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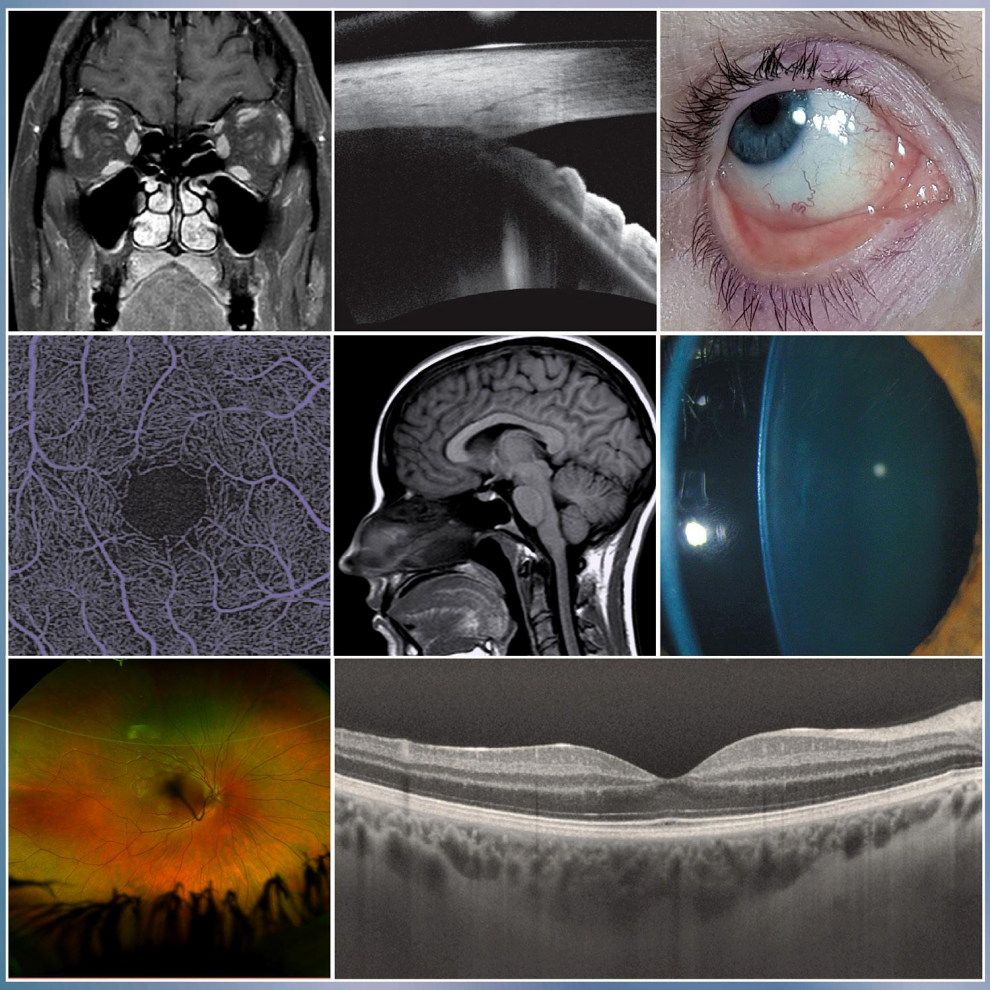

CLINICAL ANATOMY *and* PHYSIOLOGY *of the* VISUAL SYSTEM

Fourth Edition

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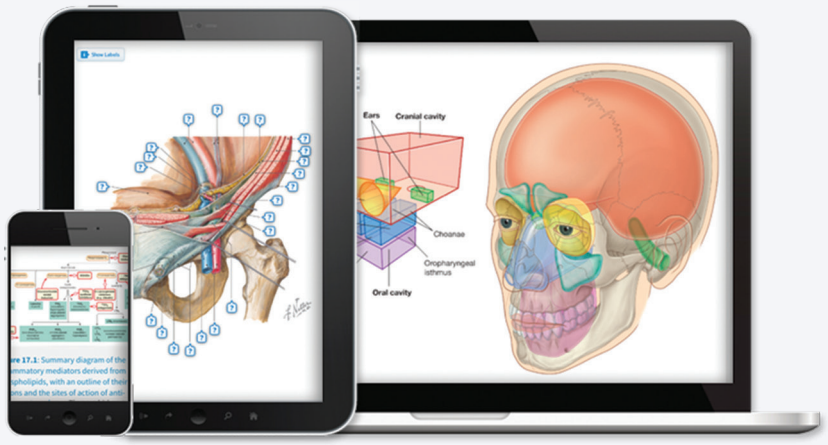

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CLINICAL ANATOMY *and* PHYSIOLOGY *of the* VISUAL SYSTEM

FOURTH EDITION

Fourth Edition

CLINICAL ANATOMY *and* PHYSIOLOGY *of the* VISUAL SYSTEM

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To Dan for his encouragement and support.

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To Spencer who supports me in all my crazy endeavors, and to Bob who started me writing.

DG

PREFACE

Clinical Anatomy and Physiology of the Visual System was written to provide optometry, ophthalmology, and visual science students, as well as clinicians, with a single text that describes the embryology, anatomy, histology, physiology, blood supply, and innervation of the globe and ocular adnexa. The visual and pupillary pathways are covered as well. The text is fully referenced, and information gathered from historical and current literature is well documented. An overview of the visual system, as well as a short review of histology and physiology, is provided in the introductory chapter. Thereafter, detailed discussions and images help illustrate anatomy and physiology concepts related to the visual system.

Chapters are roughly arranged anatomically, starting anteriorly and moving posteriorly. Chapter 2 details eyelid structure and histology, including the roles that the muscles and glands have in tear film secretion and drainage. Chapters 3 through 8 include the anatomy, detailed histology, and physiology of the structures constituting the globe. Each of the three coats of the eye—the cornea and sclera, uvea, and retina—is covered in separate chapters. Included in each is an emphasis on similarities and differences between regions within each coat and notations about layers that are continuous between structures and regions. Chapters 6 covers the chambers inside the globe and the production and composition of the material that occupies those spaces, and Chapter 7 describes the crystalline lens.

In our experience, students can more easily grasp the intricacies of ocular development after gaining a comprehensive understanding of the composition of the structures; therefore ocular embryology is covered in Chapter 9. The tissue and structures associated with and surrounding the globe are described in the next two chapters. Chapter 10 is a review of the bones and important foramina of the entire skull, as well as the detail regarding the orbital bones and connective tissue. Chapter 11 explains the extraocular muscles and describes movements that result from contraction of the muscles with the eye in various positions of gaze; an explanation of the clinical assessment of extraocular muscle function based on the anatomy is included.

The branches of the internal and the external carotid arteries that supply the globe and adnexa are identified in Chapter 12. The cranial nerve supply to orbital structures, including both sensory and motor pathways, is clarified in Chapter 13, with an emphasis on the clinical relevance and implications of interruptions along the pathways. Chapter 14 presents the autonomic pathways to the smooth muscles of the orbit and to the lacrimal gland. The pupillary pathway is included in this chapter, as is a discussion of the more common pupillary abnormalities and the relation between the pathway and the clinical presentation. Some of the common pharmaceutical agents and their actions and pupillary effects are covered as well. The final chapter has significant detail on the relationship between the structures of the visual pathway and neighboring structures and on the orientation of the fibers as they course through the cranium en route to the striate cortex. Examples are given of characteristic visual field defects associated with injury to various regions of the pathway.

In the format used in the text, terms and names of structures are noted in bold print when they are first described or explained. The name for a structure that is more common in usage is presented first, followed by other terms by which that structure is also known. Current nomenclature tends to use the more descriptive name rather than proper nouns when identifying structures, but that is not always the case, especially when the proper name of an individual has been linked so closely historically (e.g., Schwalbe line and Schlemm canal). When proper names are used, we have followed the example of major journals, which are phasing out the use of the possessive form of the name.

Experienced clinicians know that the knowledge of structure and function provides a good foundation for recognizing and understanding clinical situations, conditions, diseases, and treatments. For this reason, "Clinical Comments" are included throughout the book to emphasize common clinical problems, disease processes, or abnormalities that have a basis in anatomy or physiology.

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Denise Goodwin, OD, FAAO

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We have had the pleasure of interacting with many bright, engaging students while teaching at Pacific University College of Optometry. Their questions, corrections, suggestions, and enthusiasm motivate us to continually improve and update the understanding of the process we call vision. We are grateful for their kindness; they make our days richer.

We are also fortunate to work with an extraordinary group of colleagues, the faculty at Pacific, who create an enjoyable environment conducive to academic growth. We are grateful to Dean Jennifer Coyle and Dean Fraser Horn for the constant level of support they have provided and to the optometry faculty for their warm encouragement and help during this process.

Kristen Helm, our Content Development Specialist at Elsevier, championed the project and guided us with kindness and tact throughout the entire process, and for that we are grateful. Kayla Wolfe, our Content Strategist at Elsevier, competently combined the text and figures into a cohesive whole. We appreciate her thoughtful suggestions.

CONTENTS

CLINICAL ANATOMY *and* PHYSIOLOGY *of the* VISUAL SYSTEM

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1

Introduction to the Visual System

The visual system takes in information from the environment in the form of light and analyzes and interprets the data. This process of sight and visual perception involves a complex system of structures, each of which is designed for a specific purpose. The organization of each structure enables it to perform its intended function.

The eye houses the elements that take in light rays and change the light to a neural signal. It is protected by the surrounding bone and connective tissue of the orbit. The eyelids cover and protect the anterior surface of the eye and contain glands that produce the lubricating tear film. Muscles that attach to the outer coat of the eye control and direct the globe's movement, and the muscles of both eyes are coordinated to provide binocular vision. A network of blood vessels supplies nutrients, and a complex system of nerves provides sensory, motor, and autonomic innervation to the eye and surrounding structures. The neural signal that carries visual information passes through a complex and intricately designed pathway within the central nervous system, enabling an accurate view of the surrounding environment. This information, evaluated by a process called visual perception, influences a myriad of decisions and activities.

This book examines the macroscopic and microscopic anatomy and physiology of the components in this complex system, as well as the supporting structures.

ANATOMIC FEATURES OF THE EYE

The eye, also called the globe, is a special sense organ made up of three coats, or tunics (Fig. 1.1):

1. The outer fibrous layer of connective tissue forms the cornea and sclera.
2. The middle vascular layer is composed of the iris, ciliary body, and choroid.
3. The inner neural layer is the retina.

The outer dense connective tissue of the eye offers protection for the structures within, maintains the shape of the globe, and provides resistance to the pressure of the fluids inside. The **sclera** is the opaque white area of the eye and is covered by a transparent tissue, the **conjunctiva**. The transparent **cornea**, at the anterior part of the globe, allows light rays to enter the globe and, by refraction, helps bring these light rays into focus on the retina. The region at which the cornea transitions to sclera and conjunctiva is the **limbus**.

Inner to the sclera and cornea is a vascular layer of the eye, the **uvea**. The uvea is made up of three structures, each having a separate but interconnected function. Some of the histological layers are continuous throughout all three structures and are derived from the same embryonic germ cell layer. The **iris** is the most anterior portion of the uvea, acting as a diaphragm to regulate the amount of light entering the pupil. Two iris muscles control the shape and diameter of the pupil and are supplied by the autonomic nervous system. Continuous with the iris at its root is the **ciliary body**, which produces the components of the aqueous humor and contains the muscle that controls the shape of the lens. The posterior part of the uvea, the **choroid**, is an anastomosing network of blood vessels with a dense capillary network. The choroid surrounds the retina and supplies nutrients to the outer retinal layers.

The neural tissue of the **retina**, by complex biochemical processes, changes light energy into a signal that can be transmitted along a neural pathway. The signal passes through the retina, exits the eye through the **optic nerve**, and is transmitted to various parts of the brain for processing.

Within the globe are three spaces: the anterior chamber, posterior chamber, and vitreous chamber. The **anterior chamber** is bounded in front by the cornea and posteriorly by the iris and anterior surface of the lens. The **posterior chamber** lies behind the iris. The lens lies within the posterior chamber, and the outer border of the posterior chamber is the ciliary body. The anterior and posterior chambers are continuous with one another through the pupil, and both contain the **aqueous humor**, which is produced by the ciliary body. The aqueous humor provides nourishment for the surrounding structures, particularly the cornea and lens. The **vitreous chamber**, which is the largest space, lies adjacent to the inner retinal layer and is bounded in front by the lens. This chamber contains a gel-like substance, the **vitreous humor**.

The **crystalline lens** is located in the area of the posterior chamber and provides additional refractive power for accurately focusing images onto the retina. The lens must change shape to view an object that is close to the eye through the mechanism of **accommodation**.

ANATOMIC DIRECTIONS AND PLANES

Anatomy is an exacting science, and specific terminology is basic to its discussion. The following anatomic directions should be familiar (Fig. 1.2):

- Anterior, or ventral: toward the front
- Posterior, or dorsal: toward the back
- Superior, or cranial: toward the head
- Inferior, or caudal: away from the head
- Medial: toward the midline
- Lateral: away from the midline
- Proximal: near the point of origin
- Distal: away from the point of origin

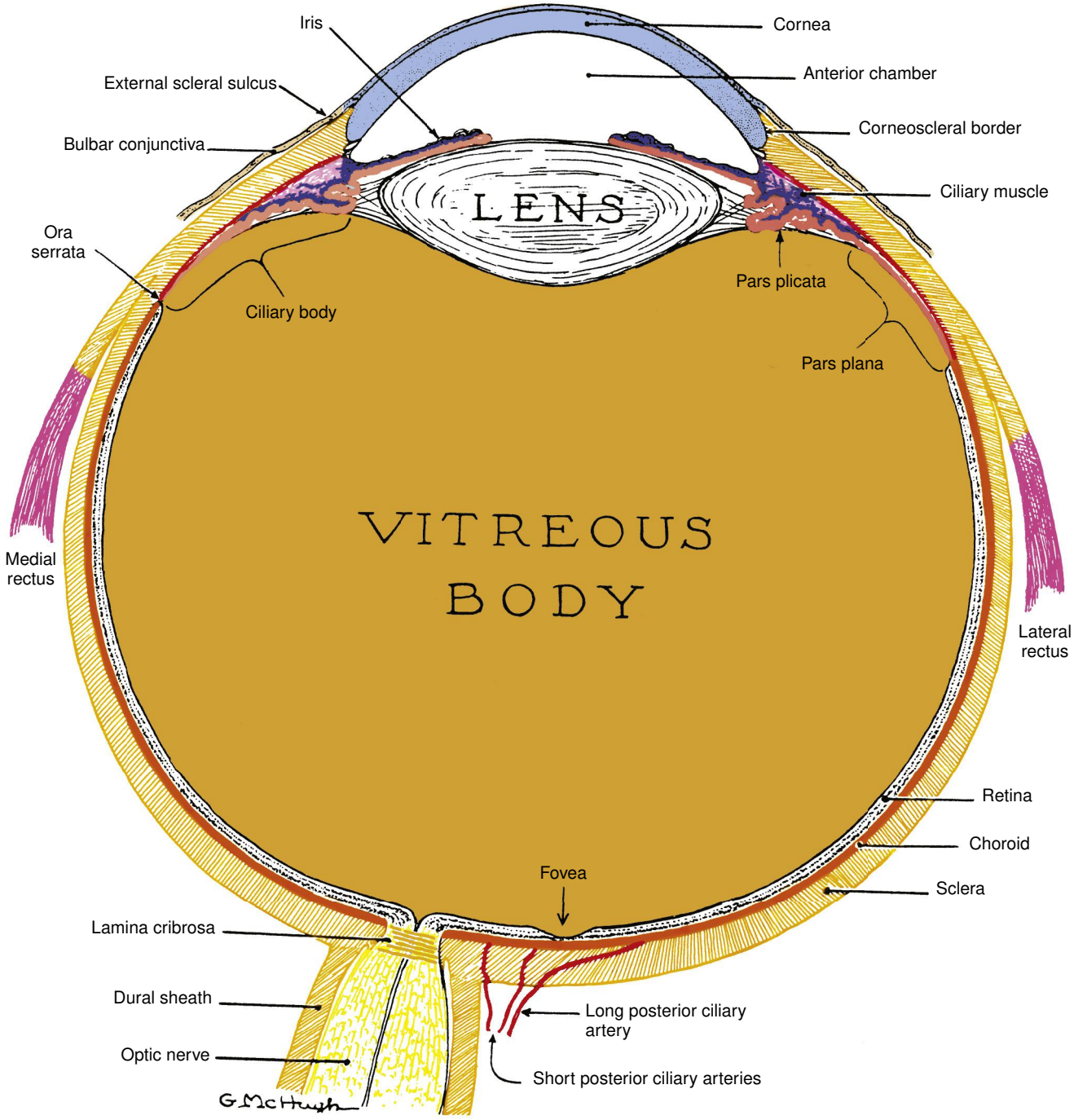

Fig. 1.1 Horizontal section of the globe showing major components.

The following planes are used in describing anatomic structures (Fig. 1.3):

- Sagittal: vertical plane running from anterior to posterior locations, dividing the structure into right and left sides.
- Midsagittal: sagittal plane through the midline, dividing the structure into right and left halves.
- Coronal or frontal: vertical plane running from side to side, dividing the structure into anterior and posterior parts.
- Axial or transverse: horizontal plane, dividing the structure into superior and inferior parts.

Because the globe is a spherical structure, references to locations can sometimes be confusing. In references to anterior and posterior locations of the globe, the anterior pole (i.e., center of the cornea) is the reference point. For example, the pupil is anterior to the ciliary body (see Fig. 1.1). When layers or structures are referred to as inner or outer, the reference is to the entire globe unless specified otherwise. The point of reference is the center of the globe, which would lie within the vitreous. For example, the retina is inner to the sclera (see Fig. 1.1). In addition, the term sclerad is used to mean toward the sclera, and vitread is used to mean toward the vitreous.

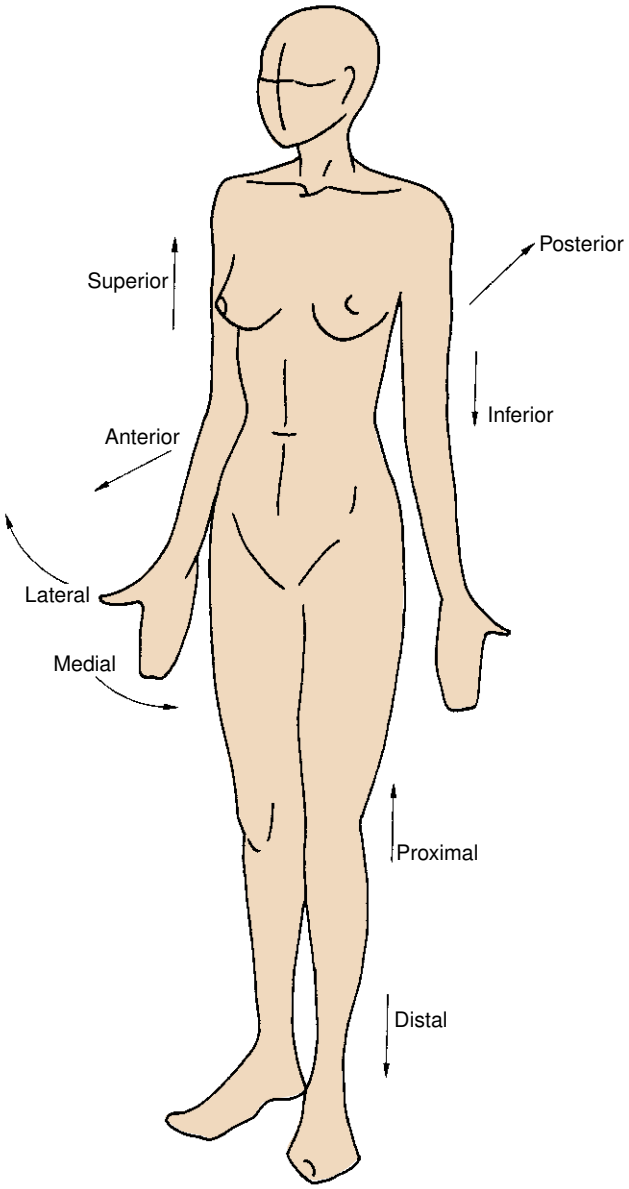

Fig. 1.2 Anatomic directions. (From Palastanga N, Field D, Soames R. *Anatomy and Human Movement*. Oxford, UK: Butterworth-Heinemann; 1989.)

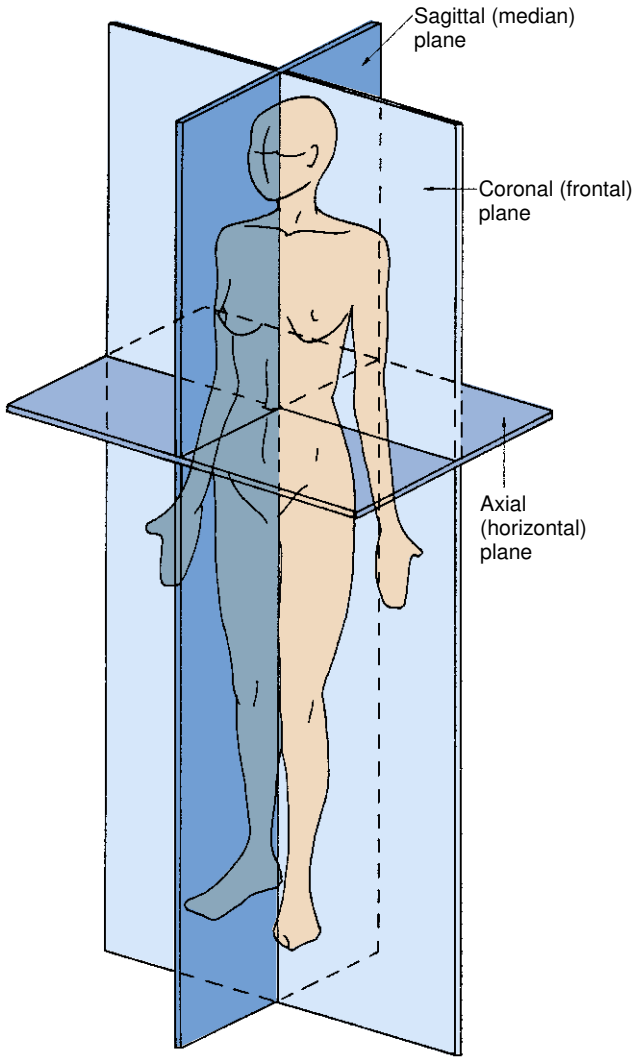

Fig. 1.3 Anatomic planes. (From Palastanga N, Field D, Soames R. *Anatomy and Human Movement*. Oxford, UK: Butterworth-Heinemann; 1989.)

REFRACTIVE CONDITIONS

If the refractive power of the optical components of the eye, primarily the cornea and lens, correlates with the distances between the cornea, lens, and retina so that incoming parallel light rays come into focus on the retina, a clear image will be seen. This condition is called **emmetropia** (Fig. 1.4A). No correction, such as glasses or contact lenses, is necessary for clear distance vision. In **hyperopia** (farsightedness), the distance from the cornea to the retina is too short for the refractive power of the cornea and lens, thereby causing images to focus behind the retina (Fig. 1.4B). Hyperopia can be corrected by placing a convex lens in front of the eye to increase the convergence of the incoming light rays. In **myopia** (nearsightedness), either the lens and cornea are too strong or, more likely, the eyeball is too long, causing parallel light rays to focus in front of the retina (Fig. 1.4C). Myopia can be corrected by placing a concave lens in front of the eye, causing the incoming light rays to diverge.

OPHTHALMIC INSTRUMENTATION

Various instruments are used to assess the health and function of elements of the visual pathway and the supporting structures. This section briefly describes some of these instruments and the structures examined.

The curvature of the cornea is one of the factors that determine the corneal refractive power. A keratometer measures the curvature of the central 3 to 4 mm of the anterior corneal surface and provides information about the power and the difference in curvature between the principle meridians at that location. An automated corneal topographer maps the corneal surface and gives an indication of the corneal curvature at selected points. This instrument is an important adjunct in the fitting of contact lenses in difficult cases.

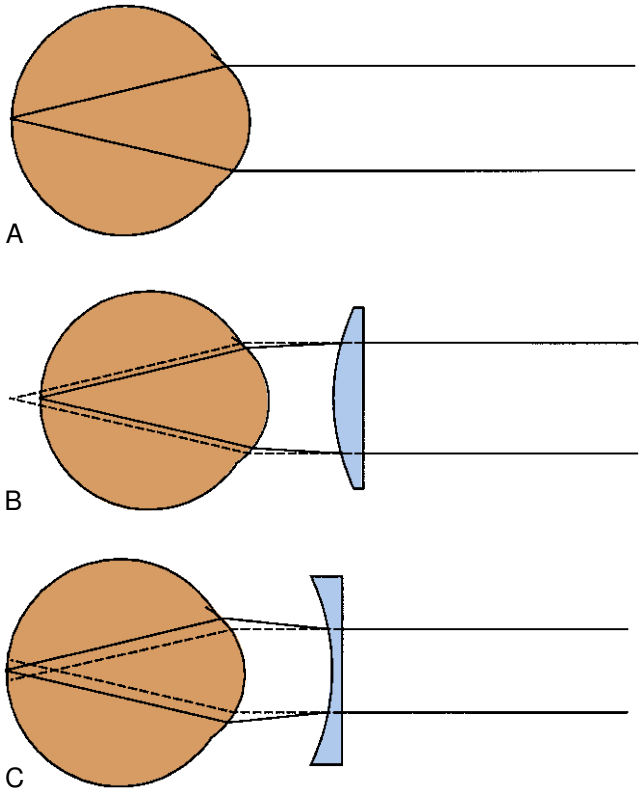

Fig. 1.4 Refractive conditions. **A**, Emmetropia, in which parallel light comes to a focus on the retina. **B**, Hyperopia, in which parallel light comes to a focus behind the retina (*dotted lines*). A convex lens is used to correct the condition and bring the light rays into focus on the retina. **C**, Myopia, in which parallel light comes to a focus in front of retina (*dotted lines*). A concave lens is used to correct the condition and bring the light rays into focus on the retina. (Courtesy Karl Citek, O.D., Pacific University College of Optometry, Forest Grove, Ore.)

The inside portion of the eye surrounding the vitreous chamber is called the **fundus**. This is examined using an ophthalmoscope, which illuminates the interior of the eye with a bright light. The retina, optic nerve head, and blood vessels can be assessed and information about ocular and systemic health obtained. This is the only place in the body in which blood vessels can be viewed directly and noninvasively. Various systemic diseases, such as diabetes, hypertension, and arteriosclerosis, can alter ocular vessels. To obtain a more complete view of the inside of the eye, topical drugs are administered to influence the iris muscles, causing the pupil to become enlarged, or mydriatic. A binocular indirect ophthalmoscope allows stereoscopic viewing of the fundus.

The outside of the globe and the eyelids can be assessed with a biomicroscope. This combination of an illumination system and a binocular microscope allows stereoscopic views of various parts of the eye. Particularly beneficial is the view of the transparent ocular structures, such as the cornea and lens. A number of auxiliary instruments can be used with the biomicroscope to measure intraocular pressure and to view the interior of the eye.

Optical coherence tomography (OCT) uses light waves to noninvasively obtain a cross-sectional image of optical structures. It provides three-dimensional mapping of the retina and the optic nerve head and can measure the thickness of specific retinal layers. OCT angiography detects motion of blood and uses this to produce high resolution images of the retinal and choroidal vasculature. This does not require the use of injectable dyes, and the images can be obtained within seconds. Additional instrumentation can allow visualization of corneal layers, cells, and nerves and can aid in the differentiation of bacterial, viral, parasitic, and fungal infection in corneal tissue.

The visual field is the area that a person sees, including those areas seen in the periphery. A perimeter is used to test the extent, sensitivity, and completeness of this visual field. Computerized perimeters provide extremely detailed maps of the visual field, as well as statistical information on the reliability of the test and the probabilities of any defects.

Neuroimaging techniques, such as magnetic resonance imaging and computed tomography, allow increasingly detailed imaging of the globe, orbit, and visual pathway anatomy. These images provide physiological and pathological information never before available. Having a basic understanding of the normal anatomical appearance will aid in detecting pathology.

BASIC HISTOLOGICAL FEATURES

Because many of the anatomical structures are discussed in this book at the histological level, this section briefly reviews basic human histology. Other details of tissues are addressed in the pertinent chapters.

All body structures are made up of one or more of the four basic tissues: epithelial, connective, muscle, and nervous tissue. A tissue is defined as a collection of similar cells that are specialized to perform a common function.

Epithelial Tissue

Epithelial tissue often takes the form of sheets of epithelial cells that either cover the external surface of a structure or that line a cavity. Epithelial cells lie on a basement membrane that attaches them to underlying connective tissue. The **basement membrane** can be divided into two parts: the **basal lamina**, secreted by the epithelial cell, and the **reticular lamina**, a product of the underlying connective tissue layer. The free surface of the epithelial cell is the apical surface, whereas the surface that faces underlying tissue or rests on the basement membrane is the basal surface.

Epithelial cells are classified according to shape (Fig. 1.5). Squamous cells are flat and platelike, cuboidal cells are of equal height and width, and columnar cells are higher than wide. Epithelium consisting of a single layer of cells is referred to as simple: simple squamous, simple cuboidal, or simple columnar. **Endothelium** is the special name given to the simple squamous layer that lines certain cavities. Epithelium consisting of several layers is referred to as stratified and is described by the shape of the cells in the surface layer. Only the basal or deepest layer of cells is in contact with the basement membrane, and this layer usually consists of columnar cells.

Keratinized, stratified squamous epithelium has a surface layer of squamous cells with cytoplasm that has been transformed into a substance called keratin, a tough protective material relatively resistant to mechanical injury, bacterial invasion, and water loss. These keratinized surface cells constantly are sloughed off and are replaced from the layers below where cell division takes place.

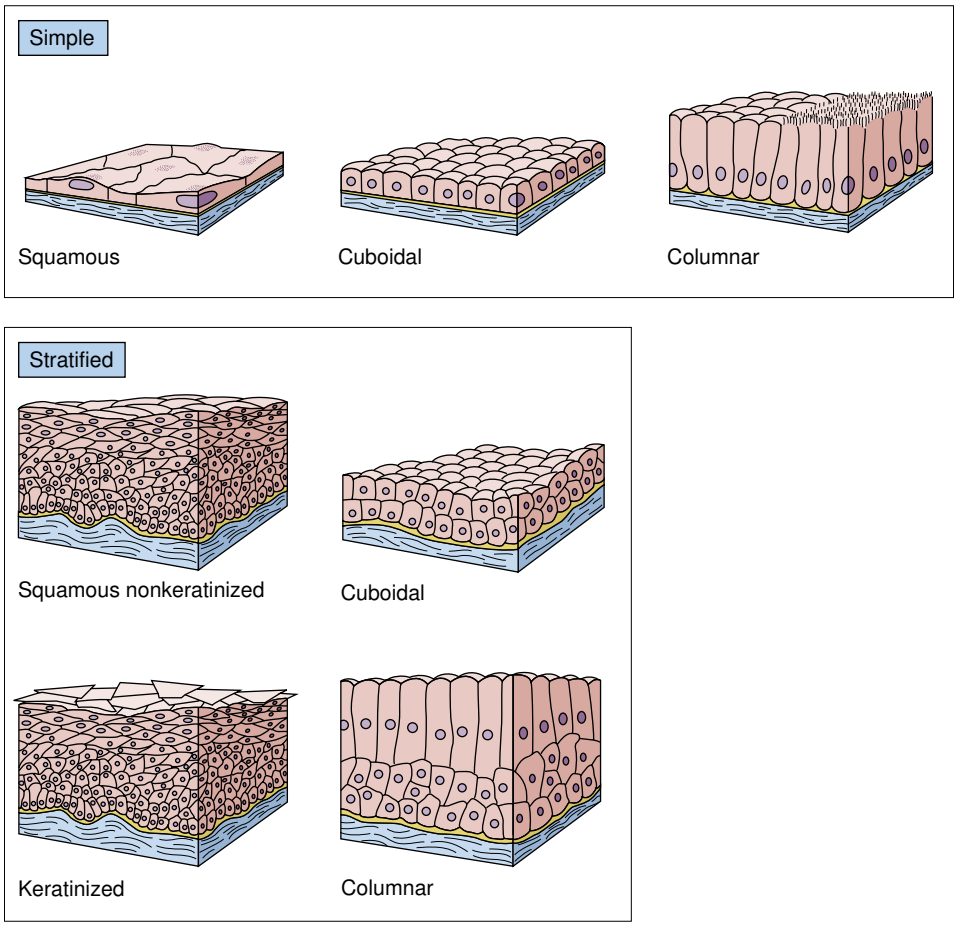

Fig. 1.5 Types of epithelia. (From Gartner LP, Hiatt JL. *Color Textbook of Histology*. 3rd ed. Philadelphia: Saunders; 2007, p 87.)

Many epithelial cells are adapted for secretion and, when gathered into groups, are referred to as glands. Glands can be classified according to the manner of secretion—exocrine glands secrete through a duct onto the epithelial surface, whereas endocrine glands secrete directly into the bloodstream. Glands can also be classified according to the process of secretion production—holocrine glands secrete complete cells laden with the secretory material; apocrine glands secrete part of the cell cytoplasm in the secretion; and the secretion of merocrine glands is a product of the cell without loss of any cellular components (Fig. 1.6). Glands can also be named according to the composition of their secretion: mucous, serous, or sebaceous.

Connective Tissue

Connective tissue provides structure and support and fills the space not occupied by other tissue. Types of connective tissue include bone, muscle, tendons, blood, lymph, and adipose tissue. Connective tissue consists of cells, fibers, and ground substance. A combination of insoluble protein fibers within the ground substance is called the extracellular matrix. Connective

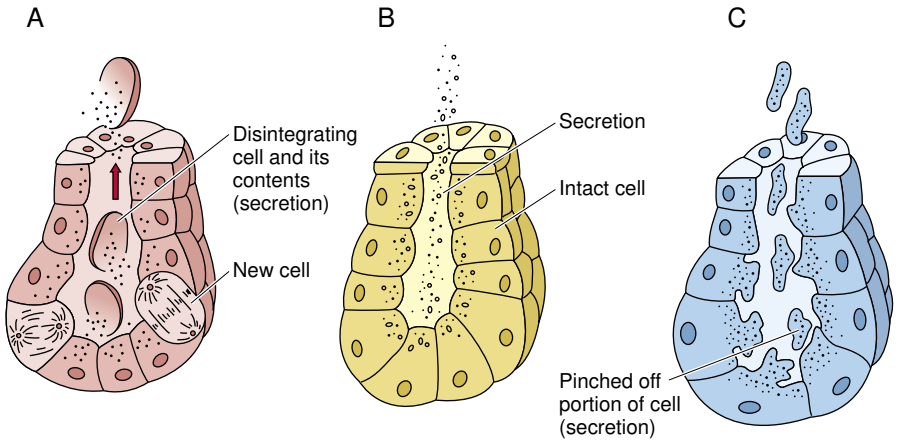

Fig. 1.6 Modes of glandular secretion. **A**, Holocrine. **B**, Merocrine. **C**, Apocrine. (From Gartner LP, Hiatt JL. *Color Textbook of Histology*. 3rd ed. Philadelphia: Saunders; 2007, p 105.)

tissue can be classified as loose or dense. Loose connective tissue has relatively fewer cells and fibers per area than dense connective tissue, in which the cells and fibers are tightly packed. Dense connective tissue can be characterized as regular or irregular on the basis of fiber arrangement.

Among the cells that may be found in connective tissue are fibroblasts (flattened cells that produce and maintain the fibers and ground substance), macrophages (phagocytic cells), mast cells (which contain heparin and histamine), and fat cells. Connective tissue composed primarily of fat cells is called adipose tissue.

The fibers found in connective tissue include flexible collagen fibers with high tensile strength, delicate reticular fibers, and elastic fibers, which can undergo extensive stretching. **Collagen fibers** are a major component of much of the eye's connective tissue. These fibers are composed of protein macromolecules of tropocollagen that have a coiled helix of three polypeptide chains. The individual polypeptide chains can differ in their amino acid sequences, and the tropocollagen has a banded pattern because of the sequence differences. Collagen is separated into various types on the basis of such differences, and several types are components of ocular connective tissue structures.

The amorphous ground substance, in which the cells and fibers are embedded, consists of water bound to glycosaminoglycans, proteoglycans, and glycoproteins.

Muscle Tissue

Muscle tissue is contractile tissue. It can be classified as striated or smooth and may be under voluntary or involuntary control. **Striated muscle** has a regular pattern of light and dark bands and is subdivided into skeletal and cardiac muscle. Skeletal muscle is under voluntary control, whereas cardiac muscle is controlled involuntarily. The structure of skeletal muscle and the mechanism of its contraction are discussed in Chapter 11.

The **smooth muscle** fiber is an elongated, slender cell with a single centrally located nucleus. This tissue is under the involuntary control of the autonomic nervous system.

Nerve Tissue

Nerve tissue encompasses two types of cells: **neurons**, which are specialized cells that react to a stimulus and conduct a nerve impulse, and **neuroglia**, which are cells that provide structure and metabolic support to the neurons. The neuron cell body, called the soma, has several cytoplasmic projections. The projections that conduct impulses to the cell body are **dendrites**, and the projection that conducts impulses away from the cell body is an **axon**.

A nerve impulse, in the form of an action potential, passes between nerves at a specialized junction, a synapse. As the action potential reaches the presynaptic membrane of the first axon, a neurotransmitter is released into the synaptic gap, triggering an excitatory or an inhibitory response in the postsynaptic membrane of the second neuron.

Neuroglia in the central nervous system include oligodendrocytes, astrocytes, and microglial cells. Schwann cells are the only neuroglial cell in the peripheral nervous system. Cytoplasmic extensions of **Schwann cells** in the peripheral nervous system encircle nerve fibers to form a myelin sheath, and **oligodendrocytes** do the same in the central nervous system (including forming the myelin for the optic nerve). Nerve fibers thus are either myelinated or unmyelinated. Myelinization improves impulse conduction speed. **Astrocytes** have a number of functions, including providing physical and metabolic support, maintaining extracellular homeostasis, and participating in the blood brain barrier. **Microglial cells** mediate the immune response in the central nervous system. They possess phagocytic properties and increase in number in areas of damage or disease.

BRIEF REVIEW OF HUMAN CELLULAR PHYSIOLOGY

A **cell membrane** surrounds each cell and is composed of a double layer of hydrophilic lipids surrounding a hydrophobic intermediate area (Fig. 1.7). The two hydrophilic phospholipid layers face the aqueous solutions on both the inside (intracellular area) and outside (extracellular area) of the cell. A hydrophobic fatty acid chain extending from each phospholipid layer projects toward the center of the membrane. Cholesterol molecules found in the central fatty acid portion decrease the membrane's permeability to water soluble molecules. Carbohydrates may form a glycocalyx coating on the extracellular cell membrane. Protein molecules may be embedded in both surfaces of the lipid bilayer, and membrane-spanning proteins have portions both inside and outside the cell.

The **cellular cytoplasm** (cytosol) contains various protein fibers. Microtubules are the largest and are composed of the protein tubulin. Other fibers may be tissue specific: keratin fibers in epithelium, microfilaments of actin and myosin fibers in the sarcoplasm of muscles, and neurofilaments in neurons. The **cytoskeleton** is a three-dimensional scaffolding within the cytoplasm that gives the cell structure and support and provides intracellular transport. The **nucleus**, the control center for the cell, directs cellular function and contains most of the genetic material within its deoxyribonucleic acid (DNA), which is organized into **chromosomes**. The genes within the chromosomes are the **genome. Ribosomes**, granules of ribonucleic acid and proteins within the cytoplasm, manufacture proteins as directed by the cellular DNA. The **endoplasmic reticulum** within the cytoplasm provides sites for protein and lipid synthesis. Smooth endoplasmic reticulum does not have embedded ribosomes. It is involved in steroid and lipid synthesis. Rough endoplasmic reticulum houses ribosomes and is involved in producing proteins. The **Golgi apparatus** modifies and packages proteins. **Mitochondria**, the powerhouse of the cell, produce the cell's supply of energy in the form of adenosine triphosphate (ATP). The inner wall of the double-walled mitochondria is folded into cisternae. This is where biochemical processes occur that result in the production of ATP. **Lysosomes**, intracellular digestive systems containing powerful enzymes, take up bacteria or old organelles and break them down into component molecules that are reused or reabsorbed into the cytoplasm and transported out of the cell.

Fluid and solute transport across a cell membrane can occur passively either by diffusion down a concentration gradient or by facilitated diffusion using membrane transport proteins (Fig. 1.8). Molecules can be transported against the concentration gradient with the use of active transport, which requires energy. Diffusion occurs when molecules pass from a higher to a lower concentration and no energy is expended. Facilitated diffusion may occur

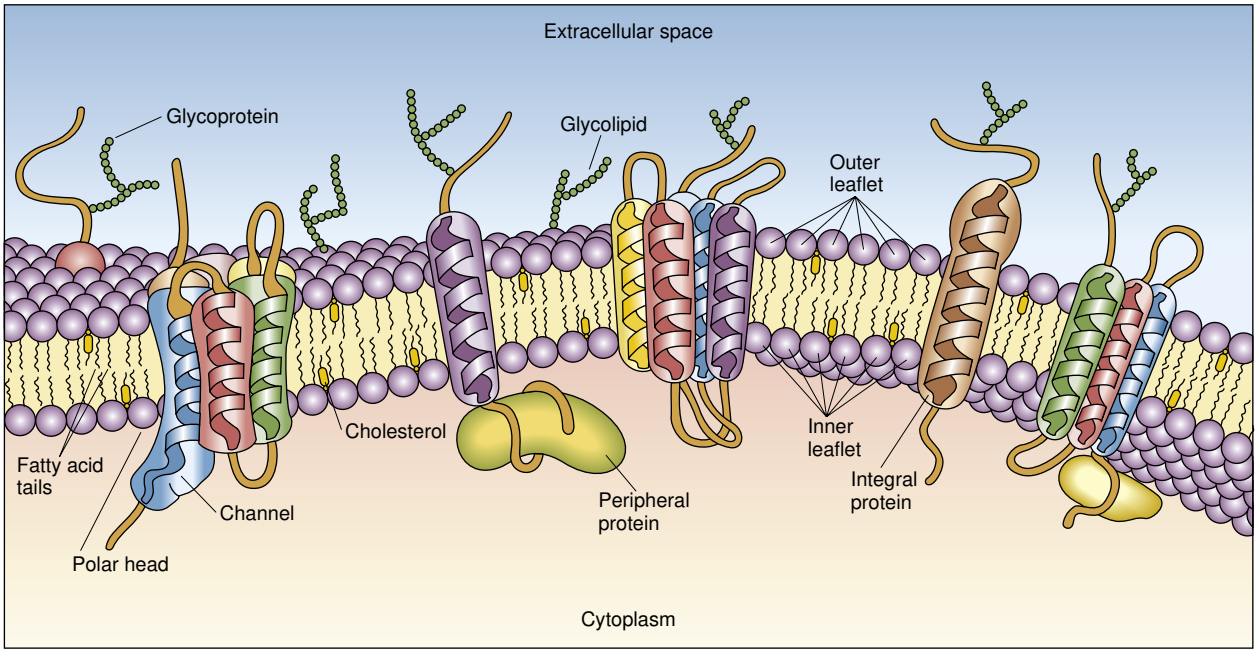

Fig. 1.7 Model of the cell membrane. (From Gartner LP, Hiatt JL. *Color Textbook of Histology*. 3rd ed. Philadelphia: Saunders; 2007, p 16.)

through channel proteins or carrier proteins. Channel proteins within the cell membrane create water-filled passages linking the intracellular and extracellular spaces. These channels facilitate ion movement across the lipid bilayer and move ions without the expenditure of energy. The channels control entrance into the cell using gates. Voltage-gated channels open with depolarization. Ligand-gated channels open when a signaling molecule, such as a neurotransmitter or a nucleotide like cyclic guanosine monophosphate, binds to the channel. Mechanical-gated channels open with physical contact like cilia deformation. Some channels are not gated, such as potassium (K^+) channels or aquaporins, and are always open. Transport across a cell membrane using carrier proteins requires internal binding sites for the ion or molecule being transferred. The carrier proteins never form a direct connection between the intracellular and extracellular environments. This method is slower and selective but can carry larger molecules. Molecules, such as glucose and amino acids, are moved in this way. Carrier proteins can function passively (facilitated diffusion) or with the use of energy (active transport). The most well-known active transport pump is the Na^+/K^+ ATPase pump. Here, transporters and cotransporters move substances against the concentration gradient and need a steady supply of ATP. Transporting epithelia are polarized and the apical and basal membranes have differing properties. Both often contain ion channels; however, the Na^+/K^+ ATPase pumps are generally located in the basolateral membranes. **Aquaporins** are bidirectional channels composed of major intrinsic proteins that specifically allow water passage but may not allow other materials to pass through the channel. Aquaporins are numerous in ocular tissues, including the cornea, lens, ciliary body epithelia, and retina.

Cellular metabolic functions are complex activities that maintain the viability of the cell. Amino acids, carbohydrates, and lipids are used as building blocks in the construction of cellular components or are broken down as a source of energy. A myriad of biochemical pathways and processes function in cellular metabolism and are regulated by signals from either inside or outside the cell. Integrins are membrane-spanning proteins that can carry information from the extracellular matrix into the cell and activate intracellular enzymes that then influence cellular processes. Energy for metabolic processes is supplied by ATP molecules, produced either through aerobic or anaerobic metabolism. Aerobic metabolism is more efficient, with 36 to 38 molecules of ATP produced per molecule of glucose. Anaerobic glycolysis yields two ATP per molecule.

INTERCELLULAR JUNCTIONS

Intercellular junctions join epithelial cells to one another and to adjacent tissue. There are three main types of junctions. Tight junctions, which form fused connections between membranes of adjoining cells, include zonula occludens and macula occludens. Zonula adherens, macula adherens (desmosomes), and hemidesmosomes form anchoring junctions between adjacent cells or between the cell and the basal lamina. Gap junctions allow communication between adjacent cells by permitting passage of ions and small molecules between cells. Physical changes, such as pressure and biochemical or pharmaceutical factors, can modulate junctions and alter the junctional proteins. This allows changes in the extracellular environment to be relayed to the interior cell and may affect intracellular processes.

With tight (occluding) junctions, the outer leaflet of the cell membrane of one cell comes into direct contact with its neighbor. Ridgelike elevations on the surface of the cell membrane fuse with complementary ridges on the surface of a neighboring cell. As the paired strands meet, the neighboring cell membranes are fused. The fibers of tight junctions are connected to the cytoskeleton within the cell. This forms an impermeable barrier that prevents passage of unwanted material between

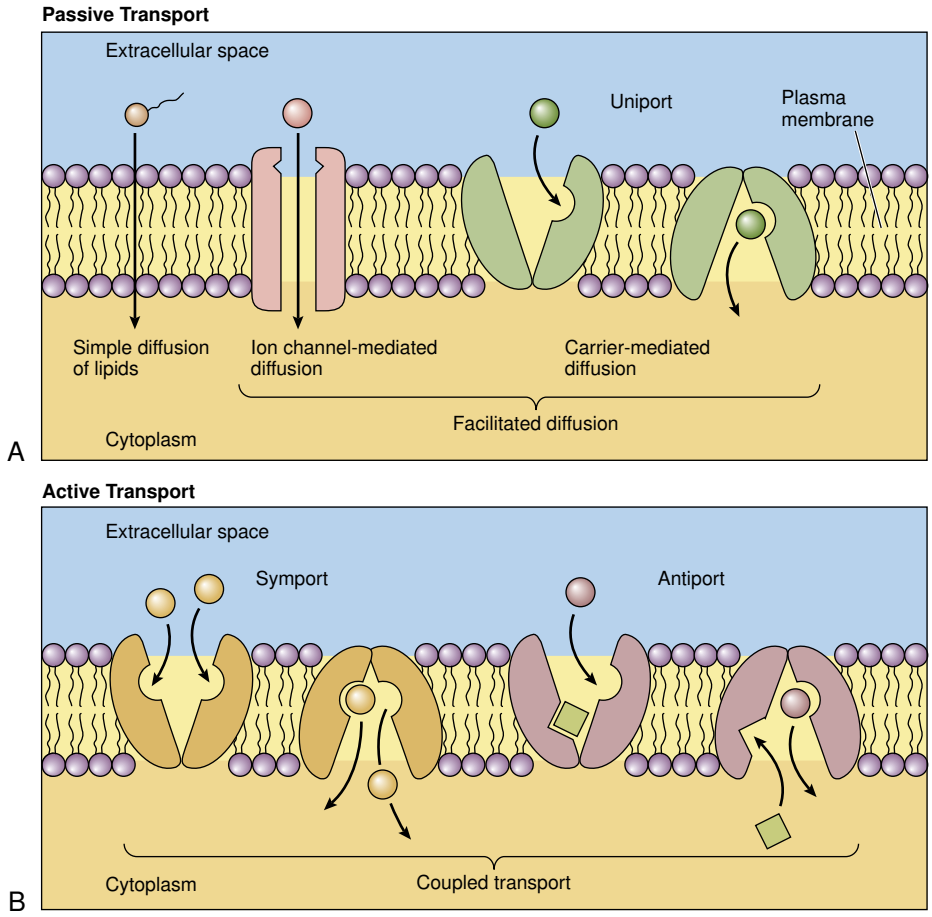

Fig. 1.8 Types of transport. **A**, Passive transport that does not require the input of energy. **B**, Active transport is an energy requiring mechanism. (From Gartner LP, Hiatt JL. *Color Textbook of Histology*. 3rd ed. Philadelphia: Saunders; 2007, p 18.)

adjacent cells. **Zonula occludens** forms a belt-like zone of tight junctions around the entire apical portion of the cell, joining it with each of the adjacent cells (Fig. 1.9). In these zones, row on row of intertwining ridges effectively occlude the intercellular space. A substance cannot pass through a sheet of epithelium whose cells are joined by zonula occludens by passing between the cells. Instead the substance must pass through the cell. In stratified epithelia, where the surface layer is constantly being sloughed and replaced from below, zonula occludens, if present, will be located in the surface layer. The components of the tight junction are found in increasing numbers as a cell moves from its origin in the basal layer until, finally, when the cell reaches the surface, its occluding junction is complete. The complex formed by the junctional proteins in the zonula occludens aids in forming the blood-retinal and blood-aqueous barrier. The tight junction can be affected in some diseases, causing dysfunction of the barrier function. A **macula occludens** junction has a rounded shape.

Zonula adherens and macula adherens are anchoring junctions that bind cells together. The adjacent plasma membranes are separated, leaving a narrow intercellular space that contains a glycoprotein material. This arrangement allows substances to pass between adjacent cells despite relatively firm adhesions. Adjacent to the adhering junctions are fine microfilaments that extend from a plaque just inside the membrane to filaments of the cytoskeleton, contributing to cell stability. In general, **zonula adherens** encircles the entire cell just basal to the zonula occludens which lies nearest the cell apex (see Fig. 1.9B). **Macula adherens (desmosome)** is a strong, spotlike attachment between cells (see Fig. 1.9A). A dense disc or plaque is present within the cytoplasm adjacent to the plasma membrane at the site of the adherence. Hairpin loops of cytoplasmic filaments called tonofilaments extend from the disc into the cytoplasm and link to keratin filaments in the cytoskeleton, contributing to cell stability. Other filaments, transmembrane linkers, or cadherins extend from the plaque across the intercellular space, holding the cell membranes together and forming a strong bond. The intercellular space contains an acid-rich mucoprotein that acts as a strong adhesive.

Hemidesmosomes provide a strong connection between the cell and its basement membrane and underlying connective tissue. They contain similar components to desmosomes. The protein complex extends through the cell membrane to

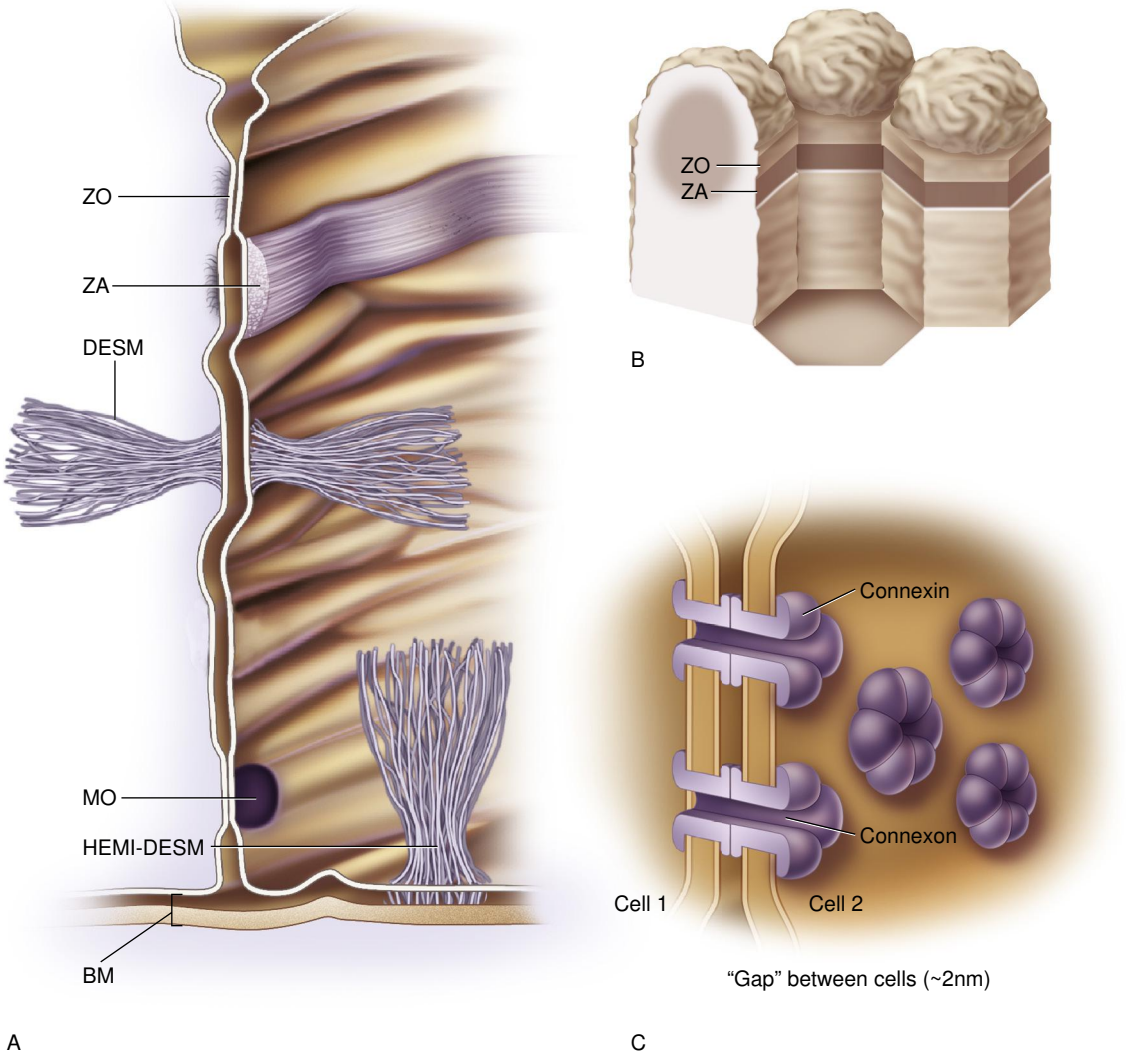

Fig. 1.9 Intercellular junctional complexes. A, The lateral cell membranes of adjacent cells. Zonula occludens joins cells with no intercellular space present. Zonula adherens joins cells without fusing the membranes. Macula adherens (desmosome) forms strong, spot-like junctions with fibers extending into the cytoplasm. Hemidesmosomes form strong junctions that join the basal aspect of the cell to its basement membrane. **B**, Zonula occludens and zonula adherens generally lie adjacent to one another at the apex of the cell. **C**, Gap junctions joining two cells. Six proteins (connexins) surround the central channel (connexon). *BM*, Basal membrane; *DESM*, desmosome; *HEMI-DESM*, hemidesmosomes; *MO*, macula occludens; *ZA*, zonula adherens; *ZO*, zonula occludens.

attach to keratin in the basement membrane. Bundles of filaments join the intracellular plaque to the underlying connective tissue matrix, often attaching to a plaque embedded in the connective tissue.

Gap junctions are formed by a group of (usually six) proteins, called connexins, that span the cell membrane and unite with connexins of a neighboring cell forming a channel called a connexon (see Fig. 1.9C). These narrow channels allow rapid cell-to-cell communication, that is, passage of small molecules and ions from one cell to another. A group of cells with such connections act like a syncytium, that is, a single cell with multiple nuclei.

2

Ocular Adnexa and Lacrimal System

The ocular adnexa includes the structures situated in proximity to the globe. This chapter discusses the eyebrows, the structures of the eyelids, the palpebral conjunctiva, and the lacrimal system, which consists of a secretory system for tear production and an excretory system for tear drainage.

EYEBROW FEATURES

The eyebrows consist of thick skin covered by characteristic short, prominent hairs extending across the superior orbital margin, usually arching slightly but sometimes merely running horizontally. In general, in men the brows run along the orbital margin, whereas in women the brows run above the margin.[1] The first body hairs produced during embryological development are those of the eyebrow.[1]

The muscles located in the forehead—the frontalis, procerus, corrugator superciliaris, and orbicularis oculi—produce eyebrow movements, an important element in facial expression (Fig. 2.1). The **frontalis** muscle originates high on the scalp and inserts into connective tissue near the superior orbital rim. The fibers are oriented vertically and raise the eyebrow, causing a look of surprise or attention. The **corrugator** originates on the inferomedial frontal bone and inserts into skin superior to the medial eyebrow. It is characterized as the muscle of trouble or concentration, and its fibers are oriented obliquely. It moves the brow down and medially, toward the nose, creating vertical furrows between the brows.[2] The **procerus,** the muscle of menace or aggression, originates on the nasal bone and inserts into the medial side of the frontalis. It pulls the medial portion of the eyebrow inferiorly and produces horizontal furrows over the bridge of the nose. The orbicularis oculi (described in more detail later) lowers the entire brow. The fibers of these muscles blend with one another and are difficult to separate.[1] All are innervated by the facial nerve—cranial nerve VII.

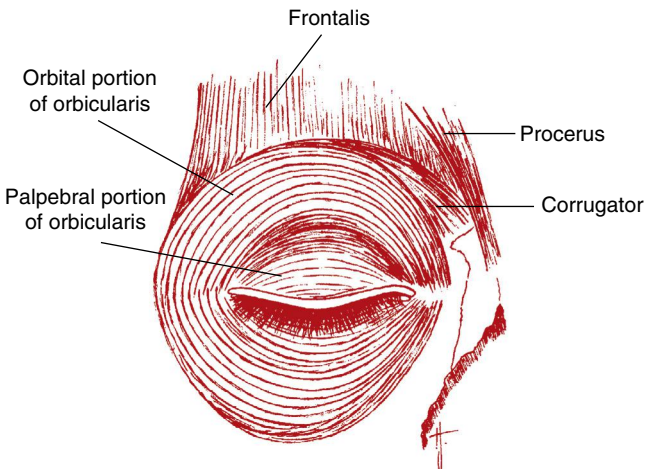

Fig. 2.1 Forehead muscles that control the eyebrows. These are called the muscles of expression.

EXTERNAL FEATURES OF THE EYELIDS

The eyelids, or palpebrae, are folds of skin and tissue that, when closed, cover the globe. The eyelids have four major functions: (1) they cover the globe for protection, (2) they contain structures that produce the tear film, (3) on opening, they spread the tear film over the anterior surface of the eye, and (4) on closure, they move the tears toward drainage areas at the medial canthus. On closure, the upper eyelid moves down to cover the cornea, whereas the lower eyelid rises only slightly. When the eyes are closed gently, the eyelids should cover the entire globe.

Palpebral Fissure

The **palpebral fissure** is the area between the open eyelids. The average vertical palpebral fissure height is approximately 11 mm in Caucasians and 8.5 mm in Asians.[3,4] Although numerous variations exist in the positional relationship of the eyelid margins to the limbus (the junction of the cornea and sclera), generally the upper eyelid covers the superior limbus by 1.5 to 2 mm when the eyes are open and looking straight ahead.[5] The distance between the corneal reflex and the upper eyelid margin while the patient is in primary gaze, known as the margin to reflex distance, is approximately 5 mm in Caucasians, 4.5 mm in African Americans and Latinos, and 4 mm in Asians.[6] The lower eyelid position is more variable, usually lying within 1 mm of the inferior limbus.[7–9]

The upper and lower eyelids meet at the corners of the palpebral fissure in the lateral and medial canthi. The **lateral canthus** is located approximately 5 to 7 mm medial to the bony orbital margin and is in contact with the globe.[9] The **medial canthus** is at the medial orbital margin but is separated from the globe by a reservoir for the pooling of tears, the **lacrimal lake**. At the floor of the lacrimal lake is the **plica semilunaris** (Fig. 2.2). This narrow, crescent-shaped fold of conjunctiva, located in the medial canthus allows for lateral movement of the eye without stretching the bulbar conjunctiva. The **caruncle** is a small, pink mass of modified skin located just medial to the plica semilunaris. It is covered with epithelium that contains goblet cells, as well as fine hairs and their associated sweat and sebaceous glands.

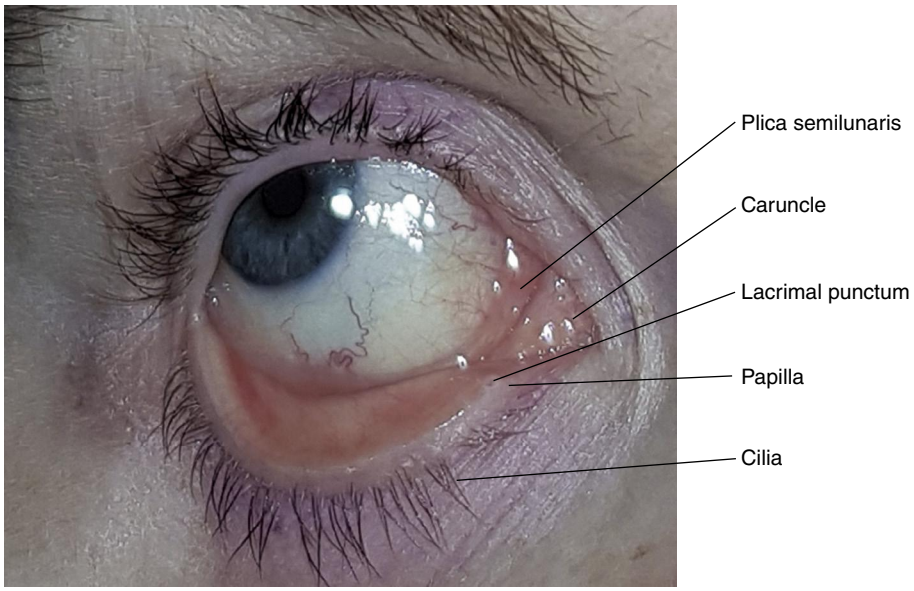

Fig. 2.2 Structures located in left medial canthus.

CLINICAL COMMENT: Lagophthalmos
Lagophthalmos refers to an incomplete closure of the eyelids (Fig. 2.3). Its cause may be physiological, mechanical (e.g., scarring), or paralytic. Lagophthalmos is most evident during sleep, when drying of the inferior cornea may result. Scratchy, irritated eyes are evident on awakening, and punctate keratitis can occur. Clinical assessment of the inferior cornea will show varying degrees of epithelial disruption, manifesting as staining with fluorescein dye.

Eyelid Topography

The upper eyelid extends to the eyebrow and is divided into tarsal and orbital or preseptal parts. The tarsal portion lies closest to the lid margin, rests on the globe, and contains the tarsal plate. The skin is thin, and the underlying loose connective tissue is devoid of adipose tissue. The orbital portion extends from the tarsus to the eyebrow, and a furrow—the **superior palpebral sulcus**—separates the tarsal portion from the orbital portion (Fig. 2.4). This sulcus separates the pretarsal skin, which is tightly adherent to the underlying tissue, from the preseptal skin, which is only loosely adherent to its underlying tissue and may contain a cushion of fat. In eyelids of those of Eastern Asian descent, the fat between the orbital septum and orbicularis muscle descends lower into the eyelid[10] eliminating the superior palpebral sulcus.[1,11–15]

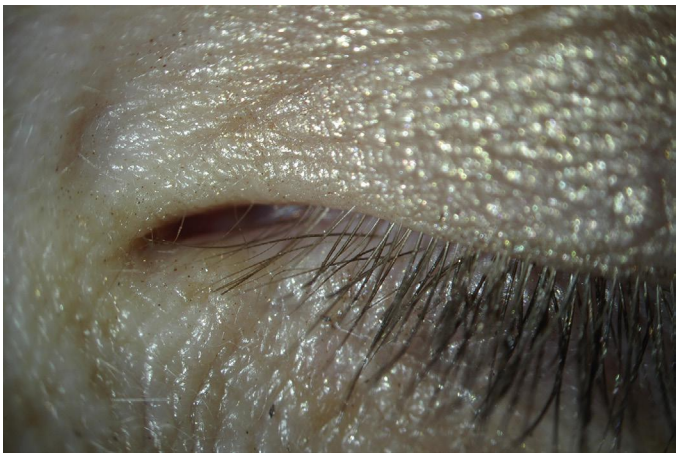

Fig. 2.3 Lagophthalmos of the left eye. The eyelids do not fully close.

In the lower eyelid, the **inferior palpebral sulcus**, which separates the lower lid into tarsal and orbital parts, is often not very distinct. The tarsal portion rests against the globe, and the orbital portion extends from the lower border of the tarsus onto the cheek, extending just past the inferior orbital margin to the nasojugal and malar sulci (see Fig. 2.4). These furrows occur at the attachment of the skin to the underlying connective tissue and become more prominent with age.

Eyelid Margin

The eyelid margin rests against the globe and contains the eyelashes and the pores of the meibomian glands. The cilia (eyelashes) are arranged at the lid margin in a double or triple row, with approximately 150 in the upper eyelid and 75 in the lower eyelid.[16] The lashes curl upward on the upper and downward on the lower lid. Replacement lashes grow to full size in approximately 10 weeks, and each lash is replaced approximately every 5 months.[9] The eyelashes are richly supplied with nerves, causing them to be sensitive to even the slightest unexpected touch, which will elicit a protective response—a blink.

CLINICAL COMMENT: Conditions Affecting the Cilia
Various epithelial diseases can cause madarosis (loss of eyelashes) or trichiasis (misdirected growth of eyelashes, in which the eyelashes grow toward rather than away from the palpebral fissure). Contact between the eyelashes and cornea can cause irritation and painful abrasions and can lead to corneal ulceration. The problem lashes can be removed by epilation.

Receptors for prostaglandin analogs have been found in the bulb and stem of eyelash follicles.[17] When these receptors are influenced by prostaglandin analogs, increased growth and pigmentation of eyelashes occur. Prostaglandin analogs are a type of medication commonly used to treat glaucoma.

The pores of the meibomian glands are located posterior to the cilia (Fig. 2.5A), and the transition from skin to conjunctiva, the **mucocutaneous junction (line of Marx)**, occurs just

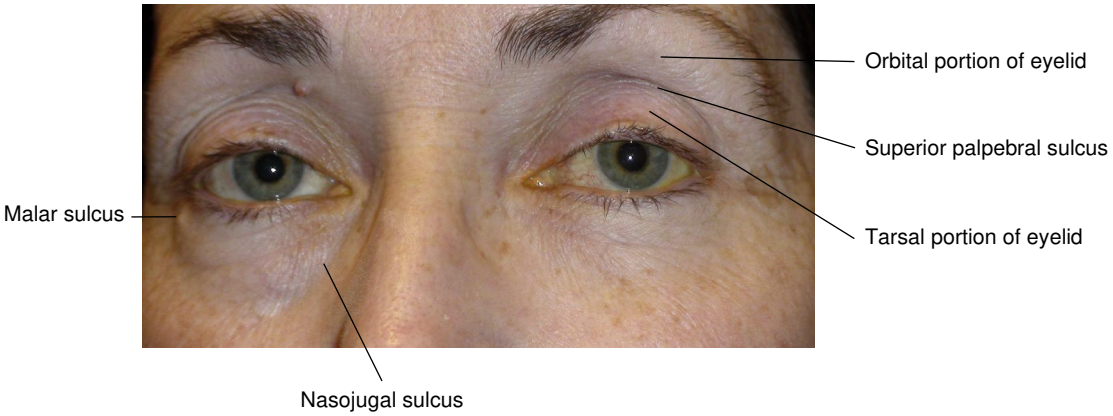

Fig. 2.4 Surface anatomy of the eyelids.

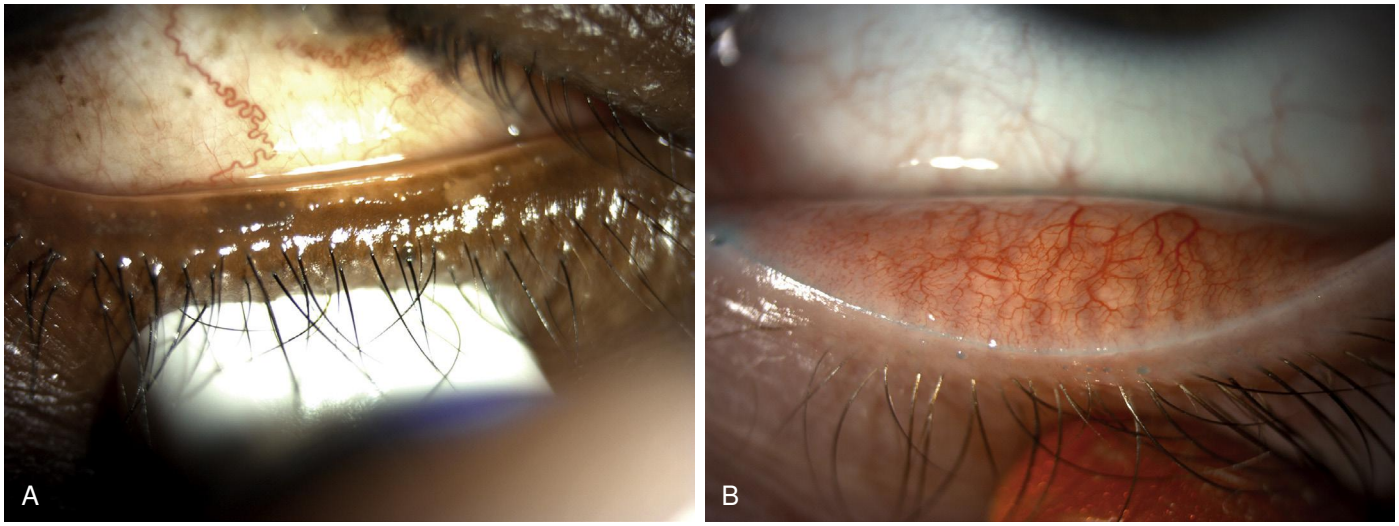

Fig. 2.5 Eyelid margin. **A**, Meibomian gland orifices; **B**, mucocutaneous junction stained with lissamine green. (Courtesy Tracy Doll, O.D., Pacific University College of Optometry, Forest Grove, Ore.)

posterior to these openings (Fig. 2.5B). A groove called the **gray line** runs along the eyelid margin between the cilia insertions and the pores of the meibomian glands. This groove is the location of a surgical plane that divides the eyelid into anterior and posterior portions.

The eyelid margin can be divided into two parts: the medial one-sixth is the lacrimal portion, and the lateral five-sixths is the ciliary portion. The division occurs at the lacrimal papilla, a small elevation containing the lacrimal punctum, the opening that carries the tears into the nasolacrimal drainage system (see Fig. 2.2). Usually, no cilia or meibomian pores are found medial to the punctum, along the lacrimal portion of the eyelid margin.

CLINICAL COMMENT: Epicanthus
Epicanthus, or an epicanthal fold, is a vertical fold of skin at the nasal canthus arising in the medial area of the upper eyelid and terminating in the nasal canthal area (Fig. 2.6). It is common in newborns and may cause the appearance of esotropia. A parent of an infant with an epicanthal fold might worry that the child's eyes are crossed; however, a cover test will identify a true esotropia. As the bridge of the nose develops, the epicanthal fold gradually disappears. An epicanthal fold is common in those of Asian descent because there is no connection between the upper and lower preseptal portions of the palpebral orbicularis muscle.[18]

GROSS ANATOMY OF THE EYELID

Orbicularis Oculi Muscle

The striated fibers of the **orbicularis oculi** muscle are located below the subcutaneous connective tissue layer. The muscle encircles the palpebral fissure and extends from the eyelid

Fig. 2.6 Epicanthal fold may give rise to pseudoesotropia. (From Kanski JJ, Nischal KK. *Ophthalmology: Clinical Signs and Differential Diagnosis*. St Louis: Mosby; 1999.)

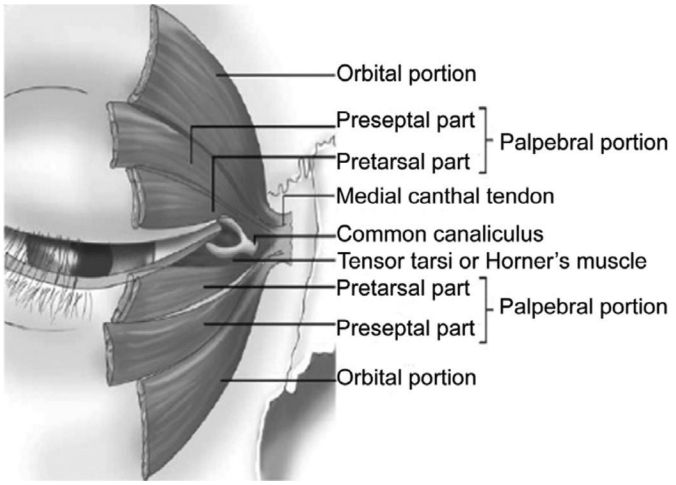

Fig. 2.7 Medial canthal structures. The orbicularis oculi muscle is composed of semicircles of muscle fibers originating at the medial orbital margin and medial canthal tendon. The fibers attach laterally to the lateral canthal tendon. (From Most SP, Mobley SR, Larrabee WF. Anatomy of the eyelids [review]. 2005;13:488.)

margin to overlap onto the orbital margin. It is fixed to the orbital bones by the orbicularis retaining ligament. The muscle can be divided into two regions: palpebral and orbital.

Palpebral Portion of the Orbicularis Muscle

The palpebral portion of the orbicularis oculi muscle occupies the area of the eyelid that rests on the globe and is closest to the eyelid margin. It is divided further into pretarsal and preseptal parts, named for the structures that the divisions overlie. The palpebral portion is composed of semicircles of muscle fibers originating at the medial orbital margin and medial canthal tendon (Fig. 2.7) and attaching to the lateral canthal tendon laterally.[19] The superior and inferior muscle fibers fuse with one another laterally.[20–22]

Deep palpebral orbicularis fibers arise from attachments on the posterior lacrimal crest and medial orbital wall.[23,24] This section of the palpebral part of the orbicularis, **Horner muscle**, encircles the lacrimal canaliculi.[25] Contraction of this portion of the orbicularis assists in moving tears through the canaliculi into the nasolacrimal drainage system.[26] Horner muscle, along with the medial rectus muscle pulley and check ligament, support the medial aspect of the tarsal plate.[24]

Another section of the palpebral orbicularis, **Riolan muscle**, lies near the lid margin on both sides of the meibomian gland openings. It maintains the eyelid margins close to the globe and may aid in regulation of meibum expression from the meibomian glands.[21,27]

CLINICAL COMMENT: Ectropion and Entropion

Abnormal eversion of the eyelid margin away from the globe is called ectropion (Fig. 2.8). A common cause of this is loss of orbicularis muscle tone, a normal occurrence in the aging process. As the eyelid margin falls away from its position against the globe, the lacrimal punctum is no longer in position to drain the tears from the lacrimal lake. Epiphora, an overflow of tears onto the cheek, may occur, causing irritation of the delicate skin in this area.

Inversion of the eyelid margin, called entropion, may result from spasm of the orbicularis oculi muscle causing the lid margin to turn inward (Fig. 2.9). This inward turning of the eyelid margin puts the eyelashes in contact with the globe and, unless relieved, can cause a corneal abrasion. Scarring of the eyelid after trauma or disease may also cause entropion. Both ectropion and entropion are more common in the lower eyelid and can be corrected surgically, if necessary. The anatomic relationship of the muscular and connective tissue components is an important consideration when repair is done.

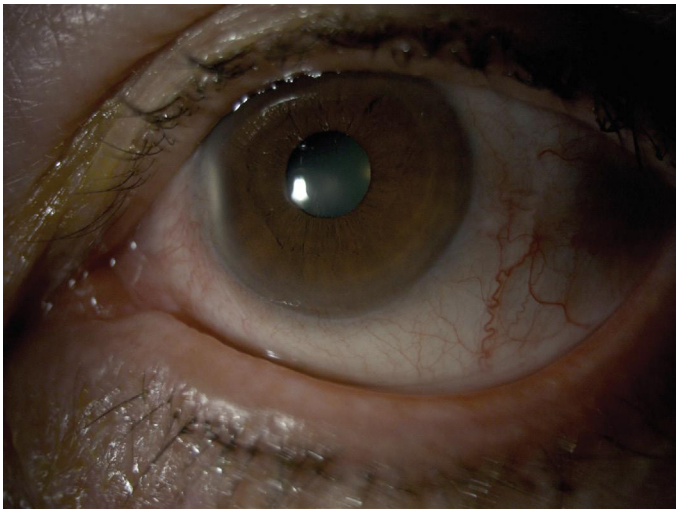

Fig. 2.8 Involutional ectropion.

Orbital Portion of the Orbicularis Muscle

The orbital portion of the orbicularis oculi muscle is attached superiorly to the orbital margin, just medial to the supraorbital notch (see Fig. 10.7). The concentric circular fibers encircle the area outer to the palpebral portion and attach inferiorly at the orbital margin, medial to the infraorbital foramen.

Orbicularis Action

The orbicularis oculi muscle is innervated by cranial nerve VII (the facial nerve). Contraction of the palpebral portion of the orbicularis closes the eyelid gently. In addition, the palpebral orbicularis is the muscle of action in an involuntary blink and a voluntary wink. Relaxation of the levator muscle occurs concurrently.[28] Spontaneous involuntary blinking renews the

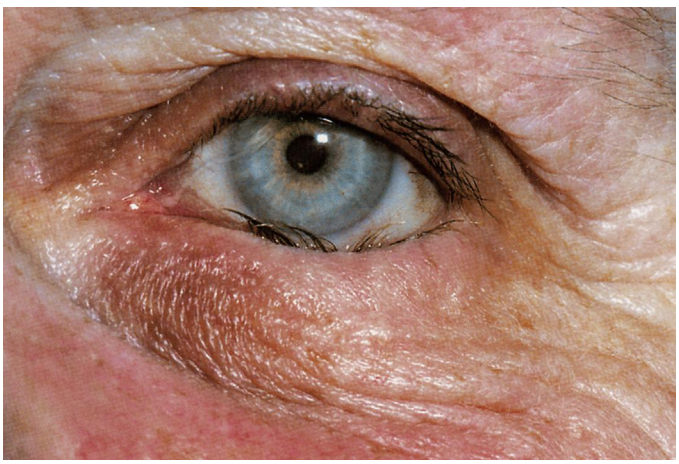

Fig. 2.9 Involutional entropion. (From Kanski JJ. *Clinical Ophthalmology: A Systematic Approach*. ed 5, Oxford, UK: Butterworth-Heinemann; 2003.)

precorneal tear film. A reflex blink is protective and may be elicited by a number of stimuli—a loud noise; corneal, conjunctival, or cilial touch; or the sudden approach of an object.

When the orbital portion of the orbicularis contracts, the eye closes tightly, and the areas surrounding the lids—the forehead, temple, and cheek—are involved in the contraction. Such eyelid closure is often a protective mechanism against ocular pain or after injury and is called reflex blepharospasm. If the lids are closed tightly in a strong contraction, forces compressing the orbital contents can significantly increase the intraocular pressure.[29]

The antagonist to the palpebral portion of the orbicularis muscle is the levator muscle. The antagonist to the orbital portion of the orbicularis muscle is the frontalis muscle.

Superior Palpebral Levator Muscle

The **superior palpebral levator muscle,** the retractor of the upper eyelid, is located within the orbit above the globe and extends into the upper eyelid. It originates on the lesser wing of the sphenoid bone above and in front of the optic foramen, and its sheath blends with the sheath of the superior rectus muscle. As the levator approaches the eyelid from its posterior origin at the orbital apex, two ligaments, the **superior transverse ligament (Whitnall ligament),** found above the levator, and the **intermuscular transverse ligament**, found below the levator, form a sleeve around the levator which changes the anteroposterior direction of the levator to superoinferior (Fig. 2.10).[10,12,30–33]

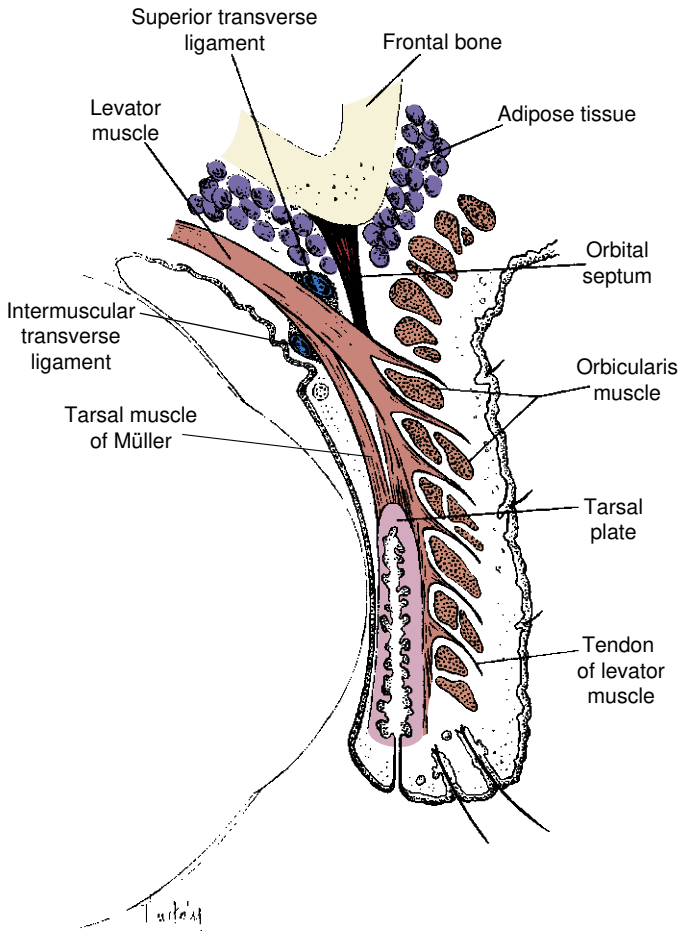

Fig. 2.10 Sagittal section of upper eyelid.

These ligaments form fibrous bands that span the anterior superior orbit from the trochlea to the lateral orbital wall. They provide support for the upper eyelid and orbital structures as well as acting as a pulley for the levator. They are located at the point where the levator muscle fibers end and the aponeurosis begins.[34]

Levator Aponeurosis

As it enters the eyelid, the levator becomes a fan-shaped tendinous expansion, the **levator aponeurosis**. Unlike a typical tendon, the aponeurosis spreads out into an extensive sheet beginning posterior to the orbital septum. The fibers of the aponeurosis penetrate the orbital septum and extend into the upper lid, fanning out across its entire width. These tendinous fibers pass through the submuscular connective tissue. Then, the posterior fibers insert into the lower third of the anterior surface of the tarsal plate, and the anterior fibers run between the muscle bundles of the orbicularis to insert primarily into the skin of the eyelid, although some insert into the intermuscular septa of the orbicularis (see Fig. 2.10).[35] The attachments between the levator aponeurosis, skin, and orbicularis anchor the skin to the underlying tissue in the pretarsal area of the eyelid and create the upper eyelid crease.[35] In those of Eastern Asian descent, the aponeurotic fibers do not attach as extensively to the cutaneous tissue causing an absent or lowered eyelid crease.[1,11,35]

The two side extensions of the aponeurosis are referred to as horns. The lateral horn helps to support the lacrimal gland by holding it against the orbital roof, dividing the gland into orbital and palpebral lobes (Fig. 2.11). The lateral horn then attaches to the lateral canthal tendon and lateral orbital tubercle. The medial horn is attached to the medial canthal tendon and posterior lacrimal crest.

Levator Action

Contraction of the levator muscle causes elevation of the eyelid. The connection between the sheath of the levator and sheath of the superior rectus muscle coordinates eyelid position with globe position so that as the eye is elevated, the lid is raised. The levator is innervated by the superior division of the oculomotor nerve, cranial nerve III.

The eyelids are closed by relaxation of the levator and contraction of the orbicularis oculi muscles. The tonic activity of the levator and the relaxation of the orbicularis hold the eyelid open. In a blink, tonic activity of the levator is suspended, and with a burst of activity, the orbicularis rapidly lowers the lid followed by a cessation of orbicularis activity and resumption of levator tonicity.[36]

Retractor of the Lower Eyelid

The retractor of the lower eyelid is the **capsulopalpebral fascia (lower eyelid aponeurosis)**.[37] This is analogous to the levator aponeurosis in the upper eyelid. The capsulopalpebral fascia, an anterior extension from the sheath of the inferior rectus muscle and the suspensory ligament, inserts into the inferior edge of the tarsal plate.[37] This insertion coordinates lid position with globe movement. The lower eyelid is depressed on globe depression, and the lower eyelid elevates slightly on upward movement of the globe. The capsulopalpebral fascia also fuses with the orbital septum and sends some fibers to insert into the inferior fornix (the junction between the palpebral and bulbar conjunctiva).[37] In contrast to the

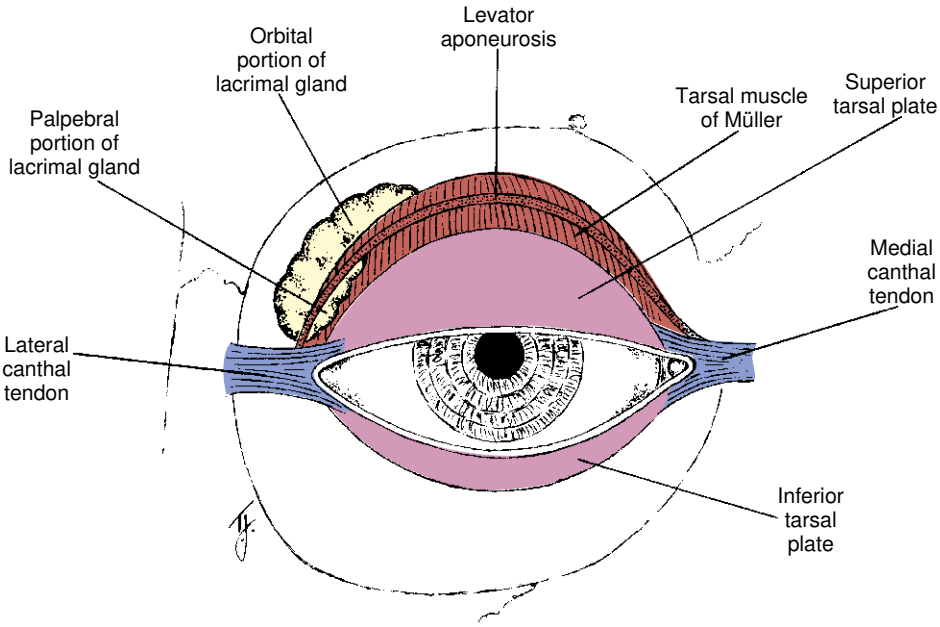

Fig. 2.11 **Orbital area viewed from the front, with skin, subcutaneous tissue, and orbital septum removed.** The levator tendon is sectioned before its insertion on the tarsal plate. The origin and insertion of Müller muscle are evident.

levator aponeurosis, there are few attachments to the skin of the lower lid. This results in a poorly formed lower lid crease.

Tarsal Muscle of Müller

The **superior tarsal muscle (Müller muscle)** is composed of smooth muscle and originates on the posteroinferior aspect of the levator muscle. These smooth muscle fibers begin to appear within the striated muscle at the point at which the muscle becomes aponeurotic. The superior tarsal muscle inserts on the superior edge of the tarsal plate (see Figs. 2.10 and 2.11). Contraction of Müller muscle can provide 2 mm of additional lid elevation.[10]

A similar smooth muscle, the **inferior tarsal muscle**, is found in the lower eyelid. It arises from the inferior rectus muscle sheath and inserts into the lower palpebral conjunctiva and possibly the lower border of the tarsal plate, although investigators disagree about whether the inferior tarsal muscle actually inserts into the tarsal plate or inserts into the tissue below the tarsal plate.[1,9,29,32,38] Both the superior and inferior tarsal muscles are innervated by sympathetic fibers that widen the palpebral fissure when activated (as in situations associated with fear or surprise).

CLINICAL COMMENT: Ptosis

Ptosis is a condition in which the upper eyelid droops or sags. It can be caused by weakness or paralysis of either the levator or Müller muscle. If Müller muscle alone is affected, a less noticeable form of ptosis occurs than when the levator is involved (Fig. 2.12). An individual with ptosis might attempt to raise the lid by using the frontalis muscle, which results in elevation of the eyebrow and wrinkling of the forehead.

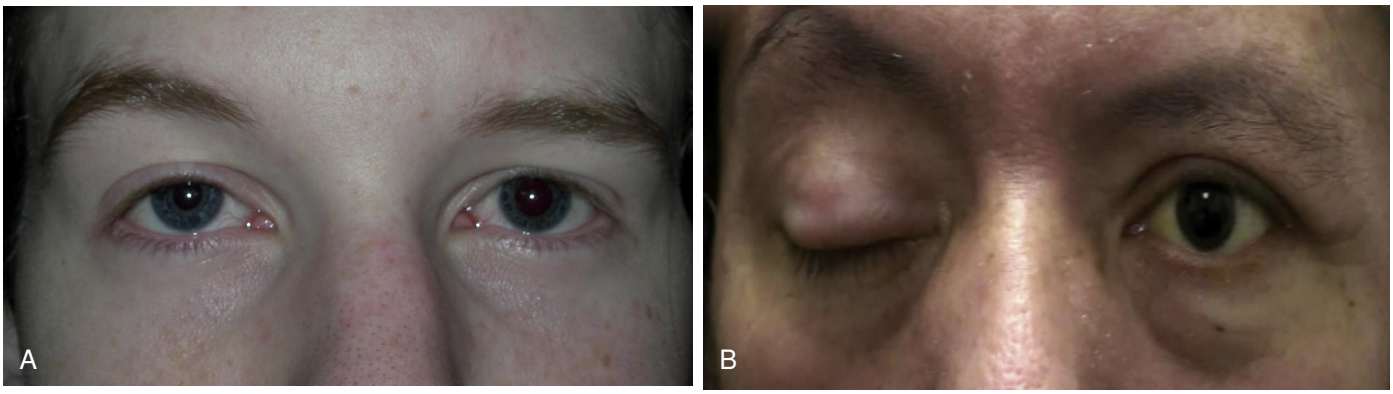

Fig. 2.12 **A**, Mild ptosis of the right eyelid associated with Horner syndrome. **B**, Severe ptosis of the right eyelid following a cranial nerve III palsy. Note the elevation of the ipsilateral eyebrow in both cases, indicating use of the frontalis muscle to aid in raising the eyelid.

Orbital Septum

The **orbital septum** is a thin sheet of fibrous connective tissue that concentrically encircles the orbit. It acts as a barrier to separate the orbital contents from the eyelid structures. The orbital septum extends from the superior orbital rim to insert into the levator aponeurosis 3.7 to 4.4 mm above the tarsal plate (see Fig. 2.10).[14,19] The orbital septum extends from the inferior orbital rim to insert into the tarsal plate of the inferior eyelid. Although the superior tarsal plate height is shorter in Asians, there is no appreciable difference in the insertion site of the orbital septum in relation to the tarsal plate in different races.[14,15]

Tarsal Plate

Each eyelid contains a **tarsal plate (tarsus)** that gives the eyelid rigidity and structure and shapes it to the curvature of the globe. In those of Asian descent, the superior tarsal plate is 8 mm high compared with 10 mm high in Caucasians.[15,39] The inferior tarsal plate is approximately 5 mm high in both Caucasians and Asians.[15,39] The anterior surface of the tarsal plate is adjacent to the submuscular connective tissue. The posterior surface is adherent to the palpebral conjunctiva. The orbital border of the superior tarsus is attached to the Müller muscle, whereas the marginal border lies at the eyelid margin. The lateral aspect of the tarsal plate is attached to the orbital margin by the lateral canthal tendon. Recent studies have shown that the medial aspect of the tarsal plate is attached to the orbital margin by the Horner muscle and the medial rectus capsulopalpebral fascia.[23,24] The medial rectus capsulopalpebral fascia consists of the medial rectus muscle pulley, the medial check ligament, and fibers attaching to the lacrimal caruncle and tarsal plate. The dense connective tissue structures connecting the tarsal plates to the orbital rim hold the tarsal plates in position against the globe during eye and lid movements.

CLINICAL COMMENT: Eyelid Eversion
When attempting to evert the upper eyelid, one should place a cotton-tipped applicator or fingertip above the superior edge of the tarsal plate. The novice experiences difficulty in everting the eyelid if the applicator is placed in the middle of the tarsal plate.

Canthal Tendons

The canthal tendons, previously known as palpebral ligaments, are the insertion points of the orbicularis muscle. The **medial canthal tendon** occupies a significant area in the medial canthal region. It was thought to divide into two limbs, but recent studies have shown only one limb that attaches to the anterior lacrimal crest.[24] Because of this, Horner muscle is now thought to play a greater role in stabilizing the tarsal plate medially. The medial canthal tendon lies anterior to the orbital septum (see Fig. 10.22).

The **lateral canthal tendon** is located posterior to the orbital septum and attaches the lateral edges of the tarsal plates to the lateral orbital margin at the lateral orbital tubercle (see Fig. 10.22). Fibrous connections between the lateral canthal tendon and the check ligament for the lateral rectus muscle allow a slight lateral displacement of the lateral canthus with extreme abduction.[40]

The upper borders of both the medial and lateral canthal tendons are joined to the expansion of the levator tendon, and their lower borders are joined to an expansion of the ligament of Lockwood.

Glands of the Eyelids

The **meibomian glands (tarsal glands)** are sebaceous glands embedded in the tarsal plate. These long, multilobed glands resemble a large bunch of grapes and are arranged vertically such that their openings are located in a row along the eyelid margin posterior to the cilia (Fig. 2.13). Approximately 25 to 40 meibomian glands are found in the upper eyelid, and 20 to 30 meibomian glands are found in the lower eyelid.[27] The length of a gland is approximately 5.5 mm in the upper lid and 2 mm in the lower lid.[27] On eyelid eversion the vertical rows of the meibomian glands can sometimes be seen as yellow streaks through the palpebral conjunctiva. These glands secrete the outer lipid layer of the tear film.

CLINICAL COMMENT: Contact Lens Wear
Some studies have identified a loss in both the number and the length of meibomian glands in contact lens wearers (Fig. 2.14). Loss does not appear to be dependent on the type of lens but rather on the duration of wear and is speculated to be caused by chronic irritation.[41]

The sebaceous **Zeis glands** secrete sebum into the hair follicle of the cilia, coating the eyelash shaft to keep it from becoming brittle.[9]

The **Moll glands** have been called modified sweat glands but are more accurately described as specialized apocrine glands.[42] They are located near the eyelid margin and their ducts empty into the hair follicle, into the Zeis gland duct, or directly onto the lid margin. Similar glands found in the axillae are scent organs, but that is likely not the function of the Moll gland.[9,16]

The **accessory lacrimal glands of Krause** are located in the stroma of the conjunctival fornix, and the **accessory lacrimal glands of Wolfring** are located along the orbital border of the tarsal plate (see Fig. 2.13). These glands are oval and display numerous acini. In the upper fornix, 20 to 40 glands of Krause are found, although only six to eight such glands appear in the lower fornix.[1] The glands of Wolfring are less numerous. The secretion of the accessory lacrimal glands appears similar to that of the main lacrimal gland and contributes to the aqueous layer of the tear film.

HISTOLOGICAL FEATURES OF THE EYELID

Skin

The skin of the eyelid contains many fine hairs, sebaceous glands, and sweat glands. It is the thinnest skin in the body, easily forms folds and wrinkles, and is almost transparent in the very young.[1] The epidermal layer of the skin consists of a basal germinal layer, a granular layer, and a superficial layer that is keratinized. The underlying dermis is abundant in elastic fibers. A very sparse areolar connective tissue layer, the subcutaneous tissue, lies below the dermis. This thin layer is devoid of adipose tissue in the tarsal portion. A pad of fat is often located in this region in the orbital portion that separates the orbicularis from the skin.[9]

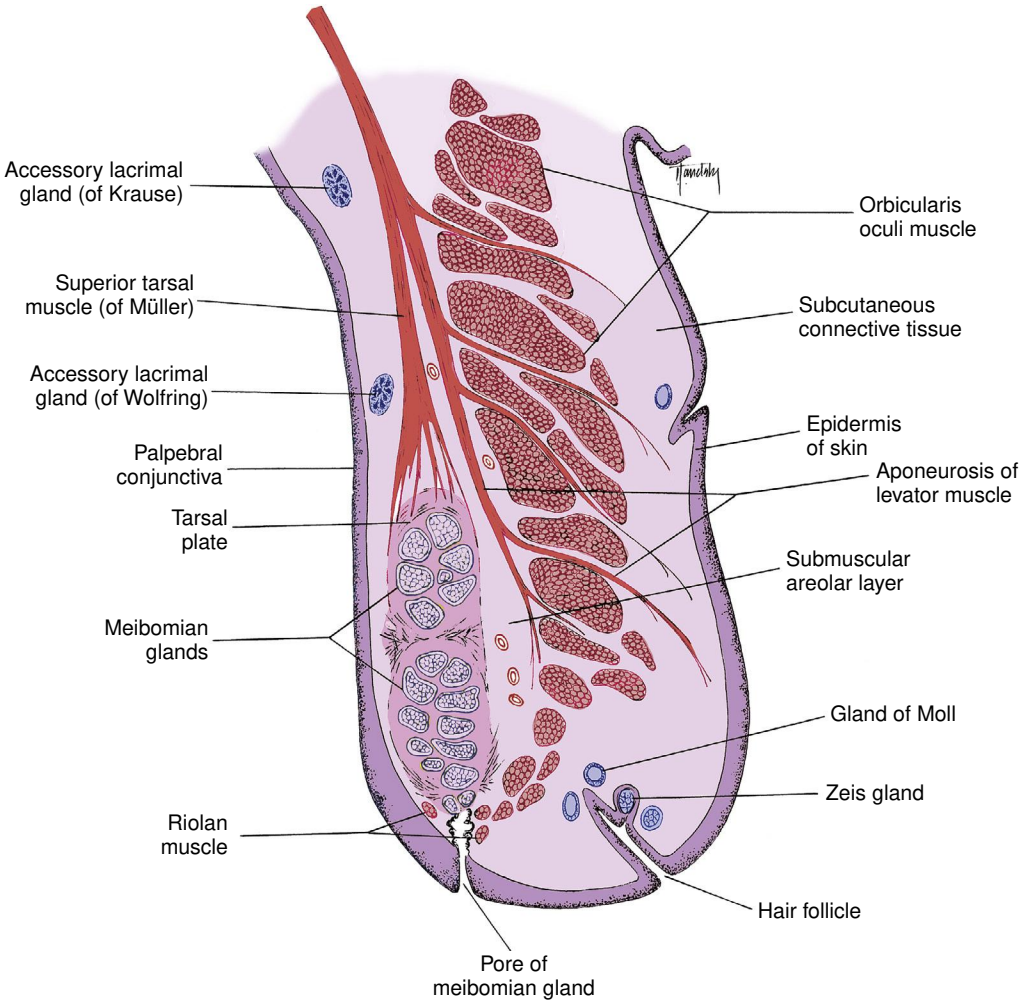

Fig. 2.13 Sagittal section of the eyelid illustrating palpebral muscles and glands.

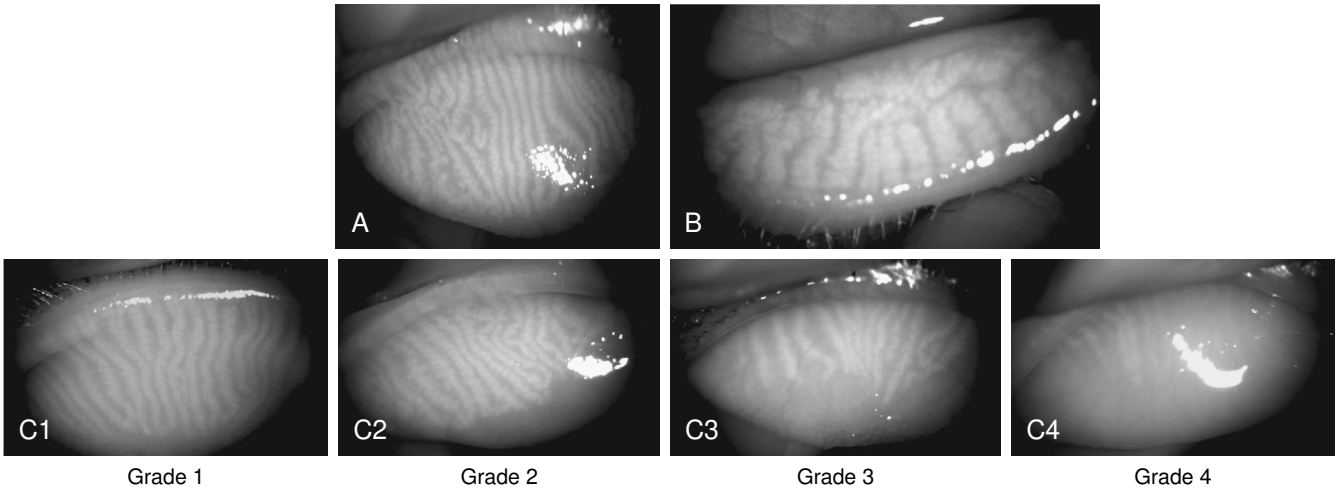

Fig. 2.14 Infrared digital photography of meibomian glands. **A**, Normal meibomian glands of the upper eyelid. **B**, Normal meibomian glands of the lower eyelid. **C**, Grading scale for meibomian gland loss. (Courtesy Patrick Caroline, C.O.T., Pacific University College of Optometry, Forest Grove, Ore.)

CLINICAL COMMENT: Fluid Accumulation in the Eyelid

The loose connective tissue layer of the eyelid can be separated easily from the underlying tissue and is the site for the accumulation of blood or edema in injuries or the accumulation of exudates in inflammatory conditions. The thinness of the skin and the fine underlying adjacent tissue allow this area to be greatly distensible, as evidenced in patients with periorbital cellulitis or ecchymosis (a black eye). This skin recovers rapidly after distention because of the elasticity of the dermis. With advancing age, however, the skin loses its elasticity, and stretching will cause exaggerated skin folds.

Muscles

The **orbicularis oculi** lies deep to the subcutaneous layer. These striated muscle bundles run throughout the eyelid. In a sagittal section of the lid prepared for microscopic examination, the orbicularis bundles are cut in cross-section (Fig. 2.15). Along the lid margin, small muscle bundles located on both sides of the meibomian glands represent a specific part of the orbicularis, the ciliary part (**Riolan muscle**), which holds the eyelid margin against the globe (see Fig. 2.15).

Posterior to the orbicularis lies another layer of loose connective tissue, the submuscular areolar layer, which separates the muscle from the tarsal plate. Between this layer and the tarsal plate is a potential space, the pretarsal space, that contains the vessels of the palpebral arcades. An analogous preseptal space is located between the orbicularis and the orbital septum.

Tendinous fibers of the **levator aponeurosis** run through the submuscular tissue layer between the orbicularis and the superior tarsal muscle to insert into the tarsal plate and the skin of the eyelid (see Fig. 2.13). It is this insertion of fibers that anchors the skin so firmly in the tarsal portion of the eyelid. The smooth muscle fibers of the **superior tarsal muscle** are located above the superior tarsal plate and insert into its upper edge.

Tarsal Plates

The **tarsal plates** are composed of dense connective tissue. The collagen fibrils of this tissue are of uniform size and run both vertically and horizontally to surround the meibomian glands.

Palpebral Conjunctiva

The **palpebral conjunctiva** lines the inner surface of the eyelid and at the fornix transitions into bulbar conjunctiva, which covers the sclera. At the **mucocutaneous junction** of the lid margin, the epithelial layer of the conjunctiva is continuous with the epithelium of the skin (see Fig. 2.15). As the conjunctiva lines the eyelid, squamous cells of the skin are replaced by cuboidal and columnar cells of the conjunctiva, forming a stratified columnar mucoepithelial layer, and the granular and keratinized layers of the skin are discontinued.[43]

The epithelial layer of the conjunctiva thickens at the mucocutaneous junction (see Fig. 2.15) and may be a location for stem cells that repopulate the palpebral conjunctival epithelium.[44] The mucocutaneous junction transitions to the **lid wiper region** at the conjunctival edge of the upper and lower eyelids. This thickened area of palpebral conjunctiva, 0.3 to 1.5 mm in height, is held tightly against the eye by the Riolan muscle and is the part of the eyelid that makes contact with the globe.[43] It is responsible for spreading tears during the blink. In the lid wiper region there are large stratified cuboidal and columnar cells interspersed with goblet cells that secrete mucin onto the ocular surface.[45]

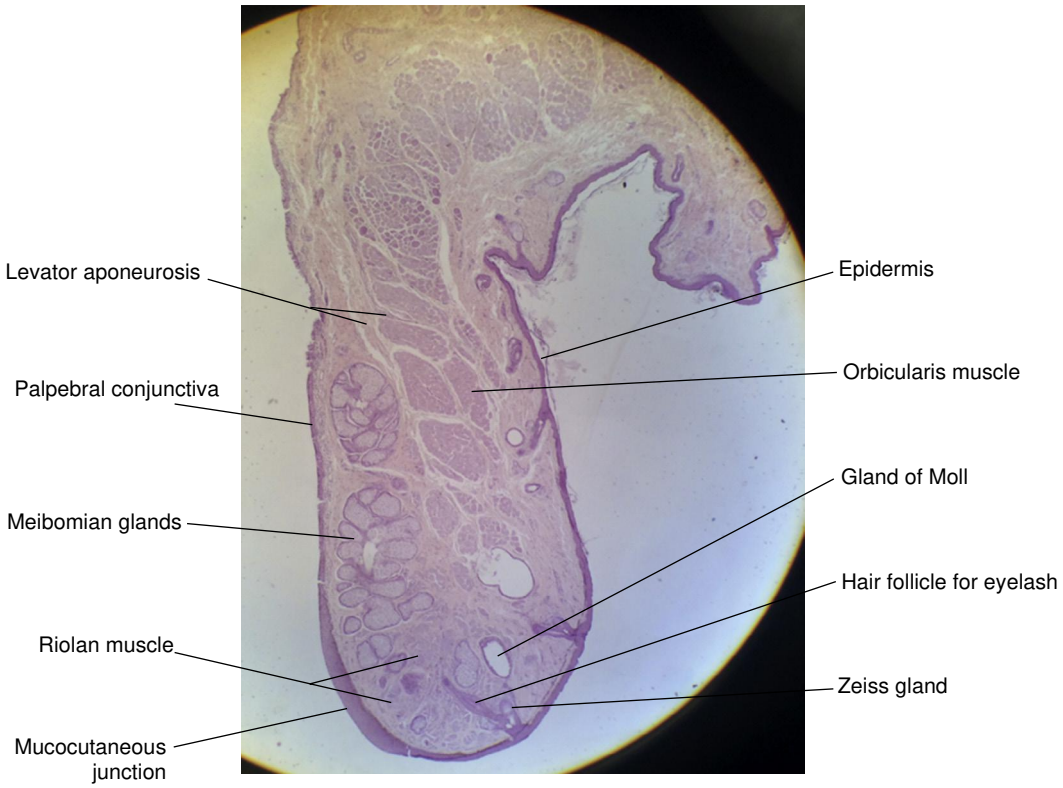

Fig. 2.15 Light micrograph of the upper eyelid.

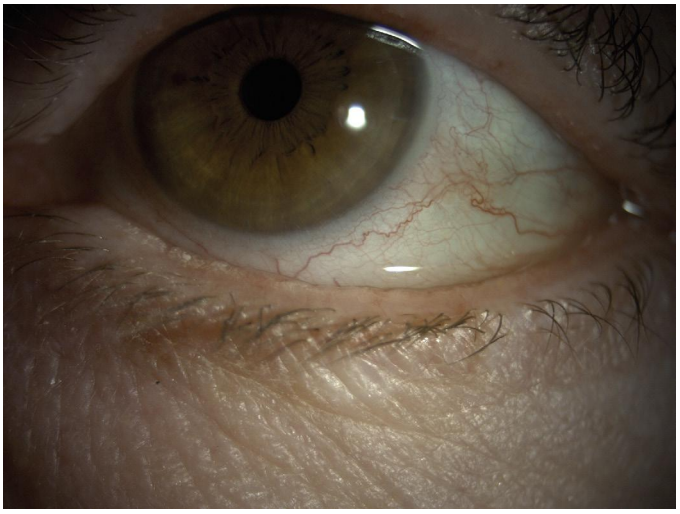

Fig. 2.16 Lid wiper epitheliopathy along the lower eyelid margin. (Courtesy Tracy Doll, O.D., Pacific University College of Optometry, Forest Grove, Ore.)

CLINICAL COMMENT: Lid Wiper Epitheliopathy
Lid wiper epitheliopathy occurs when there is alteration of the conjunctival epithelium along the eyelid margin because of increased friction between the eyelid and the ocular surface or contact lens surface (Fig. 2.16).[46] Tear instability or eyelid anatomy that causes greater pressure between the lid and cornea can contribute to this condition.[47]

Goblet cells, which produce, store, and secrete the innermost mucous layer of the tear film, are scattered throughout the stratified columnar conjunctival epithelium (Fig. 2.17). These cells are most numerous in the plica semilunaris followed by the inferior nasal aspect of the tarsal conjunctiva.[48] Their number decreases with advancing age and increases in inflammatory conditions. The goblet cell produces mucin droplets that accumulate, causing the cell to swell and become goblet shaped. The surface of the cell finally ruptures, releasing mucus into the tear layers. Parasympathetic and sympathetic nerves have been associated with goblet cells and may play a role in their secretion.[49] Invaginations of conjunctival epithelium, often located near the fornix, are called **crypts of Henle**. Goblet cells release their mucus into the cavity formed by these invaginations, and the mucus may become trapped if the opening to the crypt is narrow.

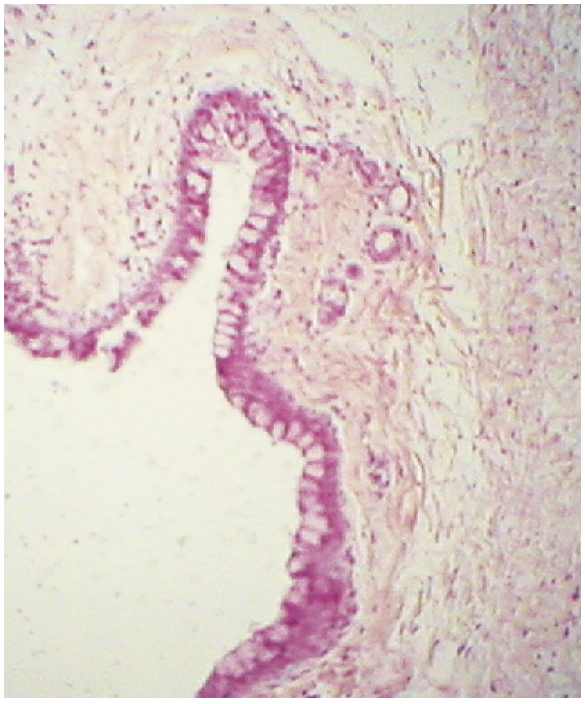

Fig. 2.17 Light micrograph of the conjunctival palpebral epithelium showing goblet cells.

The surface of the superficial conjunctival cell contains microvilli and microplicae and is covered with a glycocalyx similar to that found on the corneal surface.[50,51] Subsurface vesicles, found below the outer membrane of the superficial conjunctival cell, may be an additional source of mucous material. As these vesicles fuse with the epithelial cell membrane, chains extend outward to form a chemical bond with the mucous layer secreted by the goblet cells. These chains increase the adherence of the tear film. These vesicle membranes may also contribute to the microvilli present on the surface of the epithelial cell.[52]

CLINICAL COMMENT: Vitamin A Deficiency
Vitamin A deficiency has been associated with a loss of goblet cells. In dry-eye disorders showing a decrease in the number of goblet cells, treatment with vitamin A therapy can induce the reappearance of goblet cells.[53,54] In acute disease, cellular proteins may be activated causing keratinization of the surface epithelia.[55]

The **submucosa (stroma, substantia propria)** of the palpebral conjunctiva is very thin in the tarsal portion of the eyelid but becomes increasingly thick in the orbital portion. It is composed of loose, vascularized connective tissue that can be subdivided into an outer lymphoid layer and a deep fibrous layer. In addition to the normal connective tissue components (collagen fibrils, fibroblasts, ground substance, and a few fine elastic fibers), the lymphoid layer contains macrophages, mast cells, polymorphonuclear leukocytes, eosinophils, accumulations of lymphocytes, and occasional Langerhans cells.[56] Immunoglobulin A is found in the lymphoid layer, making the conjunctiva an immunologically active tissue.[57,58] More lymphoid tissue is found in palpebral conjunctiva than in bulbar conjunctiva.[59]

The deep fibrous layer connects the conjunctiva to underlying structures and contains a random network of collagen fibrils and numerous fibroblasts, blood vessels, nerves, and accessory lacrimal glands. This fibrous layer merges and is continuous with the dense connective tissue of the tarsal plate. The conjunctiva is so richly supplied with blood vessels that a pale palpebral conjunctiva may be a clinical sign of anemia.

CLINICAL COMMENT: Conjunctival Concretions
Conjunctival concretions are small, yellow-white nodules about the size of a pinhead and are most often located in the tarsal conjunctiva (Fig. 2.18). They are composed of fine granular material and membranous debris, products of cellular degeneration. These nodules are hardened but contain no calcium deposits.[60] Concretions are found more often in elderly patients and can be removed if they produce foreign body irritation.

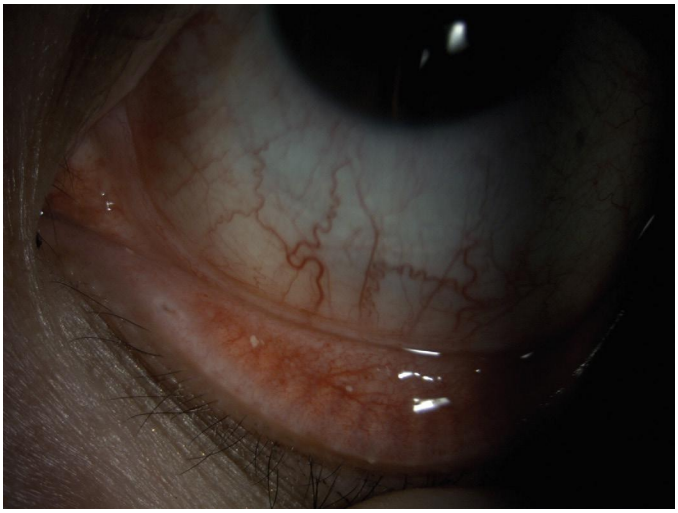

Fig. 2.18 Concretions on the inferior palpebral conjunctiva.

Glands

The **meibomian glands** are large sebaceous glands occupying the length of the tarsal plate. Each consists of 10 to 15 lobes or secretory acini attached to a large central duct.[27,61,62] The duct is arranged vertically such that the opening is located at the edge of the tarsal plate corresponding to the eyelid margin (Fig. 2.19).

Meibomian glands are holocrine glands. Their secretion is produced by the decomposition of the entire cell. Each acinus is surrounded by a layer of myoepithelial cells and is filled with actively dividing cells. The daughter cells, called meibocytes, move centrally in the acini, become large and polyhedral, and begin to synthesize lipids and fill with lipid droplets.[27,63] As each meibocyte degenerates, the nucleus begins to diminish in size, and the cell membrane disintegrates.

Cells in varying stages of decomposition pack each saccule. Decomposed cells move down the duct toward the opening. During a blink, the surrounding Riolan muscle compresses the tarsal plate releasing meibum into the tear film, at which point the secretion (lipid droplets and cell debris) forms the outermost lipid layer of the tear film. The predominant innervation of meibomian glands is parasympathetic and may act to alter the lipid production or cause cell rupture.[27,64,65]

The oily secretion of the meibomian glands has been called meibum to distinguish it from sebum secreted by the sebaceous glands of the skin and hair follicles. Meibum is much more viscous than sebum; sebum is more polar and if mixed with the tear film will contaminate and disrupt it.[66]

Histologically, the sebaceous Zeis glands are similar to the meibomian glands. The **Zeis glands**, however, are composed of just one or two acini and are associated with the eyelash follicle (Fig. 2.20). In general, two Zeis glands are present per follicle. They release sebum into the follicle, thereby preventing the cilia from becoming dry and brittle.[61]

Moll glands, modified apocrine glands, are also located near the eyelash follicle. They consist of a spiral that begins as a large cavity, the neck of which becomes narrow as it forms a duct. The large lumen often appears empty and is surrounded by a layer of cuboidal to columnar secretory cells (Fig. 2.21). Myoepithelial cells surround the secretory cells. Because the Moll gland is an

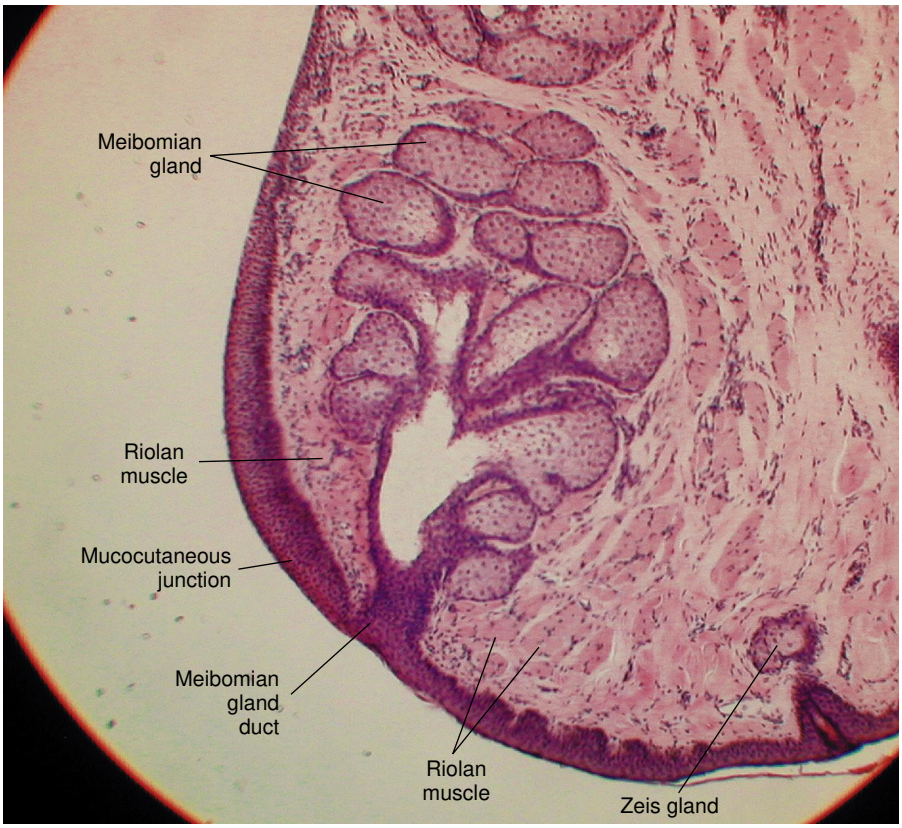

Fig. 2.19 Light micrograph of the meibomian glands embedded in the tarsal plate. The duct and pore are shown.

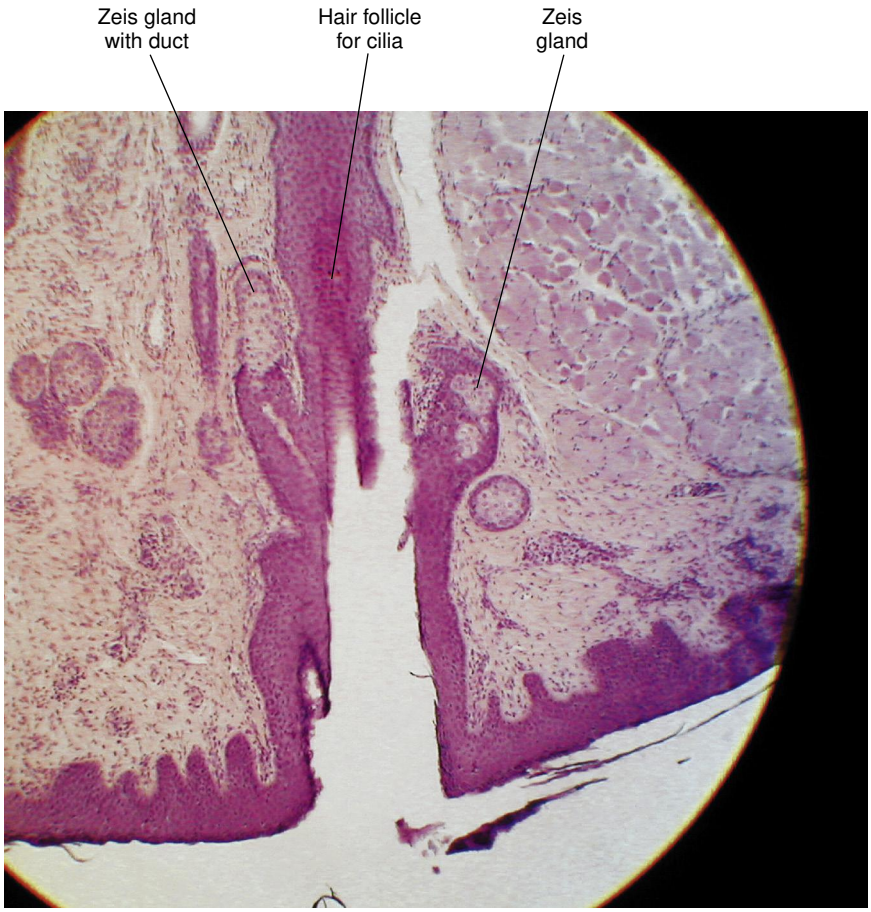

Fig. 2.20 Light micrograph of the eyelid margin. A Zeis gland is located next to a hair follicle. The duct is evident.

apocrine gland, its secretion is composed not of the whole cell but of parts of cellular cytoplasm. The duct might empty into the duct of a Zeis gland, or it might open directly onto the eyelid margin between cilia. Histochemical studies have identified antimicrobial peptides and proteins in Moll gland secretions that suggest a role in immune defense protecting the lash shaft and ocular surface.[42,67]

Accessory lacrimal glands are groups of secretory cells with a truncated-pyramid shape arranged in an oval pattern around a central lumen (Fig. 2.22). The acini are surrounded, sometimes

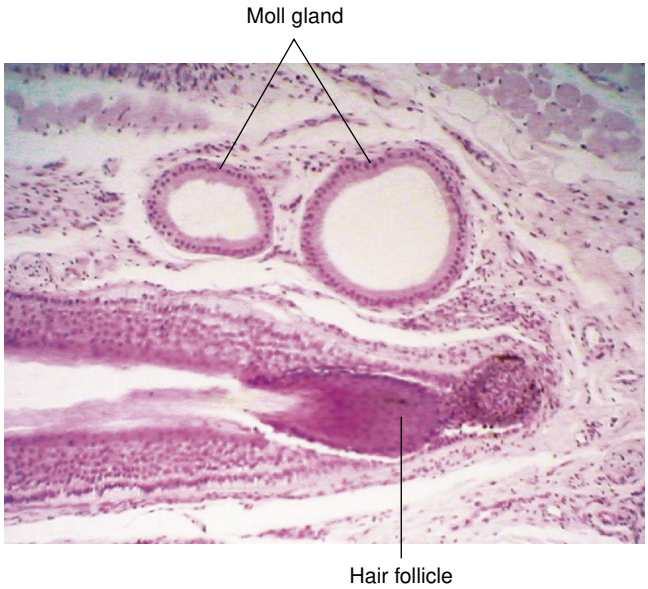

Fig. 2.21 Light micrograph of a hair follicle of a cilia. Two Moll glands are seen.

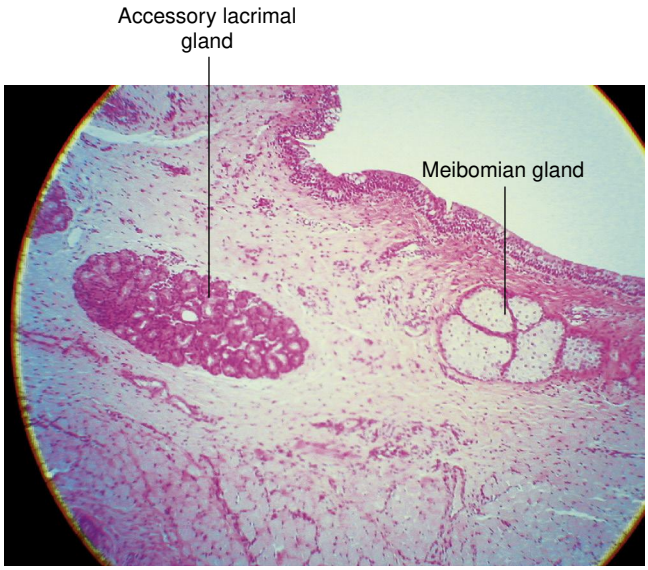

Fig. 2.22 Light micrograph of a lower eyelid. An accessory lacrimal gland is seen near the tarsal plate, within which houses a meibomian gland.

incompletely, by a row of myoepithelial cells. These are merocrine glands—that is, the cell remains intact and secretes a product—and these glands have the same histological makeup as the main lacrimal gland.[68] The secretion contains antibacterial agents, lysozyme, lactoferrin, and immunoglubulins.[69] The accessory lacrimal glands are densely innervated, as is the main lacrimal gland.[70] Animal studies suggest that the ducts of Wolfring glands have a tortuous course and open onto the palpebral conjunctiva.[68]

CLINICAL COMMENT: Common Eyelid Conditions

A hordeolum is an acute inflammation of an eyelid gland, usually caused by staphylococci.[71] An infected Zeis or Moll gland is called an external hordeolum, or common stye, and usually comes to a head on the skin of the eyelid (Fig. 2.23). A localized infection of a meibomian gland usually drains from the inside surface of the eyelid and thus is called an internal hordeolum (Fig. 2.24). Mild cases usually resolve with warm compress treatment, but more severe cases might require antibiotic treatment.

A chalazion is a localized, noninfectious, and sometimes painless swelling of a meibomian gland, often caused by an obstructed duct (Fig. 2.25). The gland may extrude its secretion into surrounding tissue, setting up a granulomatous inflammation. Medical or surgical therapy sometimes is necessary.

Blepharitis is an inflammatory disease of either the eyelid skin and lashes (anterior blepharitis) or meibomian glands (posterior blepharitis). It is often caused by a disruption of the microflora on the lid margin with increased presence of *Staphylococcus aureus*.[72] In addition, Demodex parasites increase with age and can cause blepharitis involving either the lashes or the meibomian glands.[73,74] Clinical presentation includes crusting or translucent debris surrounding the lash base, erythema of the lid margin, or plugging of the meibomian glands (Fig. 2.26). Blepharitis is typically a chronic condition that requires periodic treatments with warm compresses, lid hygiene, and antibiotic or antiparasitic agents to aid in restoring normal microflora. Long-term blepharitis can lead to loss of eyelashes, hyperkeratinization and fibrosis of the meibomian glands, and hyperemia, telangiectasia, and scarring of the lid margin.[72,75]

INNERVATION OF THE EYELIDS

The ophthalmic and maxillary divisions of the trigeminal nerve provide sensory innervation of the eyelids. The upper lid is supplied by the supraorbital, supratrochlear, infratrochlear, and lacrimal nerves, branches of the ophthalmic division of the trigeminal nerve. Innervation to the lower lid is from the infratrochlear branch of the ophthalmic nerve and the zygomaticofacial and infraorbital nerves, branches of the maxillary division of the trigeminal nerve (Fig. 2.27). Motor control of the orbicularis muscle is through the temporal and zygomatic branches of the facial nerve, and that of the levator muscle is through the superior division of the oculomotor nerve. The tarsal smooth muscles are innervated by sympathetic fibers from the superior cervical ganglion.

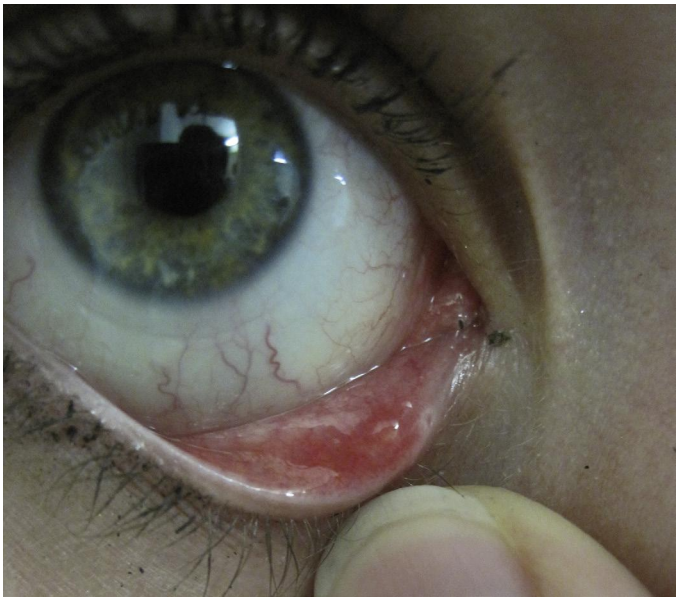

Fig. 2.24 Internal hordeolum.

BLOOD SUPPLY OF THE EYELIDS

The blood vessels are located in a series of arcades or arches in each eyelid. The marginal palpebral arcade lies near the eyelid margin, and the peripheral palpebral arcade lies near the orbital edge of the tarsal plate (Fig. 2.28). The vessels forming these arcades are anastomosing branches from the medial and lateral palpebral arteries. The medial palpebral arteries branch from either the ophthalmic artery or from the dorsonasal artery. The lateral palpebral arteries are branches of the lacrimal artery.

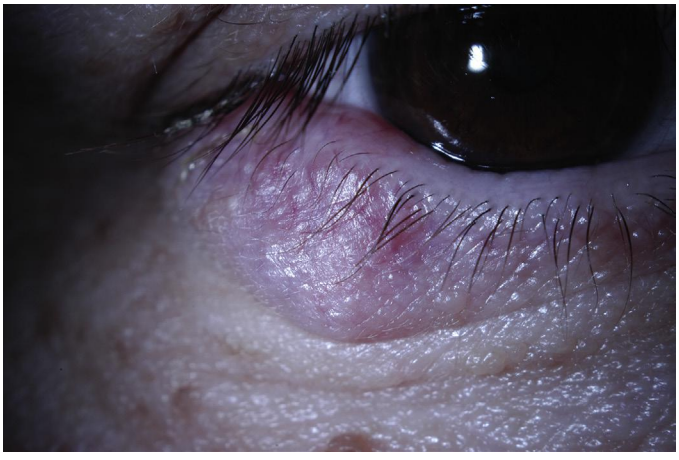

Fig. 2.23 External hordeolum.

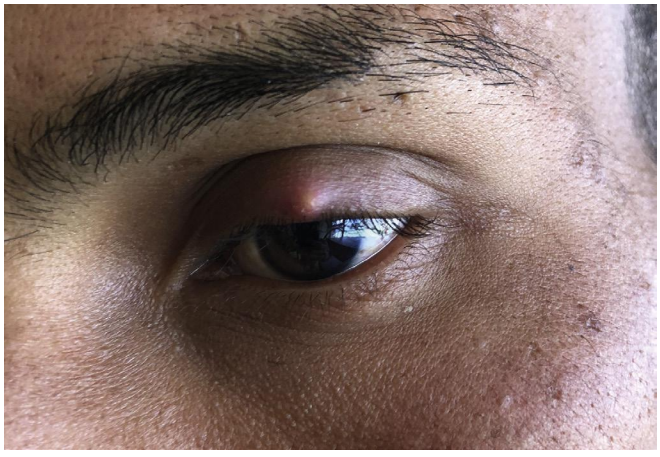

Fig. 2.25 Painless chalazion.

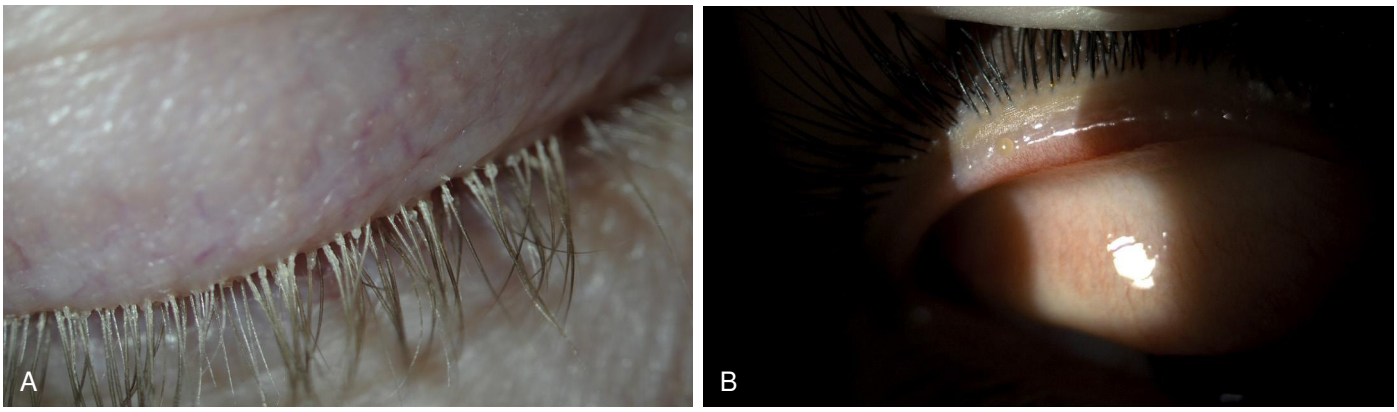

Fig. 2.26 Inflammation of Eyelids. **A**, Anterior blepharitis showing translucent debris surrounding the base of the eyelash. **B**, Plugged meibomian gland.

Normal variations occur in the blood supply, and the most common variation is a lack of the peripheral arcade in the lower lid.

LACRIMAL SYSTEM

The lacrimal system consists of the lacrimal and ancillary glands, tear film, puncta, canaliculi, and nasolacrimal duct. These structures work together to balance the inflow and outflow of the tears while providing appropriate moisture to the cornea and conjunctiva.

Tear Film

The tear film, which covers the anterior surface of the globe, has several functions: (1) it keeps the surface of the eye moist and serves as a lubricant between the globe and eyelids; (2) it traps debris and helps remove sloughed epithelial cells and debris; (3) it is the primary source of atmospheric oxygen for the cornea; (4) it provides a smooth refractive surface necessary for optimum optical function; (5) it contains antibacterial substances (lysozyme, beta-lysin, lactoferrin, and immunoglobulins) to help protect against infection;[76] (6) it helps to maintain corneal hydration through changes in tonicity that occur with evaporation; and (7) it contains various growth factors and peptides that can regulate ocular surface wound repair.[69]

Traditionally, the tear film is described as having three layers; however, there is no clear distinction between the aqueous and mucin layers (Fig. 2.29).[77] The outermost layer is a **lipid layer** containing waxy esters, cholesterol, and free fatty acids, primarily produced by the meibomian glands. The lipid layer retards evaporation, provides lubrication for smooth eyelid movement, and stabilizes the tear film by lowering surface tension, keeping

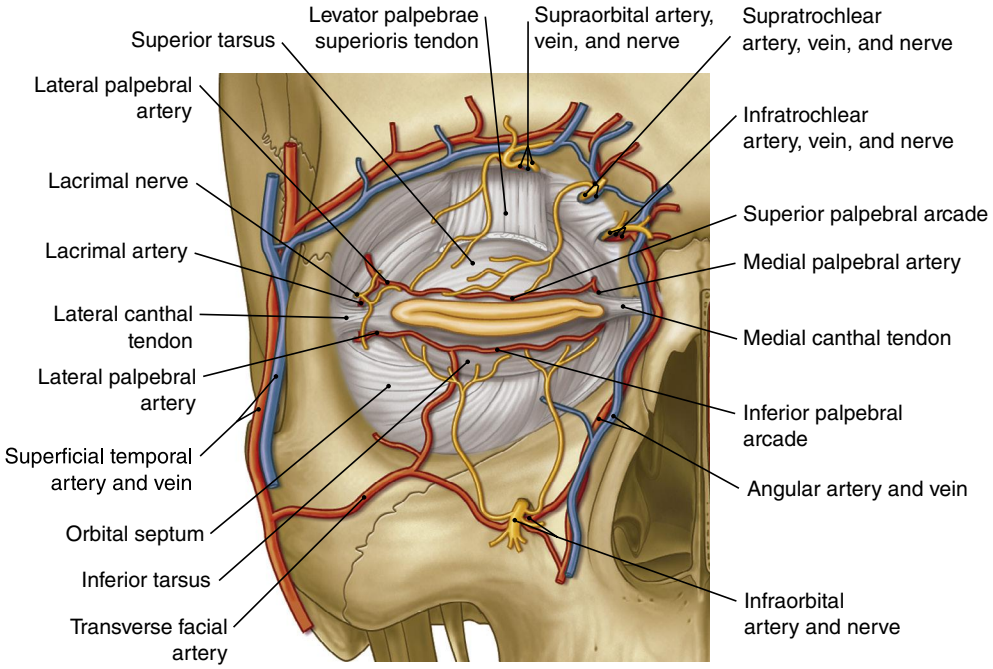

Fig. 2.27 Palpebral innervation. (From Klonisch T, Hombach-Klonisch S. Sobotta. *Clinical Atlas of Human Anatomy*. Elsevier 2019.)

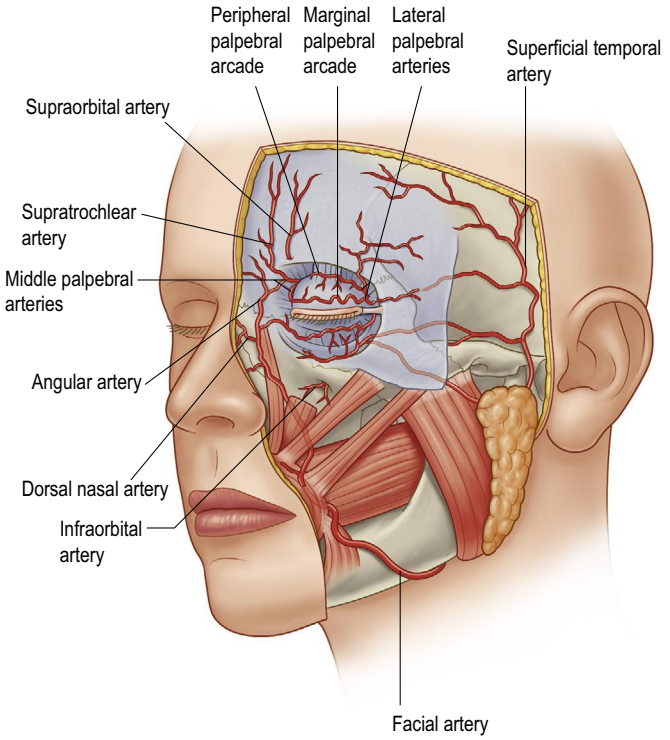

Fig. 2.28 Palpebral blood supply. (Adapted from: Lemke BN, Lucarelli MJ. Anatomy of the ocular adnexa, orbit, and related facial structures. In: Nesi FA, Lisman RD, Levine MR, eds: *Smith's Ophthalmic Plastic and Reconstructive Surgery.* 2nd ed. St Louis: 1998; Mosby.)

tears from overflowing onto the cheeks.[27] The middle or **aqueous layer** contains inorganic salts, glucose, urea, enzymes, proteins, glycoproteins, and antibacterial substances.[1] It is secreted by the main and accessory lacrimal glands. The innermost or **mucin layer** acts as an interface that facilitates adhesion of the aqueous layer of the tears to the ocular surface and provides a coating which reduces friction between the eyelid and cornea.[78] The mucin layer is composed of the glycocalyx secretion from the surface epithelia and mucin produced and secreted by the conjunctival goblet cells. Mucins can also bind and entrap bacteria and viruses blocking binding sites on microbes and preventing them from penetrating the ocular surface.[69]

According to some sources, the tear film is 4 to 8 µm thick, with the aqueous layer accounting for 90% of the thickness.[9,79–81] The lipid layer is approximately 53 nm thick.[82]

CLINICAL COMMENT: Tear Film Assessment

Various clinical procedures are used to assess the extent of tear abnormalities. In one method, fluorescein dye is instilled into the lower cul-de-sac, and it spreads throughout the tear film. After a blink, the thin lipid upper layer begins to break down, and dry spots appear. The time between the completion of the blink and the first appearance of a dry spot is termed the tear film breakup time (TBUT) and gives an indirect measure of the evaporative rate. Normally the TBUT is greater than 10 seconds and longer than the time between blinks.[83,84] A short TBUT can occur if irregularities or disturbances in the corneal surface prevent complete tear film adherence or if abnormalities exist in the lipid layer causing increased evaporation.

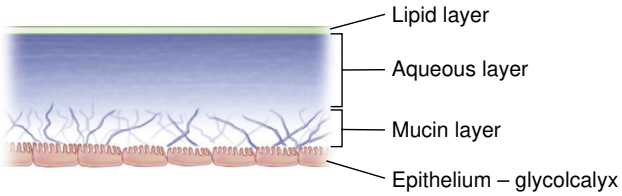

Fig. 2.29 Schematic representation of the tear film.

Lacrimal Secretory System

The lacrimal secretory system includes the main lacrimal gland, the accessory lacrimal glands, the meibomian glands, and the conjunctival goblet cells.

The main lacrimal gland is located in a fossa on the temporal side of the orbital plate of the frontal bone, just posterior to the superior orbital margin. The lacrimal gland is divided into two portions, palpebral and orbital, by the aponeurosis of the levator muscle (see Fig. 2.11). The superior orbital portion is larger and almond shaped. The superior surface lies against the periorbita of the lacrimal fossa, the inferior surface rests against the aponeurosis, the medial edge lies against the levator, and the lateral edge lies on the lateral rectus muscle. The palpebral lobe is one-third to one-half the size of the orbital lobe and is subdivided into two or three sections. If the upper lid is everted, the lacrimal gland can be seen above the edge of the upper tarsal plate. Ducts from both portions of the gland exit through the palpebral lobe.

The lacrimal gland consists of lobules made up of numerous acini. Each acinus is an irregular arrangement of secretory cells around a central lumen surrounded by an incomplete layer of myoepithelial cells. A network of ducts connects the acini and drains into one of the main excretory ducts. There are approximately 12 of these ducts, which empty into the conjunctival sac in the superior fornix.[1] The secretion is composed of water, electrolytes, and antibacterial agents, including lysozyme, lactoferrin, and immunoglobulins. The accessory glands are located in the subconjunctival tissue between the fornix area and the tarsal plate. Histologically, the accessory lacrimal glands are identical to the main lacrimal gland. Basic secretion maintains the normal volume of the aqueous portion of the tears, and reflex secretion increases the volume in response to a stimulus. Both main and accessory glands play a role in basic and reflex secretion.

The lacrimal gland is supplied by the lacrimal artery, a branch of the ophthalmic artery. Sensory innervation is through the lacrimal nerve, a branch of the ophthalmic division of the trigeminal nerve. Vasomotor sympathetic innervation causes decreased lacrimal secretion and secretomotor parasympathetic innervation results in increased lacrimation. Reflex tearing occurs when branches of the ophthalmic nerve within the cornea or conjunctiva are stimulated or in response to external stimuli, such as intense light. The afferent pathway for reflex tearing is through the trigeminal nerve, and the efferent pathway is through the parasympathetic fibers of the facial nerve.

Although it was thought that accessory glands provided the watery component of tear secretion and the main lacrimal

gland was primarily active during reflex or psychogenic stimulation,[85] it is now thought that all lacrimal glands work together to produce the aqueous layer and that production is stimulus driven.[77,86] The rate of production ranges from low levels in sleep to high levels under conditions of stimulation.[69,87]

CLINICAL COMMENT: Dry Eye

Alteration in any layer of the tear film or in eyelid anatomy or lid closure can result in depletion of the tear film and cause dry eye, one of the most common disorders seen in clinical eye care practice.

Dry eye syndrome, also known as keratoconjunctivitis sicca, has a complex etiology and may be caused by a deficiency of any of the layers of the tear film or a change in the interaction between the layers. Aqueous deficiency, often resulting in tear hyperosmolarity and ocular surface inflammation, is common, and normal aging can cause a decrease of aqueous tear production. Autoimmune diseases, such as Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus, can affect the lacrimal gland causing a deficiency in the aqueous layer. Increased meibum viscosity can cause obstruction of the meibomian glands resulting in meibomian gland dysfunction and evaporative dry eye.[27] Loss of lipid secretion can lead to alterations in the lipid layer, allowing increased evaporation of the tear film and leading to dry eye symptoms and corneal epithelial compromise. Conditions with deficient secretion of the mucin layer are associated with reduced goblet cell populations, such as chemical burns, Stevens-Johnson syndrome, and ocular pemphigoid. Complaints associated with dry eye include scratchiness and foreign body sensation.

The tear film can be augmented by the application of ocular lubricants, consisting of artificial tears during the day and ointments at night. More serious dry eye problems can be treated with procedures that decrease tear drainage. Punctual plugs are a temporary solution, and electrocautery can produce permanent closure of the punctum. Ocular surface inflammation contributing to dry eye may be successfully treated with topical antiinflammatory agents, such as cyclosporin or lifitegrast eye drops.[78]

Tear Film Distribution

The lacrimal gland fluid is secreted into the lateral part of the upper fornix and descends across the anterior surface of the globe. Contraction of the orbicularis forces meibum out of the pores and eyelid motion spreads the thin lipid layer across the surface. Each blink reforms the tear film, spreading it over the ocular surface.

At the posterior edge of both upper and lower eyelid margins, there is a meniscus of tear fluid (Fig. 2.30). The meniscus at the lower lid is more easily seen. The upper tear meniscus is continuous with the lower meniscus at the lateral canthus whereas at the medial canthus the tear menisci lead directly to the puncta and drain into them. The lacrimal lake, a tear reservoir, is located in the medial canthus. The plica semilunaris makes up the floor of the lake and the caruncle is located at its medial side.

Nasolacrimal Drainage System

Some tear fluid is lost by evaporation and some by reabsorption through conjunctival tissue, but approximately 75% passes through the nasolacrimal drainage system.[76] The nasolacrimal drainage system consists of the puncta, canaliculi, lacrimal sac, and nasolacrimal duct, which empties into the nasal cavity (Fig. 2.31).

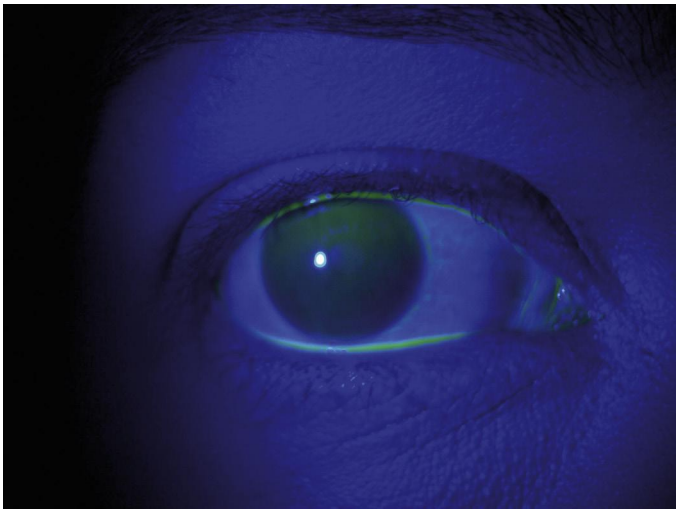

Fig. 2.30 The tear film is seen as a green fluorescence through a cobalt blue filter.

Puncta and Canaliculi

A small aperture, the **lacrimal punctum**, is located in a slight tissue elevation, the **lacrimal papilla**, at the junction of the lacrimal and ciliary portions of the eyelid margin (see Fig. 2.2). Both upper and lower lids have a single punctum which drains the tears into the upper and lower canaliculi, respectively. The width of the lower punctum varies between 0.1 and 0.9 mm.[88,89] The puncta are turned toward the globe and normally can be seen only if the eyelid edge is everted slightly.

The **canaliculi** are tubes in the upper and lower eyelids that join the puncta to the lacrimal sac. The walls of the canaliculi contain elastic tissue and are surrounded by fibers from the lacrimal portion of the orbicularis muscle (Horner muscle). The first portion of the canaliculus is vertical and extends approximately 2 mm; a slight dilation, the ampulla, is at the base of

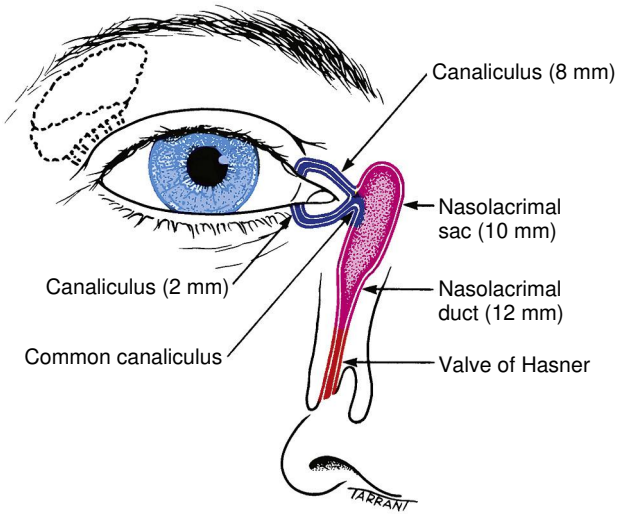

Fig. 2.31 Anatomy of the lacrimal drainage system. (From Kanski JJ. *Clinical Ophthalmology*. Ed 3, Oxford, UK: Butterworth-Heinemann; 1995.)

the vertical portion of the canaliculus.[90] The canaliculus then turns horizontally to run along the lid margin for approximately 8 mm (see Fig. 2.31). The canaliculi join to form a single common canaliculus that pierces the periorbita covering the lacrimal sac and enters the lateral aspect of the sac. The angle at which the canaliculus enters the sac produces a physiologic valve that prevents reflux.

Lacrimal Sac and Nasolacrimal Duct

The **lacrimal sac** lies within the lacrimal fossa in the anterior portion of the medial orbital wall. This fossa is formed by the frontal process of the maxillary bone and the lacrimal bone. The sac is surrounded by fascia, continuous with the periorbita, which runs from the anterior to the posterior lacrimal crests. The lacrimal sac is surrounded by the medial canthal tendon anteriorly and Horner muscle posteriorly. The orbital septum and the check ligament of the medial rectus muscle also lie behind the lacrimal sac (see Fig. 10.22).

The lacrimal sac empties into the **nasolacrimal duct** just as it enters the nasolacrimal canal in the maxillary bone. The duct is approximately 15 mm long and terminates in the inferior meatus of the nose. At this point, the **valve of Hasner** is found. This fold of mucosal tissue prevents retrograde movement of fluid up the duct from the nasal cavity.

Tear Drainage

During closure, the eyelids meet first at the temporal canthus. Closure then moves toward the medial canthus where the tears pool in the lacrimal lake. The tear menisci are pushed toward the lacrimal puncta into which they drain. Capillary attraction plays a role in moving tears into the puncta and down into the canaliculi between blinks.[76]

The underlying mechanism of tear drainage is not completely understood. One theory involves compression of the canaliculi and expansion of the lacrimal sac with eyelid closure. When the eyes are closed, Horner muscle contracts shortening the canaliculi.[91] Then, upon eyelid opening Horner muscle relaxes, and the canaliculi expand pulling fluid in from the puncta. In addition, because Horner muscle shares fascia with the lacrimal sac, muscle contraction (occurring when the eye is closed) causes lateral displacement of the lateral wall of the sac, expanding the upper half of the lacrimal sac, creating negative pressure, and pulling tears into the lacrimal sac.[25,91] Relaxation of Horner muscle causes contraction of the upper half of the lacrimal sac resulting in tears being pushed from the lacrimal sac into the nasolacrimal duct.[25]

Other theories postulating on the mechanism of tear drainage propose an increase in pressure within the lacrimal sac during lid closure.[92] With eyelid closure, the puncta rise from the lid margin and become apposed and occluded halfway into a blink.[93] The canaliculi and lacrimal sac are compressed, forcing the fluids into the nasolacrimal duct. As the eyelids start to open, compression of the canaliculi decreases, but the puncta remain occluded, creating a negative pressure in the canaliculi. When the puncta finally are opened, the negative pressure pulls the tears in immediately after the blink. Other studies support the lack of volume change within the lacrimal sac.[94,95]

Most of the tears are absorbed by the mucosal lining of the duct before the remaining tears enter the inferior meatus. Absorption through mucous membranes is very rapid and so substances, such as drugs, that are present in tears may enter the blood stream of the body.[96]

AGING CHANGES IN THE EYELIDS AND LACRIMAL SYSTEM

The aging process is apparent in the eyelids as tissue atrophies, the skin loses elasticity, and wrinkles appear. With age the distance between the center of the pupil and the lower eyelid margin increases caused by sagging of the lower lid; this change is greater in males than females.[97] More pronounced changes in eyelid margin position, including ectropion and entropion (previously described), increase in incidence with age-related changes in the orbicularis muscle tone, and elongation of the levator aponeurosis. The orbital septum weakens with age allowing orbital fat to prolapse anteriorly.

Tearing may be caused by eversion of the lower punctum because of eyelid position or by stenosis of the passages in the lacrimal drainage system. Both occur more frequently in elderly persons. Some studies find that the basal rate of tear secretion diminishes after age 40 years, contributing to dry eye, the incidence of which increases with age.[98,99] Others have determined that tear reflex secretion decreases.[100] The goblet cell population may decrease over age 80 years, and a decrease in lysozyme and lactoferrin is noted.[100] With age, meibomian glands atrophy resulting in decreased overall gland secretion and ocular dryness.[27,101,102] Causative factors include loss of glandular tissue and a change in composition of the meibomian secretion forming a more viscous material that does not flow as easily.[41,103] The incidence of vascular engorgement at the lid margin and plugged meibomian gland pores also increases with age.[103]

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3

Cornea

The outer connective tissue coat of the eye has the appearance of two joined spheres. The smaller, anterior transparent sphere is the cornea and has a radius of curvature of approximately 8 mm. The larger, posterior opaque sphere is the sclera, which has a radius of approximately 12 mm (Fig. 3.1A). The cornea and sclera merge at the limbus. The approximate diameters of the globe are 24.5 mm anteroposterior, 24 mm vertical, and 24 mm horizontal; these do not change much beyond age 1 year.[1–3]

CORNEAL DIMENSIONS

The transparent cornea appears from the front to be oval, as the sclera encroaches on the superior and inferior aspects. The anterior horizontal diameter is 12 mm, and the anterior vertical diameter is 11 mm (Fig. 3.1B).[1,2,4] If viewed from behind, the cornea appears circular, with horizontal and vertical diameters of 11.7 mm.[1]

In profile, the cornea has an elliptic rather than a spherical shape, the curvature being steeper in the center and flatter near the periphery. The radius of curvature of the central cornea at the anterior surface is 7.8 mm and at the posterior surface is 6.5 mm.[1,5,6] The central corneal thickness is 535 to 555 μm, whereas the corneal periphery is 640 to 670 μm thick (Fig. 3.1C).[7–9]

CLINICAL COMMENT: Astigmatism

Astigmatism is a condition in which light rays coming from a point source are not imaged as a single point. This results from unequal refraction of light by different meridians of the refracting element, each meridian having a different radius of curvature. The cornea, which refracts light and helps focus light rays onto the retina, contributes to astigmatism of the eye because the surface is generally not spherical. The radius of curvature of the corneal surface can be determined clinically by keratometry or topography measurements. These will give an approximation of the corneal contribution to astigmatism.

Regular astigmatism occurs when the longest radius of curvature and shortest radius of curvature lie 90 degrees apart. The most common presentation occurs when the radius of curvature of the vertical meridian differs from that of the horizontal meridian. With-the-rule astigmatism (Fig. 3.2A), occurs when the steepest curvature lies in the vertical meridian. Thus the vertical meridian has the shortest radius of curvature. Against-the-rule astigmatism (Fig. 3.2B) occurs when the horizontal meridian is the steepest; the greatest refractive power is found in the horizontal meridian. If the meridians that contain the greatest differences are not along the 180- and 90-degree axes (±30 degrees), but lie along the 45- and 135-degree axes (±15 degrees), the astigmatism is called oblique. Irregular astigmatism is a less common finding in which the meridians corresponding to the greatest differences are not 90 degrees apart.

CORNEAL ANATOMY AND HISTOLOGY

The **cornea** is the principal refracting component of the eye. Its transparency and avascularity provide optimal light transmittance. The anterior surface of the cornea is covered by the tear film, and the posterior surface borders the aqueous-filled anterior chamber. At its periphery, the cornea is continuous with the conjunctiva and the sclera. From anterior to posterior, the five layers that compose the cornea are epithelium, Bowman layer, stroma, Descemet membrane, and endothelium (Fig. 3.3).

Epithelium

The outermost corneal layer is **stratified corneal epithelium** of five to seven cells thick and measuring approximately 50 μm.[9,10] It is further broken down into surface squamous cells, wing cells, and basal columnar cells. The epithelium thickens in the periphery and is continuous with the conjunctival epithelium at the limbus.

The surface **squamous cell layer** of corneal epithelium is two cells thick and displays a very smooth anterior surface. It consists of nonkeratinized squamous cells, each of which contains a flattened nucleus and fewer cellular organelles than deeper cells. Cell size varies but a superficial cell can be 50 μm in diameter and 5 μm in height.[11] The plasma membrane of the surface epithelial cells secretes a glycocalyx component that adjoins the mucin layer of the tear film. Loss of the glycocalyx will result in poor tear stability. Many projections located on the apical surface of the outermost cells increase the surface area, also enhancing the stability of the tear film. The finger-like projections are microvilli, and the ridgelike projections are microplicae (Fig. 3.4)

Tight junctions (**zonula occludens**) join the surface cells along their lateral walls, near the apical surface.[12] These junctures provide a barrier to intercellular movement of substances from the tear layer and prevent the uptake of excess fluid from the tear film. A highly effective, semipermeable membrane is produced, allowing passage of fluid and molecules through the cells but not between them. Additional adhesion between the cells is provided by numerous desmosomes.

CLINICAL COMMENT: Evaluation of Corneal Surface

Fluorescein dye can be used to evaluate the barrier function of the surface layer. When instilled in the tear film, it will not penetrate the epithelial tissue as long as the zonula occludens are intact. If the tight junctions are disrupted, the dye can pass easily through Bowman layer and into the anterior stroma. An epithelial defect will usually appear a vivid green fluorescence when viewed with the cobalt blue filter of the slit lamp (Fig. 3.5).

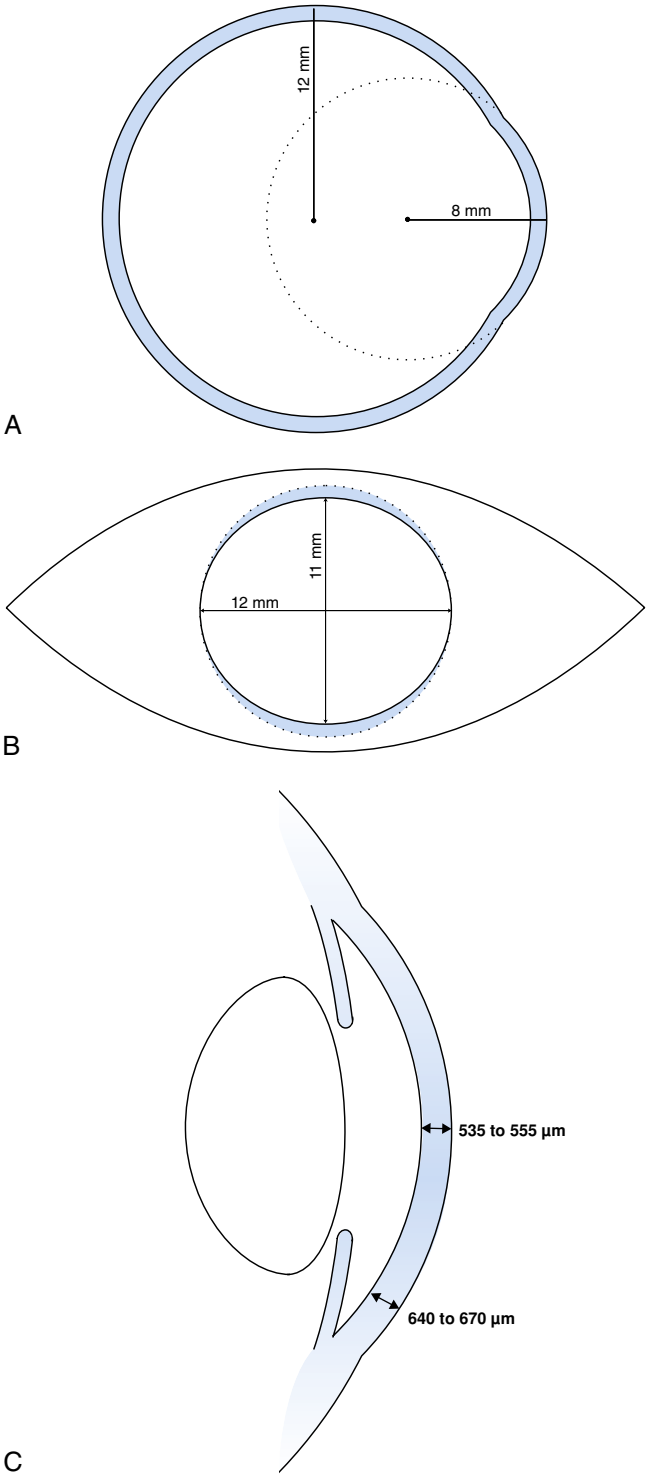

Fig. 3.1 Corneal dimensions. **A**, Radius of curvature of cornea and sclera. **B**, View from the front of the eye. The sclera encroaches on the corneal periphery inferiorly and superiorly. Dotted lines show the extent of the cornea in the vertical dimension posteriorly. **C**, Sagittal section of cornea showing central and peripheral thickness.

The middle layer of the corneal epithelium is made up of two to three layers of **wing cells**. These cells have wing-like lateral processes, are polyhedral, and have convex anterior surfaces and concave posterior surfaces that fit over the basal cells (Fig. 3.6). The diameter of a wing cell is approximately 20 µm.[11] Desmosomes and gap junctions join wing cells to each other, and desmosomes join wing cells to surface and basal cells.[13]

The innermost **basal cell layer** of the corneal epithelium is a single layer of columnar cells, with diameters ranging from 8 to 10 µm (Fig. 3.7).[11] These cells contain oval-shaped nuclei displaced toward the apex and oriented at right angles to the surface. The rounded, apical surface of each cell lies adjacent to the wing cells, and the basal surface attaches to the underlying basement membrane (basal lamina). Although less numerous here than in the wing cell layer, desmosomes and gap junctions join the columnar cells. Interdigitations and desmosomes connect the basal cells with the adjacent layer of wing cells.

The basal cells secrete the basement membrane, which attaches the cells to the underlying tissue by **hemidesmosomes**. From the hemidesmosomes, anchoring fibrils form a complex branching network that runs from the basal epithelial cells, through Bowman layer to penetrate into the anterior stroma.[14] If the basement membrane is damaged, healing of the epithelium can take up to 6 weeks.[15]

CLINICAL COMMENT: Recurrent Corneal Erosion

Recurrent corneal erosion is a condition in which the hemidesmosomes or anchoring fibrils are abnormal causing the corneal epithelium to periodically slough off. There is poor attachment between the epithelium and its basement membrane or the basement membrane and underlying stromal tissue. Recurrent corneal erosion can occur after incomplete healing of a superficial abrasion or it may be caused by an epithelial basement membrane dystrophy. Matrix metalloproteinases, which normally maintain the extracellular matrix by causing degradation and remodeling, are upregulated in recurrent corneal erosion and may cause this break down of the epithelial attachments.[16]

Age-related changes can play a role in recurrent corneal erosion. The corneal epithelium continues to secrete the basement membrane throughout life. The thickness of the basement membrane doubles by 60 years of age. In addition, reduplication in focal areas of the membrane can occur with aging.[17] As the basement membrane thickens or as reduplication occurs, the thickness of the membrane can exceed the length of the anchoring fibrils, allowing sloughing of epithelial layers.

Corneal erosions are very painful because the dense network of sensory nerve endings in the epithelium is disrupted. A number of treatments may be used. Ointment at night can help prevent the eyelid from adhering to the corneal epithelium as the tear film thins overnight. Acute cases may require antibiotic ointment to protect from opportunistic infection. Bandage soft contact lenses are applied to alleviate pain while allowing healing of the surface without the shearing effect from opening and closing the eyelids. For cases in which the suspected cause is a defective basement membrane, treatment might include debridement of the faulty tissue to enhance adhesion between the basal epithelial cells and basement membrane or corneal puncture in which multiple perforations are made through the epithelial layers to induce adhesion by producing subepithelial scar tissue (Fig. 3.8). Oral tetracycline or topical steroids may reduce breakdown of the bonds between the epithelium and basement membrane by inhibiting matrix metalloproteinases. Autologous serum supplies fibronectin which promotes epithelial attachment.

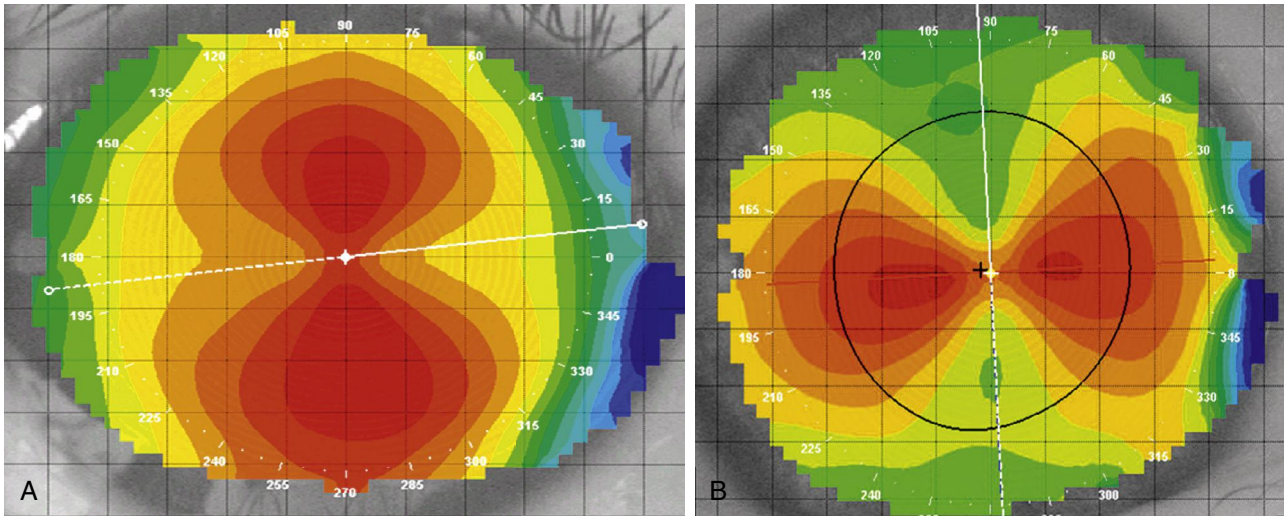

Fig. 3.2 Corneal topography showing a map of the corneal surface curvature. Colors of longer wavelength (i.e., red) indicate areas of steeper corneal curvature, whereas the shorter wavelength colors indicate a flatter corneal curvature. **A**, Corneal topography demonstrating with-the-rule corneal astigmatism. **B**, Corneal topography demonstrating against-the-rule corneal astigmatism. (Courtesy Patrick Caroline, C.O.T., Pacific University College of Optometry, Forest Grove, OR.)

Bowman Layer

The second layer of the cornea is approximately 8 to 19 μm thick (Fig. 3.9).[8–10] **Bowman layer** (anterior limiting lamina) is a dense, fibrous sheet of interwoven collagen fibrils randomly arranged in a mucoprotein ground substance. The fibrils have a diameter of 20 to 25 nm, run in various directions, and are not ordered into bundles. Bowman layer sometimes is referred to as a membrane, but it is more correctly a transition layer to the stroma rather than a true membrane. It differs from the stroma in that it is acellular and contains collagen fibrils of a smaller diameter. The pattern of the anterior surface is irregular and reflects the contour of the bases of the basal cells of the epithelium. Posteriorly, as the layer transitions into stroma, the fibrils gradually adopt a more orderly arrangement and begin to merge into bundles that intermingle with those of the stroma (Fig. 3.10). The posterior surface is not clearly defined.[18]

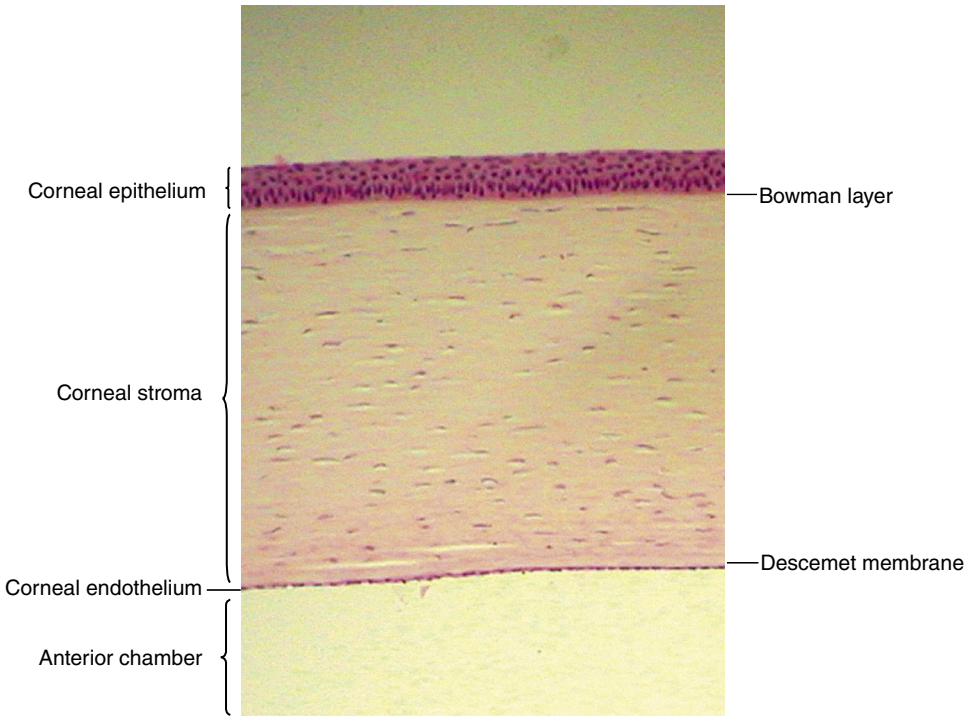

Fig. 3.3 Light micrograph of corneal layers.

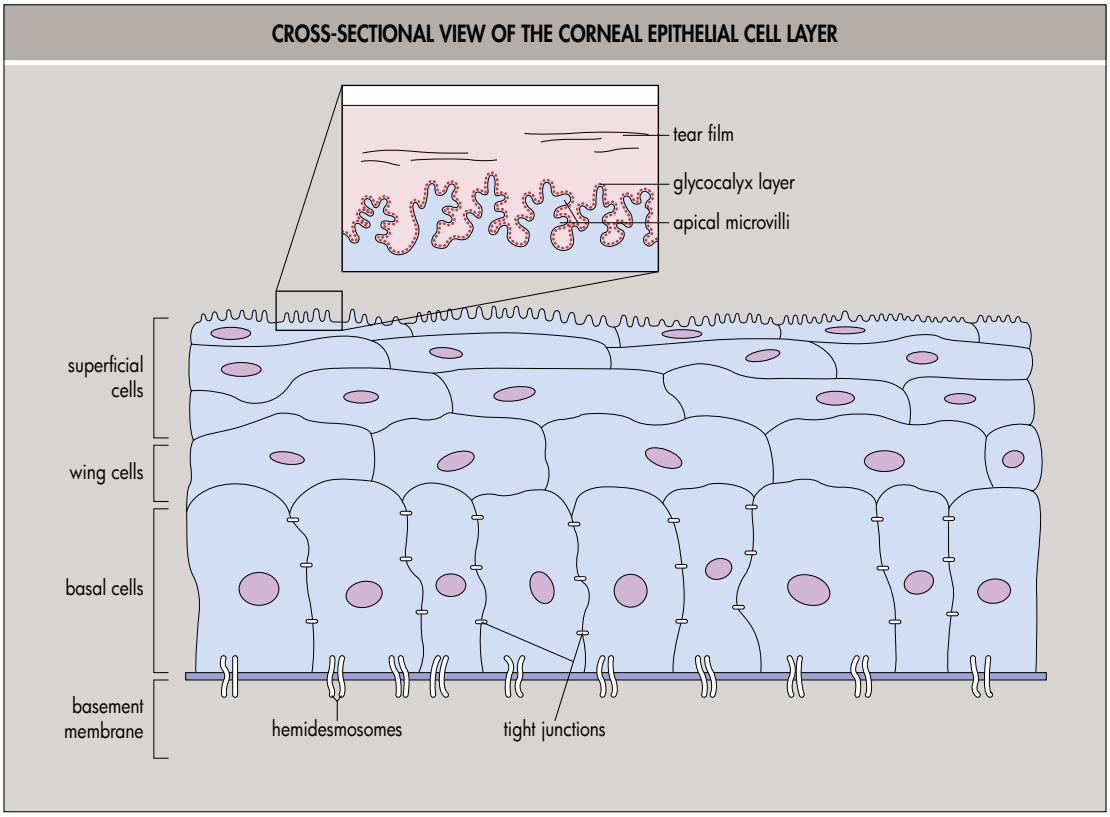

Fig. 3.4 Cross-sectional view of the corneal epithelial cell layer. (From Farjo A, Mc Dermott M, Soong HK. Corneal Anatomy, Physiology, and Wound healing. In: Yanoff M, Duker JS, eds. *Ophthalmology*, 3rd ed. St Louis, MO: Mosby; 2008, Figure 4.1.1).

Bowman layer is produced prenatally by the epithelium and is not believed to regenerate. Therefore if injured, the layer usually is replaced by epithelial cells or stromal scar tissue. However, Bowman layer is very resistant to damage by shearing, penetration, or infection. Although Bowman layer is thought to provide biomechanical rigidity and shape to the cornea, speculation continues regarding the function of Bowman layer and whether it is necessary to maintain corneal function. No long-term effects have been documented in patients with Bowman layer removed by photorefractive keratectomy, a procedure performed since the late 1980s.[19]

Corneal nerves passing through Bowman layer typically lose their Schwann cell covering and pass into the epithelium as naked nerves (see Fig. 3.6). Bowman layer tapers and ends at the corneal periphery and does not have a counterpart in either the conjunctiva or the sclera.

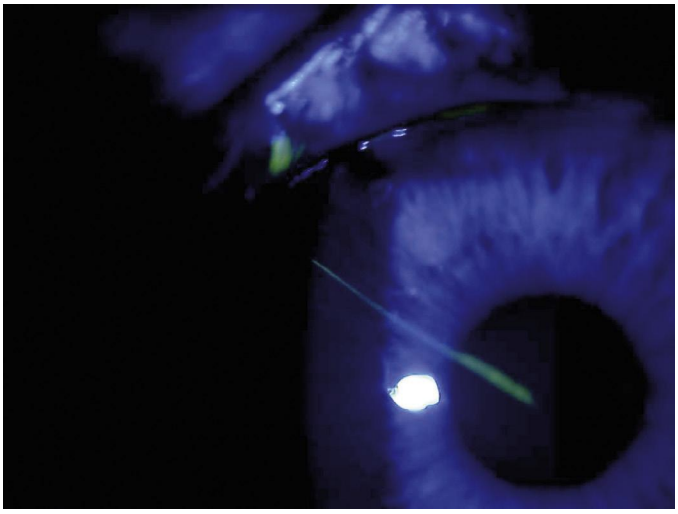

Fig. 3.5 Following a paper cut to the cornea, fluorescein dye is instilled and an epithelial defect is seen as green fluorescence through a cobalt blue filter.

Stroma

The middle layer of the cornea is approximately 450 to 500 μm thick, or about 90% of the total corneal thickness (see Fig. 3.3).[9,11,20] The **corneal stroma** (substantia propria) is composed of collagen fibrils, keratocytes, and extracellular ground substance.

The **collagen fibrils** have a uniform 25- to 35-nm diameter and run parallel to one another, forming flat bundles called **lamellae**.[18] The 200 to 300 lamellae are stacked throughout the stroma and lie parallel to the corneal surface. Adjacent lamellae lie at angles to one another, but with significant interweaving, particularly in the anterior cornea (Fig. 3.11).[21,22] Each lamellae contains uniformly straight collagen fibrils, running in the same direction and arranged with regular spacing because of the surrounding proteoglycans and glycosaminoglycans (Fig. 3.12). Each lamella extends across the entire cornea, and each fibril runs from limbus to limbus. Near the limbus the collagen fibril diameter increases and anchoring lamellae run circumferentially between the sclera and cornea.[21]

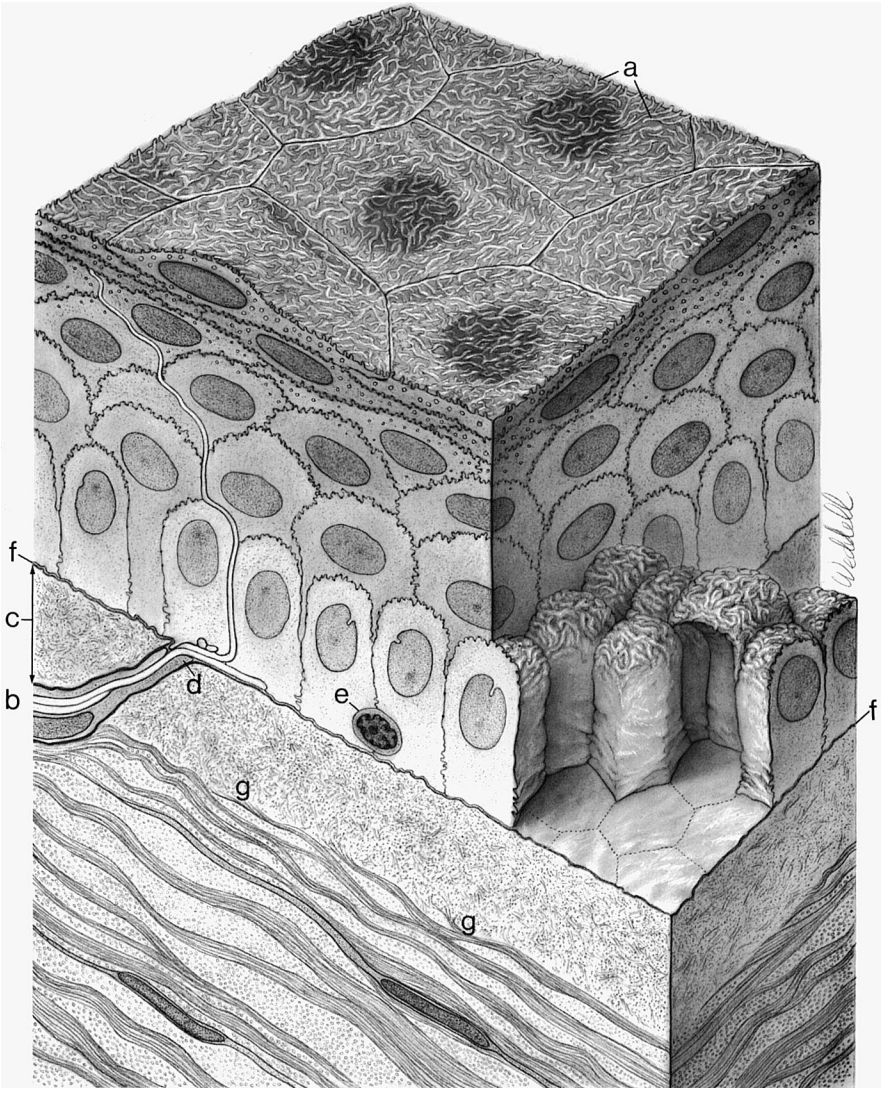

Fig. 3.6 Three-dimensional drawing of the corneal epithelium showing five layers of cells. The polygonal shape of the basal and surface cells and their relative size are apparent. Wing cell processes fill the spaces formed by the dome-shaped apical surface of basal cells. Turnover time for these cells is 7 days, and during this time the columnar basal cell gradually is transformed into a wing cell and then into a thin, flat surface cell. During this transition, cytoplasm changes and Golgi apparatus becomes more prominent. Numerous vesicles develop in the superficial wing and surface layers, and glycogen appears in surface cells. The intercellular space separating the outermost surface cells is closed by zonula occludens, forming a barrier that prevents passage of the precorneal tear film into the corneal stroma. The cell surface shows an extensive net of microplicae (*a*) and microvilli that are involved in retention of the precorneal tear film. A corneal nerve (*b*) passes through Bowman layer (*c*); the nerve loses its Schwann cell sheath near the basement membrane (*d*) of the basal epithelium. It then passes as a naked nerve between the epithelial cells toward the superficial layers. A lymphocyte (*e*) is seen between two basal epithelial cells. The basement membrane is seen at (*f*). Some of the most superficial corneal stromal lamellae (*g*) are seen curving forward to merge with Bowman layer. The regular arrangement of the corneal stromal collagen differs from the random disposition in Bowman layer. (From Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye.* Philadelphia: Saunders; 1971.)

The arrangement of the lamellae varies slightly within the stroma. In the anterior one-third of the stroma, the lamellae are thin (0.5–30 μm wide and 0.2–1.2 μm thick), and they branch and interweave more than in the deeper layers.[18,23] In the posterior two-thirds of the stroma, the arrangement is more regular, and the lamellae become larger (100–200 μm wide and 1–2.5 μm thick).[18] The anterior cornea has a higher incidence of cross-linking and is more rigid, helping to maintain the corneal curvature.[24] This arrangement is the reason that stromal swelling is directed posteriorly. This swelling causes Descemet membrane to fold, which can be seen clinically as striae.[15]

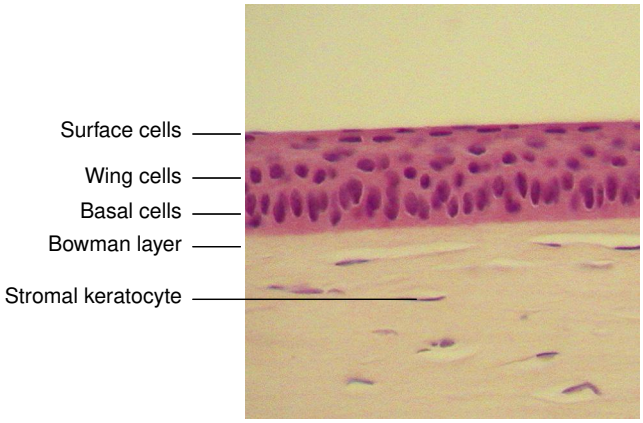

Fig. 3.7 Light micrograph of corneal epithelium showing columnar basal cells, wing cells, and squamous surface cells of the cornea. Bowman layer and the anterior stroma are also evident.

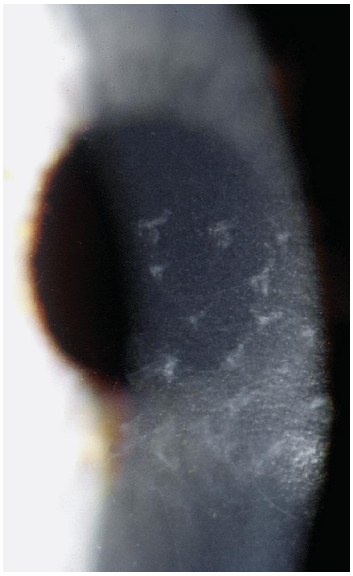

Fig. 3.8 In recurrent corneal erosion, defective adhesion of the epithelium and basement membrane complex to underlying stroma exists. One treatment option involves passing a hypodermic needle through the epithelium and anterior stroma to create focal areas of scarring that help to cause "spot welds." (From Krachmer JH, Palay DA. *Cornea Color Atlas*. St Louis: Mosby; 1995.)

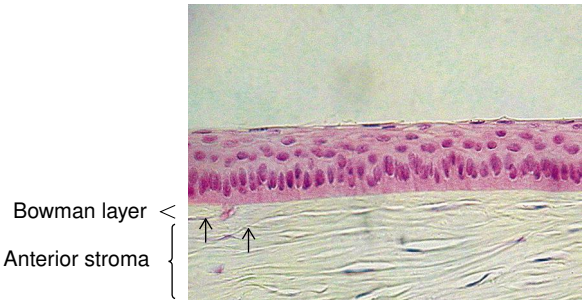

Fig. 3.10 Light micrograph of corneal epithelium, Bowman layer, and anterior stroma. There is a change in the direction of the superficial lamellae as they curve forward to merge with Bowman layer (*arrows*).

The collagen fibrils of the innermost layers of the corneal stroma, adjacent to Descemet membrane, become very compact with a random arrangement similar to what is found in Bowman layer.[25–27] The fibrils interlace with the anterior zone of Descemet membrane and add strength to the cornea. When injecting air into the corneal tissue, as is done in lamellar keratoplasty, this area (8–15 μm) of posterior stroma separates and stays attached to Descemet membrane.[21,26,27]

Keratocytes (corneal fibroblasts) are flattened cells that lie between and occasionally within the lamellae[28] (see Fig. 3.7). The cells are not distributed randomly, their density is higher in the anterior stroma.[24] Keratocytes have extensive branching processes joined by gap junctions along the lateral extensions, as well as the anteroposterior branches.[29,30] These cells become active when there is injury to the corneal tissue. Otherwise, they maintain the stroma by slowly synthesizing collagen and extracellular matrix components, including glycosaminoglycans and matrix metalloproteinases. Other cells may be found between lamellae, including white blood cells, lymphocytes, macrophages, and polymorphonuclear leukocytes, which can increase in number in pathological conditions.

Ground substance fills the areas between fibrils, lamellae, and cells. It contains proteoglycans, macromolecules consisting of a core protein with one or more attached glycosaminoglycan side chain. There are four main proteoglycans in the normal human cornea. Decorin (molecules that contain chondroitin and dermatan sulfate) is more abundant in the anterior stroma. The other three proteoglycans, lumican, keratocan, and mimican, contain

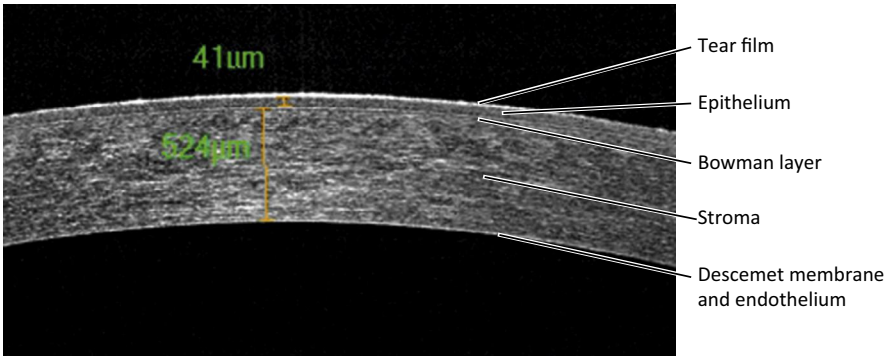

Fig. 3.9 Anterior segment optical coherence tomography demonstrating the layers of the cornea.

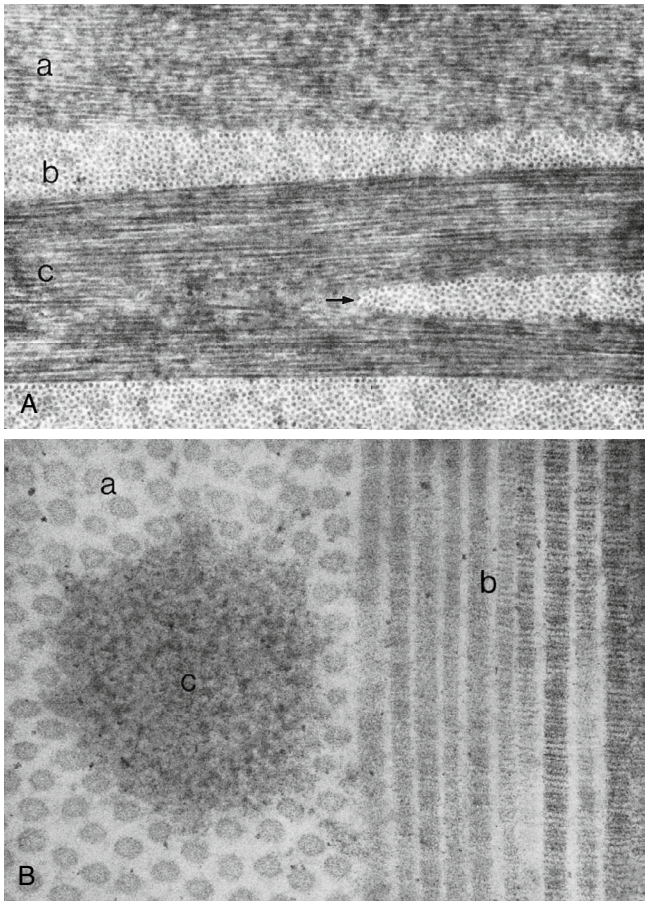

Fig. 3.11 Corneal stromal lamellae. A, View of lamellae showing three different directions of the lamellae layers. The upper lamella (*a*) is cut obliquely, the next (*b*) is cut in cross-section, and the third (*c*) is cut longitudinally. This lamella splits into two lamellae (*arrow*) (×28,000). **B**, Cross-sectional (*a*) and longitudinal (*b*) views of two lamellae. The fibrils measure 340 to 400 Å in diameter and are separated from each other by a space measuring 200 to 500 Å. A large, round granular mass (*c*) is observed within the lamella cut in cross-section. Such masses are seen in most of the collagenous tissues of the eye and may represent a stage in formation of the mature fiber (×104,000). (From Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye*. Philadelphia: Saunders; 1971.)

keratan sulfate and are more abundant in posterior stroma.[31] Decorin aids in interfibrillar spacing and adhesion which stabilizes the lamellae. Keratan regulates the diameter of the collagen fibrils,[32] and lumican, in particular, controls collagen fibril diameter keeping it within a very limited range.[33,34] Proteoglycans have a significant role in maintaining corneal tensile strength and glycosaminoglycans contribute to the relatively high stromal hydration.[31] **Glycosaminoglycans** are hydrophilic, negatively charged carbohydrate molecules located at specific sites around each collagen fibril. They attract and bind with water, maintaining the precise hexagonal lattice relationship between individual fibrils.[34]

CLINICAL COMMENT: Keratoconus

Keratoconus is a corneal dystrophy that results in progressive stromal thinning and an outward bulging of the central cornea. Environmental and genetic factors are among the possible causes. Normally corneal shape and strength are maintained by the arrangement and density of the collagen fibrils that lie parallel to each other and the corneal surface. In keratoconus, this is disrupted. Although the pathology is not completely understood, it is thought that the stromal elasticity is decreased and that an alteration of lumican, keratocan, and decorin proteoglycan levels results in interlamellar displacement.[32,35–37] The process usually begins in the central cornea. The stroma eventually degenerates and thins, and the affected area projects outward in a cone shape because of the force exerted by intraocular pressure on the weakened area of the cornea (Fig. 3.13A). The cone shape is most evident in downgaze when the lower eyelid conforms to the cone shape; this is known as Munson sign (Fig. 3.13B). With progression, folds occur in the posterior stroma and Descemet membrane (Fig. 3.13C).[38,39]

Spectacles may be used for a time for correction of refractive error, but with increasing irregular astigmatism, rigid gas-permeable contact lenses usually are necessary to achieve best corrected vision.[40] When contact lenses no longer correct vision, penetrating keratoplasty may be performed to replace the defective cornea with a donor cornea.

One treatment for progressive keratoconus is corneal collagen cross-linking. In this procedure the corneal epithelium is removed, and the stroma is saturated with topical riboflavin (vitamin B2). The cornea is then exposed to ultraviolet radiation that interacts with the riboflavin creating chemical bonds between and within the collagen fibrils. The corneal collagen stiffens, halting the progression of keratoconus.[32,41]

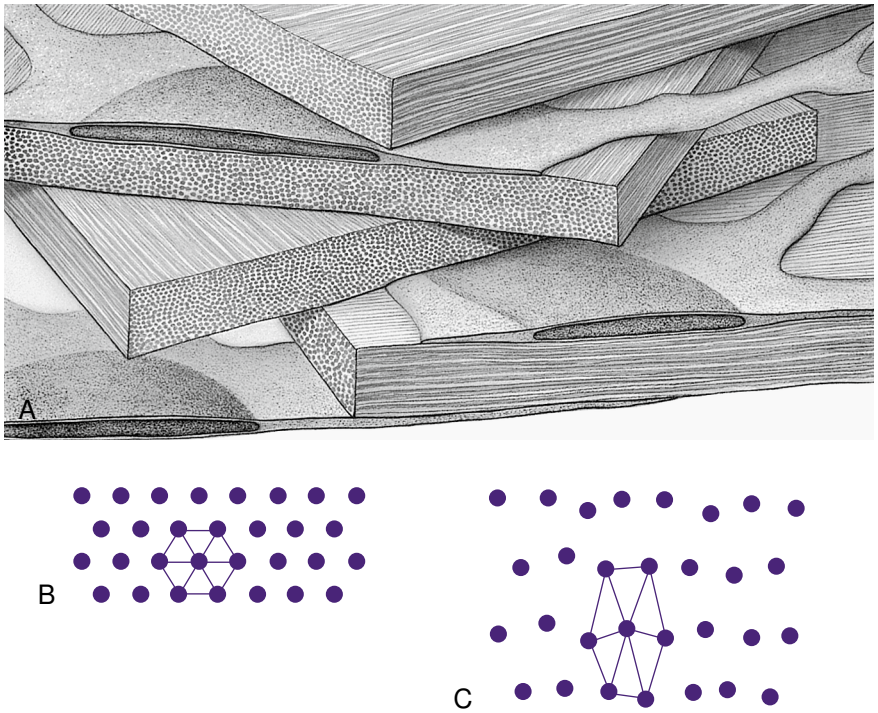

Fig. 3.12 **A**, Corneal lamellae. The cornea is composed of orderly, dense, fibrous connective tissue. Its collagen, which is a stable protein with an estimated half-life of 100 days, forms many lamellae. Collagen fibrils within a lamella are parallel to one another and run the full length of the cornea. Successive lamellae run across the cornea at an angle to one another. Three fibroblasts are seen between the lamellae. **B**, Theoretic orientation of corneal collagen fibrils. Each of the fibrils is separated from the others by an equal distance. As a result of this arrangement, stromal lamellae form a three-dimensional array of diffraction gratings. Scattered rays of light passing through such a system interact with one another in an organized way, resulting in elimination of scattered light by destructive interference. Mucoproteins, glycoproteins, and other components of ground substance are responsible for maintaining proper position of fibrils. **C**, Orientation of collagen fibrils in an opaque cornea. Diagram shows that the orderly position of fibrils has been disturbed. Because of this disarrangement, scattered light is not eliminated by destructive interference, and the cornea becomes hazy. Edematous fluid in the ground substance produces clouding of the cornea by disturbing interfibrillar distance. (Modified from Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye*, Philadelphia: Saunders; 1971.)

The very regular arrangement and diameter of the stromal fibrils, as well as the restriction of the distance between fibrils, contribute to stromal transparency. If the distance between collagen fibrils is less than one-half the wavelength of visible light (400–700 nm), destructive interference occurs, and light scattering is reduced significantly.[24,42] In the stroma, the very specific spacing between the fibrils allows destructive interference of rays reflecting from adjacent fibrils. Although the components of the epithelium, Bowman layer, and Descemet membrane are arranged irregularly, the scattering particles are separated by such small distances that light scattering is minimal in these layers.[23] Less than 1% of the light entering the cornea is scattered.[13,43]

CLINICAL COMMENT: Corneal Opacity
There are a number of reasons the cornea can lose its transparency, become opacified, and cause light scatter. Corneal edema changes the refractive index of the cornea and disrupts the collagen spacing leading to loss of destructive interference. Corneal scarring occurs when collagen fibrils are remodeled with wide, disordered fibers. During wound healing, keratocytes become active which lowers the refractive index.[21] This may cause a temporary corneal haze such as that which occurs following refractive surgery.

Descemet Membrane

Descemet membrane (posterior limiting lamina) is the basement membrane of the endothelium. It is produced continually and therefore thickens throughout life, such that it has doubled by age 40 years.[17] In children, it is 5 µm thick and will increase to approximately 15 µm over a lifetime (Fig. 3.14).

Descemet membrane consists of two laminae. The anterior lamina, approximately 3 µm thick, exhibits a banded appearance and is a latticework of collagen fibrils secreted during embryonic development. The posterior lamina is nonbanded

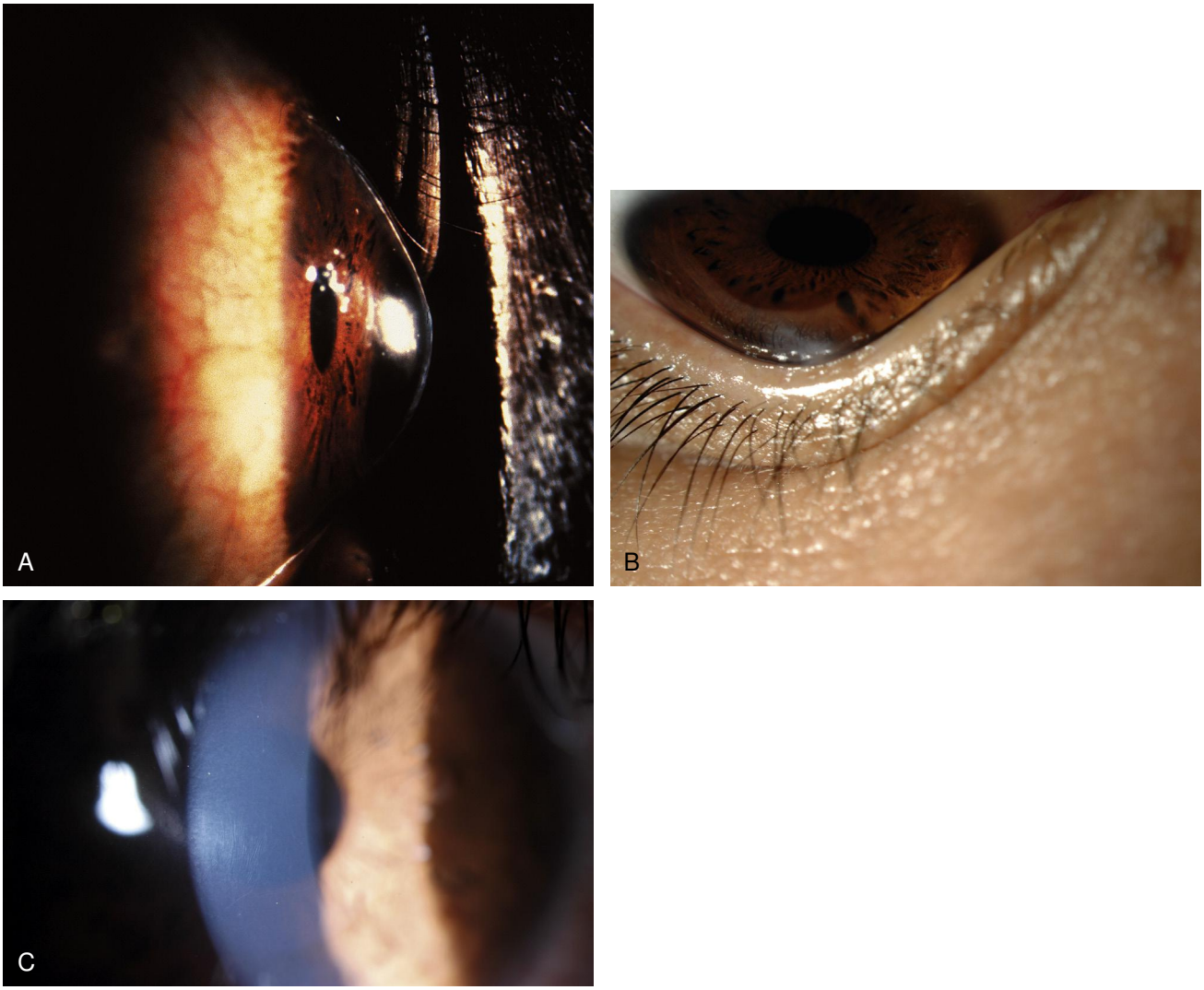

Fig. 3.13 **A**, Keratoconus. (Courtesy Patrick Caroline, C.O.T., Pacific University College of Optometry, Forest Grove, OR.). **B**, Munson sign; the lower lid conforms to the shape of the keratoconic cornea in downgaze. (Courtesy Edward B. Mallett, O.D., Pacific University, Family Vision Center, Forest Grove, OR.). **C**, Descemet folds associated with keratoconus.

and homogeneous; it is the portion secreted by the endothelium throughout life.[44]

Although no elastic fibers are present, the collagen fibrils are arranged in such a way that Descemet membrane exhibits an elastic property. If torn, the membrane will curl into the anterior chamber. Descemet membrane is very resistant to trauma, proteolytic enzymes, and some pathological conditions. It can be regenerated if damaged. A thickened area of collagenous connective tissue can be seen at the termination of Descemet membrane in the limbus; this circular structure is called **Schwalbe line**.

The method of attachment between Descemet membrane and the neighboring layers is poorly understood. Short fine fibrils have been identified with electron microscopy that extend from the posterior stroma into anterior Descemet membrane.[45] The anchoring fibrils characteristic of the connective tissue component of the hemidesmosome are not seen in Descemet membrane, and so the adhesions between Descemet membrane and the endothelium are not the typical hemidesmosomes.[46]

Endothelium

The innermost layer of the cornea, the **endothelium,** lies adjacent to the anterior chamber and is composed of a single layer of flattened cells. It is normally 5 μm thick.[13] The basal part of each cell rests on Descemet membrane, and the apical surface, from which microvilli extend, lines the anterior chamber (Fig. 3.15). Endothelial cells are polyhedral: five-sided and seven-sided cells can be found in normal cornea, but 70% to 80% are hexagonal. The hexagon is considered the most efficacious shape to provide area coverage without gaps.[47,48] The very regular arrangement of these cells is described as the endothelial mosaic (Fig. 3.16).

Although Descemet membrane is considered a basement membrane, the nature of the junctions joining it to

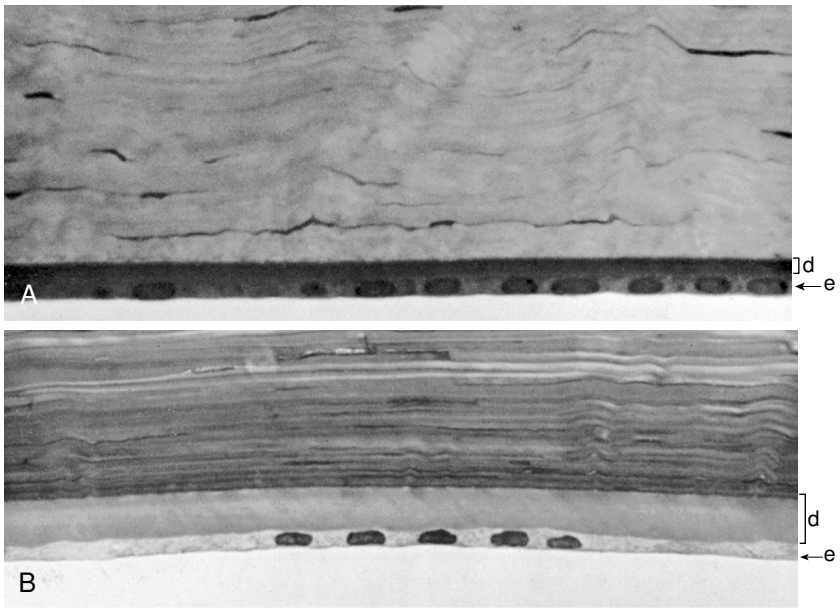

Fig. 3.14 Thickness of Descemet membrane changes with increasing age. **A**, Eye of 18-month-old child. Light micrograph showing the endothelium (*e*) and Descemet membrane (*d*), which are approximately the same thickness (×500). **B**, Eye of 50-year-old adult. Descemet membrane (*d*) is a little more than double the thickness of the endothelium (*e*) (×800). (From Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye*. Philadelphia: Saunders; 1971: p. 94.)

the endothelium are undefined. Extensive interdigitations join the lateral walls of the cells, and gap junctions provide intercellular communication.[13] Tight junctional complexes joining the endothelial cells are located near the cell apex; these are a series of macula occludens rather than zonula occludens.[49,50]

The barrier formed by adhesions between endothelial cells is slightly leaky. Large molecules can penetrate the intercellular spaces.[51] This incomplete barrier allows the entrance of nutrients, including glucose and amino acids, from the aqueous humor. Excess water that accompanies these nutrients must be moved out of the cornea if proper hydration is to be maintained. Ionic pumps present in the endothelium are critical in maintaining the hydration of the stroma. These mechanisms are active throughout the endothelial cells and function continually to move ions across the cell membranes. Lateral infoldings increase the surface area providing space necessary for the number of ionic pumps needed. With changes in solute concentration caused by these pumps, water flows down the concentration gradient, thus maintaining a balance of fluid movement across the endothelium. The endothelial cell is rich in cellular organelles. Mitochondria reflect high metabolic activity and are more numerous in these cells than in any other cells of the eye except the retinal photoreceptor cells.[13]

Endothelial cells do not divide and replicate. Endothelial cells in the adult possess proliferative capacity but are in an arrested phase in the cell cycle. The cell-to-cell contact may be one factor that maintains this layer in the nonproliferative state.[52–54] The lack of proliferation may be necessary for the layer to maintain its barrier and pump functions.[52] Even in children, cells migrate and spread out to cover a defect, with resultant cell thinning. The cell density (cells per unit area) of the endothelium decreases normally with aging because of cell disintegration. Density ranges from 3000 to 4000 cells/mm^2 in children to 1000 to 2000 cells/mm^2 at age 80 years.[47,49,55–57] The minimum cell density necessary for adequate function is in the range of 400 to 500 cells/mm^2.[58,59]

Disruptions to the endothelial mosaic can include endothelial cell loss or an increase in the variability of cell shape (pleomorphism) or size (polymegathism) (Fig. 3.17). The active pump function can be detrimentally affected by polymegathism or morphological changes, although the endothelial barrier function is not compromised by a moderate loss of cells.[60] An excessive loss of cells can disrupt the intercellular junctions and allow excess aqueous to flow into the stroma. The endothelial pumps may be unable to compensate for this loss of barrier function.

CLINICAL COMMENT: Hassall-Henle Bodies and Guttata

The endothelium can produce mounds of basement membrane material, which are seen as periodic thickenings in Descemet membrane that bulge into the anterior chamber. Those located near the corneal periphery are called Hassall-Henle bodies. These bodies are a common finding, and their incidence increases with age. Such deposits of basement membrane in the central cornea are called corneal guttata and are indicative of endothelial dysfunction. The endothelium that covers these mounds is thinned and altered, and the endothelial barrier may be compromised. Both Hassall-Henle bodies and guttata are visible as dark areas when viewed with specular reflection with the biomicroscope. These may be interpreted as holes in the endothelium, but the endothelium is merely displaced posteriorly from the plane of reflection (Fig. 3.18).