# The Endocrine System

- Is a group of glands that regulate physiological functions by releasing hormones into the blood stream.

- *Intercellular signaling* is the way by which a cell exerts its effects on another cell ( or on itself ) and it subdivided into the following classifications:
  1) ***Intracrine*** signals are produced within the target cell.
  2) ***Autocrine*** signals target the cell itself.
  3) ***Juxtacrine*** signals target adjacent (touching) cells.
  4) ***Paracrine*** signals target cells in the vicinity of the emitting cell ( e.g. neurotransmitters)
  5) ***Endocrine*** signals target distant cells by producing hormones that travel through the blood to reach all parts of the body.

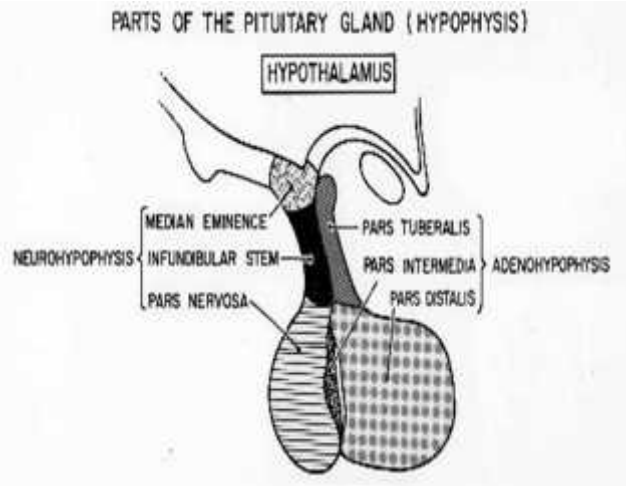
- **The endocrine system includes**:

  1. Endocrine glands, such as the pituitary, thyroid and parathyroid, adrenal, and the pineal gland;
  2. Clusters of endocrine cells located in the organs such as islets of Langerhans in the pancreas; and
  3. Isolated endocrine cells in certain tissues, such as the enteroendocrine cells in the epithelium of the respiratory and digestive tracts.

- The organs or tissues that are activated by released hormones are called target organs or tissues. The cells in the target organ/tissue have appropriate receptors, which are able to recognize and respond to specific hormones.

- *Hormone:* a chemical substance produced in the body that controls and regulates the activity of certain cells or organs.
- The hormones can be divided into three classes based on their structure:
  1. **Steroid hormones** are lipid hormones that have the characteristic ring structure of steroids and are formed from cholesterol. (e.g. estrogen, testosterone, cortisone, and aldosterone ).
  2. **Peptide hormones** are composed of amino acids. The majority of hormones of this type are secreted by the pituitary gland (ACTH, TSH, FSH, GH, and prolactin) and parathyroid glands (PTH).
  3. **Amine hormones** are derived from the amino acid tyrosine**.**(e.g. T3&T4 released by the thyroid and adrenaline & noradrenaline secreted by the adrenal medulla).

# PITUITARY GLAND (HYPOPHYSIS)



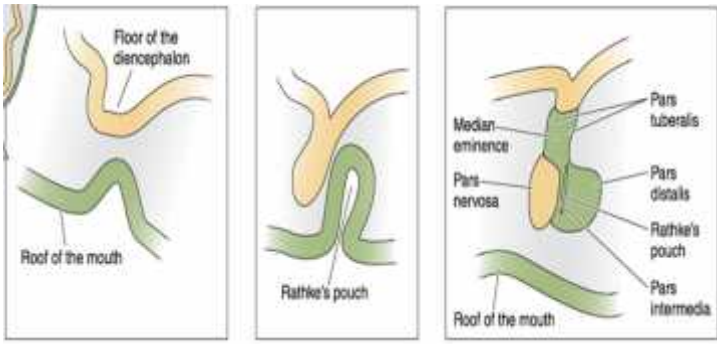

- The pituitary gland is a neuroendocrine organ located inside the skull (in the sella turcica of the sphenoid bone) and considered a part of the brain.
- It weighs about 0.5 g in adults &has dimensions of about 10 x 13 x 6 mm.
- **Embryogenesis:**

The hypophysis develops partly from oral ectoderm and partly from nerve tissue.

*The neural component* arises as an evagination from the floor of the diencephalon and grows caudally as a stalk without detaching itself from the brain.

*The oral component* arises as an out pocketing of ectoderm from the roof of the primitive mouth of the embryo and grows cranially, forming a structure called ***hypophyseal (Rathke's) pouch***. Later, a constriction at the base of this pouch separates it from the oral cavity. At the same time, its anterior wall thickens, reducing the lumen of Rathke's pouch to a small fissure.

- Because of its dual origin, the pituitary actually consists of two glands
  1. **The posterior Neurohypophysis**
  2. **The anterior Adenohypophysis**
- United anatomically but with different functions.
- ***The Neurohypophysis*** consists of :




a) **Pars Nervosa**
b) **Infundibulum**
   i. Stalk
   ii. Median eminence.

- ***The Adenohypophysis:***

a) **Pars Distalis ( Anterior Lobe)**
b) **Pars Tuberalis**
c) **Pars Intermedia.**

## o *Blood Supply & the Hypothalamo-Hypophyseal Portal System:*

The blood supply of the hypophysis derives from the internal carotid artery:

- From above, the ***superior hypophyseal arteries*** supply the median eminence and the neural stalk;
- From below, ***inferior hypophyseal arteries*** provide blood mainly for the neurohypophysis, with a small supply to the stalk.

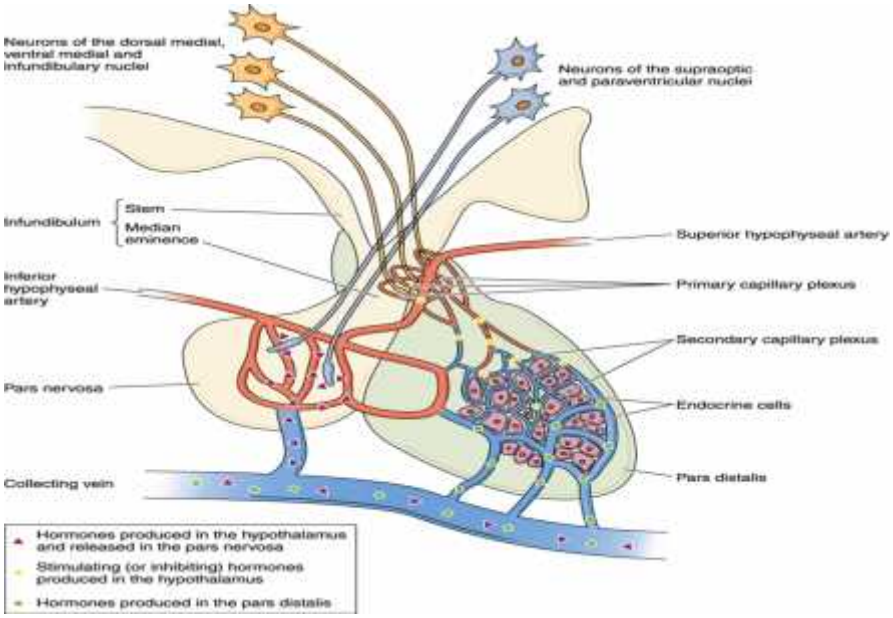
The superior hypophyseal arteries form a ***primary capillary network*** irrigating the stalk and median eminence. The capillaries then rejoin to form venules that branch again as a larger ***secondary capillary network*** in the adenohypophysis, Capillaries of both networks are fenestrated.

❖ ***In the HHPS there are three groups of hormones released at three sites :***

1. Peptide hormones synthesized by neurons in the hypothalamus (the supraoptic and the paraventricular nuclei) undergo axonal transport and accumulate distally in these axons, which are situated in the pars nervosa.

2. Another group of peptides is produced by neurons in other hypothalamic nuclei and carried in axons for temporary axonal storage and secretion in the median eminence. Then enter the capillaries of the primary plexus and are transported to the adenohypophysis where they diffuse among endocrine cells and control hormone release from their target cells.

3. The third group of hormones consists of proteins and glycoproteins released from the endocrine cells of the adenohypophysis (under the control of the neuropeptides just mentioned) and picked up by capillaries of the secondary plexus, from which they enter the general circulation.



# Adenohypophysis (Anterior Pituitary)

## Pars Distalis ( anterior lobe)

- It accounts for 75% of the mass of the hypophysis, it mainly consists of cords of epithelial cells (hormone-secreting cells) interspersed with fenestrated capillaries. With few fibroblasts producing reticular fibers that support these cords.
- These secretory cells are classified as **Chromophobes** and **Chromophils**.
    - The ***Chromophobes*** do not effectively take a stain, so they appear clear in the Mallory trichrome stain. These cells are undifferentiated cells but are capable of differentiating into chromophils.
    - The ***Chromophils*** include:
        - **Basophils** (appear blue in Mallory stain) and
        - **Acidophils** (appear red in Mallory stain)
- Subtypes of basophilic and acidophilic cells are identified by TEM or more easily by IHC and are named for their specific hormones or target cells.
    - Acidophils include the ***somatotropic*** and ***mammotropic*** cells, while the
    - Basophilils are the ***gonadotropic***, ***corticotropic***, and ***thyrotropic*** cells.

## Pars Tuberalis

The pars tuberalis is the neck of the adenohypophysis; it wraps around the infundibular stalk of the pituitary gland.

It contains a rich capillary network and some low columnar basophilic cells that are commonly arranged in cords.

Most of the cells of the pars tuberalis are basophilic gonadotropic cells that secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

## Pars Intermedia

The pars intermedia, which develops from the dorsal portion of Rathke's pouch is (in humans) a rudimentary region made up of cords and follicles of weakly basophilic cells that contain small secretory granules.

Melanocyte stimulating hormone (MSH) is probably produced in the intermediate zone, and probably also by basophils of the pars distalis.

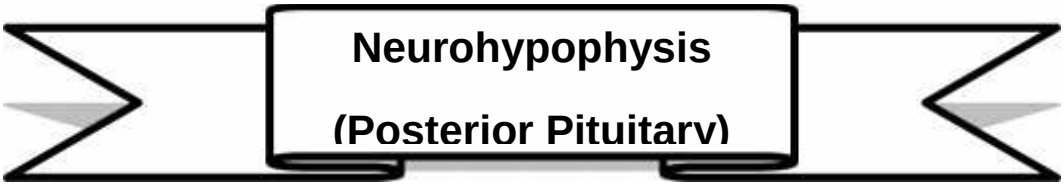
MSH increases melanocyte activity and cells of the pars intermedia are often referred to as melanotropic cells, but the overall physiological significance of this region remains uncertain, especially in adults.

## ⌘ Control of Secretion in the Adenohypophysis:

- The activities of the cells of the anterior pituitary are controlled primarily by **peptide hormones** produced in hypothalamic nuclei and stored in their axons that run to the median eminence. Most of these hormones are *hypothalamic-releasing hormones*; liberated from the axons, they are transported by capillaries to the pars distalis where they stimulate hormone synthesis and/or release.
  Two of the hypothalamic factors, however, act to inhibit hormone release by specific cells of the pars distalis (*hypothalamic-inhibiting hormones).*

- Another mechanism 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.

- Finally, hormone secretion in the pars distalis is affected by **other hormones from outside the feedback loop or even outside the major target tissues**. Examples: inhibin and activin produced in the gonads, control release of FSH and LH; the oxytocin, liberated in the posterior pituitary in the course of breast feeding, which increases secretion of prolactin.




The pars nervosa, does not contain secretory cells. It is composed of neural tissue, containing unmyelinated axons of secretory neurons whose cell bodies situated 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 (in hypothalamus) have larger diameter axons and well-developed synthetic components related to the production of hormones ***vasopressin*** (also called antidiuretic hormone, ADH) and **oxytocin**.

These hormones are transported axonally into the pars nervosa and accumulate in axonal dilations called ***neurosecretory bodies or Herring bodies***, visible in the LM as faintly eosinophilic structures. These bodies contain numerous membrane-enclosed granules with either oxytocin or vasopressin bound to a carrier protein 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 nuclei are mainly concerned with vasopressin secretion, whereas most of the fibers from the paraventricular nuclei are concerned with oxytocin secretion.

## CLINICAL CORRELATION

**Pituitary Adenomas**

Pituitary adenomas are benign tumors of the anterior pituitary gland. Clinically, they can be divided into nonsecreting and secreting forms.

Historically, adenomas were classified by their staining properties, the degree to which they took up the H&E stains. They were classified as basophilic, acidophilic, or chromophobic adenomas. With modern immunocytochemical techniques, however, tumor cells can be classified by the type of hormone they produce. Some cells do not mark with any antibody, and their tumors are called null-cell adenomas.

Classification by secretory status may reflect, for example, excess cortisol
(Cushing disease) or prolactin (prolactinoma) or the overproduction of growth hormone (gigantism or acromegaly).

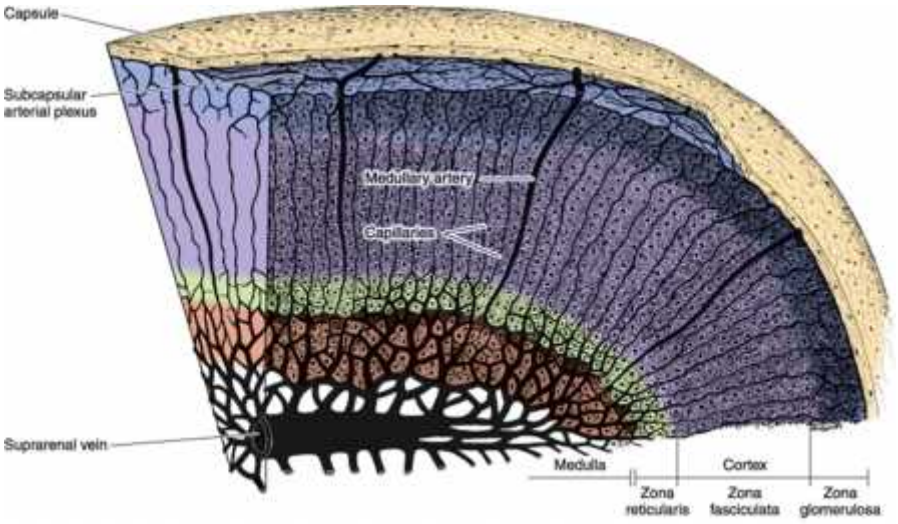
A bitemporal hemianopia is commonly seen in patients suffering from compression of the optic nerve.

# ADRENAL GLAND

- The **adrenal (suprarenal) glands** are paired organs that lie near the superior poles of the kidneys.
- They are flattened structures with a half-moon shape, about 4–6 cm long, 1–2 cm wide, and 4–6 mm thick in adults. Together they weigh about 8 g.
- Each gland covered by a dense connective tissue capsule that sends thin septa to the interior of the gland as trabeculae. The stroma consists mainly of a rich network of reticular fibers that support the secretory cells.
- The gland consists of two concentric layers:
    - A yellowish peripheral layer, the ***Adrenal Cortex(AC),*** and
    - A reddish-brown central layer, the ***Adrenal Medulla (AM)***.
- The AC & AM are 2 organs with distinct origins, functions, and morphology that become united during embryonic development.
- They arise from different embryonic germ layers:
    - The AC arises from mesoderm and
    - The AM derived from the neural crest.

### Blood Supply

- The adrenals are supplied by several arteries that enter at various points around their periphery. The branches of these arteries form three groups:
  those supplying the capsule; the ***cortical arterioles,*** which quickly form capillaries and sinusoids that irrigate all cells of the cortex and eventually join the ***medullary capillaries***; and ***medullary arterioles***, which pass directly through the cortex and form an extensive capillary network in the medulla.
- The cells of the adrenal medulla, thus, receive both arterial blood from the medullary arteries and venous blood originating from capillaries of the cortex.
- The capillary and sinusoidal endothelium is highly attenuated and fenestrated.
- Capillaries of both the cortex and the medulla form the central **medullary veins**, which join to leave the gland as the adrenal or suprarenal vein.




## Adrenal Cortex

- Cells of the AC have characteristic features of steroid-secreting cells.
- These include:
  (1) Central nuclei and acidophilic cytoplasm, usually rich in lipid droplets.
  (2) Their cytoplasm have profuse SER of interconnected tubules, which contain the enzymes for cholesterol synthesis and conversion of the steroid prohormone pregnenolone into specific active steroid hormones.
  (3) The mitochondria are often spherical, with tubular rather than shelf like cristae containing the enzymatic equipment for converting cholesterol to pregnenolone and for some steps in steroid hormone synthesis.
- Steroid hormone-secreting cells do not store their product in granules; rather, they synthesize and secrete steroid hormones upon demand. Steroids (being LMW lipid-soluble molecules) diffuse through the plasma membrane and do not require the specialized process of exocytosis for their release.

The adrenal cortex has three concentric zones in which the cords of epithelial cells are arranged somewhat differently and are specialized to produce different classes of steroid hormones:

I. Immediately inside the connective tissue capsule is the **zona glomerulosa**, consisting of closely packed, rounded or arched cords of columnar or pyramidal cells surrounded by many capillaries and comprising about 15% of the cortex.

II. The middle zone, the **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 most densely filled with cytoplasmic lipid droplets and, as a result of lipid dissolution during tissue preparation, often appear vacuolated or spongy in common histological preparations. Because of their vacuolization, the cells of the fasciculata are also called **spongyocytes.**

III. The innermost **zona reticularis** comprises about 10% of the cortex and contacts the adrenal medulla. It consists of smaller cells disposed in a network of irregular cords interwoven 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.

## ⌘ *Cortical Hormones & Their Actions:*

- The main product of the Z.G is a **mineralocorticoid** called **aldosterone;** the Z. F and possibly the Z.R secrete **glucocorticoids**, especially **cortisol;** the Z. R produces **dehydroepiandrosterone (DHEA),** a weak androgen.
- The **mineralcorticoids,** so called because they affect uptake of Na+, K+, and water by epithelial cells. The principal product is **aldosterone**, the major regulator of salt balance, which acts to stimulate Na+ reabsorption in the distal convoluted tubules of the kidneys. Aldosterone secretion in the zona glomerulosa is stimulated primarily by angiotensin II and also by an increase in plasma K+ concentration, but only weakly by ACTH.
- The **glucocorticoids**, especially **cortisol**, affect CHO metabolism by stimulating production of glucose from amino acids or fatty acids (gluconeogenesis) in many cells and glucose conversion into glycogen in the liver. Cortisol induces fat mobilization in subcutaneous adipose tissue and protein breakdown in muscle. Cortisol also suppresses many aspects of the immune response, including cytokine release and lymphopoiesis. Secretion of glucocorticoids in the Z.F is controlled by ACTH and negative feedback proportional to the concentration of circulating glucocorticoids is exerted at both the pituitary and hypothalamic levels. Cells of the Z.F also secrete small amounts of androgens.
- **DHEA** is the only sex hormone that is secreted in significant physiological quantities by the AC. It is a weak androgen that circulates in the blood as a sulfate and exerts its actions after being converted into testosterone in several tissues. Secretion by these cells is also stimulated by ACTH and is under feedback regulation with the pituitary and hypothalamus.

## Fetal Adrenal Cortex

- At birth in humans, the adrenal gland is larger than that of the adult and produces up to 200 mg of corticosteroids per day, twice that of an adult. At this age, a layer known as the fetal or **provisional cortex**, comprising 80% of the total gland, is present between the thin permanent cortex and an underdeveloped medulla. The fetal cortex is thick and contains mostly cords of large, steroid-secreting cells under the control of the fetal pituitary.
- The principal function of the cells is secretion of sulfated DHEA which is converted in the placenta to active estrogens (and androgens), which mostly enter the maternal circulation.
- The fetal adrenal cortex is an important part of a **fetoplacental unit** which affects both endocrine systems during pregnancy but whose physiological significance remains largely unclear.
- After birth, the provisional cortex undergoes involution while the permanent cortex organizes the three layers (zones) described above.

## 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. Chromaffin cells can be considered modified sympathetic postganglionic neurons, lacking axons and dendrites and specialized as secretory cells.
- Unlike cells of the cortex, medullary chromaffin cells contain many electron-dense granules for hormone storage and secretion. These granules contain one or the other of the catecholamines, **epinephrine(adrenalin)** or **norepinephrine (noradrenaline)**.
- Ultrastructurally the granules of epinephrine-secreting cells are less electron-dense and generally smaller than those of norepinephrine-secreting cells. Catecholamine, together with Ca2+ and ATP, are bound in a granular storage complex with a proteins called **chromogranins**.
- 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 NE to E occurs only in chromaffin cells of the AM.
- About 80% of the catecholamine secreted from the adrenalis epinephrine.
- Medullary chromaffin cells are innervated by cholinergic endings of preganglionic sympathetic neurons, from which impulses trigger hormone release by exocytosis.
- Epinephrine & norepinephrine are released to the blood in large quantities during intense emotional reactions, such as fright, and produce vasoconstriction, increased blood pressure, changes in heart rate, and metabolic effects such as elevated blood glucose. These effects facilitate various defensive reactions to the stressor (the fight-or-flight response).
- During normal activity, the adrenal medulla continuously secretes small quantities of the hormones.

# CLINICAL CORRELATION

Because of the feedback mechanism of adrenal cortex control, patients who are treated with corticoids for long periods should never stop taking these hormones suddenly: secretion of ACTH in these patients is inhibited, and thus the cortex will not be induced to produce corticoids, causing a severe misbalance in the levels of sodium and potassium.

## **Pheochromocytoma**S

Are neoplasms of the AM characterized by the production of catecholamines, such as epinephrine and norepinephrine, which cause significant hypertension, often episodic, in affected patients.

Grossly, most of these tumors are well circumscribed and range in size from a few grams to kilograms. Microscopically, pheochromocytomas can have a diverse appearance, from spindle cells to large, bizarre cells. The cells are often arranged in nests, or cell packets called **zellballen**.

Histologic features alone do not reliably separate benign tumors from malignant ones; therefore, the demonstration of metastases is necessary to ascertain malignancy.

## Adrenocortical disorders

- Disorders of the AC can classified as **hyperfunctional** or **hypofunctional.**
- Tumors of the adrenal cortex can result in excessive production of glucocorticoids (***Cushing syndrome***) or aldosterone (***Conn syndrome***).
- Cushing syndrome is most often (90%) due to a ***pituitary adenoma*** that produces excessive ACTH; it is rarely caused by adrenal hyperplasia or an adrenal tumor.
- Excessive production of ***adrenal androgens*** has little effect in men. However, hirsutism is seen in women, and precocious puberty (in boys) and virilization (in girls) are seen in prepubertal children. These adrenogenital syndromes are the result of several enzymatic defects in steroid metabolism that cause increased biosynthesis of androgens by the adrenal cortex.
- Adrenocortical insufficiency (**Addison disease**) is caused by destruction of the AC in some diseases. The signs and symptoms result from failure of secretion of both glucocorticoids and mineralocorticoids by the AC.
- Carcinomas of the AC are rare, but most are highly malignant. About 90% of them produce steroids.

# Endocrine Pancreas (Islets of Langerhans)

- The **pancreatic islets** are compact spherical or egg-shaped masses of endocrine tissue embedded within the acinar exocrine tissue of the pancreas.
- There are more than 1 million islets in the human pancreas, most numerous in the tail of the gland, but they only constitute 1–2% of the organ's volume.
- A very thin capsule of reticular fibers surrounds each islet, separating it from the adjacent acinar tissue.
- Islets have the same embryonic origin as the acinar tissue: (endoderm).
- Each islet consists of polygonal or rounded cells, smaller and more lightly stained than the surrounding acinar cells, arranged in cords that are separated by a network of fenestrated capillaries. Autonomic nerve fibers contact some of the endocrine cells and the blood vessels.
- Routine stains or trichrome stains show that most islet cells are acidophilic or basophilic with fine cytoplasmic granules.
- The major hormone-producing islet cells are most easily identified and studied by immunohistochemistry:

i. **Alfa** or **A cells** secrete primarily **glucagon** and are usually located near the periphery of islets.

ii. **Beta** or **B cells** produce **insulin** , are located centrally in islets and are the most numerous cell type.

iii. **Delta** or **D cells**, secreting **somatostatin**, scattered and much less abundant.
Insulin is a heterodimeric protein and the other two hormones are smaller single-chain polypeptides.

iv. A minor fourth cell type, more common in islets located within the head of the pancreas, are **F** or **PP cells,** which secrete **pancreatic polypeptide**.

❖ Pancreatic islets also normally contain a few enterochromaffin cells, like those of the digestive tract, which secrete other polypeptidehormones having other effects within the digestive system and which are also scattered in the pancreatic acini and ducts.

See table: 20 –4 in your textbook

## CLINICAL CORRELATIO

**Type 1 diabetes mellitus** is the most common type of diabetes in childhood and adolescence (65% of total cases). It is characterized by insulin deficiency and sudden onset of severe hyperglycemia, diabetic ketoacidosis, and death if patients are left without insulin treatment. Symptoms also include polyuria, polydipsia, lethargy, and weight loss. The major cause of the disease is autoimmune destruction of the insulin-secreting beta cells in the islets of Langerhans by T cells and humoral mediators (TNF,interleukin-1, nitric oxide).

**Type 2 diabetes mellitus** is characterized by hyperglycemia with normal or elevated insulin levels. In type 2 DM, insulin is present, but insulin-sensitive tissues, such as skeletal muscle and adipose tissues, manifest resistance to the action of insulin. Defects in beta cell function also contribute to the disease process. Type 2 DM generally has an insidious onset and typically affects adults. Risk factors include genetic factors and a strong association with obesity. Approximately 85% of type 2 diabetes is associated with obesity.

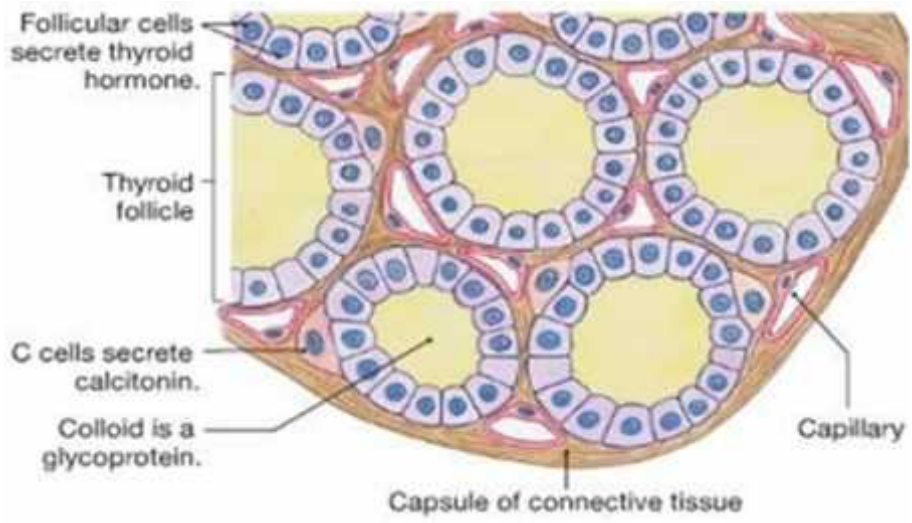
## DIFFUSE NEUROENDOCRINE SYSTEM

- The enterochromaffin cells scattered in both the islets and small ducts of the pancreas are similar to those of the digestive tract. Collectively these dispersed cells, as well as similar cells in the respiratory mucosa, make up the **diffuse neuroendocrine system (DNES)**.
- Like the pancreatic islets, most of these cells are derived from endodermal cells of the embryonic gut.
- Cells of the DNES are also referred to as **gastroenteropancreatic (GEP) endocrine cells**.
- Many cells of the DNES are stained by solutions of chromium salts and have therefore been called **enterochromaffin cells**. Those cells that stain with silver nitrate are sometimes called **argentaffin cells**.
- Those DNES cells secreting serotonin or certain other amine derivatives demonstrate amine precursor uptake and decarboxylation and are often referred to acronymically as **APUD cells**. Such names are still widely used but have been largely replaced by letter designations like those used for pancreatic islet cells.
- Whatever name is used, cells of the DNES are highly important due to their role in regulating motility and secretions of all types within the digestive system.

# THYROID GLAND

- The thyroid gland, located in the cervical region anterior 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 future tongue.
- Its function is to synthesize the thyroid hormones: **thyroxine** (tetra-iodothyronine or **T4**) and **tri-iodothyronine** (**T3**), which are important for growth, cell differentiation, and control of the BMR and O2 consumption in cells of the body, and affect protein, lipid, and CHO metabolism.
- The parenchyma of the thyroid is composed of millions of rounded epithelial structures called **follicles**. Each follicle consists of a simple epithelium and a central lumen filled with a gelatinous substance called **colloid.**
- The thyroid is the only endocrine gland in which a large quantity of secretory product is stored. Moreover, the accumulation is outside the cells, in the colloid of the follicles, which is also unusual. In humans there is sufficient hormone in follicles to supply the body for up to three months with no additional synthesis. Thyroid colloid contains the large glycoprotein **thyroglobulin**, the precursor for the active thyroid hormones.
- The gland is covered by a **fibrous capsule, which** sends septa 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. This stroma is very well vascularized with an extensive network of fenestrated capillaries closely surrounding the follicles, which facilitates molecular transfer between the follicles and blood.
- **Follicular cells** range in shape from squamous to low columnar. The size and cellular features of follicles vary with their functional activity. Active glands have more follicles of low columnar epithelium; glands with mostly squamous follicular cells are considered hypoactive.
- The follicular epithelial cells have typical junctional complexes apically 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 in the center of the cell. Basally the cells are rich in rough ER and apically, facing the follicular lumen, are Golgi complexes, secretory granules filled with colloidal material, large phagosomes and abundant lysosomes. The cell membrane of the apical pole has a moderate number of microvilli. Mitochondria and other cisternae of rough ER are dispersed throughout the cytoplasm.

- Another endocrine cell type, the **parafollicular,** or **clear cell (C cell)**, is also found inside the basal lamina of the follicular epithelium or as isolated clusters between follicles. Parafollicular cells, derived from neural crest cells migrating into the area of the embryonic foregut, 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 granules containing polypeptide hormone.
  These cells synthesize and secrete **calcitonin,** one function of which is to suppress bone resorption by osteoclasts. Calcitonin secretion is triggered by elevated blood Ca2+ levels.




## ❖ Control of Thyroid Function

- The major regulator of the anatomic and functional state of thyroid follicles is TSH, which is secreted by the anterior pituitary.
- TSH increases the height of the follicular epithelium and stimulates all stages of thyroid hormone production and release.
- Thyroid hormones inhibit the release of TSH, maintaining an adequate quantity of T4 and T3 in the organism.
- TSH receptors are abundant on the basal cell membrane of follicular cells.
- Secretion of TSH is also increased by exposure to cold and decreased by heat and stressful stimuli.

## ❖ *Synthesis & Accumulation of Hormones by Follicular Cells*

Synthesis and accumulation of hormones take place in four stages:

1) Synthesis of thyroglobulin.
2) Uptake of iodide from the blood.
3) Activation of iodide.
4) Iodination of the tyrosine residues of thyroglobulin.

## ❖ *Liberation of $T_3$& $T_4$*

- When stimulated by TSH, thyroid follicular cells take up colloid by endocytosis.
- The colloid within the endocytic vesicles is then digested by lysosomal enzymes.
- Hydrolysis of thyroglobulin results in $T_4$, $T_3$, diiodotyrosine, and monoiodotyrosine, which are liberated into the cytoplasm.
- The free $T_4$ and $T_3$ cross the basolateral cell membrane and are discharged into the capillaries.
- Monoiodotyrosine and diiodotyrosine are not secreted into the blood, and their iodine is removed by a deiodinase. The products of this enzymatic reaction (iodine and tyrosine) are reused by the follicular cells.
- $T_4$ is the more abundant compound, constituting 90% of the circulating thyroid hormone, although $T_3$ acts more rapidly and is more potent.

## CLINICAL CORRELATION

HYPOTHYROIDISM

Hypothyroidism in the fetus may present at birth as **cretinism**, characterized by arrested or retarded physical and mental development.

Adult hypothyroidism may result from diseases of the thyroid gland (eg, due to defects in hormone synthesis or release) or may be secondary to pituitary o rhypothalamic failure.

Autoimmune diseases of the thyroid, such as **Hashimoto disease**, may impair its function, with consequent hypothyroidism.

A diet low in iodide hinders the synthesis of thyroid hormones, causing increased secretion of TSH and compensatory growth of the thyroid gland, a condition known as **iodine deficiency goiter**. Goiters are endemic in some regions of the world, where dietary iodide is scarce and addition of iodide to table salt is no trequired.

The signs and symptoms related to hypothyroidism include fatigue, increased sensitivity to cold, pale skin, constipation, muscle pain and weakness, and weight gain.

HYPERTHYROIDISM

Hyperthyroidism may be caused by a variety of thyroid diseases, of which the most common form is **Graves' disease**, characterized by inflammation and growth of the extraocular adipose tissue, which leads to the bulging of the eyes (exophthalmos). In this thyroid disorder hyperfunction is due to an autoimmune response involving antibodies to TSH receptors. These antibodies can bind the receptors on follicular cells and act as long-lasting thyroid stimulators, continuously stimulating thyroid hormone secretion and producing many effects of hyperthyroidism such as decreased body weight and accelerated heart rate.

# Parathyroid Gland

- The four small **parathyroid glands** typically lie on the posterior surface of the thyroid gland and are separated from the thyroid gland by a connective tissue capsule. Connective tissue septa with blood vessels divide each parathyroid gland into many incomplete lobules.
- The parathyroid glands are derived from the endoderm of pharyngeal pouch 3 (the inferior glands) and pouch 4 (the superior parathyroid glands).
- There are two types of cells in the gland: **chief (principle) cells** and **oxyphilcells.** Adipocytes are commonly found in the glands in older individuals.
- The **chief cells** are small polygonal cells with round nuclei and pale-staining, slightly acidophilic cytoplasm. Ultrastructurally the cytoplasm is seen to be filled with irregularly shaped granules. These are secretory granules containing the polypeptide **parathyroid hormone** (**PTH**).
- Much smaller, often clustered, populations of **oxyphil cells** are sometimes present. These are much larger than the principal cells and are characterized by acidophilic cytoplasm filled with abnormally shaped mitochondria. Some oxyphil cells show low levels of PTH synthesis, suggesting these cells are transitional derivatives from chief cells. The oxyphil cells appear at puberty, and their numbers increase with age. Their functions are unclear.

### *Action of Parathyroid Hormone & Its Interrelation with Calcitonin*

- PTH binds to receptors in osteoblasts. This is a signal for these cells to produce an ***osteoclast-stimulating factor***, which increases the number and activity of osteoclasts and thus promotes the absorption of the calcified bone matrix and the release of $Ca^{2+}$ into the blood. The resulting increase in the concentration of $Ca^{2+}$ in the blood suppresses the production of PTH.
- Calcitonin from the thyroid gland also influences osteoclasts by inhibiting both their resorptive action on bone and the liberation of $Ca^{2+}$. Calcitonin thus lowers blood $Ca^{2+}$ concentration and increases osteogenesis; its effect is opposite to that of PTH.
- These two hormones constitute a dual mechanism to regulate blood levels of $Ca^{2+}$, an important factor in homeostasis.
- PTH indirectly increases the absorption of $Ca^{2+}$ from the GIT by stimulating the synthesis of vitamin D, which is necessary for this absorption.
- In addition to increasing the concentration of $Ca^{2+}$, PTH reduces the concentration of phosphate in the blood. This effect is a result of the activity of PTH on kidney tubule cells, diminishing the absorption of phosphate and causing an increase of phosphate excretion in urine.
- The secretion of parathyroid cells is regulated by blood $Ca^{2+}$ levels.

# PINEAL GLAND

- The **pineal gland**, also known as the pineal body or epiphysis cerebri. It is a very small, pine cone-shaped organ in the brain. It develops with the brain from neuroectodermin the roof of the diencephalon and is found in the posterior of the third ventricle, attached to the brain by a short stalk.
- The gland is covered by C.T of the pia mater, from which emerge septa containing small blood vessels and dividing the gland in to lobules.
- It is composed of two types of cells: **pinealocytes** and **Interstitial glial cells**.
- The prominent and abundant secretory cells are the **pinealocytes**, which have slightly basophilic cytoplasm and large, irregular euchromatic nuclei and nucleoli. 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 LMW tryptophan derivative. Unmyelinated sympathetic nerve fibers enter the pineal gland and end among pinealocytes, with some forming synapses.
- **Interstitial glial cells** of the pineal gland stain positively for glial fibrillary acidic protein and thus most closely resemble astrocytes. They have elongated nuclei more heavily stained than those of pinealocytes, long cytoplasmic processes, and are usually found in perivascular areas and between the groups of pinealocytes. Pinealastrocytes represent only about 5% of the cells in the gland.
- 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, which form by precipitation around extracellular protein deposits. Such concretions appear during childhood and gradually increase in number and size with age, with no apparent effect on the gland's function.
- Accumulations of brain sand are opaque to x-rays and allow the pineal to serve as a good midline marker in radiological and CT studies of the brain.

### Role of the Pineal Gland in Controlling Biological Cycles

Melatonin release from pinealocytes is promoted by darkness and inhibited by daylight and 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 pinealocytes 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 nerve input regarding light and darkness into variations in many hormonal functions.

*The End*