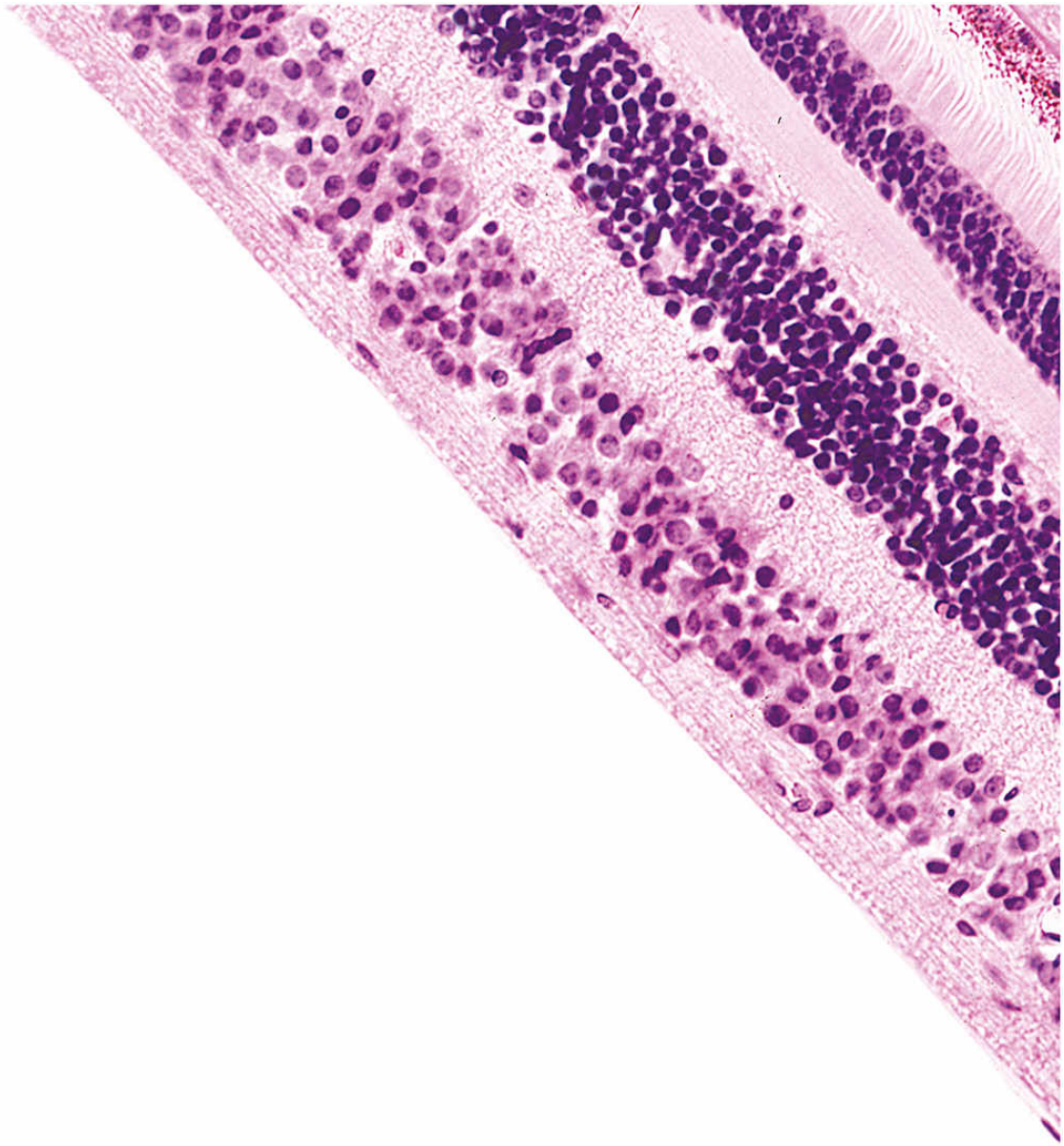

24 EYE

OVERVIEW OF THE EYE

GENERAL STRUCTURE OF THE EYE

Layers of the Eye
Chambers of the Eye
Development of the Eye

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Corneoscleral Coat
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ACCESSORY STRUCTURES OF THE EYE

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HISTOLOGY

OVERVIEW OF THE EYE

The **eye** is a complex sensory organ that provides the sense of sight. In many ways, the eye is similar to a digital camera. Like the optical system of a camera, the **cornea** and **lens** of the eye capture and automatically focus light, whereas the iris automatically adjusts the diameter of the pupil to differences in illumination. The light detector in a digital camera, the charge-coupled device (CCD), consists of closely spaced photodiodes that capture, collect, and convert the light image into a series of electrical impulses. Similarly, the **photoreceptor cells** in the **retina** of the eye detect light intensity and color (wavelengths of visible light that are reflected by different objects) and encode these parameters into electrical impulses for transmission to the brain via the **optic nerve**. The retina has other capabilities beyond those of a CCD: It can extract and modify specific impulses from the visual image before sending them to the central nervous system (CNS).

In other ways, the optical system of the eye is far more elaborate and complex than a camera. For example, the eye is able to track moving objects with coordinated eye movements. The eye can also protect, maintain, self-repair, and clean its transparent optical system.

Because the eyes are paired and spatially separated, two slightly different and overlapping views (visual fields) are sent to the brain. The brain integrates these two slightly different images from each eye into a single **three-dimensional (3D) image** in a process called **stereopsis**. The primary visual cortex located in the occipital lobes processes the differences between the two images to create the perception of depth. The final image is then projected onto the visual cortex. In addition, other complex neural mechanisms coordinate eye movements, enabling refinements in the perception of depth and distance. Therefore, the way in which we see the world around us largely depends on impulses processed within the retina and the analysis and interpretation of these impulses by the CNS.

GENERAL STRUCTURE OF THE EYE

The eye measures approximately 25 mm in diameter. It is suspended in the bony orbital socket by six extrinsic muscles that control its movement. A thick layer of adipose tissue partially surrounds and cushions the eye as it moves within the orbit. The extraocular muscles are coordinated so that the eyes move symmetrically around their own central axes.

Layers of the Eye

The wall of the eye consists of three concentric layers or coats.

The eyeball is composed of three concentric structural layers (Fig. 24.1):

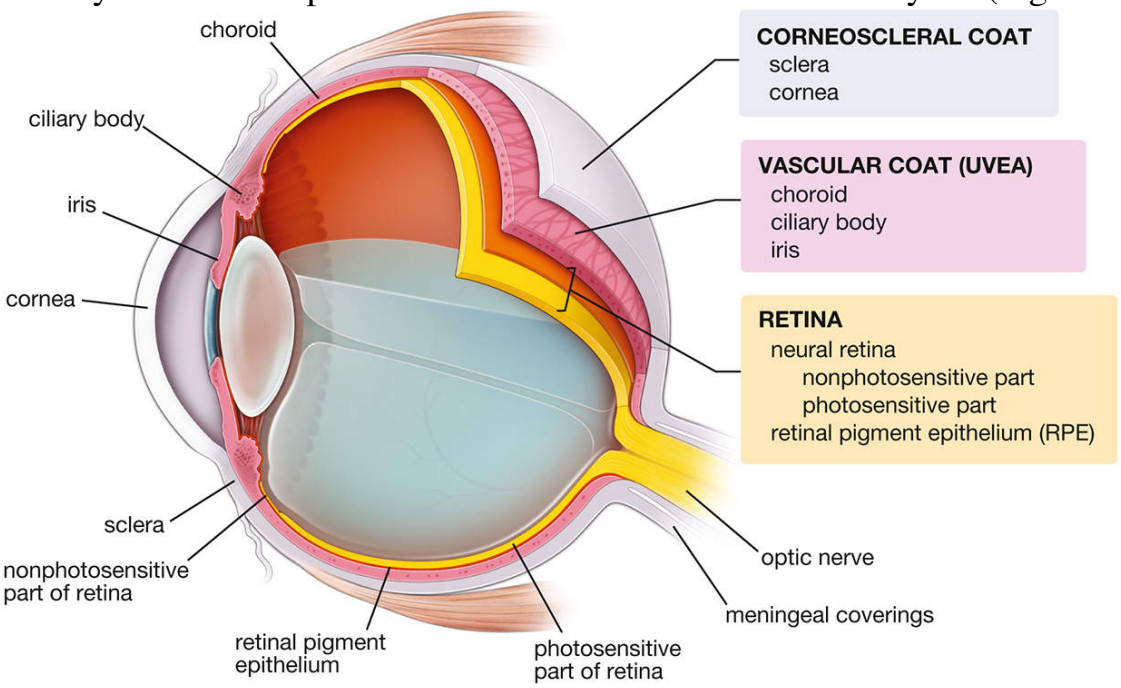


FIGURE 24.1. Schematic diagram of the layers of the eye. The wall of the eyeball is organized in three separate concentric layers: an outer supporting

fibrous layer, the corneoscleral coat; a middle vascular coat or uvea; and an inner layer consisting of the retina. Note that the retina has two layers: a neural retina (*yellow*) and a retinal pigment epithelium (*orange*). The photosensitive and nonphotosensitive parts of the neural retina occupy different regions of the eye. The photosensitive part of the retina is found in the posterior part of the eye and terminates anteriorly along the ora serrata. The nonphotosensitive region of the retina is located anterior to the ora serrata and lines the inner aspect of the ciliary body and the posterior surface of the iris. The vitreous body (*partially removed*) occupies considerable space within the eyeball.

- The **corneoscleral coat**, the outer or fibrous layer, includes the **sclera**, the white portion, and the **cornea**, the transparent portion.
- The **vascular coat**, the middle layer, or **uvea**, includes the **choroid** and the stroma of the **ciliary body** and **iris**.
- The **retina**, the inner layer, includes an outer pigment epithelium, the inner neural retina, and the epithelium of the ciliary body and iris. The neural retina is continuous with the CNS through the **optic nerve**.

The corneoscleral coat consists of the transparent cornea and the white opaque sclera.

The **cornea** covers the anterior one-sixth of the eye (see Fig. 24.1). In this window-like region, the surface of the eye has a prominence or convexity. The cornea is continuous with the **sclera** *[Gr. skleros, hard]*. The sclera is composed of dense fibrous connective tissue that provides attachment for the extrinsic muscles of the eye. The corneoscleral coat encloses the inner two layers, except where it is penetrated by the optic nerve. The sclera constitutes the "white" of the eye. In children, it has a slightly blue tint because of its thinness; in elderly people, it is yellowish because of the accumulation of lipofuscin in its stromal cells. A noticeable feature of patients with **jaundice** is a yellow discoloration of the sclera (**scleral icterus**) caused by a high level of circulating bilirubin.

The uvea consists principally of the choroid, the vascular layer that provides nutrients to the retina.

Blood vessels and melanin pigment give the **choroid** an intense dark brown color. The pigment absorbs scattered and reflected light to minimize glare within the eye. The choroid contains numerous venous plexuses and layers of capillaries and is firmly attached to the retina (see Fig. 24.1). The anterior rim of the uveal layer continues forward, where it forms the stroma of the **ciliary body** and **iris**.

The **ciliary body** is a ring-like thickening that extends inward just posterior to the level of the corneoscleral junction. Within the ciliary body is the **ciliary muscle**, a smooth muscle that is responsible for lens

accommodation. Contraction of the ciliary muscle changes the shape of the lens, which enables it to bring light rays from different distances to focus on the retina.

The **iris** is a contractile diaphragm that extends over the anterior surface of the lens. It also contains smooth muscle and melanin-containing pigment cells scattered in the connective tissue. The **pupil** is the central circular aperture of the iris. It appears black because one looks through the lens toward the heavily pigmented back of the eye. In the process of **adaptation**, the iris contracts or expands, changing the size of the pupil in response to the amount of light that passes through the lens to reach the retina.

The retina consists of two components: the neural retina and pigment epithelium.

The **retina** is a thin, delicate layer (see Fig. 24.1) consisting of two components:

- The **neural retina** is the inner layer that contains light-sensitive receptors and complex neuronal networks.
- The **retinal pigment epithelium (RPE)** is the outer layer composed of simple cuboidal melanin-containing cells.

Externally, the retina rests on the choroid; internally, it is associated with the vitreous body. The neural retina consists largely of **photoreceptor cells**, called retinal **rods** and **cones**, and interneurons. Visual information encoded by the rods and cones is sent to the brain via impulses conveyed along the optic nerve.

Chambers of the Eye

The layers of the eye and the lens serve as boundaries for three chambers within the eye.

The chambers of the eye are as follows:

- The **anterior chamber** is the space between the cornea and the iris.
- The **posterior chamber** is the space between the posterior surface of the iris and the anterior surface of the lens.
- The **vitreous chamber** is the space between the posterior surface of the lens and the neural retina (Fig. 24.2). The cornea, the anterior and posterior chambers, and their contents constitute the anterior segment of the eye. The vitreous chamber, visual retina, RPE, posterior sclera, and uvea constitute the posterior segment.

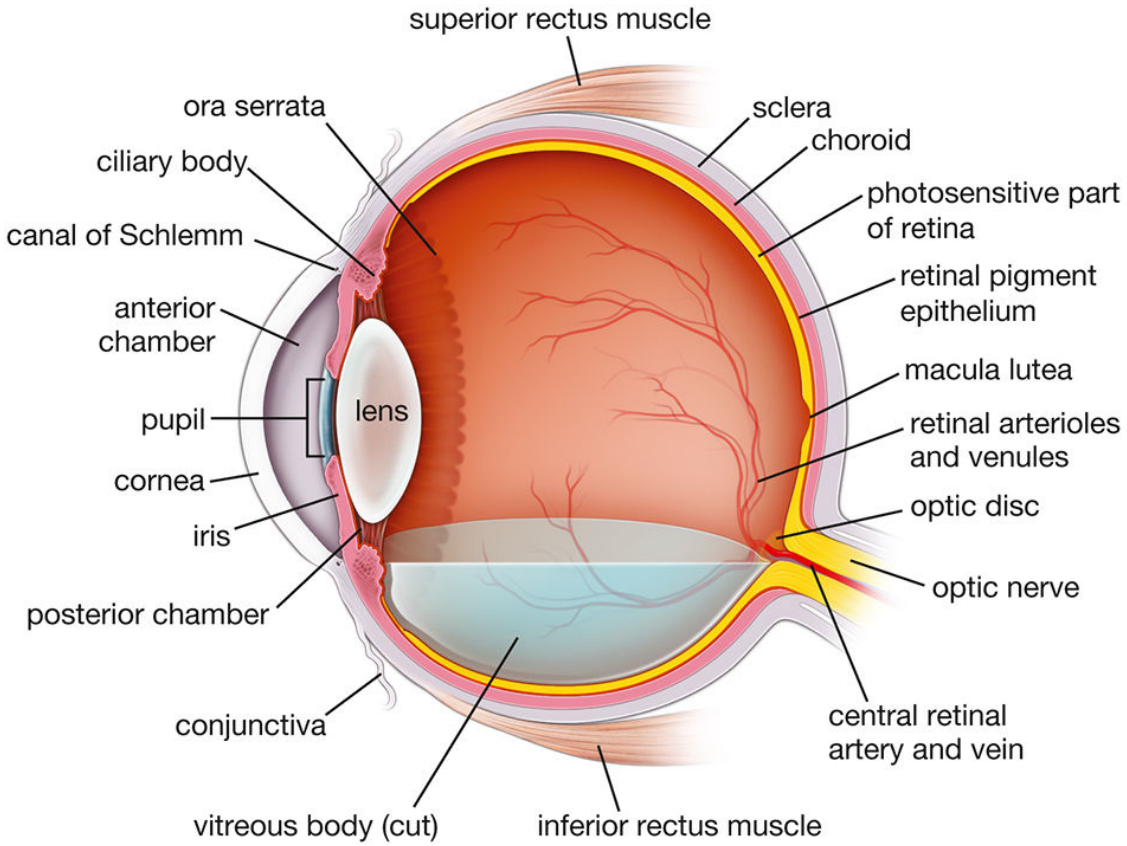


FIGURE 24.2. Schematic diagram illustrating the internal structures of the human eye. This diagram shows the relationship between the layers of the eye and internal structures. The lens is suspended between the edges of the ciliary body. Note the posterior chamber of the eye, which is a narrow space between the anterior surface of the lens and the posterior surface of the iris. It communicates through the pupil with the larger anterior chamber that is bordered by the iris and the cornea. These spaces are filled with the aqueous humor produced by the ciliary body. The large cavity posterior to the lens, the vitreous chamber, is filled with a transparent jelly-like substance called the *vitreous body*. In this figure, most of the vitreous body has been removed to illustrate the distribution of the central retinal vessels on the surface of the retina. The other layers of the eyeball and the attachment of two of the extraocular muscles to the sclera are also shown.

The refractile media components of the eye alter the light path to focus it on the retina.

As light rays pass through the components of the eye, they are refracted. Refraction focuses the light rays on the photoreceptor cells of the retina. Four transparent components of the eye, called the **refractile (or dioptric) media**, alter the path of the light rays:

- The **cornea** is the anterior window of the eye.

- The **aqueous humor** is the watery fluid located in the anterior and posterior chambers.
- The **lens** is a transparent, crystalline, biconvex structure suspended from the inner surface of the ciliary body by a ring of radially oriented fibers, the **zonule of Zinn**.
- The **vitreous body** is composed of a transparent gel-like substance that fills the vitreous chamber. It acts as a "shock absorber" that protects the fragile retina during rapid eye movement and helps maintain the shape of the eye. The vitreous body is almost 99% water with soluble proteins, hyaluronan, glycoproteins, widely dispersed collagen fibrils, and traces of other insoluble proteins. The fluid component of the vitreous body is called the **vitreous humor**.

The **cornea** is the chief refractive element of the eye. It is the single most powerful focusing element of the eye and has a refractive index of 1.376 (air has a refractive index of 1.0). The cornea provides about 80% of the eye's refractive power and is almost twice as powerful as the lens. The lens is second in importance to the cornea in refracting light rays. It is responsible for fine-tuning and focusing light onto the retina. Because of its elasticity, the shape of the **lens** can undergo slight changes in response to the tension of the ciliary muscle. These changes are important in **accommodation** for proper focusing on near objects. The aqueous humor and vitreous body have only minor roles in refraction. However, the aqueous humor plays an important role in providing nutrients to two avascular structures, the lens and cornea. In addition to transmitting light, the vitreous body helps maintain the position of the lens and helps keep the neural retina in contact with the RPE.

Development of the Eye

To appreciate the unusual structural and functional relationships in the eye, it is helpful to understand how it forms in the embryo.

The tissues of the eye are derived from neuroectoderm, surface ectoderm, and mesoderm.

By the 22nd day of development, the **eyes** are evident as shallow grooves—the **optic sulci** or **optic grooves**—located in the neural folds at the cranial end of the embryo. As the neural tube closes, the paired grooves form outpocketings called **optic vesicles** (Fig. 24.3a). As each optic vesicle grows laterally, the connection to the forebrain becomes constricted into an optic stalk, and the overlying surface ectoderm thickens and forms a **lens placode**. These events are followed by concomitant invagination of the optic vesicles and the lens placodes. The invagination of the optic vesicle results in the formation of a double-layered **optic cup** (Fig. 24.3b). The inner layer

becomes the **neural retina**. The outer layer becomes the **RPE**. The mesenchyme surrounding the optic cup gives rise to the **sclera**.

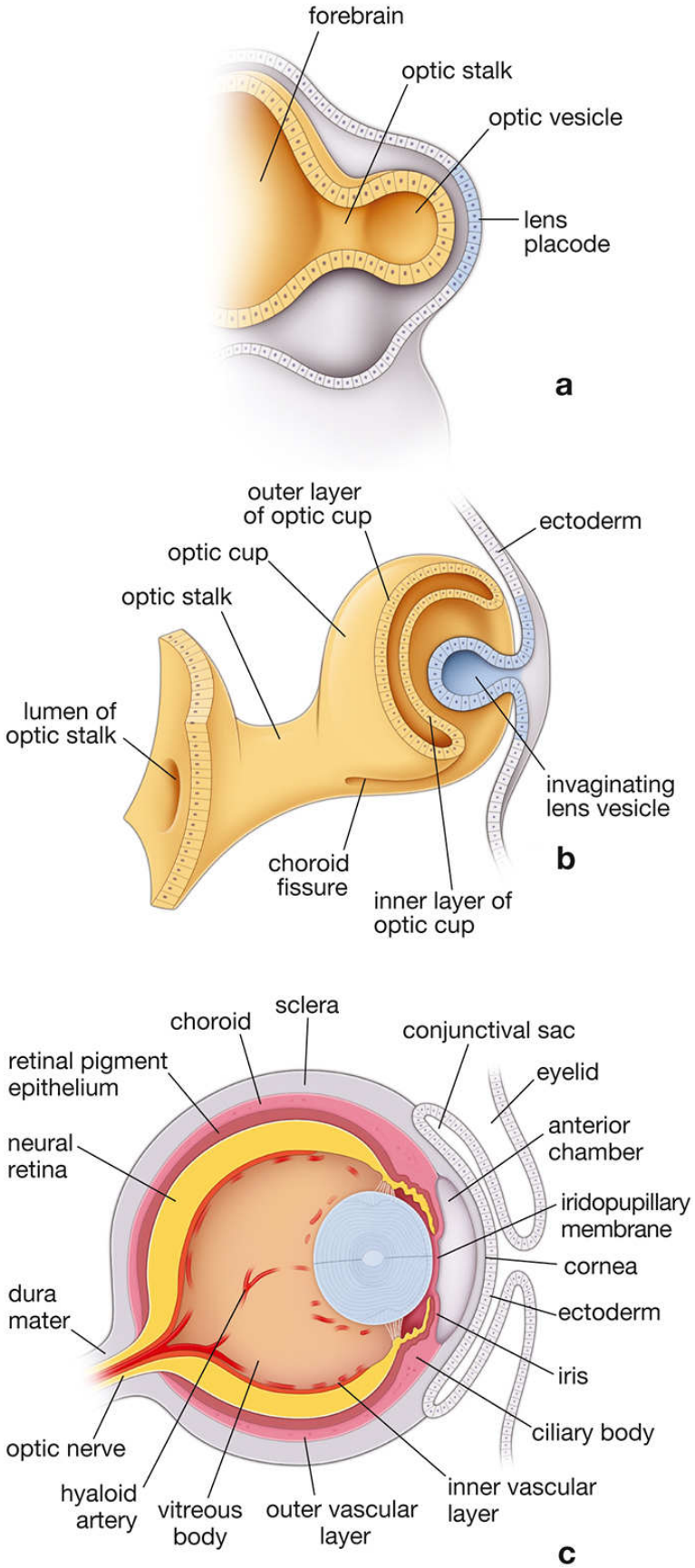


FIGURE 24.3. Schematic drawing illustrating the development of the eye. **a.** Forebrain and developing optic vesicles as seen in a 4-mm embryo. **b.**

Bilayered optic cup and invaginating lens vesicle as seen in a 7.5-mm embryo. The optic stalk connects the developing eye to the brain. **c.** The eye as seen in a 15-week fetus. All the layers of the eye are established, and the hyaloid artery traverses the vitreous body from the optic disc to the posterior surface of the lens.

Invagination of the central region of each **lens placode** results in the formation of the **lens vesicle**. By the fifth week of development, the lens vesicle loses contact with the surface ectoderm and comes to lie in the mouth of the optic cup. After the lens vesicle detaches from the surface ectoderm, this same site again thickens to form the corneal epithelium. **Mesenchymal cells** from the periphery then give rise to the **corneal endothelium** and the **corneal stroma**.

Grooves containing blood vessels derived from mesenchyme develop along the inferior surface of each optic cup and stalk. Called the **choroid fissures**, the grooves enable the hyaloid artery to reach the inner chamber of the eye. This artery and its branches supply the inner chamber of the optic cup, lens vesicle, and mesenchyme within the optic cup. The hyaloid vein returns blood from these structures. The distal portions of the hyaloid vessels degenerate, but the proximal portions remain as the **central retinal artery** and **central retinal vein**. By the end of the seventh week, the edges of the choroid fissure fuse, and a round opening, the future pupil, forms over the lens vesicle.

The **outer layer of the optic cup** forms a single layer of pigmented cells (Fig. 24.3c). Pigmentation begins at the end of the fifth week. The **inner layer** undergoes a complex differentiation into the nine layers of the **neural retina**. The photoreceptor cells (rods and cones) as well as the bipolar, amacrine, and ganglion cells and nerve fibers are present by the seventh month. The macular depression, a future site of fovea centralis, begins to develop during the eighth month and is not complete until about 6 months after birth.

During the third month, the growth of the optic cup gives rise to the **ciliary body** and the future **iris**, which forms a double row of epithelium in front of the lens. The mesoderm located external to this region becomes the stroma of the ciliary body and iris. Both epithelial layers of the iris become pigmented. In the ciliary body, however, only the outer layer is pigmented. At birth, the iris is light blue in fair-skinned people because the pigment is usually not present. The dilator and sphincter pupillary muscles develop during the sixth month as derivatives of the neuroectoderm of the outer layer of the optic cup.

The embryonic origins of the individual eye structures are summarized in Table 24.1.

TABLE 24.1 **Embryonic Origins of the Individual Structures of the Eye**

Source	Derivative
Surface ectoderm	Lens Epithelium of the cornea, conjunctiva, and lacrimal gland and its drainage system
Neural ectoderm	Vitreous body (derived partly from neural ectoderm of the optic cup and partly from mesenchyme) Epithelium of the retina, iris, and ciliary body Sphincter pupillae and dilator papillae muscles Optic nerve
Mesoderm	Sclera Stroma of the cornea, ciliary body, iris, and choroids Extraocular muscles Eyelids (except epithelium and conjunctiva) Hyaloid system (most of which degenerates before birth) Coverings of the optic nerve Connective tissue and blood vessels of the eye, bony orbit, and vitreous body

MICROSCOPIC STRUCTURE OF THE EYE

The three layers of the eye—the **corneoscleral coat**, the **vascular coat**, and the **retina**—are in turn composed of complex molecular layers and structures that reflect their various functions.

Corneoscleral Coat

The cornea is a unique tissue and the most powerful focusing element of the eye. It forms part of the anterior segment of the eye, protecting structures within the eye from the external environment. The most important characteristics of the cornea include its mechanical strength and transparency to incoming light.

The cornea consists of five layers: three cellular layers and two noncellular layers.

The transparent **cornea** (see Figs. 24.1 and 24.2) is only 0.5 mm thick at its center and about 1 mm thick peripherally. It consists of three cellular layers that are distinct in both appearance and origin. These layers are separated by two important membranes that appear homogeneous when viewed in the light microscope. Thus, the **five layers of the cornea** seen in a transverse section are the following:

- **Corneal epithelium**
- **Bowman membrane** (anterior basement membrane)
- **Corneal stroma**

- **Descemet membrane** (posterior basement membrane)
- **Corneal endothelium**

The corneal epithelium is a nonkeratinized stratified squamous epithelium.

The **corneal epithelium** (Fig. 24.4) represents **nonkeratinized stratified squamous epithelium** that consists of approximately five layers of cells and measures about 50 μm in average thickness. It is continuous with the conjunctival epithelium that overlies the adjacent sclera. The epithelial cells adhere to neighboring cells via desmosomes that are present in short interdigitating processes. Like other stratified epithelia, such as that of the skin, the cells proliferate from a basal layer and become squamous at the surface. The basal cells are low columnar with round, ovoid nuclei; the surface cells acquire a squamous or discoid shape, and their nuclei are flattened and pyknotic (Fig. 24.4b). As the cells migrate to the surface, the cytoplasmic organelles gradually disappear, indicating a progressive decline in metabolic activity. The corneal epithelium has a remarkable regenerative capacity with a turnover time of approximately 7 days.

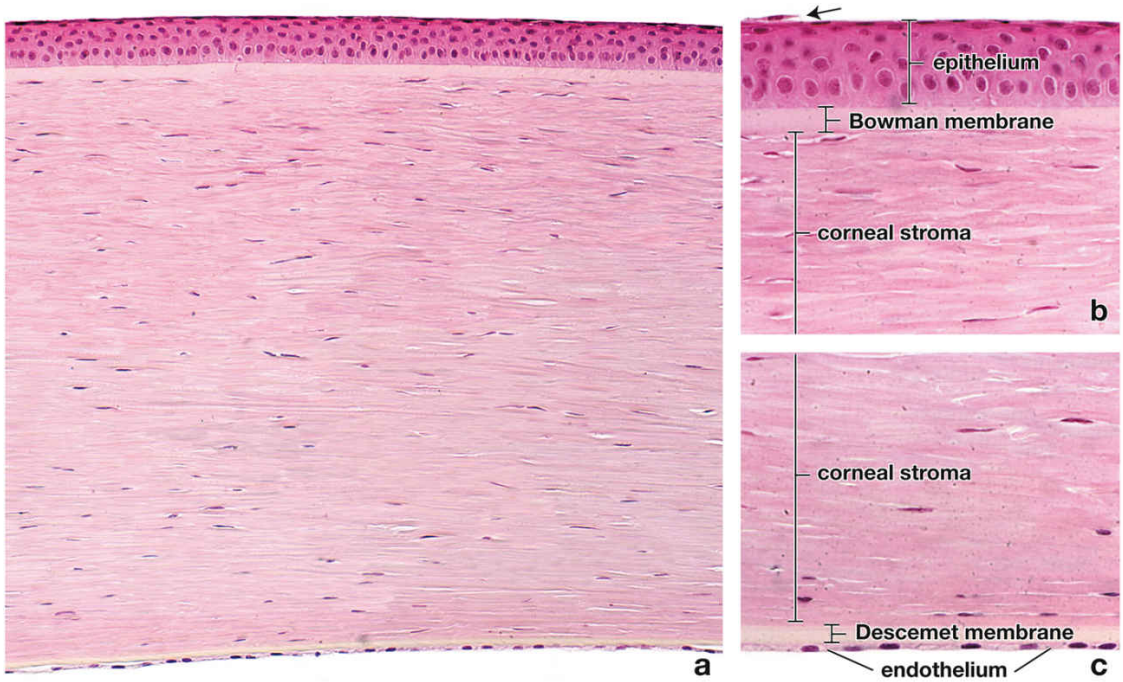


FIGURE 24.4. Photomicrograph of the cornea. a. This photomicrograph of a section through the full thickness of the cornea shows the corneal stroma and the two corneal surfaces covered by different types of epithelia. The corneal stroma does not contain blood or lymphatic vessels. ×140. **b.** A higher magnification of the anterior surface of the cornea showing the *corneal stroma* covered by a stratified squamous (corneal) *epithelium*. The basal cells that rest on *Bowman membrane*, which is a homogeneous condensed layer of corneal stroma, are low columnar in contrast to the squamous surface cells. Note that

one of the surface cells is in the process of desquamation (*arrow*). ×280. **c.** A higher magnification photomicrograph of the posterior surface of the cornea covered by a thin layer of simple squamous epithelium (corneal *endothelium*). These cells are in direct contact with the aqueous humor of the anterior chamber of the eye. Note the very thick *Descemet membrane* (basal lamina) of the corneal endothelial cells. ×280.

The actual stem cells for the corneal epithelium, called **corneolimbal stem cells**, reside at the **corneoscleral limbus**, the junction of the cornea and sclera. The microenvironment of this stem cell niche is important in maintaining the stem cell population. It also acts as a barrier that prevents migration of conjunctival epithelial cells to the corneal surface. The **corneolimbal stem cells** may be partially or totally depleted by disease or extensive injury, resulting in abnormalities of the corneal surface that lead to **conjunctivalization** of the cornea, which is characterized by vascularization, appearance of goblet cells, and an irregular and unstable epithelium. These changes cause ocular discomfort and reduced vision. Minor injuries of the corneal surface heal rapidly by inducing stem cell proliferation and migration of cells from the corneoscleral limbus to fill the defect.

Numerous free nerve endings in the corneal epithelium provide it with extreme sensitivity to touch. Stimulation of these nerves (e.g., by small foreign bodies) elicits blinking of the eyelids, flow of tears, and, sometimes, severe pain. Microvilli present on the surface epithelial cells help retain the tear film over the entire corneal surface. Drying of the corneal surface may cause ulceration.

DNA in the corneal epithelial cells is protected from UV light damage by nuclear ferritin.

Despite constant exposure of the corneal epithelium to ultraviolet (UV) light, cancer of the corneal epithelium is extremely rare. Unlike the epidermis, which is also exposed to UV light, melanin is not present as a defense mechanism in the corneal epithelium. The presence of melanin in the cornea would diminish light transmission. Instead, it has recently been shown that corneal epithelial cell nuclei contain **ferritin**, an iron-storage protein. Experimental studies with avian corneas have shown that **nuclear ferritin** protects the DNA in the corneal epithelial cells from free radical damage caused by UV light exposure.

Bowman membrane is a homogeneous-appearing layer on which the corneal epithelium rests.

Bowman membrane (anterior basement membrane) is a homogeneous, faintly fibrillar lamina that is approximately 8–10 μm thick. It lies between the

corneal epithelium and the underlying corneal stroma and ends abruptly at the corneoscleral limbus. The collagen fibrils of Bowman membrane have a diameter of about 18 nm and are randomly oriented. Bowman membrane imparts some strength to the cornea, but more significantly, it acts as a barrier to the spread of infections. It does not regenerate. Therefore, if damaged, an opaque scar forms that may impair vision. In addition, changes in Bowman membrane are associated with **recurrent corneal erosions**.

The corneal stroma constitutes 90% of the corneal thickness.

The **corneal stroma**, also called **substantia propria**, is composed of about 60 thin lamellae. Each lamella consists of parallel bundles of collagen fibrils. Located between the lamellae are nearly complete sheets of slender, flattened fibroblasts. The collagen fibrils are very uniform, measuring approximately 23 nm in diameter and as long as 1 cm in length, and are arranged at approximately right angles to those in adjacent lamellae (Fig. 24.5). The ground substance of cornea contains **small leucine-rich proteoglycans (SLRPs)**, which comprise sulfated glycosaminoglycans—chiefly, keratan sulfate proteoglycan (**lumican**) and chondroitin sulfate proteoglycan (**decorin**). They are responsible for the 3D organization of collagen fibrils. Lumican regulates the normal collagen fibril assembly in the cornea and is critical to the development of a highly organized collagenous matrix.

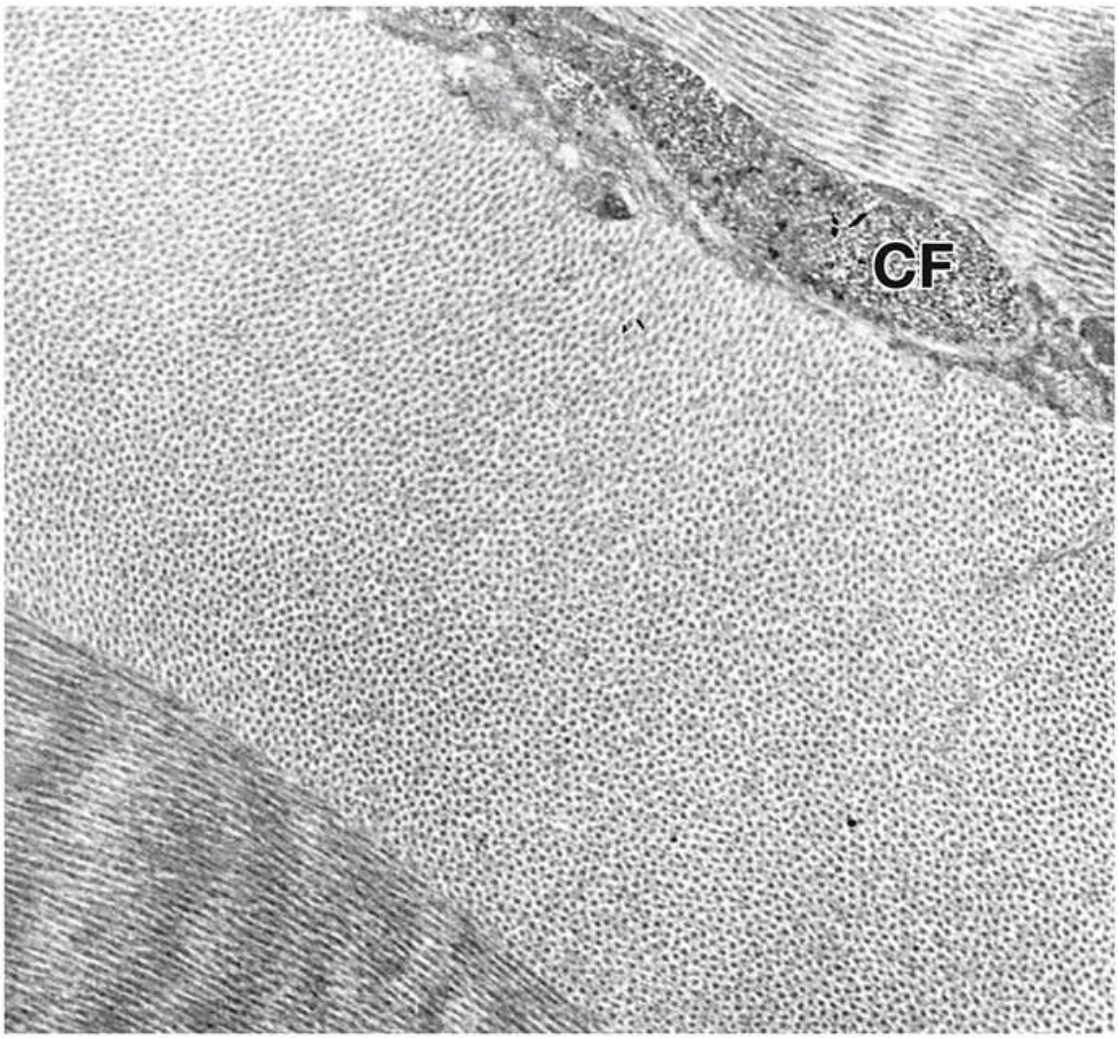


FIGURE 24.5. Electron micrograph of the corneal stroma. This electron micrograph shows parts of three lamellae and a portion of a corneal fibroblast (*CF*) between two of the lamellae. Note that the collagen fibrils in adjacent lamellae are oriented at right angles to one another. ×16,700.

Corneal transparency is achieved by the regular arrangement of small collagen fibrils and the spaces between them that are smaller than one-half of a wavelength of visible light.

The **transparency of the cornea** is directly related to the spaces between collagen fibrils containing glycosaminoglycans and the size of the collagen fibrils. If these spaces are smaller than one-half of a wavelength of visible light, the cornea is clear and transparent. The uniform spacing of type I collagen fibrils and lamellae, as well as the **orthogonal array** of the lamellae (alternating layers at right angles), helps maintain corneal transparency. Proteoglycans (**lumican**), along with **type V collagen**, regulate the precise diameter and spacing of the type I collagen fibrils, maintaining corneal clarity. The necessity for uniformity of collagen fibrils explains the ratio of type V to type I collagen, which is much higher in the corneal stroma than in other

tissues. **Corneal swelling** after injury to the epithelium or endothelium disrupts this precise array and leads to translucency or opacity of the cornea. The hazy appearance of the cornea is related to the enlargement of the spaces between collagen fibers. Lumican is overexpressed during the wound healing process following corneal injury. Normally, the cornea contains no blood vessels or pigments. During an inflammatory response involving the cornea, large numbers of neutrophils and lymphocytes migrate from the blood vessels of the corneoscleral limbus and penetrate the stromal lamellae.

Descemet membrane is an unusually thick basal lamina.

Descemet membrane (posterior basement membrane) is the basal lamina of corneal endothelial cells. It is intensely positive to periodic acid–Schiff (PAS) and can be as thick as 10 μm. Descemet membrane has a felt-like appearance and consists of an interwoven meshwork of fibers and pores. It separates the corneal endothelium from the adjacent corneal stroma. Unlike Bowman membrane, Descemet membrane readily regenerates after injury. It is produced continuously but slowly thickens with age. Descemet membrane also contributes to the diagnosis of **Wilson disease**, a rare inherited disorder of copper metabolism that causes excessive deposition of copper in organs and other tissues. A common ophthalmologic finding in individuals with Wilson disease is the presence of **Kayser–Fleischer rings**. These are caused by increased depositions of copper within Descemet membrane. A Kayser–Fleischer ring usually appears as a gold brown ring located in the periphery of the cornea.

Descemet membrane extends peripherally beneath the sclera as a trabecular meshwork forming the **pectinate ligament**. Strands from the pectinate ligament penetrate the ciliary muscle and sclera and may help maintain the normal curvature of the cornea by exerting tension on Descemet membrane.

The corneal endothelium provides for metabolic exchange between the cornea and the aqueous humor.

The **corneal endothelium** is a single layer of squamous cells covering the surface of the cornea that faces the anterior chamber (Fig. 24.4c). The cells are joined by well-developed zonulae adherentes, relatively leaky zonulae occludentes, and desmosomes. Virtually, all of the metabolic exchanges of the cornea occur across the endothelium. The endothelial cells contain many mitochondria and vesicles and an extensive rough-surfaced endoplasmic reticulum (rER) and Golgi apparatus. They demonstrate endocytotic activity and are engaged in active transport. Na^+/K^+-activated ATPase is located on the lateral plasma membrane.

Transparency of the cornea requires precise regulation of the water content of the stroma. Physical or metabolic damage to the endothelium leads to rapid **corneal swelling** and, if the damage is severe, corneal opacity. Restoration of endothelial integrity is usually followed by deturgescence (dehydration necessary to maintain the transparency), although corneas can swell beyond their ability for self-repair. Such swelling can result in permanent focal opacities caused by aggregation of collagen fibrils in the swollen cornea. Essential sulfated glycosaminoglycans that normally separate the corneal collagen fibers are extracted from the swollen cornea.

Human **corneal endothelium** has a **limited proliferative capacity**. Severely damaged endothelium can be repaired only by transplantation of a donor cornea. Recent studies indicate that the periphery of the cornea represents a regenerative zone of the corneal endothelial cells. However, soon after **corneal transplantation**, endothelial cells exhibit contact inhibition when exposed to the extracellular matrix of Descemet membrane. The discovery that inhibitory factors released by Descemet membrane prevent proliferation of endothelial cells has focused current corneal research on the reversal or prevention of this inhibition with exogenous growth factors.

The sclera is an opaque layer that consists predominantly of dense connective tissue.

The **sclera** is a thick fibrous layer containing flat collagen bundles that pass in various directions and in planes parallel to its surface. Both the collagen bundles and the fibrils that form them are irregular in diameter and arrangement. Interspersed between the collagen bundles are fine networks of elastic fibers and a moderate amount of ground substance. Fibroblasts are scattered among these fibers (Plate 24.4, page 1016).

The opacity of the sclera, like that of other dense connective tissues, is primarily attributable to the irregularity of its structure. The sclera is pierced by blood vessels, nerves, and the optic nerve (see Fig. 24.2). It is 1 mm thick posteriorly, 0.3–0.4 mm thick at its equator, and 0.7 mm thick at the corneoscleral margin or limbus.

The sclera is divided into three rather ill-defined layers:

- The **episcleral layer (episclera)**, the external layer, is the loose connective tissue adjacent to the periorbital fat.
- The **substantia propria** (**sclera proper**, also called **Tenon capsule**) is the investing fascia of the eye and is composed of a dense network of thick collagen fibers.
- The **suprachoroid lamina (lamina fusca)**, the inner aspect of the sclera, is located adjacent to the choroid and contains thinner collagen fibers and

elastic fibers as well as fibroblasts, melanocytes, macrophages, and other connective tissue cells.

In addition, the **episcleral space (Tenon space)** is located between the episcleral layer and substantia propria of the sclera. This space and the surrounding periorbital fat allow the eye to rotate freely within the orbit. The tendons of the extraocular muscles attach to the substantia propria of the sclera.

The corneoscleral limbus is the transitional zone between the cornea and the sclera that contains corneolimbal stem cells.

At the **junction of the cornea and sclera** (Fig. 24.6 and Plate 24.4, page 1016), Bowman membrane ends abruptly. The overlying epithelium at this site thickens from the 5 cell layers of the cornea to the 10–12 cell layers of the conjunctiva. The surface of the limbus is composed of two distinct types of epithelial cells: One type constitutes the conjunctival cells, and the other constitutes the corneal epithelial cells. The basal layer of the limbus contains the **corneolimbal stem cells** that generate and maintain the corneal epithelium. These cells proliferate, differentiate, and migrate to the surface of the limbus and then toward the center of the cornea to replace damaged epithelial cells. As mentioned previously, this movement of cells at the corneoscleral limbus also creates a barrier that prevents conjunctival epithelium from migrating onto the cornea. At this junction, the corneal lamellae become less regular as they merge with the oblique bundles of collagen fibers of the sclera. An abrupt transition from the avascular cornea to the well-vascularized sclera also occurs here.

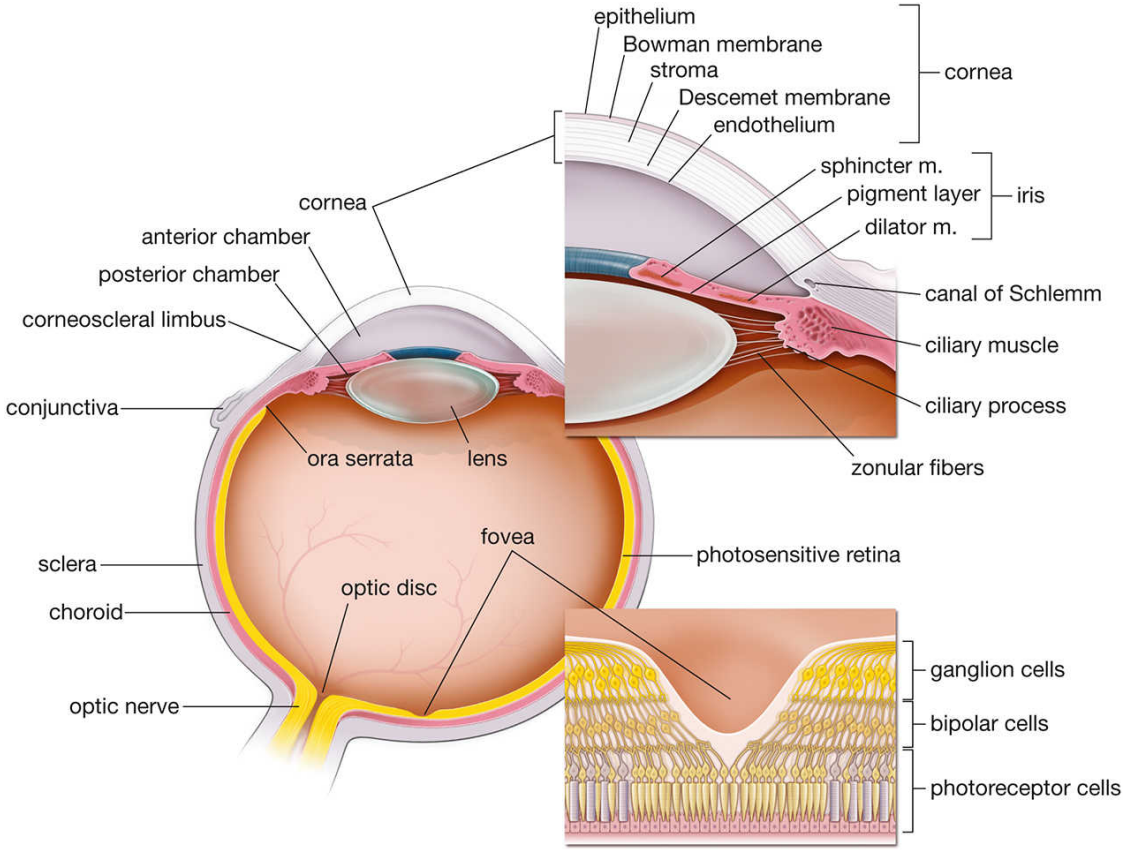


FIGURE 24.6. Schematic diagram of the structure of the eye. This drawing shows a horizontal section of the eyeball with color-coded layers of its wall. **Upper inset.** Enlargement of the anterior and posterior chambers is shown in more detail. Note the location of the iridocorneal angle and canal of Schlemm (scleral venous sinus), which drains the aqueous humor from the anterior chamber of the eye. **Lower inset.** Typical organization of the cells and nerve fibers of the fovea.

The limbus region, specifically, the **iridocorneal angle**, contains the apparatus for the outflow of aqueous humor (Fig. 24.7). In the stromal layer, endothelium-lined channels called the **trabecular meshwork** (or **spaces of Fontana**) merge to form the **scleral venous sinus (canal of Schlemm)**. This sinus encircles the eye (see Figs. 24.6 and 24.7). The aqueous humor is produced by the ciliary processes that border the lens in the posterior chamber of the eye. The fluid passes from the posterior chamber into the anterior chamber through the valve-like potential opening between the iris and lens. The fluid then passes through the openings in the trabecular meshwork in the limbus region as it continues its course to enter the scleral venous sinus. Collecting vessels in the sclera, called **aqueous veins** (of Ascher) because they convey aqueous humor instead of blood, transport the aqueous humor to episcleral and conjunctival (blood) veins located in the sclera. Changes in the **iridocorneal angle** may lead to blockage in the drainage of aqueous humor, causing **glaucoma** (see Folder 24.1, page 990). The

iridocorneal angle can be visualized during eye examination using a **gonioscope**, a specialized optical device that uses mirrors or prisms to reflect the light from the iridocorneal angle into the direction of the observer. In conjunction with a slit lamp or operating microscope, the ophthalmologist can examine this region to monitor various eye conditions associated with glaucoma. The iridocorneal angle can be also visualized using the **ultrasound biomicroscopy (UBM)**. This high-resolution imaging technique utilizes a high-frequency ultrasound transducer to visualize the narrowed iridocorneal angle in primary angle-closure glaucoma.

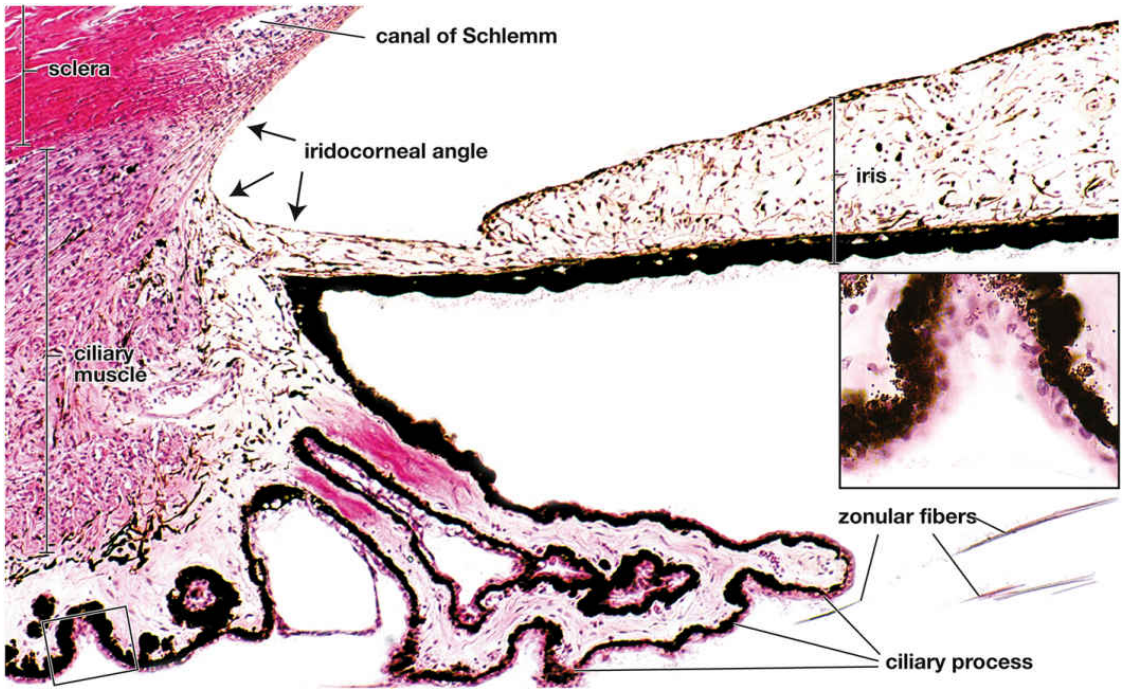


FIGURE 24.7. Photomicrograph of the ciliary body and iridocorneal angle. This photomicrograph of the human eye shows the anterior portion of the ciliary body and parts of the *iris* and *sclera*. The inner surface of the ciliary body forms radially arranged, ridge-shaped elevations, the *ciliary processes*, to which the *zonular fibers* are anchored. The ciliary body contains the *ciliary muscle*, connective tissue with blood vessels of the vascular coat, and the ciliary epithelium, which is responsible for the production of aqueous humor. Anterior to the ciliary body, between the iris and the cornea, is the *iridocorneal angle*. The scleral venous sinus (*canal of Schlemm*) is located in close proximity to this angle and drains the aqueous humor to regulate intraocular pressure. ×120. The *inset* shows that the ciliary epithelium consists of two layers, the outer pigmented layer and the inner nonpigmented layer. ×480.

FOLDER 24.1
CLINICAL CORRELATION: GLAUCOMA

Glaucoma is a clinical condition resulting from increased intraocular pressure over a sustained period of time. It can be caused by excessive secretion of aqueous humor or impedance of the drainage of aqueous humor from the anterior chamber. The internal tissues of the eye, particularly the retina, are nourished by the diffusion of oxygen and nutrients from the intraocular vessels. Blood flows normally through these vessels (including the capillaries and veins) when the hydrostatic pressure within the vessels exceeds the intraocular pressure. If the drainage of the aqueous humor is impeded, the intraocular pressure increases because the layers of the eye do not allow the wall to expand. This increased pressure interferes with normal retinal nourishment and function, causing the retinal nerve fiber layer to atrophy (Fig. F24.1.1).

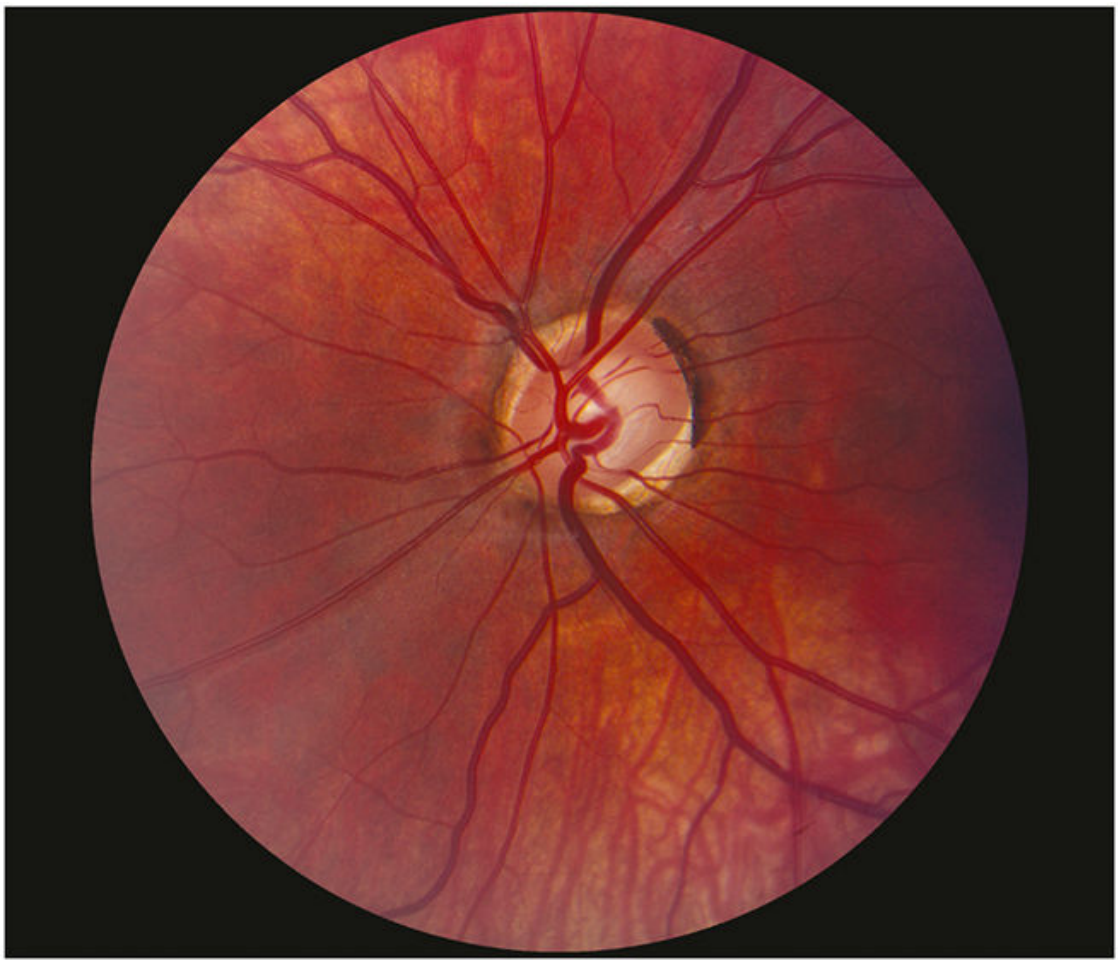


FIGURE F24.1.1. Glaucoma. This image shows a view of the fundus of the left eye in a patient with advanced glaucoma. As a result of the increased intraocular pressure, retinal nerve fibers undergo atrophy and shrink in size. Note a pale optic disc in the *center* of the image with a less pronounced rim due to atrophy of nerve fibers. Enlargement of the optic nerve cup (central area of the optic disc) is also visible and a characteristic finding for glaucoma.

Compare this image to a normal retina in Figure 24.15. (Courtesy of Dr. Renzo A. Zaldivar.) There are two major types of glaucoma:

- **Open-angle glaucoma** is the most common type of glaucoma and the leading cause of blindness among adults. The removal of aqueous humor is obstructed because of reduced flow through the trabecular meshwork of the iridocorneal angle into the scleral venous sinus (canal of Schlemm).
- **Angle-closure glaucoma (acute glaucoma)** is less common and is characterized by a narrowed iridocorneal angle that obstructs the inflow of the aqueous humor into the scleral venous sinus. Usually, it is associated with a sudden, painful, complete blockage of the scleral venous sinus and can result in permanent blindness if not treated promptly.

Visual deficits associated with glaucoma include blurring of vision and impaired dark adaptation (symptoms that indicate loss of normal retinal function) and halos around lights (a symptom indicating corneal endothelial damage). If the condition is not treated, the retina will be permanently damaged, and blindness will occur. Treatment is directed toward lowering the intraocular pressure by decreasing the rate of production of aqueous humor or eliminating the cause of the obstruction of normal drainage. Topical **prostaglandin analogs** (i.e., latanoprost, bimatoprost, travoprost) are the first line of treatment for open-angle glaucoma. They are very effective in reducing intraocular pressure by increasing the drainage of aqueous humor into the canal of Schlemm. **Carbonic anhydrase inhibitors**, which were used in the past to decrease the production of aqueous humor, have largely been replaced by prostaglandin analogs that have fewer systemic side effects.

There are two main types of laser surgery to treat glaucoma. They facilitate drainage of aqueous humor from the iridocorneal angle. Laser **trabeculoplasty** utilizes a laser beam to induce focal scarring of the trabecular meshwork. This results in mechanical stretching of the surrounding untreated regions of the meshwork, which facilitates drainage of the aqueous humor. Trabeculoplasty is often used in open-angle glaucoma when medications are not effective or cause intolerable side effects. **Iridotomy** is used in patients with angle-closure glaucoma. The laser beam incises a small opening at the base of the iris, which widens the iridocorneal angle to allow better drainage of aqueous humor.

Vascular Coat (Uvea)

The iris, the most anterior part of the vascular coat, forms a contractile diaphragm in front of the lens.

The **iris** arises from the anterior border of the ciliary body (see Fig. 24.7) and is attached to the sclera about 2 mm posterior to the corneoscleral junction. The **pupil** is the central aperture of this thin disc. The iris is pushed slightly forward as it changes in size in response to light intensity. It consists of a highly vascularized connective tissue stroma that is covered on its posterior surface by highly pigmented cells, the **posterior pigment epithelium** (Fig. 24.8). The basal lamina of these cells faces the posterior chamber of the eye. The degree of pigmentation is so great that neither the nucleus nor the character of the cytoplasm can be seen in the light microscope. Located beneath this layer is a layer of myoepithelial cells, the **anterior pigment myoepithelium**. The apical (posterior) portions of these myoepithelial cells are laden with melanin granules, which effectively obscure their boundaries with the adjacent posterior pigment epithelial cells. The basal (anterior) portions of myoepithelial cells possess processes containing contractile elements that extend radially and collectively make up the **dilator pupillae muscle** of the iris. The contractile processes are enclosed by a basal lamina that separates them from the adjacent stroma.

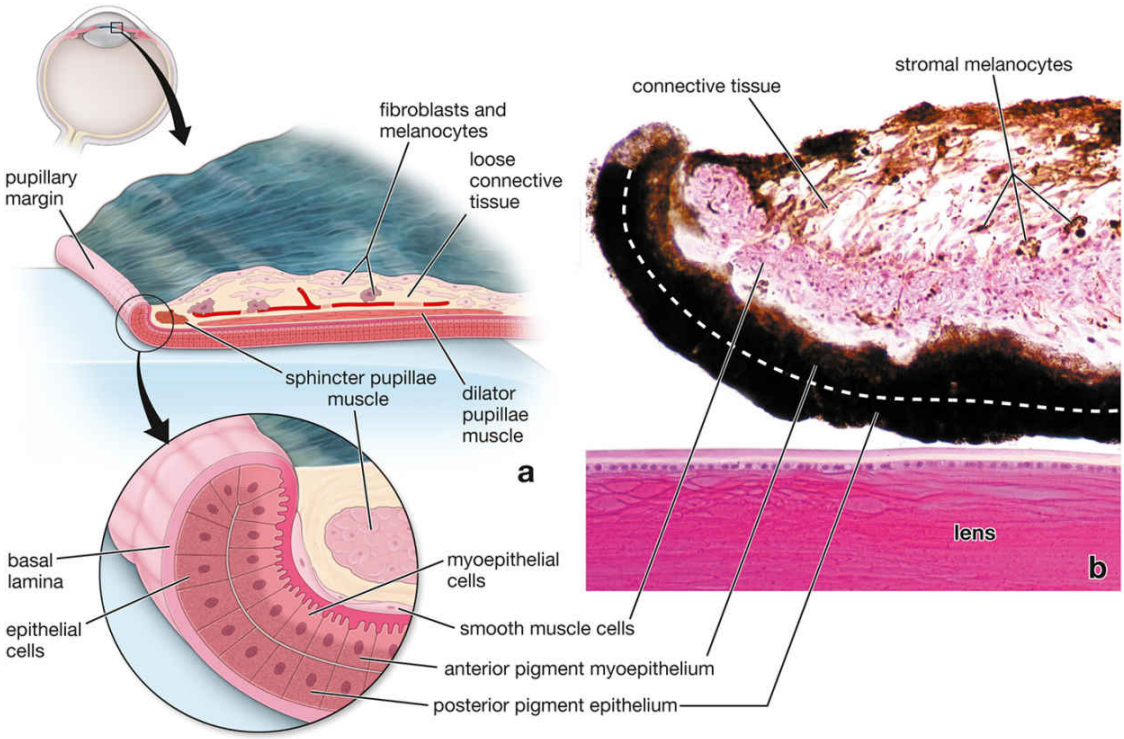


FIGURE 24.8. Structure of the iris. a. This schematic diagram shows the layers of the iris. Note that the pigmented epithelial cells are reflected as occurs at the pupillary margin of the iris. The two layers of pigmented epithelial cells are in contact with the dilator pupillae muscle. The incomplete layer of fibroblasts and stromal melanocytes is indicated on the anterior surface of the iris. **b.** Photomicrograph of the iris showing the histologic features of this structure. The *lens*, which lies posterior to the iris, is included for orientation. The iris is composed of a *connective tissue* stroma covered on its posterior

surface by the posterior pigment epithelium. The basal lamina (not visible) faces the posterior chamber of the eye. Because of intense pigmentation, the histologic features of these cells are not discernible. Just anterior to these cells is the anterior pigment myoepithelium layer (the *dashed line* separates the two layers). Note that the posterior portion of the myoepithelial cells contains melanin, whereas the anterior portion contains contractile elements forming the dilator pupillae muscle of the iris. The sphincter pupillae muscle is evident in the stroma. The color of the iris depends on the number of *stromal melanocytes* scattered throughout the connective tissue stroma. At the *bottom*, note the presence of the lens. ×570.

Constriction of the pupil is produced by smooth muscle cells located in the stroma of the iris near the pupillary margin of the iris. These circumferentially oriented cells collectively compose the **sphincter pupillae muscle**.

The anterior surface of the iris reveals numerous ridges and grooves that can be seen in clinical examination with the ophthalmoscope. When this surface is examined in the light microscope, it appears as a discontinuous layer of fibroblasts and melanocytes. The number of melanocytes in the stroma is responsible for variation in eye color. The function of these **pigment-containing cells** in the iris is to absorb light rays. If there are few melanocytes in the stroma, the color of the iris is derived from light reflected from the pigment present in the cells of the iris's posterior surface, giving it a blue appearance. With increasing amounts of pigment present in the stroma, the iris color changes from blue to shades of greenish blue, gray, and, finally, brown.

The sphincter pupillae is innervated by parasympathetic nerves; the dilator pupillae muscle is under sympathetic nerve control.

The **size of the pupil** is controlled by contraction of the sphincter pupillae and dilator pupillae muscles. The process of **adaptation** (increasing or decreasing the size of the pupil) ensures that only the appropriate amount of light enters the eye. Two muscles are actively involved in adaptation:

- The **sphincter pupillae muscle**, a circular band of smooth muscle cells (Plate 24.3, page 1014), is innervated by parasympathetic nerves carried in the oculomotor nerve (cranial nerve III) and is responsible for reducing pupillary size in response to bright light. Failure of the pupil to respond when light is shined into the eye—"**pupil fixed and dilated**"—is an important clinical sign showing a lack of nerve or brain function.
- The **dilator pupillae muscle** is a thin sheet of radially oriented contractile processes of pigmented myoepithelial cells constituting the anterior pigment epithelium of the iris. This muscle is innervated by sympathetic nerves from the superior cervical ganglion and is responsible for increasing pupillary size in response to dim light.

Just before **ophthalmoscopic examination**, mydriatic agents such as **atropine** are given as eye drops to cause dilation of the pupil. Acetylcholine (ACh) is the neurotransmitter of the parasympathetic nervous system (it innervates the sphincter pupillae muscle); the addition of atropine blocks muscarinic acetylcholine receptors, temporally blocking the action of the sphincter muscle, and leaving the **pupil wide open** and unreactive to light originating from ophthalmoscope.

The ciliary body is the thickened anterior portion of the vascular coat and is located between the iris and the choroid.

The **ciliary body** extends about 6 mm from the root of the iris posterolaterally to the **ora serrata** (see Fig. 24.2). As seen from behind, the lateral edge of the ora serrata bears 17–34 grooves or crenulations. These grooves mark the anterior limit of both the retina and the choroid. The anterior third of the ciliary body has approximately 75 radial ridges or **ciliary processes** (see Fig. 24.7). The fibers of the zonule arise from the grooves between the ciliary processes.

The layers of the ciliary body are similar to those of the iris and consist of a stroma and an epithelium. The stroma is divided into two layers:

- An **outer layer** of smooth muscle, the **ciliary muscle**, makes up the bulk of the ciliary body.
- An **inner vascular region** extends into the ciliary processes.

The epithelial layer covering the internal surface of the ciliary body is a direct continuation of the two layers of the retinal epithelium (see Fig. 24.1).

The ciliary muscle is organized into three functional portions or groups of smooth muscle fibers.

The smooth muscle of the ciliary body has its origin in the scleral spur, a ridge-like projection on the inner surface of the sclera at the corneoscleral junction. The muscle fibers spread out in several directions and are classified into three functional groups on the basis of their direction and insertion:

- The **meridional (or longitudinal) portion** consists of the outer muscle fibers that pass posteriorly into the stroma of the choroid. These fibers function chiefly in stretching the choroid. It also may help open the iridocorneal angle and facilitate drainage of the aqueous humor.
- The **radial (or oblique) portion** consists of deeper muscle fiber bundles that radiate in a fan-like manner to insert into the ciliary body. Its contraction causes the lens to flatten and thus focus on distant vision.

- The **circular (or sphincteric) portion** consists of inner muscle fiber bundles oriented in a circular pattern that forms a sphincter. It reduces the tension on the lens, causing the lens to accommodate for near vision.

Examination of a histologic preparation does not clearly reveal the arrangement of the muscle fibers. Rather, the organizational grouping is based on microdissection techniques.

Ciliary processes are ridge-like extensions of the ciliary body from which zonular fibers emerge and extend to the lens.

Ciliary processes are thickenings of the inner vascular region of the ciliary body. They are continuous with the vascular layers of the choroid. Scattered macrophages containing melanin pigment granules and elastic fibers are present in these processes (Plate 24.3, page 1014). The processes and the ciliary body are covered by a double layer of columnar epithelial cells, the **ciliary epithelium**, which was originally derived from the two layers of the optic cup. The ciliary epithelium has three principal functions:

- Secretion of **aqueous humor**
- Participation in the **blood–aqueous barrier** (part of the **blood–ocular barrier**)
- Secretion and anchoring of the **zonular fibers** that form the **suspensory ligament of the lens**

The inner cell layer of the ciliary epithelium has a basal lamina facing the posterior and vitreous chambers. The cells in this layer are nonpigmented. The cell layer that has its basal lamina facing the connective tissue stroma of the ciliary body is heavily pigmented and is directly continuous with the pigmented epithelial layer of the retina. The **double-layered ciliary epithelium** continues over the iris, where it becomes the posterior pigmented epithelium and anterior pigmented myoepithelium. The zonular fibers extend from the basal lamina of the nonpigmented epithelial cells of the ciliary processes and insert into the lens capsule (the thickened basal lamina of the lens).

The blood–aqueous barrier separates the interior environment of the eye from the blood entering the ciliary body.

The **cells of the nonpigmented layer** have all the characteristics of a fluid-transporting epithelium, including complex cell-to-cell junctions with a well-developed zonula occludens, extensive lateral and basal plications, and localization of Na^+/K^+-ATPase in the lateral plasma membrane. In addition, they have an elaborate rER and Golgi complex, consistent with their role in the secretion of zonular fibers. Tight junctions (zonulae occludentes) between the

nonpigmented ciliary epithelial cells are responsible for maintaining the **blood–aqueous barrier**. This barrier restricts free diffusion across the ciliary epithelium to maintain the unique environment of the aqueous humor, which is quite different from that of blood vessels and stroma of the ciliary body. The blood–aqueous barrier contributes to the nutrition and function of the cornea and the lens. **Disruption of the blood–aqueous barrier** may be observed in ocular inflammation, intraocular surgery, trauma, or vascular diseases. The aqueous humor becomes cloudy because of the leakage of plasma proteins (fibrinogen) and migration of inflammatory cells from the stroma of the ciliary body and iris into the posterior and anterior chambers of the eye.

The **cells of the pigmented layer** have a less developed junctional zone and often exhibit large, irregular lateral intercellular spaces. Both desmosomes and gap junctions hold together the apical surfaces of the two cell layers, creating discontinuous "luminal" spaces called **ciliary channels**.

The aqueous humor is derived from plasma and maintains intraocular pressure.

The **aqueous humor** is secreted by the double-layered ciliary epithelium and originates from blood capillaries. It is similar in ionic composition to plasma but contains less than 0.1% protein (compared to 7% protein in plasma). The main functions of the aqueous humor are to maintain **intraocular pressure** and to provide nutrients and remove metabolites from the avascular tissues of the cornea and lens. The aqueous humor passes from the ciliary body toward the lens and then between the iris and the lens, before it reaches the anterior chamber of the eye (see Fig. 24.6). In the anterior chamber of the eye, the aqueous humor passes laterally to the angle formed between the cornea and the iris. Here, it penetrates the tissues of the limbus as it enters the labyrinthine spaces of the limbus's trabecular meshwork in the iridocorneal angle and finally reaches the **canal of Schlemm**, which communicates with the veins of the sclera (see Folder 24.1). Normal turnover of the aqueous humor in the human eye is approximately once every 1.5–2 hours.

The choroid is the portion of the vascular coat that lies deep into the retina.

The **choroid** is a dark brown vascular sheet only 0.25 mm thick posteriorly and 0.1 mm thick anteriorly. It lies between the sclera and the retina (see Fig. 24.1).

Two layers can be identified in the choroid:

- **Choriocapillary layer**, an inner vascular layer
- **Bruch membrane**, a thin, amorphous hyaline membrane

The choroid is attached firmly to the sclera at the margin of the optic nerve. A potential space, the **perichoroidal space** (between the sclera and the retina), is traversed by thin, ribbon-like branching lamellae or strands that pass from the sclera to the choroid. These lamellae originate from the **suprachoroid lamina** (lamina fusca) and consist of large, flat melanocytes scattered between connective tissue elements, including collagen and elastic fibers, fibroblasts, macrophages, lymphocytes, plasma cells, and mast cells. The lamellae pass inward to surround the vessels in the remainder of the choroid layer. Free smooth muscle cells, not associated with blood vessels, are present in this tissue. Lymphatic channels called **epichoroid lymph spaces**, long and short posterior ciliary vessels, and nerves on their way to the front of the eye are also present in the suprachoroid lamina.

Most of the blood vessels decrease in size as they approach the retina. The largest vessels continue forward beyond the ora serrata into the ciliary body. These vessels can be seen with an ophthalmoscope. The large vessels are mostly veins that course in whorls before passing obliquely through the sclera as vortex veins. The inner layer of vessels, arranged in a single plane, is called the **choriocapillary layer**. The vessels of this layer provide nutrients to the cells of the retina. The fenestrated capillaries have lumina that are large and irregular in shape. In the region of the fovea, the choriocapillary layer is thicker, and the capillary network is denser. This layer ends at the ora serrata.

Bruch membrane, also called the **lamina vitrea**, measures 1–4 μm in thickness and lies between the choriocapillary layer and the pigment epithelium of the retina. It runs from the optic nerve to the ora serrata, where it undergoes modifications before continuing into the ciliary body. Bruch membrane is a thin, amorphous refractile layer. The transmission electron microscope (TEM) reveals that it consists of a multilaminar sheet containing a center layer of elastic and collagen fibers. Five different layers are identified in Bruch membrane:

- The basal lamina of the endothelial cells of the choriocapillary layer
- A layer of collagen fibers approximately 0.5 μm thick
- A layer of elastic fibers approximately 2 μm thick
- A second layer of collagen fibers (thus forming a “sandwich” around the intervening elastic tissue layer)
- The basal lamina of the RPE cells

At the ora serrata, the collagenous and elastic layers disappear into the ciliary stroma, and Bruch membrane becomes continuous with the basal lamina of the RPE of the ciliary body.

Retina

The retina represents the innermost layer of the eye.

The **retina**, derived from the inner and outer layers of the optic cup, is the innermost of the three concentric layers of the eye (see Fig. 24.1). It consists of two basic layers:

- The **neural retina** or **retina proper** is the inner layer that contains the photoreceptor cells.
- The **retinal pigment epithelium (RPE)** is the outer layer that rests on and is firmly attached through the Bruch membrane to the choriocapillary layer of the choroid.

A potential space exists between the two layers of the retina. The two layers may be separated mechanically in the preparation of histologic specimens. Separation of the layers, "**retinal detachment**" (see Folder 24.2), also occurs in the living state because of eye disease or trauma.

FOLDER 24.2

CLINICAL CORRELATION: RETINAL DETACHMENT

A potential space exists in the retina as a vestige of the space between the apical surfaces of the two epithelial layers of the optic cup. If this space expands, the neural retina separates from the retinal pigment epithelium (RPE), which remains attached to the choroid layer. This condition is called **retinal detachment**. As a result of retinal detachment, the photoreceptor cells are no longer supplied by nutrients from the underlying vessels in the choriocapillary plexus of the choroid.

Clinical symptoms of retinal detachment include visual sensations commonly described as a "shower of pepper" or floaters. These are caused by red blood cells extravasated from the capillary vessels that have been injured during the retinal tear or detachment. In addition, some individuals describe sudden flashes of light as well as a "web" or "veil" in front of the eye in conjunction with the onset of floaters. A detached retina can be observed and diagnosed during ophthalmoscopic eye examination (Fig. F24.2.1).

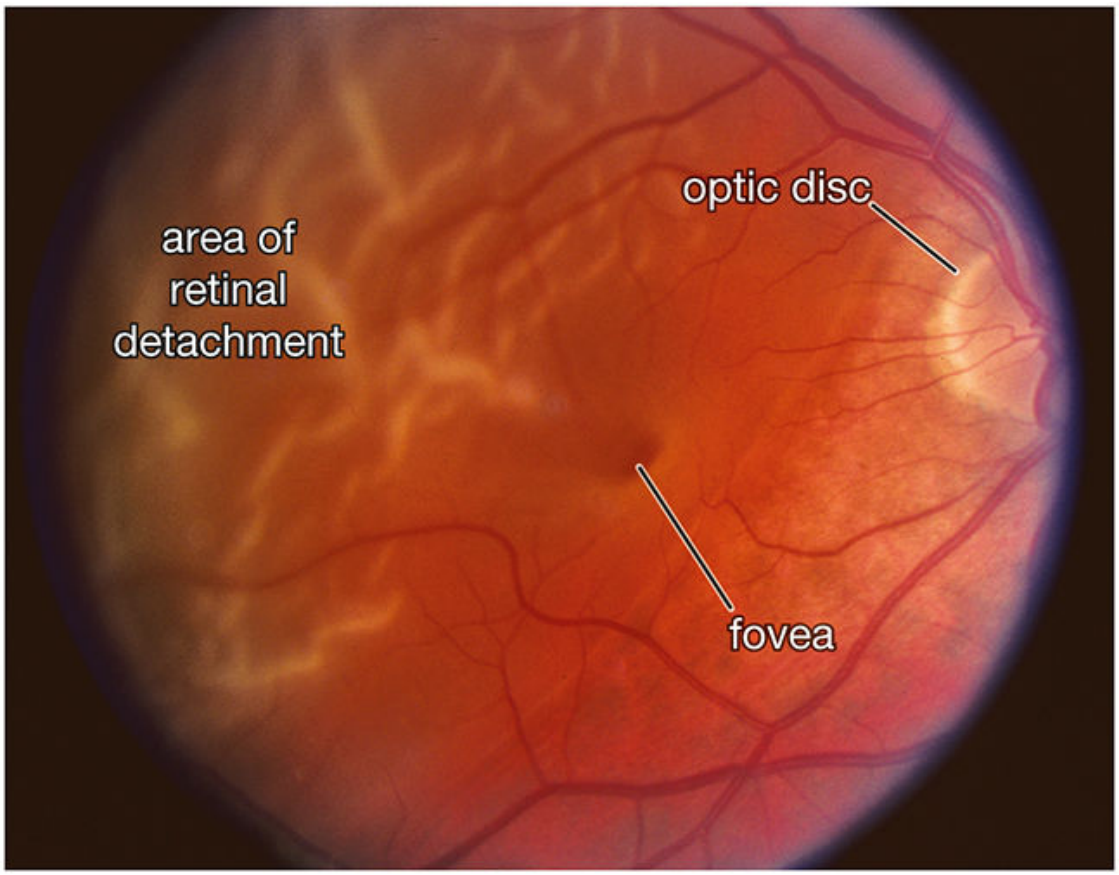


FIGURE F24.2.1. Retinal detachment. This image shows a view of the fundus of the right eye in a patient with retinal detachment. The central retinal vessels emerging from the optic disc are in focus, but in the *area of the retinal detachment,* they appear to be out of focus. Because the area of retinal detachment is elevated (note multiple ridges and shadows), it is located anterior to the plane of focus of the ophthalmoscope. (Courtesy of Dr. Renzo A. Zaldivar.) Another common retinal condition occurs with aging. As the vitreous body ages (in the sixth and seventh decades of life), it tends to shrink and pull away from the neural retina, which causes single or multiple tears in the neural retina.

If not repositioned quickly, the detached area of the retina will undergo necrosis, resulting in blindness. An argon laser is often used to repair retinal detachment by photocoagulating the edges of the detachment and producing scar tissue. This method prevents the retina from further detachment and facilitates the repositioning of photoreceptor cells.

In the neural retina, two regions or portions that differ in function are recognized:

- The **nonphotosensitive region** (nonvisual part), located anterior to the ora serrata, lines the inner aspect of the ciliary body and the posterior surface of the iris (this portion of the retina is described in the sections on the iris and ciliary body).

- The **photosensitive region** (optic part) lines the inner surface of the eye posterior to the ora serrata, except where it is pierced by the optic nerve (see Fig. 24.1).

The site where the optic nerve joins the retina is called the **optic disc** or **optic papilla**. Because the optic disc is devoid of photoreceptor cells, it is a blind spot in the visual field. The **fovea centralis** is a shallow depression located about 2.5 mm lateral to the optic disc. It is the area of greatest visual acuity. The visual axis of the eye passes through the fovea. A yellow-pigmented zone called the **macula lutea** surrounds the fovea. In relative terms, the fovea is the region of the retina that contains the highest concentration and most precisely ordered arrangement of visual elements. The region of the retina surrounding the macula lutea may be affected in older individuals by **age-related macular degeneration** (see Folder 24.3).

FOLDER 24.3

CLINICAL CORRELATION: AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (ARMD) is the most common cause of blindness in older individuals. Although the cause of this disease is still unknown, evidence suggests both genetic and environmental (ultraviolet [UV] irradiation, drugs) components. The disease causes loss of central vision, although peripheral vision remains unaffected. Two forms of ARMD are recognized: a dry (atrophic, nonexudative) form and a wet (exudative, neovascular) form. The latter is considered a complication of the first. **Dry ARMD** is the most common form (90% of all cases) and involves degenerative lesions localized in the area of the macula lutea. The degenerative lesions include **drusen**, which are focal thickenings of Bruch membrane, atrophy, depigmentation of the RPE, and obliteration of capillaries in the underlying choroid layer. These changes lead to the deterioration of the overlying photosensitive retina, resulting in the formation of blind spots in the visual field (Fig. F24.3.1). **Wet ARMD** is a complication of dry ARMD caused by neovascularization of blind spots of the retina in the large drusen. These newly formed, thin, fragile vessels frequently leak and produce exudates and hemorrhages in the space just beneath the retina, resulting in fibrosis and scarring. These changes are responsible for the progressive loss of central vision over a short time. The treatment of wet ARMD includes conventional **laser photocoagulation** therapy and pharmacologic therapy with intravitreal injection of ranibizumab, a **vascular endothelial growth factor (VEGF) inhibitor**. Other surgical methods, such as **macular translocation**, have been recently introduced. In this procedure, the retina is detached, translocated, and reattached in a new location, away from the choroid neovascular

tissue. Conventional laser treatment is then applied to destroy pathologic vessels without destroying central vision.

FIGURE F24.3.1. Photograph depicting the visual field in individuals with age-related macular degeneration. Note that central vision is absent because of the changes in the macula region of the retina. To maximize their remaining vision, individuals with this condition are instructed to use eccentric fixation of their eyes.

Layers of the retina

Ten layers of cells and their processes constitute the retina.

Before discussing the **ten layers of the retina**, it is important to identify the types of cells found there. This identification will aid in understanding the functional relationships of the cells. Studies of the retina in primates have identified at least 15 types of neurons that form at least 38 different types of synapses. For convenience, neurons and supporting cells can be classified into

four groups of cells (Fig. 24.9):

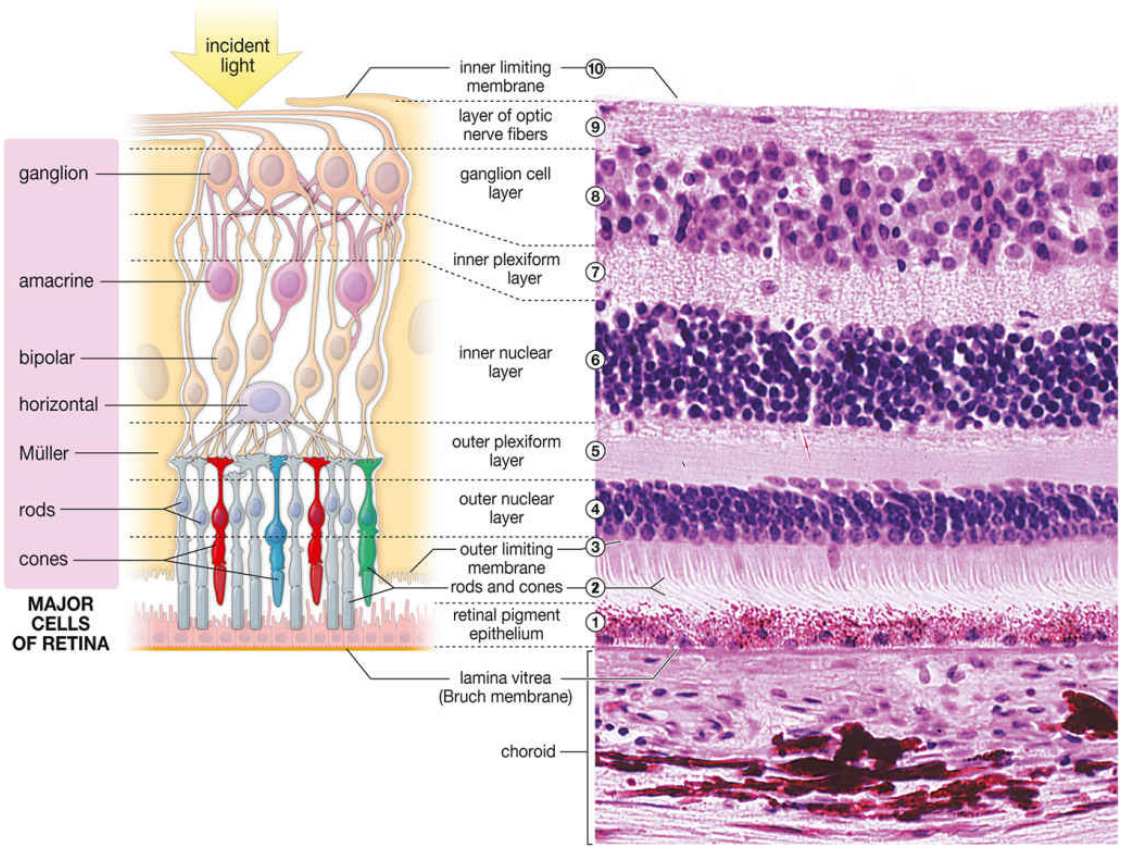


FIGURE 24.9. Schematic drawing and photomicrograph of the layers of the retina. On the basis of histologic features that are evident in the photomicrograph *on right*, the retina can be divided into 10 layers. The layers correspond to the diagram *on left*, which shows the distribution of major cells of the retina. Note that light enters the retina and passes through its inner layers before reaching the photoreceptors of the rods and cones that are closely associated with the retinal pigment epithelium. Also, the interrelationship between the bipolar neurons and ganglion cells that carry electrical impulses from the retina to the brain is clearly visible. Bruch membrane (lamina vitrea) separates the inner layer of the vascular coat (choroid) from the retinal pigment epithelium. ×440.

- **Photoreceptor cells**—the retinal rods and cones
- **Conducting neurons**—bipolar neurons and ganglion cells
- **Association neurons** and others—horizontal, centrifugal, interplexiform, and amacrine neurons
- **Supporting (neuroglial) cells**—Müller cells, microglial cells, and astrocytes

The specific arrangement and associations of the nuclei and processes of these cells form 10 retinal layers that can be seen with the light microscope. The layers of the retina can also be imaged and examined in living individuals using spectral-domain optical coherence tomography (see

Folder 24.4). The 10 layers of the retina, from outside inward, are as follows (see Fig. 24.9): FOLDER 24.4

CLINICAL CORRELATION: CLINICAL IMAGING OF THE RETINA

The standard ophthalmoscopic examination of the eye has been recently supplemented by a new examination technique that utilizes **spectral-domain optical coherence tomography** (SD OCT). This noninvasive and noncontact examination is not only useful in visualizing the retinal surface, but it also provides a high-resolution cross-sectional image of the retina in vivo. All histologic layers of the retina can be easily differentiated with SD OCT (Fig. F24.4.1), and they can be objectively measured for tissue thickness and change. SD OCT technology is based on comparisons of spectral characteristics of the reflected light beam from the retina with those of the reference beam. For this purpose, an infrared laser beam (~840 nm wavelength with 50 nm bandwidth) is used that is able to produce images at 5-μm resolution. The laser beam passes through the structures of the eye and is partially absorbed and partially reflected depending on tissue characteristics. The reflected light is detected by a multichannel spectrometer, and the interference pattern is compared to the reference beam using complex computer algorithms. The spectral differences are used to construct the cross-sectional (line) scans as shown in Figure F24.4.1 or the three-dimensional images of the retina as shown in Figure F24.4.2. Introduced in the 1990s, the SD OCT has revolutionized the management and diagnosis of many eye diseases. SD OCT established itself as an imaging modality of choice in **glaucoma** (measurement of optic nerve and retinal nerve fiber layer) and retinal diseases. It is used for the early and accurate detection of **macular degeneration**, **retinal detachment**, **macular holes**, **epiretinal membranes**, and **optic disc pits** and for the detection of fluid accumulation within the retina that occurs in conditions such as **diabetic retinopathy**, **cystoid macular edema**, and **central serous choroidopathy**.

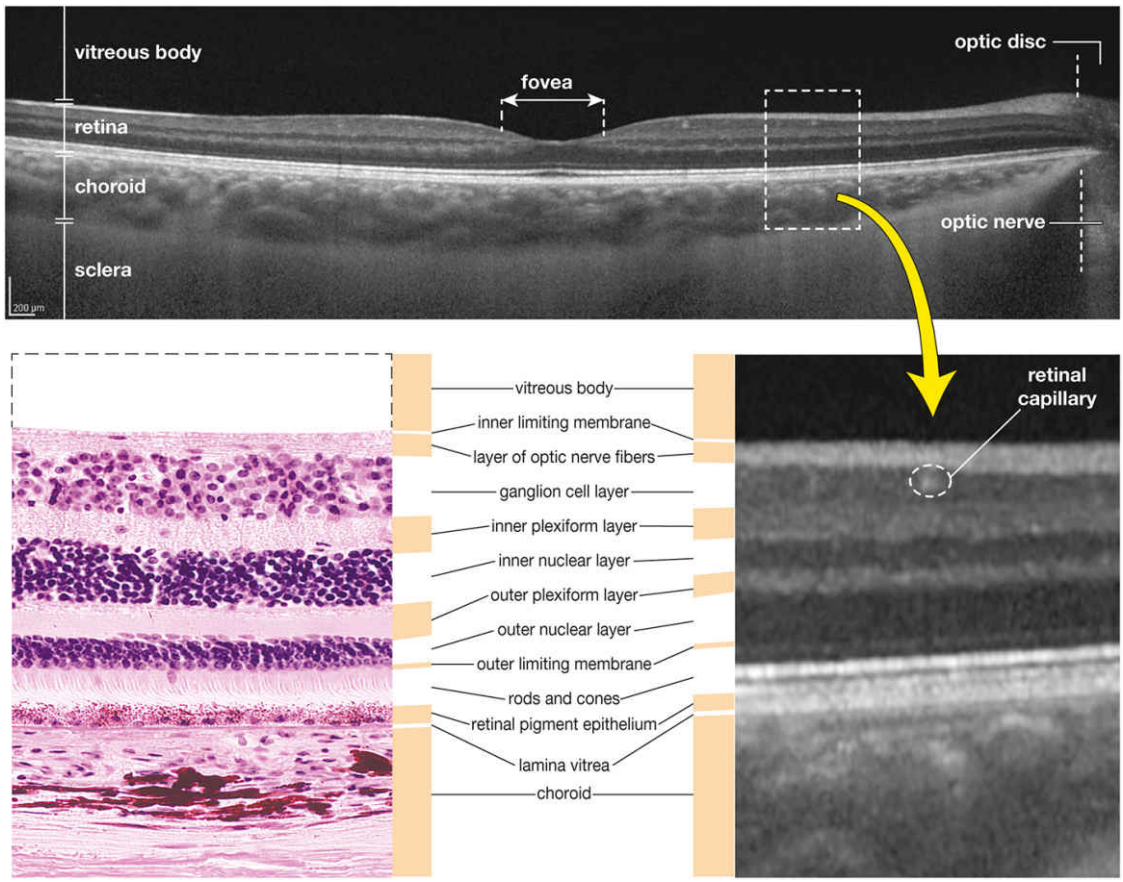


FIGURE F24.4.1. Spectral-domain optical coherence tomography (SD OCT) cross-sectional (line) image of the retina in a healthy eye. The *upper* image represents a normal cross-sectional image of the retina containing fovea and optic disc on the *right* side of the image. The optically transparent vitreous body is invisible and appears as the *black* region in the upper part of the image. Hyperreflective and hyporeflective bands of retinal tissue correspond to the histologic layers of the retina. Note the photoreceptor layer containing rods and cones as well the retinal pigment epithelium are well defined and are separated from the choroid layer containing blood vessels. (Courtesy of Drs. Andrew J.

Barkmeier and Denise M. Lewison.)

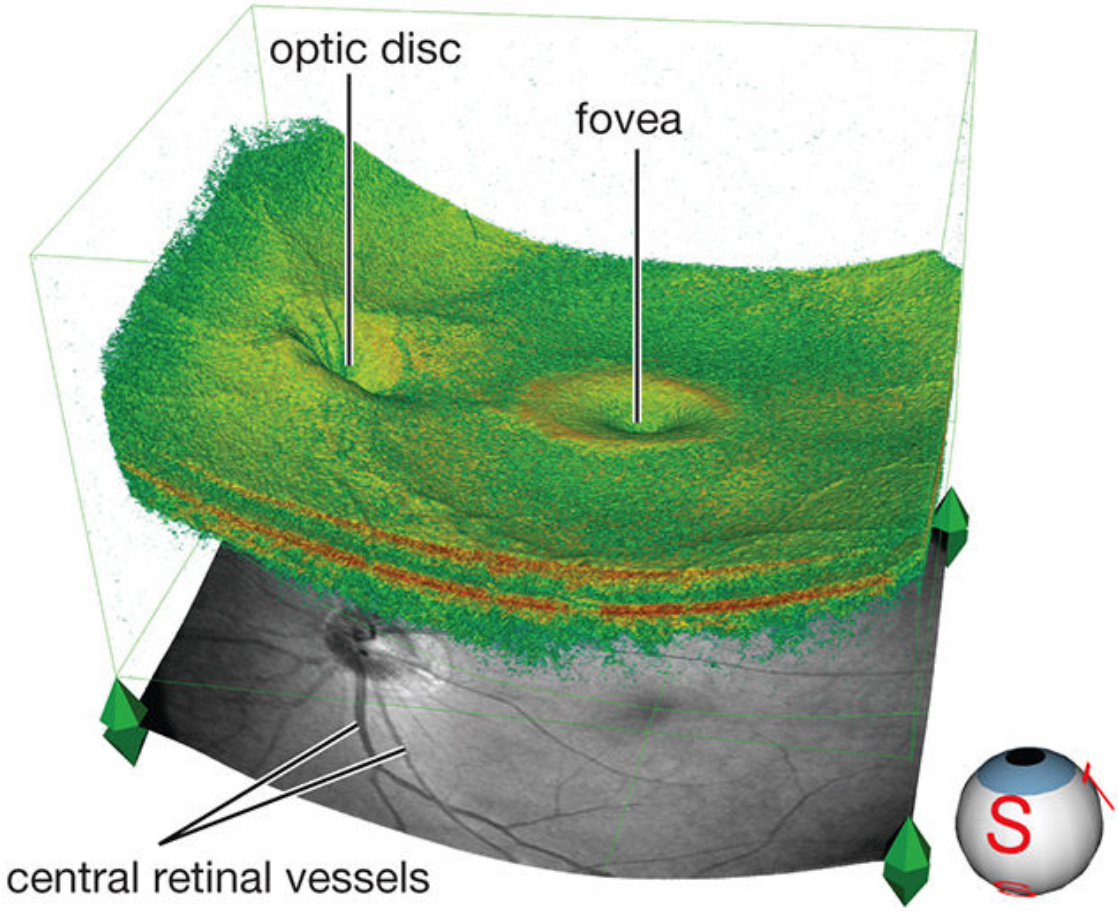


FIGURE F24.4.2. Spectral-domain optical coherence tomography (SD OCT) three-dimensional image of the retina of a healthy right eye. The scan area is ~12 mm × 9 mm in size and includes a portion of the optic disc (*on the left*) and fovea (*on the right*). A three-dimensional data set is acquired from four scans (two vertical and two horizontal), which is then processed with a motion-correction technology (MCT) algorithm. The MCT algorithm analyzes and compares the vascular pattern in each of the scans and reduces artifacts and image distortions associated with eye movement. This image has two parts. The upper false-color image (optical densities are coded in different colors) shows the surface and thickness of all layers of the retina and represents a motion-corrected, three-dimensional volume rendering of the entire data set. The lower grayscale vascular map image (optical densities are coded in grayscale) is a two-dimensional image created by summing all the pixels in each column. It is curved to match the curvature of the eye. The letters S (for superior) and T (for temporal) on the eye orientation icon in the *lower right corner* provide reference to the positioning of the scan in the patient's eye. (Image courtesy of Dr. Pravin Dugel, Phoenix, Arizona.)

1. **Retinal pigment epithelium (RPE)**—the outer layer of the retina, actually not part of the neural retina but intimately associated with it

2. **Layer of rods and cones**—contains the outer and inner segments of photoreceptor cells
3. **Outer limiting membrane**—the apical boundary of Müller cells
4. **Outer nuclear layer**—contains the cell bodies (nuclei) of retinal rods and cones
5. **Outer plexiform layer**—contains the processes of retinal rods and cones and processes of the horizontal, amacrine, and bipolar cells that connect to them
6. **Inner nuclear layer**—contains the cell bodies (nuclei) of horizontal, amacrine, bipolar, and Müller cells
7. **Inner plexiform layer**—contains the processes of horizontal, amacrine, bipolar, and ganglion cells that connect to each other
8. **Ganglion cell layer**—contains the cell bodies (nuclei) of ganglion cells
9. **Layer of optic nerve fibers**—contains processes of ganglion cells that lead from the retina to the brain
10. **Inner limiting membrane**—composed of the basal lamina of Müller cells

Each of the layers is more fully described in the following sections (see corresponding numbers).

The cells of the retinal pigment epithelium (layer 1) have extensions that surround the processes of the rods and cones.

The **RPE** is a single layer of cuboidal cells about 14 μm wide and 10–14 μm tall. The cells rest on Bruch membrane of the choroid layer. The pigment cells are tallest in the fovea and adjacent regions, which account for the darker color of this region.

Adjacent RPE cells are connected by a junctional complex consisting of gap junctions and elaborate zonulae occludentes and adherentes. This junctional complex is the site of the **blood–retina barrier**. This barrier makes the retinal vessels impermeable to molecules larger than 20–30 kDa.

The pigment cells have cylindrical sheaths on their apical surface that are associated with, but do not directly contact, the tip of the photoreceptor processes of the adjacent rod and cone cells. Complex cytoplasmic processes project for a short distance between the photoreceptor cells of the rods and cones. Numerous elongated melanin granules, unlike those found elsewhere in the eye, are present in many of these processes. They aggregate on the side of the cell nearest the rods and cones and are the most prominent feature of the cells. The nucleus with its many convoluted infoldings is located near the basal plasma membrane adjacent to Bruch membrane.

The cells also contain material phagocytosed from the processes of the photoreceptor cells in the form of lamellar debris (lipofuscin) contained in residual bodies or phagosomes. These lipofuscin granules reside in the basal cytoplasm of the RPE cell and are relatively difficult to detect in routine

hematoxylin and eosin (H&E) preparation. Because the lipofuscin pigment is fluorescent, it can be clearly seen in the UV fluorescent microscope. A supranuclear Golgi apparatus and an extensive network of smooth-surfaced endoplasmic reticulum (sER) surround the melanin granules and residual bodies that are present in the cytoplasm.

The **RPE** serves several important functions, including the following:

- It **absorbs light** passing through the neural retina to **prevent reflection** and resultant glare.
- It isolates the retinal cells from blood-borne substances. It serves as a major component of the **blood–retina barrier** via tight junctions between RPE cells.
- It participates in **restoring photosensitivity** to visual pigments that were dissociated in response to light. The metabolic apparatus for visual pigment resynthesis is present in the RPE cells.
- It **phagocytoses and disposes of membranous discs** from the rods and cones of the retinal photoreceptor cells.

The rods and cones of the photoreceptor cell (layer 2) extend from the outer layer of the neural retina to the pigment epithelium.

The **rods** and **cones** are the outer segments of photoreceptor cells whose nuclei form the outer nuclear layer of the retina (Figs. 24.9 and 24.10). The light that reaches the photoreceptor cells must first pass through all of the internal layers of the neural retina. The rods and cones are arranged in a palisade manner; therefore, in the light microscope, they appear as vertical striations.

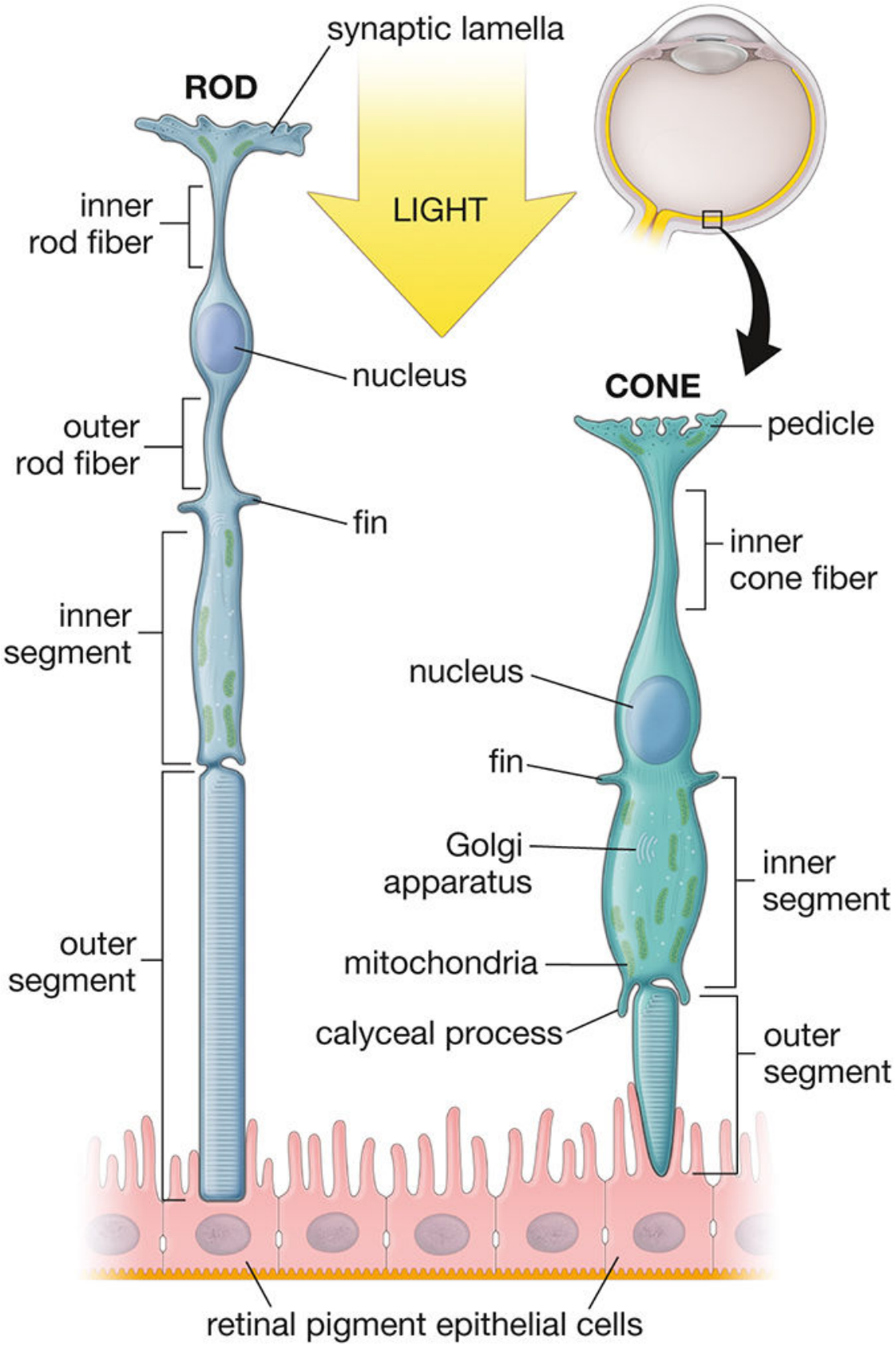


FIGURE 24.10. Schematic diagram of the ultrastructure of rod and cone cells. The outer segments of the rods and cones are closely associated with the adjacent pigment epithelium.

The retina contains approximately **120 million rods** and **7 million cones**. They are not distributed equally throughout the photosensitive part of the retina. The **highest density of cones** is detected in the **fovea centralis**, which corresponds to the highest visual acuity and best color vision (Fig. 24.11). The highest density of rods is outside the fovea centralis, and their density steadily decreases toward the periphery of the retina. Rods are not present in the fovea centralis nor at the optic disc, which is devoid of any photoreceptors (see Fig. 24.11). The rods are about 2 μm thick and 50 μm long (ranging from about 60 μm at the fovea to 40 μm peripherally). The cones vary in length from 85 μm at the fovea to 25 μm at the periphery of the retina.

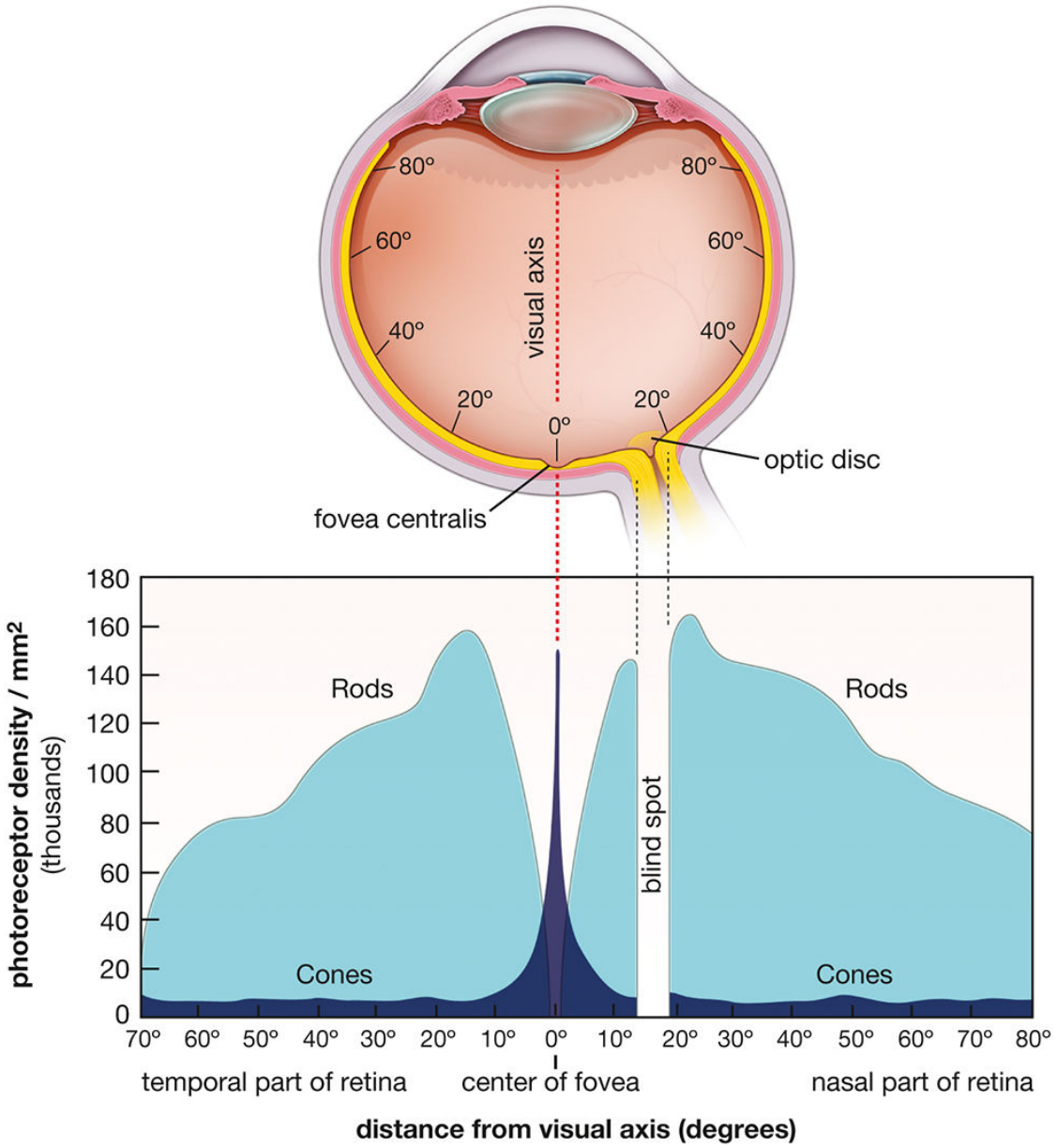


FIGURE 24.11. Distribution of rods and cones in the human eye. This graph shows the density of rods and cones per mm^2 across the retina. The peak number of cones occurs in the fovea centralis, where it reaches ~150,000

cones/mm^2. Rod density peaks about 20 degrees from the visual axis and is roughly the same as that of cones. Rods density decreases toward the periphery of the retina. Note that there are no photoreceptors at the optic disc.

Rods are sensitive in low light and produce black-and-white images; cones are less sensitive in low light and produce color images.

Functionally, the **rods** are more **sensitive to light** and are the receptors used during periods of low light intensity (e.g., at dusk or at night). The rod pigments have a maximum absorption at 496 nm of visual spectrum, and the image provided is one composed of gray tones (a "black-and-white picture"). In contrast, the **cones** exist in **three classes**: **L, M, and S** (long-, middle-, and short-wavelength sensitive, respectively) that cannot be distinguished morphologically. They are less sensitive to low light but more sensitive to red, green, and blue regions of the visual spectrum. Each class of cones contains a different visual pigment molecule that is activated by the absorption of light at the **blue** (420 nm), **green** (531 nm), and **red** (588 nm) ranges in the color spectrum. Cones provide a visual image composed of color by mixing the appropriate proportion of red, green, and blue light. For a description of different types of color blindness, see Folder 24.5.

FOLDER 24.5

CLINICAL CORRELATION: COLOR BLINDNESS

In individuals with normal color vision, the three primary colors (red, green, and blue) are combined to achieve the full spectrum of color vision. These individuals are called **trichromats** and possess three independent channels for conveying color information that are derived from three different classes of cones (L—red sensitive; M—green sensitive; and S—blue sensitive). Approximately 90% of trichromats can apperceive any given color from impulses generated in all three classes of cones. Some individuals have an impairment of normal color vision, which occurs when one of the cones is altered in its spectral sensitivity. For example, about 6% of trichromats matches colors with an unusual proportion of red and green. These individuals are called **anomalous trichromats**.

Color blindness is a condition in which individuals are missing or have a defect in a specific class of cones. True color-blind individuals are **dichromats** and have a defect either in the L, M, or S cones. In this condition, the affected cones are completely missing. Dichromats can only distinguish different colors by matching the impulses generated by the two remaining normal classes of cones.

Three major types of color blindness have been identified:

- **Protanopia** is characterized as a defect affecting the long-wavelength L cones responsible for red vision. The genes encoding L cone photoreceptor proteins are located on the X chromosome; therefore,

protanopia is a sex-linked disorder affecting mainly males (1% of the male population). These individuals have difficulty distinguishing between blue and green as well as red and green colors; thus, this color vision deficiency is a serious risk factor in driving (Fig. F24.5.1).

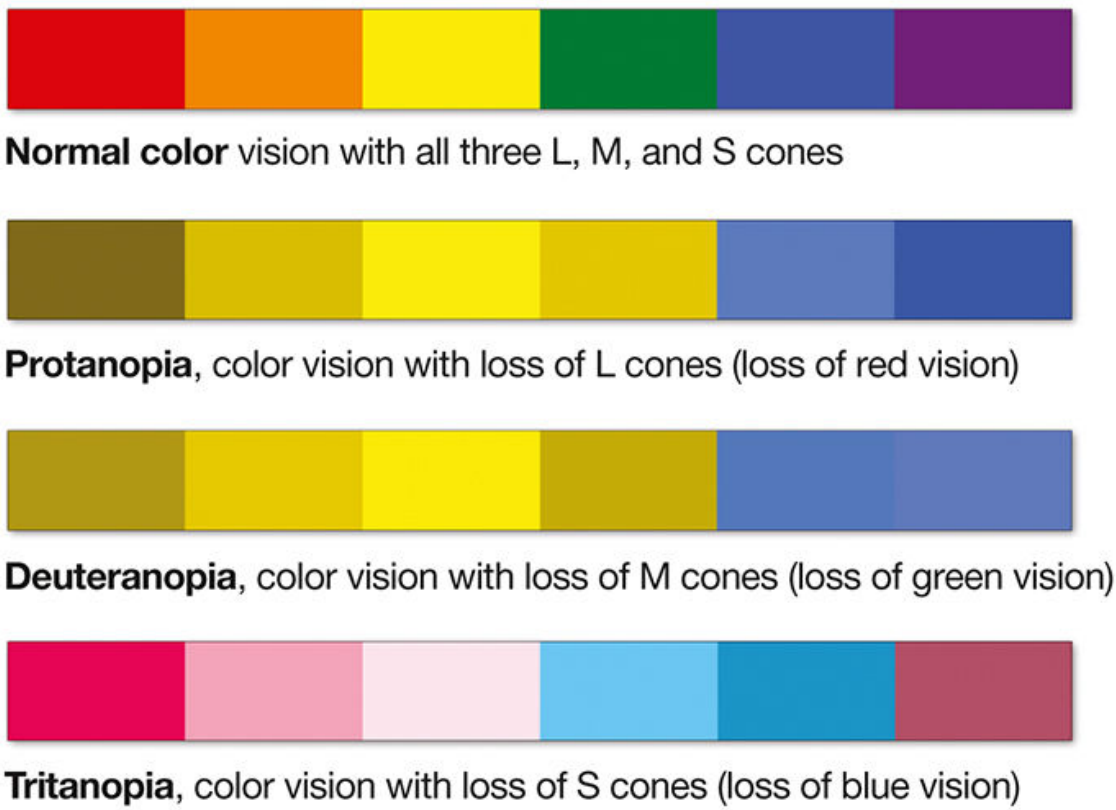


FIGURE F24.5.1. Color blindness. This chart shows the six-color spectrum in normal color vision and in individuals with the three types of color blindness.

- **Deuteranopia** is characterized as a defect affecting the middle-wavelength M cones responsible for green vision. Deuteranopia is the most common form of color blindness, affecting about 5% of the male population. It is also a sex-linked disorder because the genes encoding M cone photoreceptor proteins are located in the same region of the X chromosome as the genes for L cones. Similar to protanopia, red and green are the main problem colors (see Fig. F24.5.1).
- **Tritanopia** is characterized as a defect affecting the short-wavelength S cones responsible for blue vision (see Fig. F24.5.1). The defect is autosomal and involves mutation of a single gene encoding S cone photoreceptor proteins that reside on chromosome 7. This color blindness occurs very rarely (1 in 10,000) and affects women and men equally.

Each rod and cone photoreceptor consists of three parts:

- The **outer segment** of the photoreceptor is roughly cylindrical or conical (hence, the descriptive name **rod** or **cone**). This portion of the photoreceptor is intimately related to microvilli projecting from the adjacent pigment epithelial cells.
- The **connecting stalk** contains a cilium composed of nine peripheral microtubule doublets extending from a basal body. The connecting stalk appears as the constricted region of the cell that joins the inner to the outer segment. In this region, a thin, tapering process called the **calyceal process** extends from the distal end of the inner segment to surround the proximal portion of the outer segment (see Fig. 24.10).
- The **inner segment** is divided into an outer **ellipsoid** and an inner **myoid portion**. This segment contains a typical complement of organelles associated with a cell that actively synthesizes proteins. A prominent Golgi apparatus, rER, and free ribosomes are concentrated in the myoid region. Mitochondria are most numerous in the ellipsoid region. Microtubules are distributed throughout the inner segment. In the outer ellipsoid portion, cross-striated fibrous rootlets may extend from the basal body among the mitochondria.

The outer segment is the site of photosensitivity, and the inner segment contains the metabolic machinery that supports the activity of the photoreceptor cells. The outer segment is considered a highly modified cilium because it is joined to the inner segment by a short connecting stalk containing a basal body (Fig. 24.12a).

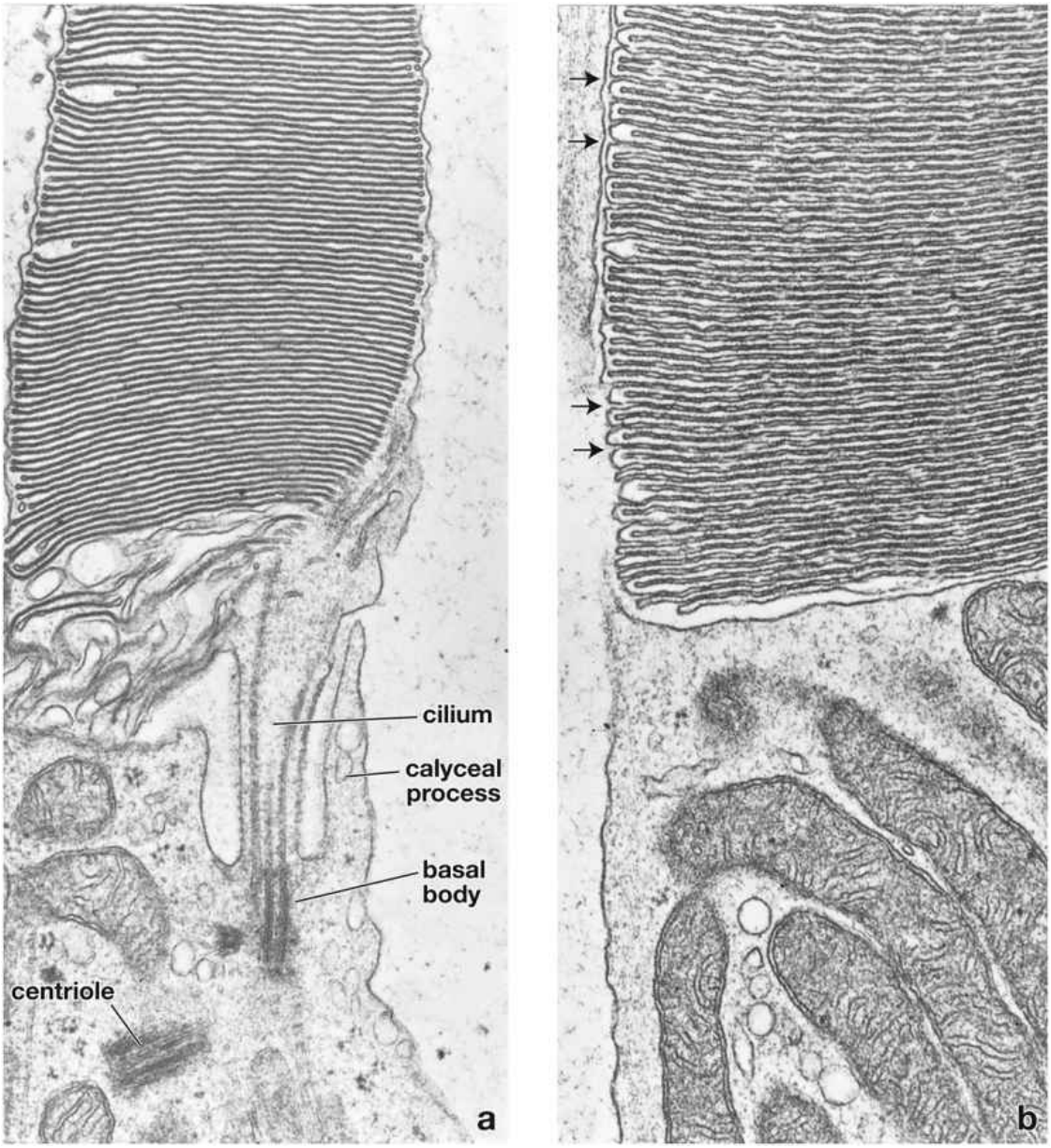


FIGURE 24.12. Electron micrographs of portions of the inner and outer segments of cones and rods. a. This electron micrograph shows the junction between the inner and outer segments of the rod cell. The outer segments contain the horizontally flattened discs. The plane of this section passes through the connecting stalk and cilium. A centriole, a cilium and its basal body, and a calyceal process are identified. ×32,000. **b.** Another electron micrograph shows a similar section of a cone cell. The interior of the discs in the outer segment of the cone is continuous with the extracellular space (*arrows*). ×32,000. (Courtesy of Dr. Toichiro Kuwabara.) With the TEM, 600–1,000 regularly spaced horizontal **membranous discs** are seen in the outer segment (Fig. 24.12). In rods, these discs are membrane-bound structures measuring about 2 μm in diameter. They are enclosed within the plasma membrane of the outer segment (see Fig. 24.12a). The parallel membranes of the discs are about 6 nm thick and are continuous at their ends. The central enclosed space is about 8 nm across. In both rods and cones, the membranous discs are

formed from repetitive transverse infolding of the plasma membrane in the region of the outer segment near the cilium. Autoradiographic studies have demonstrated that rods form new discs by infolding of the plasma membrane throughout their life span. Discs are formed in cones in a similar manner but are not replaced on a regular basis.

Rod discs lose their continuity with the plasma membrane from which they are derived soon after they are formed. They then pass like a stack of plates, proximally to distally, along the length of the cylindrical portion of the outer segment until they are eventually shed and phagocytosed by the pigment epithelial cells. Thus, each rod disc is a membrane-enclosed compartment within the cytoplasm. Discs within the cones retain their continuity with the plasma membrane (Fig. 24.12b).

Rod cells contain the visual pigment rhodopsin; cone cells contain the visual pigment iodopsin.

Rhodopsin (also called **visual purple**) is a 39-kDa protein in rod cells that initiates the visual stimulus when it is bleached by light. Rhodopsin is present in globular form on the outer surface of the lipid bilayer (on the cytoplasmic side) of the membranous discs. In the cone cells, the visual pigment protein on the membranous discs is the photopigment **iodopsin**. Each cone cell is specialized to respond maximally to one of three colors: red, green, or blue. Both rhodopsin and iodopsin contain a membrane-bound subunit called an **opsin** and a second small light-absorbing component called a **chromophore**. The opsin of rods is **scotopsin**; the opsins of cones are **photopsins**. The chromophore of rods is a vitamin A–derived carotenoid called **retinal**. Thus, an adequate intake of **vitamin A** is essential for normal vision. Prolonged dietary deficiency of vitamin A leads to the inability to see in dim light (**night blindness**).

The interior of the discs of cones is continuous with the extracellular space.

The basic difference in the structure of the rod and cone discs—that is, continuity with the plasma membrane—is correlated with the slightly different means by which the visual pigments are renewed in rods and cones. Newly synthesized rhodopsin is incorporated into the membrane of the rod disc as the disc is being formed at the base of the outer segment. It then takes several days for the disc to reach the tip of the outer segment. In contrast, although visual proteins are constantly produced in retinal cones, the proteins are incorporated into cone discs located anywhere in the outer segment.

Vision is a process by which light striking the retina is converted into electrical impulses that are transmitted to the brain.

The impulses produced by light reaching the photoreceptor cells are conveyed to the brain by an elaborate network of nerves. The conversion of the incident light into electrical nerve impulses is called **visual processing** and involves several steps:

- A photochemical reaction occurs in the outer segment of the rods and cones. In the dark, **rhodopsin** molecules contain a chromophore called retinal in its isometric form of **11-*cis*-retinal**. When rods are exposed to light, the 11-*cis*-retinal undergoes a conformational change from a bent to a more linear molecule called **all-*trans*-retinal**. The conversion of 11-*cis*-retinal to all-*trans*-retinal activates opsin, which results in the release of all-*trans*-retinal into the rod's cytoplasm (a reaction called **bleaching**).
- The activated **opsin** interacts with a G-protein called **transducin**, which subsequently activates phosphodiesterase that breaks down **cyclic guanosine monophosphate (cGMP)**. In the dark, high levels of cGMP molecules produced in the photoreceptor cells by guanylyl cyclase are bound to the cytoplasmic surface of **cGMP-gated Na^+ channels**, causing them to stay open. Steady influx of Na^+ into the cells results in **depolarization** of the plasma membrane and continuous **release of the neurotransmitter (glutamate)** at the synaptic junction with the bipolar neurons (Fig. 24.13).

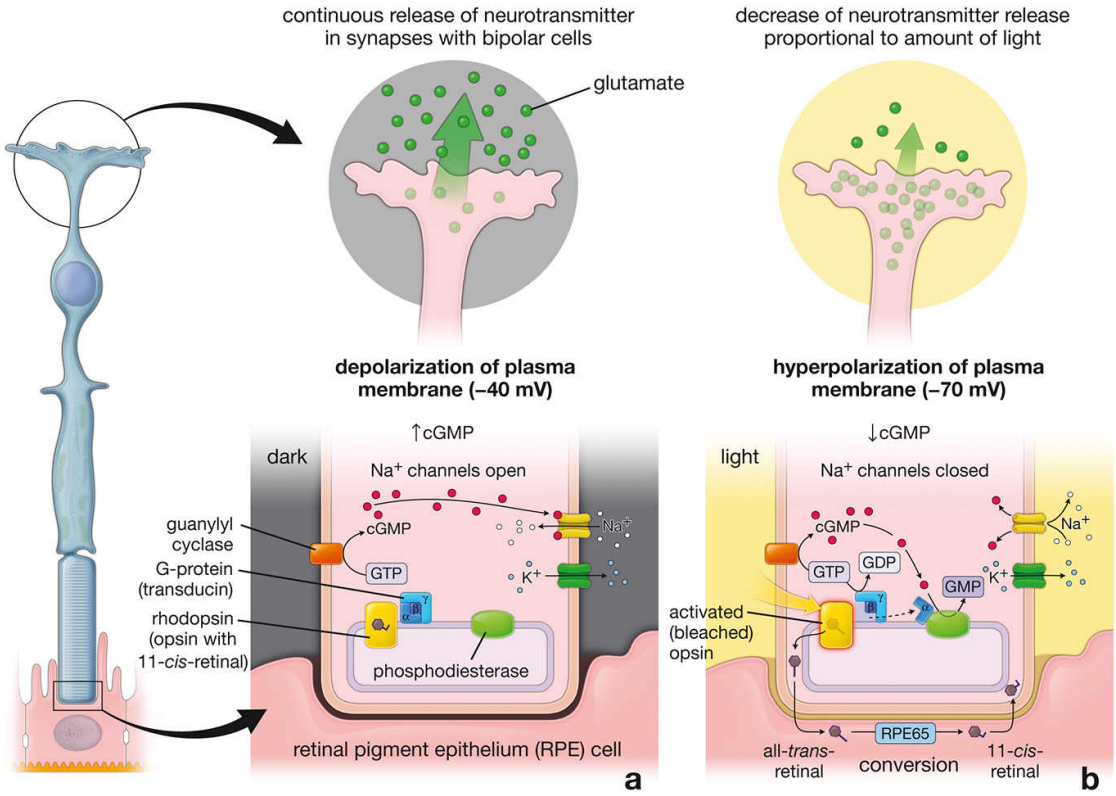


FIGURE 24.13. Schematic diagram of visual processing in the photoreceptor cell. a. In the dark, high levels of cGMP generated by

guanylyl cyclase are present in the cytoplasm of the rod. Some of the cGMP molecules are bound to the cytoplasmic surface of cGMP-gated Na^+ channels, causing them to stay open and resulting in continuous influx of Na^+ and depolarization of the plasma membrane. This results in a steady release of glutamate, a neurotransmitter, in the synaptic junctions with bipolar neurons. Also in the dark, rhodopsin molecules that contain 11-*cis*-retinal are inactive. **b.** After exposure to light, 11-*cis*-retinal undergoes a conformational change to all-*trans*-retinal. This conversion activates opsin (a reaction called *bleaching*) and releases all-*trans*-retinal into the rod's cytoplasm. The activated opsin interacts with G-protein, which subsequently activates phosphodiesterase that breaks down cGMP, effectively lowering the concentration of cGMP in the cell. In this condition, cGMP molecules dissociate from Na^+ channels, resulting in their closing and hyperpolarization of the plasma membrane. This results in a decrease in glutamate secretion, which is detected by the bipolar neurons and conveyed as electrical impulses to the brain. The released retinal from opsin is converted to its original conformation in retinal pigment epithelial (*RPE*) cells by the RPE65 enzymatic complex and is recycled to the photoreceptor cell. *cGMP*, cyclic guanosine monophosphate; *GDP*, guanosine diphosphate; *GMP*, guanosine monophosphate; *GTP*, guanosine triphosphate.

- A decrease in the concentration of cGMP within the cytoplasm of the inner segment of the photoreceptor cells is due to the action of phosphodiesterase. Dissociation of cGMP from Na^+ channels effectively closes the channels and reduces the influx of Na^+ into the cell, resulting in **hyperpolarization** of the plasma membrane. The hyperpolarization causes a **decrease of glutamate secretion** at the synapses with bipolar cells, which is detected and conveyed as electrical impulses (see Fig. 24.13).

Released retinal from opsin is converted back to its original conformation in the RPE cells and Müller cells.

After release, all-*trans*-retinal is converted to all-*trans*-retinol in the cytoplasm of rods and cones and then transported to the cytoplasm of RPE cells (from rods) or both RPE cells and Müller cells (from cones). The energy for this process is provided by the mitochondria located in the inner segment of these photoreceptors. Both Müller cells and RPE cells participate in a multistep conversion of all-*trans*-retinol to 11-*cis*-retinal, which is transported back to the photoreceptor cells for the resynthesis of rhodopsin. The **retinal pigment epithelium–specific protein 65 kDa (RPE65)** is involved in this conversion; thus, the visual cycle can begin again.

During the normal functioning of the photoreceptor cells, the membranous discs of the outer segment are shed and phagocytosed by the pigment epithelial cells (Fig. 24.14). It is estimated that each of these cells is capable of phagocytosing and disposing of about 7,500 discs per day. The discs are

constantly turning over, and the production of new discs must equal the rate of disc shedding.

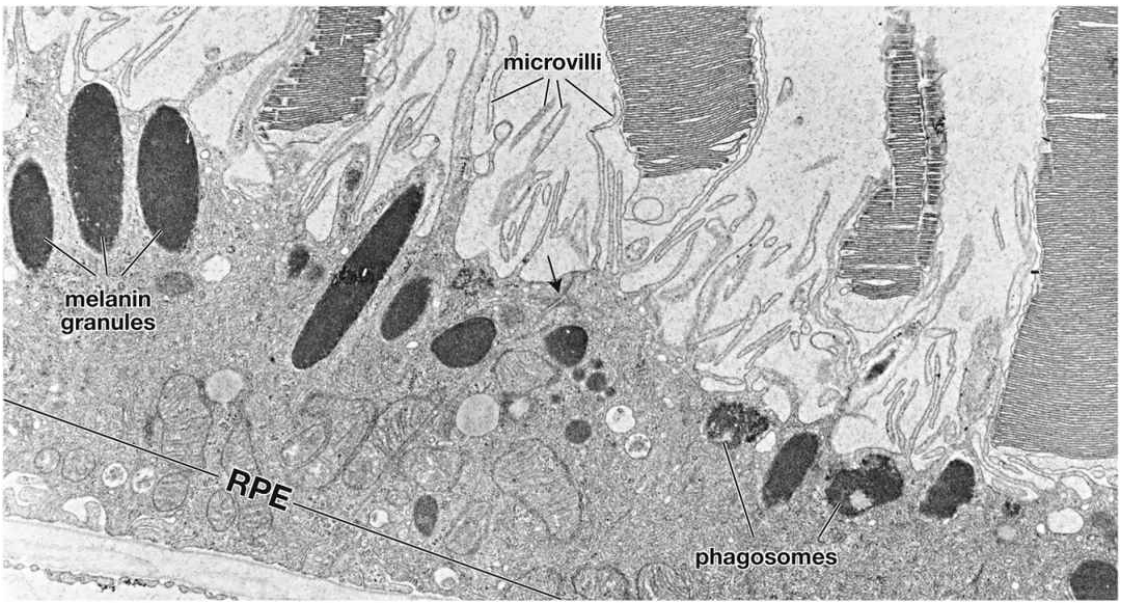


FIGURE 24.14. Electron micrograph of the retinal pigment epithelium in association with the outer segments of rods and cones. Retinal pigment epithelial (*RPE*) cells contain numerous elongated *melanin granules* that are aggregated in the apical portion of the cell, where the *microvilli* extend from the surface toward the outer segments of the rod and cone cells. The *retinal pigment epithelial* cells contain numerous mitochondria and *phagosomes*. The *arrow* indicates the location of the junctional complex between two adjacent cells. ×20,000. (Courtesy of Dr. Toichiro Kuwabara.) Discs are shed from both rods and cones.

In rods, after a period of sleep, a burst of **disc shedding** occurs as light first enters the eye. The time of disc shedding in cones is more variable. The shedding of discs in cones also enables the receptors to eliminate superfluous membrane. Although not fully understood, the shedding process in cones also alters the size of the discs so that the conical form is maintained as discs are released from the distal end of the cone.

The outer limiting membrane (layer 3) is formed by a row of zonulae adherentes between Müller cells.

The **outer limiting membrane** is not a true membrane. It is a row of zonulae adherentes that attaches the apical ends of Müller cells (i.e., the end that faces the pigment epithelium) to each other and to the rods and cones (see Fig. 24.9). Because Müller cells end at the base of the inner segments of the receptors, they mark the location of this layer. Thus, the supporting processes of Müller cells, on which the rods and cones rest, are pierced by the inner and outer segments of the photoreceptor cells. This layer is thought to be a

metabolic barrier that restricts the passage of large molecules into the inner layers of the retina.

The outer nuclear layer (4) contains the nuclei of the retinal rods and cones.

The region of the rod cytoplasm that contains the nucleus is separated from the inner segment by a tapering process of the cytoplasm. In cones, the nuclei are located close to the outer segments, and no tapering is seen. The cone nuclei stain lightly and are larger and more oval than rod nuclei. Rod nuclei are surrounded by only a thin rim of cytoplasm. In contrast, a relatively thick investment of cytoplasm surrounds the cone nuclei (see Fig. 24.10).

The outer plexiform layer (5) is formed by the processes of the photoreceptor cells and neurons.

The **outer plexiform layer** is formed by the processes of retinal rods and cones and the processes of horizontal, interplexiform, amacrine, and bipolar cells. The processes allow the electrical coupling of photoreceptor cells to these specialized interneurons via synapses. A thin process extends from the region of the nucleus of each rod or cone to an inner expanded portion with several lateral processes. The expanded portion is called a **spherule** in a rod and a **pedicle** in a cone. Normally, many photoreceptor cells converge onto one bipolar cell and form interconnecting neural networks. Cones located in the fovea, however, synapse with a single bipolar cell. The fovea is also unique in that the compactness of the inner neural layers of the retina causes the photoreceptor cells to be oriented obliquely. Horizontal cell dendritic processes synapse with photoreceptor cells throughout the retina and further contribute to the elaborate neuronal connections in this layer.

The inner nuclear layer (6) consists of the nuclei of horizontal, amacrine, bipolar, interplexiform, and Müller cells.

Müller cells form the scaffolding for the entire retina. Their processes invest the other cells of the retina so completely that they fill most of the extracellular space. The basal and apical ends of Müller cells form the inner and outer limiting membranes, respectively. Microvilli extending from their apical border lie between the photoreceptor cells of the rods and cones. Capillaries from the retinal vessels extend only to this layer. The rods and cones carry out their metabolic exchanges with extracellular fluids transported across the blood–retina barrier of the RPE.

The four types of conducting cells—bipolar, horizontal, interplexiform, and amacrine—found in this layer have distinct orientations (see Fig. 24.9):

- **Bipolar cells** and their processes extend to both the inner and outer plexiform layers. In the peripheral regions of the retina, the axons of bipolar

cells pass to the inner plexiform layer where they synapse with several ganglion cells. Through these connections, the bipolar cells establish communication with multiple cells in each layer, except in the fovea, where they may synapse only with a single ganglion cell to provide greater visual acuity in this region.

- **Horizontal cells** and their processes extend to the outer plexiform layer where they intermingle with processes of bipolar cells. The cells have synaptic connections with rod spherules, cone pedicles, and bipolar cells. This electrical coupling of cells is thought to affect the functional threshold between rods and cones and bipolar cells.
- **Amacrine cells'** processes pass inward, contributing to a complex interconnection of cells. Their processes branch extensively to provide sites of synaptic connections with axonal endings of bipolar cells and dendrites of ganglion cells. Besides bipolar and ganglion cells, the amacrine cells synapse in the inner plexiform layer with interplexiform and other amacrine cells (see Fig. 24.9).
- **Interplexiform cells** and their processes have synapses in both inner and outer plexiform layers. These cells convey impulses from the inner plexiform to the outer plexiform layer.

The inner plexiform layer (7) consists of a complex array of intermingled neuronal cell processes.

The **inner plexiform layer** consists of synaptic connections between axons of the bipolar neurons and dendrites of ganglion cells. It also contains synapses between intermingling processes of amacrine cells and bipolar neurons, ganglion cells, and interplexiform neurons. The course of these processes is parallel to the inner limiting membrane, thus giving the appearance of horizontal striations to this layer (see Fig. 24.9).

The ganglion cell layer (8) consists of the cell bodies of large multipolar neurons.

The cell bodies of large **multipolar nerve cells**, measuring as much as 30 μm in diameter, constitute the ganglion cell layer. These nerve cells have lightly staining round nuclei with prominent nucleoli and Nissl bodies in their cytoplasm. An axonal process emerges from the rounded cell body, passes into the **nerve fiber layer**, and then enters **the optic nerve**. The dendrites extend from the opposite end of the cell to ramify in the inner plexiform layer. In the peripheral regions of the retina, a single ganglion cell may synapse with 100 bipolar cells. In marked contrast, in the macular region surrounding the fovea, the bipolar cells are smaller (some authors refer to them as *midget bipolar cells*), and they tend to make one-to-one connections with ganglion cells. Over most of the retina, the ganglion cells are only a single layer of cells. At the

macula, however, they are piled as many as eight deep, although they are absent over the fovea itself. Scattered among the ganglion cells are small neuroglial cells with densely staining nuclei (see Fig. 24.9).

The layer of optic nerve fibers (9) contains axons of the ganglion cells.

The axonal processes of the ganglion cells form a flattened layer running parallel to the retinal surface. This layer increases in depth as the axons converge at the **optic disc** (Fig. 24.15). The axons are thin, nonmyelinated processes measuring as much as 5 μm in diameter (see Fig. 24.9). The retinal vessels, including the superficial capillary network, are primarily located in this layer.

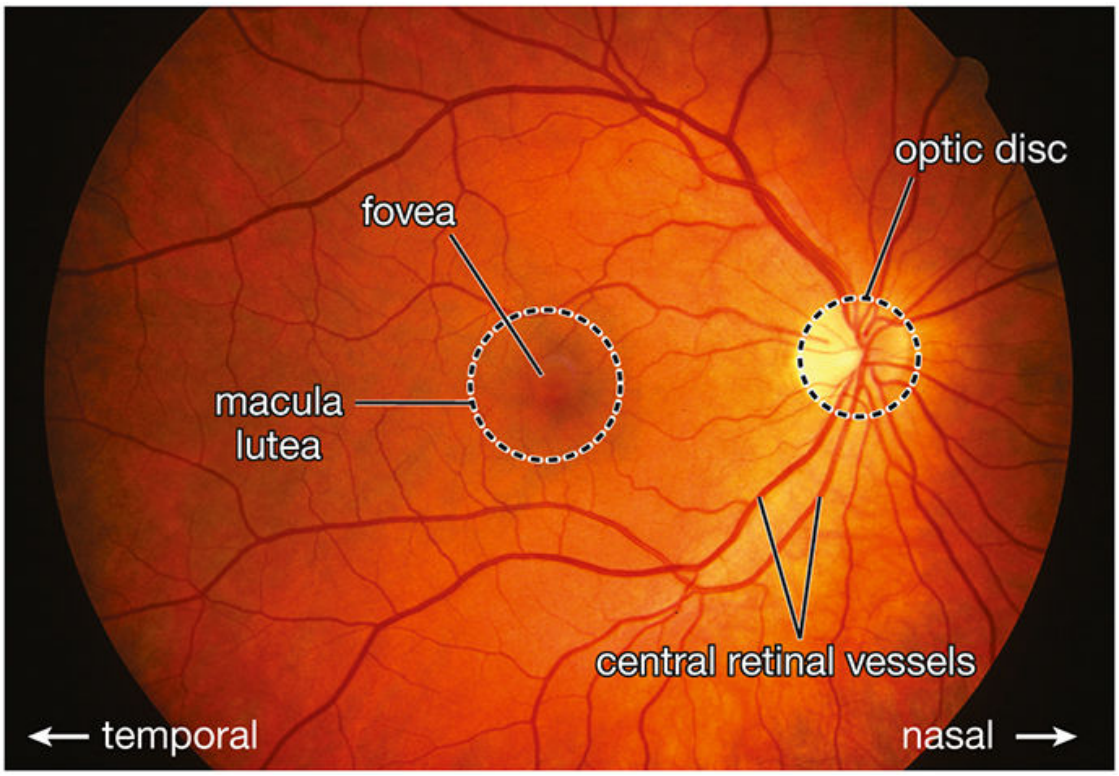


FIGURE 24.15. Normal view of the fundus in ophthalmoscopic examination of the right eye. The site where the axons converge to form the optic nerve is called the *optic disc*. Because the optic disc is devoid of photoreceptor cells, it is a blind spot in the visual field. From the center of the optic nerve (clinically called the *optic cup*), *central retinal vessels* emerge. The artery divides into upper and lower branches, each of which further divides into nasal and temporal branches (note the nasal and temporal directions on the image). Veins have a similar pattern of tributaries. Approximately 17 degree or 2.5 times optic disc diameters lateral to the disc, the slightly oval-shaped, blood vessel–free, and pigmented area represents the macula lutea. The *fovea centralis*, a shallow depression in the center of the *macula lutea*, is also visible.

(Courtesy of Dr. Renzo A. Zaldivar.) The inner limiting membrane (layer 10) consists of a basal lamina separating the retina from the vitreous body.

The **inner limiting membrane** forms the innermost boundary of the retina. It serves as the basal lamina of Müller cells (see Fig. 24.9). In younger individuals, reflections from the internal limiting membrane produce a **retinal sheen** that is seen during ophthalmoscopic examination of the eye. In older individuals, a semitranslucent sheet of cells and extracellular matrix can be formed on the inner surface of the retina in conjunction with the inner limiting membrane. This condition is called **epiretinal membrane (ERM)** or **macular pucker** and is responsible for variable clinical symptoms, including optical distortion and blurred vision. ERM is initially formed by cells from within the retina (RPE cells, Müller cells, and astrocytes) that begin proliferating and migrating onto the surface of the internal limiting membrane. Later, the membrane is infiltrated by macrophages, fibroblasts, and myofibroblasts. To prevent damage to the underlying retina, surgical removal of the ERM may be performed.

Specialized regions of the retina

The **fovea (fovea centralis)** appears as a small (1.5 mm in diameter), shallow depression located at the posterior pole of the visual axis of the eye. Its central region, known as the **foveola**, is about 200 μm in diameter (see Fig. 24.15). Except for the photoreceptor layer, most of the layers of the retina are markedly reduced or absent in this region (see Fig. 24.6). Here, the photoreceptor is composed entirely of cones (~4,000) that are longer and more slender and rod like than they are elsewhere. The fovea is the area of the retina specialized for the discrimination of details and color vision. The ratio between cones and ganglion cells is close to 1:1. Retinal vessels are absent in the fovea, allowing light to pass unobstructed into the cones' outer segments. The adjacent pigment epithelial cells and choriocapillaris are also thickened in this region.

The **macula lutea** is the area surrounding the fovea and is approximately 5.5 mm in diameter. It is yellowish because of the presence of yellow pigment (xanthophyll). The macula lutea contains approximately 17,000 cones and gains rods at its periphery. Retinal vessels are also absent in this region. Here, the retinal cells and their processes, especially the ganglion cells, are heaped up on the sides of the fovea so that light may pass unimpeded to this most sensitive area of the retina.

Vessels of the retina

The **central retinal artery** and **central retinal vein**, the vessels that can be seen and assessed with an ophthalmoscope, pass through the center of the

optic nerve to enter the bulb of the eye at the optic disc (see Fig. 24.2 and pages 982-983, the section on the development of the eye). The central retinal artery provides nutrients to the inner retinal layers. The artery branches immediately into the upper and lower branches, each of which divides again into nasal and temporal branches (see Fig. 24.15). Veins undergo a similar pattern of branching. The vessels initially lie between the vitreous body and the inner limiting membrane. As the vessels pass laterally, they also move deeper within the inner retinal layers. Branches from these vessels form a capillary plexus that reaches the inner nuclear layer and, therefore, provides nutrients to the inner retinal layers (layers 6–10; see pages 993-994). Nutrients to the remaining layers (layers 1–5) are provided by diffusion from the vascular choriocapillary layer of the choroid. The branches of the **central retinal artery** do not anastomose and, therefore, are classified as **anatomic end arteries**. Evaluation of the retinal vessels and appearance of the optic disc during ophthalmoscopy not only gives important information on the state of the eye but also may reveal early clinical signs of a number of conditions, including increased **intracranial pressure**, **hypertension**, **glaucoma**, and **diabetes**.

Crystalline Lens

Like the lens in a camera, the basic function of the eye lens is to transmit and focus light onto the retina.

The **lens** is a transparent, biconvex structure that has no vessels or nerves and is almost totally devoid of connective tissue, except for an enveloping capsule of basal lamina. It is suspended between the edges of the ciliary body by the **zonular fibers**. The pull of the zonular fibers keeps the lens in a flattened condition. Release of tension causes the lens to widen or **accommodate** to bend light rays originating close to the eye so that they focus on the retina.

The lens has three principal components (Fig. 24.16):

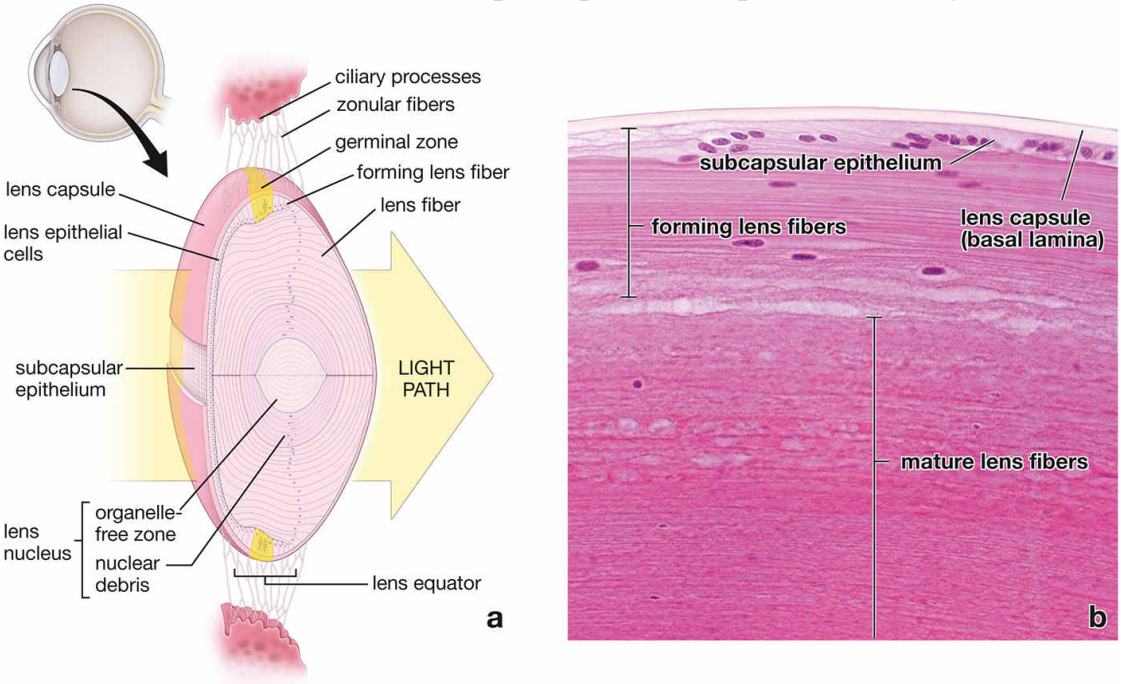


FIGURE 24.16. Structure of the lens. a. This schematic drawing of the lens suspended from ciliary processes by zonular fibers indicates its structural components. Note that the capsule of the lens is formed by the basal lamina of the lens fibers and the subcapsular epithelium located on the anterior surface of the lens. A strip of capsule was removed on this drawing to show underlying epithelium. Also note the location of the germinal zone (*yellow*) at the lens equator, where cells divide and differentiate into the lens fiber cells. The organelle-free center of the lens is occupied by the lens nucleus. **b.** This high-magnification photomicrograph of the germinal zone of the lens (near its equator) shows the active process of lens fiber formation from the *subcapsular epithelium*. Note the thick *lens capsule* and the underlying layer of nuclei of lens fibers during their differentiation. The *mature lens fibers* do not possess nuclei. ×570.

- The **lens capsule** is a thick basal lamina that surrounds the outer surface of the lens. It originates as the basal lamina of the embryonic lens vesicle. The anterior part of the capsule is thick, measuring approximately 10–20 μm, and is produced by the anterior lens cells. The posterior part of the capsule is much thinner, measuring approximately 5–10 μm. The lens capsule, composed primarily of type IV collagen and proteoglycans (i.e., laminin, entactin, perlecan), is elastic. It is thickest at the equator where the zonular fibers attach to it.
- The **subcapsular epithelium** is derived from the epithelial cells of the anterior part of the embryonic lens vesicle. It represents a single cuboidal layer of **lens epithelial cells** present only on the anterior surface of the lens. The epithelial cells of the posterior part of the vesicle elongate

anteriorly and form the **primary lens fibers** that fill the cavity of the optic vesicle.

- **Secondary lens fibers (lens fiber cells)** are formed at the periphery near the **lens equator**. Here, epithelial cells proliferate and migrate along the posterior lens capsule to differentiate into mature lens fiber cells. In the center of the lens, epithelial cells are quiescent. As lens fiber cells differentiate, they undergo massive elongation and lose all of their organelles, including nuclei, forming the **organelle-free zone**.

Gap junctions connect the cuboidal cells of the subcapsular epithelium. They have few cytoplasmic organelles and stain faintly. The apical region of the cell is directed toward the internal aspect of the lens and the **lens fibers**, with which they form **junctional complexes**. The lens increases in size during normal growth and then continues to produce new lens fibers at an ever-decreasing rate throughout life. The new lens fibers develop from the subcapsular epithelial cells located near the equator (see Fig. 24.16) are laid down peripherally as concentric lamellae in an onion-like arrangement. Cells in this region increase in height and then differentiate into lens fibers.

As the lens fibers develop, they become highly elongated and appear as thin, flattened structures. They lose their nuclei and other organelles as they become filled with proteins called **crystallins**. Mature lens fibers attain a length of 7–10 mm, a width of 8–10 μm, and a thickness of 2 μm. In the adult lens, only lens fibers in the outermost region maintain their nuclei and organelles. Near the center, in the **lens nucleus**, the fibers are compressed and condensed to such a degree that individual fibers are impossible to recognize. The lens nucleus is an organelle-free zone and is composed of primary lens fiber cells laid down during embryonic and fetal development. The lens fibers are joined at their apical and basal ends by specialized junctions called **sutures**. Despite its density and protein content, the lens is normally transparent (see Fig. 24.16). The high density of lens fibers makes it difficult to obtain routine histologic sections of the lens that are free from artifacts.

Changes in the lens are associated with aging.

With increasing age, the lens gradually loses its elasticity and ability to accommodate. This condition, called **presbyopia**, usually occurs in the fourth decade of life. It is easily corrected by wearing reading glasses or using a magnifying lens.

Loss of transparency of the lens or its capsule is also a relatively common condition associated with aging. This condition, called **cataract**, may be caused by conformational changes or cross-linking of proteins. The development of a cataract may also be related to disease processes, metabolic or hereditary conditions, trauma, or exposure to a

deleterious agent (such as ultraviolet radiation). Cataracts that significantly impair vision can usually be corrected surgically by removing the lens and replacing it with a plastic lens implanted in the posterior chamber.

Vitreous Body

The vitreous body is the transparent jelly-like substance that fills the vitreous chamber in the posterior segment of the eye.

The **vitreous body** is loosely attached to the surrounding structures, including the inner limiting membrane of the retina. The main portion of the vitreous body is a homogeneous gel containing approximately 99% water (the vitreous humor), collagen, glycosaminoglycans (principally hyaluronan), and a small population of cells called **hyalocytes**. These cells are believed to be responsible for the synthesis of collagen fibrils and glycosaminoglycans. Hyalocytes in routine H&E preparations are difficult to visualize. Often, they exhibit a well-developed rER and Golgi apparatus. Fibroblasts and tissue macrophages are sometimes seen in the periphery of the vitreous body. The **hyaloid canal** (or **Cloquet canal**), which is not always visible, runs through the center of the vitreous body from the optic disc to the posterior lens capsule. It is the remnant of the pathway of the hyaloid artery of the developing eye.

■ ACCESSORY STRUCTURES OF THE EYE

The primary functions of the eyelids are to cover, protect, and lubricate the eyes.

The **eyelids** represent folds of modified skin containing highly modified epidermal appendages to cover, protect, and lubricate the anterior portions of the eyes. The anterior surface of the eyelid is covered by thin **skin**, and its posterior surface is lined by a specialized mucous membrane, the **conjunctiva**. The skin of the eyelids is loose and elastic to accommodate their movement. Within each eyelid is a flexible support, the **tarsal plate**, consisting of dense fibrous and elastic tissue. In the upper eyelid, the lower free edge of the tarsal plate extends to the lid margin, and its superior border serves for the attachment of smooth muscle fibers of the **superior tarsal muscle (of Müller)**. The undersurface of the tarsal plate is covered by the conjunctiva (Fig. 24.17). The striated **orbicularis oculi muscle**, a facial expression muscle, forms a thin oval sheet of circularly oriented skeletal muscle fibers overlying the tarsal plate. In addition, the connective tissue of the upper eyelid contains tendon fibers of the **levator palpebrae superioris muscle** that open the eyelid (see Fig. 24.17). A mucocutaneous junction

between eyelid skin and conjunctiva occurs near the lid margin. The **eyelashes** emerge from the most anterior edge of the lid margin. They are short, stiff, curved hairs and may occur in double or triple rows. The lashes on the same eyelid margin may have different lengths and diameters.

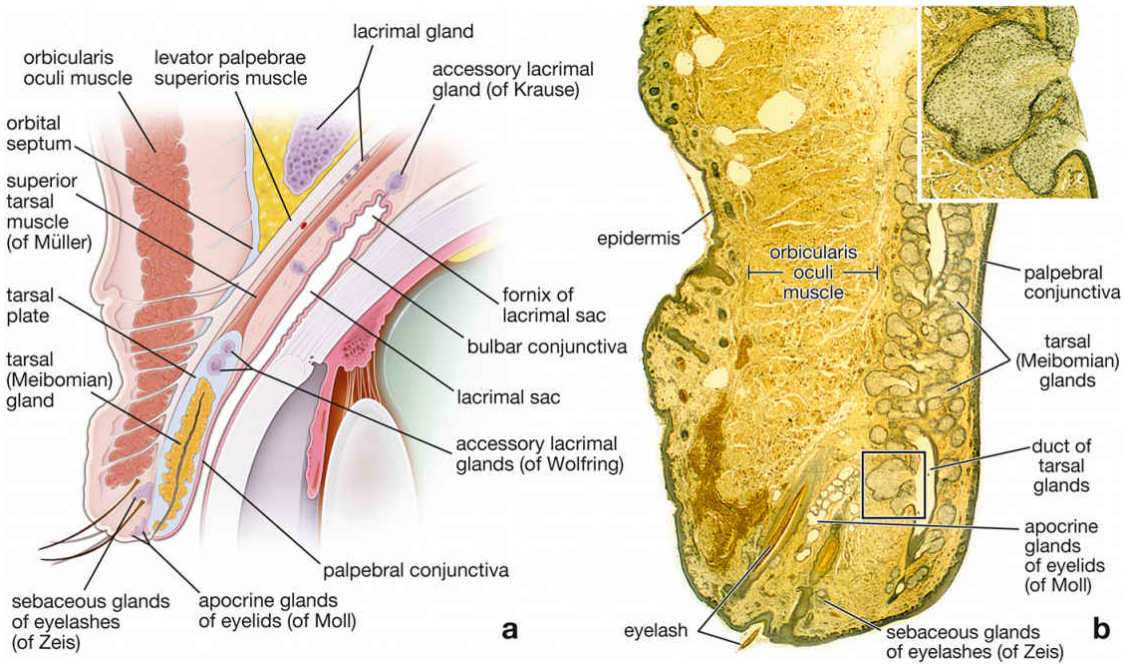


FIGURE 24.17. Structure of the eyelid. a. This schematic drawing of the eyelid shows the skin, associated skin appendages, muscles, tendons, connective tissue, and conjunctiva. Note the distribution of multiple small glands associated with the eyelid and observe the reflection of the palpebral conjunctiva in the fornix of the lacrimal sac to become the bulbar conjunctiva. **b.** Photomicrograph of a sagittal section of the eyelid stained with picric acid for better visualization of epithelial components of the skin and the numerous glands. In this preparation, muscle tissue (i.e., *orbicularis oculi muscle*) stains *yellow*, and the epithelial cells of the skin, conjunctiva, and glandular epithelium are *green*. Note the presence of numerous glands within the eyelid. The *tarsal (Meibomian) gland* is the largest gland, and it is located within the dense connective tissue of the tarsal plates. This sebaceous gland secretes into ducts opening onto the eyelids. ×20. **Inset.** Higher magnification of a tarsal gland from the *boxed area* showing the typical structure of a holocrine gland. ×60.

The conjunctiva lines the space between the inner surface of the eyelids and the anterior surface of the eye without covering the cornea.

The **conjunctiva** is a thin, transparent mucous membrane that extends from the corneoscleral limbus located on the peripheral margin of the cornea across the sclera (**bulbar conjunctiva**) and covers the internal surface of the eyelids (**palpebral conjunctiva**). The palpebral conjunctiva merges with the bulbar

conjunctiva at the fornices of the conjunctival sac; this part is called the **forniceal conjunctiva** (Fig. 24.18). Bulbar, palpebral, and forniceal conjunctiva form a conjunctival sac, a space between the eyelid and eyeball that opens anteriorly at the palpebral fissure. The conjunctival sac can hold fluid up to 30 μL. Because a standard eyedropper dispenses about 50 μL of suspended medicine per drop, one drop is more than enough to overfill the conjunctival sac.

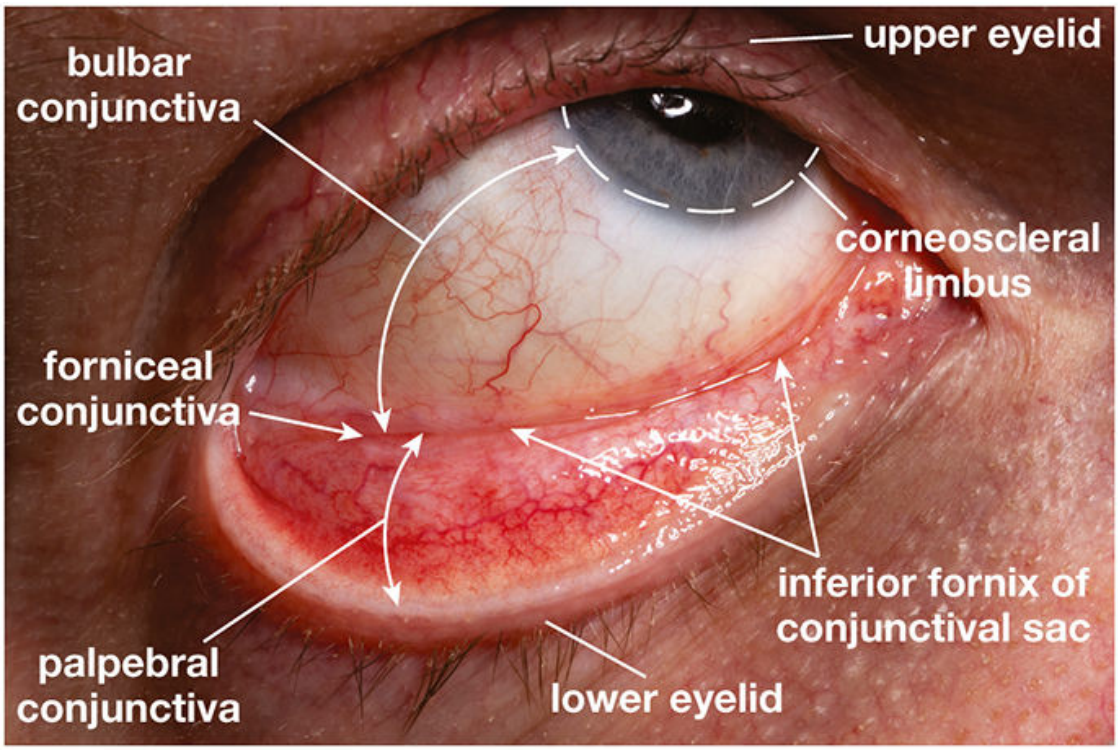


FIGURE 24.18. Conjunctiva and conjunctival sac. This photograph of the lower part of the eyeball with a reflected lower eyelid shows different regions of the conjunctiva that line the conjunctival sac. The area shown is located between the inner surface of the eyelid and the anterior surface of the eye. The bulbar conjunctiva extends from the corneoscleral limbus covering the sclera of the eye (it does not cover the cornea) to its reflections onto the internal surface of the eyelid, at which point it is called the *palpebral conjunctiva*. This photograph shows the inferior point of reflection onto the lower eyelid (called the *inferior fornix* of the conjunctival sac). The conjunctiva in these regions is recognized as the forniceal conjunctiva.

The conjunctiva consists of a **stratified columnar epithelium** containing numerous **goblet cells** and rests on a lamina propria composed of loose connective tissue. The goblet cells secrete a component of the tears that bathe the eye. Melanocytes are present in the basal epithelial layer and, like melanocytes in the skin, transfer melanosomes into neighboring epithelial cells. Accumulation of diffuse lymphatic tissue is evident, especially deep to

the forniceal conjunctiva (Fig. 24.19). These specialized collections of T and B lymphocytes underlying the conjunctiva are called **conjunctiva-associated lymphatic tissue (CALT)** (Fig. 24.20). It functions to recognize and process antigens and trigger an appropriate immune response against the microbial invasion of the ocular surface. The conjunctiva is supplied with blood by the branches of arteries of the eyelid (marginal tarsal arcades) and from the eyeball (anterior ciliary arteries). The conjunctiva receives sensory innervation from the branches of the trigeminal nerve. **Conjunctivitis**, an inflammation of the conjunctiva, commonly called **pinkeye**, is characterized by redness, irritation, and watering of the eyes. For more clinical information about this condition, see Folder 24.6.

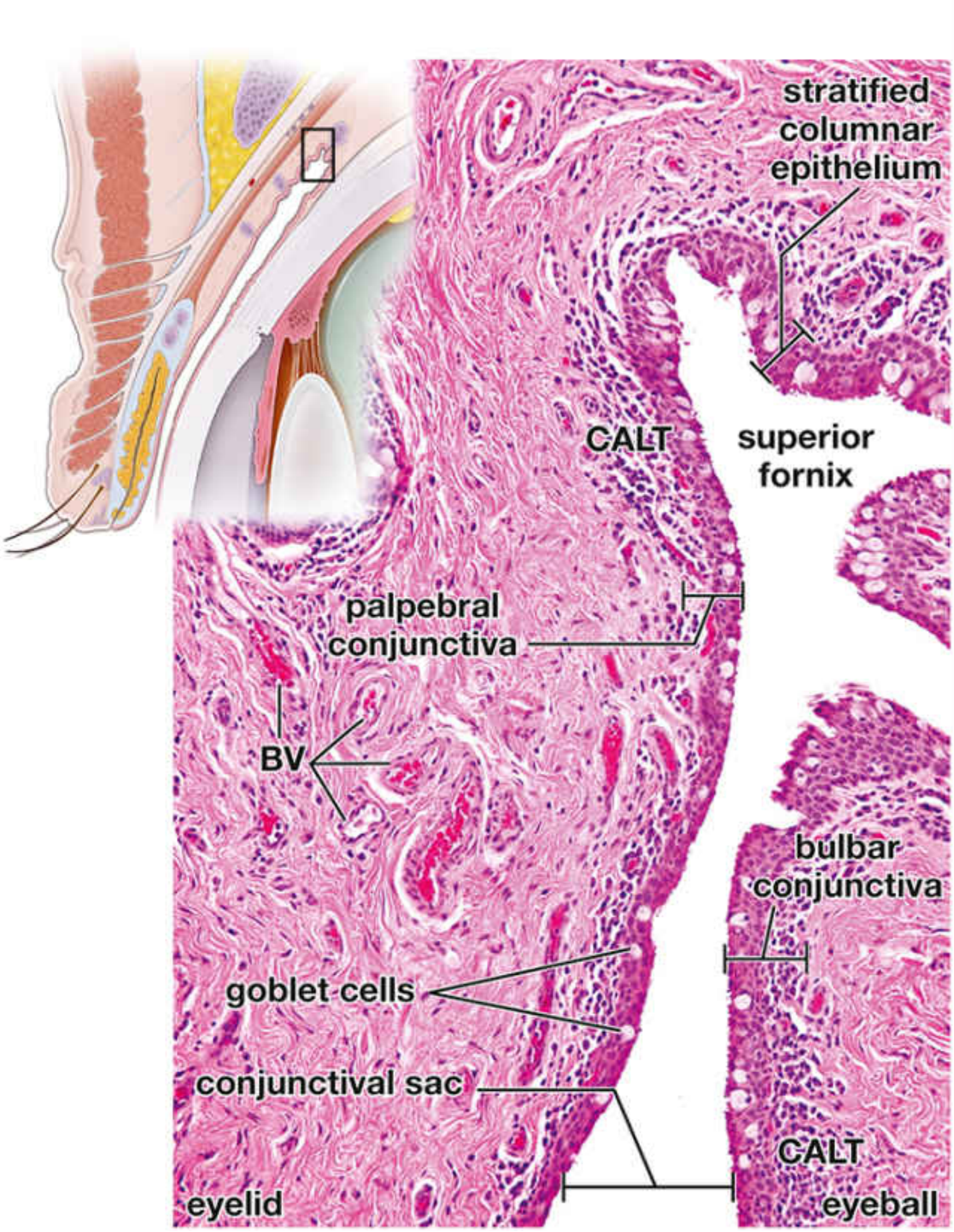


FIGURE 24.19. Superior fornix of the conjunctival sac. This low-magnification hematoxylin and eosin (H&E)-stained specimen was obtained from the superior fornix of the conjunctival sac as indicated by the *rectangle* in the inset. The palpebral conjunctiva lines the inner surface of the eyelid, and in the superior fornix of the conjunctival sac, it reflects onto the eyeball (bulbar conjunctiva). This reflection is identified as the forniceal conjunctiva and is composed of stratified columnar epithelium containing numerous goblet cells. Accumulations of lymphatic tissue called *conjunctiva-associated lymphatic tissue* (*CALT*) are clearly visible. There are numerous blood vessels (*BV*) underlying the palpebral conjunctiva. ×120. (Courtesy of Dr. Nick Mamalis,

University of Utah, Moran Clinical Ophthalmology Resource for Education [CORE], Salt Lake City, Utah.)

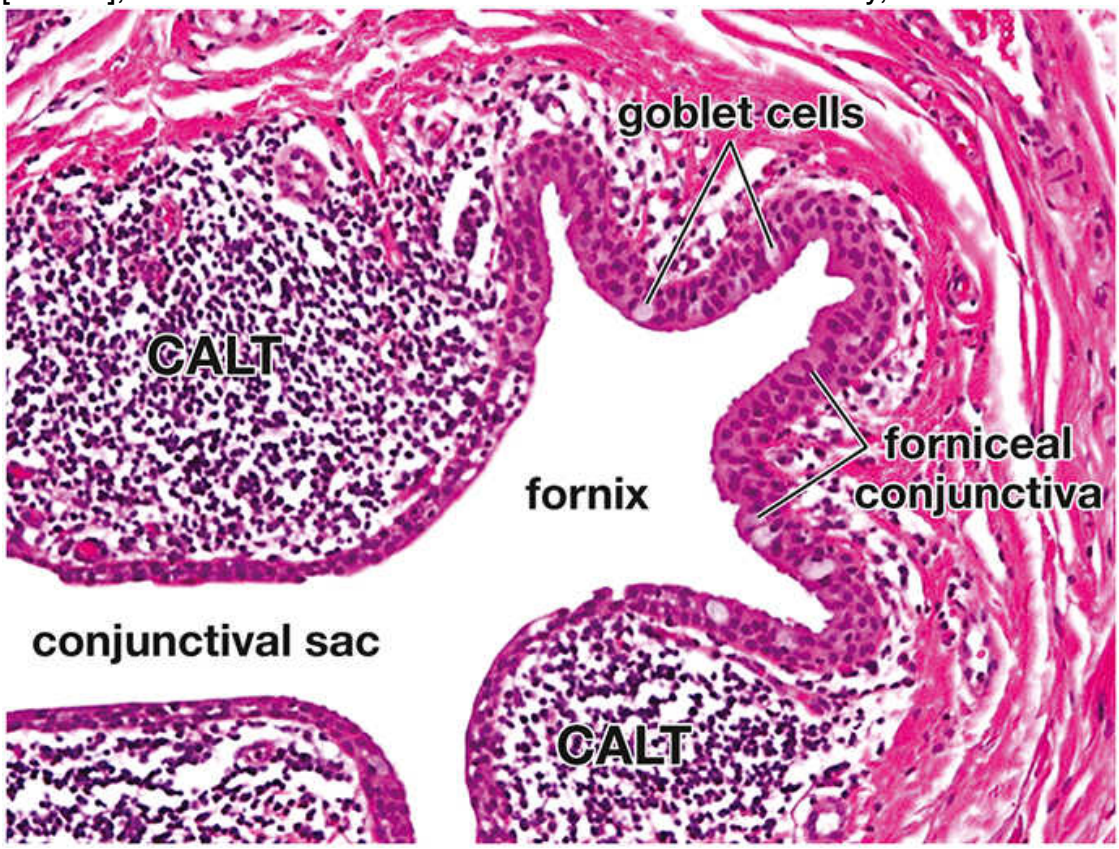


FIGURE 24.20. Forniceal conjunctiva. This high-magnification hematoxylin and eosin (H&E)-stained specimen shows the fornix of the conjunctival sac. The forniceal conjunctiva shows a typical pattern of the stratified columnar epithelium containing goblet cells that rests on a lamina propria composed of loose connective tissue. The stratified columnar epithelium farther away from the fornix may change into columnar stratified or squamous stratified nonkeratinized epithelium (*lower right corner of conjunctival sac*). Note the accumulations of diffuse lymphatic tissue deep into the conjunctiva known as *conjunctiva-associated lymphatic tissue* (*CALT*). ×220. (Courtesy of Dr. Nick Mamalis, University of Utah, Moran Clinical Ophthalmology Resource for Education [CORE], Salt Lake City, Utah.) FOLDER 24.6

CLINICAL CORRELATION: CONJUNCTIVITIS

Conjunctivitis, otherwise known as pinkeye, is an inflammation of the conjunctiva. It may be localized in either the palpebral conjunctiva or the bulbar conjunctiva. Individuals may present with relatively nonspecific symptoms and signs that include redness, irritation, and watery discharge from the eye (Fig. F24.6.1). The symptoms can also mimic a foreign-body sensation. Extended use of contact lenses can cause allergic or bacterial conjunctivitis and may be the first sign of more serious ocular disease (i.e., corneal ulcer). In general, symptoms that last <4 weeks are classified as

acute conjunctivitis, and those extending for a longer period are referred to as **chronic conjunctivitis**.

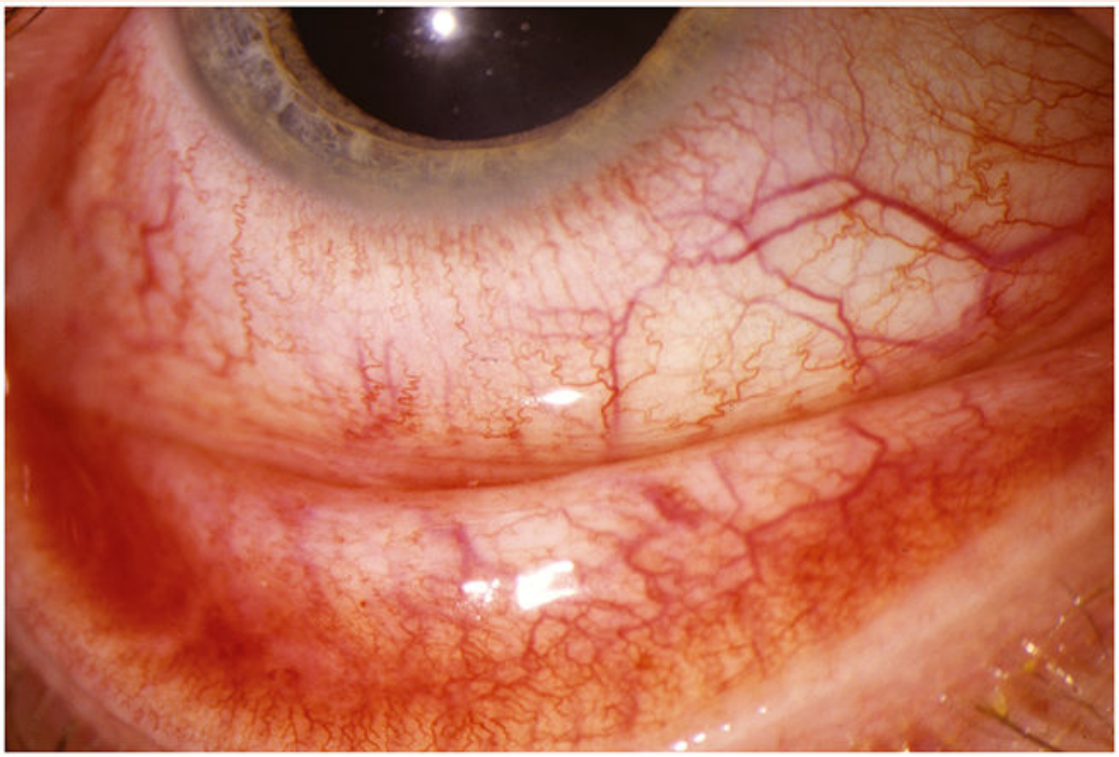


FIGURE F24.6.1. Conjunctivitis. This photograph of the lower part of the eyeball with reflected lower eyelid shows an infected conjunctiva. The enlarged blood vessels of the conjunctiva are responsible for moderate redness of the eye with conjunctival swelling. Moderately, clear (in allergic conjunctivitis) or purulent (in bacterial conjunctivitis) discharge is visible. (Courtesy of Dr. Renzo A. Zaldivar.) Acute conjunctivitis is most commonly caused by bacteria; a variety of viruses, including HIV, varicella-zoster virus (VZV), and herpes simplex virus (HSV); or allergic reactions. Bacterial conjunctivitis often causes an opaque purulent discharge containing white cells and desquamated epithelial cells. On eye examination, the purulent discharge and conjunctival papillae help differentiate between bacterial and viral etiology. Viral conjunctivitis is most common in adults. Clinically, it presents as a diffuse pinkness of the conjunctiva with particularly numerous lymphoid follicles on the palpebral conjunctiva, often accompanied by enlarged preauricular lymph nodes. Viral conjunctivitis is very contagious and usually associated with a recent upper respiratory infection. Patients need to be advised to avoid touching their eyes, to wash their hands frequently, and to avoid sharing towels and washcloths.

Bacterial conjunctivitis is usually treated with antibiotic eye drops or ointments. For viral conjunctivitis, no antimicrobial therapy is needed. However, conservative management with artificial tears to keep the eye lubricated may relieve symptoms. For severe cases, topical corticosteroid drops may be prescribed to reduce the discomfort of inflammation. However, prolonged use of corticosteroid drops increases the risk of side effects. Antibiotic drops may also be used for the treatment of secondary

infections. Viral conjunctivitis usually resolves within 3 weeks. However, in the worst cases, it may take more than a month.

Secretions from modified glands in the eyelid provide additional protection to the eye.

In addition to eccrine sweat glands, which discharge their secretions directly onto the skin, the eyelid contains four other major types of glands (see Fig. 24.17):

- The **tarsal glands (Meibomian glands)**, long sebaceous glands embedded in the tarsal plates, appear as vertical yellow streaks in the tissue deep into the conjunctiva. Their elongated ducts open at the lid margin behind rows of eyelashes. About 25 tarsal glands are present in the upper eyelid, and 20 are present in the lower eyelid. The sebaceous secretion of the tarsal glands produces an oily layer on the surface of the tear film that retards the evaporation of the normal tear layer. Blockage of the tarsal gland secretion leads to **chalazion** (tarsal gland lipogranuloma), an inflammation of the tarsal gland. It presents as a painless cyst usually on the upper eyelid that disappears after a few months without therapeutic intervention.
- **Sebaceous glands of eyelashes (glands of Zeis)** are small, modified sebaceous glands that are connected with and empty their secretion into the follicles of the eyelashes. Bacterial infection of these sebaceous glands causes a **stye** (also called a **hordeolum**), a painful tenderness and redness of the affected area of the eyelid.
- **Apocrine glands of eyelashes (glands of Moll)** are small sweat glands with unbranched sinuous tubules that begin as a simple spiral.
- **Accessory lacrimal glands** are compound serous tubuloalveolar glands that have distended lumina. They are located on the inner surface of the upper eyelids (**glands of Wolfring**) and in the fornix of the conjunctival sac (**glands of Krause**).

All glands of the human eyelid are innervated by neurons of the autonomic nervous system, and their secretion is synchronized with the lacrimal glands by a common neurotransmitter, vasoactive intestinal polypeptide (VIP).

The lacrimal gland produces tears that moisten the cornea and flow to the nasolacrimal duct.

Tears are produced by the **lacrimal glands** and, to a lesser degree, by the accessory lacrimal glands. The lacrimal gland is located beneath the conjunctiva on the upper lateral side of the orbit (Fig. 24.21). The lacrimal gland consists of several separate lobules of tubuloacinar serous glands. The

acini have large lumina lined with columnar cells. Myoepithelial cells, located below the epithelial cells within the basal lamina, aid in the release of tears (Fig. 24.22). Approximately 12 ducts drain from the lacrimal gland into the reflection of conjunctiva just beneath the upper eyelid, known as the **fornix of the conjunctival sac**.

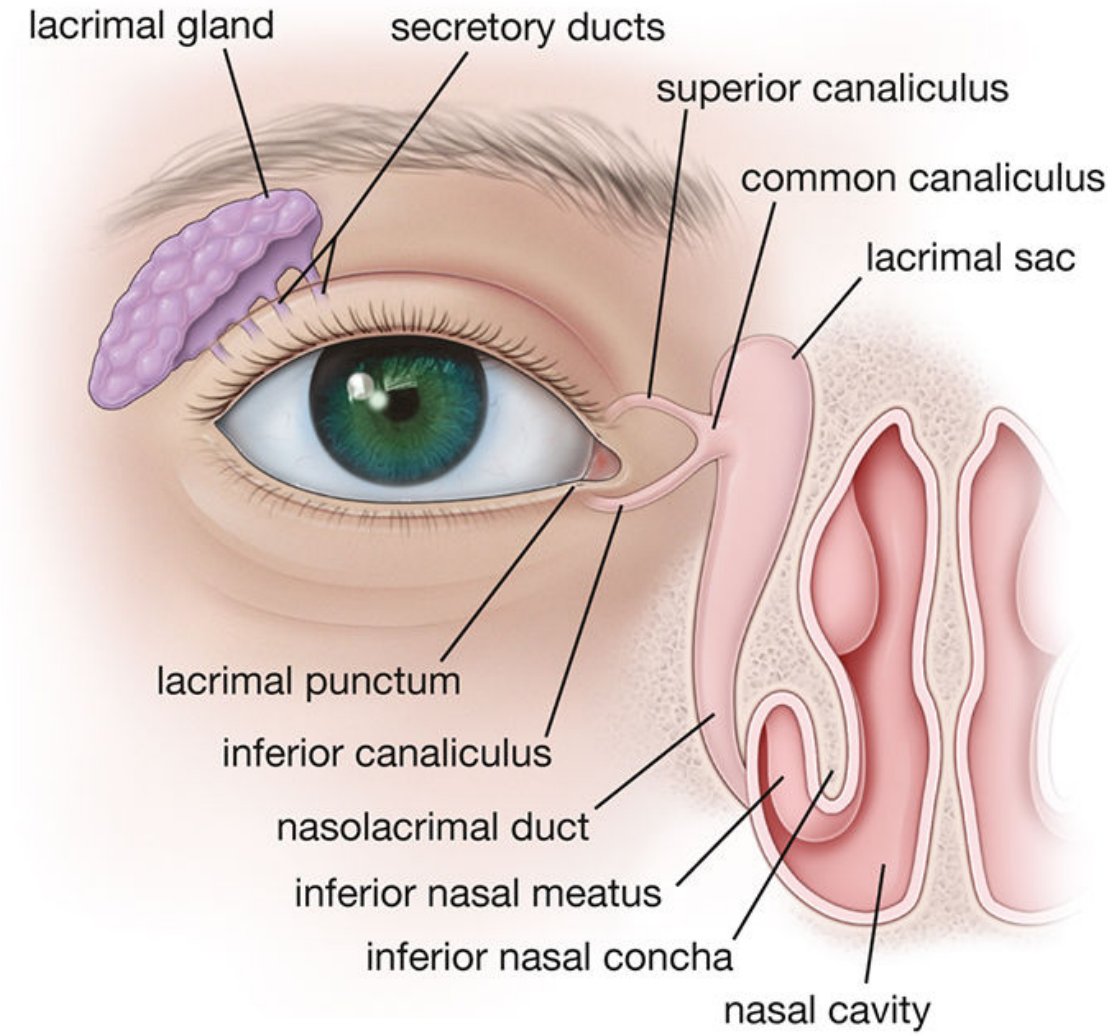


FIGURE 24.21. Schematic diagram of the eye and lacrimal apparatus. This drawing shows the location of the lacrimal gland and components of the lacrimal apparatus, which drains the lacrimal fluid into the nasal cavity.

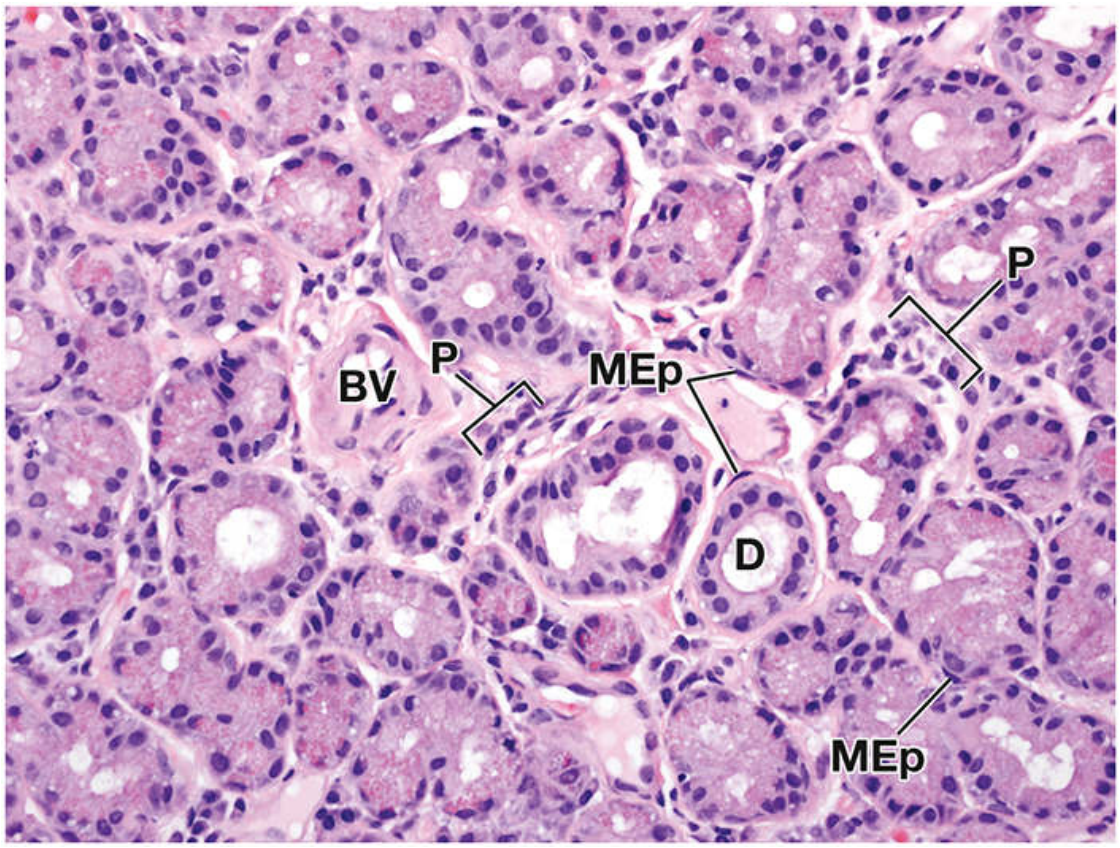


FIGURE 24.22. Photomicrograph of lacrimal gland. The lacrimal gland consists of tubuloacinar serous secretory units. The acini are lined with serous secretory columnar cells. Myoepithelial cells (*MEp*) are present below the epithelial cells within the basal lamina. Cytoplasm of the secretory cells contains small lipid droplets and mucin-containing granules. Intralobular ducts (*D*) lined by serous cells also contain myoepithelial cells. Occasional plasma cells (*P*) and lymphocytes are present between acini of the lacrimal gland. *BV*, blood vessels. ×450.

Tears drain from the eye through **lacrimal puncta**, the small openings of the **lacrimal canaliculi**, located at the medial angle. The upper and lower canaliculi join to form the **common canaliculus**, which opens into the lacrimal sac. The sac is continuous with the **nasolacrimal duct**, which opens into the nasal cavity below the inferior nasal conchae. A pseudostratified ciliated epithelium lines the lacrimal sac and the nasolacrimal duct. **Dacryocystitis** is an inflammation of the lacrimal sac that is frequently caused by an obstruction of the nasolacrimal duct. It can be acute, chronic, or congenital. It usually affects older individuals and is most often secondary to stenosis (narrowing) of the lacrimal canaliculi.

Tears protect the corneal epithelium and contain antibacterial and UV-protective agents.

Tears keep the conjunctiva and corneal epithelium moist and wash foreign material from the eye as they flow across the corneal surface toward the medial angle of the eye (see Fig. 24.21). The thin film of tears covering the corneal surface is not homogeneous but a mixture of products secreted by the lacrimal glands, the accessory lacrimal glands, the goblet cells of the conjunctiva, and the tarsal glands of the eyelid. The tear film contains proteins (tear albumins and lactoferrin), enzymes (lysozyme), lipids, metabolites, electrolytes, and medications, the latter secreted during therapy.

The tear cationic protein lactoferrin increases the activity of various natural antimicrobial agents, such as lysozyme.

The eye is moved within the orbit by coordinated contraction of extraocular muscles.

Six muscles of the eyeball (also called **extraocular** or **extrinsic muscles**) attach to each eye. These are the medial, lateral, superior, and inferior rectus muscles and the superior and inferior oblique muscles. The superior oblique muscle is innervated by the trochlear nerve (cranial nerve IV). The lateral rectus muscle is innervated by the abducens nerve (cranial nerve VI). All of the remaining extraocular muscles are innervated by the oculomotor nerve (cranial nerve III). The combined, precisely controlled action of these muscles allows vertical, lateral, and rotational movement of the eye. Normally, the actions of the muscles of both eyes are coordinated so that the eyes move in parallel (called **conjugate gaze**).

EYE

OVERVIEW OF THE EYE

- The **eye** is a paired, specialized sensory organ that provides the sense of sight.
- The tissues of the eye are derived from **neuroectoderm** (retina), **surface ectoderm** (lens, corneal epithelium), and **mesoderm** (sclera, corneal stroma, vascular coat).
- The eyeball is composed of three structural layers: the outer **corneoscleral (fibrous) coat** consisting of the transparent cornea and

the opaque white sclera; the middle **vascular coat** consisting of the choroid, ciliary body, and iris; and the inner layer, the **retina**.

- The layers of the eye and the lens serve as boundaries for three chambers: the **anterior chamber** and **posterior chamber**, which are filled with **aqueous humor**, and the **vitreous chamber**, which is occupied by a transparent gel, the **vitreous body**.
- **Aqueous humor** is secreted by the ciliary processes into the posterior chamber. From there it flows through the pupil into the anterior chamber, where it drains inside the **iridocorneal angle** to the **scleral venous sinus (canal of Schlemm)**.

COATS IN THE WALL OF THE EYE

- The **cornea** is transparent and consists of five layers (beginning from the anterior surface): **corneal epithelium** (nonkeratinized stratified squamous epithelium), **Bowman membrane** (anterior basement membrane for corneal epithelium), a thick avascular **corneal stroma**, **Descemet membrane** (posterior basement membrane for corneal endothelium), and **corneal endothelium**.
- The **sclera** is opaque and consists predominantly of dense connective tissue. It communicates with the cornea at the **corneoscleral limbus**, which contains **corneolimbal stem cells**.
- The **iris** arises from the ciliary body, and the diameter of its opening (**pupil**) is controlled by smooth muscle fibers of the **sphincter pupillae muscle** and the myoepithelial cell layer of the **dilator pupillae muscle**. Its posterior surface is covered by pigment epithelium and contains a stroma that is abundant with melanocytes.
- The **ciliary body** is located between the iris and the choroid. It contains **ciliary processes** that secrete aqueous humor, anchors **zonular fibers** that suspend the lens, and contains **ciliary muscle** that alters the shape of the lens during **lens accommodation**.
- The **lens** is a transparent, avascular, biconvex structure that is suspended between the edges of the ciliary body. It consists of a **lens capsule**, **subcapsular epithelium**, and **lens fiber cells**.
- The **choroid** is part of the vascular coat and has an inner **choriocapillary layer** containing blood vessels that provide nutrients to the retina and an outer **Bruch membrane** that serves as the basal lamina for both the endothelial and RPE cells.
- The **retina** is derived from the inner and outer layers of the optic cup. It consists of two basic layers: the **neural retina** is the inner layer containing photoreceptor cells, and the **retinal pigment epithelium (RPE)** is the outer layer that attaches to the choroid.

RETINA

- The **retina** contains 10 layers of cells and their processes. Major cells in the retina include **photoreceptors** (rods and cones), **conducting neurons** (bipolar neurons and ganglion cells), **association neurons**, and **supporting cells** (e.g., Müller cells).
- **Retinal pigment epithelium** (layer 1) is the outermost layer of the retina and **absorbs scattered light**, contributes to the **blood–retina barrier, restores photosensitivity** to visual pigments, and **phagocytoses membranous discs** from the rods and cones.
- **Rods** (layer 2) are most numerous (120 million) in the retina and detect light intensity with their cylindrical outer segments. **Cones** (layer 2) are less numerous (7 million) and, with their conical outer segment, detect three different wavelengths of light corresponding to the primary colors: blue, green, and red.
- Rods contain the visual pigment **rhodopsin** that consists of **opsin** and a small light-absorbing compound, **retinal**. Cone cells contain the visual pigment **iodopsin**.
- Conversion of light into nerve impulses in the photoreceptors is called **visual processing**. It involves a photochemical reaction based on the conversion of **11-cis-retinal** into **all-trans-retinal** in the rhodopsin. This results in the activation of opsin, which, in turn, activates G-protein and initiates hyperpolarization of the photoreceptor cell membrane that is detected by the bipolar neurons as a nerve impulse.
- The **outer limiting membrane** (layer 3) is formed by a row of zonulae adherentes between Müller cells.
- The **outer nuclear layer** (layer 4) contains the nuclei of rods and cones, and the **outer plexiform layer** (layer 5) contains their processes, which synapse with the horizontal, amacrine, and bipolar cells (the nuclei of which reside in the **inner nuclear layer** [layer 6]).
- Axons from cells in the outer plexiform layer synapse in the **inner plexiform layer** (layer 7) with ganglion cells, the cell bodies of which reside in the **ganglion cell layer** (layer 8). These cells send axons to the **layer of optic nerve fibers** (layer 9), which forms the optic nerve.
- The **inner limiting membrane** (layer 10) consists of a basal lamina separating the retina from the vitreous body.

ACCESSORY STRUCTURES OF THE EYE

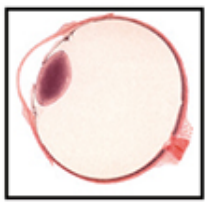
- The **eyelids** consist of skin, tarsal plates, part of the **orbicularis oculi muscle**, tendon fibers of the **levator palpebrae superioris muscle** (in the upper eyelid), and the palpebral conjunctiva.

- The **conjunctiva** consists of **stratified columnar epithelium** with **goblet cells**. It lines the space between the inner surface of the eyelid and the anterior surface of the eye lateral to the cornea.
- A diffuse lymphatic tissue called **conjunctiva-associated lymphatic tissue (CALT)** is underlying conjunctiva at the superior and inferior fornices of the conjunctival sac.
- The **tarsal glands (Meibomian glands)** are long sebaceous glands embedded in the tarsal plates of the upper and lower eyelids.
- The **lacrimal gland** produces tears that moisten the cornea and flow to the nasolacrimal duct and into the nasal cavity.

PLATE 24.1 ■ EYE I

The human **eye** is a complex sensory organ that provides sight. The wall of the eye consists of **three concentric layers or coats**: the **retina**, the inner layer; the **uvea**, the middle or vascular layer; and the **corneosclera**, the outer fibrous layer. The eye is often compared to a simple camera with a lens to capture and focus light, a diaphragm to regulate the amount of light, and film to record the image. In the eye, the **cornea** and **lens** concentrate and focus light on the **retina**. The **iris**, located between the cornea and lens, regulates the size of the pupil through which light enters the eye. **Photoreceptor cells (rods and cones)** in the retina detect the intensity (rods) and color (cones) of the light that reaches them and encode the various parameters for transmission to the brain via the optic nerve (cranial nerve II).

The eye measures 25 mm in diameter. It is suspended in the bony orbit by six extrinsic striated muscles that control its movement. The extraocular muscles are coordinated so that both eyes move synchronously, with each moving symmetrically around its own central axis. A thick layer of adipose tissue partially surrounds and cushions the eye as it moves within the orbit.



Modified drawing of human eye, meridional perspective by E. Sobotta.

The innermost layer is the **retina** (*R*), which consists of several layers of cells. Among these are receptor cells (rods and cones), neurons (e.g., bipolar and ganglion cells), supporting cells, and a pigment epithelium (see Plate 24.2, page 1012). The receptor components of the retina are situated in the posterior three-fifths of the eyeball. At the anterior boundary of the receptor layer, the **ora serrata** (*OS*), the retina becomes reduced in thickness, and nonreceptor components of the retina continue forward to cover the posterior or inner surface of the **ciliary body** (*CB*) and the **iris** (*I*). This anterior nonreceptor extension

of the inner layer is highly pigmented, and the pigment (melanin) is evident as the black inner border of these structures.

The **uvea**, the middle layer of the eyeball, consists of the choroid, the ciliary body, and the iris. The choroid is a vascular layer; it is relatively thin and difficult to distinguish in the accompanying figure, except by location. On this basis, the **choroid** (*Ch*) is identified as being just external to the pigmented layer of the retina. It is also highly pigmented; the choroidal pigment is evident as a discrete layer in several parts of the section.

Anterior to the ora serrata, the uvea is thickened; here, it is called the ciliary body (*CB*). This contains the ciliary muscle (see Plate 24.3, page 1014), which brings about adjustments of the lens to focus light. The ciliary body also contains processes to which the zonular fibers are attached. These fibers function as suspensory ligaments of the lens (*L*). The iris (*I*) is the most anterior component of the uvea and contains a central opening, the pupil.

The outermost layer of the eyeball, the **fibrous layer**, consists of the **sclera** (*S*) and the **cornea** (*C*). Both of these contain collagenous fibers as their main structural element; however, the cornea is transparent, and the sclera is opaque. The extrinsic muscles of the eye insert into the sclera and affect the movements of the eyeball. These are not included in the preparation, except for two small pieces of a muscle insertion (*arrows*) in the *lower left* and *top center* of the illustration. Posteriorly, the sclera is pierced by the emerging **optic nerve** (*ON*). A deep depression in the neural retina lateral to the optic nerve (above the *ON* in this figure) is the fovea centralis (*FC*), the thinnest and most sensitive portion of the neural retina.

The lens is considered in Plate 24.4 (page 1016). Just posterior to the lens is the large cavity of the eye, the **vitreous cavity** (*V*), which is filled with a thick jelly-like material, the vitreous humor or body. Anterior to the lens are two additional, fluid-filled chambers of the eye, the **anterior chamber** (*AC*) and the **posterior chamber** (*PC*), separated by the iris.

AC, anterior chamber **C,** cornea
CB, ciliary body
Ch, choroid
FC, fovea centralis **I,** iris
L, lens
ON, optic nerve
OS, ora serrate
PC, posterior chamber **R,** retina
S, sclera
V, vitreous cavity
arrows, muscle insertions

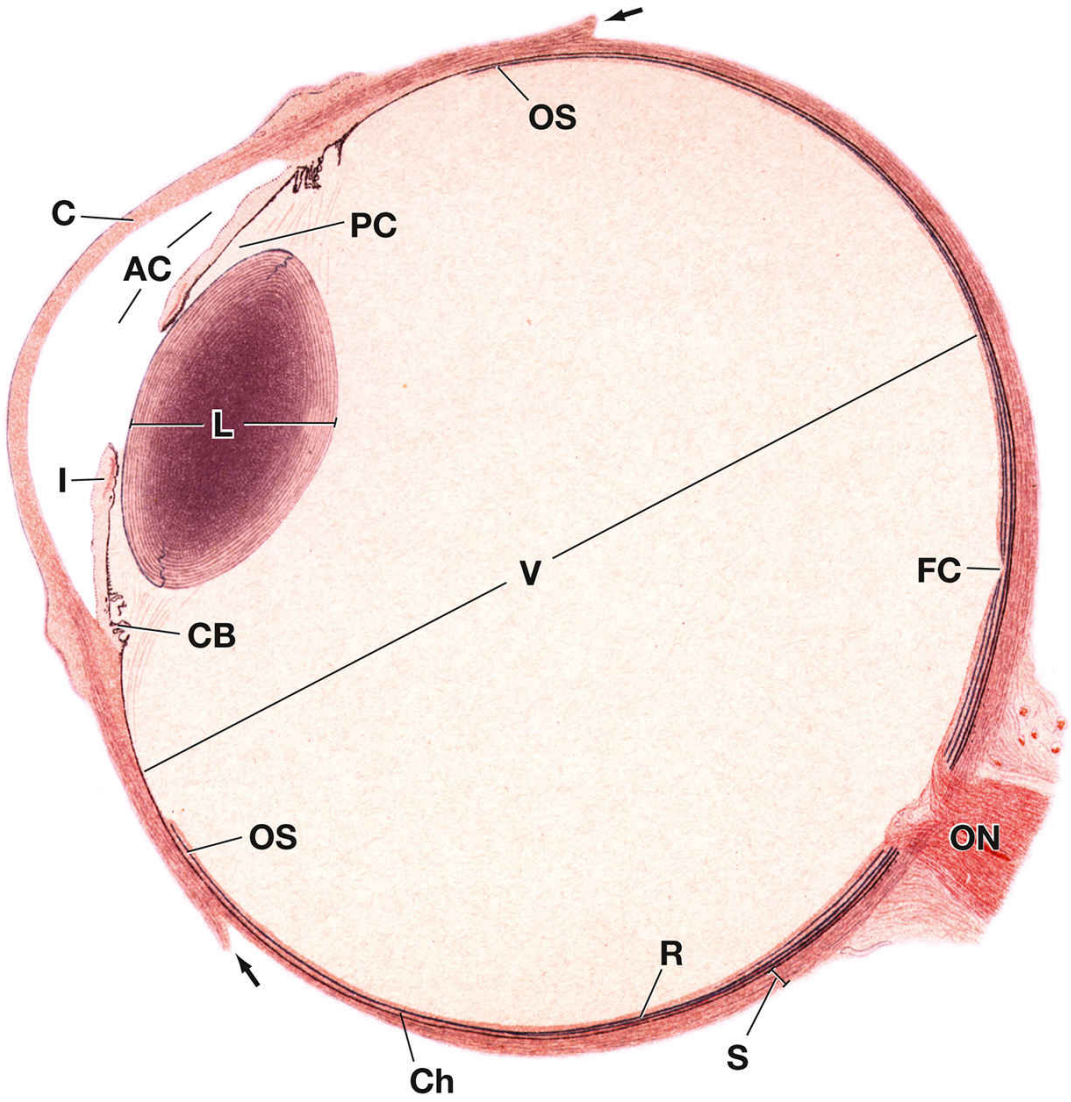


PLATE 24.2 ■ EYE II: RETINA

The **retina** and **optic nerve** are projections of the forebrain. The fibrous cover of the optic nerve is an extension of the meninges of the brain. The neural retina is a multilayered structure consisting of photoreceptors (rods and cones); neurons, some of which are specialized as conducting and associating neurons; and supporting cells (**Müller cells**). External to the neural retina is a layer of simple columnar **retinal pigment epithelium (RPE)**. The Müller cells are comparable to neuroglia in the rest of the central nervous system. Processes of Müller cells ramify virtually through the entire thickness of the retina. The internal limiting membrane is the basal lamina of these cells; the external limiting membrane is actually a line formed by the junctional complexes between processes of these cells and the **photoreceptor cells**.

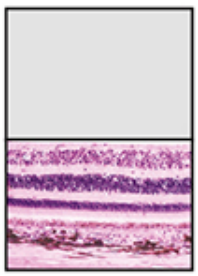
The neurons of the retina are arranged sequentially in three layers: (1) a deep layer of rods and cones; (2) an intermediate layer of **bipolar**, **horizontal**, and **amacrine** cells; and (3) a superficial layer of **ganglion** cells. Nerve impulses originating in the rods and cones are transmitted to the intermediate layer and then to the ganglion cells. Synaptic connections occur in the **outer plexiform**

layer (between the rods and cones and the intermediate neuronal layer) and the **inner plexiform layer** (between the intermediate layer and the ganglion cells), resulting in summation and neuronal integration. Finally, the ganglion cells send their axons to the brain as components of the optic nerve.

Optic disc and nerve, eye, human, hematoxylin and eosin (H&E) ×65.

The site where the optic nerve leaves the eyeball is called the **optic disc** (*OD*). It is characteristically marked by a depression, evident here. Receptor cells are not present at the optic disc, and because it is not sensitive to light stimulation, it is sometimes referred to as the *blind spot*.

The fibers that give rise to the optic nerve originate in the retina, more specifically, in the ganglion cell layer (see later). They traverse the sclera through a number of openings (*arrows*) to form the **optic nerve** (*ON*). The region of the sclera that contains these openings is called the **lamina cribrosa** (*LC*) or cribriform plate. The optic nerve contains a central artery and vein (not seen here) that also traverse the lamina cribrosa. Branches of these blood vessels (*BV*) supply the inner portion of the retina.



Retina, eye, human, H&E ×325.

On the basis of structural features that are evident in histologic sections, the retina is divided into 10 layers, from posterior to anterior, as listed herein and labeled in this figure:

1. **Retinal pigment epithelium** (*RPE*), the outermost layer of the retina
2. **Layer of rods and cones** (*R&C*), the photoreceptor layer of the retina
3. **External limiting membrane** (*ELM*), a line formed by the junctional complexes of the photoreceptor cells
4. **Outer nuclear layer** (*ONL*), containing nuclei of rod and cone cells
5. **Outer plexiform layer** (*OPL*), containing neural processes and synapses of rod and cone cells with bipolar, amacrine, interplexiform, and horizontal cells

6. **Inner nuclear layer** (*INL*), containing nuclei of bipolar, horizontal, interplexiform, amacrine, and Müller cells
7. **Inner plexiform layer** (*IPL*), containing processes and synapses of bipolar, horizontal, interplexiform, amacrine, and ganglion cells
8. **Layer of ganglion cells** (*GC*), containing cell bodies and nuclei of ganglion cells
9. **Nerve fiber layer** (*NFL*), containing axons of ganglion cells
10. **Internal limiting membrane** (*ILM*), consisting of the external (basal) lamina of Müller cells

This figure also shows the innermost layer of the choroid (*Ch*), a cell-free membrane, the lamina vitrea (*LV*), also called Bruch membrane. Electron micrographs reveal that it corresponds to the basement membrane of the pigment epithelium. Immediately external to the lamina vitrea is the capillary layer of the choroid (lamina choriocapillaris). These vessels supply the outer part of the retina.

BV, blood vessels
Ch, choroid
ELM, external limiting membrane **GC,** layer of ganglion cells **ILM,** internal limiting membrane **INL,** inner nuclear layer (nuclei of bipolar, horizontal, amacrine, and Müller cells) **IPL,** inner plexiform layer **LC,** lamina cribrosa **LV,** lamina vitrea
NFL, nerve fiber layer **OD,** optic disc
ON, optic nerve
ONL, outer nuclear layer (nuclei of rod and cone cells) **OPL,** outer plexiform layer **RPE,** retinal pigment epithelium **R&C,** layer of rods and cones **arrows,** openings in sclera (lamina cribrosa)

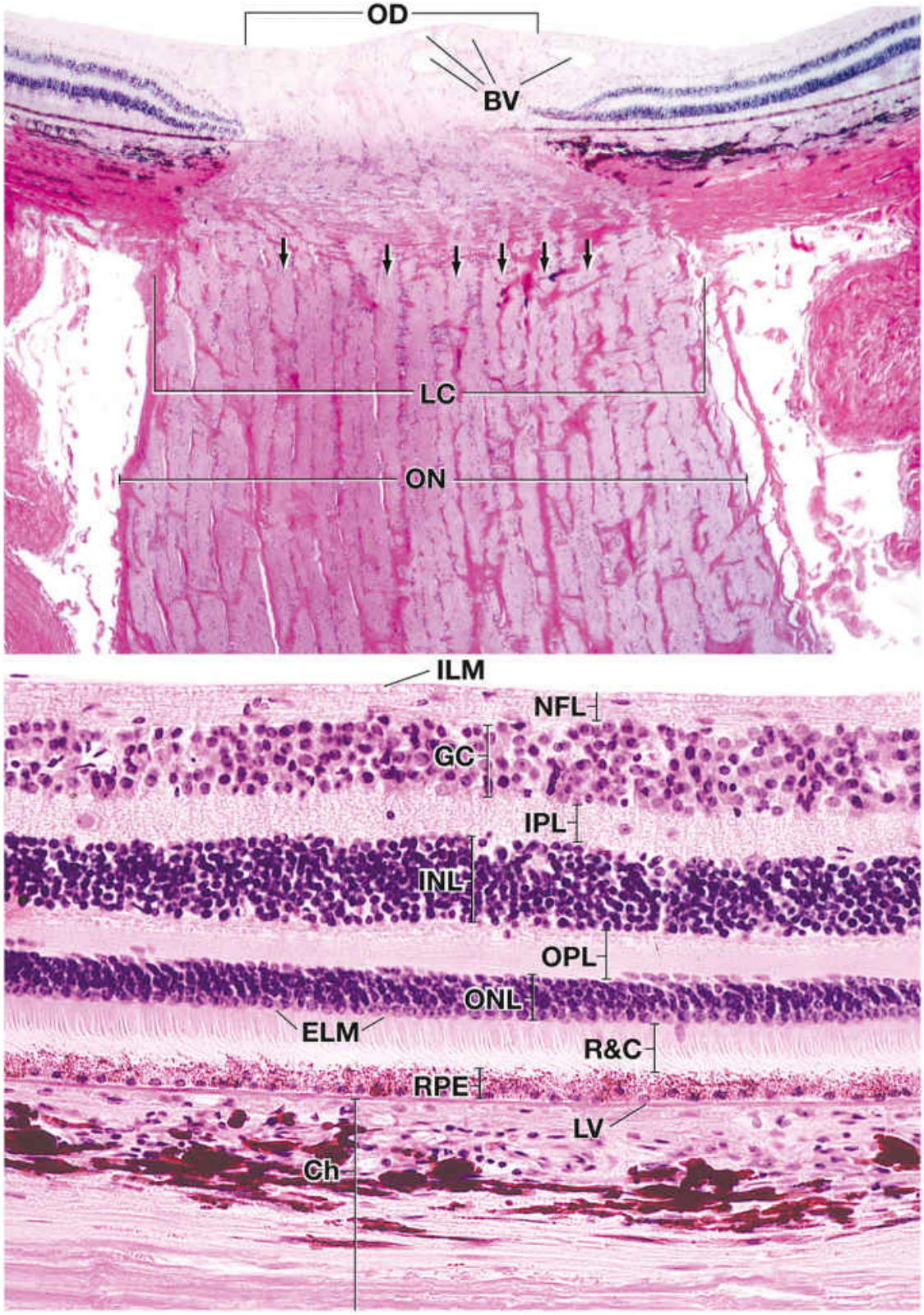


PLATE 24.3 ■ EYE III: ANTERIOR SEGMENT

The **anterior segment** is that part of the eye anterior to the **ora serrata**, the most anterior extension of the neural retina, and includes the **anterior** and **posterior**

chambers and the structures that define them. These include the cornea and sclera, the iris, the lens, the ciliary body, and the connections between the basal lamina of the ciliary processes and the lens capsule (thick basal lamina of the lens epithelium) that form the suspensory ligament of the lens, the **zonular fibers**. The posterior chamber is bounded posteriorly by the anterior surface of the lens and anteriorly by the posterior surface of the iris. The ciliary body forms the lateral boundary. Aqueous humor flows through the pupil into the anterior chamber, which occupies the space between the cornea and the iris, and drains into the **canal of Schlemm**.

Anterior segment, eye, human, hematoxylin and eosin (H&E) ×45; inset ×75.

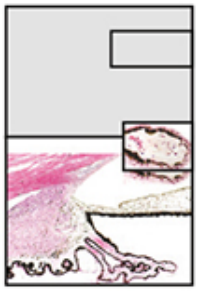
A portion of the **anterior segment** of the eye, shown in this figure, includes parts of the cornea (*C*), sclera (*S*), iris (*I*), ciliary body (*CB*), anterior chamber (*AC*), posterior chamber (*PC*), lens (*L*), and zonular fibers (*ZF*).

The relationship of the cornea to the sclera is illustrated to advantage here. The junction between the two (*arrows*) is marked by a change in staining, with the substance of the cornea appearing lighter than that of the sclera. The **corneal epithelium** (*CEp*) is continuous with the **conjunctival epithelium** (*CjEp*) that covers the sclera. Note that the epithelium thickens considerably at the corneoscleral junction and resembles that of the oral mucosa. The conjunctival epithelium is separated from the dense fibrous component of the sclera by a loose vascular connective tissue. Together, this connective tissue and the epithelium constitute the conjunctiva (*Cj*). The epithelial–connective tissue junction of the conjunctiva is irregular; in contrast, the undersurface of the corneal epithelium presents an even profile.

Just lateral to the junction of the cornea and sclera is the **canal of Schlemm** (*CS*; see also the next figure). This canal takes a circular route about the perimeter of the cornea. It communicates with the anterior chamber through a loose trabecular meshwork of tissue, the spaces of Fontana. The canal of Schlemm also communicates with episcleral veins. By means of its communications, the canal of Schlemm provides a route for the fluid in the anterior and posterior chambers to reach the bloodstream.

The *inset* shows the tip of the iris. Note the heavy pigmentation on the posterior surface of the iris, which is covered by the same double-layered epithelium as the ciliary body and ciliary processes. In the ciliary epithelium, the outer layer is pigmented and the inner layer is nonpigmented. In the iris, both layers of the iridial epithelium (*IEp*) are heavily pigmented. A portion of the iridial constrictor muscle (*M*) is seen beneath the epithelium.

Anterior segment, eye, human, H&E ×90; inset ×350.



Immediately internal to the anterior margin of the sclera (*S*) is the **ciliary body** (*CB*). The **iris** (*I*) arises from the anterior border of the ciliary body. The inner surface of the ciliary body forms radially arranged, ridge-shaped elevations, the **ciliary processes** (*CP*), to which the zonular fibers (*ZF*) are anchored. From the outside, the components of the ciliary body are the ciliary muscle (*CM*), the connective tissue (vascular) layer (*VL*) containing small arteries (*A, inset*) and veins (*V, inset*) representing the choroid coat in the ciliary body, the lamina vitrea (*LV, inset*), and the ciliary epithelium (*CiEp*, *inset*). The ciliary epithelium consists of two layers (*inset*), the pigmented layer (*PE*) and the nonpigmented layer (*npE*). The lamina vitrea is a continuation of the same layer of the choroid; it is the basement membrane of the pigmented ciliary epithelial cells.

The **ciliary muscle** is arranged in three patterns. The outer layer is immediately deep into the sclera and contains the meridionally arranged fibers of Brücke. The outermost of these fibers continues more posteriorly into the choroid and is referred to as the *tensor muscle of the choroid*. The middle layer is the radial group. It radiates from the region of the sclerocorneal junction into the ciliary body. The innermost layer of muscle cells is circularly arranged. These are seen in cross section. The circular artery (*CA*; barely discernible) and vein (*CV*) for the iris, also cut in cross section, are just anterior to the circular group of muscle cells.

A, artery
AC, anterior chamber **C,** cornea
CA, circular artery **CB,** ciliary body
CEp, corneal epithelium **CiEp,** ciliary epithelium **Cj,** conjunctiva
CjEp, conjunctival epithelium **CM,** ciliary muscle
CP, ciliary processes **CS,** canal of Schlemm **CV,** circular vein
I, iris
IEp, iridial epithelium **L,** lens
LV, lamina vitrea
M, iridial constrictor muscle **npE,** nonpigmented layer of ciliary epithelium **PC,** posterior chamber **PE,** pigmented layer of ciliary epithelium **S,** sclera
V, vein
VL, vascular layer (of ciliary body) **ZF,** zonular fibers
arrows, junction between cornea and sclera

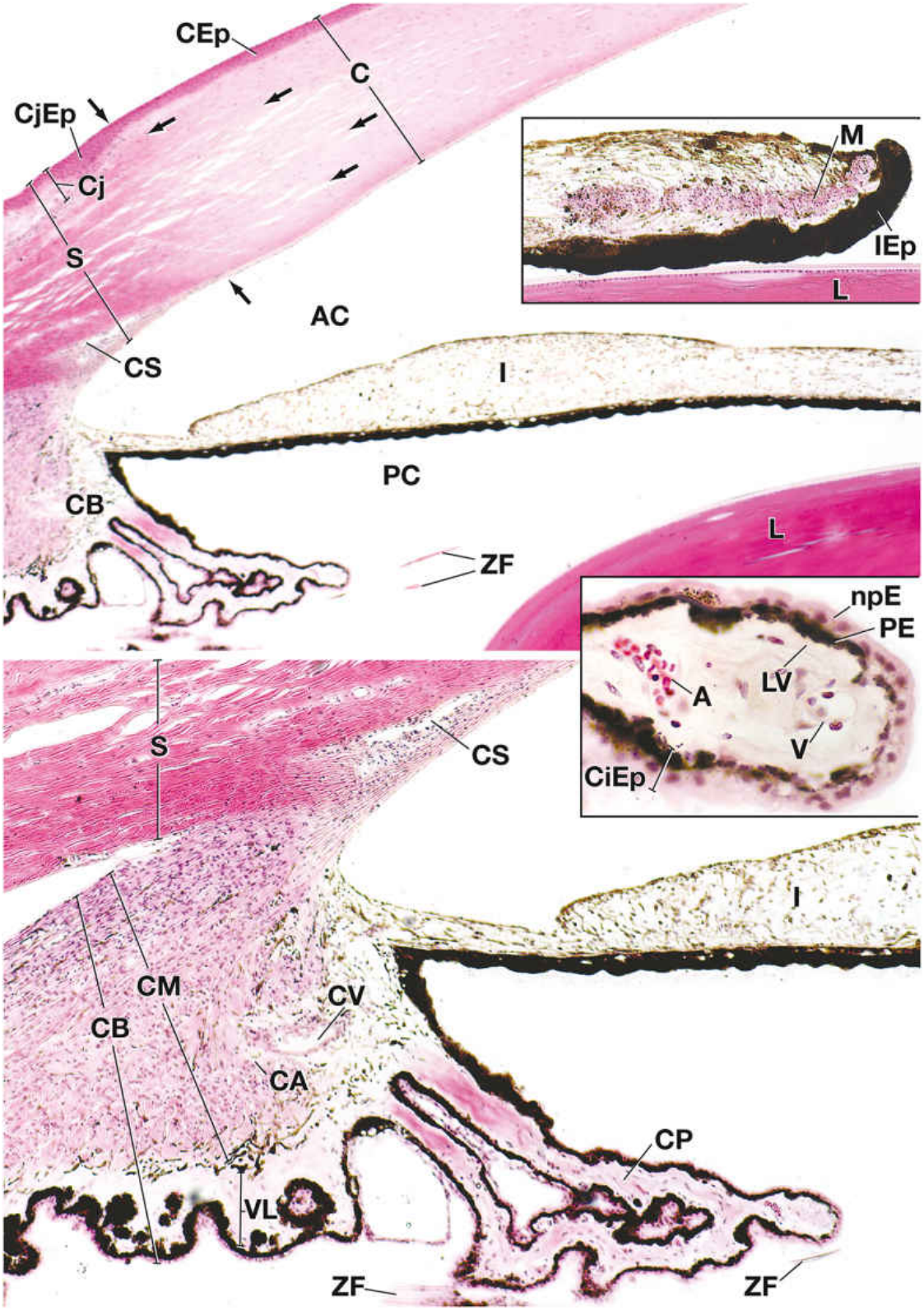


PLATE 24.4 ■ EYE IV: SCLERA, CORNEA, AND LENS

The transparent **cornea** is the primary dioptric (refractive element) of the eye and is covered with nonkeratinized stratified squamous epithelium. Its stroma consists

of alternating lamellae of collagen fibrils and fibroblasts (**keratocytes**). The fibrils in each lamella are extremely uniform in diameter and uniformly spaced; fibrils in adjacent lamellae are arranged at approximately right angles to each other. This orthogonal array of highly regular fibrils is responsible for the transparency of the cornea. The posterior surface is covered with a single layer of low cuboidal cells, the **corneal endothelium**, which rests on a thickened basal lamina called **Descemet membrane**. Nearly all of the metabolic exchanges of the avascular cornea occur across the endothelium. Damage to this layer leads to corneal swelling and can produce temporary or permanent loss of transparency.

The **lens** is a transparent, avascular, biconvex epithelial structure suspended by the zonular fibers. Tension on these fibers keeps the lens flattened; reduced tension allows it to fatten or **accommodate** to bend light rays originating close to the eye to focus them on the retina.

Corneoscleral junction, eye, human, hematoxylin and eosin (H&E) ×130.

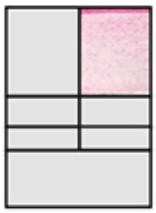
This low-magnification micrograph shows the full thickness of the sclera just lateral to the **corneoscleral junction** or limbus. To the *left* of the *arrow* is sclera; to the *right* is a small amount of corneal tissue. The **conjunctival epithelium** (*CjEp*) is irregular in thickness and rests on a loose vascular connective tissue. Together, this epithelium and underlying connective tissue represent the **conjunctiva** (*Cj*). The white opaque appearance of the sclera is due to the irregular dense arrangement of the collagen fibers that make up the stroma (*S*). The **canal of Schlemm** (*CS*) and small blood vessels (*BV*) are seen at the *left* close to the inner surface of the sclera near the border with anterior chamber (*AC*) of the eye.

Corneoscleral junction and canal of Schlemm, eye, human, H&E ×360.

Uppermost figure is a higher magnification micrograph showing the transition from the corneal epithelium (*CEp*) to the irregular and thicker conjunctival epithelium (*CjEp*) covering the sclera. Note that Bowman membrane (*B*), lying under the corneal epithelium, is just discernible but disappears beneath the conjunctival epithelium. The next figure shows a higher magnification of the canal of Schlemm (*CS*) than does the *top left* figure. That the space shown here is not an artifact is evidenced by the endothelial lining cells (*En*) that face the lumen.

Cornea, eye, human, H&E ×175.

This low-magnification micrograph shows the full thickness of the **cornea** (*C*) and can be compared with the sclera shown in the figure at the *left*. The **corneal**



epithelium (*CEp*) presents a uniform thickness, and the underlying stroma (*S*) has a more homogeneous appearance than the stroma of the sclera (the white spaces seen here and in the figure at the *left* are artifacts). Nuclei (*N*) of the keratocytes of the stroma lie between lamellae. The corneal epithelium rests on a thickened anterior basement membrane called **Bowman membrane** (*B*). The posterior surface of the cornea facing the anterior chamber (*AC*) is lined by a simple squamous epithelium called the **corneal endothelium** (*CEn*); its thick posterior basement membrane is called **Descemet membrane** (*D*).

Corneal epithelium and endothelium, eye, human, H&E ×360.

Uppermost is a higher magnification micrograph showing the **corneal epithelium** (*CEp*) with its squamous surface cells, the very thick homogeneous-appearing **Bowman membrane** (*B*), and the underlying stroma (*S*). Note that the stromal tissue has a homogeneous appearance, a reflection of the dense packing of its collagen fibrils. The flattened nuclei belong to the keratocytes. Lowermost figure shows the posterior surface of the cornea. Note the thick homogeneous **Descemet membrane** (*D*) and the underlying **corneal endothelium** (*CEn*).

Lens, eye, human, H&E ×360.

This micrograph shows a portion of the lens near its equator. The lens consists entirely of epithelial cells surrounded by a homogeneous-appearing **lens capsule** (*LC*) to which the zonular fibers attach. The lens capsule is a very thick basal lamina of the epithelial cells. Simple cuboidal lens epithelial cells are present on the anterior surface of the lens, but at the lateral margin, they become extremely elongated and form layers that extend toward the center of the lens. These elongated columns of epithelial cytoplasm are referred to as **lens fibers** (*LF*). New cells are produced at the margin of the lens and displace the older cells inwardly. Eventually, the older cells lose their nuclei, as evidenced by the deeper portion of the cornea in this micrograph.

AC, anterior chamber **B,** Bowman membrane
BV, blood vessels
C, cornea
CEn, corneal endothelium **CEp,** corneal epithelium **Cj,** conjunctiva
CjEp, conjunctival epithelium **CS,** canal of Schlemm **D,** Descemet membrane **En,** endothelial lining cells **LC,** lens capsule
LF, lens fibers

N, nuclei
S, stroma