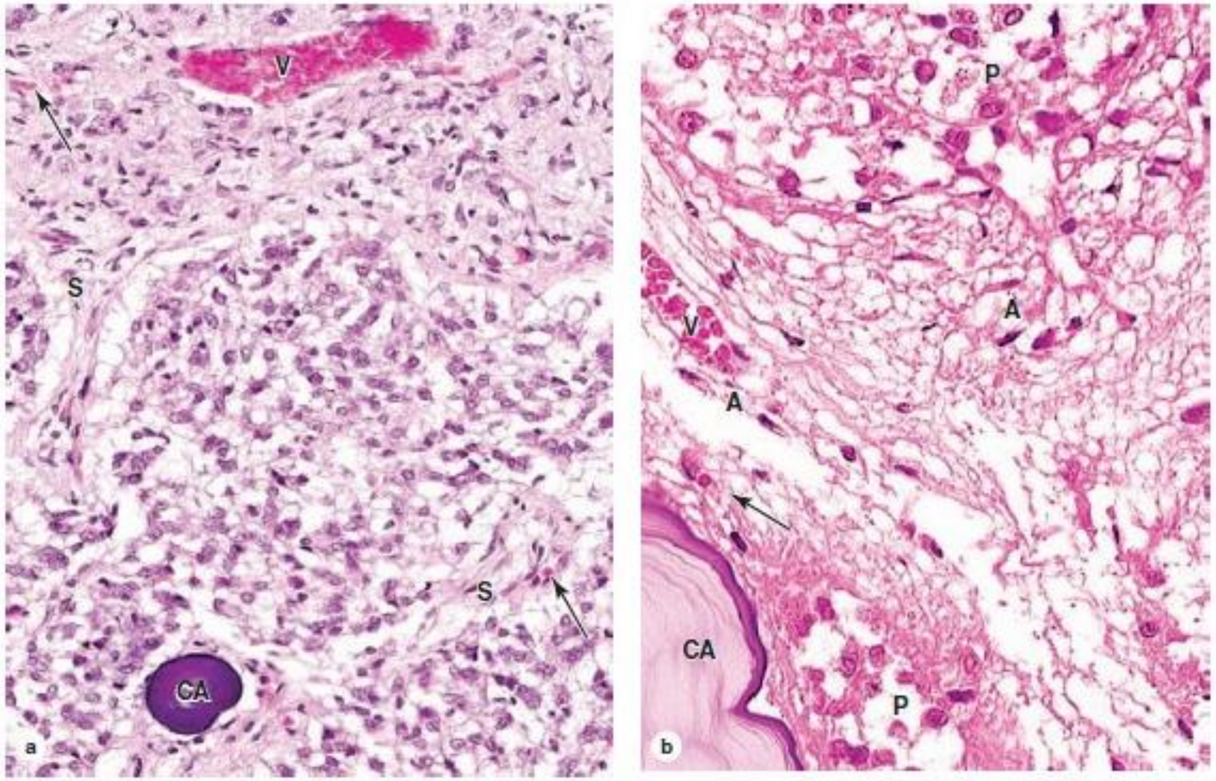
- Prominent and abundant secretory cells called **pinealocytes** have slightly basophilic cytoplasm and irregular euchromatic nuclei. Ultrastructurally pinealocytes are seen to have secretory vesicles, many mitochondria, and long cytoplasmic processes extending to the vascularized septa, where they end in dilatations near capillaries, indicating an endocrine function. These cells produce **melatonin**, a low-molecular-weight tryptophan derivative. Unmyelinated sympathetic nerve fibers enter the pineal gland and end among pinealocytes, with some forming synapses.



5. PINEAL GLAND

- Melatonin release from pinealocytes is promoted by darkness and inhibited by daylight. The resulting diurnal fluctuation in blood melatonin levels induces rhythmic changes in the activity of the hypothalamus, pituitary gland, and other endocrine tissues that characterize the circadian (24 hours, day/night) rhythm of physiological functions and behaviors.

- In humans and other mammals, the cycle of light and darkness is detected within the retinas and transmitted to the pineal via the retinohypothalamic tract, the suprachiasmatic nucleus, and the tracts of sympathetic fibers entering the pineal. The pineal gland acts, therefore, as a neuroendocrine transducer, converting sensory input regarding light and darkness into variations in many hormonal functions.



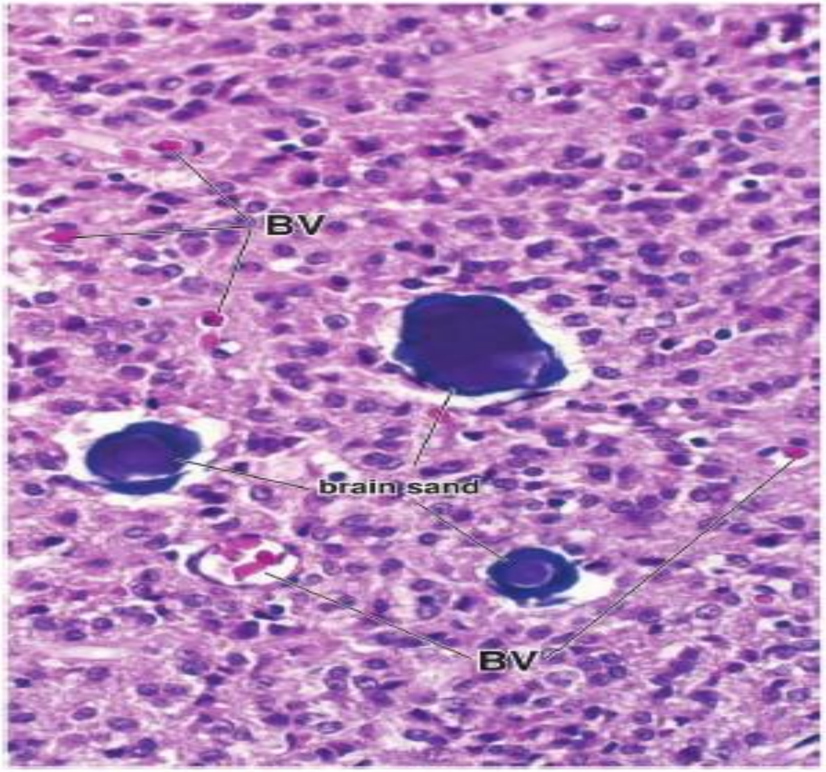
(a) The micrograph shows a group of pinealocytes surrounded by septa (**S**) containing venules (**V**) and capillaries (arrows). Also seen is an extracellular mineral deposit called a **corpus arenaceum** (**CA**) of unknown physiologic significance but an excellent marker for the pineal. (X200; H&E)

(b) At higher magnification the numerous large pinealocytes (**P**) with euchromatic nuclei can be compared to much fewer astrocytes (**A**) that have darker, more elongated nuclei and are located mainly within septa and near small blood vessels (**V**). Capillaries (arrow) are not nearly as numerous as in other endocrine glands. At the lower left is a part of a very large corpus arenaceum (**CA**), the calcified structures also known as **brain sand**. Along the septa run unmyelinated tracts of sympathetic fibers, associated indirectly with photoreceptive neurons in the retinas and running to the pinealocytes to stimulate melatonin release in periods of darkness. Levels of circulating melatonin are one factor determining the diurnal rhythms of hormone release and physiologic activities throughout the body. (X400; H&E)

5. Pineal Gland

- The pineal gland also has interstitial glial cells that are modified **astrocytes**, staining positively for glial fibrillary acidic protein, which represent about 5% of the cells. These have elongated nuclei more heavily stained than those of pinealocytes and are usually found in perivascular areas and between the groups of pinealocytes.

- A characteristic feature of the pineal gland is the presence of variously sized concretions of calcium and magnesium salts called **corpora arenacea**, or brain sand, formed by mineralization of extracellular protein deposits. Such concretions may appear during childhood and gradually increase in number and size with age, with no apparent effect on the gland's function



Photomicrograph of human pineal gland. This higher magnification photomicrograph shows the characteristic concretions called *brain sand* or *corpora arenacea*. Pinealocytes (chief cells of the pineal gland) account for the majority of the cells seen in the specimen. They are arranged in clumps or cords. Those blood vessels (BV) that contain red blood cells are readily apparent; numerous other blood vessels are also present but are not recognized at this magnification without evidence of the blood cells. ×250.

6. ADRENAL GLAND

- The **adrenal** (or suprarenal) **glands** are paired organs lying near the superior poles of the kidneys, embedded in the pararenal adipose tissue and fascia. They are flattened structures with a half-moon shape. Adrenal glands are each covered by a dense connective tissue capsule that sends thin trabeculae into the gland’s parenchyma. The stroma consists mainly of reticular fibers supporting the secretory cells and microvasculature. Each gland has two concentric regions: a yellowish **adrenal cortex** and a reddish-brown central **adrenal medulla**.

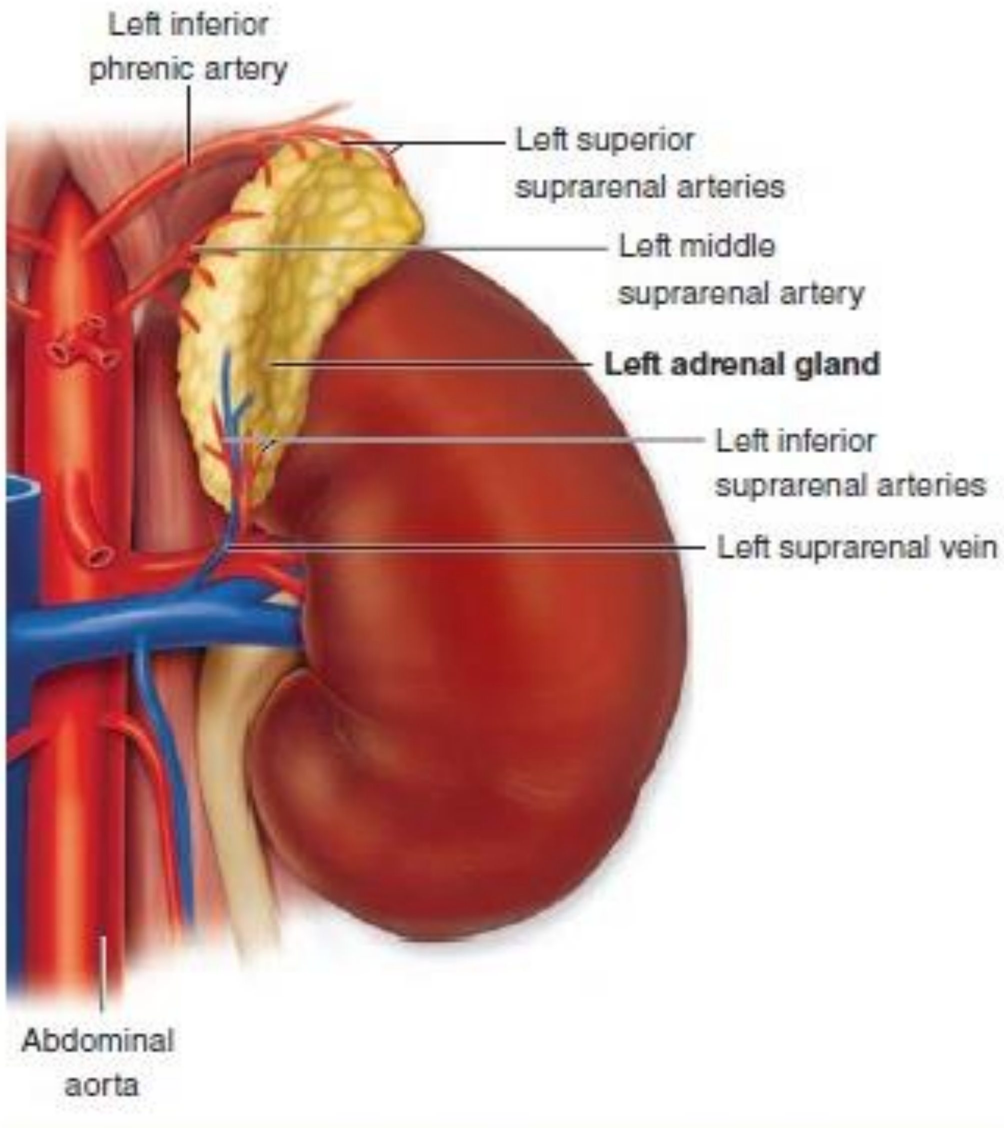
- The adrenal cortex and medulla can be considered two different organs with distinct embryonic origins, functions, and morphologic characteristics that become united during embryonic development. The cortex arises from mesoderm and the medulla from the neural crest. The general histologic appearance of the adrenal gland is typical of an endocrine gland in which cells of both cortex and medulla are grouped in cords along wide capillaries.

6. ADRENAL GLAND

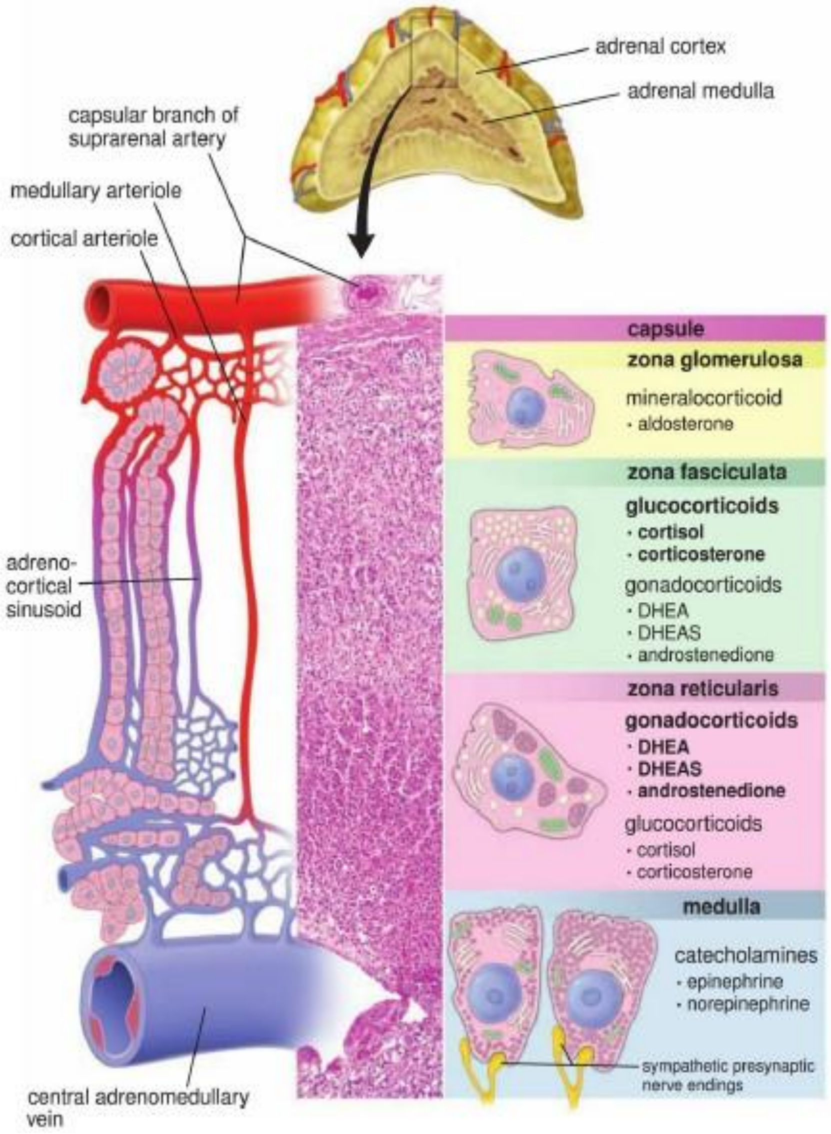
A) Adrenal cortex

1. Zona glomerulosa or arcuata
2. Zona fasciculata
3. Zona reticularis

B) Adrenal medulla



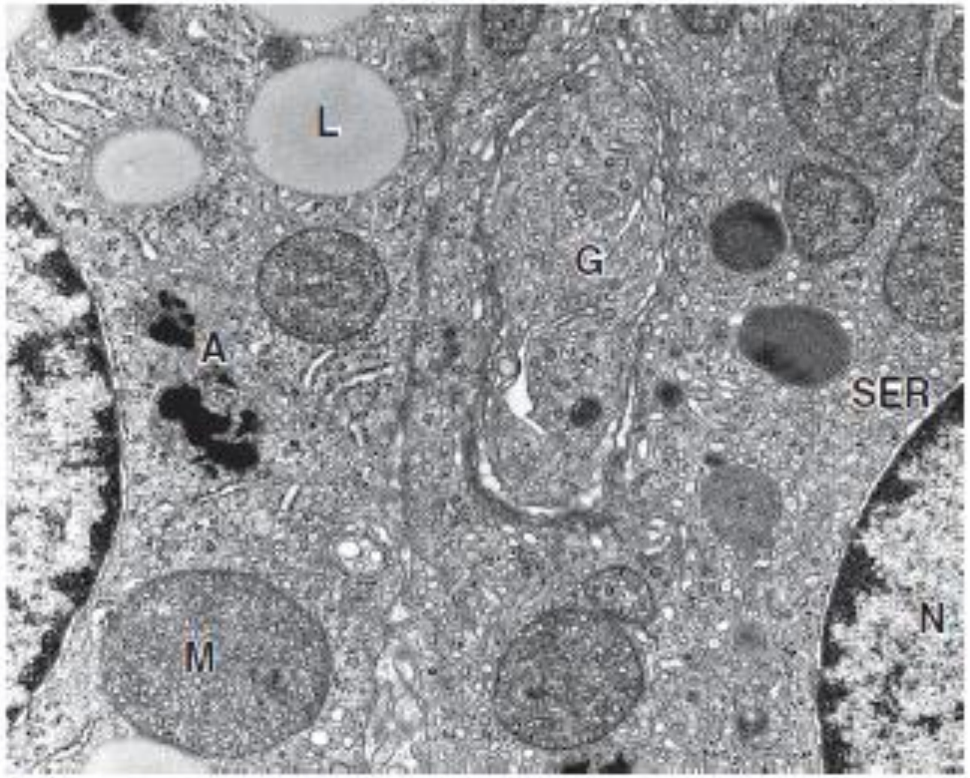
The paired adrenal glands are located at the superior pole of each kidney and each consists of an outer cortex producing a variety of steroid hormones and an inner medulla producing epinephrine and norepinephrine. This anterior view of the left adrenal gland and kidney shows the blood vessels supplying these glands.



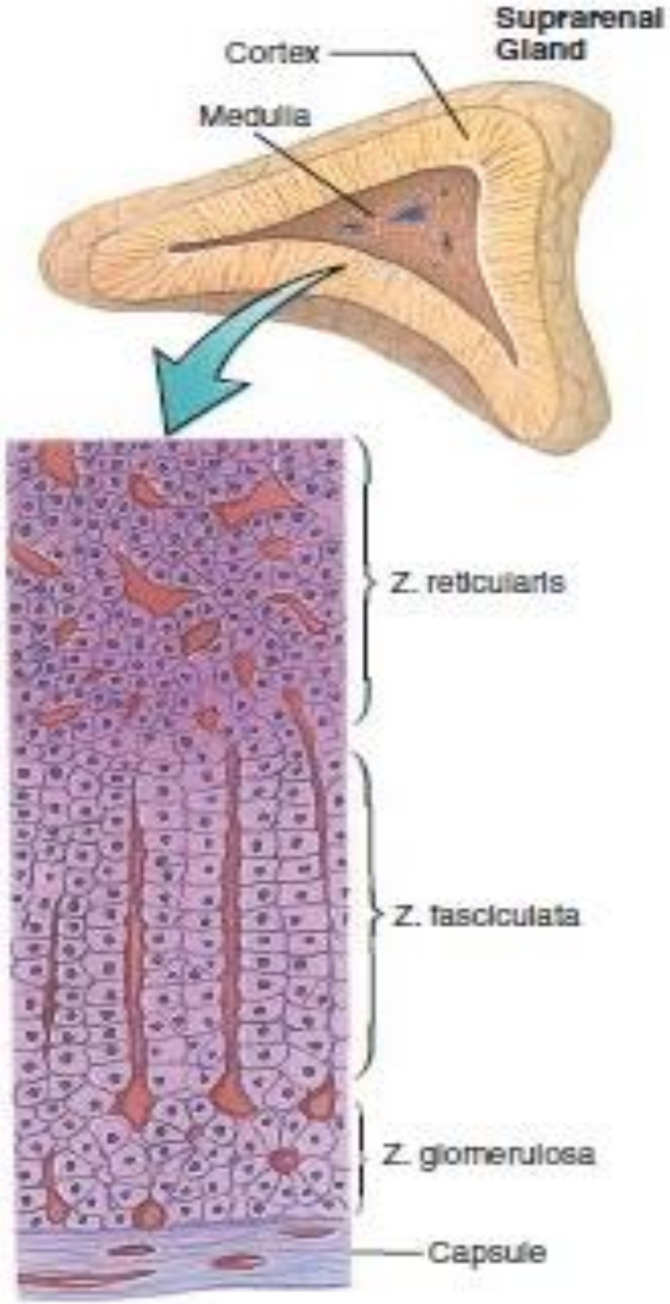
Organization and blood supply of the human adrenal gland. This diagram shows the blood supply to the adrenal cortex and medulla. The cortical arterioles form a cortical network of capillaries, which drain into a second capillary network in the medulla. The medullary capillary network is formed primarily by the medullary arterioles and drains into the central medullary vein. Adrenal medulla, zones of the cortex, and features of basic cell types and their secretory products are noted.

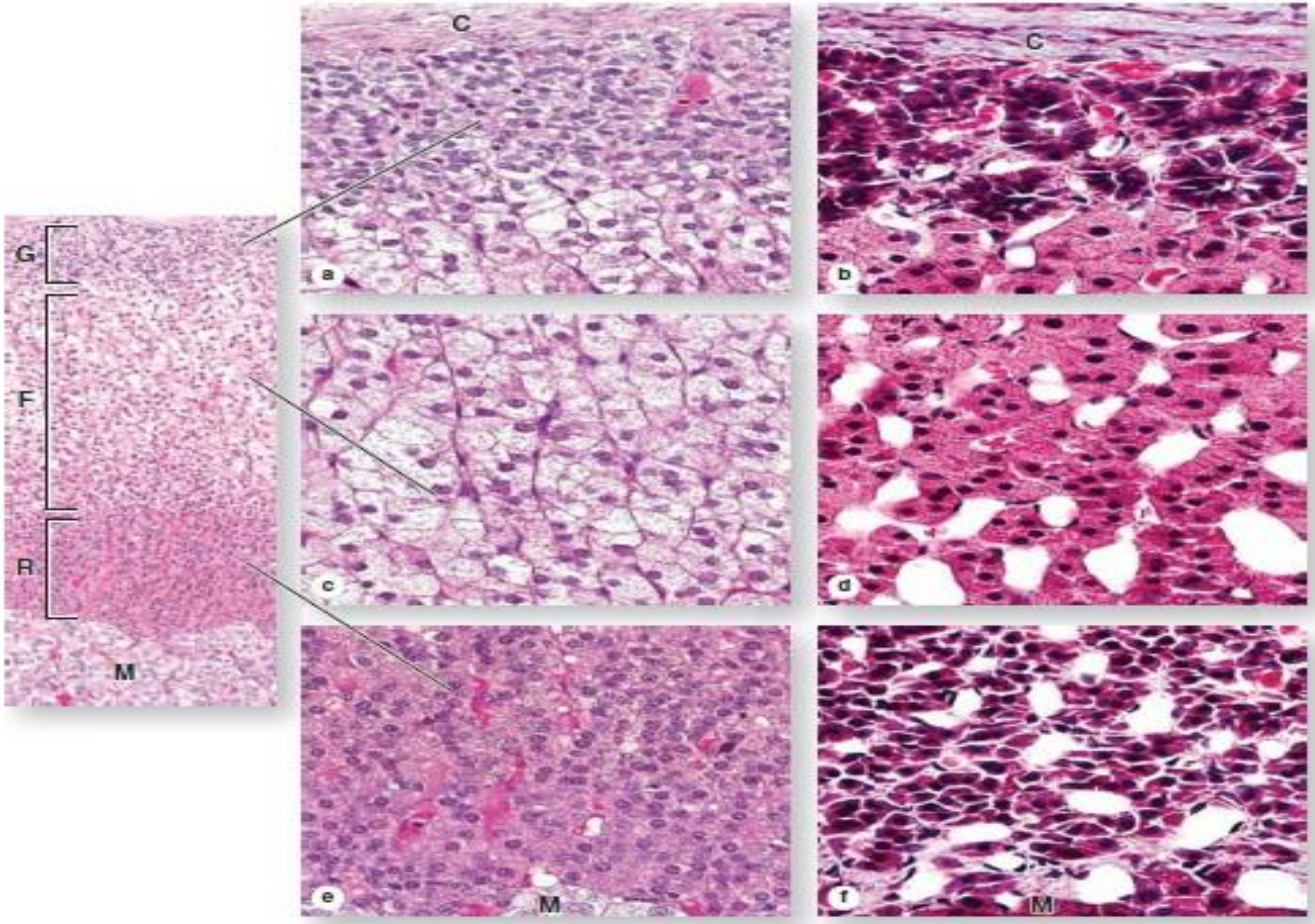
A) ADRENAL CORTEX

- Cells of the adrenal cortex have characteristic features of steroid-secreting cells: acidophilic cytoplasm rich in lipid droplets, with central nuclei. Ultrastructurally their cytoplasm shows an exceptionally profuse smooth ER (SER) of interconnected tubules, which contain the enzymes for cholesterol synthesis and conversion of the steroid prohormone pregnenolone into specific active steroid hormones. The mitochondria are often spherical, with tubular rather than shelflike cristae. These mitochondria not only synthesize ATP but also contain the enzymes for converting cholesterol to pregnenolone and for some steps in steroid synthesis. The function of steroid-producing cells involves close collaboration between SER and mitochondria.
- Steroid hormones are not stored in granules like proteins nor undergo exocytosis. As small lipid-soluble molecules, steroids diffuse freely from cells through the plasma membrane.
- The adrenal cortex has three concentric zones in which the cords of epithelial steroid-producing cells are arranged somewhat differently and which synthesize different classes of steroid hormones.



TEM of two adjacent steroid-secreting cells from the zona fasciculate 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)





The steroid-secreting cells of the adrenal cortex are arranged differently to form three fairly distinct concentric layers, the zonae glomerulosa (**G**), fasciculata (**F**), and reticularis (**R**), surrounding the medulla (**M**). As with all endocrine glands, the layers of the adrenal cortex all contain a rich microvasculature. Shown here are sections from two adrenal glands, stained with H&E (left) and Mallory trichrome, in which the sparse collagen appears blue (right).

(a, b) Immediately beneath the capsule (**C**), the **zona glomerulosa** consists of rounded clusters of columnar or pyramidal cells principally secreting the mineral corticoid aldosterone. Blood-filled regions are parts of the subcapsular arterial plexus.

(c, d) The thick middle layer, the **zona fasciculata**, consists of long cords of large, spongy-looking cells mainly secreting glucocorticoids such as cortisol.

(e, f) Cells of the innermost **zona reticularis**, next to the medulla (**M**), are small, have fewer lipid droplets and are therefore better stained, arranged in a close network and secrete mainly sex steroids, including the androgen precursor DHEA. Cells of all the layers are closely associated with capillaries and sinusoids.

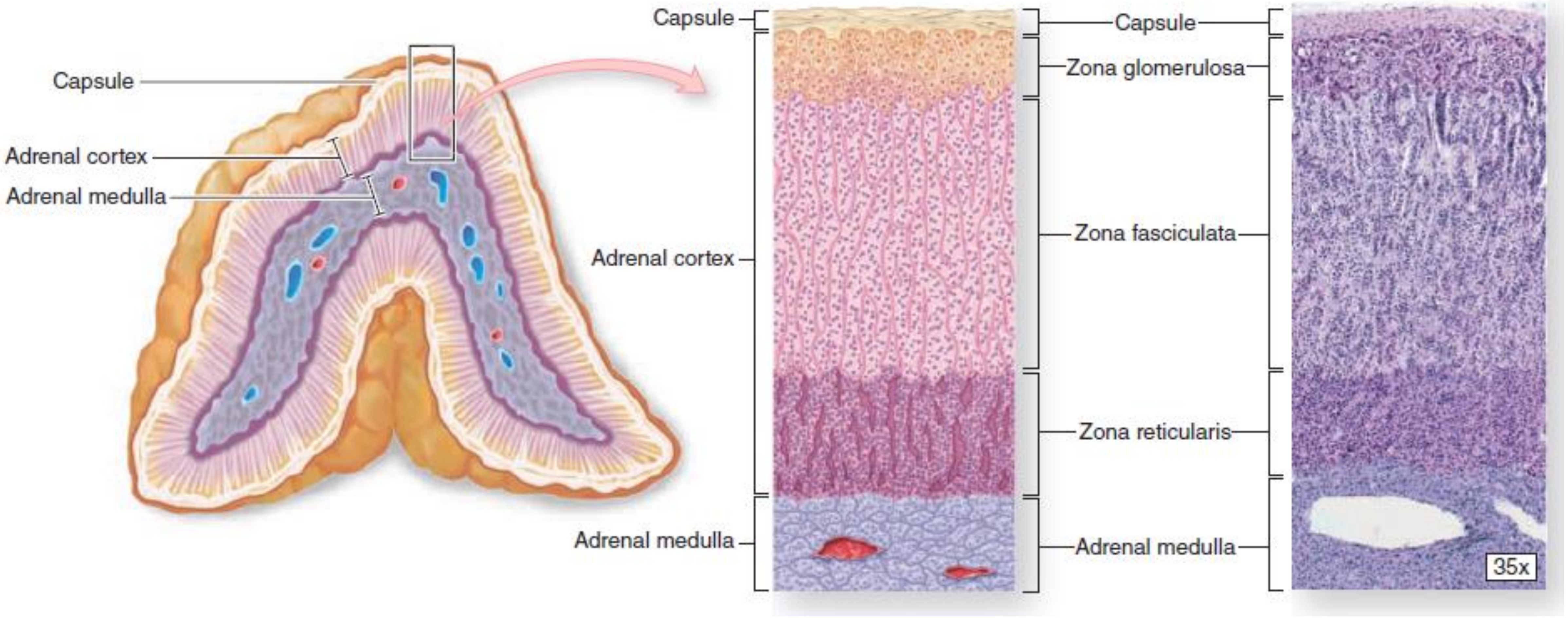
Left: (X20); a–f: (X200)

1. ZONA GLOMERULOSA/ARCUATA

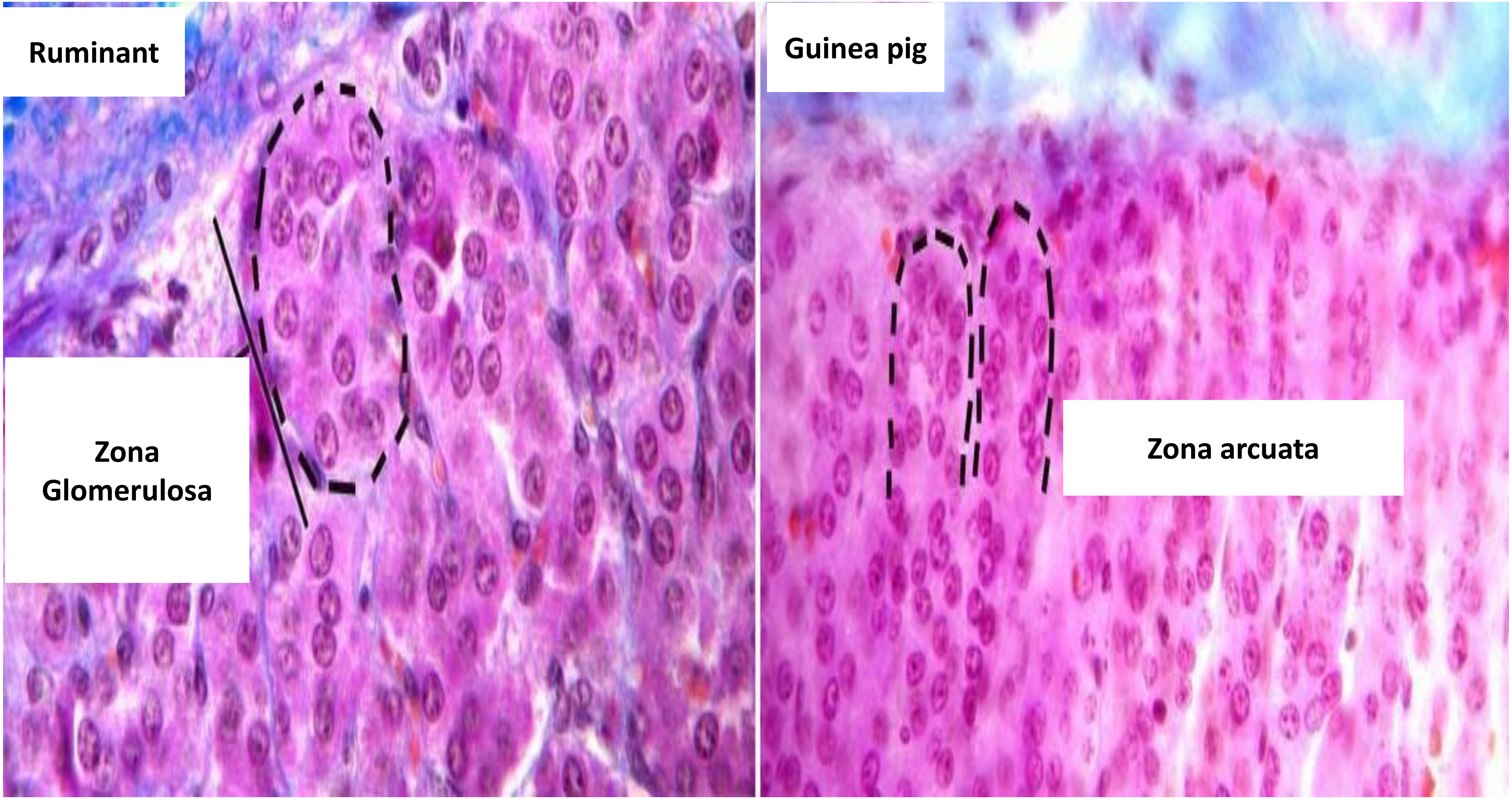
- The **zona glomerulosa**, immediately inside the capsule and comprising about 15% of the cortex, consists of closely packed, rounded or arched cords of columnar or pyramidal cells with many capillaries. The steroids made by these cells are called **mineralocorticoids** because they affect uptake of Na^+, K^+ and water by cells of renal tubules.

- The **zona arcuata** is the narrow area immediately beneath the capsule. This part is so named due to the fact that, **except in humans and ruminants**, the cellular cord alignment resembles an arch.

- The principal product is **aldosterone**, the major regulator of salt balance, which acts to stimulate Na^+ reabsorption in the distal convoluted tubules. Aldosterone secretion is stimulated primarily by angiotensin II and also by an increase in plasma K^+ concentration, but only weakly by ACTH.



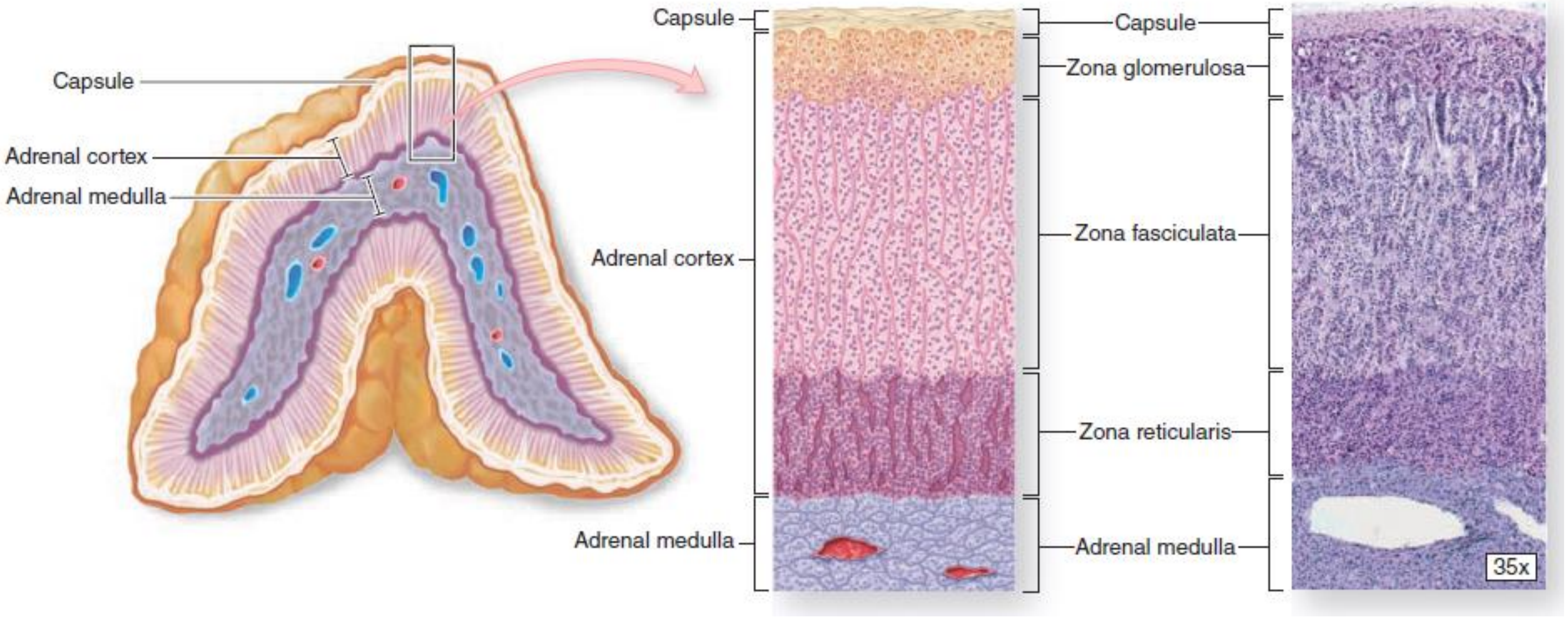
Capsule
Adrenal cortex
Adrenal medulla
Capsule
Adrenal cortex
Adrenal medulla
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenal medulla
35x


Ruminant
Zona Glomerulosa
Guinea pig
Zona arcuata

2. ZONA FASCICULATA

- The middle **zona fasciculata**, occupies 65%-80% of the cortex and consists of long cords of large polyhedral cells, one or two cells thick, separated by fenestrated sinusoidal capillaries. The cells are filled with lipid droplets and appear vacuolated in routine histologic preparations.

- These cells secrete **glucocorticoids**, especially **cortisol**, which affect carbohydrate metabolism by stimulating gluconeogenesis in many cells and glycogen synthesis in the liver. Cortisol also suppresses many immune functions and can induce fat mobilization and muscle proteolysis. Secretion is controlled by ACTH with negative feedback proportional to the concentration of circulating glucocorticoids. Small amounts of weak androgens are also produced here.

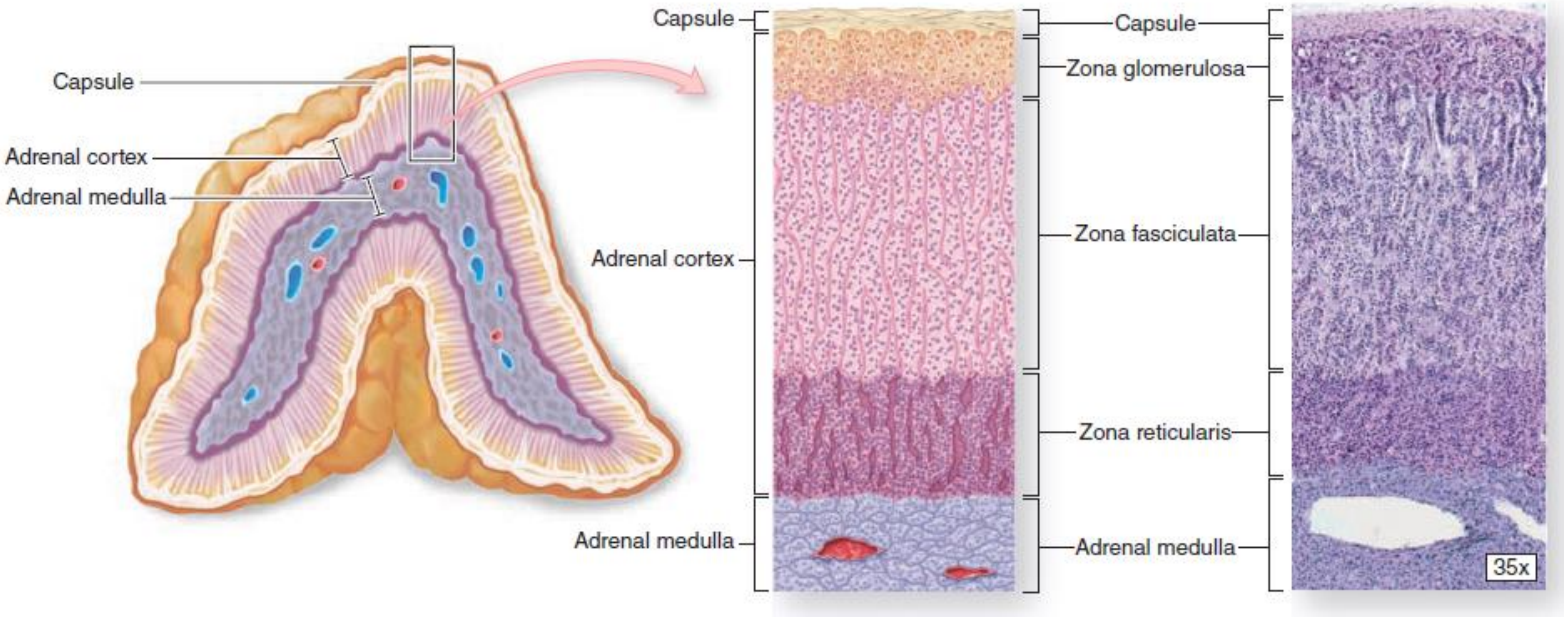


Capsule
Adrenal cortex
Adrenal medulla
Capsule
Adrenal cortex
Adrenal medulla
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenal medulla
35x

3. ZONA RETICULARIS

The innermost **zona reticularis** comprises about 10% of the cortex and consists of smaller cells in a network of irregular cords interspersed with wide capillaries. The cells are usually more heavily stained than those of the other zones because they contain fewer lipid droplets and more lipofuscin pigment.

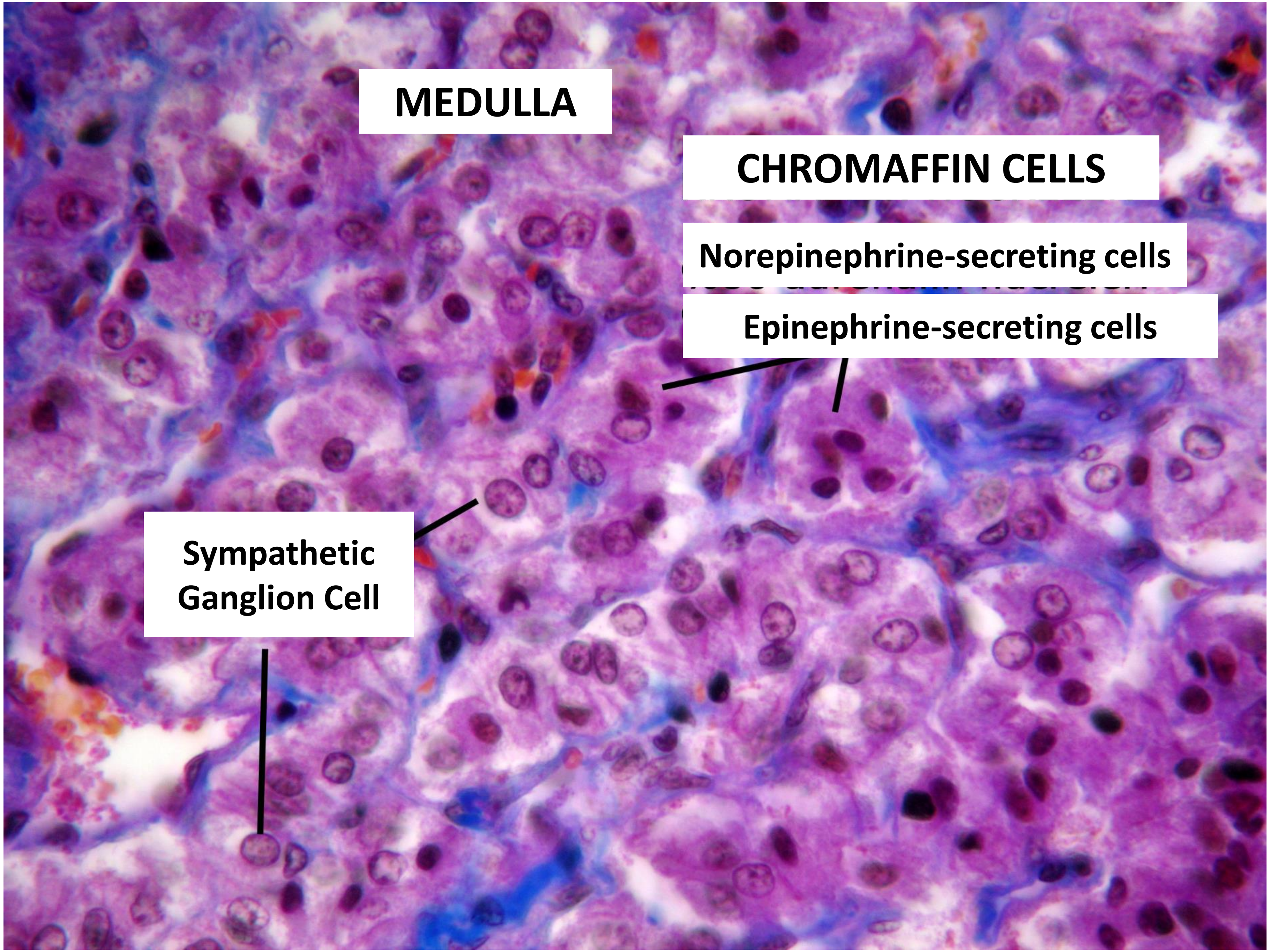
Cells of the zona reticularis also produce cortisol but primarily secrete the **weak androgens**, including **dehydroepiandrosterone (DHEA)** that is converted to testosterone in both men and women. Secretion by these cells is also stimulated by ACTH with regulatory feedback.


Capsule
Adrenal cortex
Adrenal medulla
Capsule
Adrenal cortex
Adrenal medulla
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenal medulla
35x

B) ADRENAL MEDULLA

- The adrenal medulla is composed of large, pale-staining polyhedral cells arranged in cords or clumps and supported by a reticular fiber network. A profuse supply of sinusoidal capillaries intervenes between adjacent cords and a few parasympathetic ganglion cells are present. Medullary parenchymal cells, known as **chromaffin cells**, arise from neural crest cells, as do the postganglionic neurons of sympathetic and parasympathetic ganglia. Chromaffin cells can be considered modified sympathetic postganglionic neurons, lacking axons and dendrites and specialized as secretory cells.

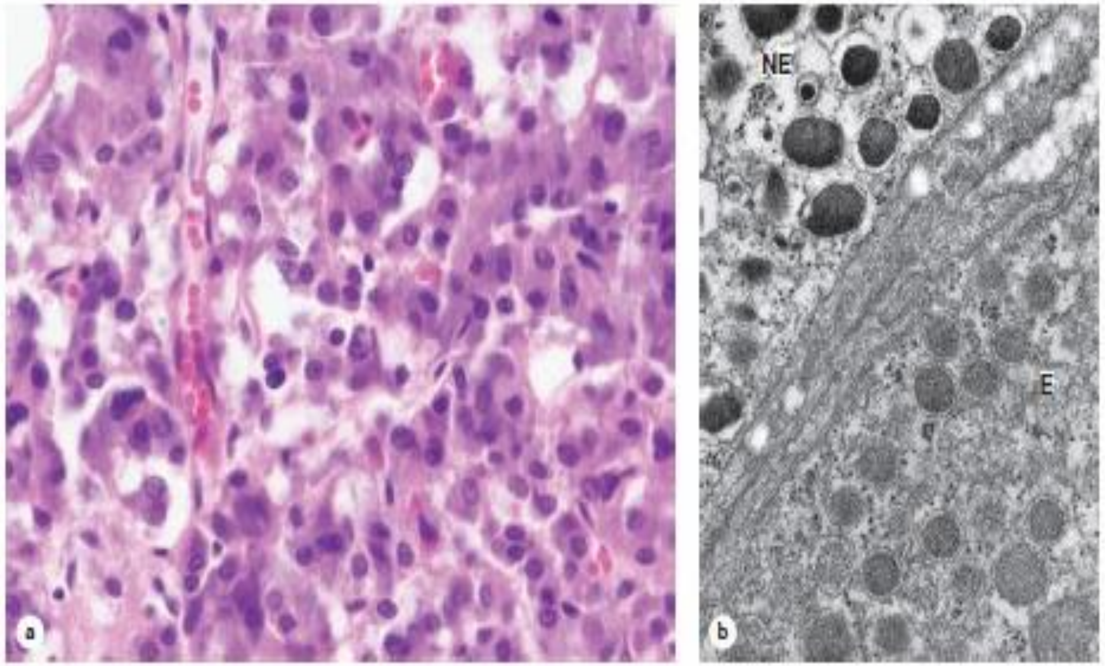
- Unlike cells of the adrenal cortex, chromaffin cells contain many electron-dense granules, 150-350 nm in diameter, for storage and secretion of catecholamines, either **epinephrine** or **norepinephrine**. The granules of epinephrine-secreting cells are less electron-dense and generally smaller than those of norepinephrine-secreting cells. Both catecholamines, together with Ca^{2+} and ATP, are bound in granular storage complexes with 49-kDa proteins called **chromogranins**.


MEDULLA
CHROMAFFIN CELLS
Norepinephrine-secreting cells
Epinephrine-secreting cells
Sympathetic
Ganglion Cell

B) Adrenal Medulla

- Norepinephrine-secreting cells are also found in paraganglia (collections of catecholamine-secreting cells adjacent to the autonomic ganglia) and in various viscera. The conversion of norepinephrine to epinephrine (adrenalin) occurs only in chromaffin cells of the adrenal medulla. About 80% of the catecholamine secreted from the adrenal is epinephrine.

- Medullary chromaffin cells are innervated by preganglionic sympathetic neurons, which trigger epinephrine and norepinephrine release during stress and intense emotional reactions. Epinephrine increases heart rate, dilates bronchioles, and dilates arteries of cardiac and skeletal muscle. Norepinephrine constricts vessels of the digestive system and skin, increasing blood flow to the heart, muscles, and brain.



The hormone-secreting cells of the adrenal medulla are chromaffin cells, which resemble sympathetic neurons.

(a) The micrograph shows that they are large pale-staining cells, arranged in cords interspersed with wide capillaries. Faintly stained cytoplasmic granules can be seen in most chromaffin cells. (X200; H&E)

(b) TEM reveals that the granules of norepinephrine-secreting cells (**NE**) are more electron-dense than those of cells secreting epinephrine (**E**), which is due to the chromogranins binding the catecholamines. Most of the hormone produced is epinephrine, which is only made in the adrenal medulla. (X33,000)

THE PARAGANGLION

- Paraganglions are the group of cells that originates from the crista neuralis during embryonic development. They gain the ability to perform a glandular character.

- Paraganglial cells transform gland cells, losing their neural features and their extension (axons and dendrites).

- These cells synthesize effective substances such as **adrenaline, noradrenaline,** and **acetylcholine**.

THE PARAGANGLION

Since all paraganglia cells receive innervation from the central nervous system, they are kept under control of the nervous system.

However, after a certain period of lifespan, they might regress or disappear.

THE PARAGANGLION

- Adrenal medulla is the largest and most important organ of the paraganglia and remains throughout life.
- Cells in paraganglia secrete chemical substances that are either sympathetic or parasympathetic.
- For this reason, they are also referred to as the sympathetic and parasympathetic paraganglia.
- When stained after fixation with chrome salts, Cells that secrete substances with adrenergic activity like adrenaline and noradrenaline can be demonstrated under light microscopy. Thus, they are termed as chromaffin cells. These cells get involved in the sympathetic group.
- In contrast, cells that do not show chromaffin properties can not be demonstrated by this method of staining; these cells containing acetylcholine are included in the parasympathetic group.

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