# CHAPTER 19
# Endocrine System

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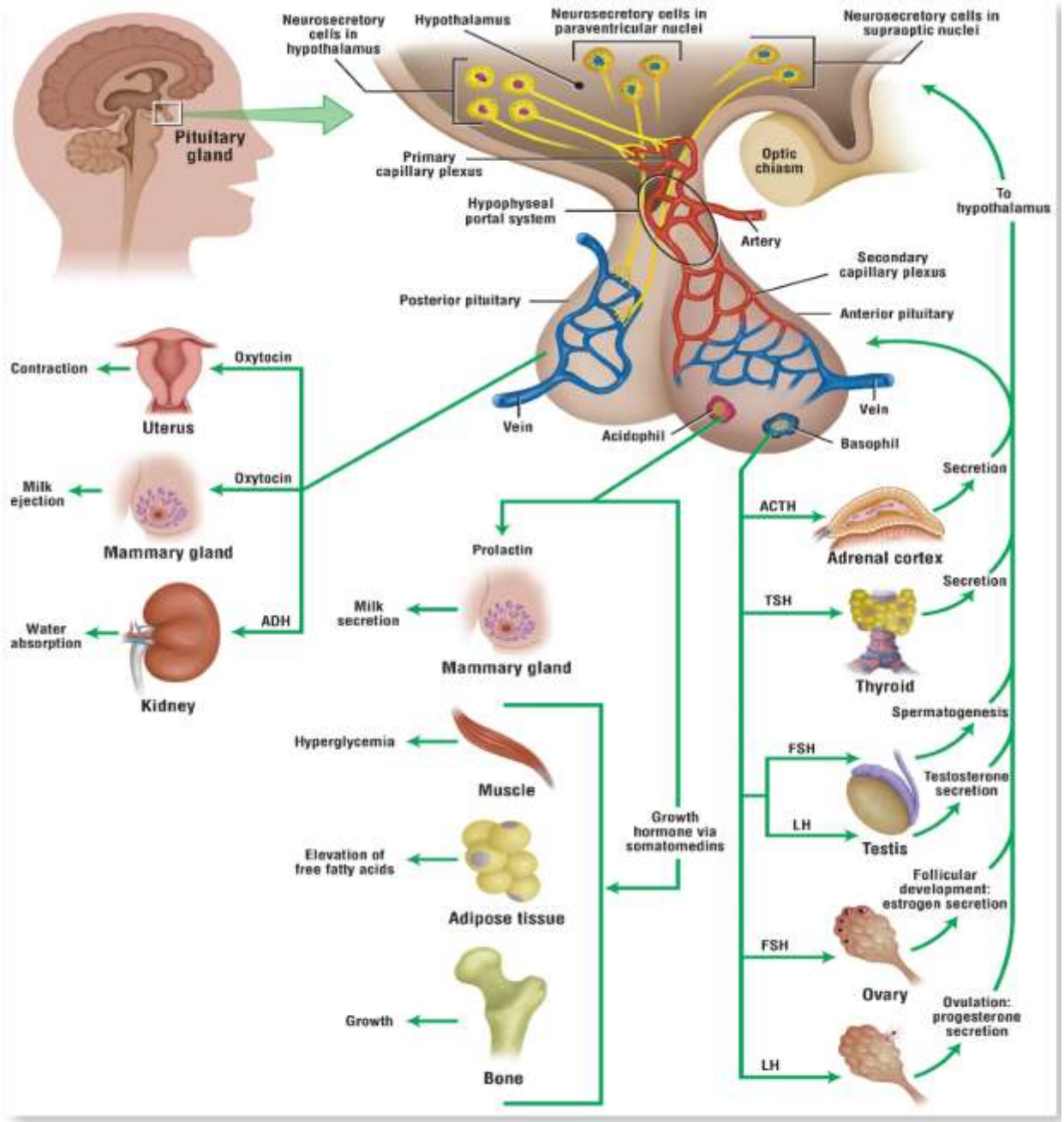



**OVERVIEW FIGURE 19.1** ■ Hypothalamus and hypophysis (pituitary gland). A section of hypothalamus and hypophysis illustrates the neuronal, axonal, and vascular connections between the hypothalamus and the hypophysis. Also illustrated are the major target cells, tissues, and organs of the hormones that are produced by both the anterior (adenohypophysis) and posterior (neurohypophysis) pituitary gland. ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

# SECTION 1 Hormones and Pituitary Gland

The endocrine system consists of cells, tissues, and organs that synthesize and secrete products called **hormones**. The hormones are then released into the interstitial connective tissue from which the hormones pass directly into blood or lymph circulation. As a result, endocrine cells, tissues, glands, and organs are called **ductless** because they do not have excretory ducts for the release of their hormones. Furthermore, the cells in most endocrine tissues and organs are arranged into **cords** and **clumps** and are surrounded by an extensive **capillary network** that allows for more efficient transport of hormones.

Hormones produced by endocrine cells include polypeptides, proteins, steroids, amino acid derivatives, and catecholamines. Because hormones act at a distance from the site of their release, they enter the circulatory system to be transported to the **target organs**. Here, they influence the structure and the programmed function of the target organ cells in the organs by binding to and interacting with specific hormone receptors.

**Hormone receptors** can be located either on the cell membrane, in the cytoplasm, or in the nucleus of target cells. Nonsteroid receptors for protein and peptide hormones are usually located on cell surfaces because the hormones do not penetrate the cell membrane. Their interaction and activation by the hormone results in the production of intracellular molecules called **second messengers**, which is **cyclic adenosine monophosphate (cAMP)** for numerous hormones. cAMP then activates a specific sequence of enzymes and various cellular events of the cytoplasm and/or nucleus in specific response to the particular hormone.

Other receptors are **intracellular** and are usually localized in the **nucleus**. These receptors are activated by hormones that diffuse through cellular and nuclear membranes. Steroid hormones and thyroid hormones are soluble in lipids and can easily cross these membranes. Once inside the target cells, these steroid hormones combine with specific protein receptors. The resulting hormone–receptor complex binds in the nucleus to a particular DNA sequence that either activates or inhibits specific genes. The activated genes initiate the synthesis of messenger RNA, which enters the cytoplasm to initiate the production of new hormone-specific proteins. The new proteins induce cellular changes that are specifically associated with the influence of the particular hormone. The hormones that combine with the intracellular receptors do not use the second messenger. Instead, they directly influence **gene expression** of the affected cell.

Numerous organs in the body contain individual endocrine cells or endocrine tissues mixed with other tissues. Such mixed (endocrine-exocrine) organs are the pancreas, kidneys, reproductive organs of both sexes, placenta, and gastrointestinal tract. Endocrine cells and endocrine tissues are discussed with the specific exocrine organs in their respective chapters.

There are also complete endocrine organs or glands (Overview Fig. 19.1). These include the **hypophysis,** or **pituitary gland** (described below), **thyroid gland, adrenal (suprarenal) glands**, and **parathyroid glands** (described in Section 2).

## Embryologic Development of Hypophysis (Pituitary Gland)

The pituitary gland, or hypophysis, is often called the master endocrine organ because it secretes many hormones that can influence the action of numerous peripheral tissues or organs in the body. However, the pituitary gland itself is controlled by the **hypothalamus** of the brain from

which regulatory hormones are transported to the pituitary. To understand this functional relationship, it is important to understand the embryologic development of the pituitary gland.

The structure and function of the hypophysis reflect its dual embryologic origin. During embryonic development, the epithelium of the **pharyngeal roof** (oral cavity) forms an outpocketing called the **hypophyseal (Rathke) pouch**. As development proceeds, the hypophyseal pouch detaches from the oral cavity to become the cellular or glandular portion of the hypophysis, now called the **adenohypophysis (anterior pituitary)**. At the same time, the downgrowth from the developing brain (diencephalon) forms the neural portion of the hypophysis, called the **neurohypophysis (posterior pituitary)**. The two separately developed structures then unite to form a single pituitary gland, the hypophysis. The hypophysis remains attached to a ventral extension of the brain called the **hypothalamus**. A short neural stalk, called the **infundibulum**, is a neural pathway that attaches and connects the hypophysis to the hypothalamus. The neurons that are located in the hypothalamus control the release of hormones from the adenohypophysis as well as secrete hormones that are then transported to and stored in the neurohypophysis until needed.

After development, the hypophysis rests in a bony depression of the sphenoid bone of the skull called the **sella turcica** that is located inferior to the hypothalamus at the base of the brain.

## Subdivisions of the Hypophysis

The epithelial-derived adenohypophysis has three subdivisions: pars distalis, pars tuberalis, and pars intermedia. The **pars distalis** is the largest part of the hypophysis. The **pars tuberalis** surrounds the neural stalk, or infundibulum. The **pars intermedia** is a thin cell layer between the pars distalis and the neurohypophysis. It represents the remnant of the hypophyseal (Rathke) pouch that becomes rudimentary in humans but prominent in other mammals.

The neurohypophysis, situated posterior to the adenohypophysis, also consists of three parts: median eminence, infundibulum, and pars nervosa. The **median eminence** is located at the base of the hypothalamus of the brain from which extends the pituitary stalk, or **infundibulum**. In the infundibulum is found a multitude of unmyelinated axons that extend from the neurons in the hypothalamus. The large portion of the neurohypophysis is the **pars nervosa**. This region contains the terminal ends of unmyelinated axons for the storage of hormones that have been secreted by the neurons in the hypothalamus. Surrounding the axons are the nonsecretory **pituicytes** that support and nourish the axons.

## Vascular and Neural Connections of Hypophysis

### Adenohypophysis

Because the adenohypophysis does not develop from the neural tissue, its connection to the **hypothalamus** of the brain is via a rich vascular network. **Superior hypophyseal arteries** from the internal carotid artery supply the pars tuberalis, median eminence, and infundibulum. These arteries form a **primary capillary plexus** in the median eminence at the base of the hypothalamus. Secretory neurons that are located in the hypothalamus synthesize hormones that have a direct influence on cell functions in the adenohypophysis. The axons from these neurons terminate on the fenestrated capillaries of the primary capillary plexus into which they release their hormones.

Small **hypophyseal portal venules** then drain the primary capillary plexus and deliver the blood with the hormones to a **secondary capillary plexus** that surrounds the cells in the pars distalis of the adenohypophysis. The venules that connect the primary capillary plexus of the hypothalamus with the secondary capillary plexus in the adenohypophysis form the **hypophyseal portal system**. To ensure efficient transport of hormones from the blood to the cells, the capillaries in the primary and secondary capillary plexuses are **fenestrated** (contain small pores).

#### *Cells of the Adenohypophysis*

The cells of the adenohypophysis were initially classified as **chromophobes** and **chromophils** based on the affinity of their cytoplasmic granules for specific stains. The pale-staining chromophobes are believed to be either degranulated chromophils with few granules or undifferentiated stem cells. The chromophils were further subdivided into **acidophils** and **basophils** because of their staining properties. Immunocytochemical techniques now identify these cells on the basis of

their specific hormones. The adenohypophysis includes two types of acidophils, the **somatotrophs** and **mammotrophs**, as well as three types of basophils: **gonadotrophs**, **thyrotrophs**, and **corticotrophs**.

The hormones released from these cells are carried in the bloodstream to the target organs, where they bind to specific receptors that influence the structure and function of the target cells. Once the target cells are activated and release their secretory products, a **feedback mechanism** (positive or negative) controls the synthesis and release of these hormones by directly acting on cells in the adenohypophysis or neurons in the hypothalamus that have initially produced these hormones.

## Neurohypophysis

In contrast to the adenohypophysis, the neurohypophysis has a direct neural connection with the brain. As a result, there are no neurons or hormone-producing cells in the neurohypophysis, and it remains connected to the brain by a multitude of unmyelinated axons and supportive cells, the pituicytes. The **neurons** (cell bodies) of these axons are located in the **supraoptic** and **paraventricular nuclei** (a collection of neurons) in the hypothalamus. The unmyelinated axons that extend from the hypothalamus into the neurohypophysis form the **hypothalamohypophyseal tract** and the bulk of the neurohypophysis. These axons also terminate near the fenestrated capillaries in the pars nervosa.

Neurons in the hypothalamus first synthesize the hormones that are released from the neurohypophysis. These hormones bind to the carrier glycoprotein **neurophysin** and are then transported from the hypothalamus down the axons by **axonal transport** to the neurohypophysis. Here, the hormones accumulate and are stored in the distended terminal ends of unmyelinated axons as **Herring bodies**. When needed, hormones from the neurohypophysis are directly released into the fenestrated capillaries of the pars nervosa by nerve impulses from the hypothalamus.

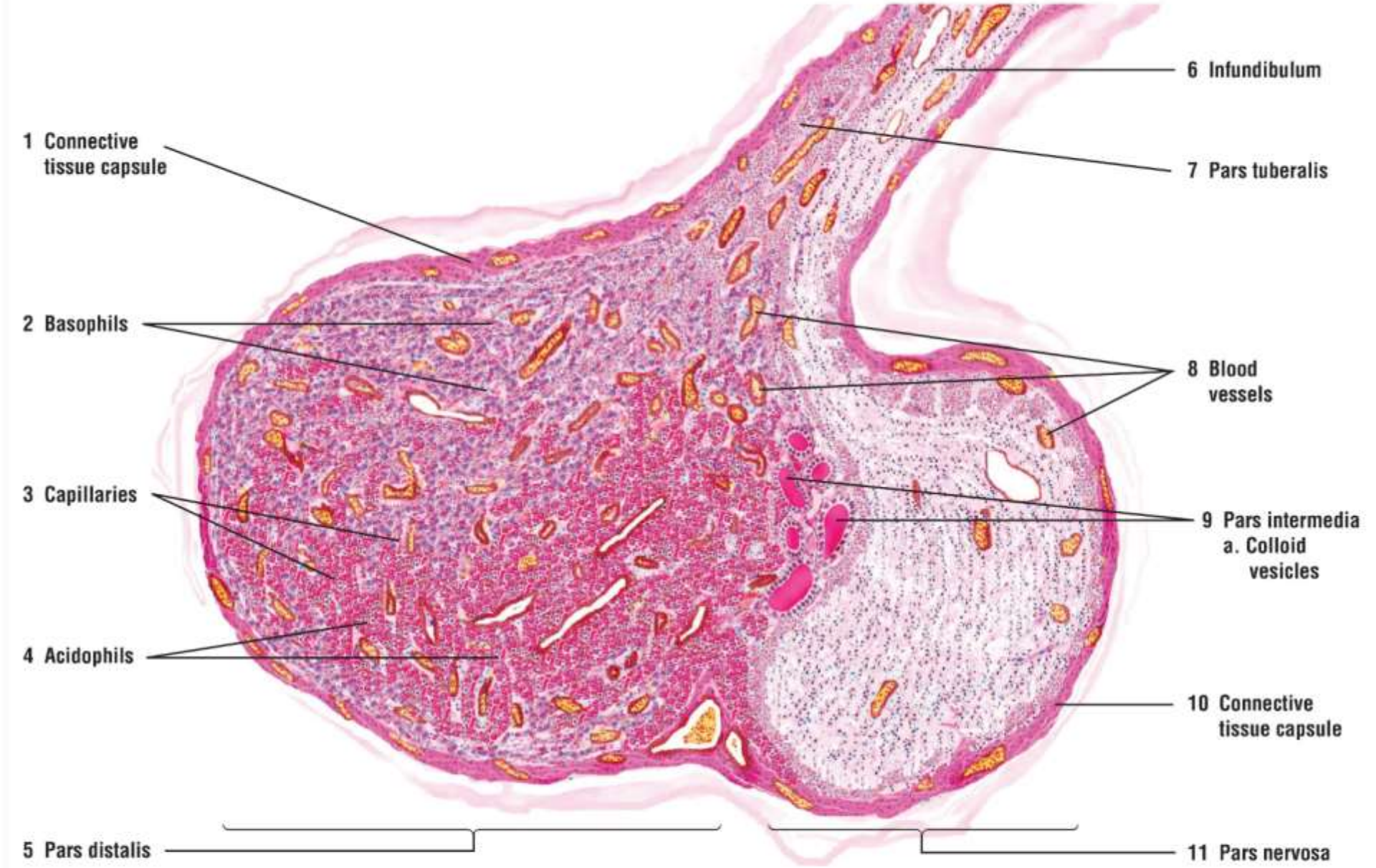



**FIGURE 19.1** ■ Hypophysis (panoramic view, sagittal section). Stain: hematoxylin and eosin. Low magnification.

## FIGURE 19.1 | Hypophysis (Panoramic View, Sagittal Section)

The hypophysis (pituitary gland) consists of two major subdivisions: the adenohypophysis and neurohypophysis. The adenohypophysis is further subdivided into the **pars distalis (anterior lobe) (5), pars tuberalis (7)**, and **pars intermedia (9)**. The neurohypophysis is divided into the **pars nervosa (11), infundibulum (6)**, and the median eminence (not illustrated). The pars tuberalis (7) surrounds the infundibulum (6) and is visible above and below the infundibulum (6) in a sagittal section. The infundibulum (6) connects the hypophysis with the hypothalamus at the base of the brain.

The pars distalis (5) contains two main cell types: chromophobe cells and chromophil cells. The chromophils are subdivided into **acidophils (alpha cells) (4)** and **basophils (beta cells) (2)**, illustrated at a higher magnification in Figure 19.2.

The pars intermedia (9) and pars nervosa (11) form the posterior lobe of the hypophysis. The pars nervosa (11) consists primarily of unmyelinated axons and supporting pituicytes. A **connective tissue capsule (1, 10)** surrounds the pars distalis (5) and pars nervosa (11) portions of the gland.

The pars intermedia (9) is situated between the pars distalis (5) and the pars nervosa (11) and represents the residual lumen of the Rathke pouch. The pars intermedia (9) normally contains **colloid-filled vesicles (9a)** that are surrounded by the cells of the pars intermedia (9).

Both the pars distalis (5) and pars nervosa (11) are supplied by numerous **blood vessels (8)** and **capillaries (3)** of different sizes.

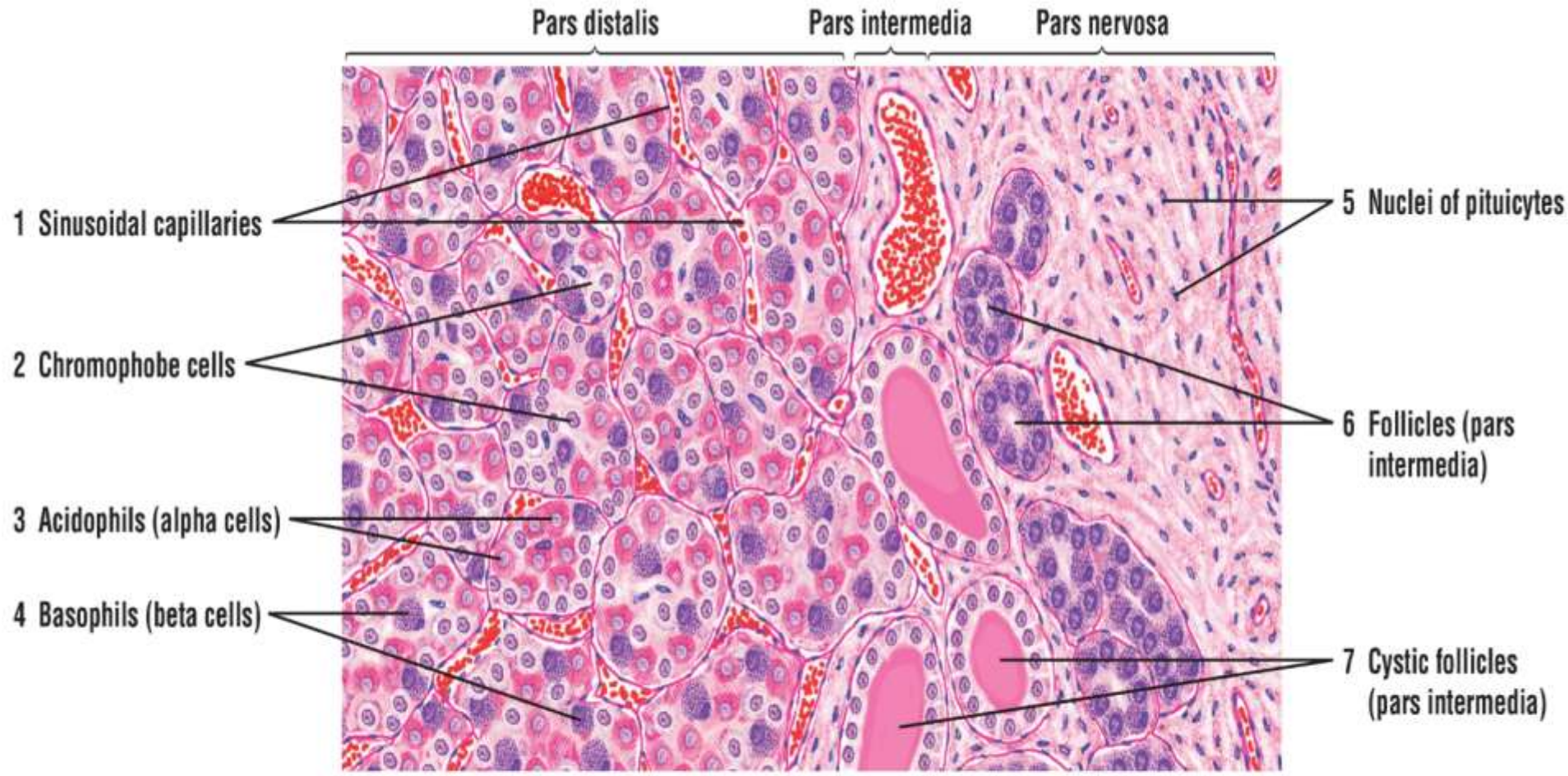



**FIGURE 19.2** ■ Hypophysis: sections of pars distalis, pars intermedia, and pars nervosa. Stain: hematoxylin and eosin. Medium magnification.

**FIGURE 19.2 | Hypophysis: Sections of Pars Distalis, Pars Intermedia, and Pars Nervosa**

At a higher magnification, numerous **sinusoidal capillaries (1)** and different cell types are visible in the **pars distalis**. **Chromophobe cells (2)** have a light-staining, homogeneous cytoplasm and are normally smaller than the chromophils. The cytoplasm of chromophils stains reddish in the **acidophils (3)** and bluish in the **basophils (4)**.

The **pars intermedia** contains **follicles (6)** and colloid-filled **cystic follicles (7)**. Follicles lined with basophils (8) are often present in the pars intermedia.

The **pars nervosa** is characterized by unmyelinated axons and the supportive **pituicytes (5)** with oval nuclei.

## FUNCTIONAL CORRELATIONS 19.1 | Hormones of the Hypophysis

Hormones produced by neurons in the **hypothalamus** directly influence and control the synthesis and release of six specific hormones from the adenohypophysis. Most of the hormones are **releasing hormones** produced by neurons in the hypothalamus for each hormone that is released from the adenohypophysis. For two hormones, growth hormone (GH) and prolactin, **inhibitory hormones** are also produced. These releasing hormones are thyrotropin-releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, and growth hormone–releasing hormone. The inhibitory hormones are **somatostatin**, which inhibits the release of GH, and **dopamine** (prolactin-inhibiting hormone), which inhibits the secretion of prolactin.

The releasing and inhibitory hormones secreted from the hypothalamic neurons are carried from the primary capillary plexus of the median eminence of the hypothalamus to the second capillary plexus in the adenohypophysis via the **hypophyseal portal system**. On reaching the adenohypophysis, the hormones bind to specific receptors on cells and either stimulate the cells to secrete and release a specific hormone into the circulation or inhibit this function.

In contrast, the neurohypophysis does not secrete hormones. Instead, the neurohypophysis stores and releases only two hormones when needed, **oxytocin** and **vasopressin** (antidiuretic hormone), that were synthesized in the hypothalamus by the neurons in the **paraventricular nuclei** and **supraoptic nuclei**. These hormones are then transported along unmyelinated axons and stored as tiny dilations in the axon terminals of the neurohypophysis as **Herring bodies** from which they are released into the capillaries of the par nervosa as needed. Herring bodies are visible with a light microscope.

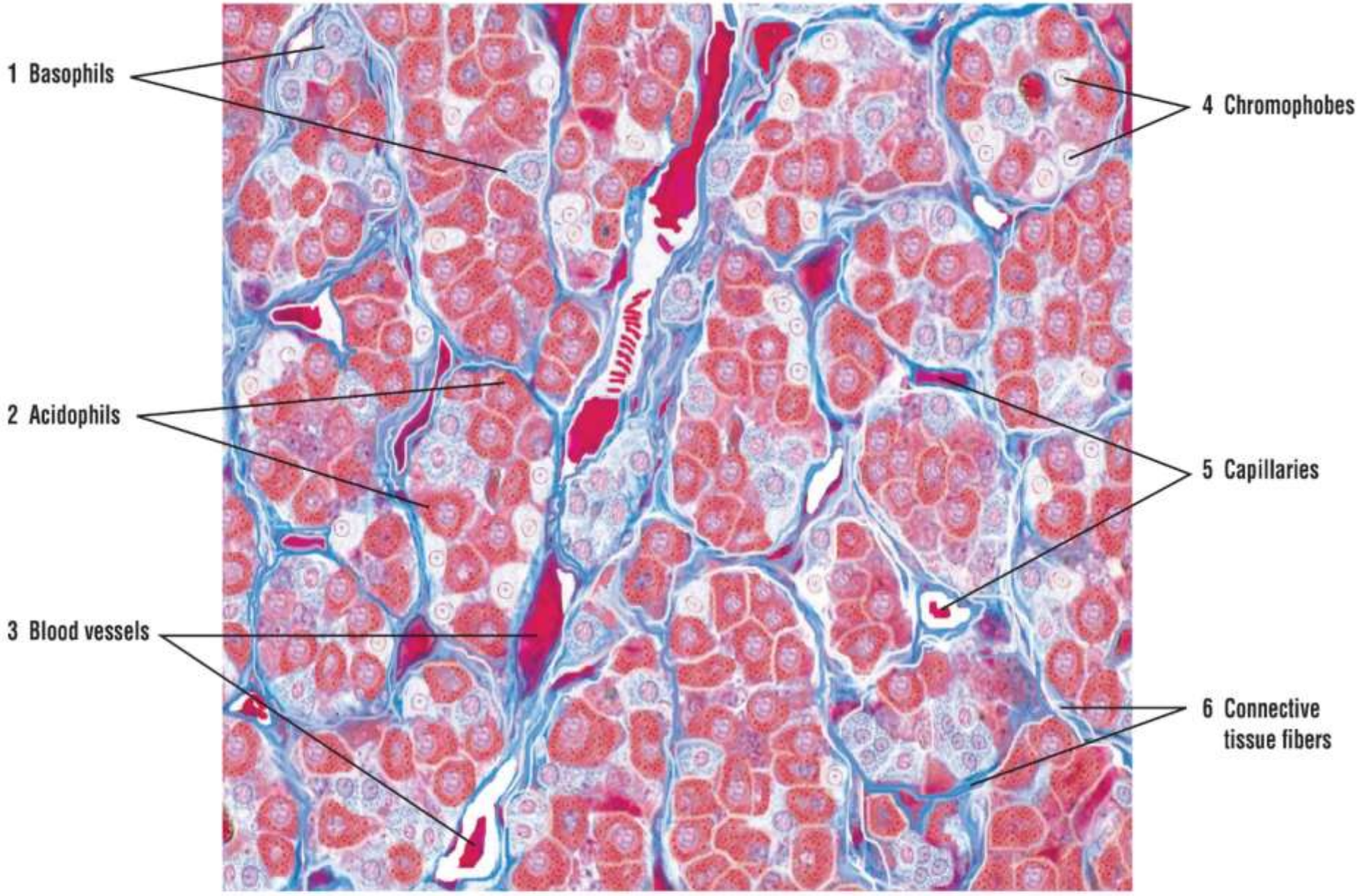



**FIGURE 19.3** ■ Hypophysis: pars distalis (sectional view). Stain: Azan. High magnification.

**FIGURE 19.3** | **Hypophysis: Pars Distalis (Sectional View)**

This illustration shows the two main populations of cells in the pars distalis of the adenohypophysis. The cells here are arranged in clumps. Between the clumps are seen the numerous **capillaries (5)**, **blood vessels (3)**, and thin **connective tissue fibers (6)** that separate the clumps. Cell types in the pars distalis can be identified with special fixation and the staining affinity of the cytoplasmic granules.

The **chromophobes (4)** usually exhibit pale nuclei and pale cytoplasm with poorly defined cell outlines. The aggregation of chromophobes in groups or clumps is seen in this illustration.

The **acidophils (2)** are more numerous and can be distinguished by their red-staining granules in the cytoplasm and blue nuclei.

The **basophils (1)** are less numerous and appear as cells that contain blue-staining granules in their cytoplasm. The degree of granularity and the stain density vary in different cells.

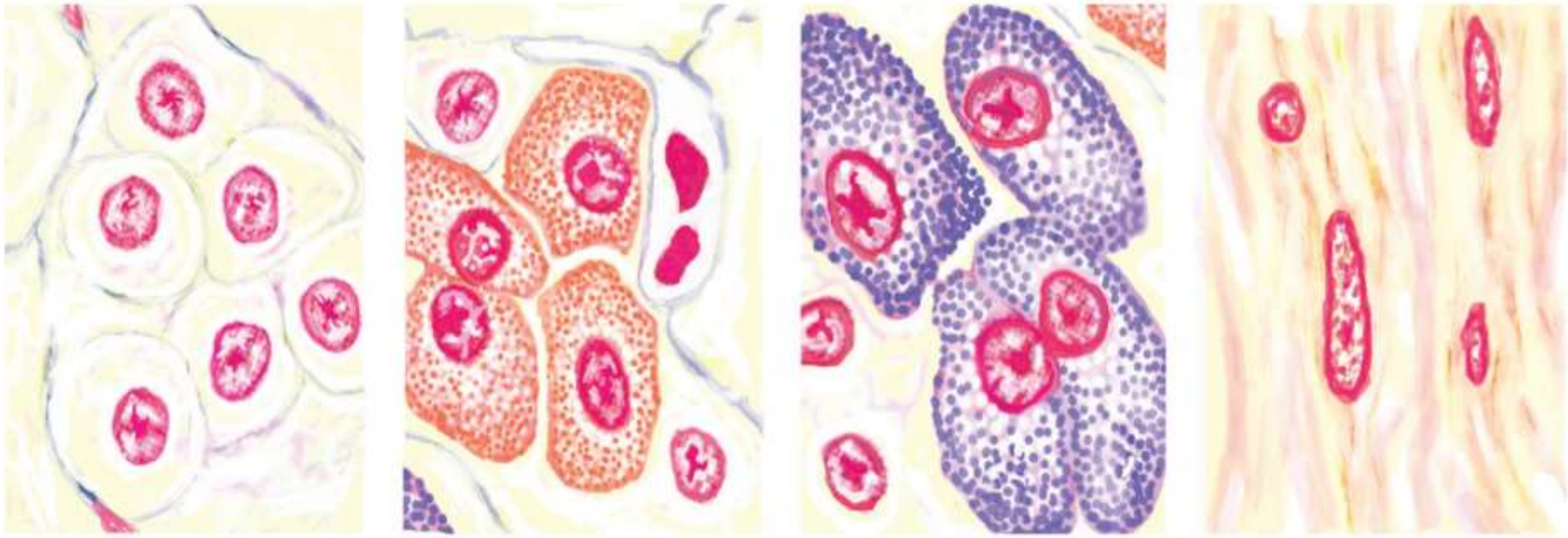



**FIGURE 19.4** ■ Cell types in the hypophysis. Stain: modified Azan. Oil immersion.

## FIGURE 19.4 | Cell Types in the Hypophysis

Groups of different cell types of the hypophysis are illustrated at a higher magnification after modified Azan staining. The nuclei of all cells are stained orange-red.

The **chromophobes** (**a**) exhibit a clear and very light orange cytoplasm. The appearance of clear cytoplasm indicates that the cells do not have granules, and as a result, their cell boundaries are indistinct.

The cytoplasmic granules of **acidophils** (**b**) stain intensely red, and the cell outlines are distinct. A sinusoid capillary surrounds the acidophils.

The **basophils** (**c**) exhibit variable cell shapes and granules that vary in size.

The **pituicytes** (**d**) of the pars nervosa have variable cell shape and cell size. The small, orange-stained cytoplasm is diffuse and barely visible.

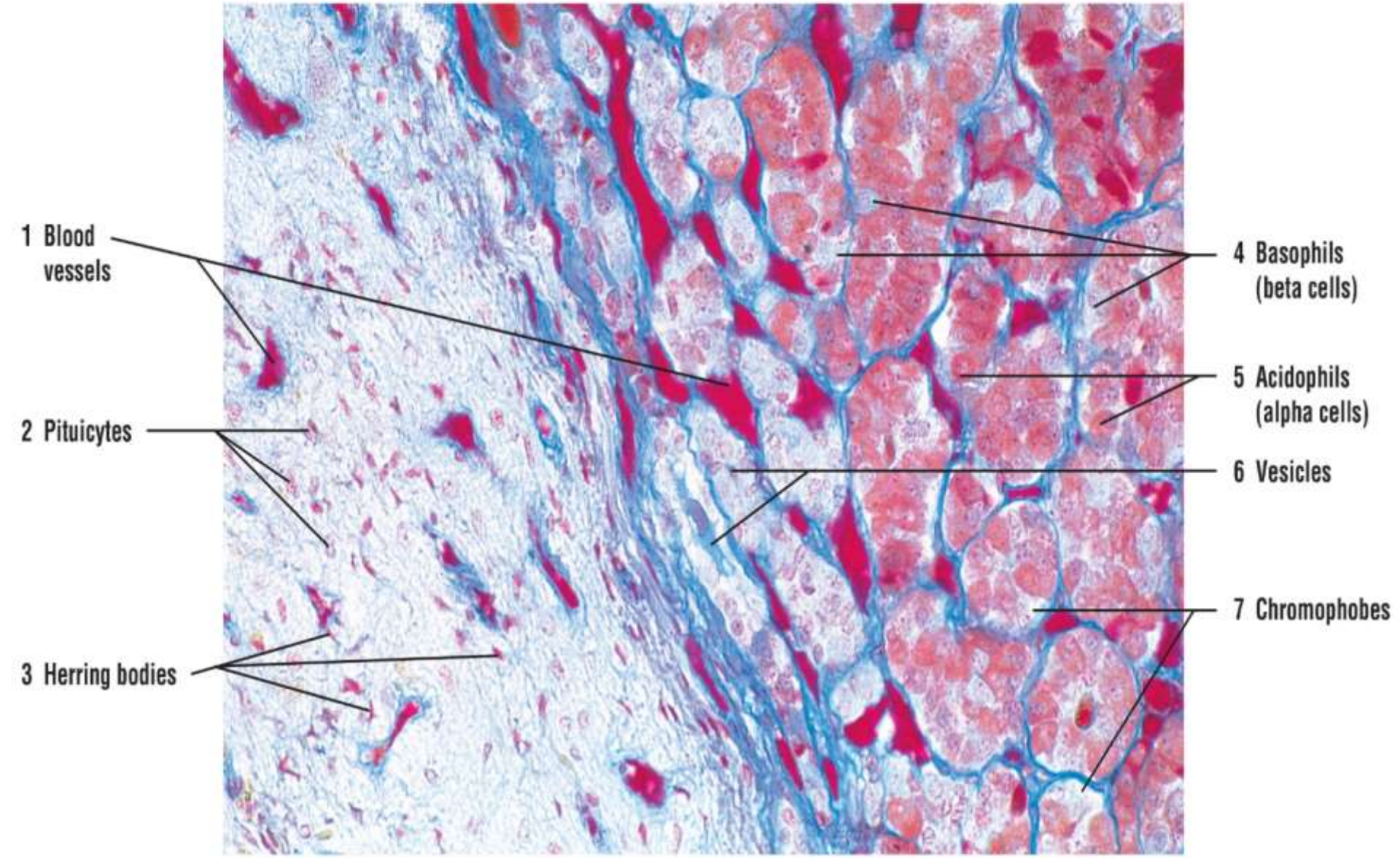



**FIGURE 19.5** ■ Hypophysis: pars distalis, pars intermedia, and pars nervosa. Stain: Mallory-Azan and orange G. ×80.

**FIGURE 19.5 | Hypophysis: Pars Distalis, Pars Intermedia, and Pars Nervosa**

This higher-power photomicrograph illustrates the cellular pars distalis and pars intermedia of the adenohypophysis and the light-staining pars nervosa of the neurohypophysis. With this stain, different cell types can be identified in the pars distalis. The red-staining, or eosinophilic, cells are the **acidophils (5)**. The cells with bluish cytoplasm are the **basophils (4)**. The light, unstained cells scattered among the acidophils (5) and basophils (4) are the **chromophobes (7)**. The pars intermedia exhibits small cysts, or **vesicles (6),** filled with colloid.

The pars nervosa is filled with the unmyelinated, light-staining axons of secretory cells, whose cell bodies are located in the hypothalamus. Most of the red-staining nuclei in the pars nervosa are the supportive cell **pituicytes (2)**. Accumulations of the neurosecretory material at the end of the axon terminals in the pars nervosa are the irregular-shaped, red-staining structures called the **Herring bodies (3)**. Herring bodies (3) are closely associated with capillaries and **blood vessels (1)**. Surrounding the secretory cells and axon terminals in the neurohypophysis are blood vessels (1) and fenestrated capillaries.

## FUNCTIONAL CORRELATIONS 19.2 | Cells and Hormones of the Adenohypophysis

### ACIDOPHILS

**Somatotrophs** secrete **somatotropin**, also called growth hormone, or GH. This hormone targets the whole body and its general growth. It stimulates cellular metabolism, uptake of amino acids, and protein synthesis. Somatotropin also stimulates the liver to produce **somatomedins**, also called insulin-like growth factor 1 (IGF-1). These hormones increase proliferation of cartilage cells (chondrocytes) in the **epiphyseal plates** of developing or growing long bones to increase the bone length. There is also an increase in the growth of the skeletal muscle and increased release of fatty acids from the adipose cells for energy production by body cells. GH-inhibiting hormone, also called **somatostatin**, has an inhibitory effect on the release of GH from somatotrophs in the pituitary gland.

**Mammotrophs** produce the lactogenic hormone **prolactin** that stimulates the development of mammary glands during pregnancy. After parturition (birth), prolactin maintains milk production in the developed mammary glands during lactation. The release of prolactin from mammotrophs is inhibited by a prolactin release inhibitory hormone, also called **dopamine**.

## BASOPHILS

**Thyrotrophs** secrete **thyroid-stimulating hormone** (**thyrotropin** or **TSH**). TSH stimulates follicular cells in the thyroid gland to synthesize and secrete thyroglobulin and the hormones **thyroxin** and **triiodothyronine** from the thyroid gland.

**Gonadotrophs** secrete **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**. In females, FSH promotes growth and maturation of ovarian follicles and the subsequent **estrogen** secretion by developing follicles. In males, FSH promotes **spermatogenesis** in the testes and secretion of **androgen-binding protein** into seminiferous tubules by **Sertoli cells**. The androgen-binding protein maintains the needed concentration of testosterone in the seminiferous tubules to ensure proper spermatogenesis.

In females, LH in association with FSH induces **ovulation**, promotes the final maturation of ovarian follicles, and stimulates the formation of the **corpus luteum** after ovulation. LH also promotes the secretion of estrogen and progesterone from the corpus luteum. In males, LH maintains and stimulates the **interstitial cells** (of Leydig) in the testes to produce the hormone **testosterone**. As a result, LH is sometimes called interstitial cell–stimulating hormone.

**Corticotrophs** secrete **adrenocorticotropic hormone (ACTH)**. ACTH influences the function of the cells in **adrenal cortex**. ACTH also stimulates the synthesis and release of glucocorticoids from the zona fasciculata and zona reticularis of adrenal cortex.

## PARS INTERMEDIA

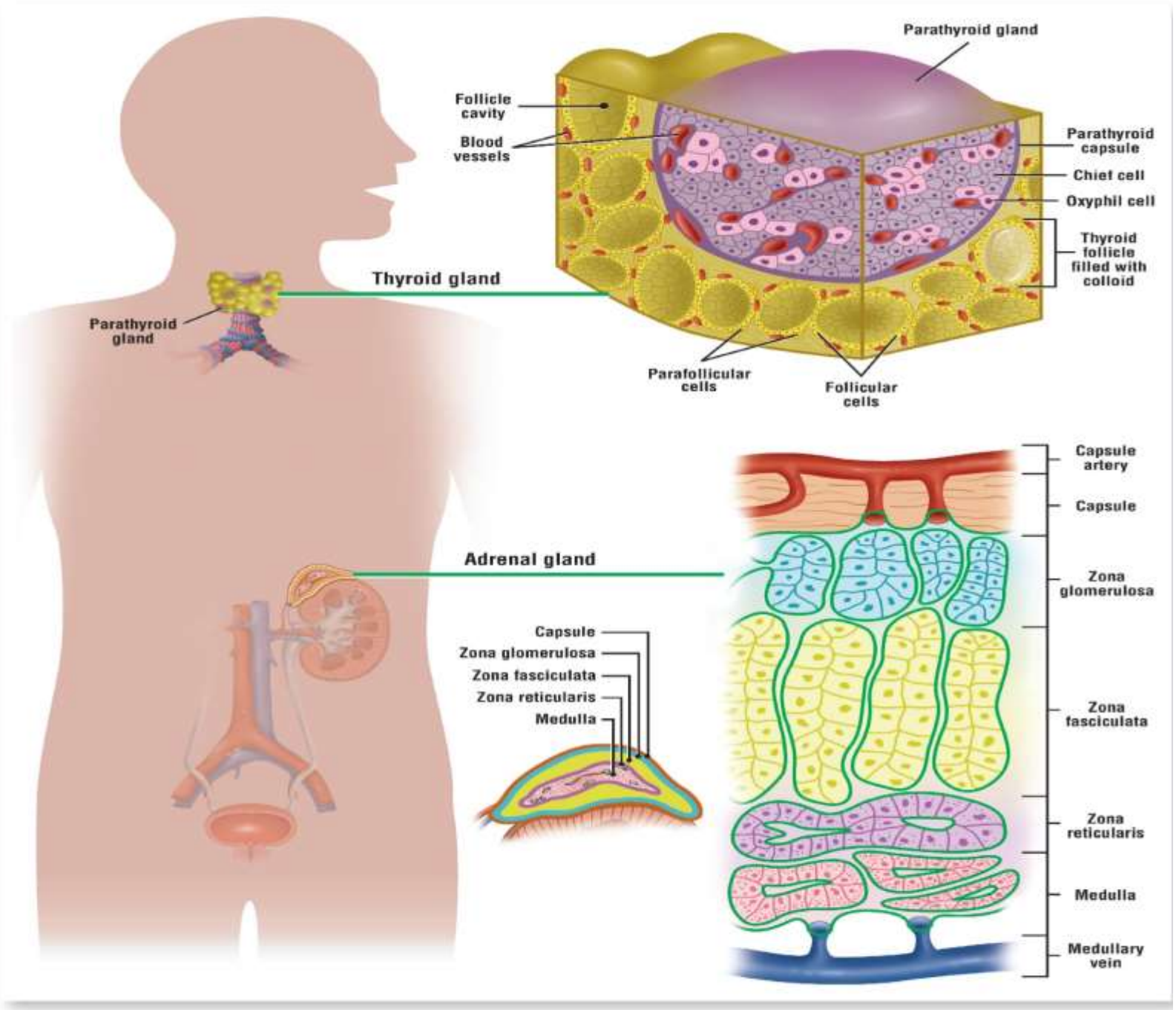
In lower vertebrates (amphibians and fishes), the pars intermedia is well developed and produces **melanocyte-stimulating hormone (MSH)**. MSH increases skin pigmentation by causing the dispersion of melanin granules. In humans and most mammals, the pars intermedia is rudimentary.

## OXYTOCIN

The two hormones, oxytocin and antidiuretic hormone (ADH), that are released from the neurohypophysis are synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. The release of oxytocin is stimulated by vaginal and cervical distension before birth and nursing of the infant after birth. The main targets of **oxytocin** are the smooth muscles of the pregnant uterus. During labor, oxytocin is released to induce strong contractions of smooth muscles in the uterus, resulting in childbirth (parturition). After parturition, the suckling action of the infant on the nipple stimulates and activates the **milk-ejection reflex** in the lactating mammary glands. Afferent impulses from the nipple stimulate neurons in the hypothalamus, causing oxytocin release. Oxytocin then stimulates the contraction of **myoepithelial cells** around the alveoli and ducts in the lactating mammary glands, ejecting milk into the excretory ducts and the nipple.

## ANTIDIURETIC HORMONE (VASOPRESSIN)

The main action of ADH is to increase **water permeability** in the **distal convoluted tubules** and **collecting ducts** of the kidney. As a result, more water is reabsorbed from the filtrate into the interstitium and retained in the body, creating more concentrated urine. A sudden decrease of blood pressure is also a stimulus for the release of ADH. It is believed that in large doses, ADH may cause smooth muscle contraction in arteries and arterioles. However, physiologic doses of ADH appear to have minimal effects on blood pressure.




**OVERVIEW FIGURE 19.2** ■ Thyroid gland, parathyroid gland, and adrenal gland. The microscopic organization and general location in the body of the thyroid, parathyroid, and adrenal glands are illustrated.

# SECTION 2 Thyroid Gland, Parathyroid Glands, and Adrenal Gland

The location in the body and histologic appearance of the thyroid gland, parathyroid glands, and adrenal glands are illustrated in Overview Figure 19.2.

## Thyroid Gland

The **thyroid gland** is located in the anterior neck inferior to the larynx. It is a single gland that consists of large right and left lobes, connected in the middle by an isthmus. Most endocrine cells, tissues, or organs are arranged in cords or clumps and store their secretory products within their cytoplasm. The thyroid gland is a unique endocrine organ in that its cells are arranged into spherical structures, called **follicles**, where the hormones are stored. Each follicle is lined with a single layer of follicular cells and surrounded by reticular fibers. The adjacent vascular network of capillaries surrounds the follicles for the easy entrance of thyroid hormones from the follicles into the bloodstream. The follicular epithelium can be simple squamous, cuboidal, or low columnar, depending on the state of activity of the thyroid gland.

Follicles are the structural and functional units of the thyroid gland. The cells that surround the follicles, the **follicular cells**, also called principal cells, synthesize, release, and store their product outside their cytoplasm, or extracellularly, in the lumen of the follicles as a gelatinous substance called **colloid**. Colloid is composed of **thyroglobulin**, an iodinated glycoprotein that is the inactive storage form of the thyroid hormones.

In addition to follicular cells, the thyroid gland also contains larger, pale-staining **parafollicular** cells. These cells are found either peripherally in the follicular epithelium or within the follicle. When parafollicular cells are located in the confines of a follicle, they are always separated from the follicular lumen by neighboring follicular cells.

## Parathyroid Glands

Mammals generally have four **parathyroid glands**. These small oval glands are embedded on the posterior surface of the thyroid gland but are separated from the thyroid gland by a thin connective tissue **capsule**. Normally, one parathyroid gland is located on the superior pole and one on the inferior pole of each lobe of the thyroid gland. In contrast to the thyroid gland, the cells of the parathyroid glands are arranged into cords or clumps, surrounded by a rich network of capillaries, and normally they do not exhibit follicles that are seen in the adjacent thyroid gland.

There are two types of cells in the parathyroid glands: functional **principal**, or **chief, cells** and **oxyphil cells**. Oxyphil cells are larger, are found singly or in small groups, and are less numerous than the principal (chief cells). In routine histologic sections, these cells stain deeply acidophilic. On rare occasions, small colloid-filled follicles may be seen in the parathyroid glands.

## Adrenal (Suprarenal) Glands

The **adrenal glands** are endocrine organs situated near the superior pole of each kidney. Each adrenal gland is surrounded by a dense irregular connective tissue capsule and embedded in the adipose tissue around the kidneys. The secretory portion of each adrenal gland consists of an outer **cortex** and an inner **medulla**. Although these two regions of the adrenal gland are located in one organ and are linked by a common blood supply, they have separate and distinct embryologic origins, structures, and functions.

### Cortex

The adrenal cortex exhibits three concentric zones: the zona glomerulosa, zona fasciculata, and zona reticularis.

The **zona glomerulosa** is a thin zone inferior to the adrenal gland capsule. It consists of cells arranged in small clumps.

The **zona fasciculata** is intermediate and the thickest zone of the adrenal cortex. This zone exhibits vertical columns of one-cell thickness adjacent to straight capillaries. This layer is characterized by pale-staining cells owing to the increased presence of numerous lipid droplets.

The **zona reticularis** is the innermost zone that is adjacent to the adrenal medulla. The cells in this zone are arranged in cords or clumps.

In all three zones, the secretory cells are adjacent to fenestrated capillaries. The cells of these zones in the adrenal cortex produce three classes of steroid hormones: **mineralocorticoids, glucocorticoids**, and **sex hormones**.

## Medulla

The medulla lies in the center of the adrenal gland. The cells of the adrenal medulla, also arranged in small cords, are modified postganglionic sympathetic neurons that have lost their axons and dendrites during development. Instead, they have become secretory cells that synthesize and secrete **catecholamines** (primarily epinephrine and norepinephrine). Preganglionic axons of the sympathetic neurons innervate the adrenal medulla cells, which are surrounded by an extensive capillary network. As result, the release of epinephrine and norepinephrine from the adrenal medulla is very efficient and under the direct control of the sympathetic division of the **autonomic nervous system**. Ganglion cells are also present in the adrenal medulla.

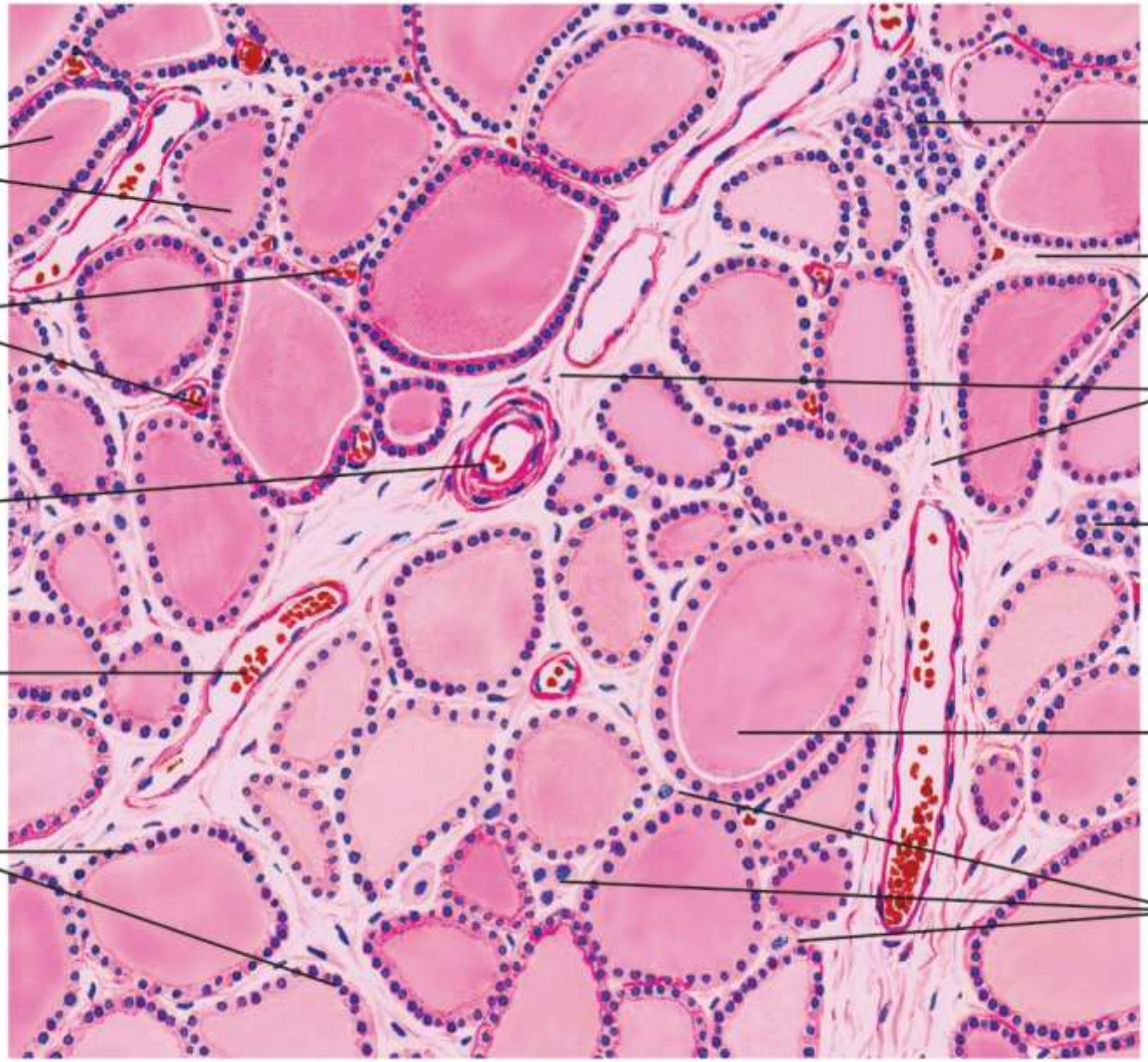



**FIGURE 19.6** ■ Thyroid gland: canine (general view). Stain: hematoxylin and eosin. Low magnification.

## FIGURE 19.6 | Thyroid Gland: Canine (General View)

The thyroid gland is characterized by numerous and variable-sized **follicles (1, 10)** that are filled with an acidophilic secretory product called **colloid (1, 10)**. The follicles are usually lined with a simple cuboidal epithelium consisting of **follicular** (principal) **cells (5, 6)**. The **follicles (6, 9)** that are sectioned peripherally or tangentially do not exhibit follicular content and appear as separate cell clumps (6, 9). The follicular cells (5, 6) synthesize and secrete the colloid and the thyroid hormones. In routine histologic preparations, colloid often retracts from the follicular wall of the follicle (10).

Within the thyroid gland are also found another cell type called **parafollicular cells (11)**. These cells occur as single cells or in clumps on the periphery of the follicles. The parafollicular cells (11) stain somewhat lighter than the follicular cells (5) and are readily visible in the canine thyroid. Parafollicular cells (11) synthesize and secrete the hormone calcitonin.

**Connective** tissue **septa (8)** from the thyroid gland capsule extend into the gland's interior and divide the gland into lobules. Numerous blood vessels—**arterioles (3), venules (4)**, and **capillaries (2)**—are seen in the connective tissue septa (8) and around individual follicles (2). A small amount of **interfollicular connective tissue (7)** is found between individual follicles.

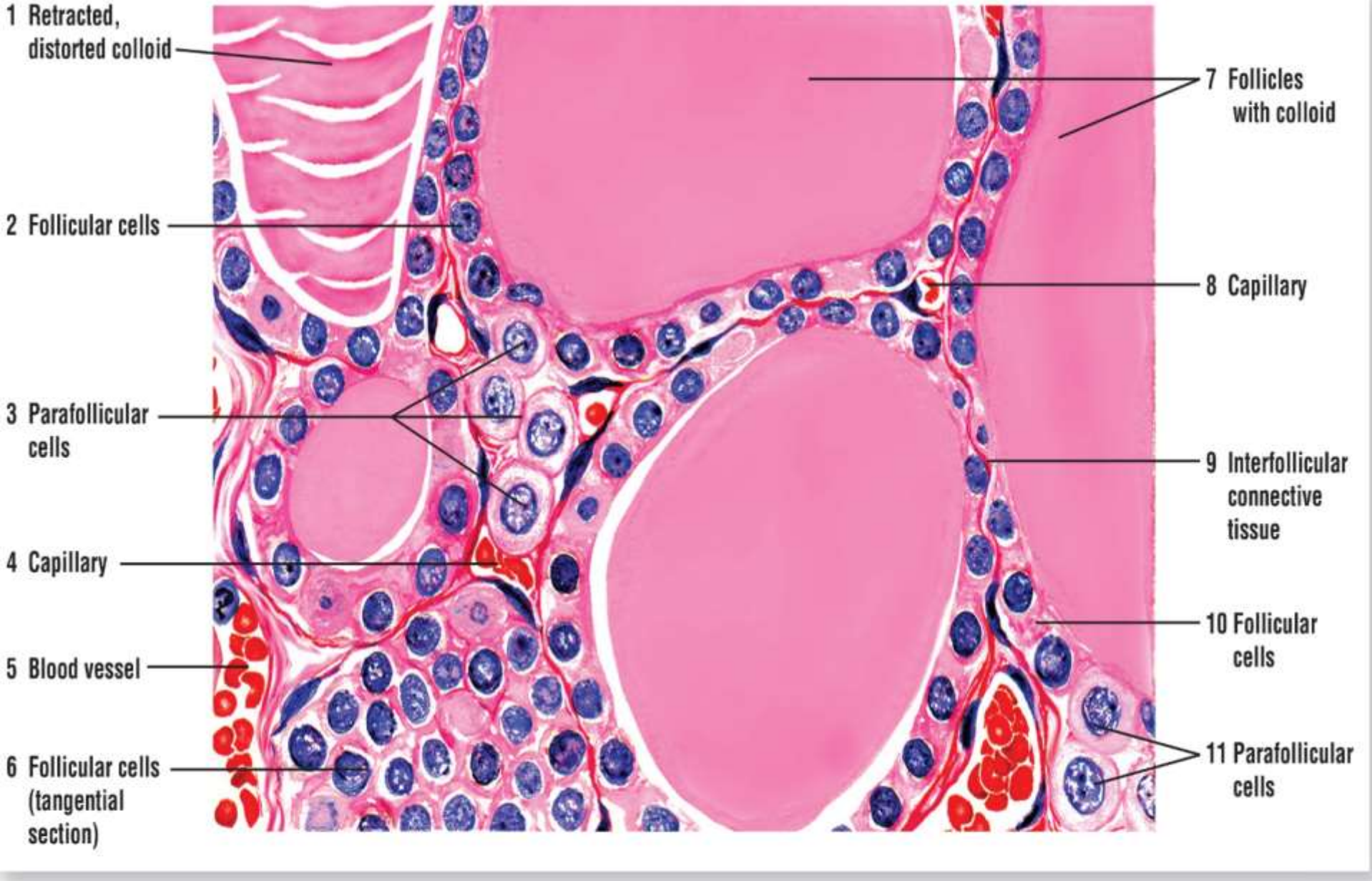



**FIGURE 19.7** ■ Thyroid gland follicles: canine (sectional view). Stain: hematoxylin and eosin. High magnification.

## FIGURE 19.7 | Thyroid Gland Follicles: Canine (Sectional View)

This higher magnification of a section of the thyroid gland shows greater detail of individual **thyroid follicles (7)** with secretory colloid material. The height of the **follicular cells (2, 6, 10)** depends on the function of the individual follicles. In highly active follicles, the epithelium is cuboidal (2, 10). In less active follicles, the epithelial cells appear flattened. All thyroid follicles (7) are filled with the secretory material, **colloid (7)**, some of which show **retraction (1)** from the follicular wall or **distortion (1)** as a result of chemicals used in slide preparation.

At a higher magnification, the location of **parafollicular cells (3, 11)** is seen to be adjacent to the follicular cells (2, 10) or in small clumps (3) adjacent to the thyroid follicles (7). The parafollicular cells (3, 11) are larger than the follicular cells (2, 10) and oval in shape with cytoplasm staining lighter than the cytoplasm of the follicular cells (2, 10). Although the parafollicular cells (3, 11) appear to be directly located on the follicular lumen, they are, instead, separated from the lumen by the processes of neighboring follicular cells (2, 10).

Surrounding the thyroid follicles (7), the follicular cells (2, 10), and the parafollicular cells (3, 11) is a thin **interfollicular connective tissue (9)** with numerous **blood vessels (5)** and **capillaries (4, 8)** that are very close to the individual follicles.

## FORMATION OF THYROID HORMONES

The secretory functions of **follicular cells**, which are responsible for the production of thyroid hormones in the thyroid gland, are controlled by **thyroid-stimulating hormone (TSH)** released from the adenohypophysis. **Iodide** is an essential element for the production of the active thyroid hormones **triiodothyronine ($T_3$)** and **tetraiodothyronine**, or **thyroxine ($T_4$)**, that are released into the bloodstream by the thyroid gland.

Low levels of thyroid hormones in the blood stimulate the release of TSH from the adenohypophysis. In response to TSH stimulus, the follicular cells in the thyroid gland take up **iodide** into their cytoplasm from the circulation via the iodide pump located in the follicular basal cell membrane. Iodide is then oxidized to iodine in the follicular cells and transported into the follicular lumen that contains colloid material. In the follicular lumen, iodine combines with amino acid tyrosine groups to form **iodinated thyroglobulin**, of which the hormones ($T_3$ and $T_4$) are the principal products. $T_3$ and $T_4$ remain bound to the iodinated thyroglobulin in thyroid follicles in an inactive form until needed. TSH released from the adenohypophysis also stimulates the thyroid gland cells to release the thyroid hormones into the bloodstream.

## RELEASE OF THYROID HORMONES

The release of thyroid hormones involves endocytosis (uptake) of thyroglobulin by follicular cells, hydrolysis of the iodinated thyroglobulin by lysosomal proteases, and release of the principal **thyroid hormones ($T_3$ and $T_4$)** at the base of follicular cells into the surrounding capillaries. Most of the released thyroid hormones are tightly bound to specific thyroxin-binding protein. The thyroid secretes greater quantities of $T_4$ than $T_3$ into the circulation; however, $T_3$ is physiologically much more potent than $T_4$. The presence of thyroid hormones in the general circulation accelerates the metabolic rate of the body and increases cell metabolism, growth, differentiation, and development throughout the body. In addition, thyroid hormones increase the rate of protein, carbohydrate, and fat metabolism.

## PARAFOLLICULAR CELLS

The thyroid gland also contains **parafollicular cells**. These cells appear on the periphery of the follicular epithelium as single cells or as cell clusters between the follicles. Parafollicular cells are not part of thyroid follicles and are not in contact with colloid in the follicular lumen.

The parafollicular cells synthesize and secrete the hormone **calcitonin (thyrocalcitonin)** into capillaries, which regulates calcium metabolism in the body. The main function of calcitonin is to lower blood calcium levels in the body. This is primarily accomplished by inhibiting the resorptive action of **osteoclasts**, reducing calcium release, and increasing calcium deposition in bones. Calcitonin also promotes increased excretion of calcium and phosphate ions from the kidneys into the urine. The production and release of calcitonin by the parafollicular cells depends on increased blood calcium levels and is completely **independent** of the pituitary gland hormones. Thus, the secretion and release of calcitonin into the bloodstream is regulated by calcium levels through a simple **feedback** mechanism.

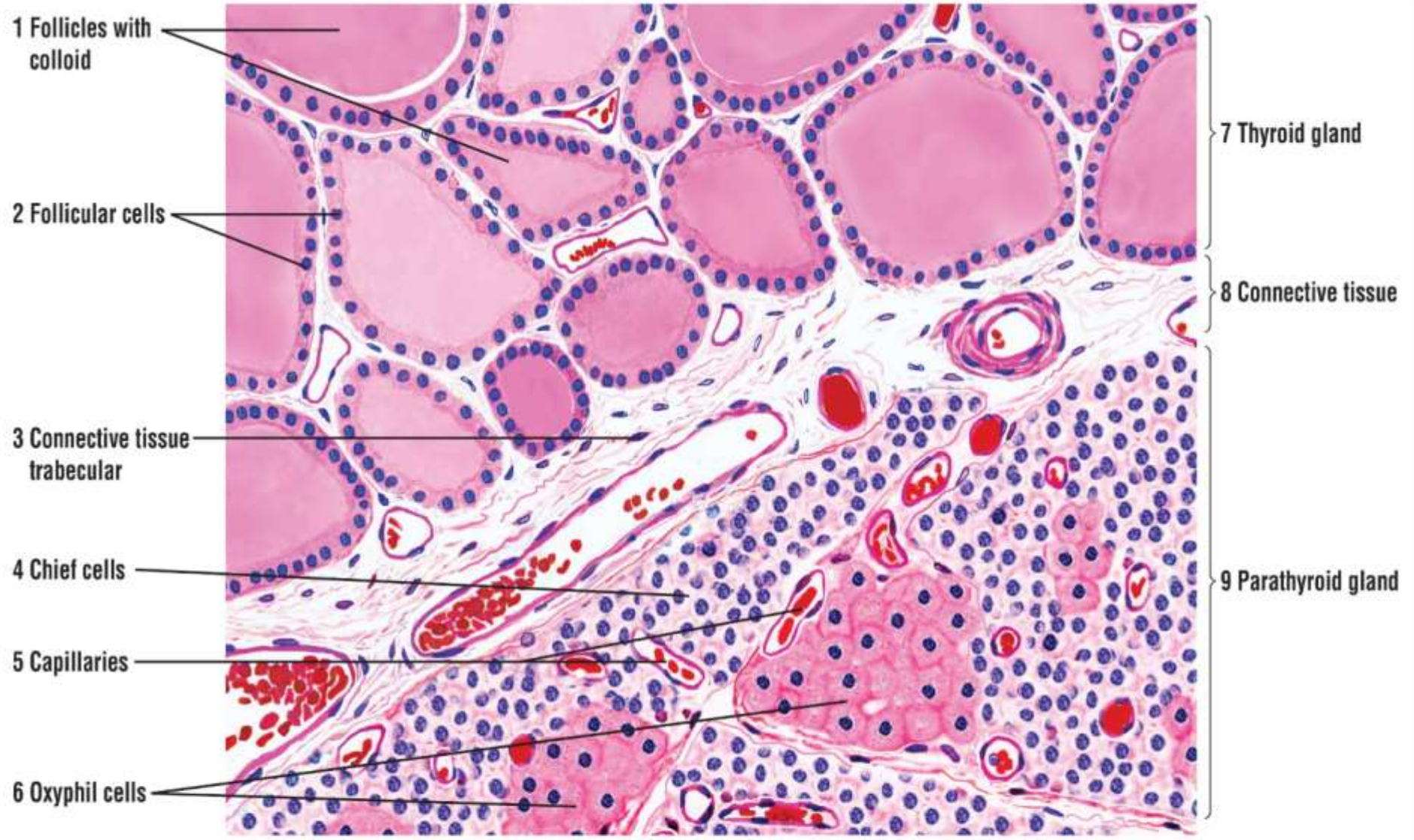



**FIGURE 19.8** ■ Thyroid and parathyroid glands: canine (sectional view). Stain: hematoxylin and eosin. Low magnification.

## FIGURE 19.8 | Thyroid and Parathyroid Glands: Canine (Sectional View)

The **follicles (1)** filled with the secretory material colloid of the **thyroid gland (7)** are closely associated with the different cell types of the **parathyroid gland (9)**. Thin **connective tissue (3, 8)** septa from the surrounding glandular capsule extend into the thyroid gland to separate the parathyroid gland (9) cells from the thyroid gland (7) follicles. In the connective tissue (3, 8) are found larger blood vessels that eventually branch into numerous **capillaries (5)** to surround the parathyroid cells (9) as well as the follicles (1) in the thyroid gland (7).

The parathyroid gland (9) cells are arranged into anastomosing cords and clumps, instead of the follicles (1) filled with the secretory material colloid surrounded by **follicular cells (2)** of the thyroid gland (7). However, occasionally, an isolated small follicle with colloid material may be observed in the parathyroid gland. The parathyroid gland (9) contains two cell types: the **chief (principal) cells (4)** and the **oxyphil cells (6)**. The chief cells (4) of the parathyroid gland are the most numerous cells. They are round and have a pale, slightly acidophilic cytoplasm. In contrast, the oxyphil cells (6) are larger and less numerous than the chief cells (4) and exhibit an acidophilic cytoplasm with dark nuclei (6). The oxyphil cells (6) are found as single cells or in small clumps throughout the parathyroid gland (9); these cells increase in number with increasing age of the individual.

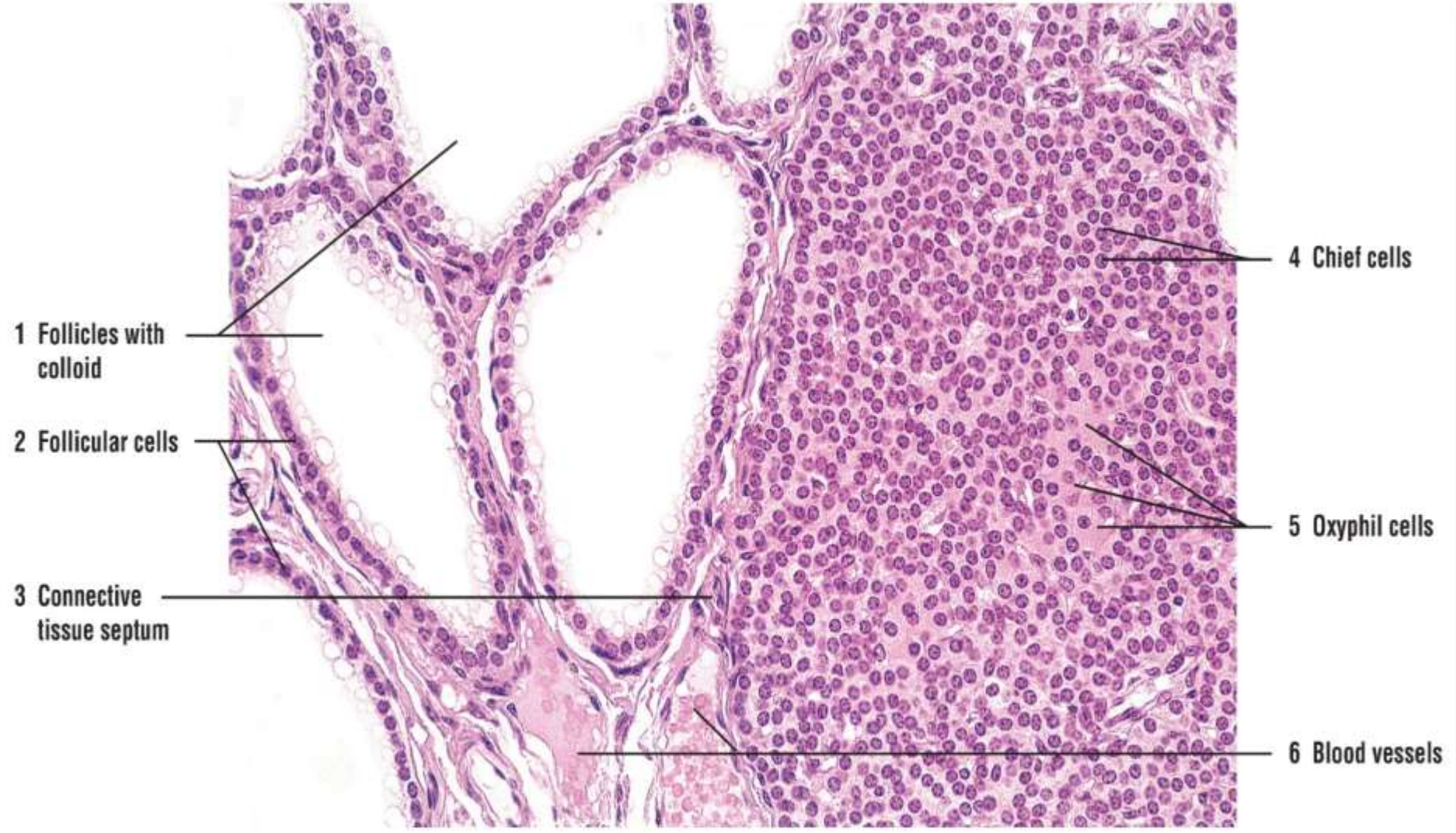



**FIGURE 19.9** ■ Thyroid gland and parathyroid gland. Stain: hematoxylin and eosin. ×80.

**FIGURE 19.9** | Thyroid Gland and Parathyroid Gland

This photomicrograph shows a section of parathyroid gland adjacent to the thyroid gland. A thin **connective tissue septum (3)** separates the two glands. Different size **follicles with colloid (1)** and lined with **follicular cells (2)** characterize the thyroid gland.

Instead of follicles, the parathyroid gland contains two cell types: **Chief cells (4)** are smaller and more numerous, whereas the **oxyphil cells (5)** are larger and less numerous and exhibit a highly eosinophilic cytoplasm. Numerous **blood vessels (6)** surround the secretory cells in both organs.

## FUNCTIONAL CORRELATIONS 19.5 | Parathyroid Glands

The **chief cells** of the parathyroid glands produce **parathyroid hormone (parathormone)**. The main function of this hormone is to maintain proper calcium and phosphate levels in the extracellular body fluids by elevating calcium levels in the blood. This action is opposite, or antagonistic, to that of calcitonin, which is produced by parafollicular cells in the thyroid glands.

The release of parathyroid hormone indirectly stimulates differentiation and increases the activity of the **osteoclasts** in bones. However, because parathyroid hormone receptors are found on osteoprogenitor cells and osteoblasts, and not on osteoclasts, the osteoclasts are indirectly activated by the signaling mechanism from the osteoblasts. Parathyroid hormone initially targets **osteoblasts** that produce **receptor activator of nuclear factor κ B ligand (RANKL)**. Also, osteoclast precursors express receptor molecules called **receptor activator of nuclear factor κ B (RANK)**.

The RANKL of osteoblasts directly interacts and controls osteoclast differentiation by activating the RANK on osteoclast precursors. Thus, the activation of the osteoclast–osteoblast/RANK–RANKL pathway becomes essential for the differentiation, proliferation, and activity of osteoclasts. This action leads to increased bone resorption and release of calcium and phosphates into the bloodstream, thereby raising and maintaining proper calcium levels. As the calcium concentration in the bloodstream increases, further production of parathyroid hormone is suppressed.

Parathyroid hormone also targets the kidneys and intestines. The distal convoluted tubules in the kidneys increase reabsorption of calcium from the glomerular filtrate and increase elimination of more phosphate, sodium, and potassium ions into urine. Parathyroid hormone also influences the kidneys to produce the hormone **calcitriol**, the active form of vitamin D, which results in increased calcium absorption from the gastrointestinal tract into the bloodstream.

The secretion and release of parathyroid hormone depends primarily on the concentration of calcium levels in the blood and not on any pituitary hormones. Thus, the secretion of parathyroid hormone is regulated by calcium levels through a simple **feedback** mechanism. Because parathyroid hormone maintains optimal levels of calcium in the blood, parathyroid glands are essential to life because calcium is utilized by different organs for many vital functions of the body.

The function of **oxyphil cells** in the parathyroid glands is presently not known, but they may represent old chief cells that are no longer secreting the parathyroid hormone.

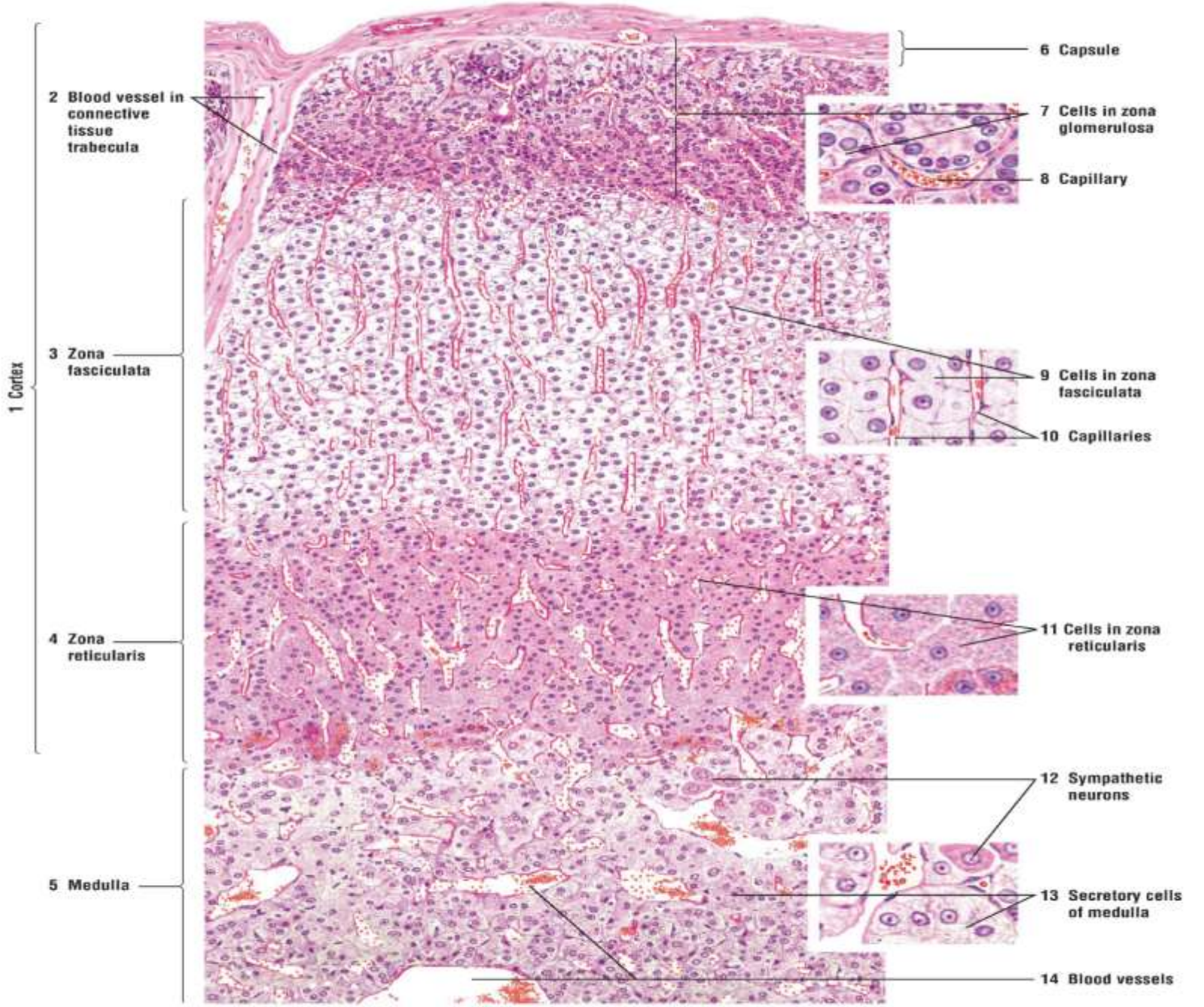



**FIGURE 19.10** ■ Adrenal (suprarenal) gland. Stain: hematoxylin and eosin. Low magnification.

**FIGURE 19.10** | Adrenal (Suprarenal) Gland

The adrenal (suprarenal) gland consists of an outer **cortex (1)** and an inner **medulla (5)**, surrounded by a thick connective tissue **capsule (6)** that contains branches of adrenal blood vessels, veins, nerves (largely unmyelinated), and lymphatics. A **connective tissue septum** with a **blood vessel (2)** passes from the capsule (6) into the cortex. Other connective tissue septa carry the blood vessels to the medulla (5). Fenestrated sinusoidal **capillaries (8, 10)** and large **blood vessels (14)** are found throughout the cortex (1) and medulla (5).

The adrenal cortex (1) is subdivided into three concentric zones. Directly under the connective tissue capsule (6) is the outer **zona glomerulosa (7)**. The **cells (7)** in the zona glomerulosa (7) are arranged into ovoid groups or clumps and surrounded by numerous sinusoidal capillaries (8). The cytoplasm of these cells (7) stains pink and contains few lipid droplets.

The middle and the widest cell layer is the **zona fasciculata (3, 9)**. The **cells of the zona fasciculata (9)** are arranged in vertical columns, or radial plates. Because of the increased amount of lipid droplets in their cytoplasm, the cells of the zona fasciculata (9) appear light or vacuolated after a normal slide preparation. Sinusoidal capillaries (10) between the cell columns follow a similar vertical or radial course.

The third and the innermost cell layer is the **zona reticularis (4, 11)**. This cell layer borders on the adrenal medulla (5). The **cells (11)** of the zona reticularis (4) form anastomosing cords surrounded by sinusoidal capillaries.

The medulla (5) is not sharply demarcated from the cortex. The cytoplasm of the **secretory cells of the medulla (13)** appears clear. After tissue fixation in potassium bichromate, called the chromaffin reaction, fine brown granules become visible in the cells of the medulla. These granules indicate the presence of the catecholamines epinephrine and norepinephrine in the cytoplasm.

The medulla also contains **sympathetic neurons (12)** that are seen singly or in small groups. The neurons (12) exhibit a vesicular nucleus, prominent nucleolus, and a small amount of peripheral chromatin.

Sinusoidal capillaries drain the contents of the medulla (5) into the prominent medullary blood vessels (14).

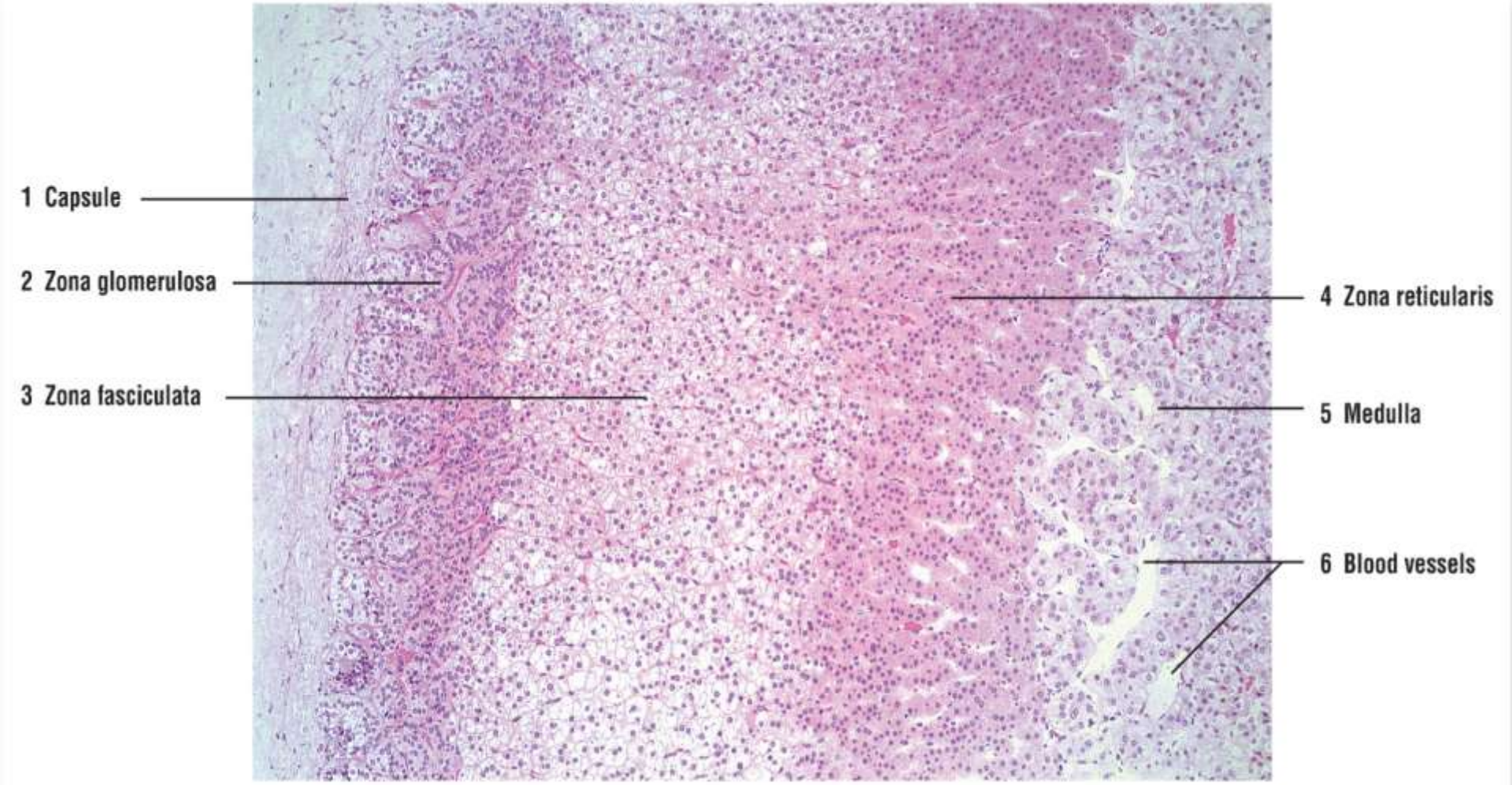



**FIGURE 19.11** ■ Adrenal (suprarenal) gland: cortex and medulla. Stain: hematoxylin and eosin. ×25.

**FIGURE 19.11** | Adrenal (Suprarenal) Gland: Cortex and Medulla

This lower-magnification photomicrograph illustrates a section of the adrenal gland. The cortex is surrounded by a dense connective tissue **capsule (1)**. Beneath the capsule (1) is the **zona glomerulosa (2)**, containing irregular ovoid clumps of cells. The intermediate and widest zone is the **zona fasciculata (3)**. Here, the cells are arranged into light-staining, narrow cords, between which are found capillaries and fine connective tissue fibers. The innermost zone of the adrenal cortex is the **zona reticularis (4)**, in which the cells are arranged into groups of branching cords and clumps.

The adrenal **medulla (5)** is located adjacent to the zona reticularis (4). In the medulla (5), the cells are larger and also arranged into clumps. Large **blood vessels (6)** (veins) drain the medulla (5).

## FUNCTIONAL CORRELATIONS 19.6 | Adrenal Gland Cortex and Medulla

### ADRENAL GLAND CORTEX

The adrenal gland cortex is under the influence of the anterior pituitary gland hormone adrenocorticotropic hormone (ACTH). Cells of the adrenal gland cortex synthesize and release three types of steroids: mineralocorticoids, glucocorticoids, and androgens.

The cells of the **zona glomerulosa** in the adrenal cortex produce **mineralocorticoid hormones**, primarily **aldosterone** that is released into the fenestrated capillaries. Aldosterone release is initiated via the kidney **renin–angiotensin** pathway in response to decreased arterial filtration blood pressure and low levels of sodium in the glomerular filtrate. These changes are detected by the **juxtaglomerular apparatus** (juxtaglomerular cells in the afferent arteriole and macula densa in the distal convoluted tubule) located in the kidney cortex near the renal corpuscles.

Aldosterone has a major influence on fluid and electrolyte balance in the body, with the main target being the distal convoluted tubules in the kidneys. The primary function of aldosterone is to increase **sodium reabsorption** from the glomerular filtrate by cells in the distal convoluted tubules of the kidney and increase potassium excretion into urine. As water follows sodium, there is an increase in fluid volume in the circulation. As the blood pressure, blood volume, and electrolyte balance are restored to normal physiologic levels in response to aldosterone effects, the release of renin from the juxtaglomerular apparatus is decreased or stopped.

The cells of the zona fasciculata—and probably those of the zona reticularis—secrete **glucocorticoids**, of which **cortisol** and **cortisone** are the most important. Glucocorticoids are released into the circulation in response to stress. These steroids stimulate protein, fat, and carbohydrate metabolism, especially by increasing circulating blood **glucose** levels. Glucocorticoids also suppress immune and inflammatory responses by reducing the number of circulating lymphocytes from lymphoid tissues and decreasing their production of antibodies. In addition, cortisol suppresses the tissue response to injury by decreasing cellular and humoral immunity.

Although the cells of the zona reticularis are believed to produce sex steroids, they are mainly weak androgens and have little physiologic significance. Glucocorticoid secretions and the secretory functions of zona fasciculata and zona reticularis are regulated by feedback control from the pituitary gland and ACTH.

## FUNCTIONAL CORRELATIONS 19.6 | Adrenal Gland Cortex and Medulla *(Continued)*

### ADRENAL GLAND MEDULLA

The functions of the adrenal medulla are controlled by the hypothalamus through the sympathetic division of the autonomic nervous system. Cells in the adrenal medulla are called the **chromaffin cells** because they stain with chromium salts. These cells arise from neural crest, just like the postganglionic neurons of sympathetic and parasympathetic ganglia, and can, therefore, be considered as ganglion cells that lack dendrites and axons. They are activated by sympathetic axons in response to fear or acute emotional stress, causing them to release the catecholamines **epinephrine** and **norepinephrine**. The release of these chemicals prepares the individual for a "fight" or "flight" response, resulting in increased heart rate, increased cardiac output and blood flow, and a surge of glucose into the bloodstream from the liver for added energy. Catecholamines produce the maximal use of energy and physical effort to overcome the stress.