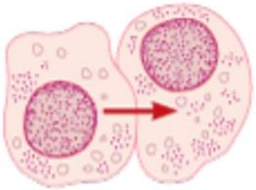
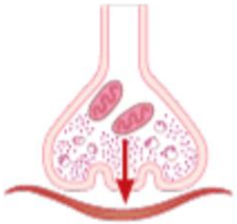
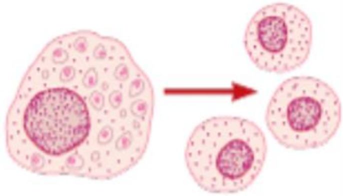
Endocrine glands

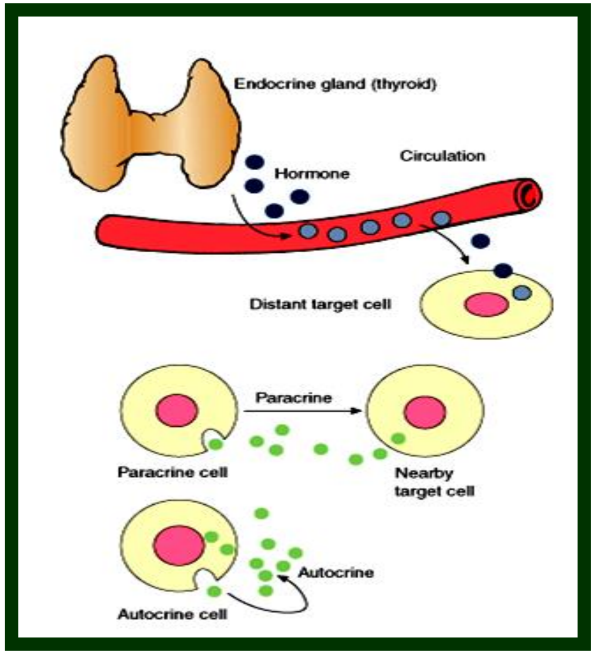
Professor Zbigniew Kmieć, MD, PhD

From: Chapter 4. Hypothalamus and Pituitary Gland: **Intercellular communication by chemical mediators.**

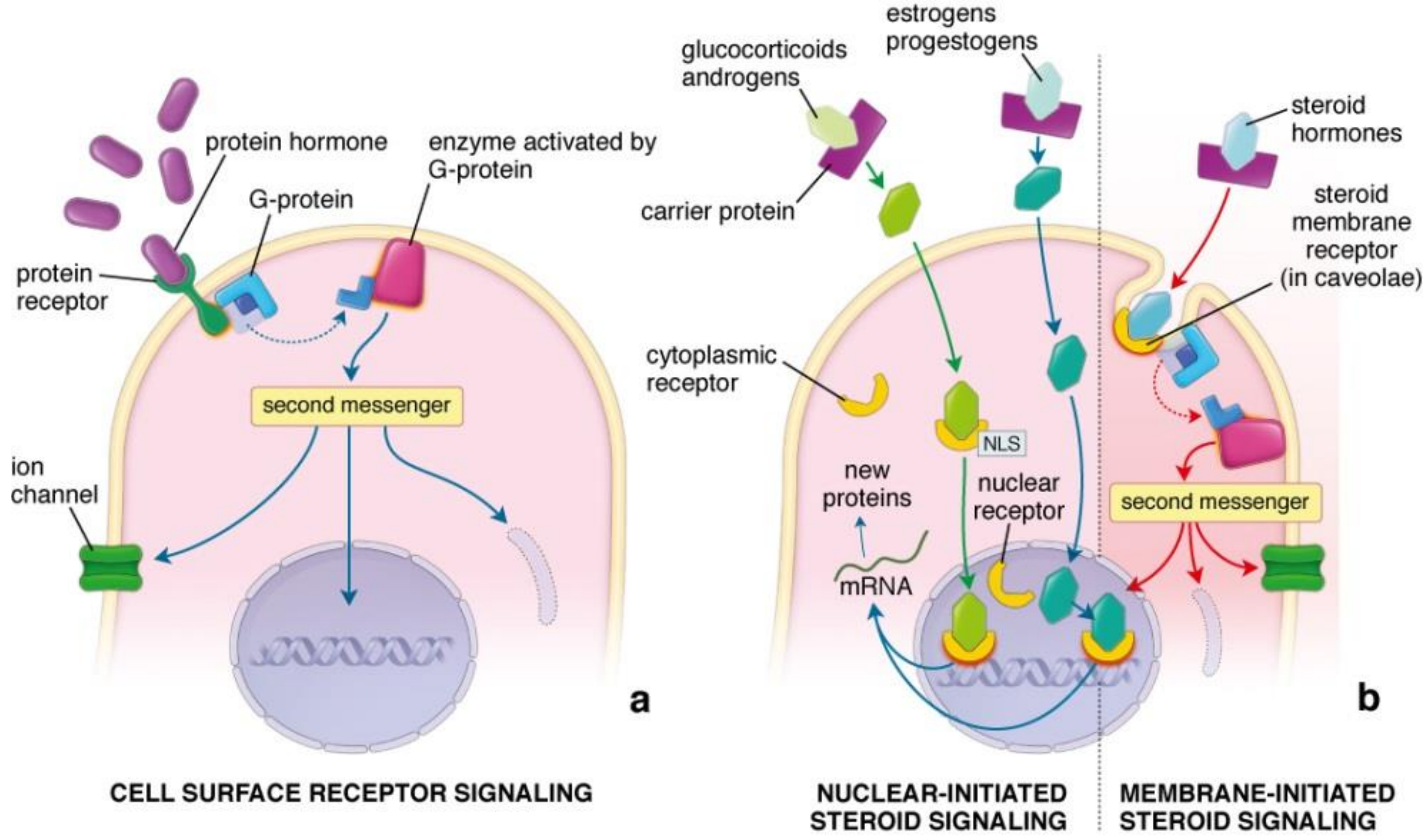
Greenspan’s Basic & Clinical Endocrinology, 9e, 2011

	Gap junctions	Synaptic	Paracrine	Endocrine
				
Message transmission	Directly from cell to cell	Across synaptic cleft	By diffusion in interstitial fluid	By circulating body fluids
Local or general	Local	Local	Locally diffuse	General
Specificity depends on	Anatomic location	Anatomic location and receptors	Receptors	Receptors

Source: Gardner DG, Shoback D: *Greenspan’s Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com



General mechanisms of protein and steroid hormone actions

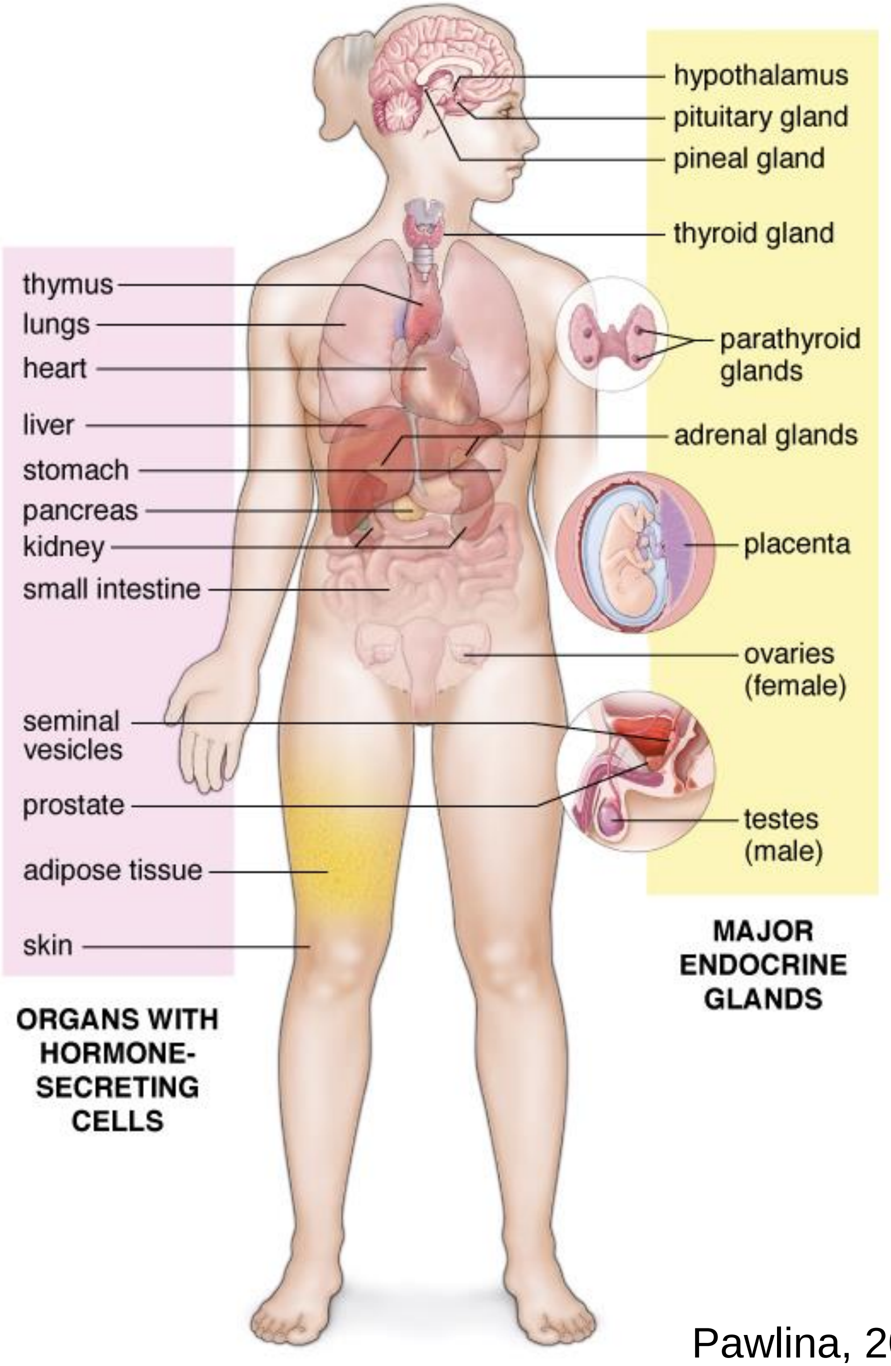


Pawlina W, Ross MH. Histology: A text and atlas with correlated cell and molecular biology. 2020, 8th ed.

a. **Protein hormones** bind to the cell surface receptors and initiate a cascade of intracellular signaling reactions (involving G-protein, various protein kinases, and second-messenger molecules), influencing channel proteins, nuclear transcription, and protein synthesis or degradation.

b. In the **nuclear-initiated steroid signaling**, some steroid hormones (e.g., glucocorticoids, androgens) cross the plasma membrane and bind to specific cytoplasmic receptors. This binding of the hormone causes allosteric transformation of the receptor, and the resulting complex travels to the nucleus (guided by the nuclear localization signal, *NLS*), where it binds to DNA and regulates the transcription of specific genes. Other steroid hormones (e.g., estrogens, progestogens) bind to their specific receptors directly in the nucleus (*blue arrows*). In **membrane-initiated steroid signaling**, the steroid receptors are expressed on the cell membrane, usually in the caveolae, and their pathway is similar to that of the cell surface receptor signaling.

Locations of the major endocrine glands



Pawlina, 2020

Not shown are **adipocytes**, which exert important endocrine functions, and the **DNES cells** in many tissues, e.g. GI tract, in which **both endocrine and paracrine signalling** is important.

Embryonal origin of endocrine glands

ENDODERM: derived form diverticuli of the digestive tube

- Thyroid
- Parathyroid
- Endocrine Pancreas

MESODERM: Glands that secrete steroid hormones.

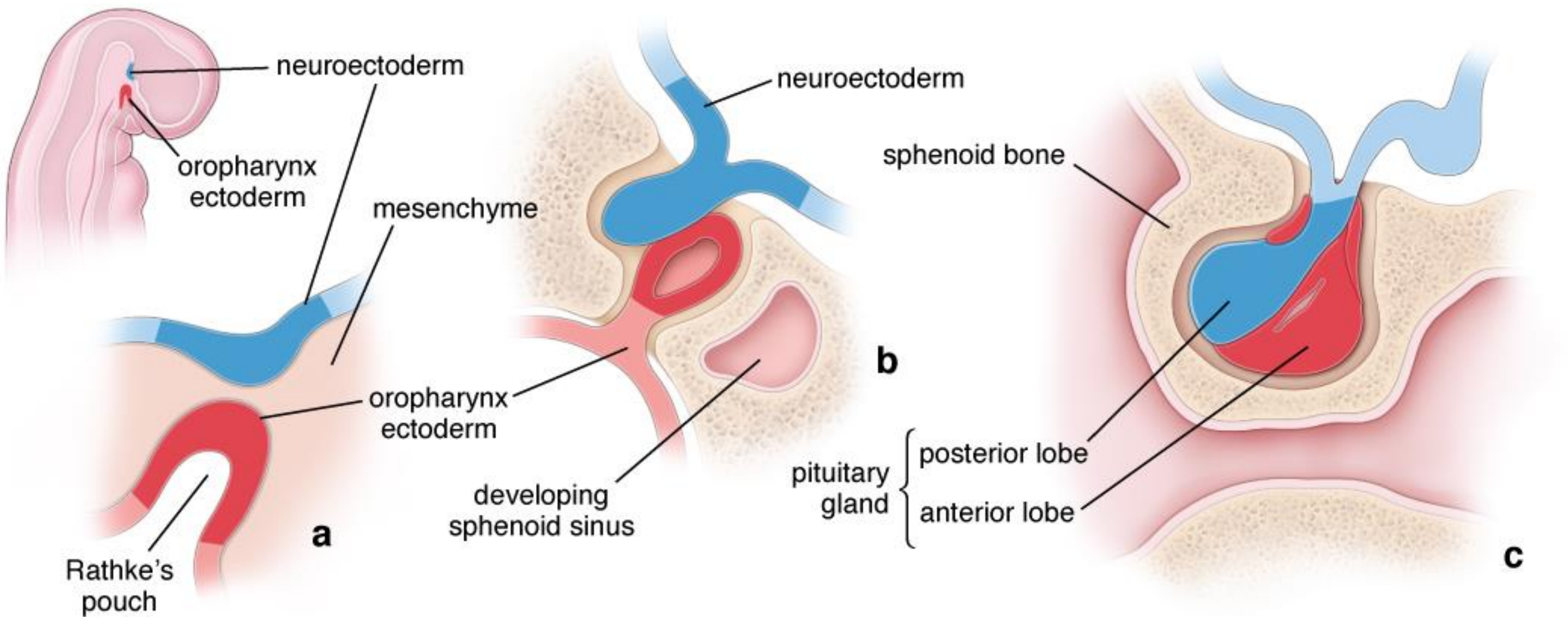
- Gonads
- Adrenal Cortex

ECTODERM: Glands that secrete peptide and amino-acid derived hormones.

- Adrenal Medulla – derivatives of neural crest cells
- Anterior Pituitary - derivative oral cavity ectoderm
- Posterior Pituitary (neuroectodermal, however,

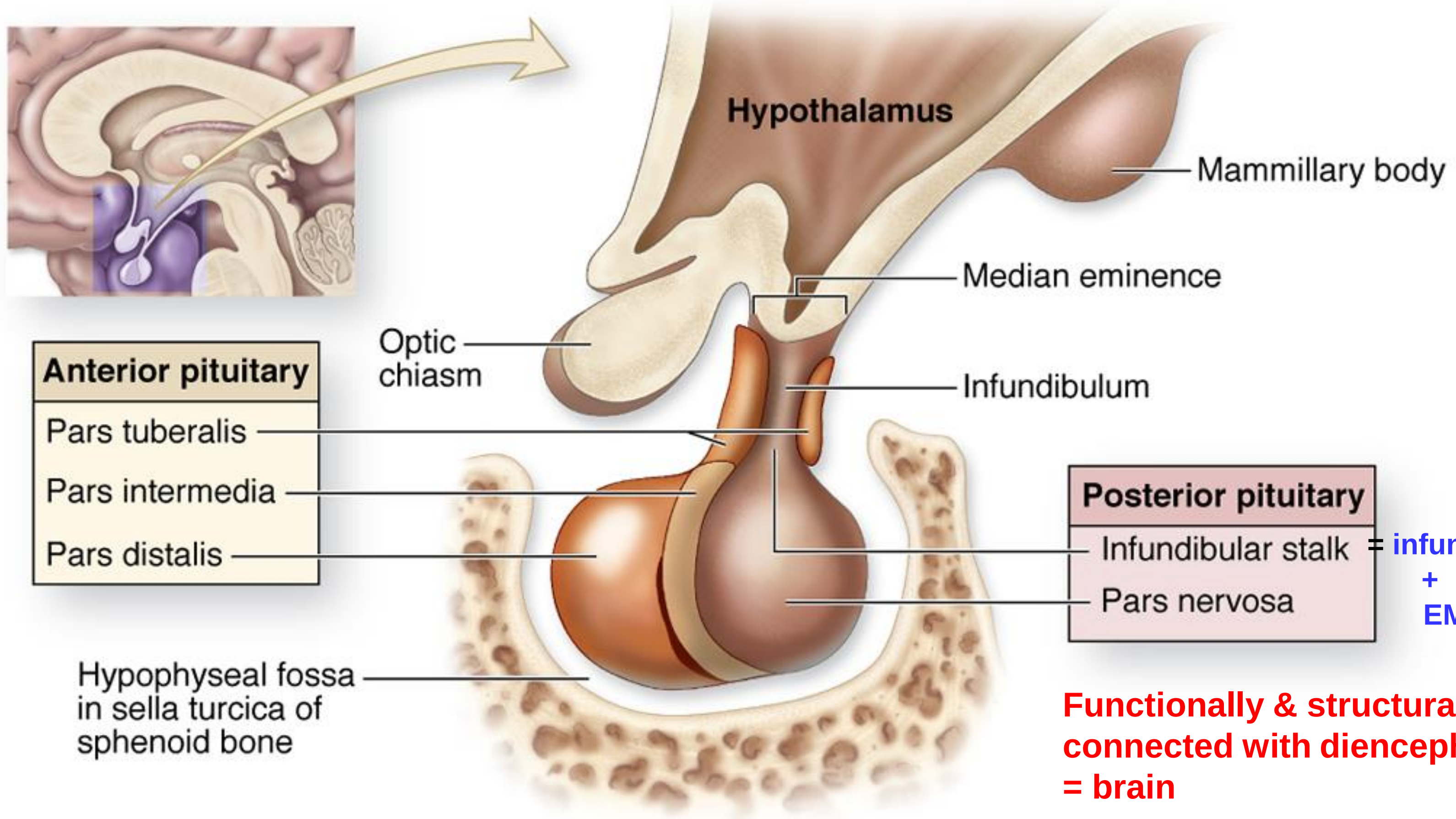
  HORMONES ARE NOT PRODUCED HERE!

Double origin of the pituitary gland



Pawlina, Histology, 2020

Pituitary gland is composed of an **anterior** part (adenohypophysis) and a **posterior** part (neurohypophysis) , which is directly attached to the hypothalamus region of the brain by a stalk called the **infundibulum**.

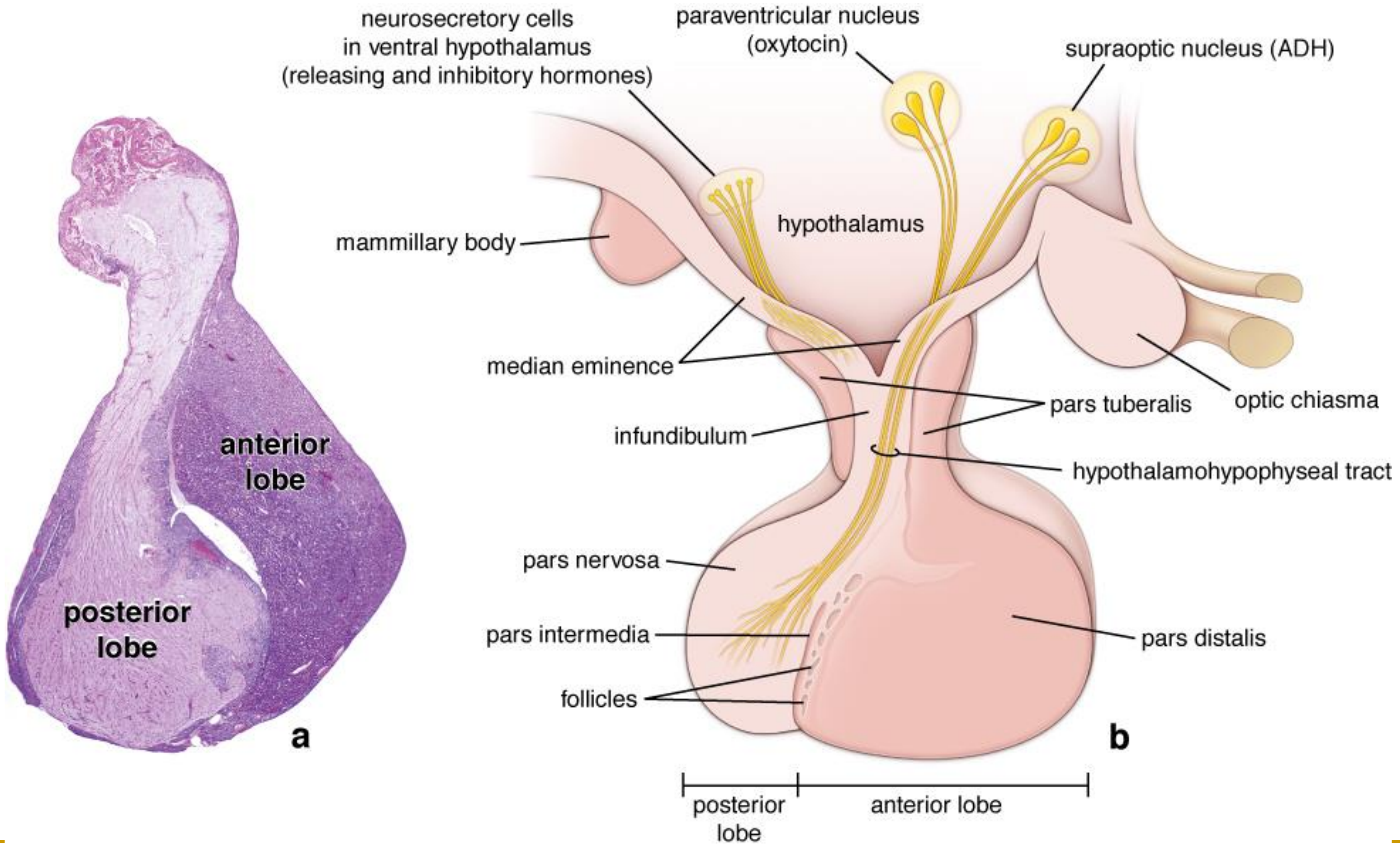


= infundibulum + MEDIAN EMINENCE

Functionally & structurally connected with diencephalon = brain

Basic Histology, 12th ed.

Anatomy of hypothysis and its connections with hypothalamus



Pawlina, Histology, 2020

Cell types present in the pars distalis of adenohypohysis:

CHROMOPHILES (ca. 50%, active forms of secretory pituitary cells)

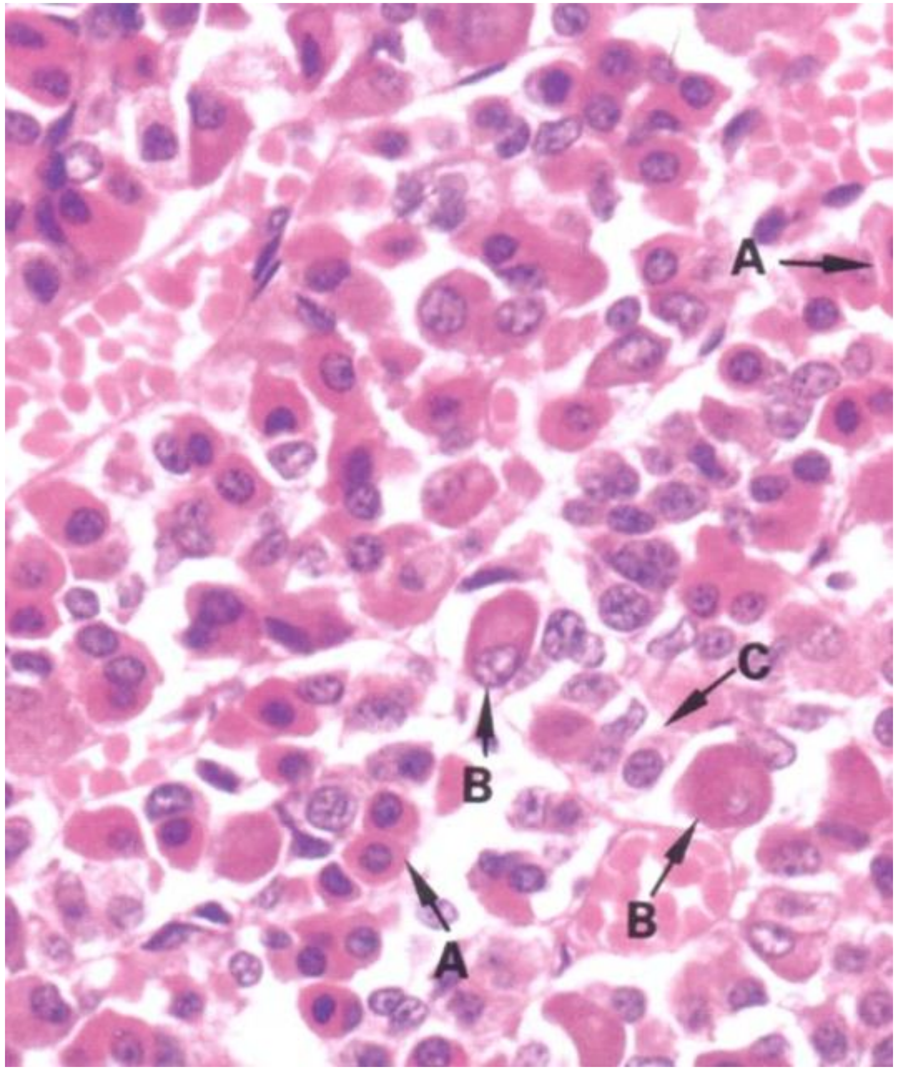
Acidophilic – 40% (red or pink, however, various staining methods have been used)

- Basophilic – 10% (blue or purple)

depending on the type of secretory material present

- CHROMOPHOBES (ca. 50% of cells, pale, inactive forms of secretory pituitary cells, *do not stain clearly*), they include:

- **Folliculostellate cells** – nonsecretory, have long processes joined by GAP jcts; MAY: phagocytose,
  support other cells of pituitary,
  function as **stem cells**,
  stimulate chromophils to release hormones



Functional Histology, 2004

ACIDOPHILS (A):

GH, somatotrophs

PRL, lactotrophs

BASOPHILS (B):

ACTH (MSH, LPH)

TSH

FSH, LH

CHROMOPHOBS (C)

Hormones of the pituitary gland and their targets

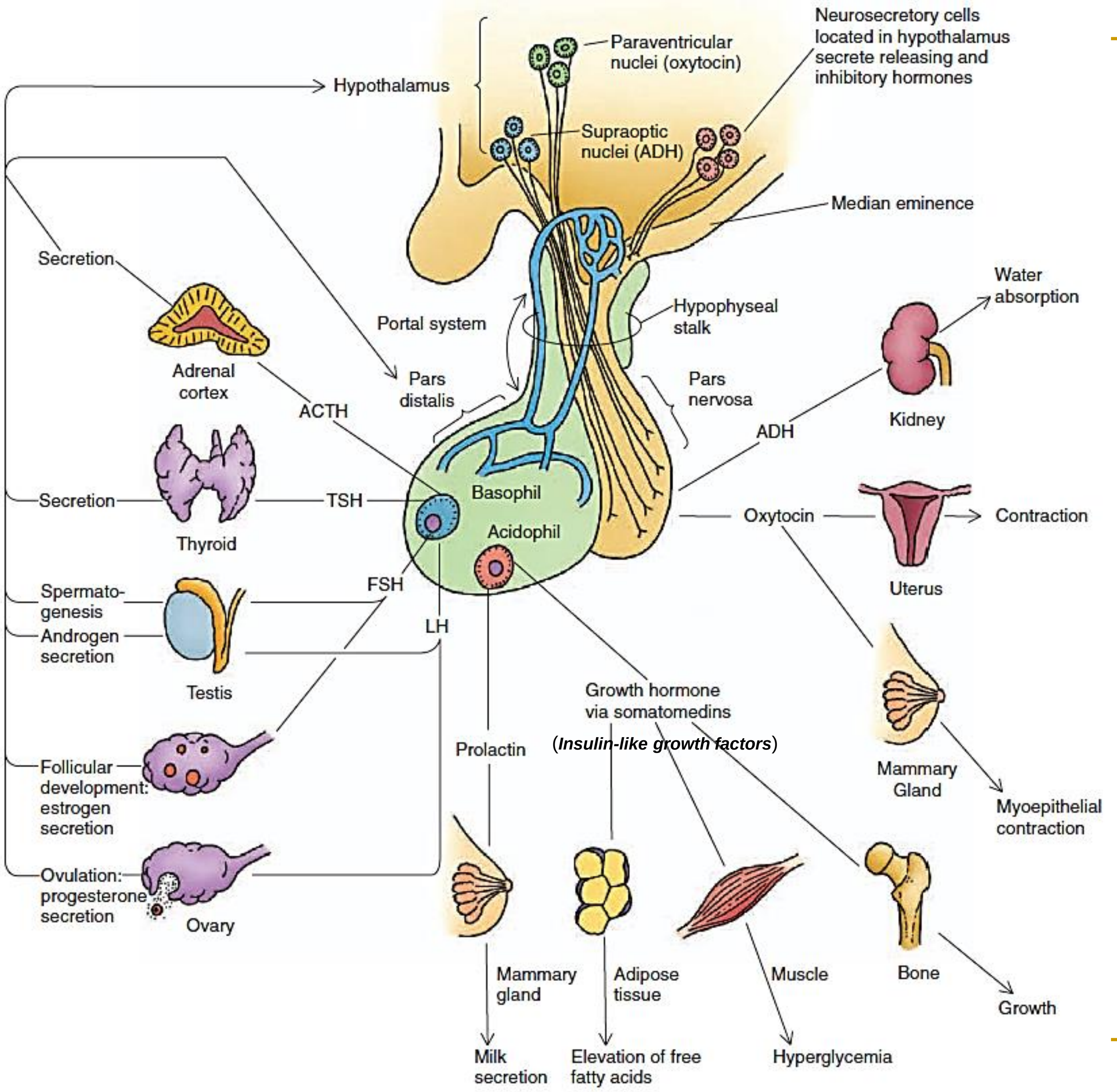


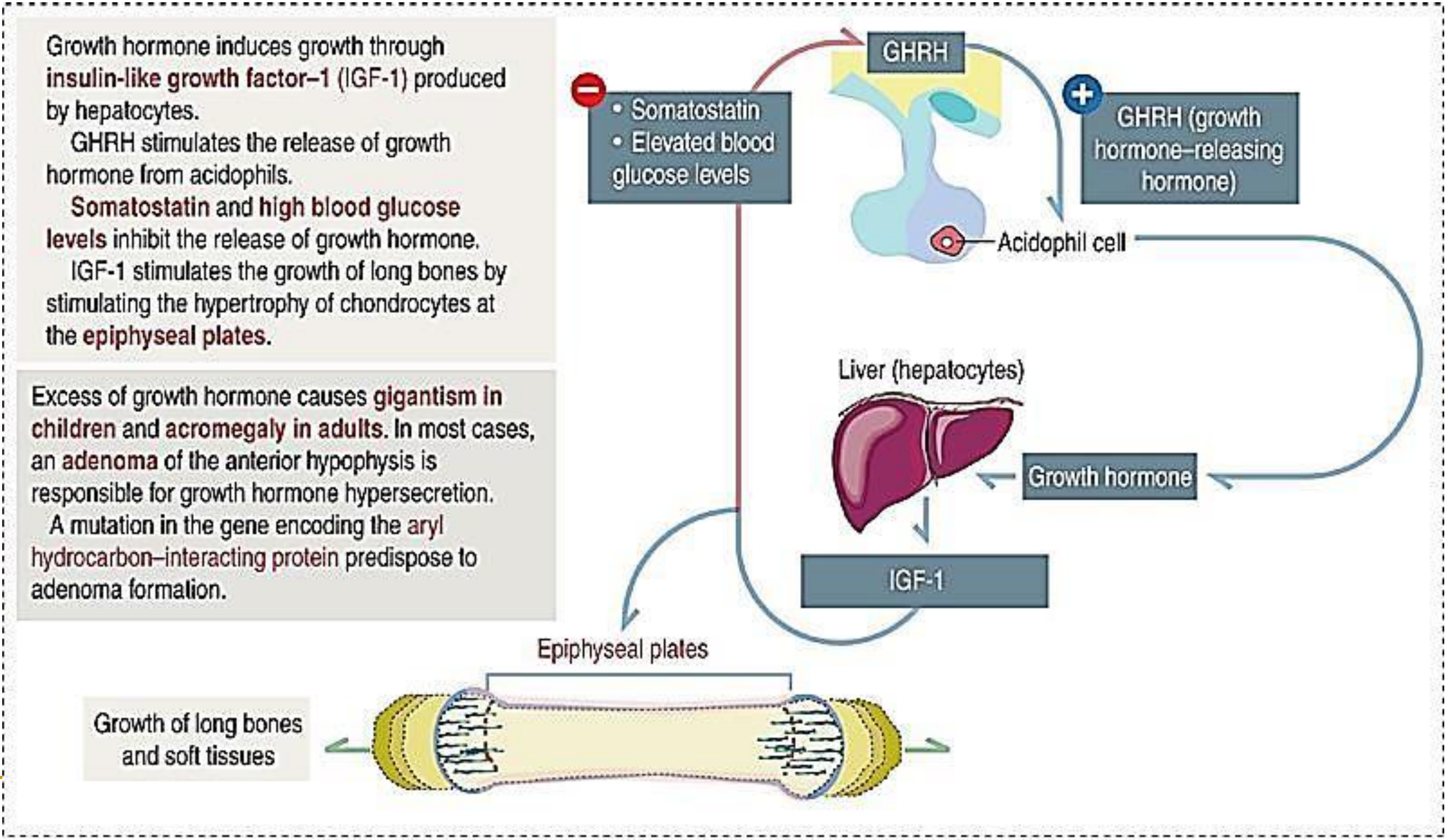
Figure 13.2 The pituitary gland and its target organs. *(From Gartner LP, Hiatt JL: Color Textbook of Histology, 3rd ed. Philadelphia, Saunders, 2007, p 305.)*

- **CHROMOPHILS and their products**:
  - **SOMATOTROPHS**: **Growth Hormone (peptide)**
  - **MAMMOTROPHS**: **Prolactin (protein)**
  - **CORTICOTROPHS**: **ACTH** (**glycoprotein**)
  - **THYROTROPHS**: **TSH** (**glycoprotein**)
    - Smallest % of cells -- less than 10% of basophils
  - **GONADOTROPHS**: **FSH, LH** (glycoproteins)

The gonadotropins are produced in the same cell type and can even be found in the same secretory granule.

They are secreted at the same time, althougth in different amounts, under the influence of ***GnRH = gonadotropin-releasing hormone***.

Somatotropin (STH; growth hormone, GH) has a generalized effect of increasing cellular metabolic rates. This hormone also INDUCES LIVER CELLS to produce **insulin-like growth factor I (IGF-1** and **IGF-2**) which increase mitotic rates of epiphyseal plate chondrocytes, promoting the **elongation of long bones and hence stimulating growth.**



Klerszenbaum & Tres: Histology and Cell Biology: An Introduction to Pathology, 3e

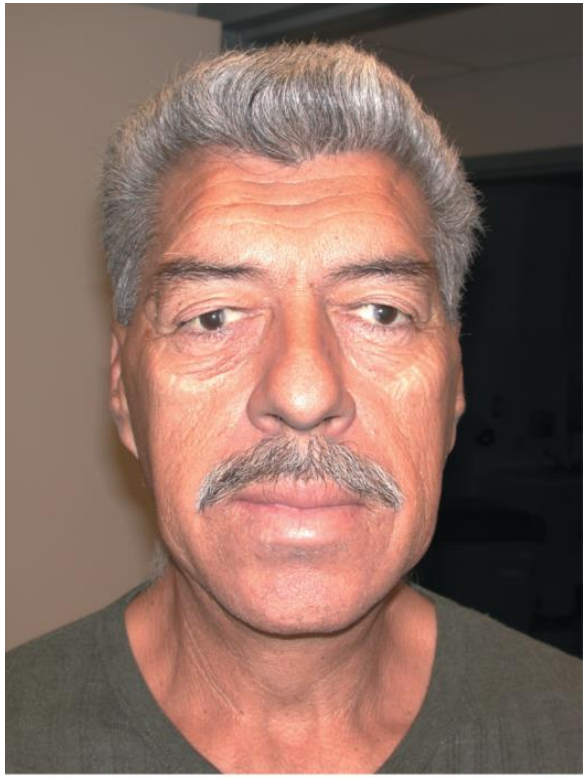
From: Chapter 228. Acromegaly.

The Color Atlas of Family Medicine, 2e, 2013

A 60-year-old man presents to his family physician with severe headache and weakness (Figure 228-1). He also noted enlargement of his hands (Figure 228-2), which made him remove his wedding ring when it became too tight, and feet (his shoe size had increased). He said his voice seemed to be deeper and his hands feel doughy and sweaty.

Laboratory testing reveals an elevated insulin-like growth factor (IGF)-I, and there is a failure of growth hormone (GH) suppression following an oral glucose load confirming the diagnosis of **acromegaly**.

Computed tomography (CT) scan of the head demonstrates a pituitary adenoma.

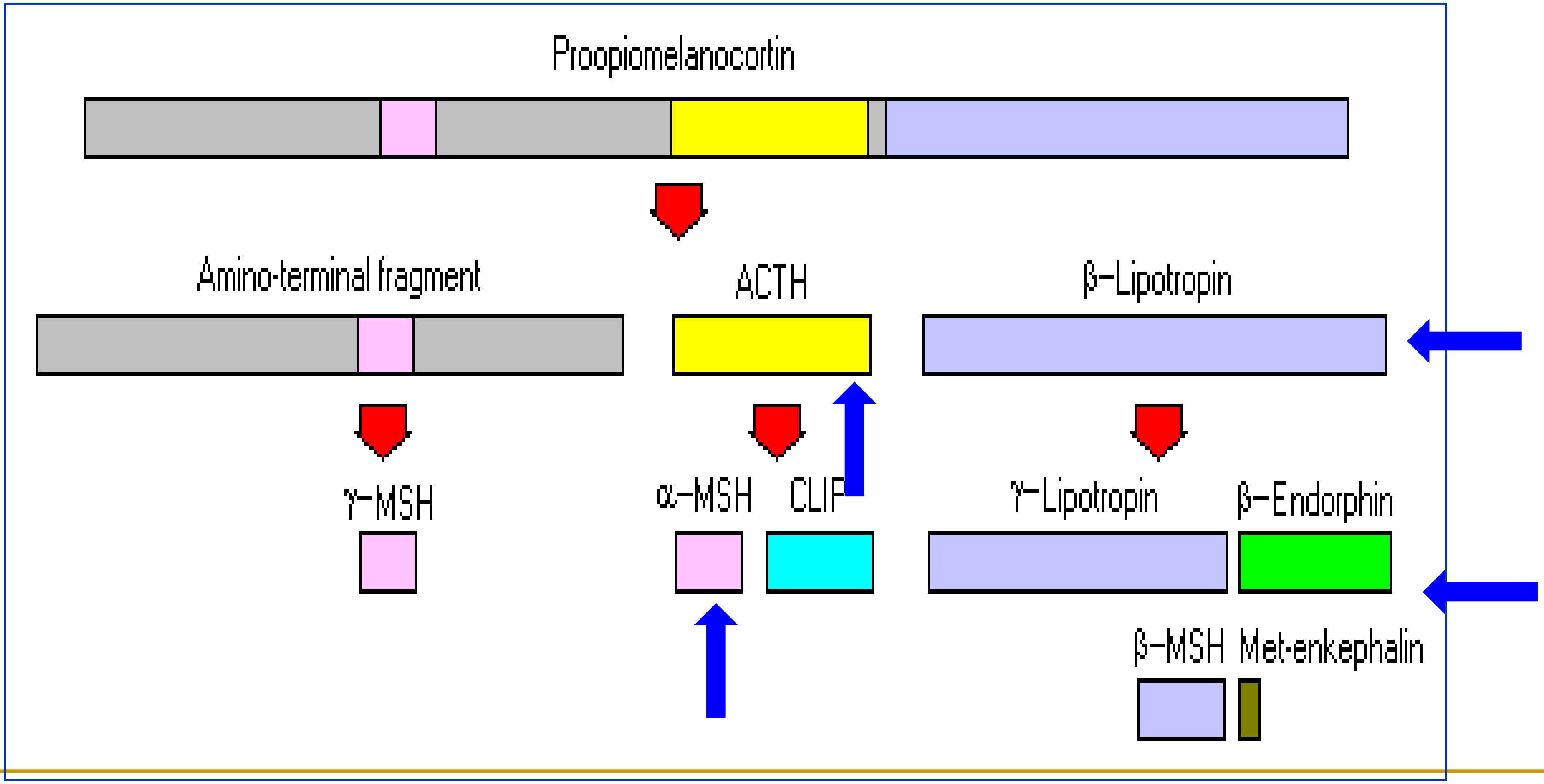


Note the coarse facial features and moderate prognathism (protrusion of the lower jaw).
(Courtesy of Richard P. Usatine, MD.)

The man in Figure 228-1 with acromegaly producing hands that are large and doughy with widened fingers.

Proopiomelanocortin POMC is a precursor of 4 different polypeptide hormones that arise from the proteolysis of the prohormone (POMC) present in orticotrophs:

Adrenocorticotropic hormone (ACTH);
Melanocyte-Stimulating Hormone (alfa-MSH);
Beta-lipotropin (LPH);
Beta-endorphin

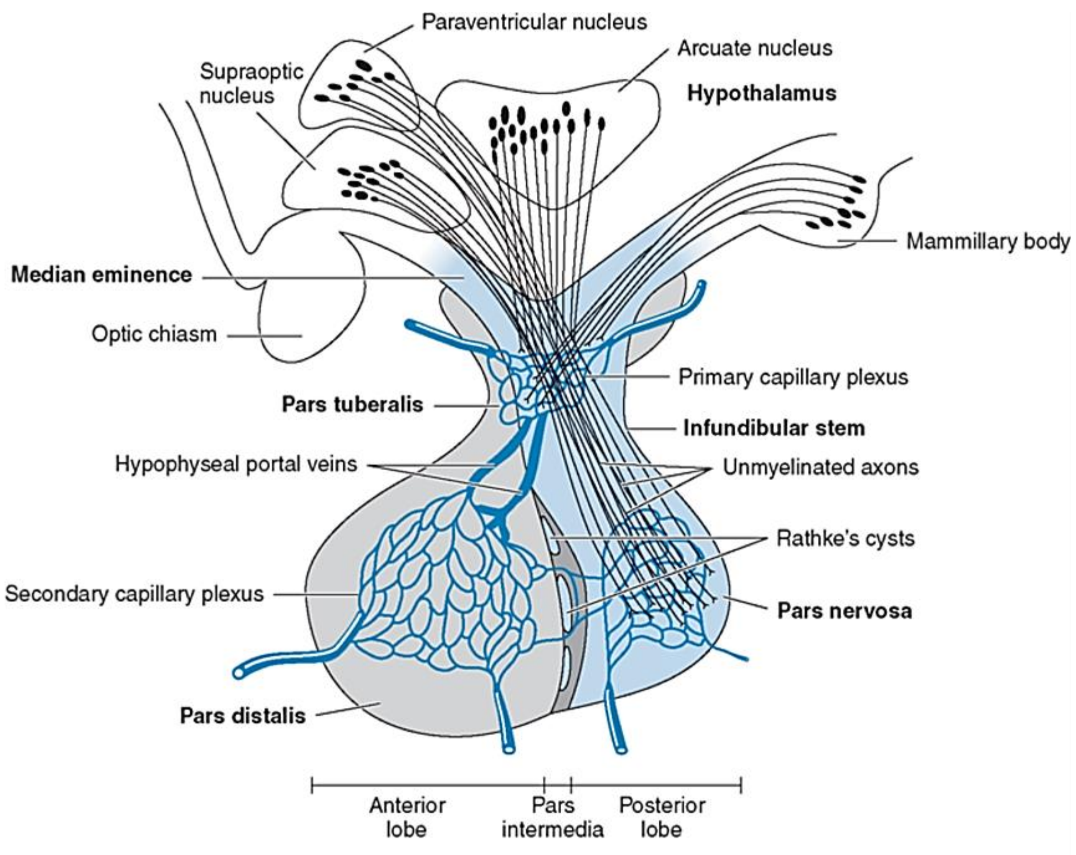


Kierszenbaum 2002

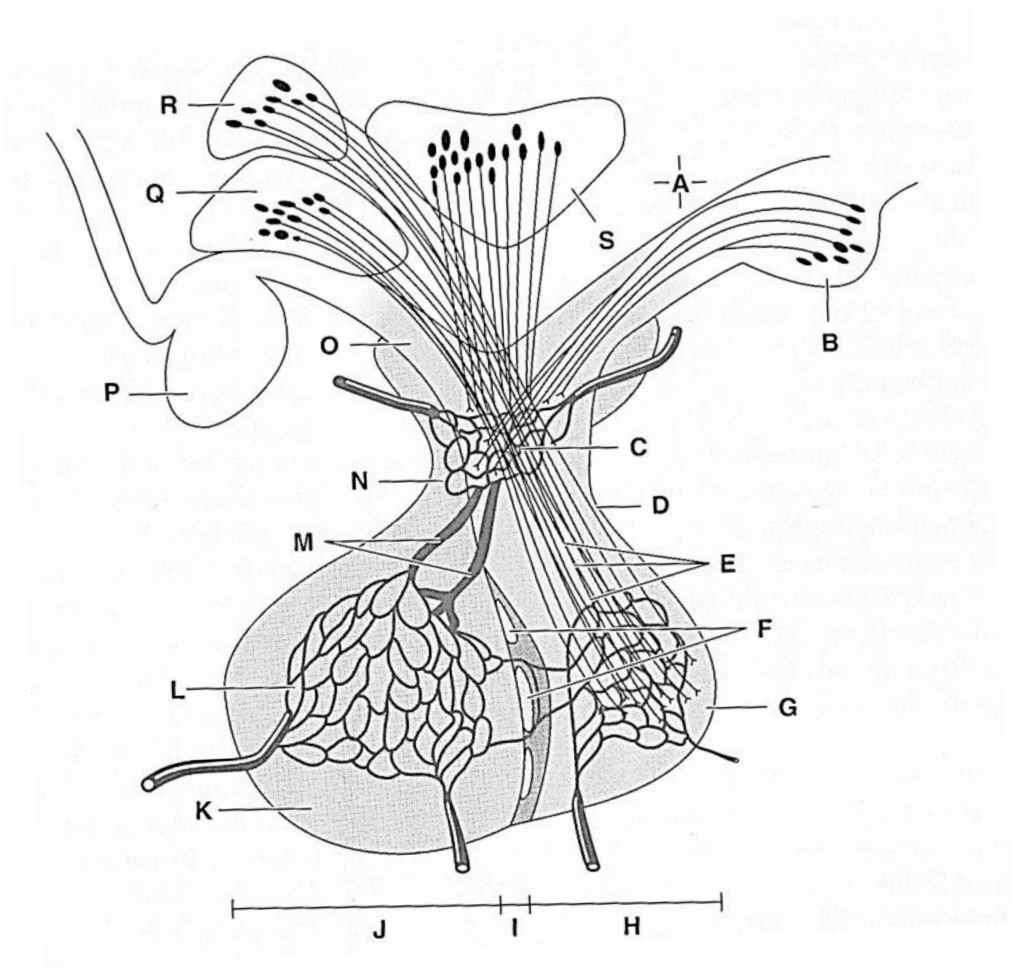
From: Chapter 20. Pituitary Gland & **Hypothalamus and Hypophysis.**

Describe the right diagram on your own!

Histology & Cell Biology: Examination & Board Review, 5e, 2010



Source: Paulsen DF: *Histology & Cell Biology: Examination & Board Review*, 5th Edition: www.accessmedicine.com



Schematic diagram of the subdivisions, blood supply, and innervation of the pituitary gland and hypothalamus.

The adenohypophysis (gray, left) lies anterior to the neurohypophysis (right). For simplicity, only a few of the many nuclei of the hypothalamus (top) are shown. Major subdivisions are shown in boldface.

Neurosecretion and neurohypophysis

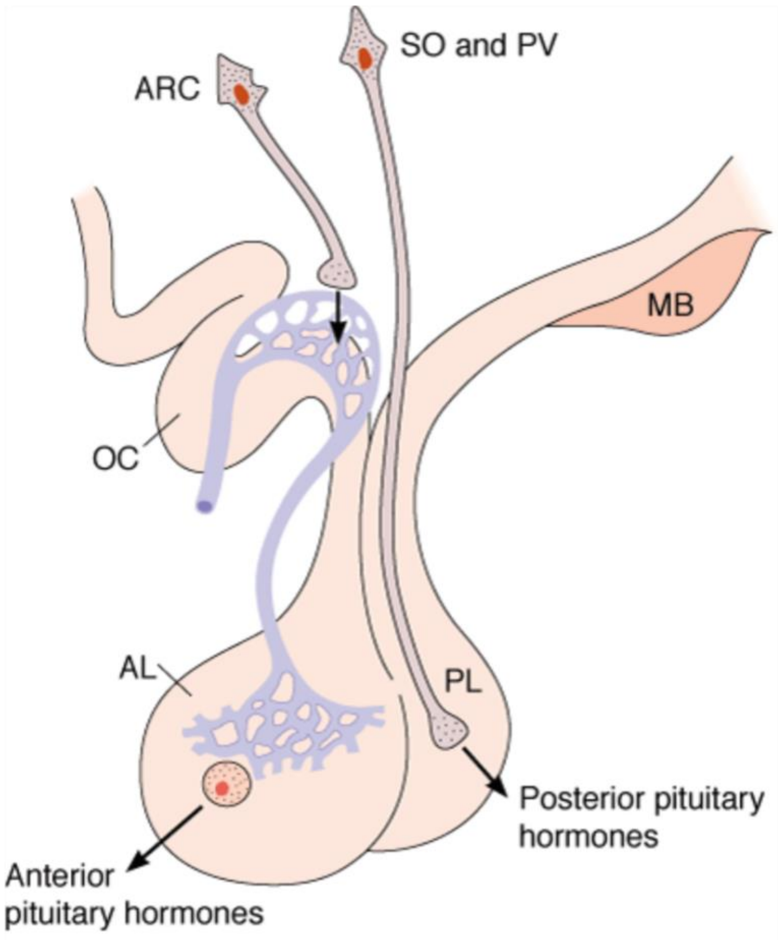
Neurosecretion: neurons are able to synthesize and release hormones

- posterior lobe = pars nervosa
  AND
- infundibulum = pituitary stalk = neural stalk (stem + median eminence)

Contains non-myelinated axons of neurosecretory cells

+ pituicytes similar to neuroglial cells

+ rich network of small capillaries



Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

The hormones of the posterior lobe (PL) are released into the general circulation from the endings of supraoptic (SO) and paraventricular (PV) neurons (*long axons*).

The hypophysiotropic hormones are secreted into the portal hypophysial circulation from the endings of arcuate (ARC) and other hypothalamic neurons (*short axons*).

(AL, anterior lobe; ARC, arcuate and other nuclei; MB, mamillary bodies; OC, optic chiasm; PV, paraventricular nucleus; SO, supraoptic nucleus).

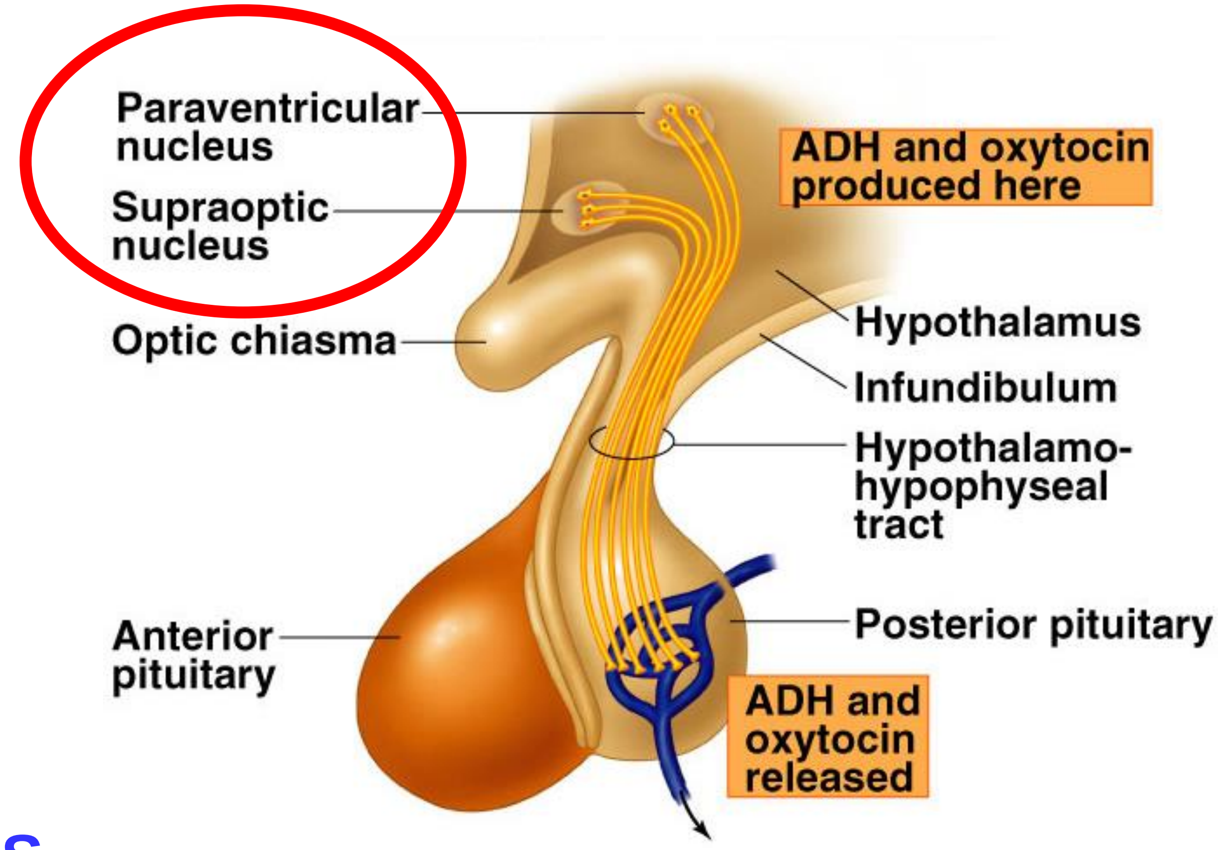
Hormones RELEASED in pars nervosa:

OF NOTE: THEY ARE PRODUCED IN ANTERIOR HYPTHALAMIC NUCLEI: PVN and SO

Hormone	Composition	Source	Major Functions
Oxytocin	Polypeptide containing nine amino acids	Cell bodies of neurons located in the supraoptic and paraventricular nuclei of the hypothalamus	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 aa; 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	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

Pawlina W, Ross MH. Histology: A text and atlas with correlated cell and molecular biology. 2020, 8th ed.

NON-OBLIGATORY



Kierszenbaum 2002

HERRING BODIES

Dilations along the unmyelinated axons (and at their endings) of hypothalamic neurons that contain granules with ADH and oxytocin connected to → Neurophysins = proteins that carry hormones from perikaryons of the hypothalamic neurons along their axons to posterior pituitary.

Moreover, Hering bodies contain ATP and acetylocholine.

The hypothalamo-hypophyseal portal system and hormone release in the pituitary

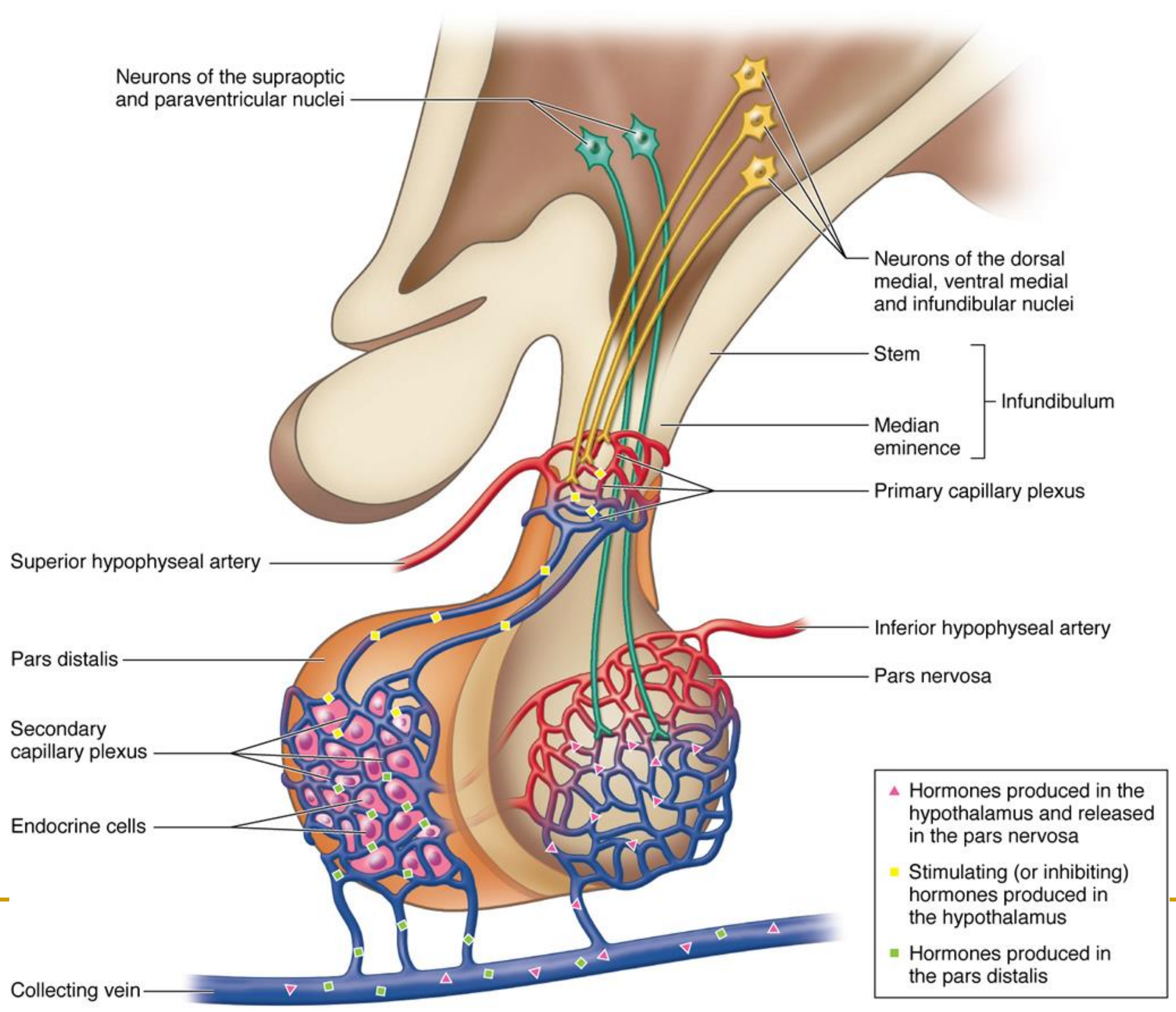
Hypothalamo-hypophyseal tract: **neurons produce hormones → pituitary stalk → posterior pitutary:** **release of oxytocin and vasopressin**

The **neurosecretory nuclei in the hypothalamus: paraventricular and supraoptic nuclei** produce **oxytocin** and **antidiuretic hormone (*ADH*)**.

These hormones are **released in the pars nervosa** of the posterior lobe. Neurosecretory cells in **the middle hypothalamus** secrete **releasing and inhibitory hormones** that are discharged into **primary capilary plexus** (located in the median eminence and infundibulum).

This network is drained by the **hypophyseal portal veins**, which give rise to a **secondary capillary plexus** in the pars distalis.

Here, the neuroendocrine secretions produced in the hypothalamus are released and act on secretory cells..

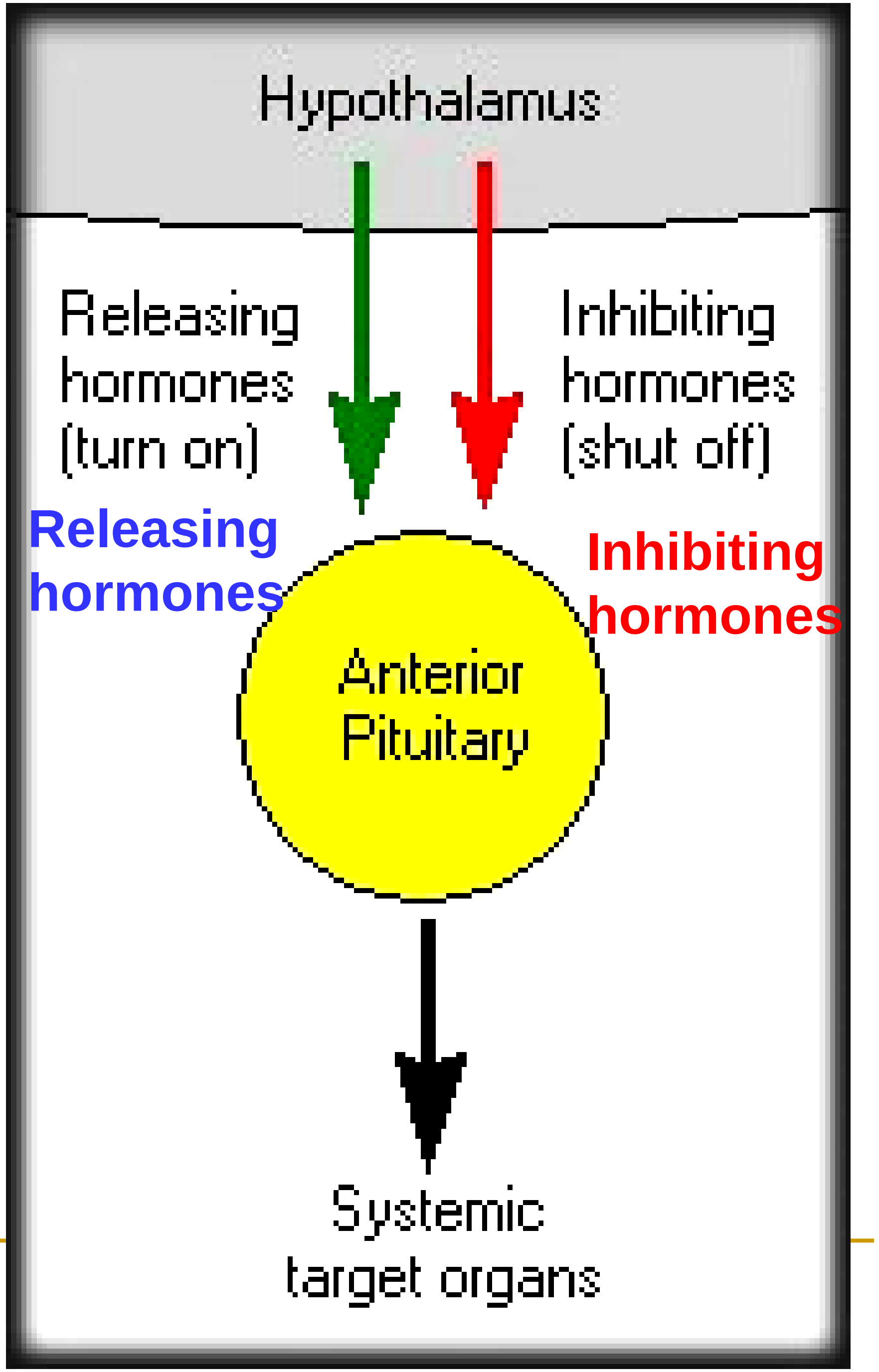


Superior hypophyseal arteries (from internal carotids) form **primary capillary plexus** (in median eminence)

Portal veins course downward to join sinusoids in pars distalis to form **secondary capillary plexus.**

Inferior hypophyseal arteries form capillaries in pars nervosa.

Basic Histology, 12th ed.



Hypothalamus = part of diencephalon:

controls secretion of all hormones of

We know 5 HYPOTHALAMIC RELEASING HORMONES:

CRH - releases ACTH,

GRH - releases GH (STH),

TRH - releases TSH

GnRH - releases FSH and LH

PRH - releases PRL = prolactin

We know 2 hypothalamic INHIBITORY HORMONES

SRIF, GIH - inhibits GH (STH) release, SOMATOSTATIN

PIH - inhibits PRL release

MIH is a tripeptide, product of an enzymatic degradation of oxitocin that inhibits MSH release

Hypothalamic-regulating hormones

NON-OBLIGATORY

Hormone	Composition	Source	Major Functions
Growth hormone–releasing hormone (GHRH)	Two forms in human: polypeptides containing 40 and 44 amino acids	Cell bodies of neurons located in the arcuate nucleus of hypothalamus	Stimulates secretion and gene expression of GH by somatotropes
Somatostatin (SRIF)	Two forms in human: polypeptides containing 14 and 28 amino acids	Cell bodies of neurons located in the periventricular, paraventricular, and arcuate nuclei of the hypothalamus	Inhibits secretion of GH by somatotropes and TSH by thyrotropes; inhibits insulin secretion by B cells of pancreatic islets
Dopamine	Catecholamine (amino acid derivative)	Cell bodies of neurons located in the arcuate nucleus of hypothalamus	Inhibits secretion of PRL by lactotropes
Corticotropin-releasing hormone (CRH)	Polypeptide containing 41 amino acids	Cell bodies of neurons located in the arcuate, periventricular, and medial paraventricular nuclei of hypothalamus	Stimulates secretion of ACTH by corticotropes; stimulates gene expression for POMC in corticotropes
Gonadotropin-releasing hormone (GnRH)	Polypeptide containing 10 amino acids	Cell bodies of neurons located in the arcuate, ventromedial, dorsal, and paraventricular nuclei of hypothalamus	Stimulates secretion of LH and FSH by gonadotropes
Thyrotropin-releasing hormone (TRH)	Polypeptide containing 3 amino acids	Cell bodies of neurons located by the ventromedial, dorsal, and para ventricular nuclei of hypothalamus	Stimulates secretion and gene expression of TSH by thyrotropes; stimulates synthesis and secretion of PRL

GH, growth hormone; *TSH*, thyroid-stimulating hormone; *PRL*, prolactin; *ACTH*, adrenocorticotropic hormone; *POMC*, proopiomelanocortin; *LH*, luteinizing hormone; *FSH*, follicle-stimulating hormone.

Pawlina W, Ross MH. Histology: A text and atlas with correlated cell and molecular biology. 2020, 8th ed.

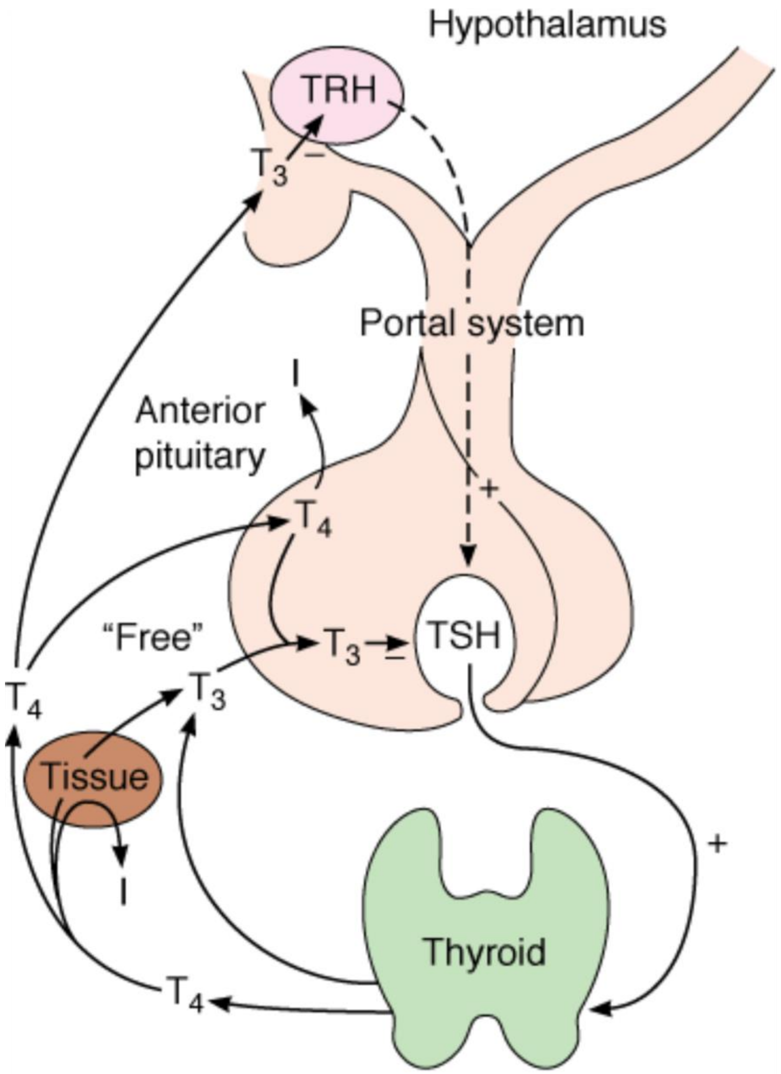
From: Chapter 7. The Thyroid Gland: **The hypothalamic-hypophysial-thyroidal axis**

Greenspan's Basic & Clinical Endocrinology, 9e, 2011

TRH produced in the hypothalamus reaches the **thyrotrophs in the anterior pituitary** by the hypothalamo-hypophysial portal system and stimulates the synthesis and release of **TSH**.

In both the hypothalamus and the pituitary, it is primarily **T3 that inhibits TRH and TSH secretion**, respectively.

T4 undergoes monodeiodination to T3 in neural cells and pituitary as well as in peripheral tissues.



Negative feedback loops affecting anterior pituitary secretion of FSH and LH (gonadotropins)

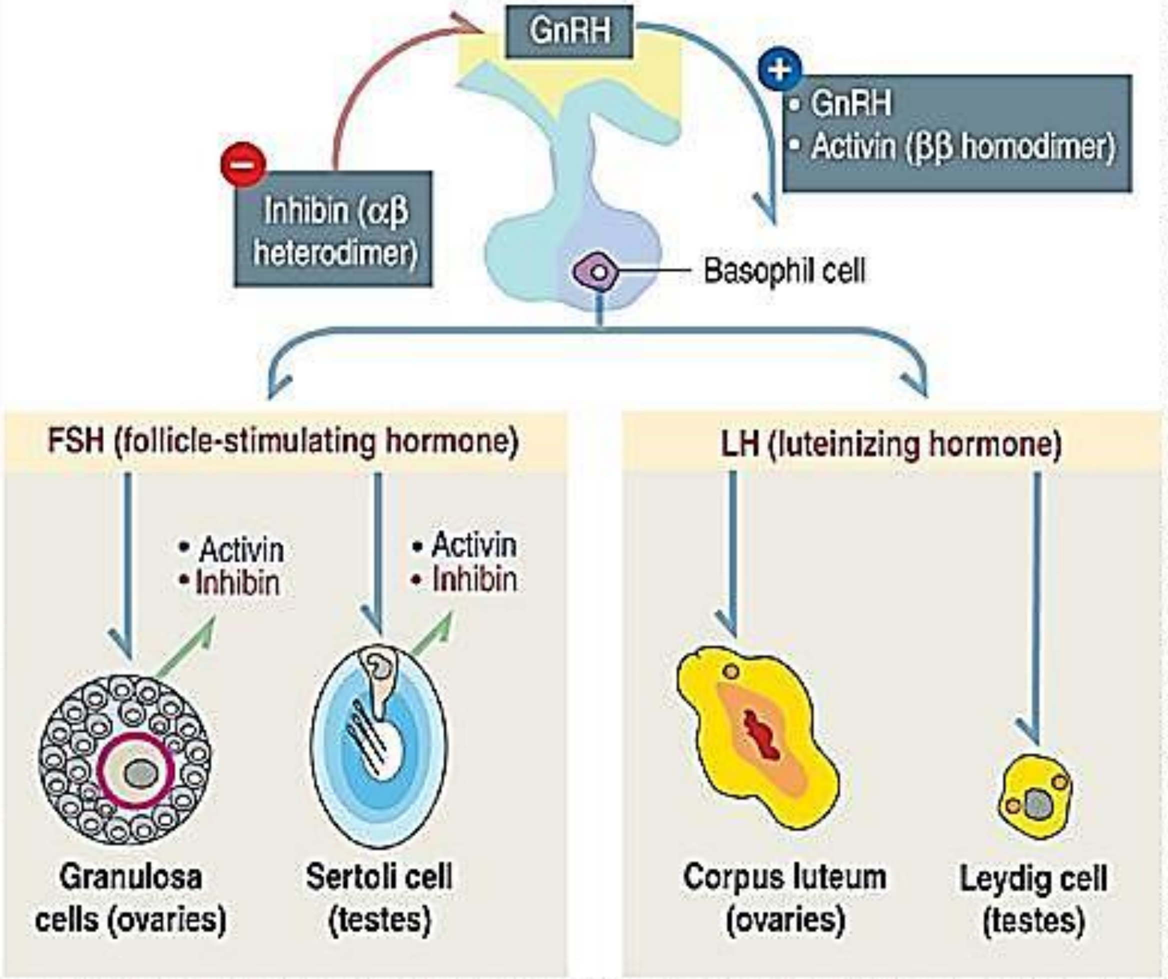
NON-OBLIGATORY

Neurons in the **arcuate nucleus** of the hypothalamus secrete **GnRH** (gonadotropin-releasing hormone). GnRH is secreted **in** pulses at 60- to 90-minute intervals and stimulates the pulsatile secretion of **gonadotropins** by the basophilic gonadotrophs.

In the female, FSH stimulates **granulosa cells** of the ovarian follicle to proliferate and secrete **estradiol**, **inhibin**, and **activin**. LH stimulates progesterone secretion by the **corpus luteum**.

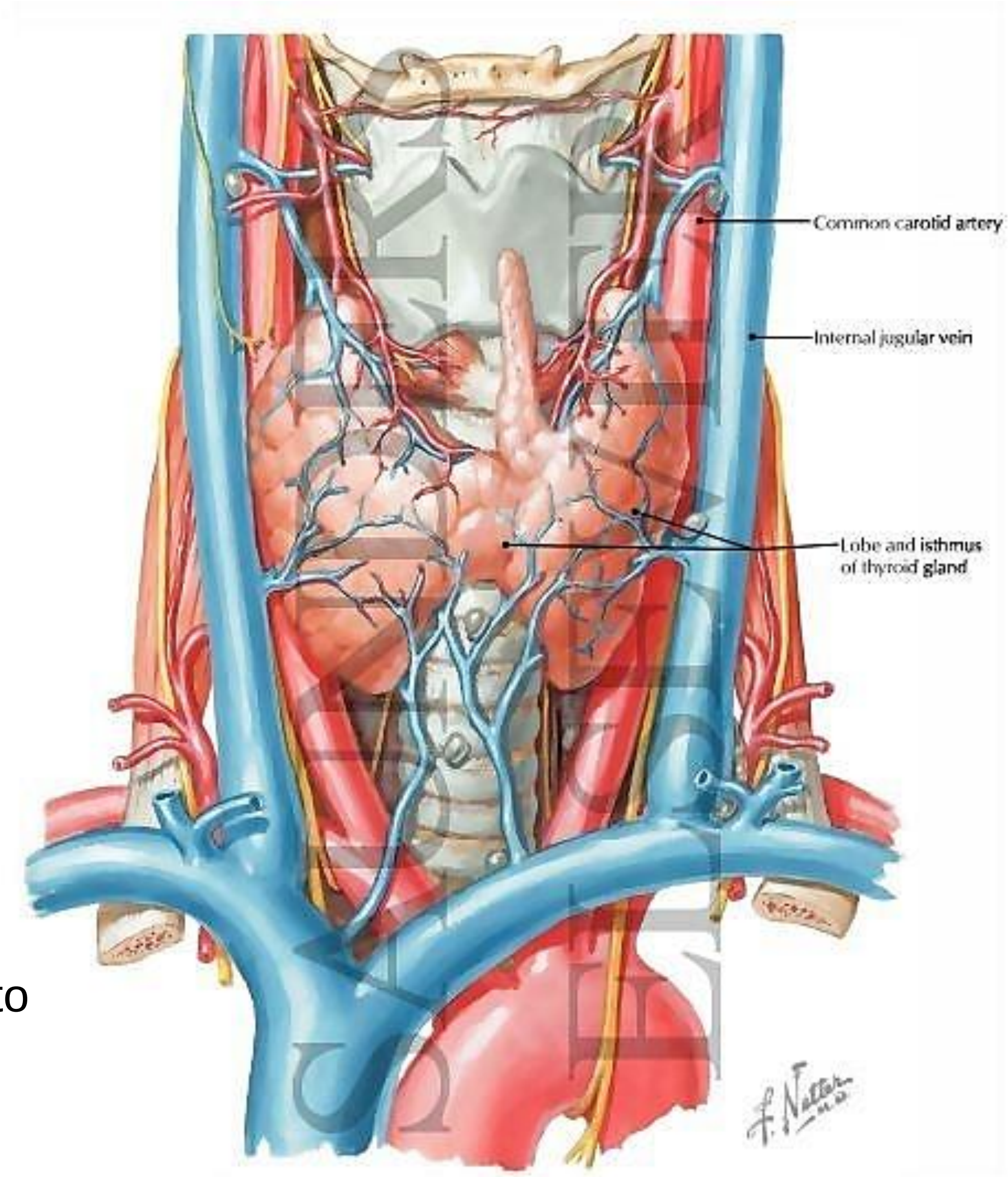
In the male, FSH stimulates **Sertoli cell** function in the seminiferous epithelium (synthesis of **inhibin**, **activin**, and **androgen-binding protein**). LH stimulates the production of **testosterone** by **Leydig cells**.

A lack of FSH and LH in females and males leads to **infertility**.



Thyroid gland

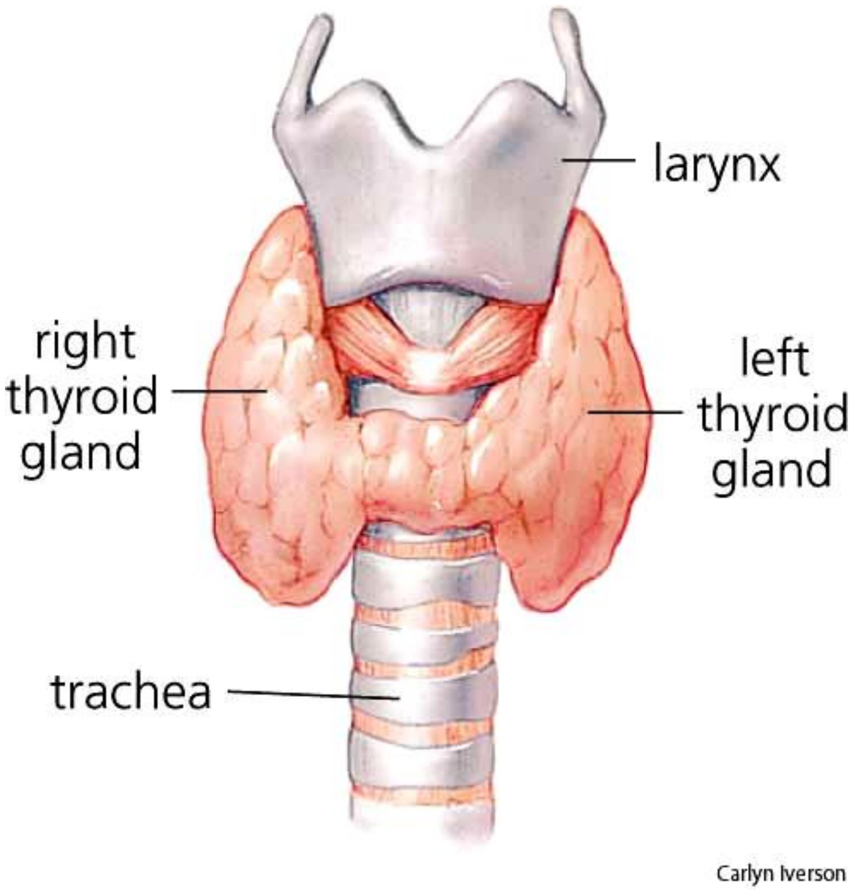
- **Blood supply**
  - **Superior thyroid artery**
    - ***From external carotid***
  - **Inferior thyroid artery**
    - ***From thyrocervical trunk***
- **Thin connective tissue capsule**
- **Two lobes connected by isthums**
- **Pyramidal lobe (40%) is a remnant of thyroglossal duct**
- **Secretory cells arranged into follicles**



The nerves supplying the laryngeal musculature (i.e., ***external laryngeal and recurrent laryngeal nerve***s) are closely applied to the thyroid gland and must be isolated and protected during **thyroidectomy**.
Damage to either of these two nerves results in hoarseness and, possibly, loss of speech.

Thyroid produces thyroxin (T4), triiodothyronin (T3) and calcitonin

- **outer capsule of loose CT and inner capsule of fibro-elastic tissue**
- **Capsule gives rise to fine collagenous septa breaking gland into lobules**
- **Secretory units are follicles that have inside colloid and one layer of epithelial=follicular cells called also thyreocytes**

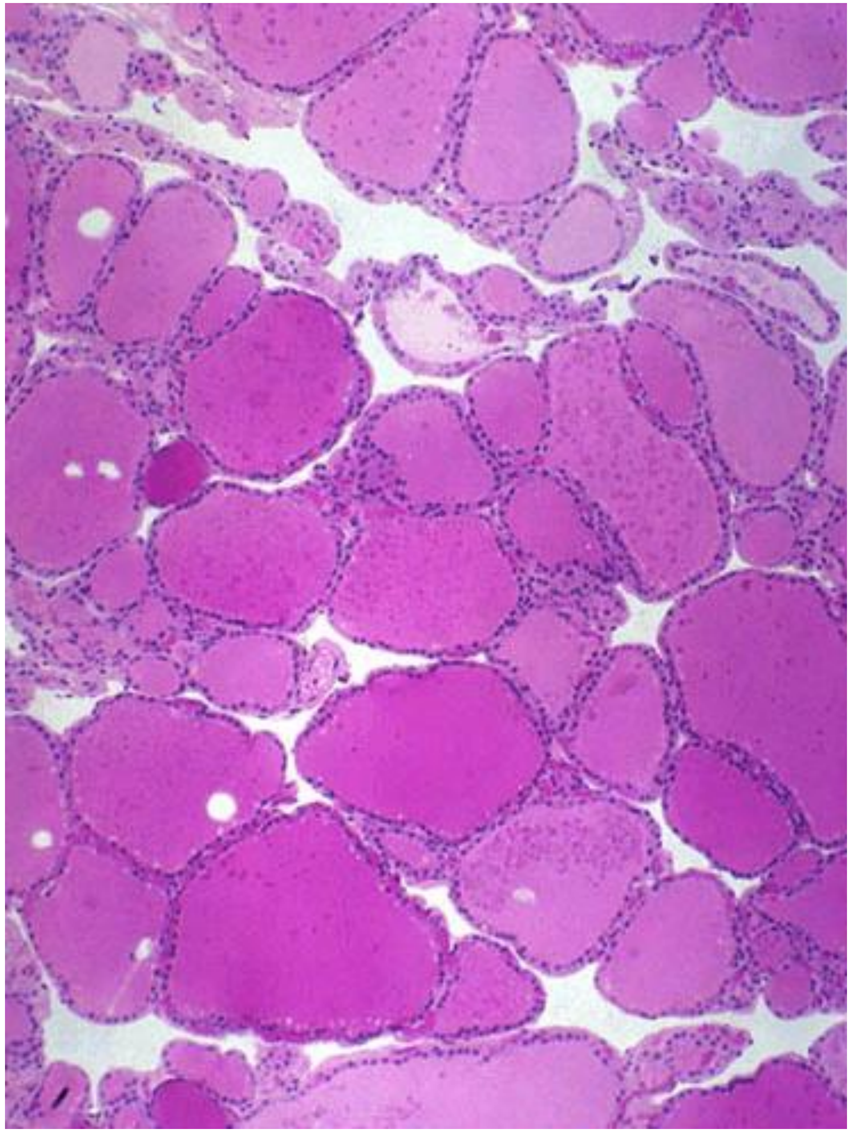


Thyroid Gland Histology

Follicular epithelium

- **Usually simple cuboidal**
- ***Height varies with functional state***
- **Have short microvilli**
- **Extensive RER, Golgi apparatus & lysosomes**
- **Produces thyroid hormones**
  - Thyroxine (T4)
  - Triiodothyronine (T3) and

Thyroglobulin is a major protein of the colloid that fills up the lumen of follicle



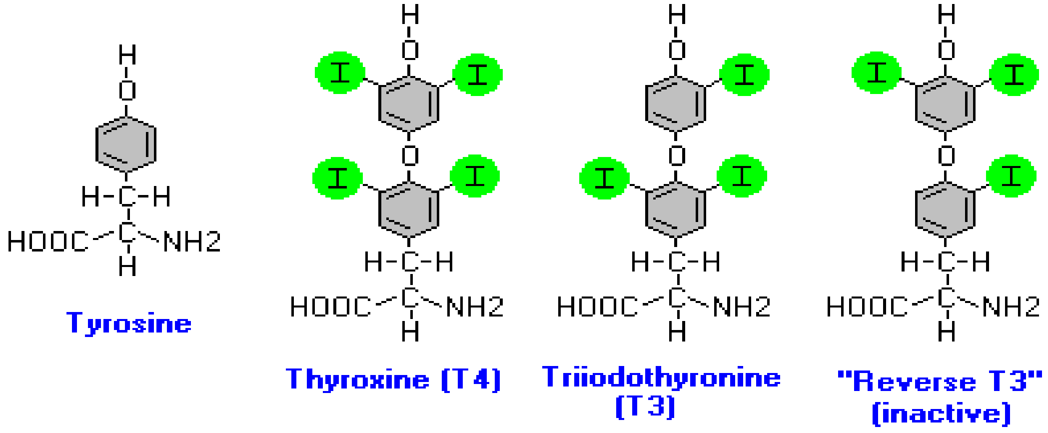
Histology Image Review: A complete illustrated review course in basic histology

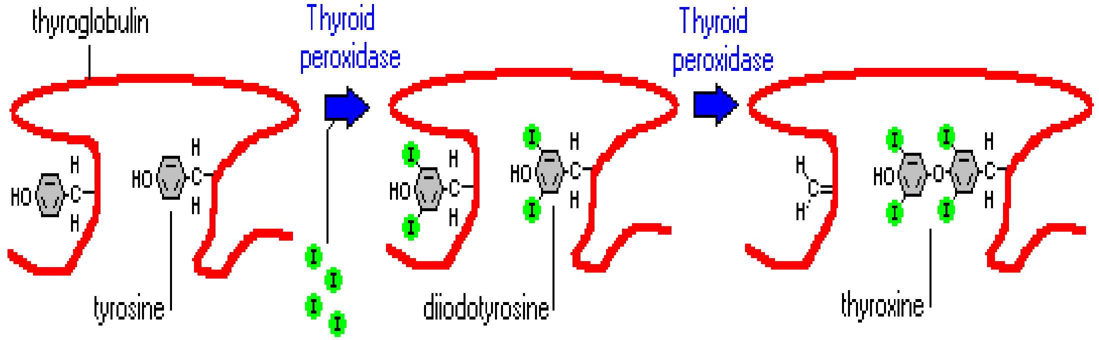
I = iodine; I^- = iodide

Iodine is reduced to iodide (I^-) within the alimentary canal and is preferentially absorbed and transported by the bloodstream to the thyroid gland.

Follicular cells produce two hormones that contain iodine:

- **tetraiodothyronine = T4 = thyroxine**
  - **contains 4 iodine atoms**
  - **T4 is converted to T3 in blood and tissues**
- **triiodothyronine = T3**
  - **contains 3 iodine atoms**
  - **far more potent (bioactive) than T4**



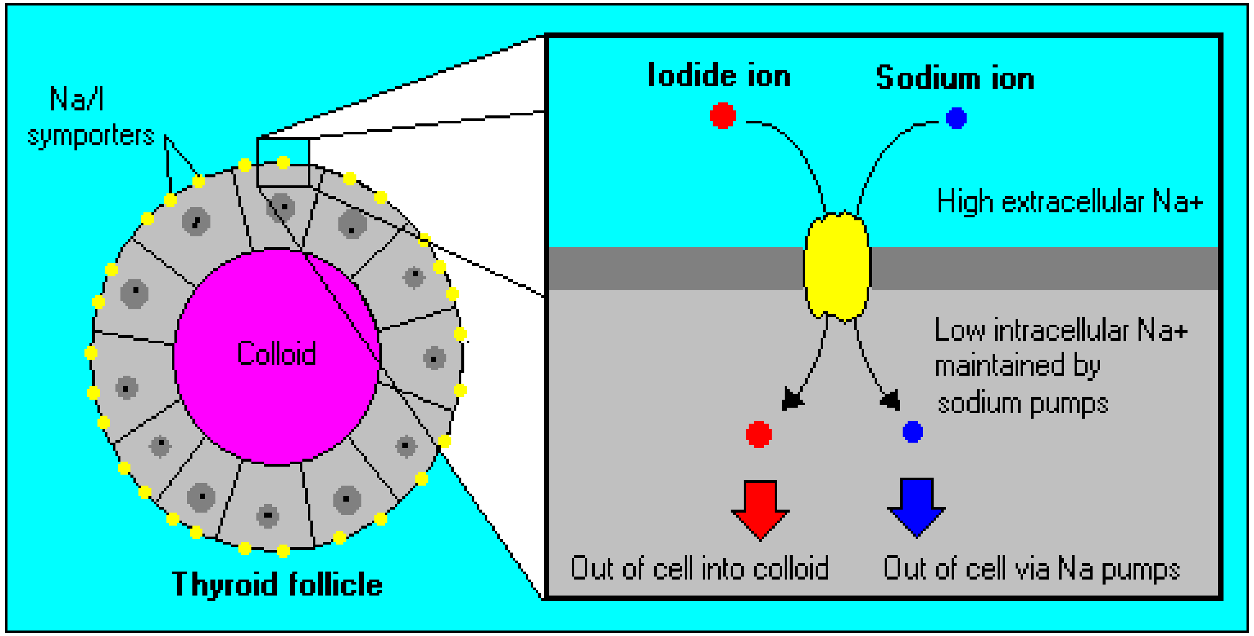


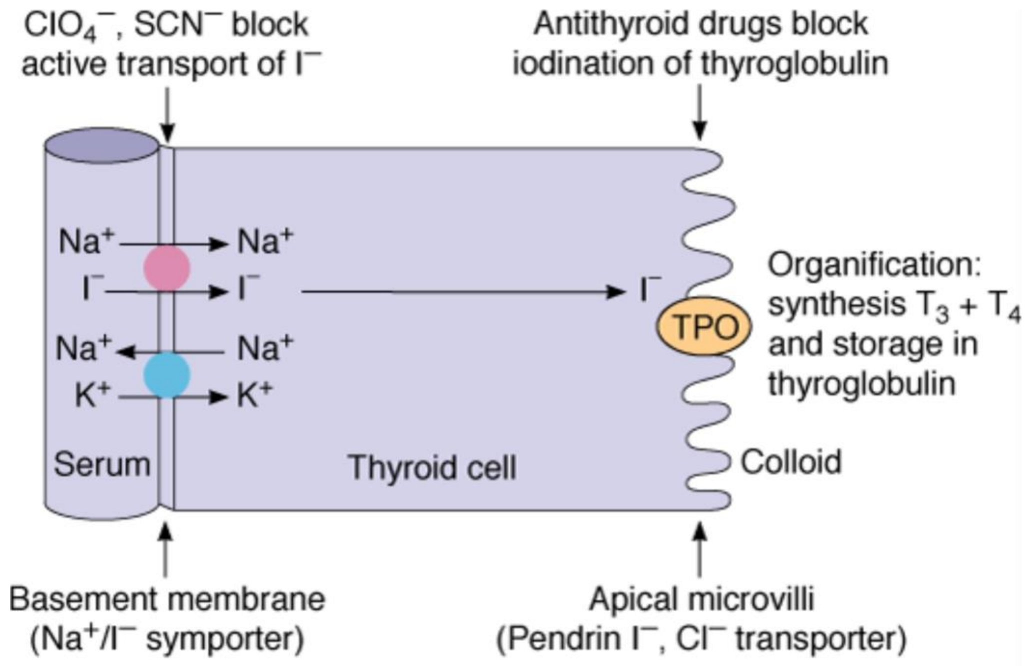
Thyroid peroxidase, TPO, present in the secretory granules together with thyroglobulin, and **activated at the apical plasma membrane**, catalyzes two sequential reactions:

- Iodination of tyrosines on thyroglobulin, and
- synthesis of thyroxine or triiodothyronine from two iodotyrosines.

From: Chapter 7. The Thyroid Gland: **The iodide transporter in the thyroid cell.**

Greenspan's Basic & Clinical Endocrinology, 9e, 2011





Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

The sodium-iodide symporter (NIS) simultaneously transports both Na^+ and I^- (iodide) ions from the extracellular fluid (i.e. blood) into the thryoid epithelial cell. This process is an example of secondary active transport. Energy is provided by the electrochemical gradient of Na+ across the cell membrane; the low intracellular concentration of Na+ is maintained by Na+K+ pump.

The large solid circle represents the Na+/I− symporter actively transporting I− into the cell; the large blue circle represents Na+-K+ ATPase supplying the ion gradient which drives the reaction. *I− is transported across the APICAL membrane into colloid space* by pendrin.

Hormone synthesis takes place in the colloid at the colloid-apical membrane interface, catalyzed by thyroperoxidase (TPO).

Iodine (J2) is reduced in gut's wall to **iodide** (**I-)** and transported by blood to reach the basal plasma membrane to be incorporated into thyrocyte by the NIS (sodium-iodide symporter) system.

1. Secretion of **TGB** (thyroglobulin) into colloid

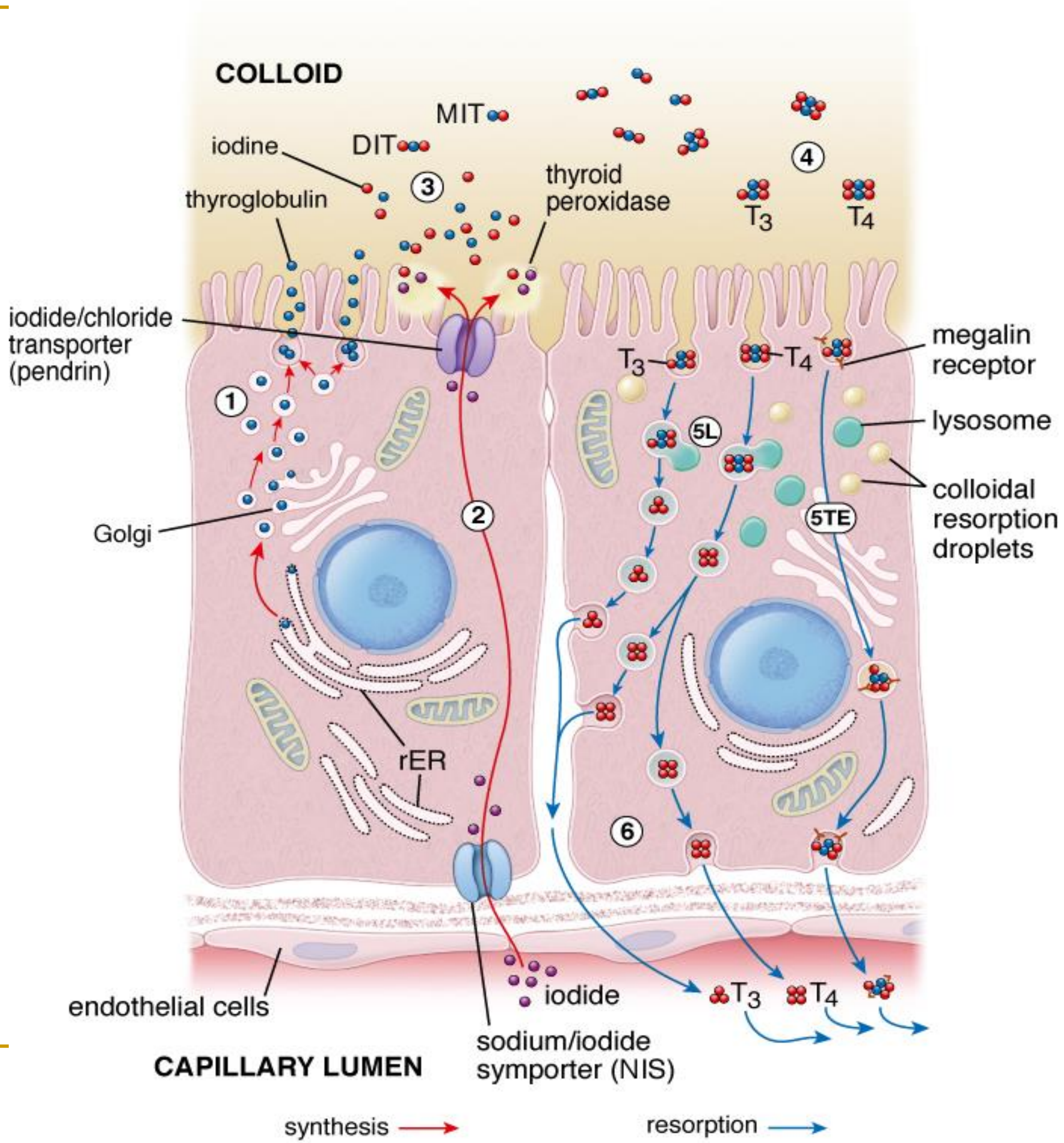
2. **Pendrin** transports **iodide** (**I-)** to apical membrane at colloid (TBG) interface

3. **Iodide is oxidized to iodine (J2)** by **TPO (**thyroid peroxidase) at apical plasma membrane and transported into follicular lumen

4. **TPO iodides tyrosine residues of TGB and catalyzes** T3 & T4 formation from iodothyrosines

5. **TGB endocytosis** leads to its degradation in lysosomes and as result

6. T3 and T4 are released from thyrocytes.



Pawlina, Histology, 2020

FUNCTIONS OF THE THYREOCYTE

LEFT

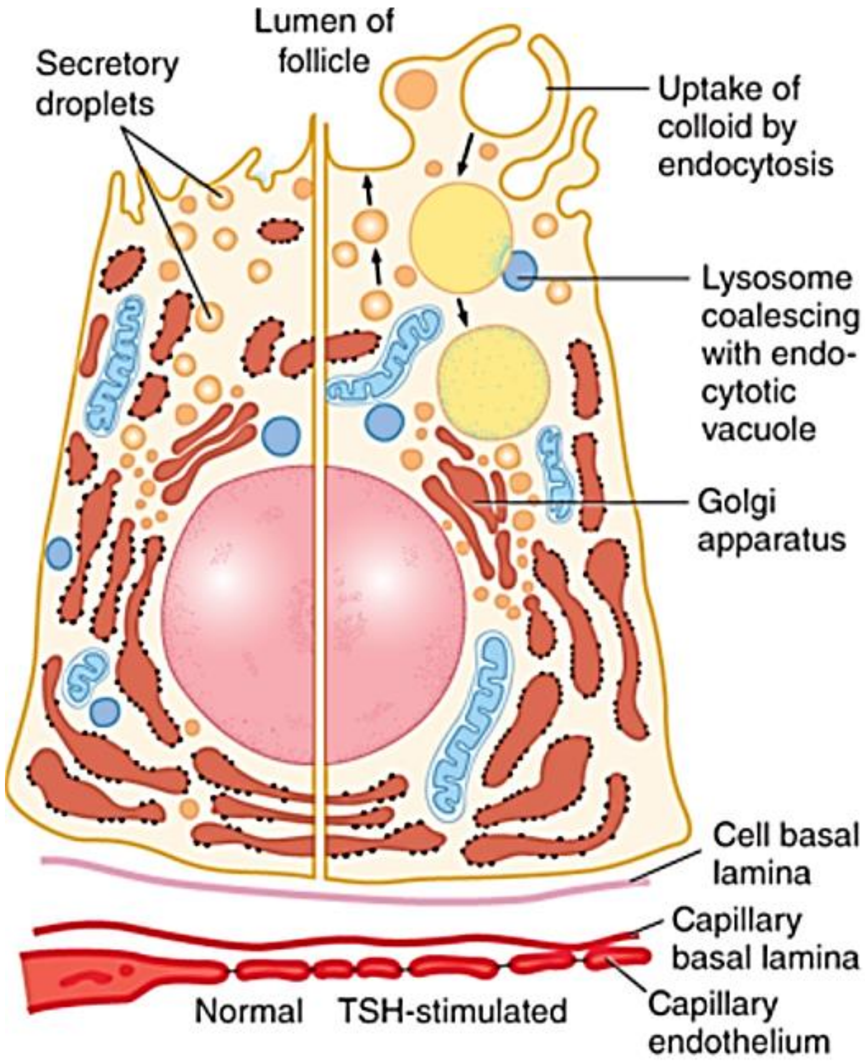
Synthesis and secretion of T3, T4 and thyroglobulin (TGB), protein of the colloid which binds and stores iodothyronines inside follicule.

RIGHT

Endocytosis of **thyreoglobulin** (TGB), its proteolysis in lysosomes and

release of T3 and T4 into blood.

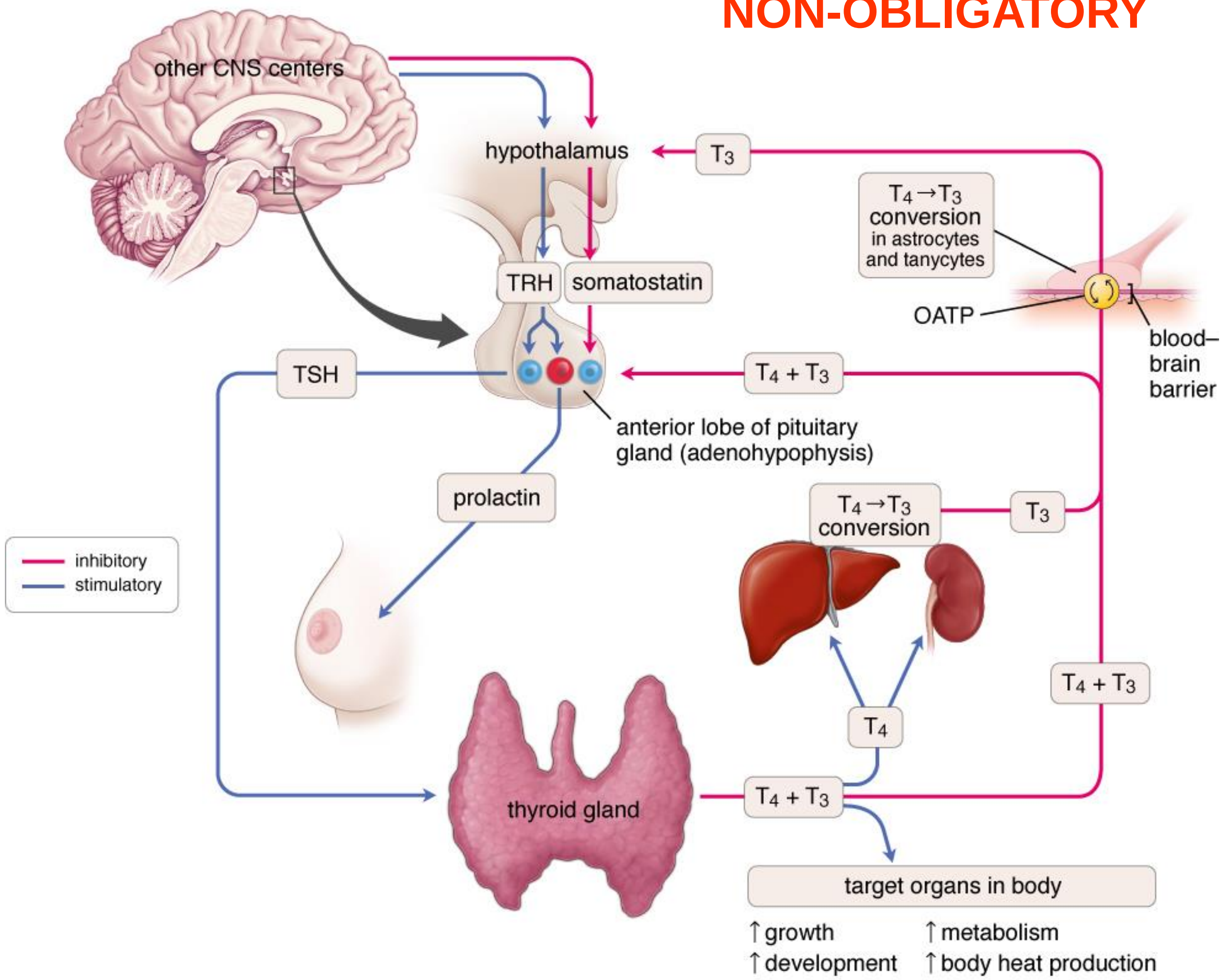
LEFT *RIGHT*



The arrows on the left show the secretion of thyroglobulin into the colloid. On the right, endocytosis of the colloid and merging of a colloid-containing vacuole with a lysosome are also shown.
The cell rests on basement membrane with nearby capillary with fenestrations in the endothelial wall.

Source: Kim E. Barrett, Susan M. Barman, Scott Boitano, Heddwen L. Brooks: Ganong's Review of Medical Physiolog
www.accessmedicine.com

Production, transport, and regulation of thyroid hormones



CNS, central nervous system; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone (thyrotropin); *OATP*, organic anion transporting polypeptides.

Pawlina W, Ross MH. Histology. 2020, 8th ed.

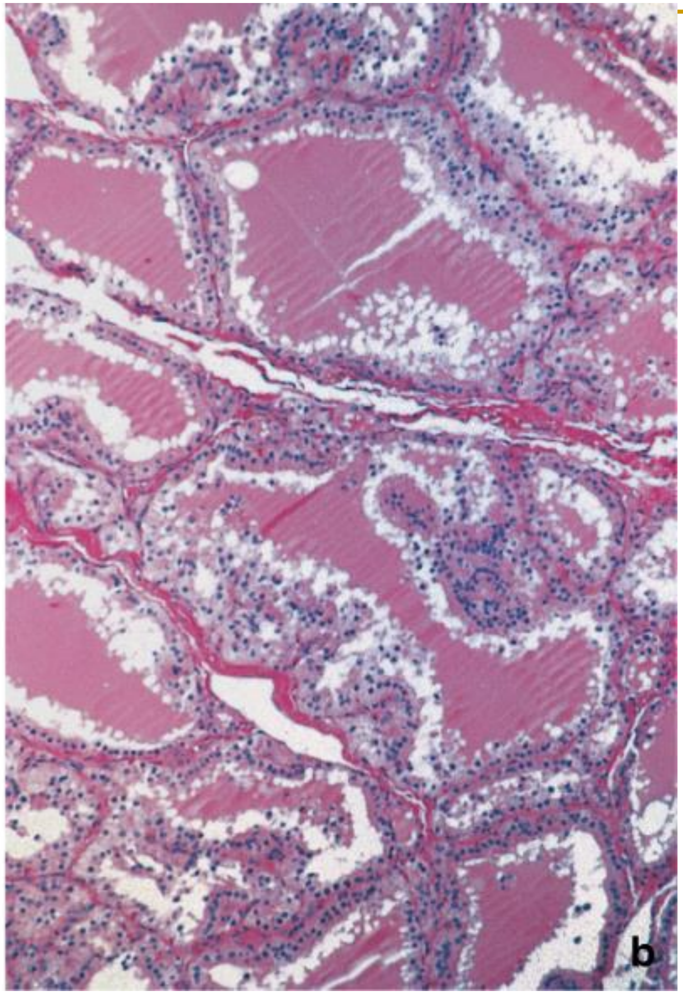
- Production of T_4 and T_3 is regulated through a **negative feedback system**. T_4 (the predominant product) is converted in the peripheral organs (e.g., liver, kidney) to a **more active form of T_3**.
- 99% of T_4 and T_3 released into the circulation bind to specific plasma proteins, while the unbound T_4 and T_3 exert negative feedback on the anterior lobe of the **pituitary gland** and the **hypothalamus**. T_4 and T_3 inhibit secretion of TSH by thyrotropes of the pituitary gland. To elicit an inhibitory effect on the hypothalamus, T_4 and T_3 need to cross the blood–brain barrier by utilizing the **OATP thyroid hormone transporter** expressed on the membrane of the endothelial cells. After crossing the blood–brain barrier, T_4 and T_3 are transferred into neighboring astrocytes, and then neurons. T_4 and T_3 are also secreted into the cerebrospinal fluid and are taken up by the tanycytes (specialized ependymal cells) and astrocytes, where T_4 is converted to T_3.
- In addition to **TRH**, which also stimulates production of prolactin in lactotropes, the hypothalamus secretes **somatostatin** that has an inhibitory effect on TSH production by thyrotropes.
- The feedback system is activated in response to **low thyroid hormone levels** in the blood or **metabolic needs**. In addition, a variety of **nerve endings in the hypothalamus** regulate secretion of TRH. For example, cold stress increases secretion of TRH, whereas increased body temperature inhibits TRH secretion.

A 32-year-old woman presents with fatigue and “eye strain” (Figure 227-1). She had been working as a secretary and noticed difficulty focusing her eyes. She said she was anxious and was having difficulty writing. She reported that her sister was taking medication for “thyroid trouble.”

A low thyroid-stimulating hormone (TSH) and an elevated free thyroxin level (T_4) were found on laboratory testing, and the patient was diagnosed with **Graves disease (GD)**. Her thyroid scan showed an enlarged thyroid with increased iodide uptake (Figure 227-2).

The patient chose radioactive iodine (RAI) as her treatment and her symptoms resolved. One year later she required levothyroxine treatment.

This patient displays the following common findings of Graves disease: Lid retraction and mild proptosis (*exophthalmos*), particularly evident on the left eye, and SIMPLE GOITER. (Courtesy of Dan Stulberg, MD.)



A young woman with **signs of hyperthyroidism**. Note the enlarged mass on the neck and the typical ocular symptoms known as ***exophthalmos*** and enlargment of the thyroid called **goiter**
b. Photomicrograph of a thyroid gland specimen from an individual with Graves disease. Due to the increased utilization of colloid, there is a ***lack of staining at the periphery*** of the colloid near the apical surface of the follicular cell. Note that the majority of the cells are columnar in shape.

MEDICAL APPLICATION 2

Graves disease is an autoimmune disorder in which IgG autoantibodies that bind to TSH receptors stimulate the follicular cells to synthesize and release of thyroid hormones. The disease is characterized by hyperplasia of the follicular cells, increasing the size of the thyroid gland two to three times above normal. T3 and T4 production is also greatly increased from 5 to 15 times normal **(hyperthyroidism)**. This results in a hypermetabolic state marked by weight loss, nervousness, sweating, heat intolerance, **exophthalmos** or protrusion of the eyeballs and other features.

MEDICAL APPLICATION 1

Insufficient dietary intake of iodine inhibits thyroid hormone production what results in the excessive production of TSH by thyrotrophs of the anterior pituitary gland.
This leads to excessive growth of thyroid follicles and enlargement of the thyroid gland, a condition known as **goiter**. Goiter usually is NOT associated with hyperthyroidism or hypothyroidism.
This condition can be treated with iodine in the diet, e.g. iodinated salt (NaCl).

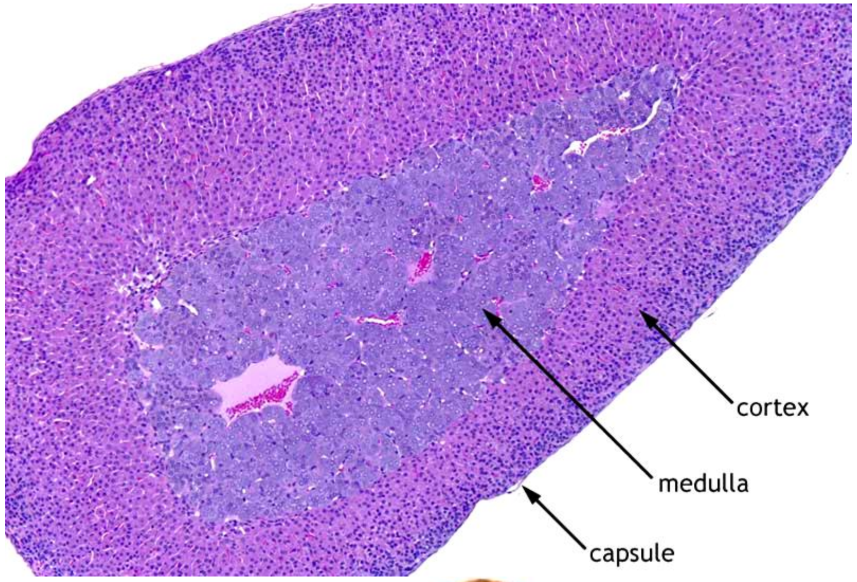
Adrenal gland

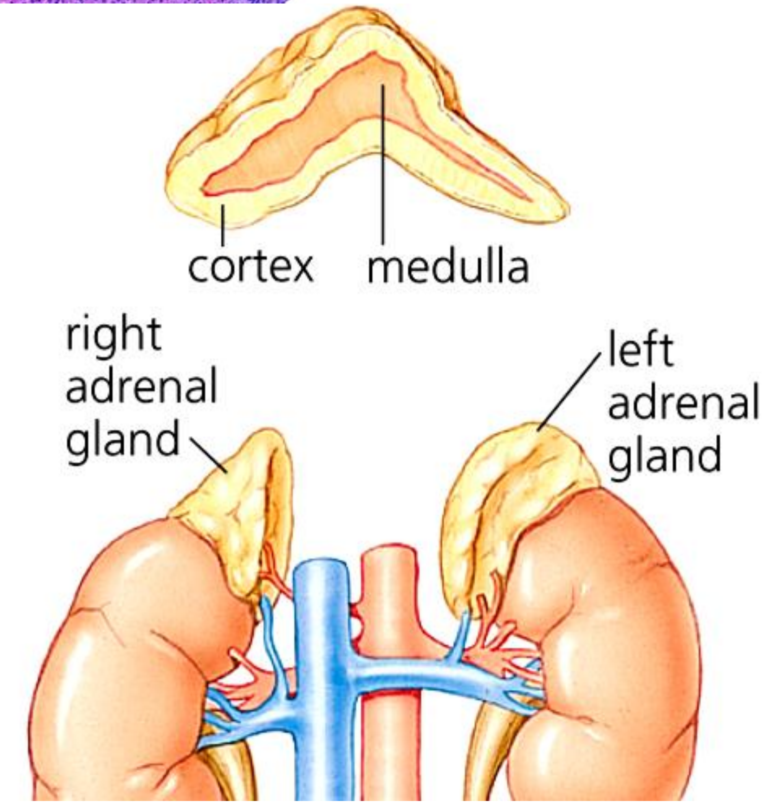
- Adrenal cortex
  - mesodermal origin
- Adrenal medulla
  - neuroectodermal origin

medulla contains

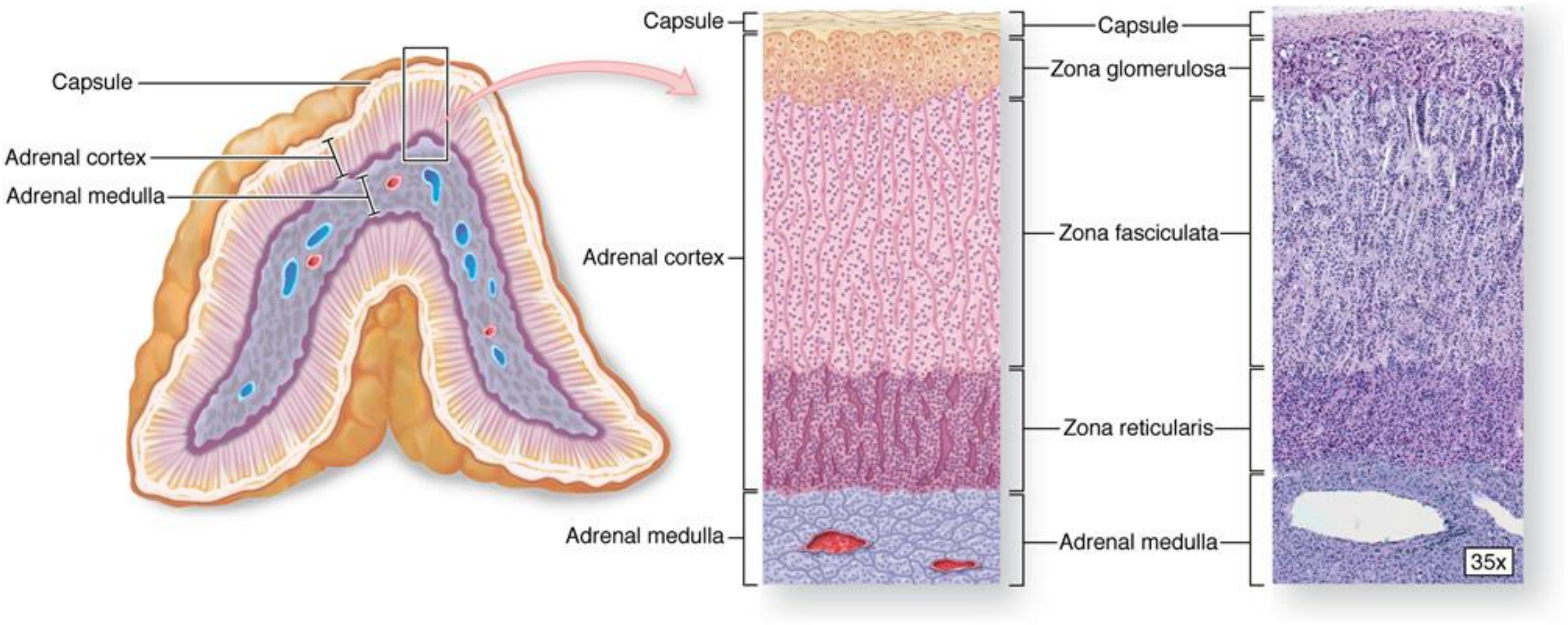
prominent central vein with many myocytes in its media

Kierszenbaum 2002





Adrenal gland. Inside the capsule of each adrenal gland is an adrenal cortex, formed from embryonic **mesodermal cells**, which completely surrounds an innermost adrenal medulla derived embryologically from **neural crest** cells. i.e. from **ectoderm**. Both regions are very well vascularized with fenestrated sinusoidal capillaries.



Basic Histology, 12th ed.

Adrenal Gland Blood Supply

- **Arterial flow:**

• Three suprarenal arteries derived from branches of inferior phrenic artery, abdominal aorta, and renal arteries

• Arteries branch into many small arteries that penetrate capsule

•**Subcapsular plexus forms short cortical arteries (arterioles)**

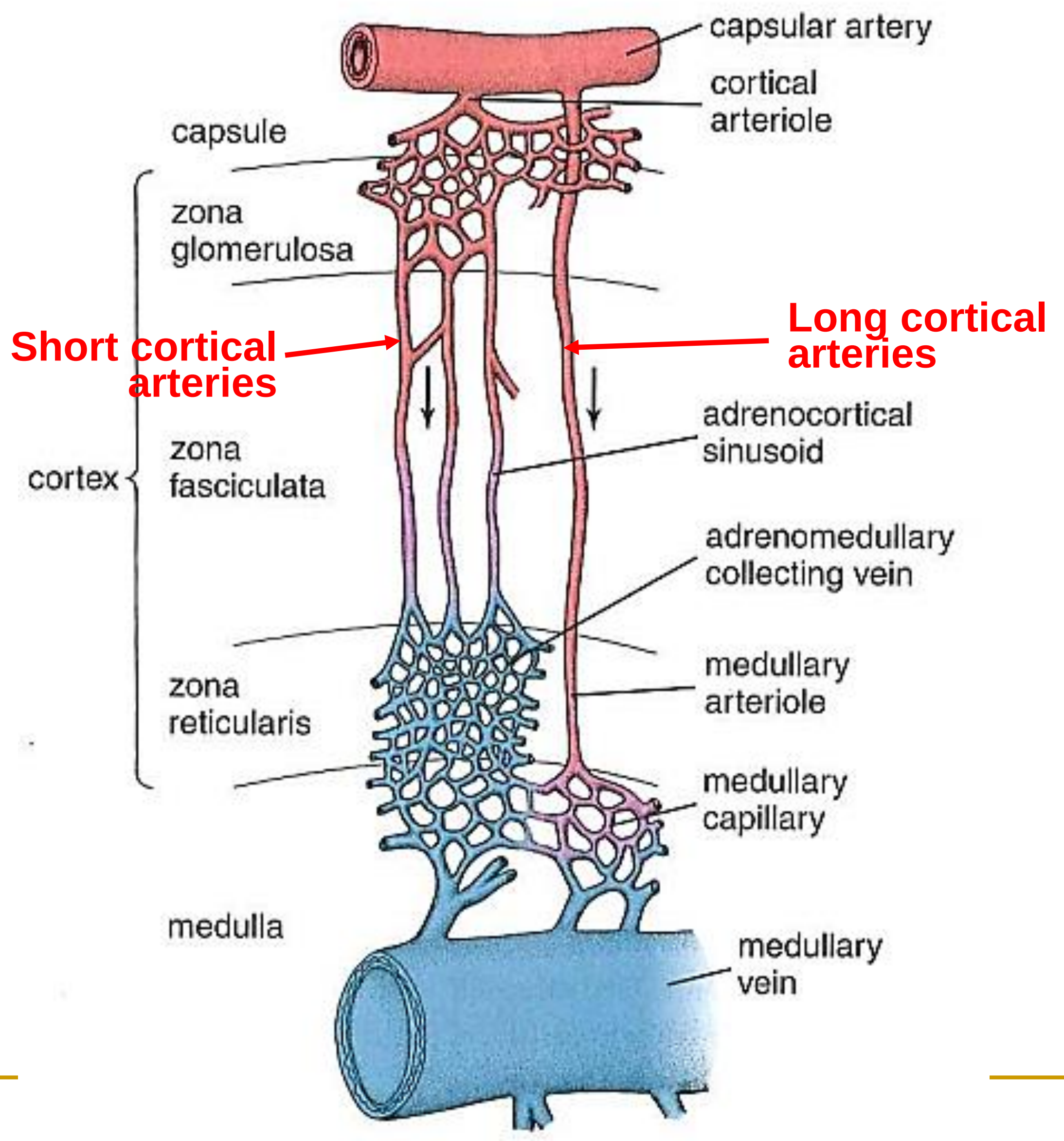
• **Sinusoidal capillaries** (fenestrated with diaphragms) deliver blood into medullary veins

• **Long cortical arteries** which bypass cortex without branching, supply blood to medulla which has, thus, ***a dual blood supply***

- **Venous drainage**

• medullary venous sinusoids join into small medullary veins which coalesce to form the large **one central medullary vein**

• Its tunica media contains longitudinally-oriented bundles of smooth muscles – regulation of the efflux of hormones

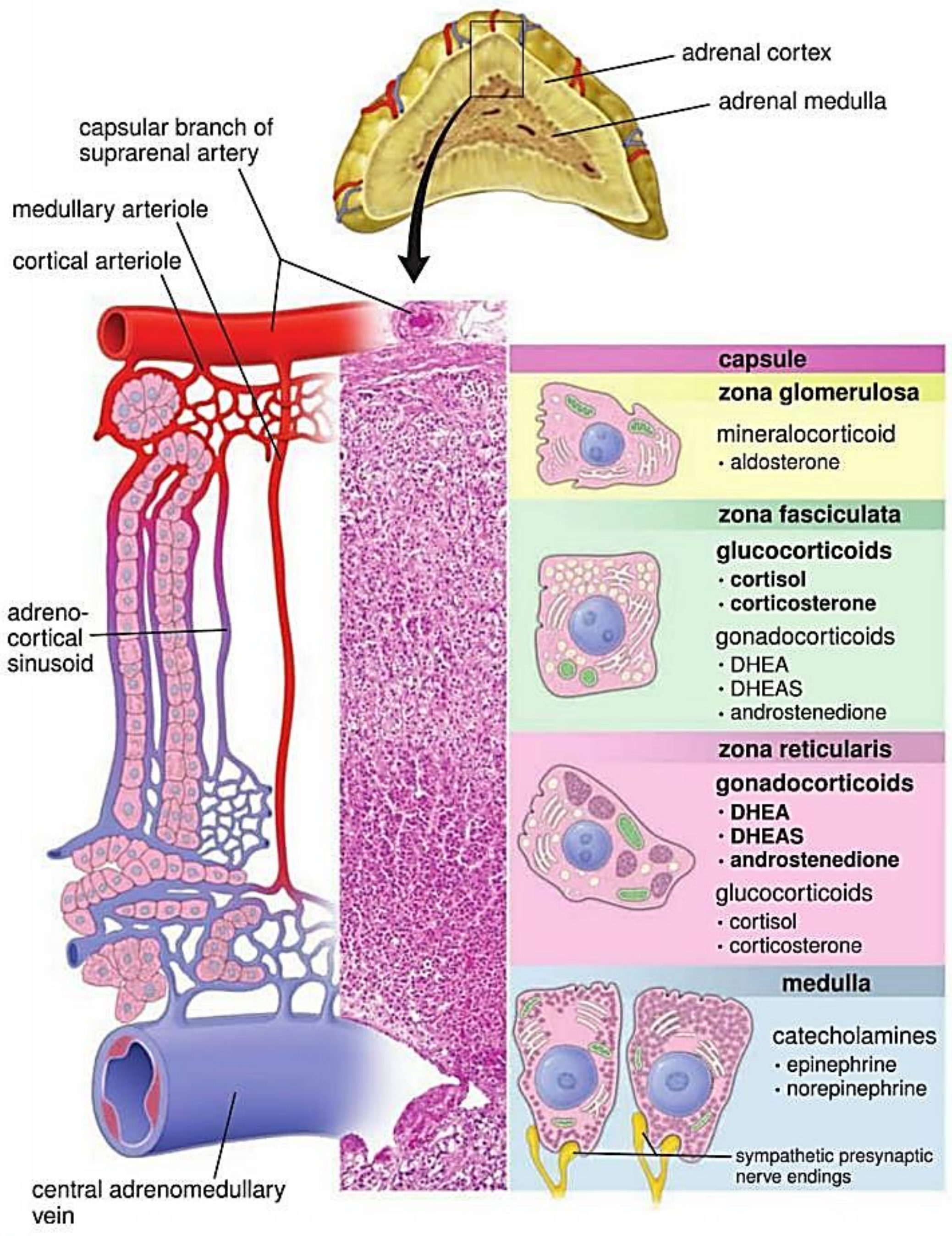


Ross 4th ed. Histology: a text and atlas

- **Cortex**
  The cortical arterioles form a cortical network of capillaries, which drain into a second capillary network in the medulla.
    - Zona glomerulosa
    - Zona fasciculata
    - Zona reticularis

Medulla

- In addition to the ***secondary capillary network*** formed by cortical veins, the medullary capillary network is formed primarily by the **medullary arterioles**.
- Blood drains into the **central medullary vein**.



"Histology: A Text

Adrenal cortex and its secretions

- steroid secretory cell: mitochondria with unusual tubular cristae, abundant SER

secretes steroid hormones

- structurally related to common precursor cholesterol
- regulated by ACTH released by the anterior hypophysis

- 3 structural and functional groups:
  - mineralocorticoids (aldosterone)
  - Glucocorticoids (cortisol, cortisone, corticosterone)
  - sex hormones (weak androgens, lack of testosterone and few estrogens

Hormones of the adrenal glands

NON-OBLIGATORY

Hormone	Composition	Source	Major Functions
Adrenal Cortex			
Mineralocorticoids: aldosterone (95% of mineralocorticoid activity in aldosterone)	Steroid hormones (cholesterol derivatives)	Parenchymal cells of the zona glomerulosa	Aid in controlling electrolyte homeostasis (act on distal tubule of kidney to increase sodium reabsorption and decrease potassium reabsorption); function in maintaining the osmotic balance in the urine and in preventing serum acidosis
Glucocorticoids: corticosterone and cortisol (95% of glucocorticoid activity is in cortisol)	Steroid hormones (cholesterol derivatives)	Parenchymal cells of the zona fasciculata (and to a lesser extent of the zona reticularis)	Promote normal metabolism, particularly carbohydrate metabolism (increase rate of aa. transport to live, promote removal of protein from skeletal muscle and its transport to liver, reduce rate of glucose metab. by cells and stimulate glycogen synthesis by liver, stimulate mobilization of fats from storage deposits for energy use); provide resistance to stress; suppress inflammatory response and some allergic reactions
Gonadocorticoids (androgens): **dehydroepiandrosterone (DHEA), dehydroepiandro-sterone sulfate (DHEAS), and androstenedione** (produced in both men and	Steroid hormones (cholesterol derivatives)	Parenchymal cells of the zona reticularis (and to a lesser extent of the zona fasciculata)	As weak androgens, they induce development of axillary and pubic hair at puberty in women; cause masculinizing effect; at normal serum levels, usually their function is insignificant
Norepinephrine and **epinephrine** (in humans, 80% epinephrine)	Catecholamines (amino acid derivatives)	Chromaffin cells	Sympathomimetic (effects similar to those induced by the sympathetic division of the autonomic nervous system); increase heart rate, increase blood pressure, reduce blood flow to viscera and skin; stimulate conversion of glycogen to glucose; increase sweating; induce dilation of bronchioles; increase rate of respiration; decrease digestion; decrease enzyme production by digestive system glands; decrease

Pawlina W, Ross MH. Histology: A text and atlas with correlated cell and molecular biology. 2020, 8th ed.

Adrenal Cortex Layers

▪*Zona glomerulosa* (glomerular layer)

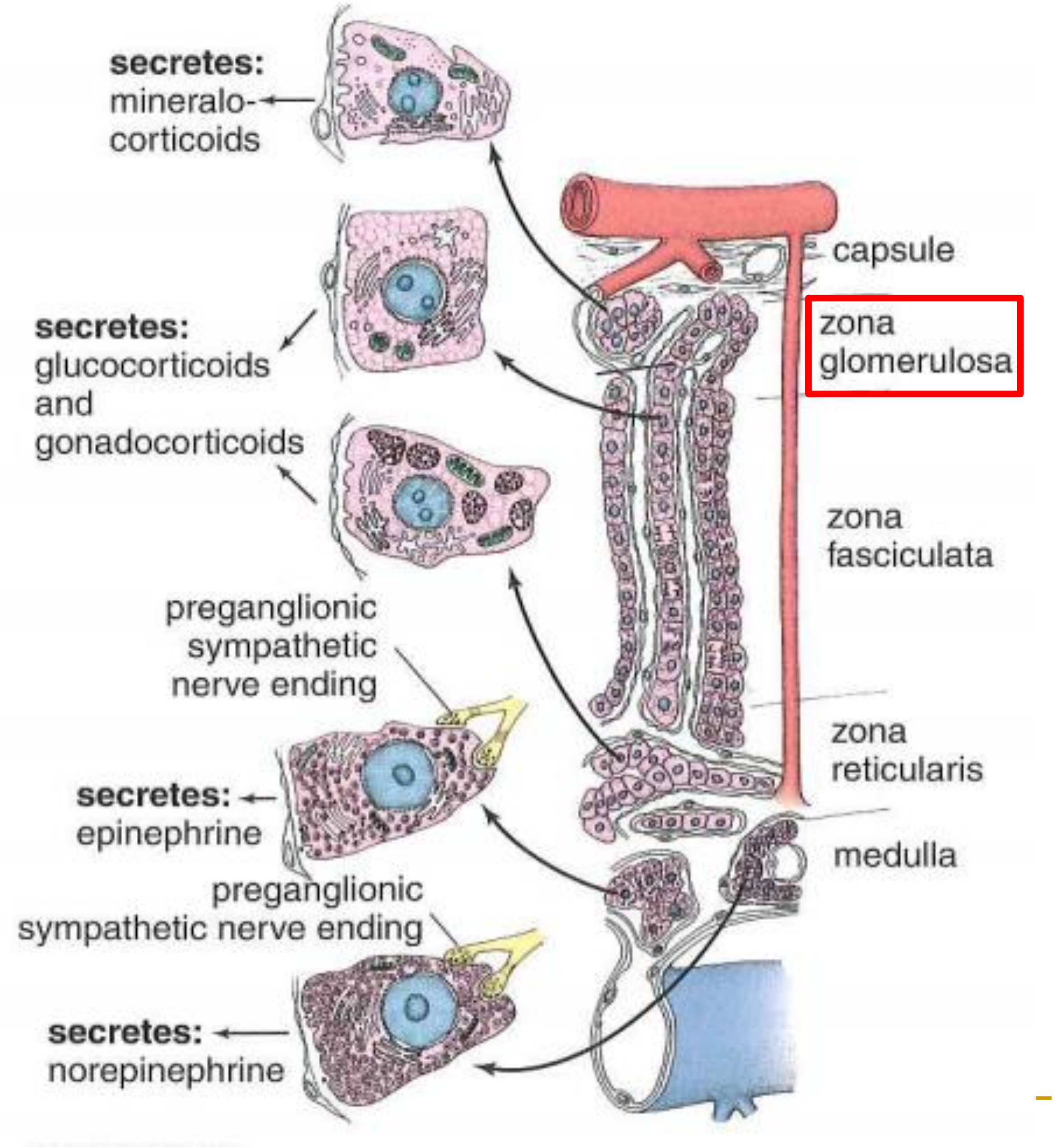
• Cells below the capsule are grouped in ovoid configuration (semi-acinar)

• Produces aldosterone and other mineralocorticoids

- Synthesized in response to angiotensin II and ACTH and increased K+

- Increases water and sodium resorbtion in distal and connecting tubules of kidney

- Increases blood volume and blood pressure



Ross 4th ed. Histology: a text and atlas

Zona fasciculata of adrenal cortex (fascicular layer)

makes up 65% of the cortex volume,

polyhedral cells are arranged in cords (radial columns that are separated by sinusoidal capillaries

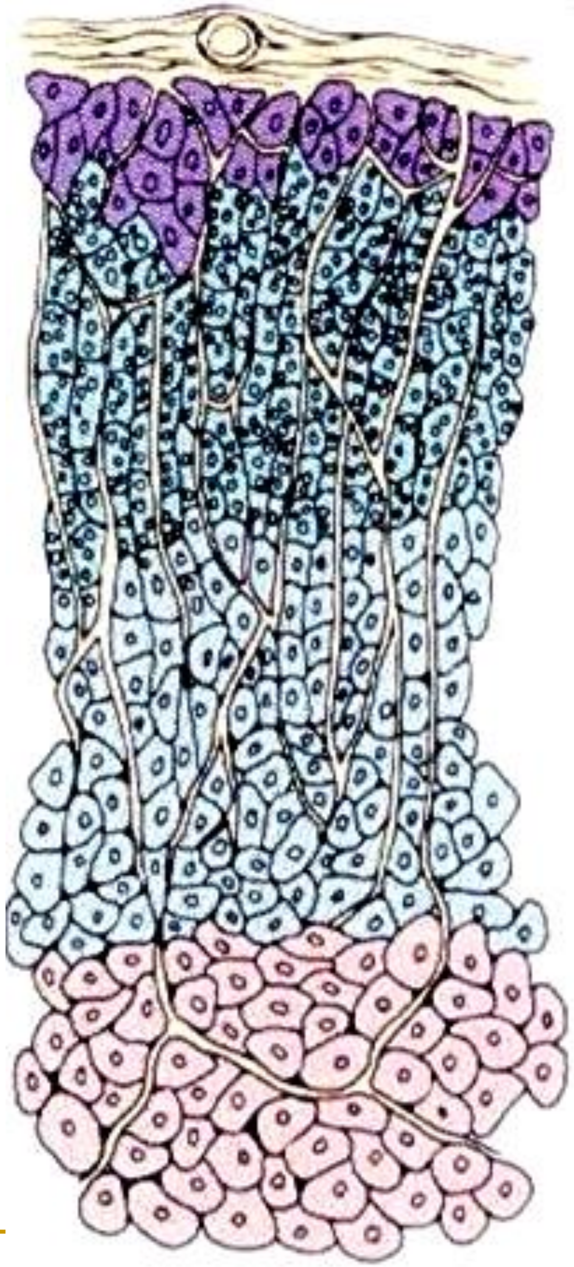
Lipid droplets are common in these cells

Produces glucocorticoids (cortisol) that:

- Increase metabolic availability of glucose and fatty acids to cells
- Supresse inflammatory and immune responses

Secretion controlled by ACTH released from adenohypophysis

Cells secrete also weak androgens (DHEA = dehydroepiandrosterone)

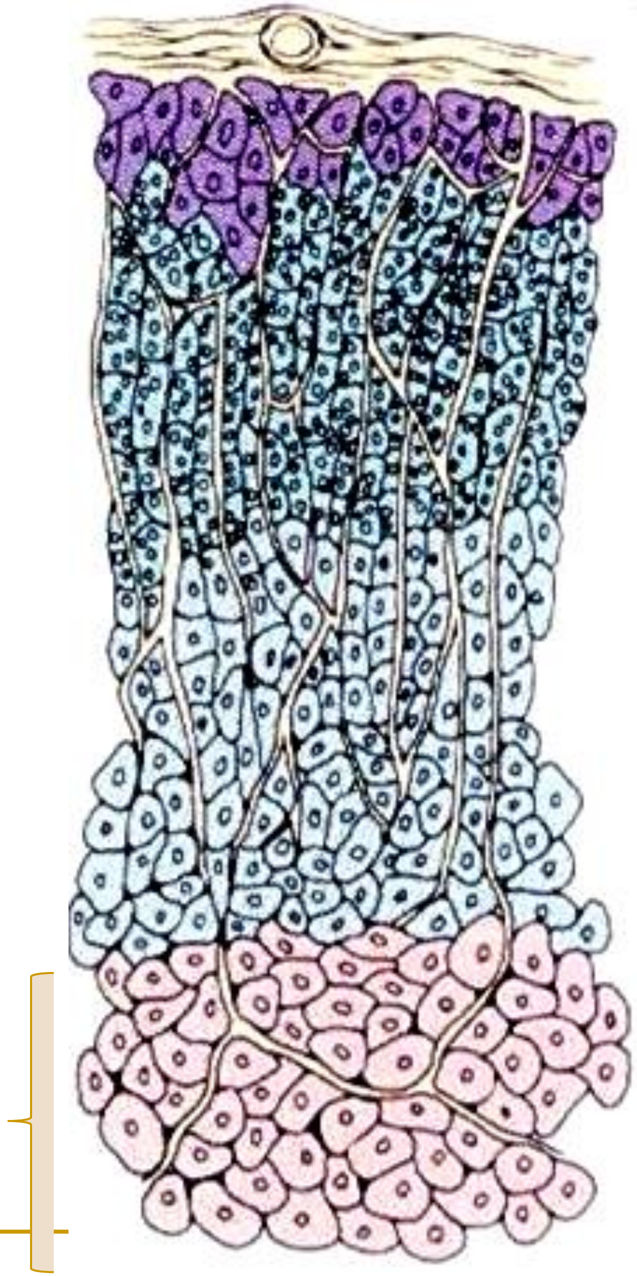


Ross 4th ed. Histology: a text and atlas

Zona reticularis **of adrenal cortex (reticular layer)**

Cells are arranged in irregular cords forming anastomosing networks, the smallest cells of the cortex, contain lipofuscin pigment granules

Stimulated by ACTH secrete cortisol & weak androgens (DHEA) as well as few estrogens

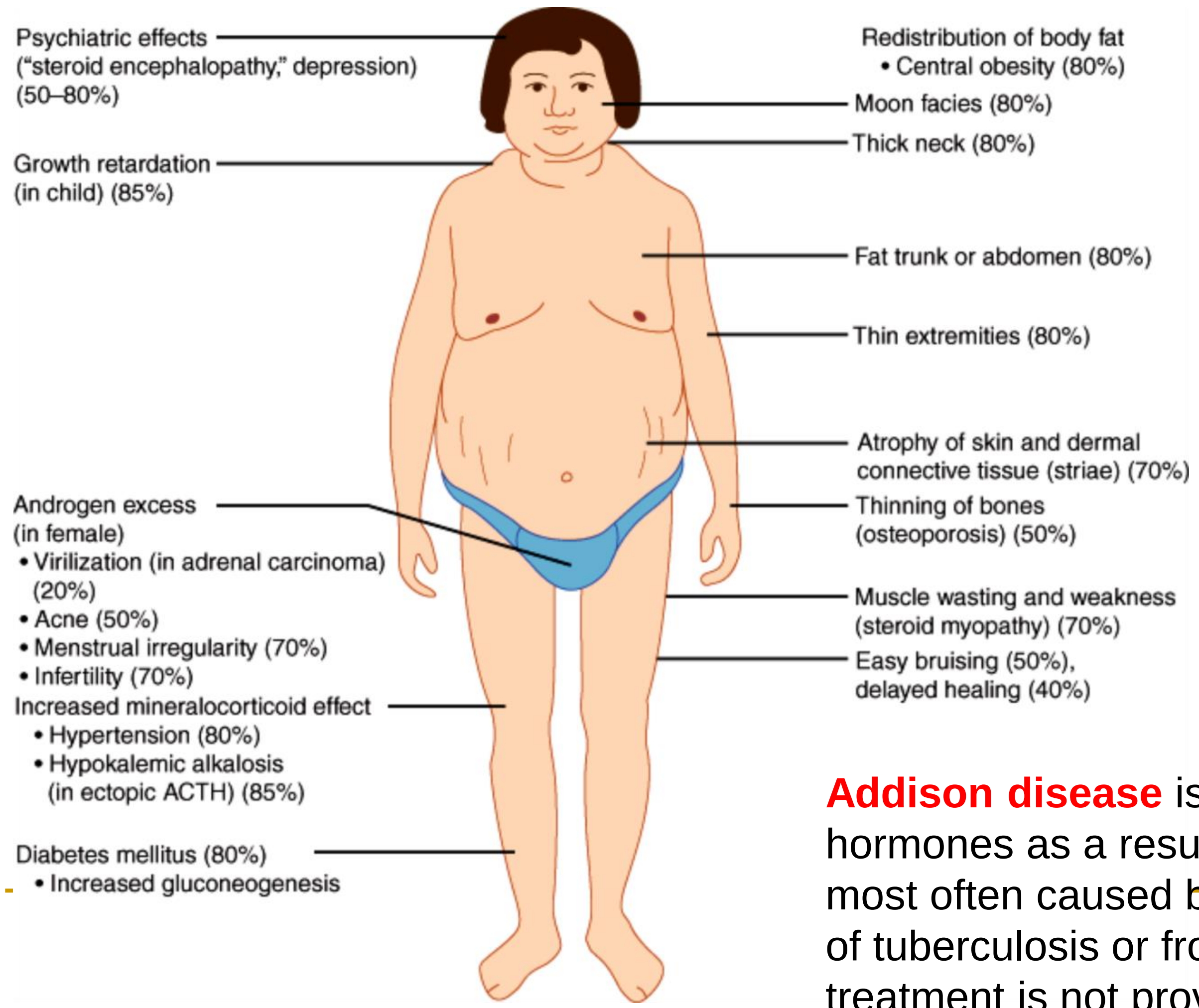


From: Disorders of the Adrenal Cortex: **Typical findings in Cushing syndrome / disease.**

Pathophysiology of Disease: An Introduction to Clinical Medicine, 7e, 2013

NON-OBLIGATORY

Cushing syndrom is caused by the **hypertrophy of adrenal cortex**, usually resulting from the presence of non-malignant tumor – ***adenoma***, or from ***chronic therapy*** with glucocorticoids such as prednison and its derivates.
Cushing disease is caused is caused by **excessive secretion of ACTH** by adenoma of anterior pituitary gland. Clinical symptoms are similar as in Cushing syndrom.



Some characteristic features of Cushing's syndrome — moon face, hirsutism (‚beard' in women), and acne (inflammation of sebaceous glands).

Men become impotent, and women have amenorrhea.

Addison disease is characterized by decreased secretion of the adrenocortical hormones as a result of ***destruction of the suprarenal cortex***. This disease is most often caused by an autoimmune process; it also can develop as a sequela of tuberculosis or from some other infectious diseases. Death occurs if steroid treatment is not provided.

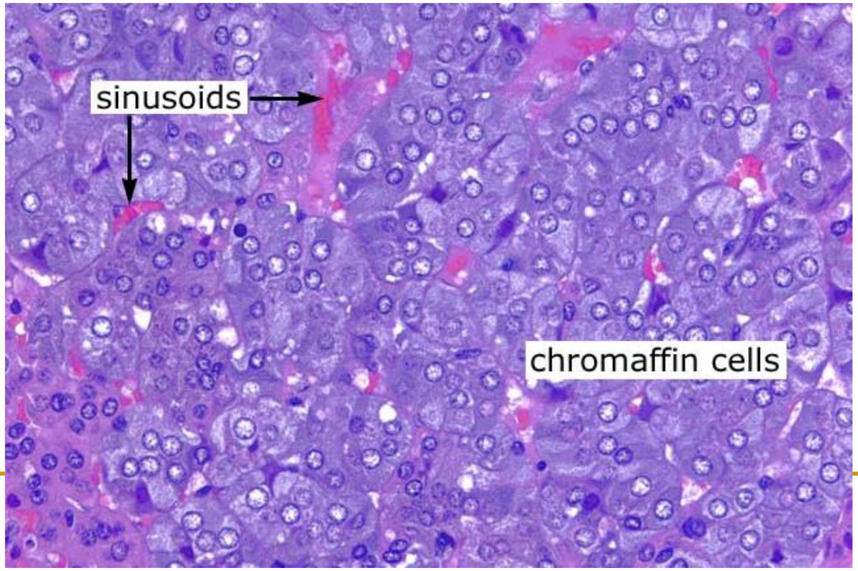
Adrenal medulla is surrounded by adrenal cortex

Cells are arranges in cords around medullary sinusoids, derivates of neural crest

Chromaffin cells ("chrome-affinity") cells are major cell type. They release catecholamine hormones

- **adrenaline (epinephrine, E, with N-methyl group)**
- **noradrenaline (norepinephrine, NE, lacking methyl group)**

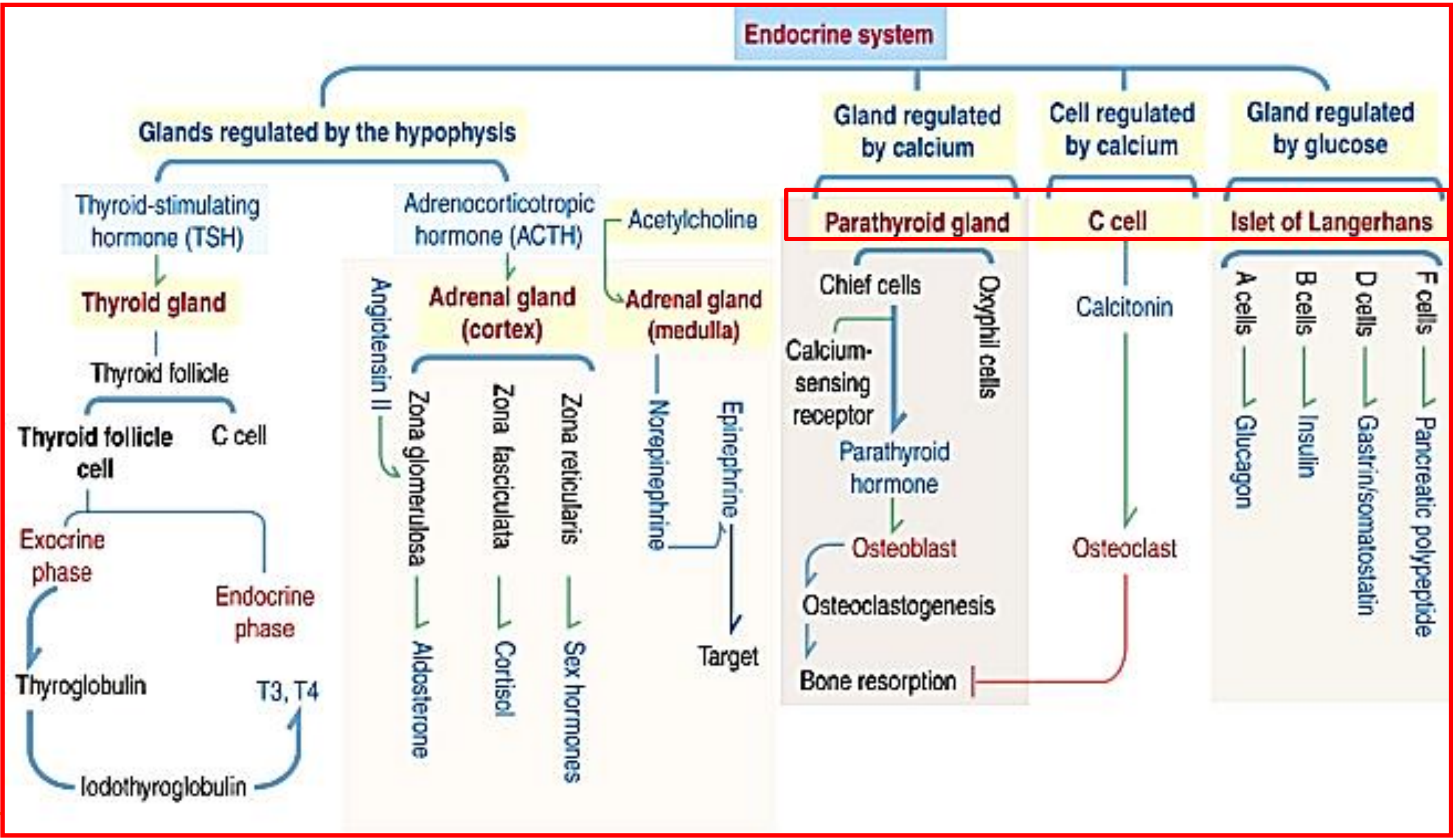
- **large, granular nuclei, extensive, strongly basophilic cytoplasm**
- **These post-ganglionic neuroendocrine cells are innervated by preganglionic sympathetic neurons** which release acetylocholine as nurotransmitter)
- **Hormones are stored in secretory granules**, together with Ca^{2+} and ATP, and are bound with 49-kDa proteins called **chromogranins.**
- **NE and E are released in response to nervous stimulation**



MEDICAL APPLICATION

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

Which extrapituitary hormonal glands are NOT dependent on the control by pituitary?

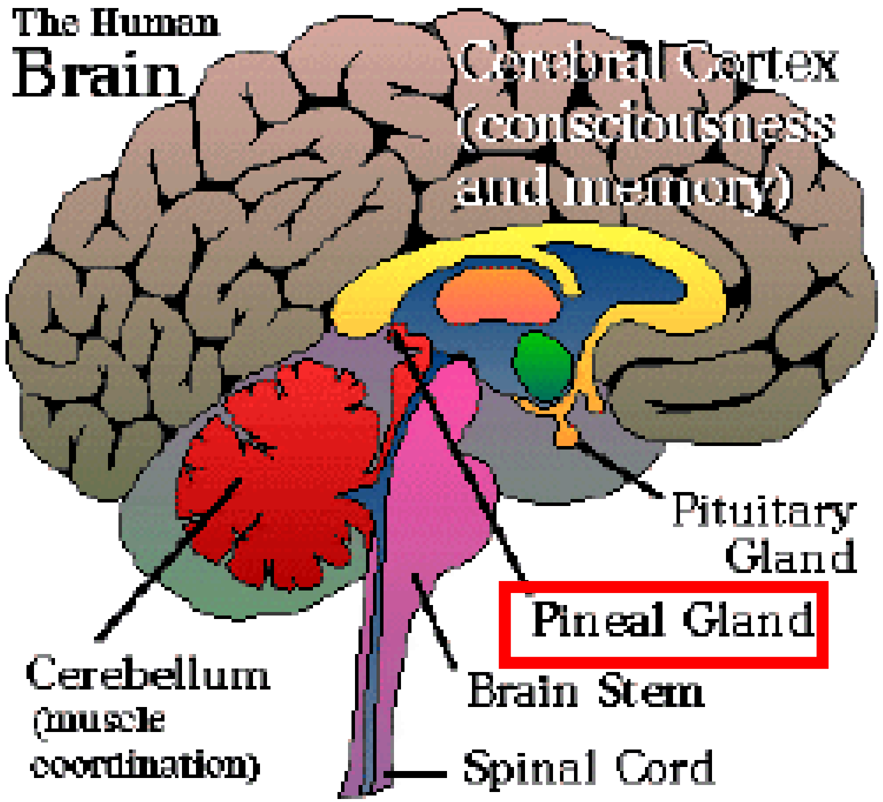


Kierszenbaum. 2002

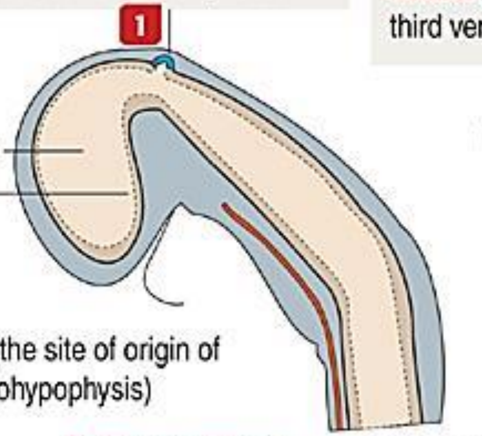
Pineal gland = ***epiphysis cerebri*,** **develops from neuroectoderm of the posterior portion of the roof of diencephalon**

a small, pine cone-like endocrine gland located near the center of the brain

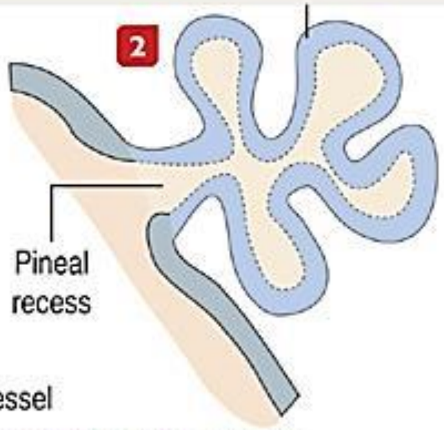
- **connected to brain via short stalk that contains nerve fibers** (indirectly from the hypothalamic suprachiasmatic nucleus via sympathetic fibers of the cervical superior ganglion)
- **pinealocytes (pineal chief cells) produce melatonin** and glial-like **interstitial cells** (5%) support them with long processes
- **pinealocytes are highly modified neurons arranged in clumps and cords surrounded by rich network of fenestrated capillaries**
- **myelinated sympathetic nerve fibers enter and ramify as unmyelinated axons inside the gland**



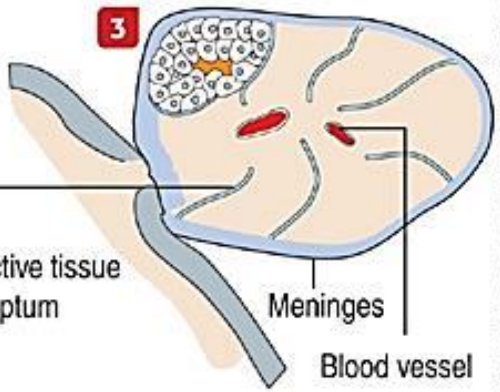
1 A dorsal diverticulum, an outpocketing of the diencephalon, initiates the formation of the pineal gland during the 10th week of development.

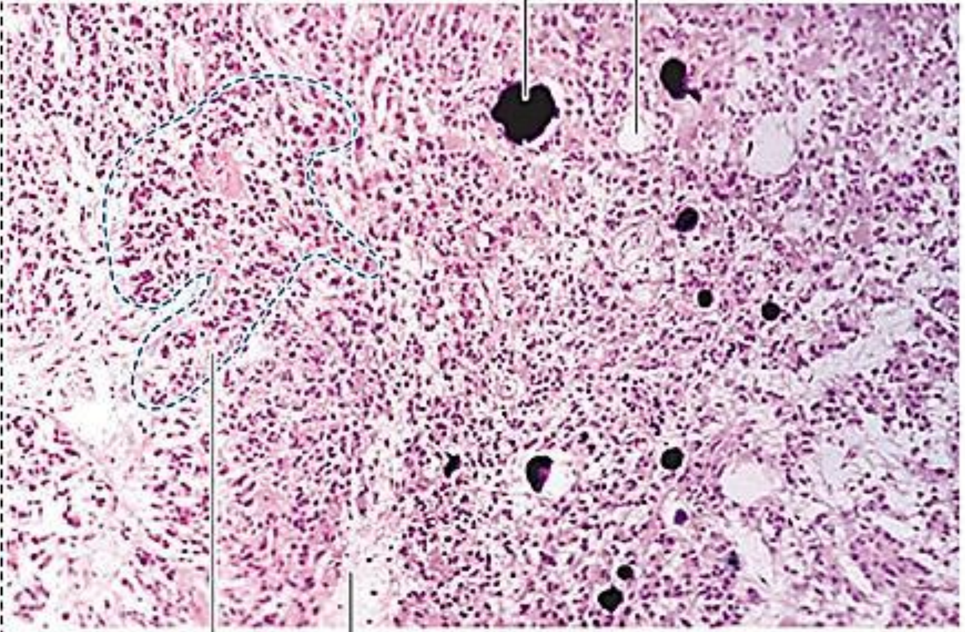


2 The wall of the vesicular evagination thickens. The lumen is occluded, except at the base of the outpocketing, where the **pineal recess** persists and communicates with the third ventricle in the adult.



3 The pineal gland becomes a compact structure containing two cell types derived from the primordial neuroepithelial cells: (1) pinealocytes; and (2) glial-like interstitial cells. Meninges envelop and invade the developing pineal gland, forming **connective tissue septa**.





The pineal gland

The pineal gland (so-called because it resembles a pine cone) consists of **melatonin-secreting pinealocytes** arranged in solid cords enclosed by processes derived from the **glial-like interstitial cells**. Cell processes projecting from the pinealocytes surround the blood vessels.

A typical feature of the histology of the pineal gland is the presence of calcium deposits, called **corpora arenacea** ("brain sand"), found in the extracellular space.

The nerve input to the pineal gland is from the **postganglionic sympathetic nerve fibers** derived from the **superior cervical ganglion**.

Pineal gland secretes melatonin at nighttime to regulate daily biological rhythms

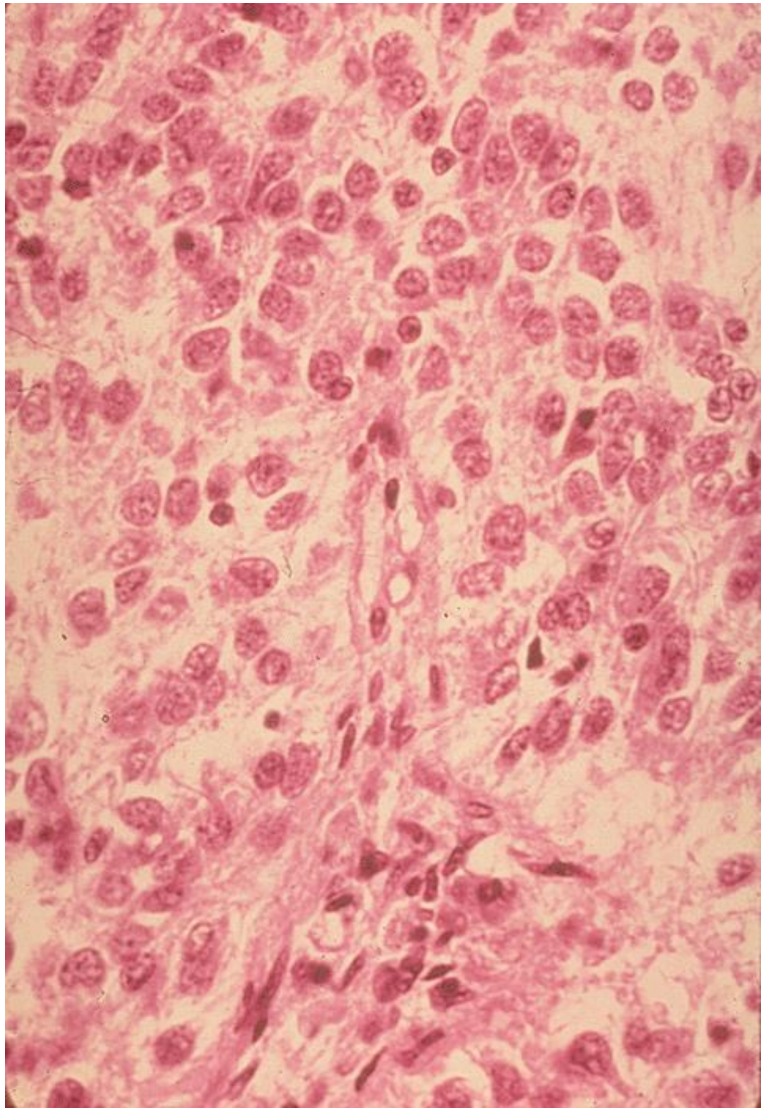
- **Melatonin**

• Regulates daily body rythms

• Antigonadotrophic in animals (*inhibits GnRH secretion from hypothalamus)*

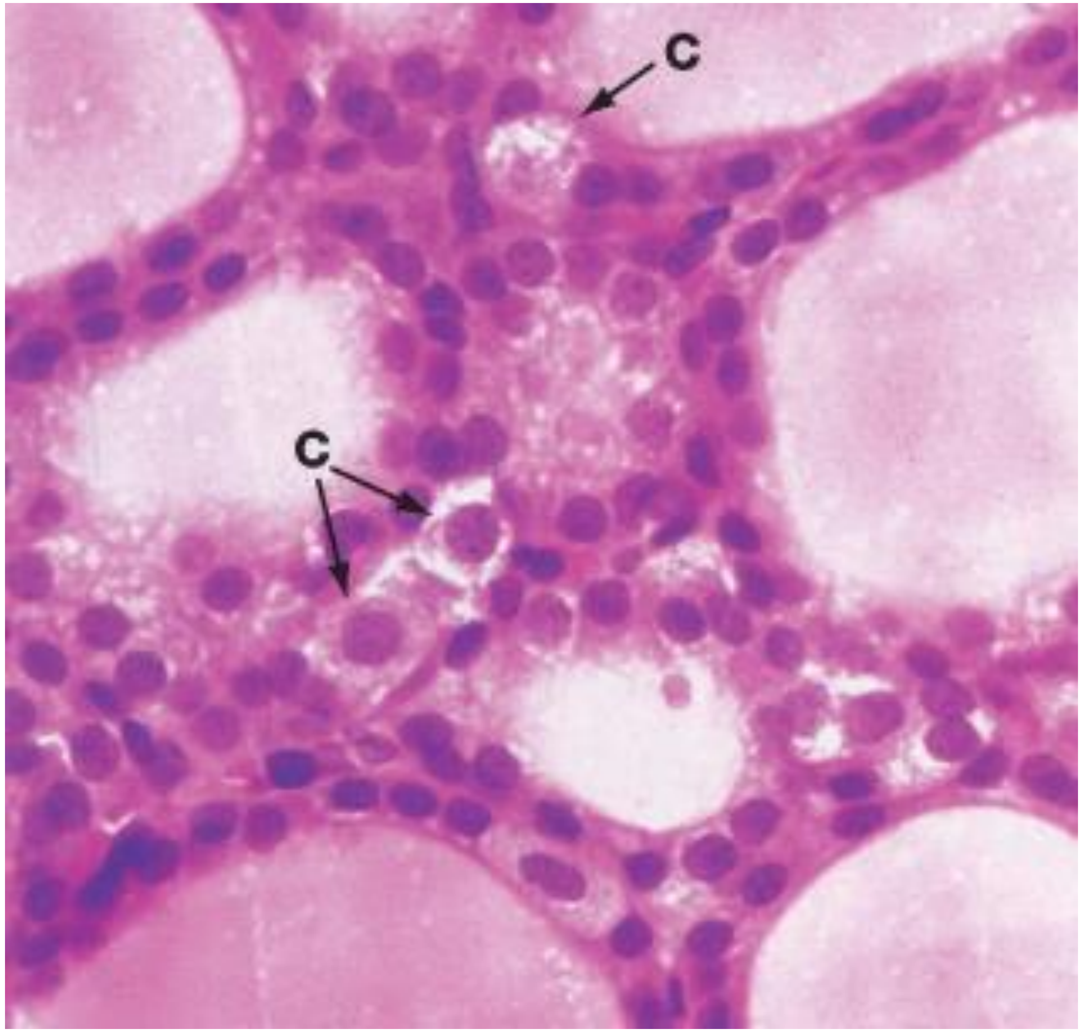
• Tumors that destroy the pineal gland are associated with precocious (early-onset) puberty

• Often used to treat *jet lag* and *insomia*



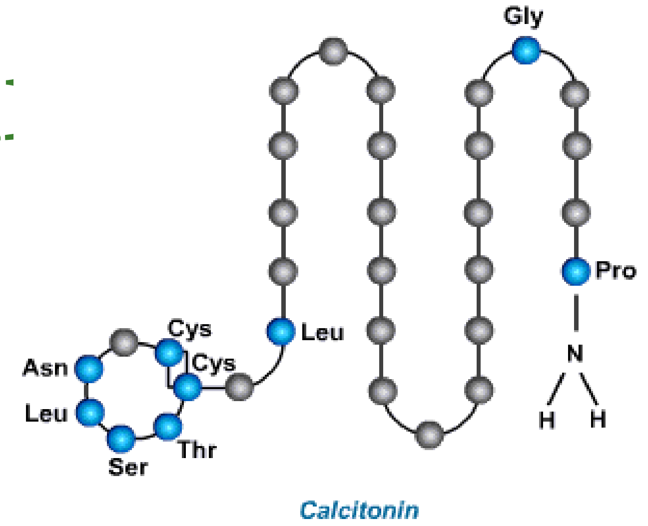
Parafollicular Cells (C cells, *clear* cells)

- **Have no contact with follicular lumen**
- **May also be present as clusters in interfollicular spaces**
- **Derived from neural crest**
- **Contain calcitonin and other agents: CGRP, SRIF, enkephalin, serotonin**



Weather's functional histology 5th ed.

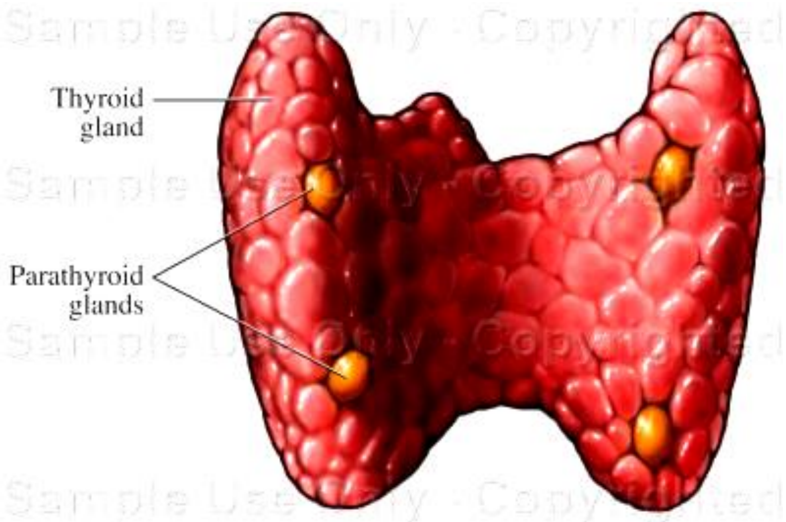
calciton



- polypeptide hormone
- lowers blood calcium by inhibiting bone resorption by osteoclasts and by stimulating activity of osteoblasts
- Synthesis and release are regulated by blood Ca^{2+} levels through plasma membrane calcium receptor

Parathyroid glands

- Four small glands located on posterior wall of thyroid gland (superior & inferior)
- Locatedwithin the thyroid capsule
- Surrounded by thin CT capsule; delicate septa divide gland into dense, cord-like masses of secretory cells



http://histology.med.umich.edu

2 types of secretory cells

chief (principal) cells

- secrete parathyroid hormone, PTH)
- apicolateral pole – surface that faces bloodstream
- prominent nucleus and relatively little cytoplasm

oxyphil cells

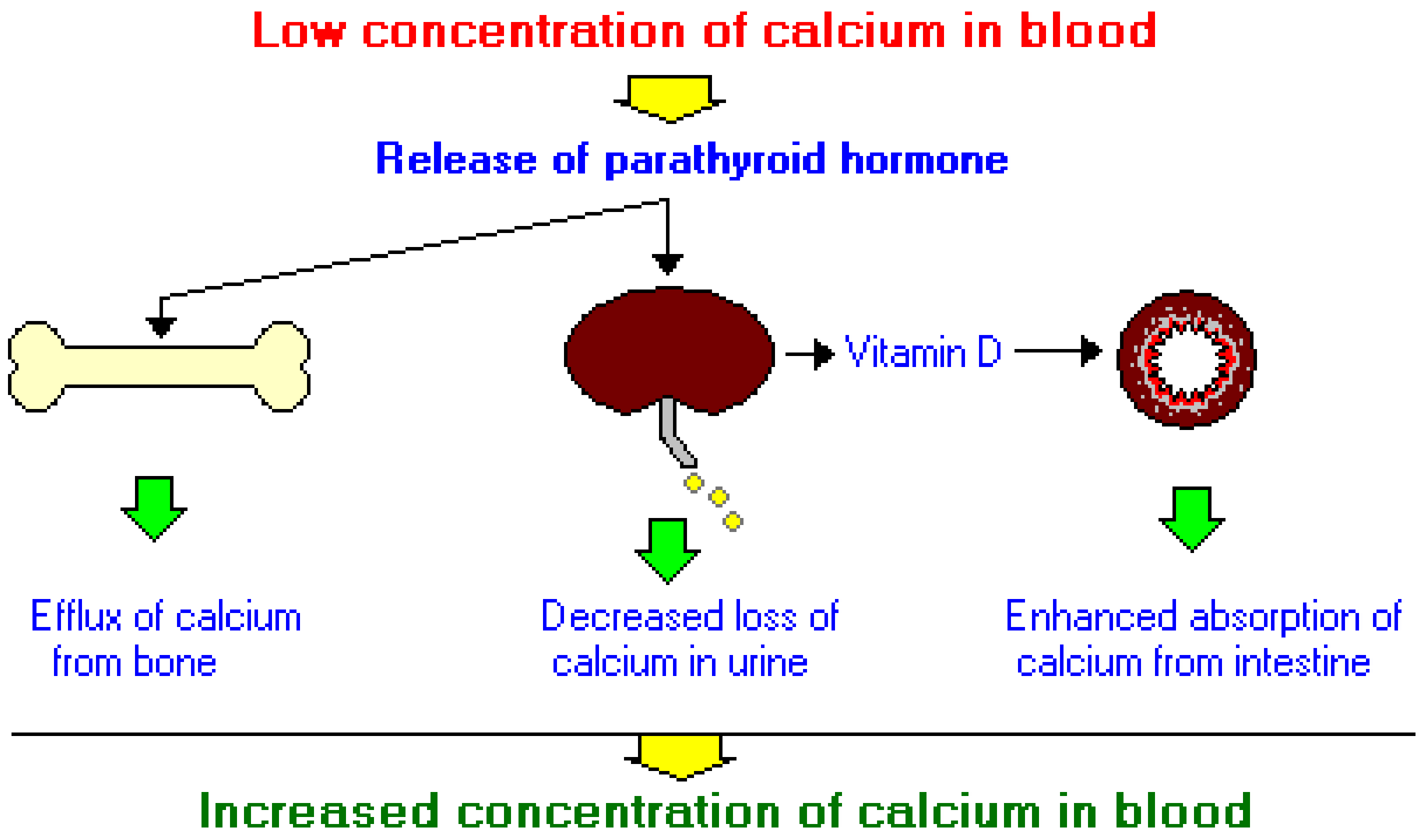
- larger, less numerous
- tend to clump among chief cells
- smaller densely stained nuclei
- Large number of mitochondria
- strongly eosinophilic cytoplasm with fine granules;
- increase in number after puberty
- function unknown

PTH is essential for life;

removal of glands cause tetanic contraction of muscles, including smooth muscle of repiratory tract, as blood calcium levels fall.

PTH = parathormone raises blood calcium level:

- indirectly increases rate of osteoclastic resorption (osteoclasts do NOT have PTH receptors!)
- increases renal tubular reabsorption of calcium ions AND inhibits reabsorption of phosphate in renal tubules,
- promotes absorption of calcium by small intestine (similarly to vit. D3)



MEDICAL CORRELATIONS

NON-OBLIGATORY

1. A condition called ***primary hyperparathyroidism*** , which may be caused by a tumor in one of the parathyroid glands, is marked by high blood calcium levels, low blood phosphate levels, loss of bone mineral, and sometimes kidney stones.

2. Secondary hyperparathyroidism may develop in patients with **rickets** , because calcium cannot be absorbed from the intestines due to vitamin D deficiency; therefore, calcium ion concentrations in the blood are low.

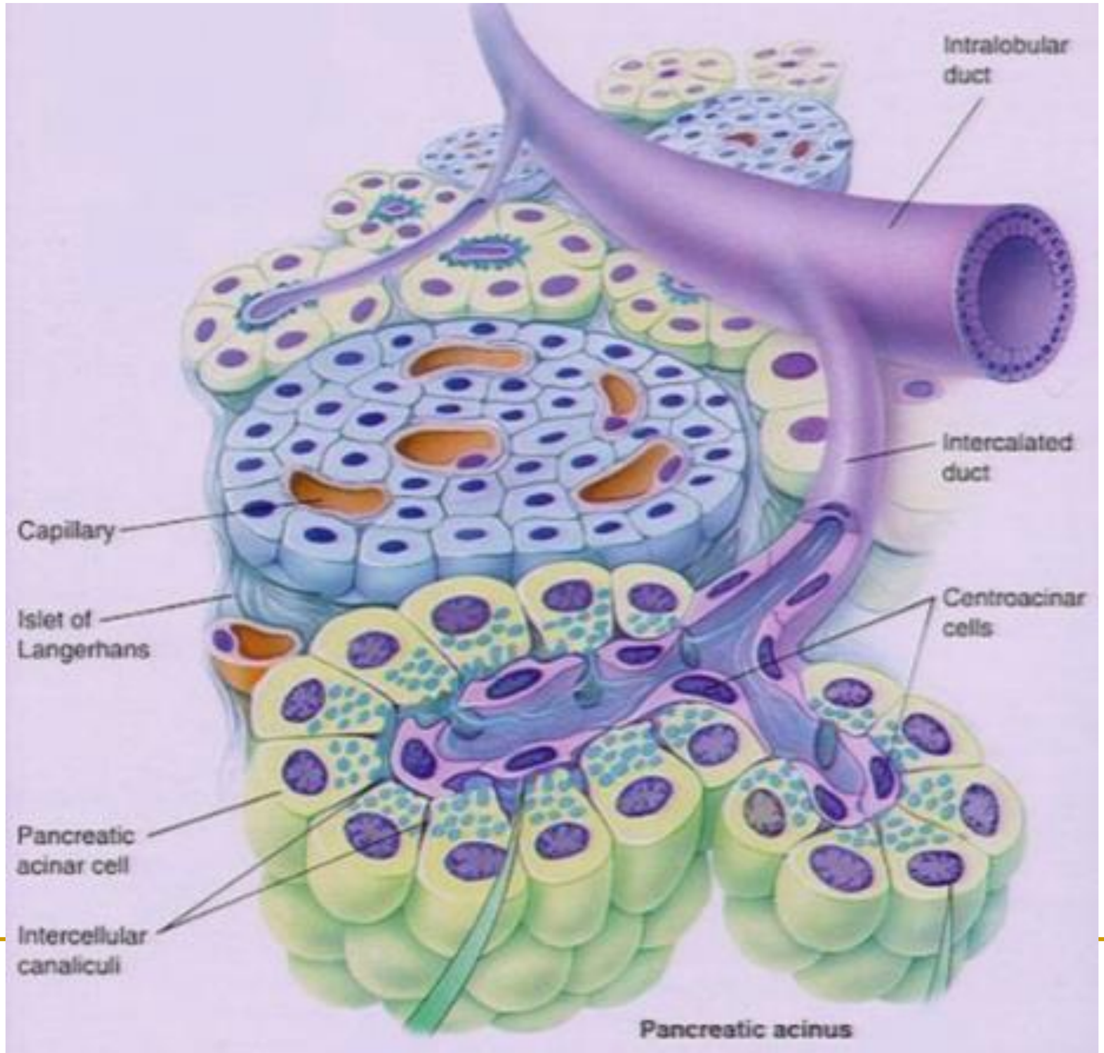
3. **Hypoparathyroidism** results from deficiency in secretion of PTH, commonly caused by injury of the parathyroid glands or by their removal during thyroid gland surgery.
This condition is marked by **low blood calcium levels, retention of bone calcium, and increased phosphate resorption in the kidney**.
The main symptoms are numbness, tingling, **carpopedal spasms** (muscle cramps) in the hands and feet, **muscle tetany** (tremors) in the facial and laryngeal muscles, mental confusion, and memory loss.

The only treatment for survival is large intravenous doses of calcium gluconate, vitamin D, and oral calcium.

Endocrine Pancreas

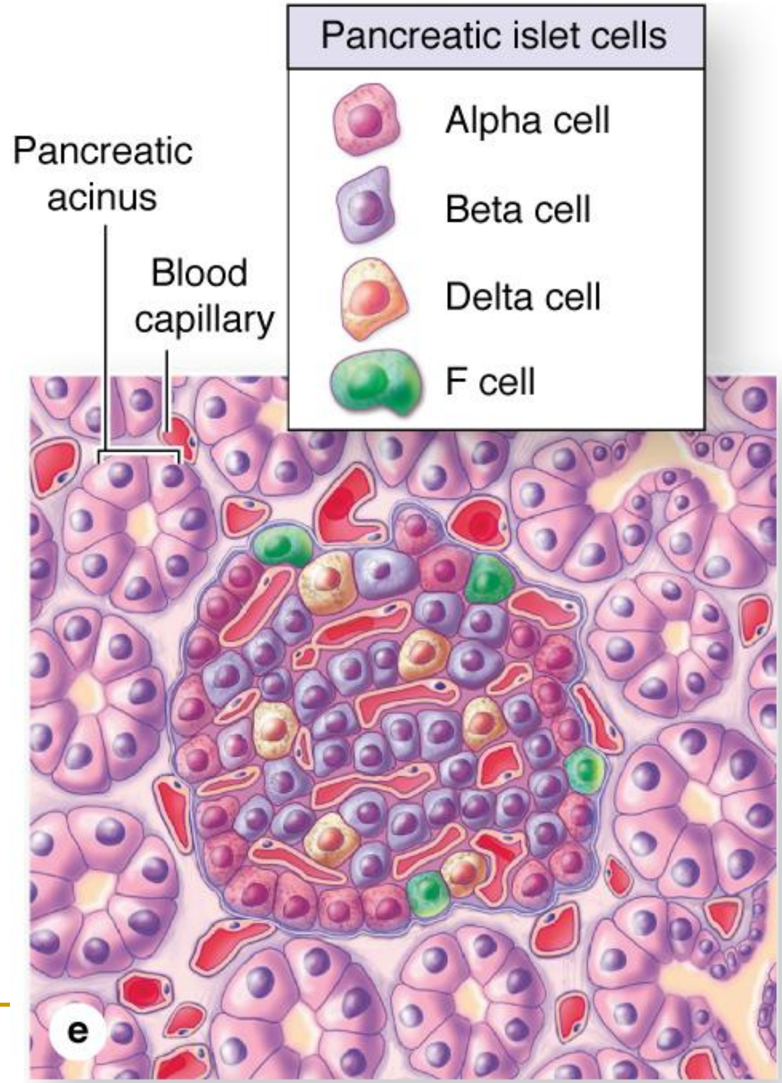
Pancreas is composed of both exocrine and endocrine components

- **Exocrine portion:**
  - Panreatic acinar cells
- **Endocrine portion:**
  - **Islets of Langerhans**
    - Spherical masses of cells
    - Highly vascularized



The four major islet hormones and the cells secreting them: α cells making glucagon, β cells making insulin, δ cells making somatostatin and gastrin, and F (PP) cells making pancreatic polypeptide.

There is also a small number of ε (epsilon, E) cells which secrete ghrelin.

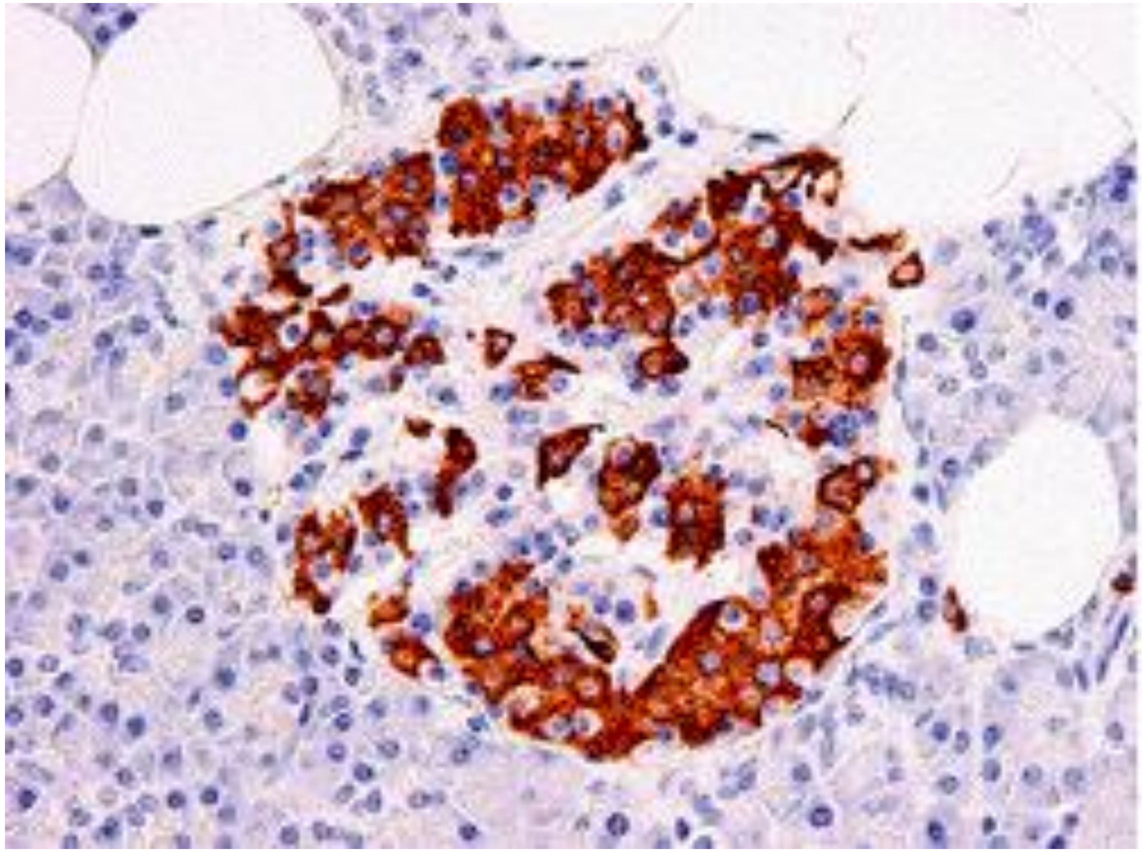


Basic Histology, 12th ed.

Pancreas Endocrine Cells

Alpha cells

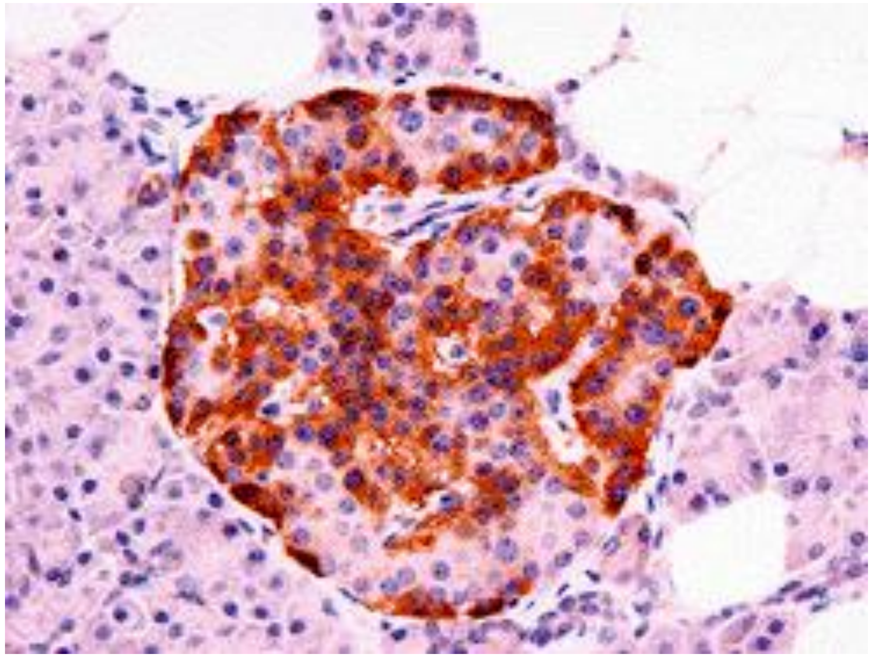
- Located mainly at periphery of islets
- Secrete glucagon - stimulates glucose synthesis and release

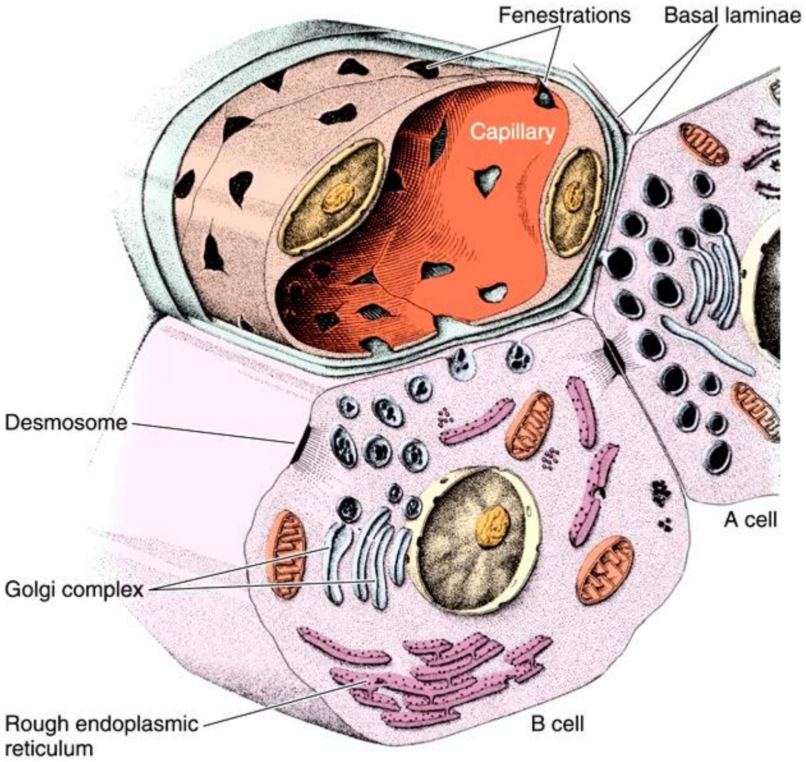


Histology for Pathologists, 3rd Edition, Lippincott Williams & Wilkins 2007

Beta cells

- **Located throughout islets**
- **Secrete insulin - promotes storage of glucose, uptake of amino acids, increases protein and lipid synthesis**

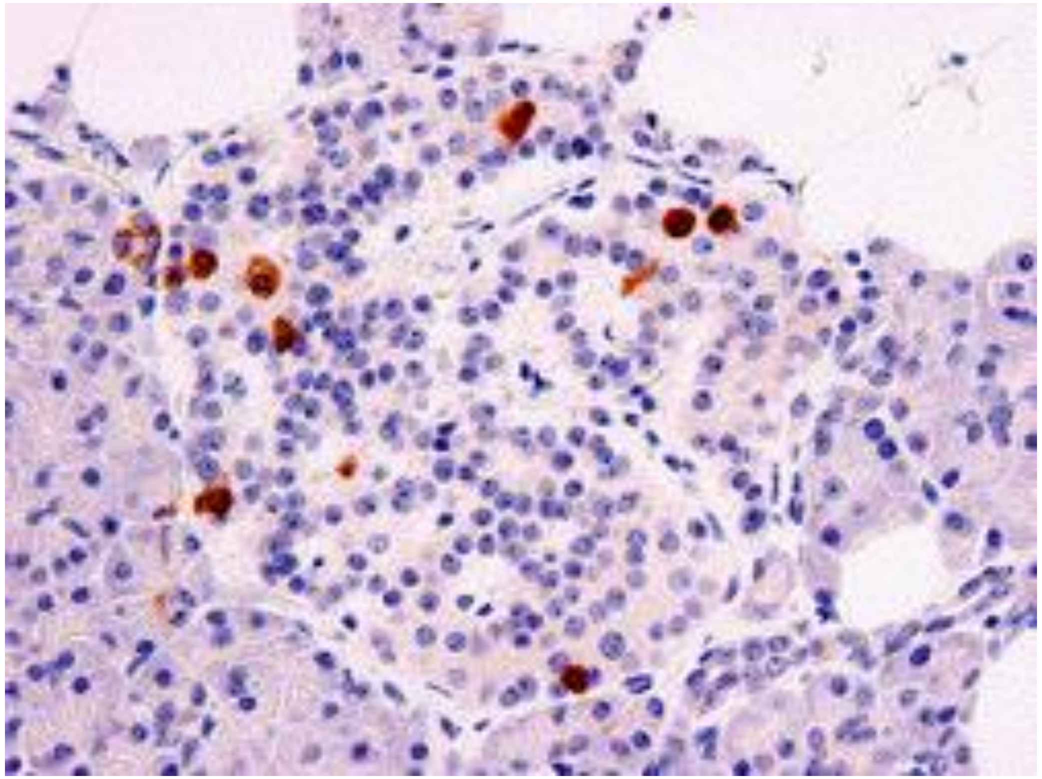




Histology for Pathologists, 3rd Edition, Lippincott Williams & Wilkins 2007

Delta cells

- **Few in number, located throughout islets**
- **Secrete somatostatin - inhibits release of somatotropin, and corticotropin, supresses alpha and beta cells**



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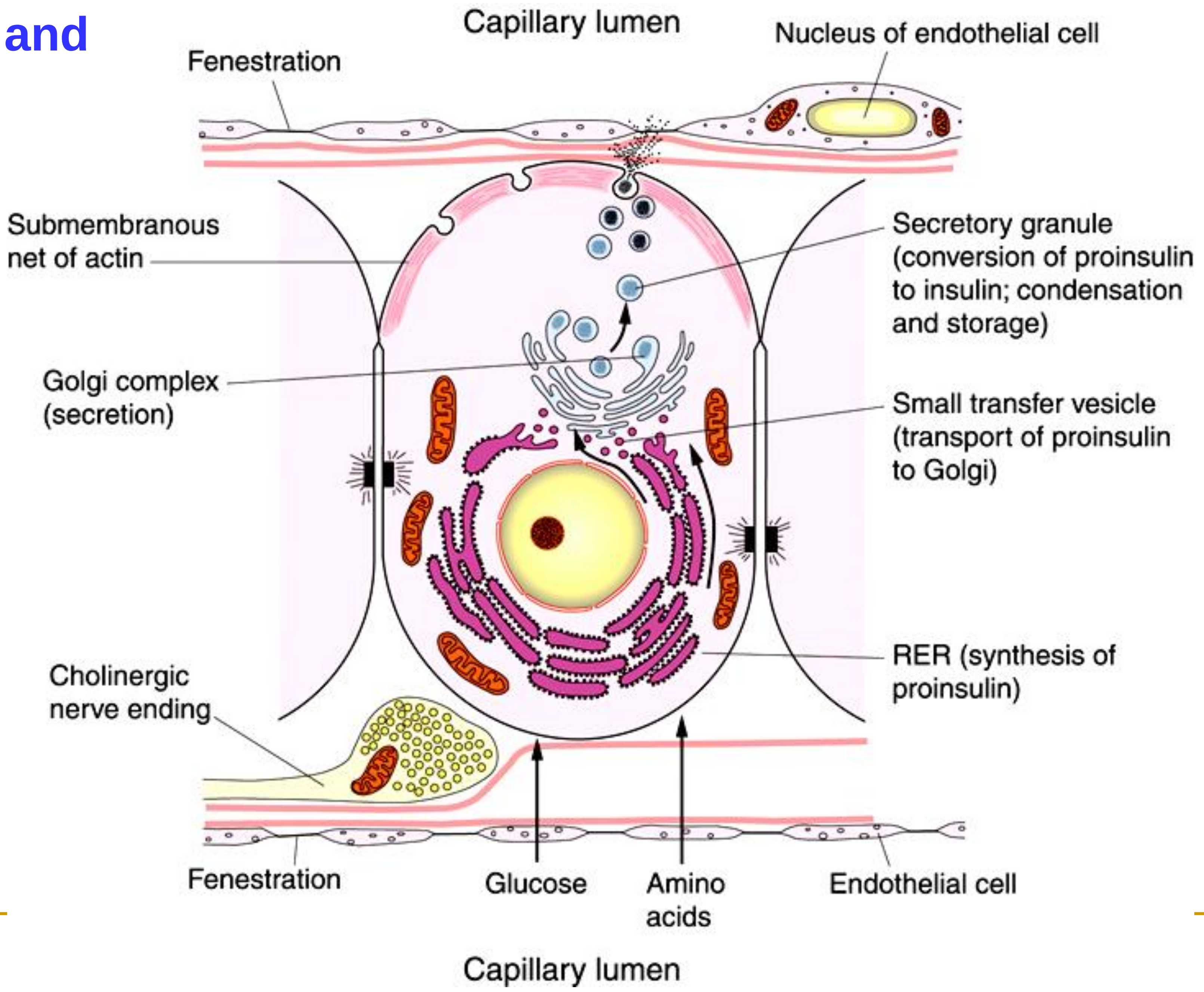
Insulin synthesis and release



Junqueira, 2004

INSULIN ACTION IN ADIPOCYTES

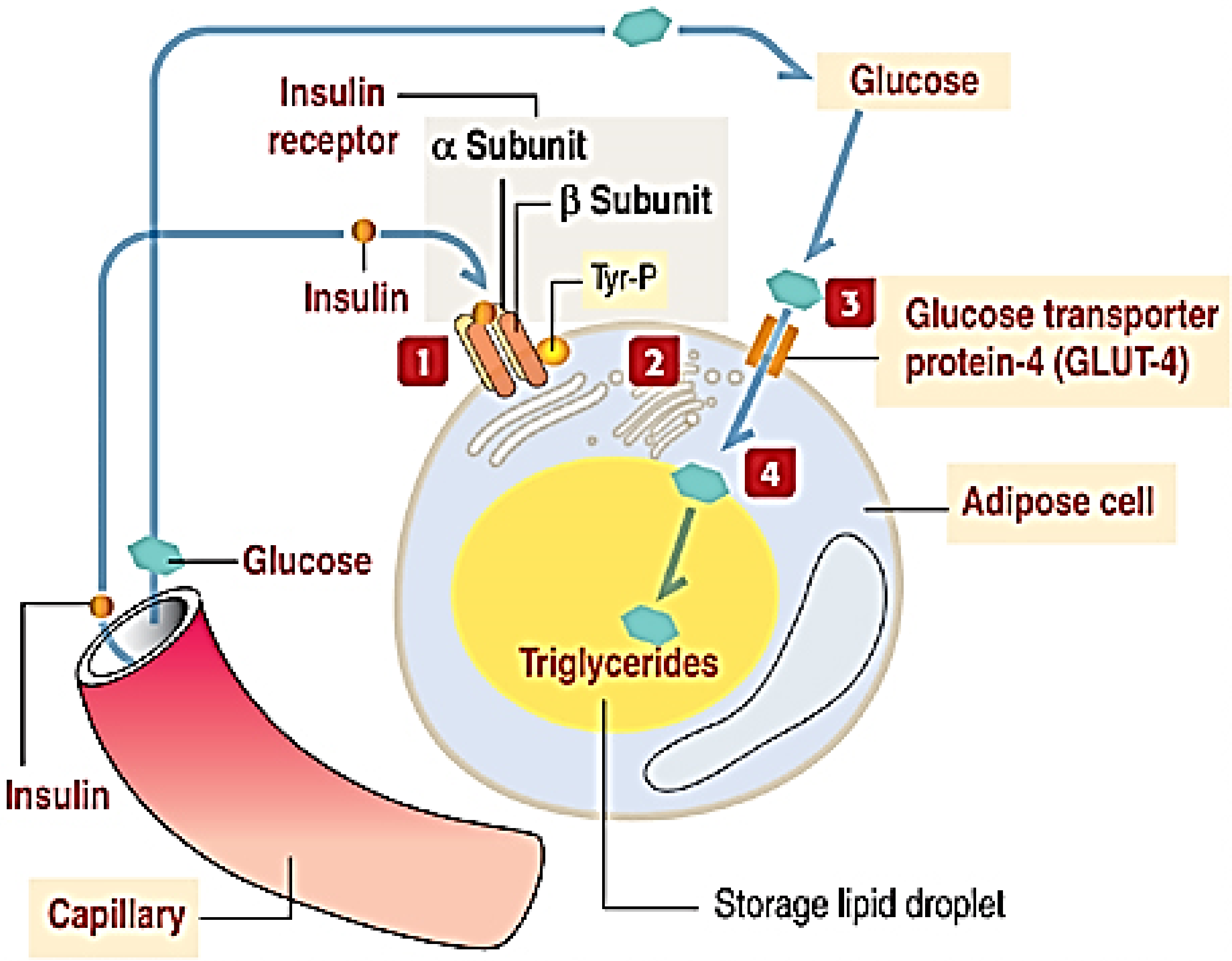
Mechanism of action of insulin in an adipose cell

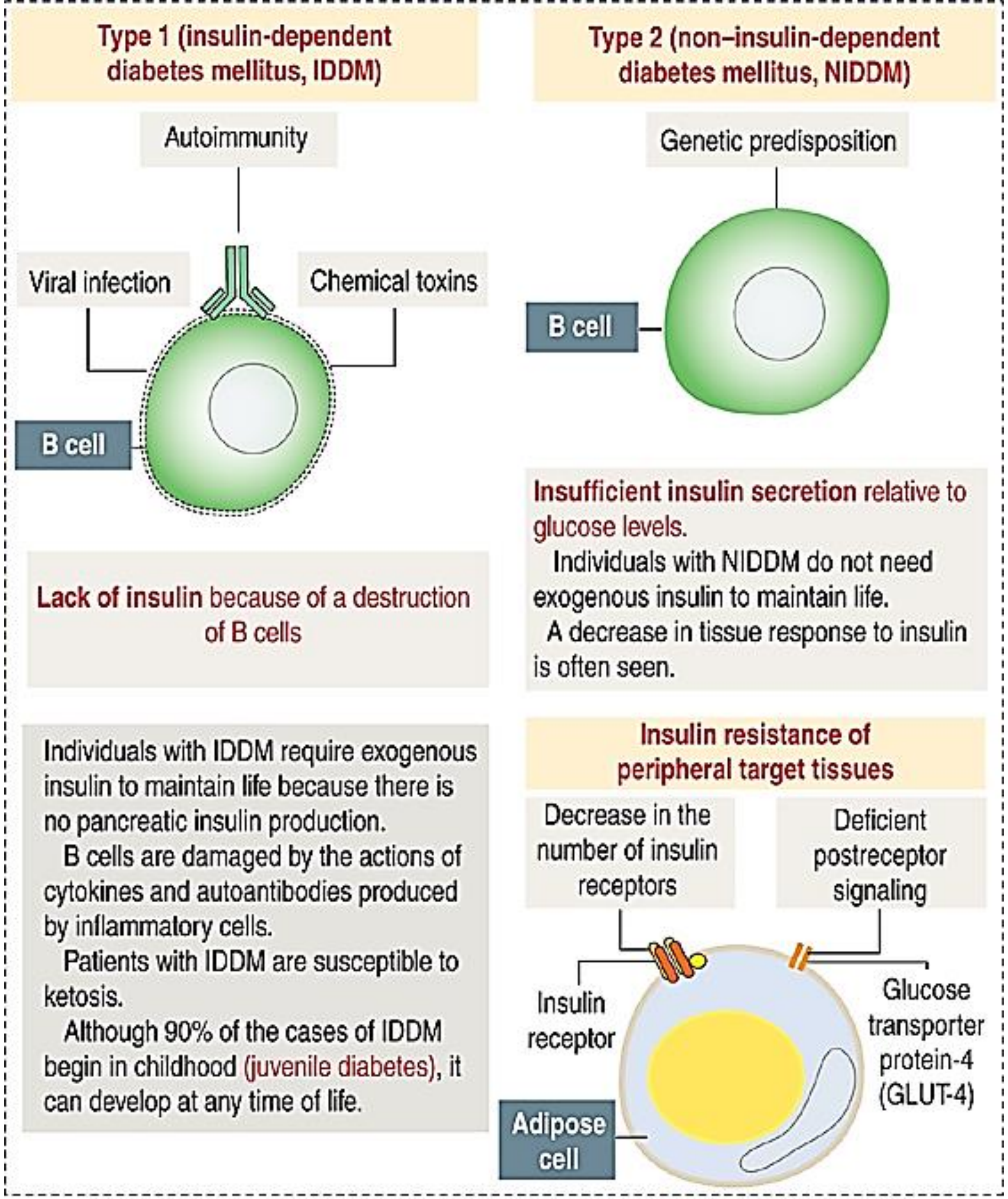
1. Insulin binds to the α subunit of the insulin receptor and activates the autophosphorylation (Tyr-P) of the adjacent β subunit (a tyrosine kinase).

2. An activated insulin receptor stimulates DNA synthesis, protein synthesis, and the translocation of insulin-dependent **glucose transporter protein-4 (GLUT-4)** from the Golgi apparatus to the plasma membrane.

3. GLUT-4 translocation facilitates the cellular uptake of glucose.

4. This mechanism demonstrates that, in diabetic individuals, a lack of insulin decreases the **utilization of glucose** in target cells.





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