

LEARNING OBJECTIVES OUTLINE

I. PITUITARY GLAND (HYPOPHYSIS)

A. Organization

1. Adenohypophysis (anterior lobe)
 - a. Pars distalis (pars anterior)
 - b. Pars intermedia
 - c. Pars tuberalis
2. Neurohypophysis (posterior lobe)
 - a. Pars nervosa (neural lobe)
 - b. Infundibulum
 - c. [Median eminence]

B. Cells of pars distalis

1. Acidophils
 - a. Lacto(=mammo-)tropes (PRL)
 - b. Somatotropes (GH)
 - c. Mammosomatotropes (GH&PRL)
2. Basophils
 - a. Gonadotropes (LH; FSH)
 - b. Thyrotropes (TSH)
 - c. Corticotropes (ACTH, LPH, β -endorphin)
3. Chromophobes
 - a. Degranulated acidophils & basophils
 - b. Stem cells
 - c. Folliculostellate cells
4. Folliculostellate cells
 - a. Specialized glia-like cells
 - i. Express S-100 protein
 - ii. Exhibit membrane excitability
 - b. Major pituitary cell expressing gap junctions
 - c. Major fxns: TBD, but may provide intrinsic control of chromophils

C. Pars intermedia

1. Cells
 - a. Basophils
 - b. Chromophobes
2. Poorly developed in humans
3. Functions: TBD

D. Pars tuberalis

1. Cells
 - a. Basophils (gonadotropes)
 - b. Undifferentiated cells
2. Function: TBD

E. Pars nervosa

1. Components
 - a. Pituitocytes (glial cells)
 - b. Unmyelinated axons
 - i. Oxytocin
 - ii. Vasopressin (ADH)
 - iii. Neurophysins (BPs)
 - iv. Herring bodies
2. Other cells
 - a. Fibroblasts
 - b. Mast cells
 - c. Endothelial cells
3. Origin of axons
 - a. Paraventricular nucleus
 - b. Supraoptic nucleus

F. Hypothalamic-pit.-endocrine axes

1. Hypothalamus
 - a. Median eminence
 - b. Releasing/inhibitory hormones
 - c. Hypophysial portal system
2. Pituitary hormones
3. Endocrine target organs (e.g., adrenal, ovary, testis, thyroid)

II. THYROID GLAND

A. Organization

1. Lobes
 - a. Lateral (right>left, typically)
 - b. Isthmus
 - c. [Pyramidal: absent or small]
2. Foramen cecum-thyroglossal duct
 - a. Accessory thyroid tissue
 - b. Thyroglossal cysts

B. Components

1. Stroma
 - a. Fibrous capsule
 - b. Interstitium
 - i. Loose CT
 - ii. Fenestrated capillaries
2. Parenchyma
 - a. Follicular elements
 - b. Parafollicular cells
3. Follicles
 - a. Follicular cells
 - b. Colloid
 - i. Thyroglobulin
 - ii. Extracellular storage of

- hormone precursors
- c. Iodination
 - i. Tyrosine residues
 - ii. Occurs at microvillous border
- d. Release of thyroid hormones
 - i. Endocytosis of colloid
 - ii. Lysosomal cleavage
 - iii. Secretion of hormones
- 4. Parafollicular ("C") cells
 - a. Clear cells
 - b. Secrete calcitonin
 - c. From ultimobranchial body (5th[4] pharyngeal pouch)

C. Hormones

- 1. Triiodothyronine (T₃) & thyroxine (T₄)
- 2. Calcitonin

III. PARATHYROID GLANDS

A. Organization

- 1. Superior
- 2. Inferior
- 3. [Accessory]

B. Cells

- 1. Principal (chief) cells
 - a. Major cell type
 - b. Secrete parathyroid hormone
- 2. Oxyphil (eosinophil) cells
 - a. Eosinophilic: many mitochondria
 - b. Function: TBD
 - c. Increase in number with age

C. Parathyroid hormone (parathormone; PTH)

- 1. 84 AA polypeptide
- 2. Secretion controlled by [Ca]
- 3. Action
 - a. Antagonistic to calcitonin
 - b. Increases blood [Ca]
- 4. Clinical significance
 - a. Hyposecretion: tetany
 - b. Hypersecretion: loss of bone mineral, hypercalcemia

IV. SUPRARENAL (ADRENAL) GLANDS

A. Organization

- 1. Capsule
- 2. Cortex
- 3. Medulla
- 4. [Accessory tissues]
 - a. Extraadrenal cortical tissue
 - b. Extraadrenal medullary (chromaffin) tissue

B. Cortex

- 1. Zones
 - a. Glomerulosa (ZG)
 - b. Fasciculata (ZF)
 - c. Reticularis (ZR)
- 2. Hormones (corticosteroids)

- a. Mineralocorticoids
 - i. Major hormone: aldosterone
 - ii. Zone: glomerulosa
 - iii. Control: renin-angiotensin
- b. Glucocorticoids
 - i. Hormones: Cortisol, corticosterone
 - ii. Zone: fasciculata>reticularis
 - iii. Control: ACTH
- c. Gonadocorticoids
 - i. Hormone: DHEA (major)
 - ii. Zone: reticularis>fasciculata
 - iii. Control: ACTH

C. Medulla

- 1. Cells
 - a. Chromaffin cells
 - i. Stain with chromium salts
 - ii. Chromaffin reaction
 - b. Origin: postganglionic sympathetic neurons
- 2. Hormones
 - a. Epinephrine (Br. =adrenalin)
 - b. Norepinephrine (Br. =noradrenalin)

D. Blood supply

- 1. Cortical and medullary
- 2. Effect on medullary output
- 3. Central vein

V. PANCREATIC ISLETS (of Langerhans)

A. Number & distribution

- 1. >1 million islets
- 2. Majority in tail of pancreas

B. Cell types

- 1. A cells
 - a. More peripheral location
 - b. 15-20%
 - c. Secrete glucagon
- 2. B cells
 - a. More central location
 - b. ~70%
 - c. Secrete insulin
- 3. D cells
 - a. Peripheral location
 - b. 5-10%
 - c. Secrete somatostatin
- 4. Other types
 - a. ~5%
 - b. Secrete PP, VIP, secretin

C. Hormones

- 1. Glucagon
 - a. 29 AA polypeptide
 - b. Elevates blood [glucose]
- 2. Insulin
 - a. Complex polypeptide
 - i. A chain: 21 AA
 - ii. B chain: 30 AA
 - iii. Disulfide bridges
 - b. Lowers blood [glucose]

3. Somatostatins
 - a. S-14: tetradecapeptide (14 AA)
 - b. S-28: 28AA (minor amounts)
 - c. Inhibit secretion of A & B cells, especially A cells.

VI. PINEAL GLAND (PINEAL BODY)

A. Components

1. Pinealocytes (cords & follicles)
2. Interstitial cells (astroglia)
3. Pineal calcifications: 2 types
 - a. Corpora arenacea (=brain sand)
 - i. Large mulberry-like concretions (LM visible)
 - ii. Hydroxyapatite, protein, glycoprotein
 - iii. Increase with age
 - b. Myeloconia (=brain dust)
 - i. 10-20µm crystals (EM visible)
 - ii. Calcite (CaCO₃), glycoprotein

B. Hormones

1. Indole amines: melatonin (major)
 - a. Roles in light-dark cycles
 - i. Circadian rhythms
 - ii. Reproductive events
 - iii. Disrupted by phase shifts (e.g., jet lag)
 - iv. Seasonal affective disorder
 - b. Important antioxidant function
 - i. Tumor suppression
 - ii. Scavenger of hydroxyl radical and singlet O
2. Polypeptides (PPs)
 - a. Neuro-epiphysins (carrier BPs)
 - b. Exchange of PPs for Ca on BPs after secretion (exocytosis) may ppt brain sand.

OVERVIEW

The Endocrine Glands consist of diverse tissues and organs that coordinate the activity of other body tissues and organs by means of specific molecules called **hormones** [Gr. *ormao*, *hormōn* =I arouse, excite, stir up, set into motion] (see Starling EH *Lancet* 166:339-441, 1905). From the glands where they are produced, these endocrine signals are transported in the blood (and other body fluids), often bound to **specific binding proteins**, to their **targets** (cells, tissues or organs) where they exercise a particular effect or response via specific **receptors**. Some endocrine glands may be under CNS influence, whereas others may be responsive to changes in their surrounding milieu. All are highly vascular and characterized by fenestrated capillaries or larger

fenestrated sinusoidal capillaries.

PITUITARY GLAND

Description. The **pituitary gland** [L. *pituita* =phlegm; originally thought to be source of nasal mucous] or **hypophysis** is an endocrine organ of dual origin that lies at the base of the brain below the hypothalamus. It is located in a bony cavity of the sphenoid bone called the **sella turcica**.

1. Major parts. Two major parts of the pituitary consist of the **adenohypophysis** and the **neurohypophysis**. The latter is connected to the **median eminence** of the hypothalamus by an isthmus of neural tissue called the **infundibulum**.

2. Control and primary function. Under the extrinsic influence of the hypothalamus, the adenohypophysis of the pituitary gland exerts its control over other endocrine glands by secretion of a variety of **tropic** [Gr. =turning, reaction] **hormones** (also referred to as trophic [Gr. =nutrition] hormones). Recent evidence also suggests that there is an important intrinsic control that may be directed by putative “conductor” cells within the local 3-D network of the adenohypophysis (e.g., Fauquier T et al. *Trends Endocrinol Metab* 13:304-309, 2002). The function of the neurohypophysis appears to be primarily directed by the NCBs in hypothalamic nuclei (i.e., paraventricular and supraoptic).

Development and Composition. The division of the pituitary into adenohypophysis and neurohypophysis is based on its embryological origins.

1. Adenohypophysis arises from an outpocketing of the oral ectoderm in the roof of the primitive mouth (stomodeum) called the **pituitary diverticulum** (=Rathke pocket/pouch).

a. Subdivisions. The adenohypophysis is subdivided into **pars distalis**, **pars tuberalis**, and **pars intermedia**.

b. Anterior lobe. Although there is some diversity in terminology, the **anterior lobe of hypophysis** is considered as an alternate term for adenohypophysis. (*Terminologia Anatomica: International Anatomical Terminology*, Thieme Stuttgart, 1998; see Table 29-1 for alternate definition).

2. Neurohypophysis is derived from neural tissue at the base of the brain (infundibular process of diencephalon; floor of 3rd ventricle) and grows

downward to take a position that is posterior to the adenohypophysis.

a. Subdivisions. This portion consists principally of the **pars nervosa** (neural lobe of hypophysis; pars nervosa) and the **infundibulum** (neural stalk). Some authors also include the **median eminence** of the tuber cinereum as a division.

b. Posterior lobe. Again, although there is some diversity in terminology, the **posterior lobe of the hypophysis** is often used synonymously with neurohypophysis. (*Terminologia Anatomica: International Anatomical Terminology*, Thieme Stuttgart, 1998; see Table 29-1 for alternate definition).

Table 29-1. Divisions of the Hypophysis in Mammals*

Neurohypophysis	Infundibulum	
	Pars nervosa	} Posterior lobe
Adenohypophysis	Pars intermedia	<-----Residual lumen
	Pars distalis	} Anterior lobe
	Pars tuberalis	

 *While this division of anterior and posterior lobes can be viewed as more historical (viz. posterior lobe consisting of those portions posterior to residual lumen), human terminology now equates adenohypophysis with anterior lobe and neurohypophysis with posterior lobe (*Terminologia Anatomica: International Anatomical Terminology*, Thieme Stuttgart, 1998)

Pars distalis functions in the production, storage, and release of various polypeptide hormones.

1. Description. With the light microscope, this area appears as clusters or cords of cells within and surrounded by a rich network of fenestrated sinusoidal capillaries.

2. Cell types. Based on their histologic staining properties, cells of the pars distalis are classically described as **acidophils**, **basophils**, and **chromophobes**. Together, acidophils and basophils are referred to as **chromophils**. Thus, anterior pituitary cells are classified in general terms as either chromophils (based on their affinity for acidic or basic dyes) or chromophobes (based on their lack of affinity for these dyes).

a. Acidophils contain large granules that stain with eosin and other acid dyes. Immunologic techniques are used as the “gold standard” to subdivide the acidophils with accuracy.

i. Somatotropes (somatotrophs), which account for about 50% of pars distalis cells, secrete growth hormone [GH; somatotropin, or somatotrophic hormone (STH)]. They are influenced by growth hormone releasing hormone (GHRH) and somatostatin from the hypothalamus.

ii. Mammotropes (mammotrophs, lactotropes/trophs) account for 15-20% and secrete prolactin (PRL); they increase in number and size during pregnancy and lactation. They are influenced by thyroid releasing hormone (TRH) and vasoactive intestinal peptide (VIP).

iii. Mammosomatotropes (mammosomatotrophs) are acidophils that not only secrete both GH and PRL, but also may be characterized by containing both hormones in the same secretory granules (Asa SL et al. *Neuroendocrinology* 48:423-431, 1988; Losinski NE et al. *Anat Anz* 172:11-16, 1991).

b. Basophils have been identified by a number of staining techniques, including the PAS reaction for those basophils which contain glycoprotein hormones. However, immunohistochemistry is also used as the “gold standard” to identify these subtypes accurately.

i. Gonadotropes (gonadotrophs), which make up less than 10% of the total, are large round cells that secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). They are influenced by gonadotropin-releasing hormone (GnRH; LHRH) from the hypothalamus.

ii. Thyrotropes (thyrotrophs), about 5% of total cells, produce thyroid-stimulating hormone (TSH). They are influenced by TRH.

iii. Corticotropes (corticotrophs) account for 15-20% of cells and produce adrenocorticotrophic hormone (ACTH). They are influenced by corticotropin-releasing hormone (CRH).

c. Chromophobes are best described as agranular cells whose cytoplasm remains unstained or poorly stained with histologic dyes. They appear to represent a diverse population of cells which include the following.

i. Stem cells that are in reserve for differentiation into other cell types.

ii. Degranulated chromophils. Acidophils and basophils that have partially or fully discharged their granules during secretion have the appearance of chromophobes.

iii. Folliculostellate cells (see next section)

d. Folliculostellate (FS) cells form a complex network of nongranular cells that extend throughout the adenohypophysis.

i. Structure. Originally “lost” in the noise levels afforded by the category of chromophobes and subsequently discovered with EM as a separate cell type, they came to be regarded as a 6th type of parenchyma cell (Rinehart, JF & Farquhar, M. *J Histochem Cytochem* 1:93-113, 1953; *Anat Rec* 121:207-240, 1955). Later FS cells were shown to exhibit two distinct morphologies: “follicular” (grouped around small cavities or follicles containing colloid) and “stellate” (cytoplasmic extensions but not associated with follicles). It is now known that they have glial properties, e.g., expression S-100 protein, highly excitable, and capable of action potentials (Fauquier, T et al. *PNAS* 98:8891-8896, 2001; *Trends Endocrinol Metab* 13:304-309, 2002). They form an extensive 3-D architecture connected together with themselves and with hormone cells via extensive gap junctions (e.g., Soji, T & Herbert, DC. *Anat Rec* 224:523-533, 1989).

ii. Function. Although the precise function(s) of FS cells remain to be determined fully, evidence is accumulating that suggests they are important for local control. They have been postulated as forming an intrinsic control function that synchronizes activities of the various hormone cells throughout the adenohypophysis. Whether this hypothesis can support the debate favoring an autonomous functioning of the anterior pituitary remains to be determined. In this regard, the dogma that the anterior pituitary is principally controlled by releasing hormones from the hypothalamus, which reach the pituitary via the hypophysial portal system, may need to be revised. It has also been suggested that FS cells may be a type of pluripotential adult stem cell (Inoue K et al. *Arch Histol Cytol* 62:205-218, 1999; Horvath E, Kovacs K. *Ultrastructural Pathol* 26:219-228, 2002).

e. One cell-one hormone theory. Although the classic description of anterior pituitary hormones has been that one cell type produces one hormone, evidence is presently available for plurihormonal cells (e.g., Horvath E *Pathol Res Practice* 183:631-633, 1988).

Pars tuberalis surrounds the infundibulum of the neurohypophysis.

1. Composition. It consists of highly vascularized cords of epithelial cells forming a thin sheath around the stalk of the infundibulum.

2. Function of this region in humans is not known with certainty.

Pars intermedia is present in humans during fetal life, but is greatly reduced in adults. This portion is

also referred to as the *intermediate lobe*. Some authors, particularly those in earlier literature, consider it to be part of the posterior lobe (see Table 29-1), because it lies posterior to the residual (or potential residual) lumen/lumina, which represent(s) remnants of the Rathke pouch.

i. Structure. In most human pituitaries, the intermedia is small and poorly represented. It consists of granular basophil cells, which are typically smaller than those in the pars distalis, and chromophobes. The basophilic cells often extend for some distance into the pars nervosa (Rasmussen AT. *Endocrinology* 2:129, 1928), a phenomenon that is referred to as *basophil invasion of the neural lobe*. Remnant(s) of Rathke pouch may occur as a cleft or more likely as a group of cysts. These cysts are largely surrounded by chromophobe-type cells and contain a colloidal fluid.

ii. Function. Due to its minimal development in adult humans, the intermediate lobe has been considered to be vestigial. However, recent studies suggest that this notion may not be correct. For example, it has been shown that *orexin type 2 receptors* are abundantly localized in cells of the human pars intermedia (Blanco M et al. *J Clin Endocrinol Metab* 86:1616-1619, 2001). **Orexins** [Gr. *orexis* =appetite] are hypothalamic peptides that have been shown to have a role in the stimulation of food intake (de Lecea L et al. *Proc Natl Acad Sci USA* 95:322-327, 1998; Sakurai T et al. *Cell* 92:573-585, 1998). In other mammals, the pars intermedia is composed of cords of weakly basophilic cells that synthesize melanocyte-stimulating hormone (MSH). Apparently, this is not the case in humans.

Paraventricular and supraoptic nuclei of the hypothalamus contain the cell bodies of the secretory neurons that produce the neurohypophysial hormones. Due to the larger size of the cell bodies of these neurons, they are often called **magnocellular** [L. *magnus* =large] neurons.

Hypothalamohypophysial tract. Extending from the paraventricular and supraoptic nuclei of the hypothalamus through the median eminence, infundibulum and into the pars nervosa is the aggregate of unmyelinated axons collectively belonging to **hypothalamohypophysial tract**.

Pars nervosa

1. Composition. The pars nervosa is composed principally of nerve cell processes, glial cells, and capillaries.

a. Nerve cell processes consist of the axons and axon termini of magnocellular neurons, whose NCBS are located in the hypothalamic

suproptic and paraventricular nuclei.

b. Glia. Surrounding the nerve terminals in the pars nervosa are numerous supporting glial cells called **pituicytes**.

c. Other components.

i. Ganglion cells resembling the magnocellular NCBs of the hypothalamus have been identified in the posterior pituitary (e.g., Horvath, E et al. *Acta Neuropathol* 100:106-110, 2000). In this case report, which also summarized controversial previous findings from 1940, large ganglion cells were clearly observed in a normal adult pituitary by histologic and immunochemical techniques at the LM level. The significance of this finding and previous observations remains to be determined, but since this occurrence appears to be rare based on the very few reports that have been published it may not be a typical feature of the pars nervosa.

ii. Basophilic cells. As mentioned above, small basophils from the intermediate lobe have been observed to extend into the pars nervosa. Their significance remains to be determined.

2. Hormones of the pars nervosa are the polypeptides **oxytocin** and **vasopressin**.

a. Production. Hormones are produced in hypothalamic NCBs, packaged into secretory granules, and moved by axoplasmic transport to the pars nervosa. Here, the hormones together with their binding proteins (**neurophysins**) accumulate in nerve terminals near capillaries awaiting secretion. Large aggregates of secretory products in the pars nervosa, which are visible with the light microscope, are called **Herring bodies**.

b. Secretion from the axon termini (=neurosecretion) occurs by exocytosis upon stimulation of their NCBs in the brain.

Vascular supply of the hypophysis is variable, but typically there are two superior hypophysial arteries on each side of the organ: the anterior and posterior superior hypophysial arteries.

1. Adenohypophysis. These vessels supply the median eminence and the stalk of the infundibulum and form primary looped sinusoidal capillaries that drain into venous trunks of the **hypophysial portal system**, which supplies the adenohypophysis. The portal system terminates in the sinusoidal capillaries in the anterior lobe. This system conducts neurohormones from the median eminence to the adenohypophysis.

2. Neurohypophysis. The anterior and posterior inferior hypophyseal arteries supply the neurohypophysis and form an arterial circle at the junction to the anterior and posterior lobes.

3. Type of capillaries. Both the adenohypophysis and the neurohypophysis are perfused with sinusoidal capillaries lined with fenestrated endothelium.

THYROID GLAND

Description. The thyroid [Gr. *thyreos* = oblong shield + *eidos* = form] gland is a lobulated organ that generally consists of two pear-shaped lateral lobes connected by an isthmus. It takes its name from the nearby thyroid cartilage, whose shape apparently reminded early anatomists of the shields used by Greek warriors.

1. Location. The thyroid is located in the cervical region, just anterior to the larynx and slightly inferior to the thyroid cartilage.

2. Variations. A pyramidal lobe is frequently present, and points upward from the isthmus near the left lobe.

a. Accessory thyroid tissues may occur along the path of the thyroglossal duct from their embryologic origin at the foramen cecum (base of tongue) of the oral cavity.

b. Thyroglossal cysts, which are cystic remnants of the thyroglossal duct, may also occur along the migratory path of the thyroid.

Function. This gland synthesizes and secretes the thyroid hormones **triiodothyronine (T₃)** and **tetraiodothyronine (T₄, thyroxine)**, which regulate cell metabolism, development, growth and differentiation; and **calcitonin**, which participates in the regulation of calcium homeostasis.

Stroma of the gland consists of a thin fibroelastic capsule from which connective tissue septa penetrate, incompletely dividing the gland into lobules. Within lobules, a delicate reticular stroma contains an extensive capillary network.

Parenchyma of the thyroid is arranged in the form of **follicles** that are lined typically by a simple cuboidal epithelium. This **follicular epithelium** surrounds a central lumen filled with colloid, which is mainly composed of a large secretory glycoprotein called **thyroglobulin**.

1. Development. Initially, epithelial parenchymal cells form clusters, which then secrete their products into a central lumen called the follicular cavity.

2. Follicles are the structural and functional units of the gland whose secretory precursor product is stored within the follicular cavity. Two cell types are associated with the follicles: **follicular cells** and **parafollicular cells**.

a. Follicular cells, which are the principal cells of the thyroid, form the continuous epithelial lining of the follicles.

i. Appearance. Typically, follicular epithelial cells are cuboidal and their nuclei are spherical in shape. The cytoplasm exhibits basal basophilia and apical PAS-positivity, which supports the presence of glycoprotein. Their apical surfaces, which face the follicular cavity and contain a fine microvillous border as seen with the EM, is where thyroglobulin is released into the follicle lumen. A basal lamina completely surrounds the follicles at the basal surfaces of the epithelial cells. *In periods of increased activity* the follicular cells are more columnar and the colloid is less abundant; *in periods of decreased activity* cell height declines toward squamous and colloid content increases.

ii. Secretory product. Follicular epithelial cells are responsible for the synthesis and secretion of the principal hormones T₄ and T₃ (see below), which are commonly referred to as thyroid hormone(s).

b. Parafollicular cells or **C cells** are also associated with the follicles, but are completely separated from the colloid by follicular cells. C cells are responsible for the secretion of calcitonin.

i. Appearance. Although difficult to find in routine histologic preparations, these cells are characterized by a pale-staining cytoplasm, which is responsible for the name C (=clear) cell. At the EM level, they contain abundant secretory granules and are located within the basal lamina of the follicle. Since all cells rest on the basal lamina but C cells do not reach the lumen, the follicular epithelium might more correctly be termed pseudostratified.

ii. Secretory product. As already indicated, C cells are responsible for the synthesis and secretion of the hormone calcitonin (=thyrocalcitonin). This peptide hormone (32 amino acids) participates in the regulation of calcium homeostasis. Specifically, calcitonin action lowers blood calcium levels.

Synthesis of thyroid hormones (T₃ and T₄) occurs as follows.

1. Translation. Thyroglobulin is synthesized on membrane-bound ribosomes of the RER where the nascent polypeptide is discharged into the cisternae of the ER.

2. Glycosylation. From the ER the polypeptide is transported to the Golgi where peripheral sugar residues are added.

3. Secretion of thyroglobulin. The glycoprotein precursor molecules are secreted into the lumen of the thyroid follicles.

4. Iodination of tyrosine residues in thyroglobulin occurs at follicular cell surfaces and is catalyzed by thyroid peroxidase enzymes localized along the microvillous borders. The thyroid gland actively extracts and accumulates iodide ions from the blood via a specific transporter.

5. Reuptake of colloid. Under stimulation of TSH, endocytosis of colloid (which now contains iodinated thyroglobulin molecules) by follicular cells occurs.

6. Intracellular processing of colloid. Endocytotic vesicles fuse with cytoplasmic lysosomes resulting in hydrolysis of thyroglobulin and liberation of T₃ and T₄ molecules.

7. Secretion of thyroid hormones. T₃ and T₄ are released from the basolateral surfaces of follicular cells and make their way into the general circulation via adjacent fenestrated capillaries.

Vascular supply of the thyroid includes a rich network of fenestrated capillaries that are closely apposed to the follicular epithelium. The thyroid is supplied by paired superior thyroid arteries (branches of the external carotids) and paired inferior thyroid arteries (branches of the thyrocervical trunks).

PARATHYROID GLANDS

Description. The parathyroids usually consist of four glands located behind the thyroid or occasionally embedded within it.

Function. These glands synthesize and secrete **parathyroid hormone (PTH)**, which is a polypeptide (84 amino acids) that participates in the regulation of calcium concentrations in bone and

body fluids.

Stroma of each gland is covered by a delicate connective tissue capsule from which septa penetrate, dividing the gland into incomplete lobules. Richly vascularized, the stroma contains many reticular fibers.

Parenchyma. The epithelial parenchymal cells, arranged in irregular cords or clusters, are composed of two cell types: **parathyroid chief cells** and **oxyphil cells**.

1. **Chief (principal) cells** of parathyroid glands are polyhedral in shape with round nuclei. They are generally arranged in cords, which often present a whorl-like appearance. Occasionally they also occur in clusters. They are responsible for the synthesis and secretion of PTH, which is released into the surrounding fenestrated capillaries.

2. **Oxyphil cells**, which have also been called Hürthle cells, are larger and much less numerous than the chief cells. They appear as strongly eosinophilic cells with smaller more heterochromatic nuclei. They may occur as solitary cells or as small to large groups surrounded by chief cells.

a. **Eosinophilia.** The prominent eosinophilic granule-like structures in their cytoplasm have been identified as mitochondria. Often these organelles may have bizarre shapes that are not typical of normal mitochondria.

b. **Significance.** Whether oxyphil cells represent different functional states of chief cells, a distinct cell type, or an abnormal cell remains to be determined.

Parathyroid hormone (PTH) increases the serum calcium concentration by acting at several levels including: increasing bone resorption, decreasing renal excretion, and increasing gastrointestinal uptake of calcium.

1. **Bone resorption.** PTH acts initially on osteocytes of bone tissue (**osteocytic osteolysis**) and eventually on osteoclasts (**osteoclastic resorption**) to resorb calcium from bone matrix and make it available to the circulation.

2. **Kidney function.** In addition to decreasing calcium excretion, PTH also increases renal excretion of phosphate.

3. **Control.** Secretion of the hormone is controlled by blood calcium and magnesium levels

and appears to be independent of endocrine or neural inputs.

Blood supply of the parathyroids is from the superior and inferior thyroid arteries.

SUPRARENAL (ADRENAL) GLANDS

Description. The suprarenals (adrenals) are paired glands, each about 4-6 cm in length, located retroperitoneally adjacent to the cranial (hence, *supra-*) poles of the kidneys.

Stroma of the adrenal glands consists of a thick connective tissue capsule that sends trabeculae of collagenous and reticular fibers into the glandular tissue.

Parenchyma. The glandular parenchyma is divided into a cortex that secretes steroid hormones (derivatives of cholesterol) and a medulla that secretes catecholamines (derivatives of tyrosine).

Adrenal cortex contains cells that synthesize and secrete **glucocorticoids**, **mineralocorticoids**, and certain **gonadocorticoids** (sex steroid hormones that are also produced in the gonads), which are all cholesterol derivatives. Typically, most cortical cells contain numerous lipid inclusions, which represent stored cholesterol ester precursors. In routine histologic preparations, these cells are characterized by a highly vacuolated cytoplasm, i.e., many delicate empty spaces where the lipid was extracted during tissue processing. This appearance is the reason why these cells are often referred to as **spongiocytes**. At the EM level spongiocytes exhibit the *characteristic features of steroid-secreting cells*: abundant smooth ER, mitochondria that typically contain tubular cristae, and the presence of lipid (cholesterol ester) inclusions.

The cortex consists of three concentric layers of epithelioid cells with abundant fenestrated capillaries.

1. **Zona glomerulosa (ZG)** [*L. glomus* = ball) is the outermost narrow zone where acidophilic columnar-like cells are arranged in groups (that often resemble “little balls” of cells) surrounded by capillary networks.

a. **Cells** in the ZG can range from cuboidal to columnar to pyramidal in shape. Typically, they contain less lipid inclusions than those in the middle zone.

b. Hormones and action. ZG cells secrete the steroid hormones known as mineralocorticoids, which in humans is mainly **aldosterone**. This hormone is important for electrolyte homeostasis and water balance. It acts principally on the distal tubules of the kidney, and also on salivary (striated ducts) and sweat glands, to influence the reabsorption of sodium.

c. Control. The synthesis and release of aldosterone is controlled principally by angiotensin II and plasma $[K^+]$, although ACTH and ANP from the heart may also stimulate secretion of mineralocorticoids to a lesser extent. Thus, the role of the ZG in sodium homeostasis appears to be controlled mainly by the renin-angiotensin system.

2. Zona fasciculata (ZF) [L. *fascis* =bundle] is a wide zone (approximately 80% of cortex by volume) with its cells organized in "little bundles" of cords, which course radially inward from the zona glomerulosa toward the medulla.

a. Cells are polyhedral or cuboidal, often binucleate, and exhibit the typical spongiocyte appearance.

b. Capillaries. A longitudinal meshwork of sinusoidal capillaries extends along the length of the cords.

c. Hormones and action.

i. Glucocorticoids. ZF cells mainly secrete glucocorticoids, including the principal hormone **cortisol**. They have major effects on carbohydrate, protein, and lipid metabolism.

ii. Sex steroids. This zone also secretes some gonadocorticoids including androgens.

d. Control. The cells of this zone are stimulated by ACTH from the adenohiphysis.

3. Zona reticularis (ZR) [L. *rete* =a net] is a smaller region adjacent to the corticomedullary junction in which the cells are arranged in "little networks" of irregular cords.

a. Cells are typically smaller than those in the ZF. They also typically contain fewer lipid inclusions.

b. Hormones. ZR cells secrete mainly androgens especially **dehydroepiandrosterone (DHEA)**, which are probably not significant in males compared to the testicular output of androgens, but may account for as much as 50% of circulating

androgens in females. This zone also secretes some glucocorticoids (cortisol).

c. Control. ZR cells also appear to be under the influence of ACTH.

Adrenal medulla consists of cells that are arranged in anastomosing cords intermingled with capillaries and venules.

1. Cells. These large, plump epithelioid cells are intimately located with sinusoidal capillaries and preganglionic sympathetic fibers.

a. Staining. Although relatively pale in routine preparations, these cells exhibit brown cytoplasmic granulations when exposed to chromium salts (**chromaffin reaction**); this coloration is due to oxidation of the catecholamines in their cytoplasmic granules. Thus, based on this reaction, medullary cells belong to a group of cells that are collectively known as **chromaffin cells**.

b. Types. Two types of chromaffin cells are identified by special histochemical techniques or TEM.

i. E-cells store epinephrine and are typically characterized by containing small granules, which often appear homogeneous in electron micrographs.

ii. NE-cells store norepinephrine and are characterized by larger granules, which typically contain dense cores giving the appearance of eccentric "bulls-eyes". These cells also typically have a more intense chromaffin reaction.

2. Hormones and action. The cells produce and secrete the catecholamine hormones, **epinephrine (E)** and **norepinephrine (NE)**, which are stored in specific secretory granules with other components including proteins called **chromogranins**. Catecholamines increase heart rate, cardiac output, blood pressure, and respiratory rate. These functions, as well as participation in the "fight or flight" response, are similar to those of the sympathetic division of the autonomic nervous system.

3. Control. The medulla is under sympathetic control, and its hormones function in concert with the sympathetic outflow in the "fight-or-flight" response.

a. Endocrine influence. Hormones (glucocorticoids) produced in the cortex pass through the medulla, and are required by medullary cells for conversion of NE to E, especially during

stress.

b. Neural influence. Exocytosis of specific chromaffin granules is controlled by acetylcholine from preganglionic sympathetic fibers. Since adrenal medullary cells are modified postganglionic sympathetic neurons, they function as such, but deliver the contents of their “synaptic vesicles” into the circulation (neurosecretion) rather than into synapses with other cells (neurotransmission).

Blood supply of the adrenals comes from the superior, middle, and inferior suprarenal arteries.

Innervation of the adrenal glands is mainly sympathetic, and is carried via the splanchnic nerves.

1. Medulla. These autonomic fibers are the principal means of regulating release of catecholamines from the medulla.

2. Cortex. Although the cortex receives some fibers, these do not appear to play an important role in regulating release of cortical hormones.

PANCREATIC ISLETS (OF LANGERHANS)

Description. The pancreatic islets are rounded clusters of endocrine cells dispersed within the pancreatic exocrine tissue.

1. Number. There are over a million islets in the human pancreas and they make up approximately 1.5% of the volume of this organ.

2. Stroma. The islets are enclosed in delicate reticular capsules, a few fibers of which penetrate the islets.

Cells. The cells of the islets are polygonal in shape and are intimately intermingled with sinusoidal capillary networks.

1. Fine structure. With the electron microscope, these cells have the structure of cells synthesizing proteins: abundant RER, prominent Golgi complex, and secretory granules.

2. Types. Special staining techniques, especially immunohistochemical procedures, have identified several cell types within the islets.

a. Alpha (A) cells constitute approximately 15-20% of the cells found in the

endocrine pancreas.

i. Location. They are found mainly in the periphery of the islets.

ii. Hormones and action. They synthesize and secrete the polypeptide (29aa) hormone **glucagon**. The action of this hormone increases blood glucose levels, stimulates gluconeogenesis and glycogenolysis, and inhibits pancreatic acinar secretion.

b. Beta (B) cells are the major cell type and constitute between 60-80% of the islet cells.

i. Location. They are localized mainly in the center of the islets.

ii. Hormones. They secrete the protein hormone **insulin**, which is composed of an alpha chain (21aa) and a beta chain (30aa) held together by disulfide linkages. Synthesized as proinsulin, this precursor is cleaved and assembled to form insulin prior to secretion.

iii. Hormone action. Insulin's important action is in the decrease of blood glucose levels. In this regard, it stimulates cellular uptake of glucose, storage of glucose as glycogen (stimulation of glycogen synthase), and promotion of glucose utilization through glycolysis. The main targets of insulin are liver, skeletal muscle, and adipose tissue. In addition, insulin has been found to increase pancreatic acinar secretion.

c. Delta (D) cells constitute less than 5% of islet cells.

i. Location. They are found scattered throughout the islets, but mainly in the periphery.

ii. Hormones and action. They secrete the peptide **somatostatins (S-14; S-28)**, which apparently act locally to inhibit the secretion of glucagon, and perhaps of insulin as well.

d. PP (F) cells, which are typically peripherally located but usually mutually exclusive with A cells, are apparently more common in the ventral lobe. These cells secrete **pancreatic polypeptide** (36 amino acids), which may have an influence on pancreatic exocrine secretion.

e. Other cells and their products that have been identified include **D1 cells** (VIP), **EC cells** (secretion, motilin, substance P), and **G cells** (gastrin).

PINEAL GLAND

Description. The **pineal gland (body)** or **epiphysis** is attached to the roof of the third ventricle by a stalk.

1. Shape and size. The pineal [L. *pinea* =pine cone] is a cone-shaped body, which is less than 1 cm (about 5-8 mm) in length.

2. Organization. It is encapsulated (except at its point of attachment) by the pia mater. Connective tissue septa containing blood vessels and unmyelinated nerve fibers originate in the pia mater and penetrate the pineal gland to form irregular lobules around cellular cords and follicles.

Cells. The major cell types of the pineal consist of pinealocytes and interstitial cells.

1. Pinealocytes are epithelial-derived cells (from roof plate of diencephalon) with large, irregularly shaped nuclei with relatively large nucleoli. They produce indolamines, the principal one of which is **melatonin**. Embryonic pinealocytes express photoreceptors and have other characteristics of photoreceptor cells.

2. Interstitial cells are characterized by elongated darkly-staining nuclei. They are located between the cords of pinealocytes and perivascular areas. They are comparable to glial cells of the brain.

Innervation of the adult pineal gland is by postganglionic sympathetic fibers which arise in the superior cervical ganglion and terminate on pinealocytes. During development, a fetal nerve (nervus pinealis) connects the caudal pineal with the posterior commissure, but then disappears during fetal life.

Melatonin, an indolamine, is apparently the principal hormone synthesized by the pineal. It is synthesized from tryptophan and exhibits highest levels during the sleep/dark phase.

1. Function(s) in humans. The precise function(s) of this hormone in humans remains speculative, but is just beginning to be dissected.

a. Time-keeping functions for daily light/dark cycles. The pineal in humans has been implicated as a photosensitive organ involved with circadian rhythms. Phase-shifts in normal patterns, both short term (e.g., jet lag, day to night work cycles) and longer term (e.g., seasonal affective disorder) appear to disrupt normal patterns.

b. Antioxidant and tumor suppression properties. Recent evidence also suggests that pineal hormones may be important tumor suppressors by acting as scavengers of hydroxyl radicals and singlet oxygen (e.g., Allegra M et al. *J Pineal Res* 34:1-10, 2003; Tan D-X et al. *J Pineal Res* 34:75-78, 2003).

2. Other animals. In mammals, pineal hormones play a role in seasonal reproductive cycles. In amphibians, melatonin induces the aggregation of pigment granules in melanophores.

Pineal calcifications. Two types of calcifications in the pineal have been identified.

1. Corpora arenacea [L. *arena* =sand], also known as **brain sand** or **pineal sand**, are small to large basophilic calcified concretions that exhibit a mulberry-like shape. They are readily seen at the LM level and increase in size and number with age. They consist of hydroxyapatite, protein, and glycoprotein components. Their function is not known, but they are convenient landmarks in clinical imaging.

2. Myeloconia, also known as **brain dust**, are small (~10-20µm) crystals of calcite (CaCO₃) and glycoprotein, which have recently been identified (Baconnier et al. *Bioelectromagnetics* 23:488-495, 2002). Although their structure is similar to the otoliths of the inner ear, their function(s) remain to be determined. They are only visible with the EM.

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