Subject II **ENDOCRINE SYSTEM**

Program of lecture

- **Features of humoral regulation.**
- **Histophysiology of secretion.**
- **Endocrine, paracrine and autocrine secretion.**
- **Endocrine system: general morpho-functional features, development.**
- **Pineal gland. Hypothalamus. Pituitary gland.**
- **Thyroid. Parathyroid.**
- **Adrenals.**
- **Diffuse endocrine system. Age features**

The endocrine system regulates metabolic activities in certain organs and tissues of the body, thereby helping to bring about homeostasis. The autonomic nervous system regulates certain organs and tissues via impulses that initiate the release of neurotransmitter substances, that produce rapid responses in the tissues that are affected. However, the endocrine system produces a slow and diffused effect via chemical substances called **hormones,** which are released into the bloodstream to influence target cells at remote sites. Although the nervous and endocrine systems function in different ways, the two systems interact to modulate and coordinate the metabolic activities of the body.

The typical mode of cell signaling in the endocrine system is endocrine signaling, that is, using the circulatory system to reach distant target organs. However, there are also other modes, i.e., paracrine, autocrine, and neuroendocrine signaling (were discussed in the couse of ñCytologyò). Purely neurocrine signaling between neurons, on the other hand, belongs completely to the nervous system.

The **endocrine system** consists of **ductless glands,** distinct clusters of cells within certain organs of the body, and **endocrine cells,** isolated in the epithelial lining of the digestive tract and in the respiratory system. The **endocrine glands,** the subject of this chapter, are abundantly and richly vascularized so that their secretory product may be released into slender connective tissue spaces between cells and the capillary beds from which they enter the bloodstream. The endocrine glands include the pineal body, the **pituitary gland,** the **thyroid gland,** the **parathyroid glands,** and the **suprarenal glands.** Unlike the endocrine glands, which are ductless, the various exocrine glands empty their secretions in a duct system and exert only local effects.

The chemical nature of a hormone dictates its mechanism of action. Most hormones elicit several effects on their target cells (e.g., short-term and long-term effects). Hormones are classified into three types based on their composition:

- **Proteins and polypeptides-**mostly water-soluble (e.g., insulin, glucagon, and follicle-stimulating hormone [FSH]).
- **Amino-acid derivatives-**mostly water-soluble (e.g., thyroxine and epinephrine).
- **Steroid and fatty acid derivatives-**mostly lipid-soluble (e.g., progesterone , estradiol , and testosterone).

PITUITARY GLAND (HYPOPHYSIS)

The pituitary gland, or **hypophysis,** is an endocrine gland that produces several hormones that are responsible for regulating growth, reproduction, and metabolism. It has two subdivisions, which develop from different embryologic sources: (1) the **adenohypophysis** develops from an evagination of the oral ectoderm **(Rathke's pouch)** that lines the primitive oral

cavity (stomadeum), and (2) the **neurohypophysis** develops from neural ectoderm as a downgrowth of the diencephalon. Subsequently, both the adenohypophysis and the neurohypophysis are joined and encapsulated into a single gland. Because each subdivision has a distinctly different embryonic origin, however, the cellular constituents and the functions of each differ.

The pituitary is connected to the brain by neural pathways; it also has a rich vascular supply from vessels that supply the brain, attesting to the intercoordination of the two systems in maintaining a physiological balance. Indeed, secretion of nearly all of the hormones produced by the pituitary gland is controlled by either hormonal or nerve signals from the hypothalamus. In addition to controlling the pituitary, the hypothalamus also receives input from various areas of the central nervous system (i.e., information regarding plasma circulating levels of electrolytes and hormones) and controls the autonomic nervous system; therefore, the hypothalamus is the brain center for the maintenance of homeostasis.

Within each subdivision of the hypophysis are various regions having specialized cells that release different hormones (Figs. 1 and 2). The subdivisions of the hypophysis and the names of the regions are:

- Adenohypophysis (anterior pituitary)
  - Pars distalis (pars anterior)
  - Pars intermedia
  - Pars tuberalis
- Neurohypophysis (posterior pituitary)
  - Median eminence
  - Infundibulum
  - Pars nervosa

The arterial supply for the pituitary gland is provided from two pairs of vessels that arise from the internal carotid artery. The **superior hypophyseal arteries** supply the pars tuberalis and the infundibulum. They also form an extensive capillary network, the **primary capillary plexus,** in the median eminence. **Inferior hypophyseal arteries** primarily supply the posterior lobe, although they also send a few branches to the anterior lobe.

Hypophyseal portal veins drain the primary capillary plexus of the median eminence, which delivers its blood into the **secondary capillary plexus,** located in the pars distalis. The capillaries of both plexuses axe fenestrated. **Hypothalamic neurosecretory hormones,** manufactured in the hypothalamus and stored in the median eminence, enter the primary capillary plexus and are drained by the hypophyseal portal veins, which course through the infundibulum and connect to the secondary capillary plexus in the anterior lobe. Here the neurosecretory hormones leave the blood to stimulate or inhibit the parenchymal cells. Thus, the hypophyseal portal system is the vascular supply system that is used for hormonal regulation of the pars distalis by the hypothalamus.

Axons of neurons that originate in various portions of the hypothalamus terminate around these capillary plexuses. The endings of these axons differ from other axons of the body, because instead of delivering a signal to another cell, they liberate either **releasing** or **inhibiting hormones (factors)** directly into the primary capillary bed. These hormones are taken by the hypophyseal portal system and delivered to the secondary capillary bed of the pars distalis, where they regulate secretion of various anterior pituitary hormones. The following are the main releasing and inhibitory hormones (factors):

- **Thyroid-stimulating hormone-releasing hormone (thyrotropin-releasing hormone [TRH])** stimulates the release of TSH.
- **Corticotropin-releasing hormone (CRH)** stimulates the release of adrenocorticotropin.

- **Somatotropin-releasing hormone (SRH)** stimulates the release of somatotropin (growth hormone).
- **Luteinizing hormone-releasing hormone (LHRH)** stimulates the release of luteinizing hormone (LH) and FSH.
- **Prolactin-releasing hormone (PRH)** stimulates the release of prolactin.
- **Prolactin inhibitory factor (PIF)** inhibits prolactin secretion.

ADENOHYPOPHYSIS

The anterior pituitary gland, the adenohypophysis, develops from Rathke's pouch, a diverticulum of the oral ectoderm. The adenohypophysis consists of the pars distalis, the pars intermedia, and the pars tuberalis (Fig.1).

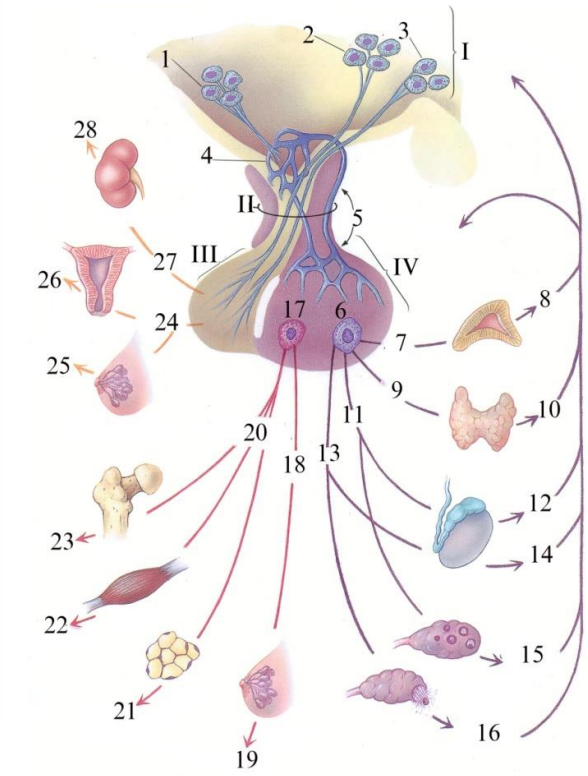

Fig. 1.

The pars distalis, or anterior lobe of the pituitary gland, is covered by a fibrous capsule and is composed of cords of parenchymal cells that are surrounded by reticular fibers; these fibers also surround the large sinusoidal capillaries of the secondary capillary plexus. Scant connective tissue is located primarily around the hypophyseal arteries and the portal veins. The endothelial lining of the sinusoids is fenestrated, which facilitates the diffusion of releasing factors to the parenchymal cells and provides entry sites for their released secretions. The parenchymal cells of the pars distalis that have an affinity for dyes are called **chromophils,** whereas those parenchymal cells that have no affinity for dyes are called **chromophobes.** Chromophils are further subdivided into **acidophils** (staining with acid dyes) and **basophils** (staining with basic dyes), which constitute the main secretory cells of the pars distalis. However, it should be noted that these latter designations refer to the affinity of the secretory granules within the cells to the dyes, not to the parenchymal cell cytoplasm (Fig.2).

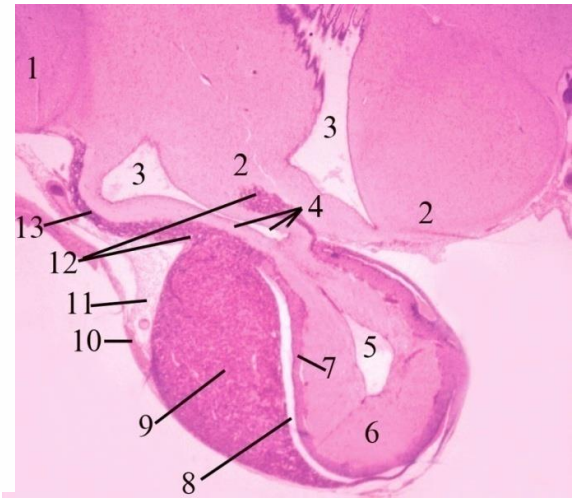

Fig. 2.

Chromophils

The most abundant cells in the pars distalis are acidophils, whose granules are large enough to be seen by the light microscope and stain orange-to-red with eosin.

Somatotrophs, one of the two varieties of the acidophils, have a centrally placed nucleus, a moderate Golgi complex, small rod-shaped mitochondria, abundant rough endoplasmic reticulum (RER), and numerous secretory granulesthat are 300 to 400 nm in diameter. These cells secrete **somatotropin (growth hormone);** thus, they are stimulated by **SRH** and inhibited by **somatostatin.** Somatotropin has a generalized effect of increasing cellular metabolic rates. This hormone also induces liver cells to produce **somatomedins (insulin-like growth factors I and II),** which stimulate mitotic rates of epiphyseal plate chondrocytes and thus promote elongation of long bones and, hence, growth.

Mammotrophs, the other variety of acidophils, are arranged as individual cells rather than as clumps or clusters. These small, polygonal acidophils have the usual unremarkable organelle population; during lactation, however, the organelles enlarge and the Golgi complex may become as large as the nucleus. These cells can be distinguished by their large secretory granules, formed by the fusion of smaller granules that are released by the *trans* Golgi network. These fused granules, which may be 600 nm in diameter, contain the hormone **prolactin,** which promotes mammary gland development during pregnancy as well as lactation after birth.

During pregnancy, circulating estrogen and progesterone inhibit secretion of prolactin. Following birth, estrogen and progesterone levels drop; thus their inhibitory effect is lost. The number of mammotrophs also increases at this time. At the conclusion of nursing, the granules are degraded and the excess mammotrophs regress. Release of prolactin from mammotrophs is stimulated by **prolactin-releasing factor (PRH)** and oxytocin , especially when nursing is taking place, and is inhibited by **PIF (Fig. 3).**

BASOPHILS

Basophils stain blue with basic dyes (especially with periodic acid-Schiff reagent) and are usually located at the periphery of the pars distalis.

Corticotrophs, which are scattered throughout the pars distalis, are round to ovoid cells, each with an eccentric nucleus and relatively few organelles. Their secretory granules are 250 to 400 nm in diameter. Corticotrophs secrete **adrenocorticotropic hormone (ACTH)** and **lipotropic hormone (LPH).** Secretion is stimulated by **CRH.** The hormone ACTH stimulates cells of the suprarenal cortex to release their secretory products.

Thyrotrophs are deeply embedded within cords of the parenchymal cells at a distance from sinusoids. These cells can be distinguished by their small secretory granules (150 nm in diameter), which contain **TSH,** also known as **thyrotropin.** Secretion is stimulated by **TRH** and inhibited by the presence of thyroxine (T_4) and triiodothyronine (T_3) (thyroid hormones) in the blood (Fig. 3).

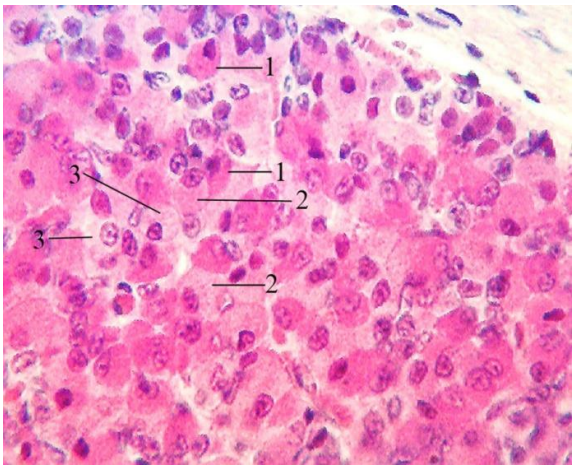

Fig. 3.

Gonadotrophs are round cells that have a well-developed Golgi complex and abundant RER and mitochondria. Their secretory granules vary in diameter from 200 to 400 nm. Gonadotrophs, situated near sinuses, secrete **FSH** and **LH;** sometimes LH is called **interstitial cell-stimulating hormone (ICSH),** because it stimulates steroid hormone production in interstitial cells of the testes. It remains unclear whether there are two subpopulations of gonadotrophs, one secreting FSH and the other LH, or whether both hormones are produced by one cell in different phases of the secretory cycle. Secretion is stimulated by **LHRH** and is inhibited by various hormones that are produced by the ovaries and testes (Fig. 4).

Groups of small, weakly staining cells in the pars distalis are called chromophobes (see Fig. 13-3). These cells generally have less cytoplasm than chromophils do, and they may represent either nonspecific stem cells or partly degranulated chromophils, although some retain secretory granules. Because there is evidence for the cyclic nature of the secretory function of the chromophils, it is probable that chromophobes are degranulated chromophils. Nonsecretory folliculostellate cells constitute a large population of cells in the pars distalis. Although their function is not clear, they have long processes that form gap junctions with those of other folliculostellate cells. Whether they physically support parenchymal cells of the anterior pituitary or provide a network of intercommunication with each other is not known.

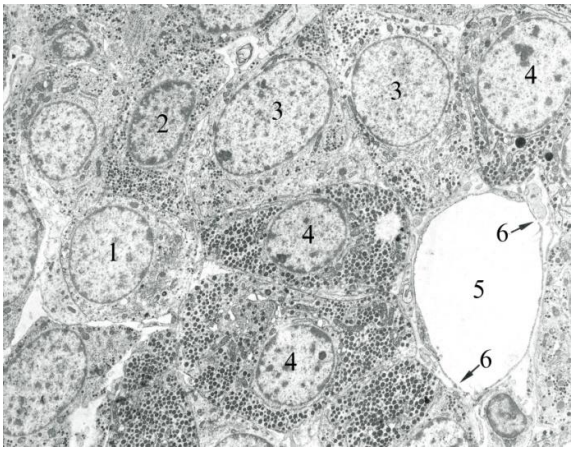

Fig. 4.

The pars intermedia is characterized by many cuboidal, cell-lined, colloid-containing cysts (Rathke's cysts), which are remnants of the ectoderm of the evaginating Rathke's pouch. The pars intermedia, or more accurately in the adult human, the **zona intermedia,** sometimes houses cords of basophils along the networks of capillaries. These basophils synthesize the prohormone **pro-opiomelanocortin (POMC),** which undergoes post-translational cleavage to form **Ŭ-melanocyte-stimulating hormone (Ŭ-MSH),** corticotropin , ɓ-lipotropin, and ɓ-endorphin. However, it has been suggested that POMC is actually produced by corticotropin cells of the anterior lobe and that the intermediate lobe (or zone) is rudimentary in humans. Although Ŭ-MSH stimulates melanin production in lower animals, in humans it may stimulate the release of prolactin and is therefore referred to as **prolactin-releasing factor.** The pars tuberalis surrounds the hypophyseal stalk but frequently is absent on its posterior aspect. Thin layers of pia arachnoid-like connective tissue separate the pars tuberalis from the infundibular stalk. The pars tuberalis is highly vascularized by arteries and the hypophyseal portal system, along which lie longitudinal cords of cuboidal to low-columnar epithelial cells. The cytoplasm of these basophilic cells contains small, dense granules, lipid droplets, interspersed colloid droplets, and glycogen. Although no specific hormones are known to be secreted by the pars tuberalis, some cells contain secretory granules that possibly contain **FSH** and **LH (Fig. 5).**

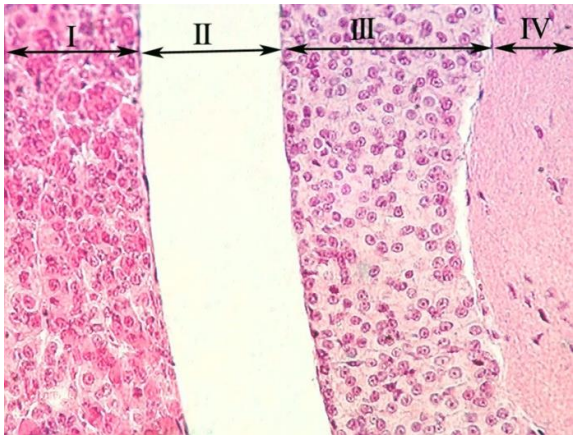

Fig. 5.

NEUROHYPOPHYSIS

The posterior pituitary gland, the neurohypophysis, develops from a downgrowth of the hypothalamus. The neurohypophysis is divided into the median eminence, the infundibulum (continuation of the hypothalamus), and the pars nervosa.

Unmyelinated axons of neurosecretory cells, the cell bodies of which lie in the **supraoptic** and **paraventricular nuclei** of the hypothalamus, enter the posterior pituitary to terminate in the vicinity of the capillaries. These axons form the hypothalamohypophyseal tract and constitute the bulk of the posterior pituitary gland. Neurosecretory cells of the supraoptic and paraventricular nuclei synthesize two hormones: **vasopressin (antidiuretic hormone [ADH])** and **oxytocin .** A carrier protein, **neurophysin,** also produced by the cells of these nuclei, binds to each of these hormones as they travel down the axons to the posterior pituitary, where they are released into the bloodstream from the axon terminals.

Technically, the pars nervosa of the posterior pituitary gland is not an endocrine gland. The distal terminals of the axons of the hypothalamohypophyseal tract end in the pars nervosa and store the neurosecretions that are produced by their cell bodies, which are located in the hypothalamus. These axons are supported by glia-like cells known as pituicytes. Although only the nuclei of the pituicytes stain well enough to be evident by light microscopy, electron micrographs reveal that one population of axons contains membrane-bound granules of **vasopressin** and that another population contains **oxytocin .** Cell bodies of neurons that

secrete vasopressin are located chiefly in the supraoptic nucleus of the hypothalamus, whereas cell bodies of neurons that secrete oxytocin are located mostly in the paraventricular nucleus of the hypothalamus. Each of these peptide hormones travel down the axons of their respective neurons in association with a precursor protein known as a **neurophysin.** By the time that they reach the pars nervosa of the hypophysis, the hormones have matured and cleaved from their precursors Chrome-alum hematoxylin staining reveals blue-black distentions of the axons by light microscopy; these are called **Herring bodies,** which represent accumulations of neurosecretory granules not only at the termini but also along the length of the axons. In response to nerve stimulation, the contents of these granules are released into the perivascular space near the fenestrated capillaries of the capillary plexus (Fig. 6).

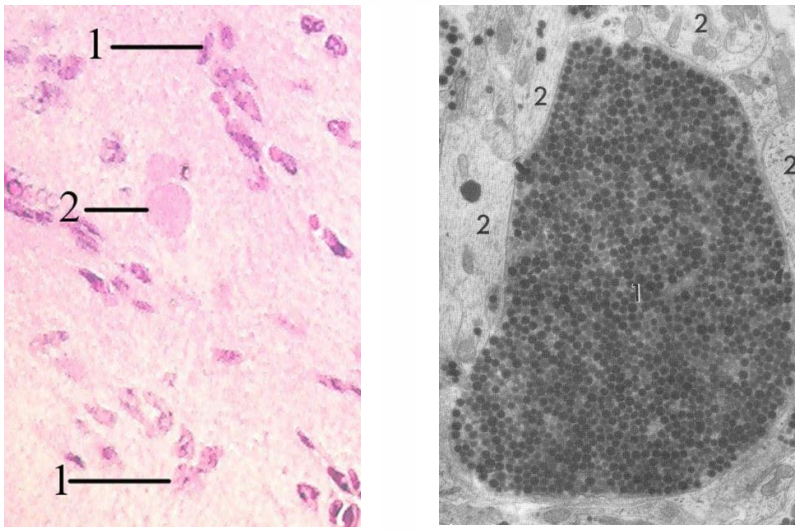

Fig. 6.

Pituicytes occupy about 25% of the volume of the pars nervosa. They are similar to neuroglial cells and help support the axons of the pars nervosa by ensheathing them as well as their dilations. Pituicytes contain lipid droplets, lipochrome pigment, and intermediate filaments; they have numerous cytoplasmic processes that contact and form gap junctions with each other. Beyond supporting the neural elements in the pars nervosa, additional functions of pituicytes have not been elucidated. However, it is believed that they may contribute a trophic function to the normal operation of the neurosecretory axon terminals and neurohypophysis.

PINEAL GLAND

The pineal gland (or **pineal body**) is an endocrine gland whose secretions are influenced by the light and dark periods of the day. It is a cone-shaped, midline projection from the roof of the diencephalon, within a recess of the third ventricle extending into the stalk that is attached to it. It is 5 to 8 mm long and 3 to 5 mm wide; it weighs approximately 120 mg. The gland is covered by pia mater, forming a capsule from which septa extend, dividing the pineal gland into incomplete lobules. Blood vessels enter the gland via the connective tissue septa. The parenchymal cells of the gland are composed primarily of **pinealocytes** and **interstitial cells** (Fig. 7).

Pinealocytes are slightly basophilic cells with one or two long processes whose terminal dilations approximate capillaries and, occasionally, other parenchymal cells. Their spherical nuclei have a single prominent nucleolus. The cytoplasm contains SER and RER, a small Golgi

apparatus, numerous mitochondria, and small secretory vesicles, some with electron-dense cores. Pinealocytes also contain a well-developed cytoskeleton composed of microtubules, microfilaments, and dense tubular structures invested by spherical vesicular elements. These unusual structures, known as **synaptic ribbons**, increase in number during the dark period of the diurnal cycle, but their function is not understood.

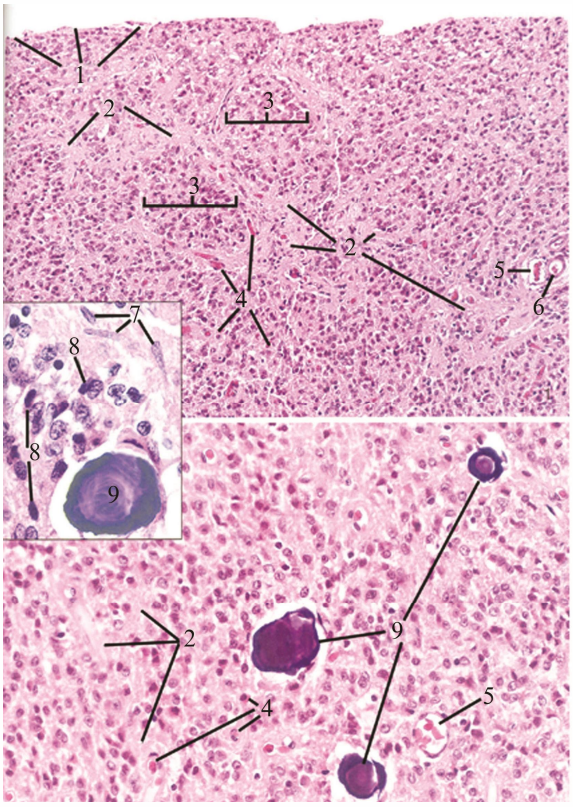

Fig. 7.

Interstitial cells, believed to be astrocyte-like neuroglial cells, are scattered throughout the pinealocytes and are particularly abundant in the pineal stalk that leads to the diencephalon. These cells have deeply staining, elongated nuclei and well-developed RER; some have deposits of glycogen. Their long cellular processes are rich in intermediate filaments, microtubules, and microfilaments.

The pineal gland also contains concretions of calcium phosphates and carbonates, which are deposited in concentric rings around an organic matrix. These structures, called **corpora arenacea ("brain sand"),** appear in early childhood and increase in size throughout life. Although it is unclear how they are formed or function, they increase during short photoperiods and are reduced when the pineal gland is actively secreting.

THYROID GLAND

The hormones $\mathbf{T_4}$ and $\mathbf{T_3}$, the secretions of which are under the control of **TSH** secreted by the anterior pituitary gland, stimulate the rate of metabolism. Another hormone, **calcitonin,** aids in decreasing blood calcium levels and facilitates the storage of calcium in bones.

The thyroid gland lies just inferior to the larynx, anterior to the junction of the thyroid and cricoid cartilages. It is composed of a **right lobe** and a **left lobe,** which are connected across the midline by an **isthmus.** In some people, the gland has an additional lobe, called the **pyramidal lobe,** that ascends from the left side of the isthmus. The pyramidal lobe is an

embryological remnant of the path of descent of the thyroid primordium from its origin in the forming tongue by way of the thyroglossal duct (Fig. 8).

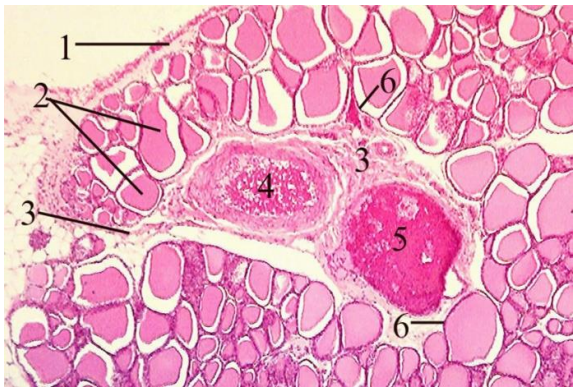

Fig. 8

The thyroid gland is surrounded by a slender, dense, irregular collagenous connective tissue capsule, a derivative of the deep cervical fascia. Septa derived from the capsule subdivide the gland into lobules. Embedded within the capsule, on the posterior aspect of the gland, are the parathyroid glands.Unlike most of the endocrine glands, which store their secretory substances within the parenchymal cells, the thyroid gland stores its secretory substances in the lumina of **follicles**. These cyst-like structures, ranging from 0.2 to 0.9 mm in diameter, are composed of a simple cuboidal epithelium surrounding a central colloid-filled lumen. Each follicle can store several weeks' supply of hormone within the **colloid.** The hormones $\mathbf{T_4}$ and $\mathbf{T_3}$ are stored in the colloid, which is bound to a large (660,000 Da) secretory glycoprotein called **thyroglobulin.** When the hormones are to be released, the hormone-bound thyroglobulin is endocytosed and the hormones are cleaved from it by lysosomal proteases. Connective tissue septa derived from the capsule invade the parenchyma and provide a conduit for blood vessels, lymphatic vessels, and nerve fibers. Slender connective tissue elements, composed mostly of reticular fibers and housing a rich capillary plexus, surround each follicle but are separated from the **follicular** and **parafollicular** cells by a thin **basal lamina.** Occasionally, follicular cells of neighboring follicles may come into contact with each other and disrupt the continuity of the basal lamina (Fig. 9).

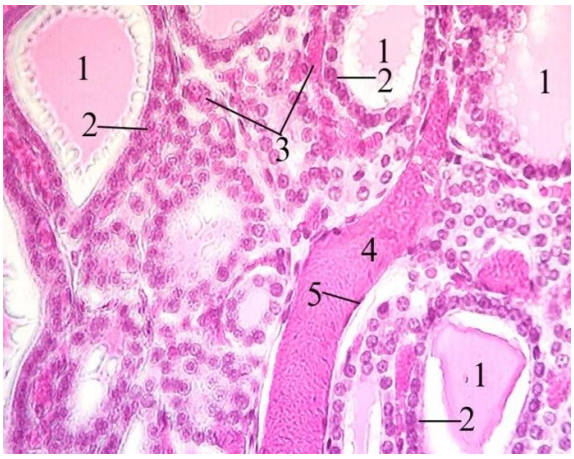

Fig. 9

Follicular cells have a round to ovoid nucleus with two nucleoli and basophilic cytoplasm. Frequently, their RER is distended and displays zones that are ribosome-free. These cells also have numerous apically located lysosomes, rod-shaped mitochondria, a supranuclear

Golgi complex, and numerous short villi that extend into the colloid. Numerous small vesicles, dispersed throughout the cytoplasm, are believed to contain thyroglobulin that was packaged in the Golgi complex and is destined for exocytosis into the follicle lumen. **Iodide** is essential for the synthesis of the thyroid hormones (T_3 and T_4); iodination of tyrosine residues occurs in the follicles at the colloid-follicular cell interface. Thus follicular cells secrete triiodothyronine (T_3) and thyroxine (T_4), which increases basal metabolic rates (Fig. 10, 12).

Synthesis of Thyroid Hormones (T_3 and T_4)

The synthesis of thyroid hormone is regulated by the iodide levels in the follicular cell as well as by the binding of TSH to TSH receptors of the follicular cells. The occupation of TSH receptors triggers cAMP production, resulting in protein kinase A activity and synthesis of T_3 and T_4.

Thyroglobulin is synthesized in the RER and subsequently glycosylated in both the RER and the Golgi apparatus. The modified protein is packaged in the *trans* Golgi network. The vesicles containing thyroglobulin are transported to the apical plasmalemma, where their contents are released into the colloid and stored in the lumen of the follicle (Fig. 10, 11).

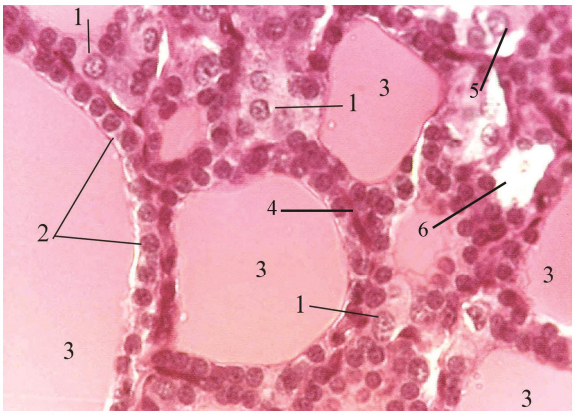

Fig. 10

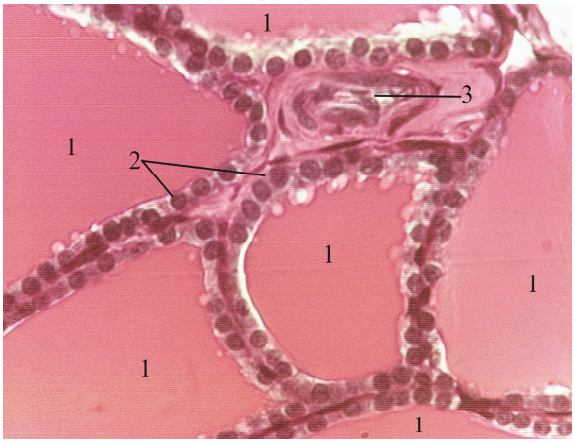

Fig. 11

Iodine is reduced to iodide (I^-) within the alimentary canal and is preferentially absorbed and transported by the bloodstream to the thyroid gland. Iodide is actively transported via sodium/iodide symporters, which are located in the basal plasmalemma of the follicular cells, so that the intracellular iodide concentration is 20-fold to 40-fold that of plasma (Fig. 11).

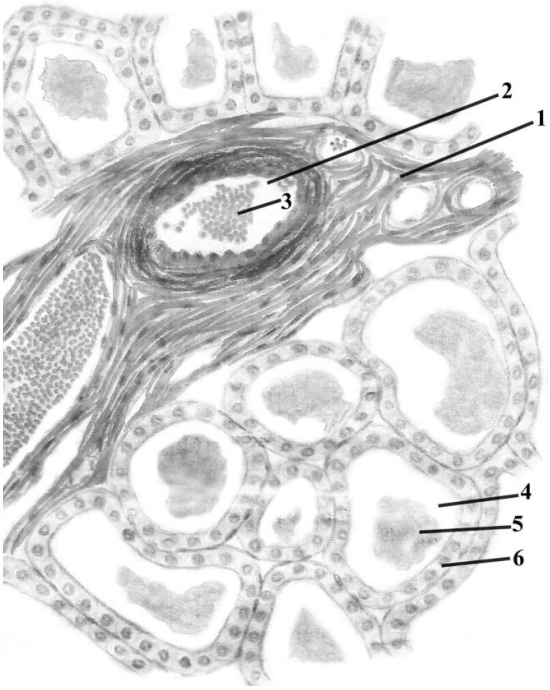

Fig. 12.

Once in the cytosol, iodide is transferred to the colloid-cell membrane interface, where iodide oxidation occurs by the enzyme **thyroid peroxidase,** a process that requires the presence of hydrogen peroxide (H_2O_2). The activated iodide enters the colloid and iodinates tyrosine residues of thyroglobulin at the interface of the colloid and the apical plasmalemma of the thyroid follicular cell. Tyrosine residues of thyroglobulin are iodinated, forming **monoiodinated tyrosine (MIT)** and **diiodinated tyrosine** (DIT). Triiodinated and tetraiodinated tyrosines are then formed by the coupling of an MIT and a DIT or of two DITs, respectively. Each thyroglobulin molecule has fewer than four T_4 molecules and fewer than 0.3 T_3 residues. The iodinated thyroglobulin is released by the follicular cells to be stored in the colloid (Fig. 13).

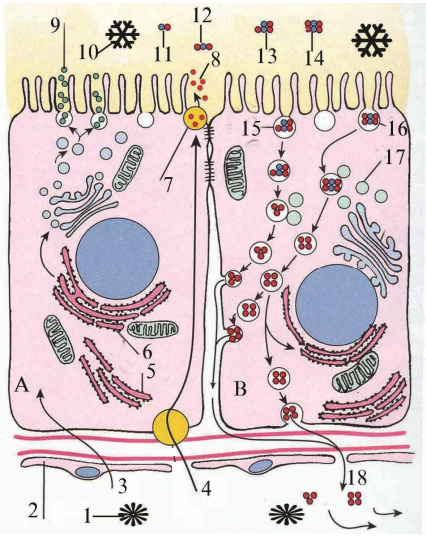

Fig. 13.

TSH, released from the basophils of the anterior pituitary, binds to TSH receptors on the basal plasmalemma of the follicular cells. Binding of TSH facilitates formation of filopodia at the apical cell membrane, resulting in endocytosis of aliquots of the colloid. Cytoplasmic vesicles containing colloid fuse with early (or late) endosomes. Within the endosomes, iodinated residues are cleaved from thyroglobulin by proteases and are transferred into the cytosol as free MIT, DIT, T_3, and T_4 (Fig. 14).

MIT and DIT are stripped of their iodine by the enzyme **iodotyrosine dehalogenase,** and both the iodine and the amino acid tyrosine become part of their respective pools within the cytosol, to be used later.

Once they enter the bloodstream, **T_3 and T_4** bind to plasma-binding proteins and are slowly released to the tissues and contact cells. As they enter the cytoplasm, they are bound to intracellular proteins and slowly used over a period of several days to weeks. Because only the free hormone has the ability to enter the cell and because T_3 is bound less avidly, more of it gains entry into the cytoplasm than does T_4. Moreover, both T_3 and T_4 bind to **nuclear thyroid hormone receptor proteins,** but T_3 binds with a much greater affinity than does T_4, which also accounts for the greater biological activity of T_3.

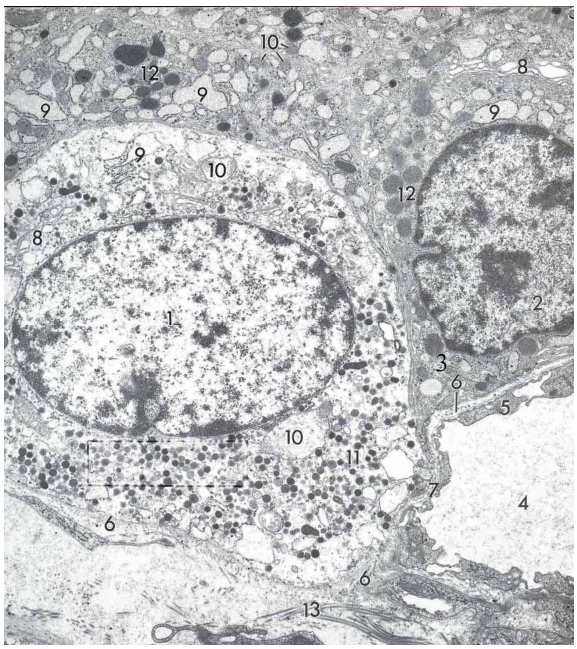

Fig. 14.

The pale-staining parafollicular cells lie singly or in clusters among the follicular cells, but they do not reach the lumen of the follicle. Although these cells are two to three times larger than follicular cells, they account for only about 0.1% of the epithelium. Electron micrographs display a round nucleus, moderate amounts of RER, elongated mitochondria, a well-developed Golgi complex, and small, dense secretory granules (0.1 to 0.4 εm in diameter) located in the basal cytoplasm. These secretory granules contain **calcitonin (thyrocalcitonin),** a peptide hormone that inhibits bone resorption by osteoclasts, thereby lowering calcium concentrations in blood. When the circulating level of calcium is high, release of calcitonin is stimulated (Fig. 14).

PARATHYROID GLANDS

The parathyroid glands, usually four in number, are located on the posterior surface of the thyroid gland; each gland is enveloped in its own thin, collagenous connective tissue capsule

(Fig. 15). The glands function in producing **PTH,** which acts on bone, kidneys, and the intestines in maintaining the optimal concentrations of calcium within blood and interstitial tissue fluid.

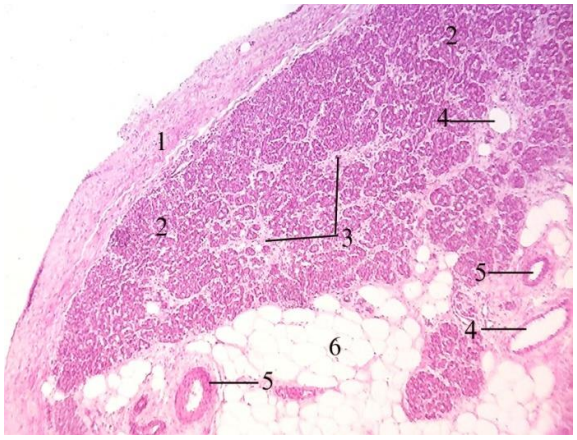

Fig. 15

The parathyroid glands develop from the third and fourth pharyngeal pouches during embryogenesis. The parathyroid glands that develop in the third pharyngeal pouches descend with the thymus (also developing in the third pouches) to become the **inferior parathyroid glands.** The parathyroid glands that develop in the fourth pharyngeal pouches descend only a short distance to become the **superior parathyroid glands.** The glands grow slowly, reaching the adult size at about 20 years of age (Fig. 16).

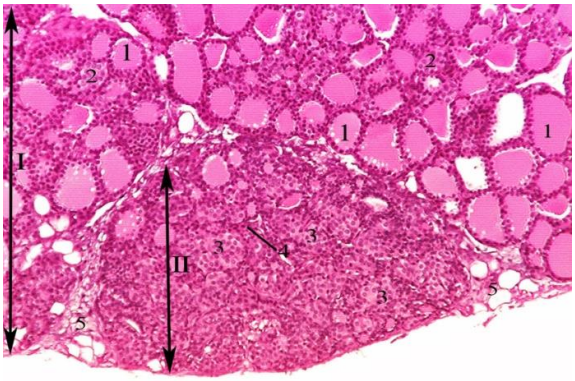

Fig. 16.

Each parathyroid gland is a small, ovoid structure about 5 mm in length, 4 mm wide, and 2 mm in thickness and weighs about 25 to 50 mg. Extensions of the connective tissue capsule enter the gland as septa, accompanied by blood vessels, lymphatics, and nerves. The septa serve mainly to support the parenchyma and consist of cords or clusters of epithelial cells surrounded by reticular fibers, which also support the parenchyma and a rich capillary network. The connective tissue stroma in older adults often contains several to many adipose cells, which may occupy up to 60% of the gland. The parenchyma of the parathyroid glands is composed of two cell types: **chief cells** and **oxyphil cells** (Fig. 17).

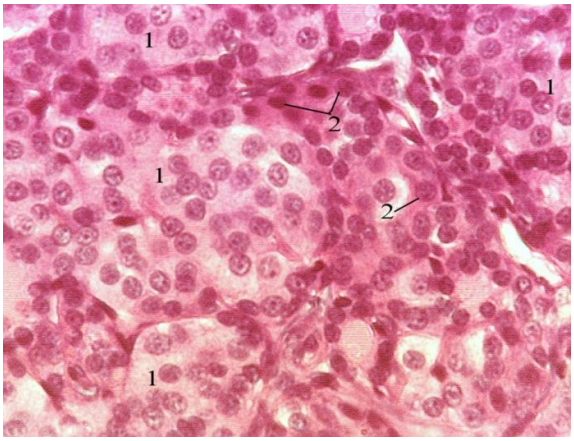

Fig. 17.

The precursor, **preproparathyroid hormone,** is synthesized on ribosomes of the RER and rapidly cleaved as it is transported to the lumen of the RER to form **proparathyroid hormone** and a polypeptide. On reaching the Golgi complex, the proparathyroid hormone is cleaved again into PTH and a small polypeptide. The hormone is packaged into secretory granules and is released from the cell surface by exocytosis (Fig. 18).

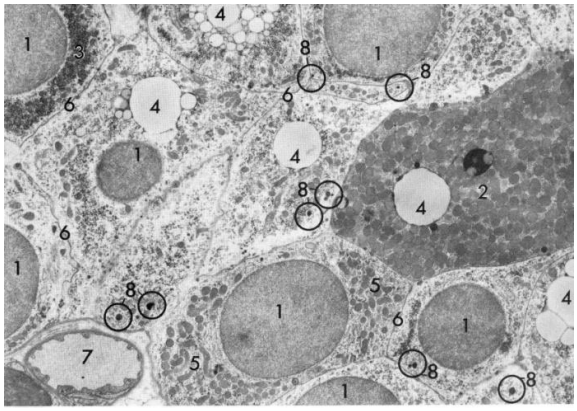

Fig. 18

The second cell type located in the parathyroid glands is the oxyphil cell. Its function is unknown, although it is believed that oxyphil cells and a third cell, described as an **intermediate cell,** probably represent inactive phases of a single cell type, with chief cells being the actively secreting phase.

Oxyphil cells are less numerous, larger (6 to 10εm in diameter), and stain more deeply with eosin than chief cells do. Oxyphils appear in groups and as isolated cells. They have more abundant mitochondria than do chief cells, but their Golgi apparatus is small and there is little RER. Glycogen is also located in the cytosol and is surrounded by mitochondria.

PTH, produced by chief cells of the parathyroid glands, helps to maintain the extracellular fluid as well as the plasma concentration of calcium ions (8.5 to 10.5 mg/dL). This hormone acts on cells of the bones, the kidneys, and, indirectly, the intestines, leading to an increased calcium ion concentration in body fluids. When calcium ion concentration in body fluids falls below normal, the chief cells increase their production and release of PTH, quickly increasing their normal secretion rate 10-fold. This rapid response is especially important because of the many functions of calcium in homeostasis, including its role in stabilizing ion

gradients across the plasmalemmae of muscle and nerve cells and its role in the release of neurotransmitter at axon terminals.

SUPRARENAL (ADRENAL) GLANDS

The suprarenal glands are located at the superior poles of the kidneys and are embedded in adipose tissue. The right and left suprarenal glands are not mirror images of each other; rather, the right suprarenal gland is pyramid-shaped and sits directly on top of the right kidney, whereas the left suprarenal gland is more crescent-shaped and lies along the medial border of the left kidney from the hilus to its superior pole.

Both glands are about 1 cm in thickness, 2 cm in width at the apex, and up to 5 cm at the base; each weighs 7 to 10 g. The parenchyma of the gland is divided into two histologically and functionally different regions: an outer yellowish portion, accounting for about 80% to 90% of the organ, called the **suprarenal cortex,** and a small, dark, inner portion called the **suprarenal medulla** (Fig. 13-10). Although both entities are endocrine in function, each develops from a different embryological origin and performs a different role. The suprarenal cortex, arising from mesoderm, produces a group of hormones called **corticosteroids,** which are synthesized from **cholesterol.** Secretion of these hormones, including **cortisol** and **corticosterone,** is regulated by **ACTH,** a hormone secreted by the anterior pituitary gland. The suprarenal medulla, arising from neural crest, is functionally related to and regulated by the sympathetic nervous system; it produces the hormones **epinephrine** and **norepinephrine (Fig. 19).**

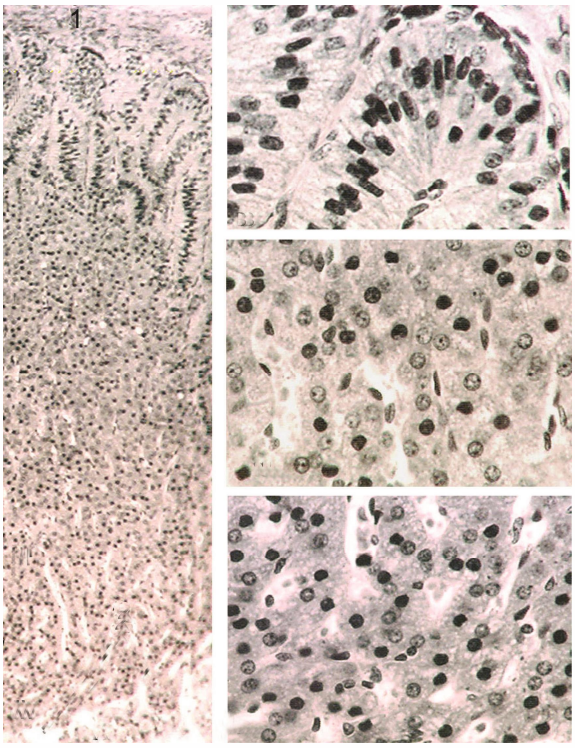

Fig.19

The suprarenal glands are retroperitoneal, located behind the peritoneum, and surrounded by a connective tissue capsule that contains large amounts of adipose tissue. Each gland has a thick capsule of connective tissue that sends septa into the parenchyma of the gland, accompanied by blood vessels and nerves (Fig.20).

The suprarenal glands have one of the richest blood supplies in the body (Fig. 21). Each suprarenal gland is served by three separate arteries that arise from three separate sources:

- The **inferior phrenic arteries,** from which the superior suprarenal arteries originate.
- The **aorta,** from which the **middle suprarenal arteries** originate.
- The **renal arteries,** from which the inferior suprarenal arteries originate.

These branches pass over the capsule, penetrate it, and form a **subcapsular plexus.**

Arising from the plexus are **short cortical arteries,** which, in the cortical parenchyma, form a network of sinusoidal fenestrated capillaries (with diaphragms). The pore diameters of the fenestrated endothelial walls of the capillaries increase from 100 nm at the outer cortex to 250 nm in the deep cortex, where the sinusoidal capillaries become confluent with a venous plexus. Small venules arising from this area pass through the suprarenal medulla and drain into a suprarenal vein, emerging from the hilus. The right suprarenal vein joins the inferior vena cava, and the left suprarenal vein drains into the left renal vein.

Additional **long cortical arteries** pass unbranched through the cortex and into the medulla, where they form networks of capillaries. Thus, the medulla receives a dual blood supply: (1) an arterial supply from the long cortical arteries and (2) numerous vessels from the cortical capillary beds.

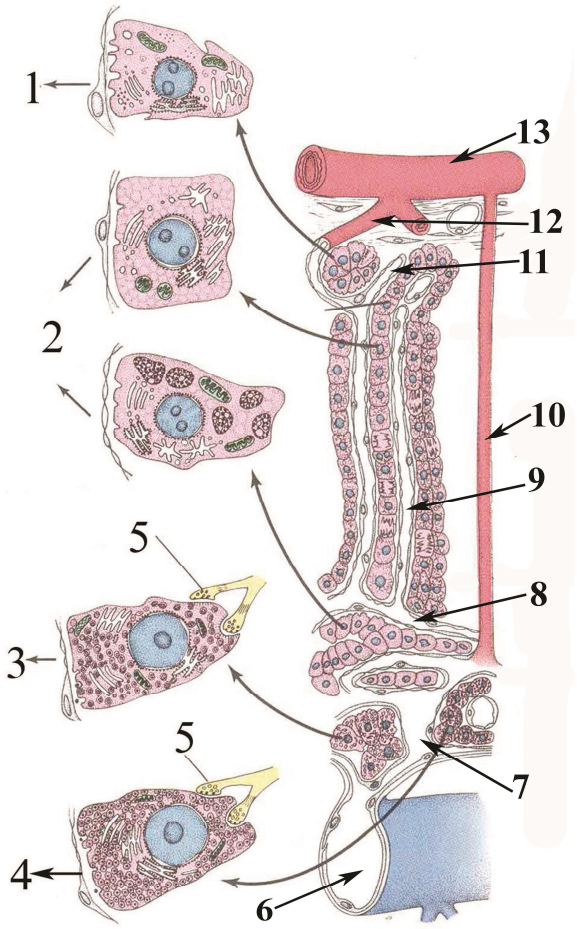

Fig. 20

The three classes of adrenocortical hormones-**mineralocorticoids, glucocorticoids,** and **androgens-**are all synthesized from **cholesterol,** the major component of **low-density lipoprotein.** Cholesterol is taken up from the blood and stored esterified in lipid droplets within the cytoplasm of the cortical cells. When these cells are stimulated, cholesterol is freed and used in hormone synthesis in the **smooth endoplasmic reticulum (SER)** by enzymes that are located there and in the mitochondria. The intermediate products of the hormone that is being synthesized are transferred between the SER and the mitochondria until the final hormone is produced (Fig. 21).

The outer concentric ring of capsular parenchymal cells, located just beneath the suprarenal capsule, is the zona glomerulosa, which constitutes approximately 13% of the total adrenal volume (Fig. 21). The small columnar cells composing this zone are arranged in cords and clusters. Their small, dark-staining nuclei contain one or two nucleoli, and their acidophilic cytoplasm contains an abundant and extensive SER, short mitochondria with shelf-like cristae, a well-developed Golgi complex, abundant RER, and free ribosomes. Some lipid droplets also are dispersed in the cyto-plasm. Occasional desmosomes and small gap junctions join cells to each other, and some cells have short microvilli

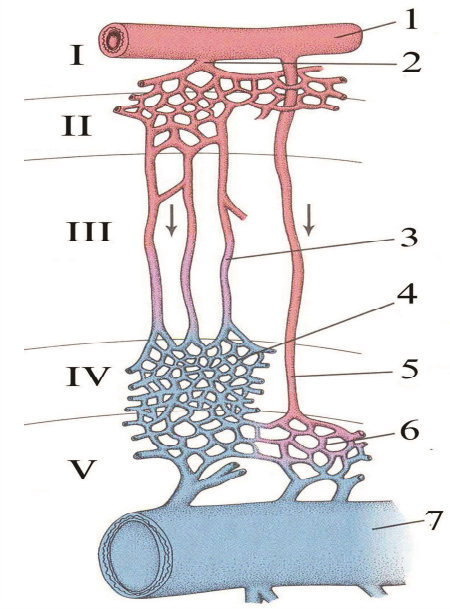

Fig. 21.

The parenchymal cells of the zona glomerulosa synthesize and secrete the **mineralocorticoid hormones,** principally **aldosterone** and some **deoxycorticosterone**. Synthesis of these hormones is stimulated by **angiotensin II** and **ACTH,** both required for normal existence of glomerulosa cells. The mineralocorticoid hormones function in controlling fluid and electrolyte balance in the body by affecting the function of the renal tubules, specifically the distal convoluted tubules.

The intermediate concentric layer of cells in the suprarenal cortex is the zona fasciculata, the largest layer of the cortex, which accounts for up to 80% of the total volume of the gland. This zone contains sinusoidal capillaries that are arranged longitudinally between the columns of parenchymal cells. The polyhedral cells in this layer are larger than the cells of the zona glomerulosa and are arranged in radial columns, one to two layers thick, and stain lightly acidophilic. Because they have many lipid droplets in their cytoplasm, which are extracted during histological processing, these cells appear vacuolated and are called **spongiocytes.** Spongiocytes have spherical mitochondria with tubular and vesicular cristae, extensive networks of SER, some RER, lysosomes, and granules of lipofuscin pigment.

Cells of the zona fasciculata synthesize and secrete the **glucocorticoid hormones cortisol** and **corticosterone.** The synthesis of these hormones is stimulated by ACTH. Glucocorticoids function in the control of carbohydrate, fat, and protein metabolism.

The innermost layer of the suprarenal cortex is the zona reticularis, constituting about 7% of gland volume. The darkly staining acidophilic cells in this layer are arranged in anastomosing cords. They are similar to the spongiocytes of the zona fasciculata but are smaller with fewer lipid droplets. They frequently contain large amounts of lipofuscin pigment granules. Several cells near the suprarenal medulla are dark with electron-dense cytoplasm and pyknotic nuclei, which suggests that this zone contains degenerating parenchymal cells.

Cells of the zona reticularis synthesize and secrete **androgens,** principally **dehydroepiandrosterone** and some **androstenedione.** Additionally, these cells may synthesize and secrete small amounts of glucocorticoids. The secretion of these hormones is stimulated by ACTH. Both dehydroepiandrosterone and androstenedione are weak, masculinizing hormones with negligible effects under normal conditions.

The three classes of hormones that are secreted by the suprarenal cortex are steroids: (1) mineralocorticoids, (2) glucocorticoids, and (3) weak androgens. ACTH from the pars distalis of the pituitary is the trophic hormone that stimulates secretion of the suprarenal cortex hormones.

The mineralocorticoids secreted by the zona glomerulosa include **aldosterone** predominantly and some deoxycorticosterone. The targets of these hormones include the gastric mucosa, salivary glands, and sweat glands, where they stimulate absorption of sodium. However, their main target are the cells of the distal convoluted tubules of the kidney, where they function to stimulate the regulation of water balance and the homeostasis of sodium and potassium by absorbing sodium and excreting potassium.

Glucocorticoids, secreted by the zona fasciculata, include **hydrocortisone (cortisol)** and **corticosterone.** These steroid hormones have a wide range of functions that affect most tissues of the body as well as control general metabolism. Glucocorticoids exert an **anabolic** effect in the liver that promotes the uptake of fatty acids, amino acids , and carbohydrates for glucose synthesis and glycogen polymerization; in other tissues, however, the effect is **catabolic.** For example, in adipocytes glucocorticoids stimulate **lipolysis,** and in muscle these hormones stimulate **proteolysis.** Glucocorticoids, when circulating at above normal levels, also influence anti-inflammatory responses by inhibiting macrophage and leukocyte infiltration at sites of inflammation. These hormones also suppress the immune response by inducing atrophy of the lymphatic system, thereby reducing the circulating lymphocyte population.

Suprarenal Medulla

The central portion of the suprarenal gland, the suprarenal medulla, is completely invested by the suprarenal cortex. The suprarenal medulla, which develops from ectodermal neural crest cells, comprises two populations of parenchymal cells: **chromaffin cells** (Fig. 20, 21), which produce the **catecholamines (epinephrine** and **norepinephrine),** and **sympathetic ganglion cells,** which are scattered throughout the connective tissue.

Chromaffin cells of the suprarenal medulla are large epithelioid cells, arranged in clusters or short cords; they contain granules that stain intensely with chromaffin salts. The reaction of the granules, which turn deep brown when exposed to chromaffin salts, indicates that the cells contain **catecholamines,** transmitters produced by postganglionic cells of the sympathetic nervous system. Thus, the suprarenal medulla functions as a modified sympathetic ganglion, housing postganglionic sympathetic cells that lack dendrites and axons. The catecholamines synthesized by the chromaffin cells are the sympathetic transmitters **epinephrine** and **norepinephrine**. These transmitters are secreted by the chromaffin cells in response to stimulation by **preganglionic sympathetic (cholinergic) splanchnic nerves.** Each chromaffin cell of primates, including the human, has the capability of producing both epinephrine and norepinephrine and storing them in secretory vesicles. Although in electron micrographs two

types of secretory vesicles, high-electron-density and low-electron-density, are evident, the density differential may be one of the maturational state of epinephrine and not necessarily indicative of the presence of two types of catecholamines.

In some animals, but not in primates including humans, two types of chromaffin cells have been identified by histochemical staining: those producing and storing norepinephrine and those producing and storing epinephrine . The granules of the norepinephrine-storing cells have an eccentric, electron-dense core within the limiting membrane of the granule, whereas the granules of chromaffin cells storing epinephrine are more homogeneous and less dense. Primate chromaffin cells have a well-developed juxtanuclear Golgi complex, some RER, and numerous mitochondria. The identifying characteristic of the chromaffin cells is the 30,000 or so small, membrane-bound, dense granules in the cytoplasm; approximately 20% of these granules contain either epinephrine or norepinephrine. The remaining granules are composed of **adenosine triphosphate, enkephalins,** and soluble proteins called **chromagranins.** Chromagranins are proteins that are believed to bind epinephrine and norepinephrine.

The diffuse endocrine system consists of a variety of individual cells with secretory endocrine morphology that appear scattered among other epithelial cells throughout the digestive tract, respiratory system etc. These cells act as chemo and mechanoreceptors of the conditions occurring in the internal organs and release their secretory peptides to neighboring cells to regulate their physiology. These cells share the common function of secreting a low molecular weight polypeptide hormone. There are several different types which secrete the hormones secretin, cholecystokinin and several others.

Diffuse Endocrine System of the Gut

The diffuse endocrine system consists of a variety of individual cells with secretory endocrine morphology that appear scattered among other epithelial cells throughout the digestive tract. These cells act as chemo and mechanoreceptors of the conditions occurring in the gut and release their secretory peptides to neighboring cells to regulate digestive physiology

Neuroendocrine cells.

Neuroendocrine cells belong to the diffuse endocrine system of the body. Although once thought to be more numerous in the fetus and newborn than in the adult, it has been shown that the numbers of these cells do not decrease with age. They are located within airway epithelium and tend to occur singly or in small organized groups contacted by nerves, called neuroepithelial bodies (NEB). Special staining procedures are required for identification at the light microscopic level; argyrophilic methods are used for paraffin sections, whereas periodic acid-Schiff (PAS)-lead hematoxylin is preferred for glycol methacrylate sections. Immunohistochemical identification can also be used. Ultrastructurally, neuroendocrine cells are characterized by small (100ï 300 nm) cytoplasmic granules that have an electron-dense core, giving the cells the commonly used name ñsmall granule cell.ò Active peptides are stored within granules; these include vasoactive intestinal peptide, bombesin, calcitonin, serotonin, neuron-specific enolase and leucine-enkephalin. These peptides are mostly released in a paracrine manner and sometimes onto nerves with regulatory-type effects. The main function of the cell appears to be the monitoring of changes in airway gases or secretions; however, their precise role in specific physiological processes is unknown. Hypoxia is known to stimulate the release of granules, whereas chronic hypoxia, hyperoxia and inhalation of NO_2 cause an increase in their number. Endocrine tumors have been induced experimentally using nitrosamines in conjunction with hyperoxia.