Vitreoretinal Disease

Diagnosis, Management, and Clinical Pearls

Second Edition

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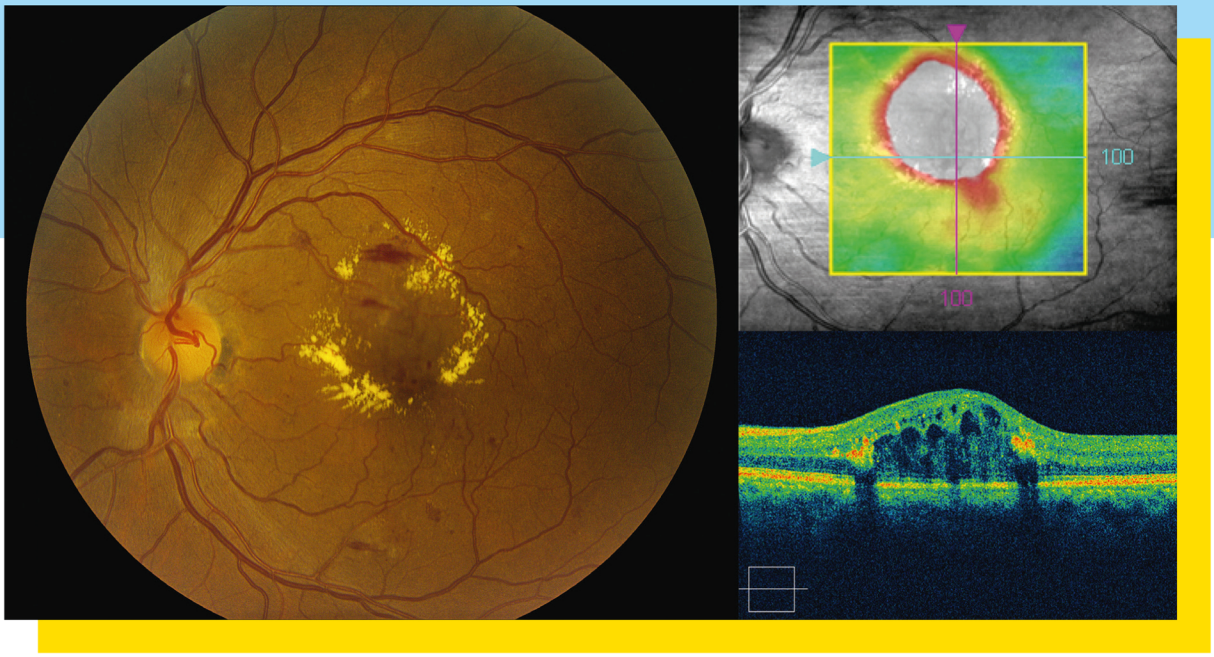

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To our families for their never-ending support and encouragement.

Contents

Foreword

Tell me and I forget. Teach me and I remember. Involve me and I learn.

- *Benjamin Franklin*

Life all around is a kind of sporting event and the best any of us can do is to try continually to improve our game.

- *Harvey Cushing to his son Bill*

This authoritative new edition of *Vitreoretinal Disease*, comprehensively updated from the classic of 1999 with the addition of the latest in cutting edge diagnostic and therapeutic technology, manages to both admirably fulfill Franklin's criteria for learning, and knock Cushing's sports metaphor out of the park. Well-written, clearly organized and engaging, it teaches and involves, capturing the reader in a voyage of exploration into all things vitreoretinal. And it helps all of us improve our game!

Carefully curated, this volume equips the practicing comprehensive ophthalmologist, resident, and fellow with a very accessible and practical clinical overview of the latest in vitreoretinal knowledge, while also satisfying the subspecialist's need for a focused and selected review and reference volume.

Vitreoretinal Disease has a game-winning guarantee in large part due to its winning hand of four editorial aces, Scott, Regillo, Brown and Flynn, whose extraordinary professional depth and the eminence of the colleagues they have martialled to selectively but comprehensively summarize the state of the art in our field represent a ne plus ultra of retina knowledge and experience.

Both teaching and engaging, this latest edition of a landmark text from the ophthalmic archives should inspire a new generation of eye physicians and surgeons, to the benefit of our profession, and our patients. In the final analysis, this book is for them.

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Preface

The field of vitreoretinal disease continues to evolve rapidly, and has expanded into a complex practice of medicine and surgery that utilizes a wide range of diagnostic and therapeutic modalities. From case reports to phase 3 multicenter clinical trials, published data accumulate in exponential fashion. As a result, it is increasingly difficult for the clinician dealing with vitreoretinal disease, both generalist and specialist alike, to synthesize and apply the amassed information to patient care.

This textbook is primarily intended to provide the practicing comprehensive ophthalmologist and ophthalmology resident with an up-to-date, clinically oriented source that covers the full spectrum of medical and surgical vitreoretinal diseases. Subspecialists in the field should also find it useful as a review and selected reference.

Although this text is meant to be comprehensive, we have tried to highlight the essential, clinically important aspects of vitreoretinal medical and surgical practice. Chapters dealing with disease states emphasize clinical features, diagnosis, and management. Entire chapters are devoted to the most commonly encountered problems. Clinical "pearls," special considerations, and controversial points are made to stand out in colored boxes.

The text is divided into four general parts. The first part provides a basic overview of posterior segment anatomy and physiology. The second part reviews the spectrum of diagnostic tools used in the field, from the relatively low-technology indirect ophthalmoscope to the latest, high-technology optical coherence tomography test. The third and largest part deals exclusively with the disease states and is subdivided by disease category. The fourth part covers specific vitreoretinal procedures. Since the last edition, each chapter has been revised and updated by experts in the field. Given the widespread integration of optical coherence tomography into vitreoretinal clinical practice since the first edition of this textbook was published in 1999, this new edition of the textbook devotes an entire chapter to optical coherence tomography and its applications in the management of vitreoretinal diseases. Due to advances in diagnostic techniques, the new edition also includes sections on multifocal electroretinography, scanning laser ophthalmoscopy, fundus autofluorescence, and adaptive optics. Since the first edition of the textbook was published, the intravitreal injection procedure has become the most commonly performed procedure by vitreoretinal specialists; accordingly, this new edition of the textbook devotes an entire chapter to the intravitreal injection procedure. Finally, many figures included in the revised edition have been updated to color.

Assembling a multiauthor textbook that attempts to have the chapters be both current and detailed in content along with being uniform in layout requires a special effort from all the contributors to adhere to strict guidelines; we are grateful to all those invited to participate in the writing of this textbook for these efforts. We wish to acknowledge the support of the staff and our colleagues at Penn State Eye Center, Wills Eye Hospital, and Bascom Palmer Eye Institute. The faculty, residents, fellows, and patients at our institutions always deserve credit as they are continued sources of inspiration for academic endeavors. We also wish to thank the editorial team at Thieme Publishers for their dedicated guidance and expertise. Finally, we thank our families for their unwavering and enthusiastic support and encouragement.

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Part I

Anatomy and Physiology

I

1 Anatomy of the Vitreous, Retina, and Choroid

Hermann D. Schubert and Marilyn C. Kincaid

1.1 Introduction

It is a truism that the anatomy of an organ, structure, or system provides the substrate for the types of pathologic processes that can affect it. This is particularly true for the retina and its associated structures, the vitreous and choroid. Understanding their structures allows the clinician to better understand diseases that can affect them and to appreciate the studies used to elucidate those diseased conditions.

1.2 Vitreous

The vitreous is a clear gel occupying the bulk of the eye, extending posteriorly from behind the lens and adhering to the internal limiting membrane of the retina (▶ Fig. 1.1). This connective tissue comprises 80% of the total volume of the globe, about 4 mL. Normal vitreous allows visible light to pass to the retina without alteration or scatter. It also acts as a stabilizer, pressure regulator, shock absorber, and metabolic sink supporting the retina.

On clinical examination, the collagenous vitreous is not homogeneous. Centrally, Cloquet's canal, a space about 1 to 2 mm in diameter, extends from just behind the lens posteriorly to the optic nerve head. It is a remnant of the embryonic hyaloid vascular system. This canal has an S-shaped course from anterior to posterior, making a dip inferiorly before rising back to the nerve head. Anteriorly, it widens as Berger's space to form the back surface of the patellar fossa.

The anterior cortical gel of the vitreous is the vitreous surface adjacent to the lens zonules and the posterior lens capsule. Biomicroscopically, the borders and structures of the gel may resemble a membrane, but ultrastructurally it consists of denser aggregations of collagen fibers.[1] The hyaloideocapsular ligament of Wieger is a circular attachment between the orbiculoposterior zonular fibers and the posterior surface of the lens capsule. It is not a true ligament,[1] and the attachments become weaker with age. The potential space formed between the lens and the patellar fossa bounded by Wieger's ligament is called *Berger's space*. A separation of Wieger's ligament from the lens represents an anterior vitreous detachment.

Posteriorly, the canal widens to cover the *area of Martegiani*, which corresponds to the surface of the optic nerve head. The vitreous is firmly attached to the margin of the area, although with age the firmness of this attachment becomes attenuated. If the vitreous detaches completely, the glial peripapillary attachment is sometimes visible as a partial or complete ring suspended in the midportion of the eye, sometimes referred to as a *Weiss ring*.

The vitreous consists of about 99% water; the remaining compounds include hyaluronic acid and collagen, as well as inorganic salts and ascorbic acid.

Most of the vitreous collagen is concentrated peripherally in the vitreous body, adjacent to lens, retina, and optic nerve head. This denser portion of the vitreous is called the *vitreous cortex*. The remainder of the nuclear vitreous, located more centrally, has less collagen. The vitreous collagens are similar, although not chemically identical, to collagens elsewhere in the body.[2]

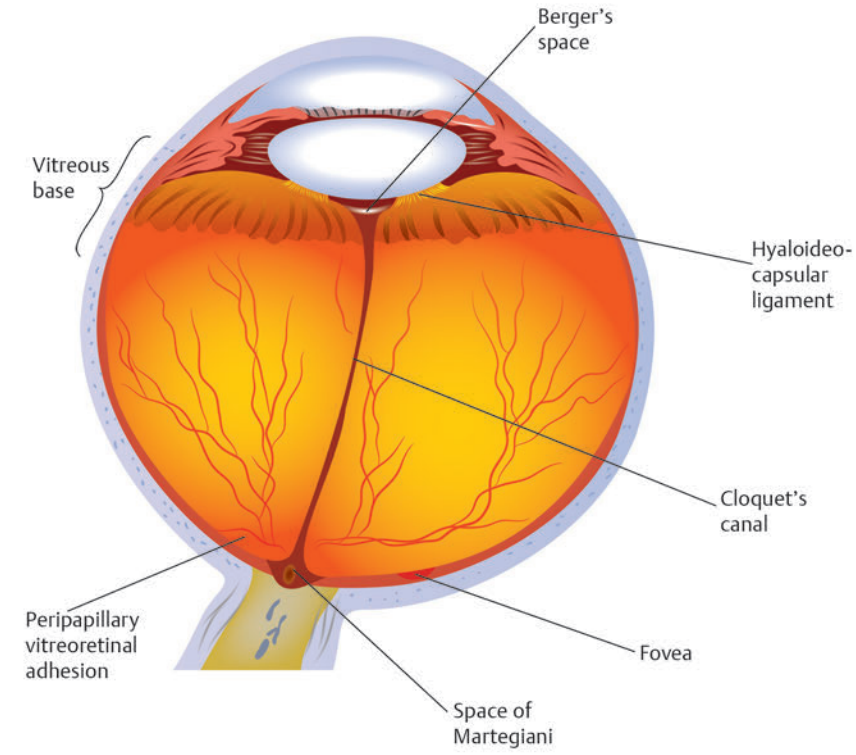

Fig. 1.1 Normal, youthful vitreous gel and associated landmarks.

The principal collagen component is type II; this is similar to the type II collagen of cartilage and suggests a support function. Type IX collagen is a minor component, also similar to the type IX collagen of cartilage.

Unlike collagen, the concentration of hyaluronic acid and other compounds is constant throughout the vitreous. The hyaluronic acid acts as a cross-link interposed between parallel fibrils of collagen forming a gel. Within the vitreous, especially in the cortex, are oval-to-spindle-shaped cells called *hyalocytes*. These cells contain organelles of synthesis and transport; in particular, they have abundant Golgi apparatus. The hyaluronic acid is believed to be synthesized in hyalocyte granules and secreted by these cells.[1]

The vitreous base overlies the posterior aspect of the pars plana and adjacent anterior aspect of the ora serrata of the retina, and is thus a ring 4 to 6 mm in width. The vitreous collagen and its attachments are most dense at the vitreous base. Traction in this area may tear the peripheral retina and adjacent pars plana epithelium.[3] The ophthalmoscopically visible phenomena of white-without-pressure and white-with-pressure appear, in some cases, to be caused by the alignment of the collagen fibrils and their insertions. Adhesions between vitreous and retina have also been observed posterior to the base, particularly in older eyes.[3] Ultrastructurally, collagen fibers insert into the basal lamina of nonpigmented ciliary epithelium and into focal breaks in the retinal internal limiting membrane.[4]

Controversial Points

- The ophthalmoscopically visible phenomena of white-without-pressure and white-with-pressure in the retinal periphery may be caused by the alignment of the cortical vitreous collagen fibrils and their insertions onto the retina in the region of the vitreous base.

The vitreous is also attached to the internal limiting membrane of the retina around the center of the foveola and alongside the larger retinal vessels; however, these attachments are not visible clinically under normal conditions. Vitreous fissures are found in front of retinal vessels and a vitreous pocket is found in front of the papilla, connecting with the premacular bursa.[5] With age, as the formed vitreous detaches and collapses anteriorly, the resultant traction on the posterior vitreous base may cause tears in the retina, sometimes accompanied by a vitreous hemorrhage if a vessel is torn.

Recently, this classic concept of posterior attachment sites has been reexamined using in vivo swept-source optical coherence tomography, corroborating and extending findings based on postmortem injections.[6] Experimental studies suggest that the vitreous is more diffusely attached in the posterior pole, at least in younger people.[7] In a study of postmortem human eyes, the vitreous was mechanically lifted away from the retina. In older eyes, the vitreous detached smoothly from the retina, leaving the internal limiting membrane intact. Ultrastructurally, the vitreal side of the membrane remained smooth. In eyes younger than 20 years, the internal limiting membrane in the posterior pole region tended to detach along with the vitreous away from the underlying retinal layers, showing the vitreous–internal limiting membrane attachment to be stronger than intraretinal attachments.

1.3 Retina

The retina is the neuroepithelium of the eye responsible for receiving light and converting it into neural impulses, which are interpreted by the cerebral cortex. It is derived from the embryonic forebrain, and is part of the central nervous system.[8] The retina is a layered and highly ordered structure. The sensory retina is transparent, except for blood vessels, so the apparent color of the fundus is derived from the retinal pigment epithelial melanin, the melanin of the choroidal melanocytes, and the choroidal vessels.

Often, the terms *retina* and *sensory retina* are used interchangeably. The term *retina* properly includes the retinal pigment epithelium as well. Both the sensory retina and retinal pigment epithelium are derived from the bilayer of the optic cup.[9] Reflecting the embryonal invagination of the optic vesicle, the cells of Müllerian glia and retinal pigment epithelium are arranged apex to apex, with the respective basement membranes (inner limiting membrane and inner aspect of Bruch's membrane) at opposite bases.

The outer neuroectodermal layer, the retinal pigment epithelium, remains a monolayer. It is discontinuous at the optic nerve head and continuous anteriorly with the pigment epithelium of the ciliary body.

The inner neuroectodermal layer proliferates, thickens, and differentiates to become the sensory retina. Except for the nerve fiber layer, the axons of which comprise the optic nerve, all layers of the sensory retina are discontinuous at the optic nerve head.

The sensory retina extends from the optic disc anteriorly to the ora serrata, where it is continuous with the nonpigmented ciliary epithelium. The ora serrata is located 6 mm behind the limbus, approximately at the insertion points of the rectus muscles, following the imaginary spiral of Tillaux.[10] The configuration of the ora serrata is discussed in more detail later.

1.3.1 Retinal Pigment Epithelium

The retinal pigment epithelium is one of the most biologically active tissues of the body. It is deeply pigmented, having become completely melanized by the sixth gestational week. Moreover, the degree of pigmentation is independent of race, unlike the pigmentation of the uveal tract, skin, and hair.[11] Biomicroscopically, this tissue is responsible for much of the color of the fundus. The macula appears darker, in part because the cells of this region are taller and narrower.

As seen in a flat preparation, the retinal pigment epithelium is a monolayer consisting of hexagonal cells with central round nuclei. Occasional cells have two nuclei, and such cells increase in number with age. Also, with age, the uniformity seen in young eyes gives way to cells more variable in size and shape.[12]

Retinal pigment epithelial cells are polar—that is, each cell has a discernible base and apex (▶ Fig. 1.2). Microvillous processes emerge from the apex of the retinal pigment epithelial cells to surround the photoreceptor outer segments. Some are fingerlike and slender, whereas others are broader and surround the outer segment like a bowl.[1] The cell nuclei are approximately spherical and lie just above the base of the cell. The unit membrane of the base is highly convoluted.

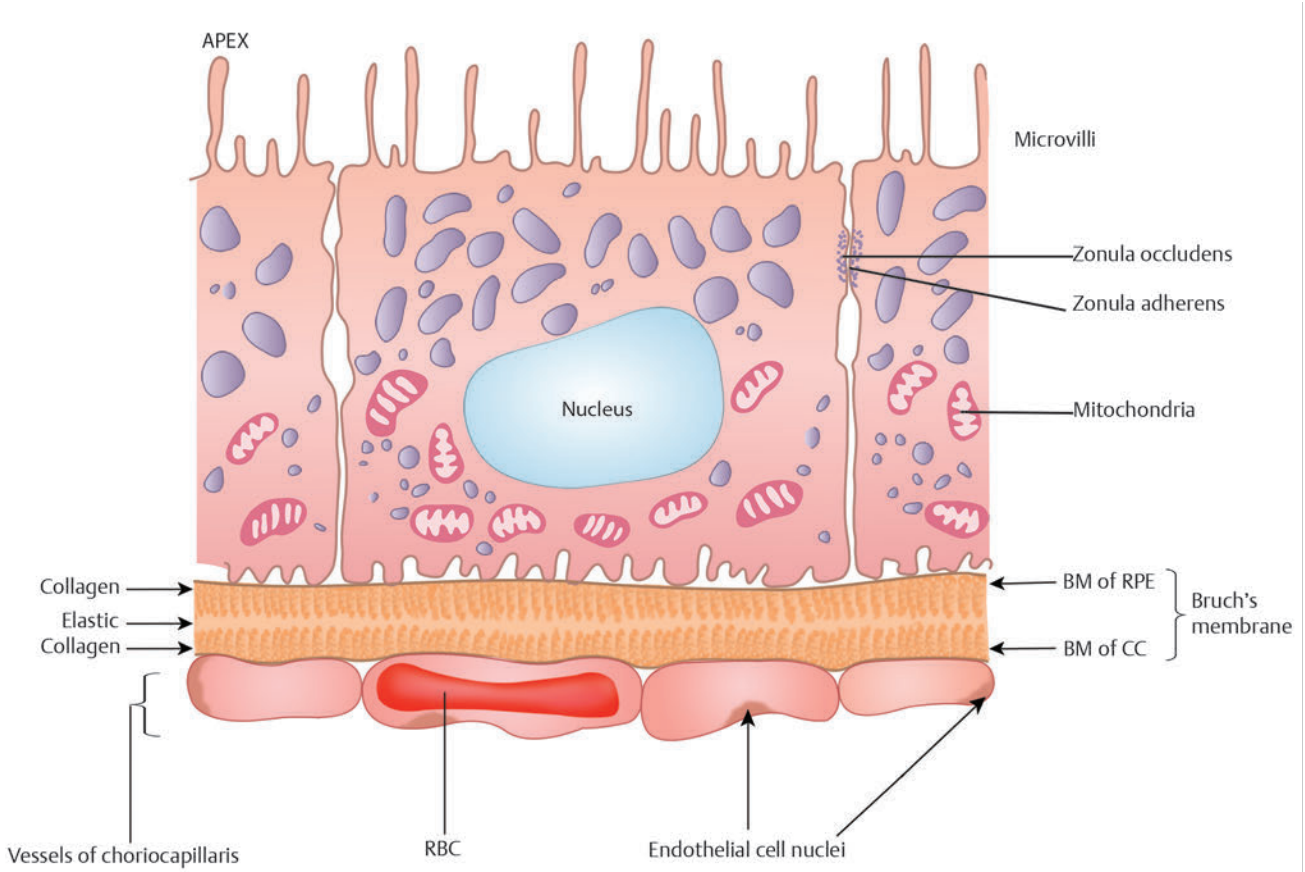

Fig. 1.2 Retinal pigment epithelial cells and the underlying Bruch's membrane. BM, basement membrane; RBC, red blood cell; RPE, retinal pigment epithelium.

A variety of conditions, such as uveitis, trauma, and retinal detachment, can stimulate the retinal pigment epithelium to proliferate. The hyperplastic retinal pigment epithelium nonetheless retains its cytologic polarity, creating tubules, acini, and rows of cells, with accompanying basement membrane formation.[13] Peripherally, the retinal pigment epithelium may proliferate in various patterns in the aging eye.[14]

Special Considerations

- A variety of pathologic conditions, such as uveitis, trauma, and retinal detachment, can stimulate the retinal pigment epithelium to proliferate. Some degree of retinal pigment epithelial proliferation is also evident in the peripheral fundus of the otherwise normal aging eye, perhaps reflecting chronic tractional forces at the vitreous base.

Each retinal pigment epithelial cell is attached to adjacent cells by tight junctions. Ultrastructurally, these junctions include a zonula adherens and an adjacent zonula occludens, both situated near the apex of the cell and encircling it.[12] The zonula adherens is a gap junction. The unit membranes of two adjacent cells are close together, but each can be separately identified. The zonula occludens, as the name implies, has no intercellular space. The peripheral margins of the unit membrane appear fused. The result is that small molecules, such as fluorescein, travel inward from the choroidal circulation only as far as the apices of the pigment epithelial cells. This barrier is referred to as the *outer blood–retinal barrier*.[15] When the junctions are lost, leakage of fluid from the choroid may be clinically evident as an exudative retinal detachment.[16]

In contrast to the convoluted unit membrane configuration at the base of the retinal pigment epithelial cell, the basement membrane is flat. It is the innermost component of Bruch's membrane, a complex consisting of five layers discerned at the ultrastructural level (▶ Fig. 1.2).[17] Extending outward from the retinal pigment epithelial side, these layers include the basement membrane of the retinal pigment epithelium, followed by a thick inner collagenous layer, an elastic layer, a thin outer collagenous layer, and the basement membrane of the choriocapillaris. Bruch's membrane thickens with age[18] and also becomes somewhat more disrupted, so that individual layers become more difficult to discern.

Special Considerations

- Ultrastructurally, Bruch's membrane has five distinct layers. However, with age, a variable degree of membrane thickening and lipid deposition make these layers less distinct.

The retinal pigment epithelium is one of the most metabolically active tissues of the body. Reflecting this, numerous organelles of synthesis and transport are seen ultrastructurally in the pigment epithelium. Mitochondria are abundant, especially in the basal half of the cell, underneath its nucleus. Smooth and rough endoplasmic reticulum, free ribosomes, and Golgi apparatus are also evident.[1]

A striking aspect of the pigment epithelium is its melanin pigment, mostly located in the apical cytoplasm of the cells. Two types of pigment granules are present in the retinal pigment epithelium- melanin and lipofuscin. Melanin is a dark brown to black pigment that is chemically poorly understood. The precursor is tyrosine, which is oxidized and polymerized through a series of enzymatic and nonenzymatic steps. Melanosomes, the site of melanogenesis, are round-to-oval membrane-bound granules morphologically similar to those of the uveal tract. In addition, there are elongated, lancet-shaped melanosomes. These granules are present in some of the apical microvilli; thus, they are in close proximity to the outer segments of the photoreceptors.[19] Recent evidence indicates that the epithelial cells do not produce additional pigment after birth, at least not through the tyrosinase enzymatic pathway. However, they do avidly take up free pigment in tissue culture.[20]

Retinal pigment epithelial hypertrophy is usually congenital. The pattern can be either solitary or grouped; the latter is sometimes called "bear tracks." The additional pigment is in the form of large, round melanosomes.[21,22]

The concentration of melanin varies regionally and also with age. The amount of melanin is actually greater at the equator than at the macula, where it is stacked up in taller and thinner cells, increasing optical density. With age, the melanin in peripheral pigment epithelium decreases, whereas that in the posterior pole remains constant for different age groups, resulting in overall greater optical density centrally.[23]

Photoreceptor outer segments are shed daily and regenerated constantly throughout life, at a rate dependent on incident light.[24,25] The shed material is engulfed and digested by the retinal pigment epithelium. However, this material is not completely digestible.[25] Lipofuscin- a complex of indigestible end products- is a golden yellow material distributed widely in the body. It is composed chiefly of vitamin A aldehyde adducts, although the composition varies even within the same tissue. With increased age, lipofuscin accumulates in the retinal pigment epithelium within secondary lysosomes due to ongoing phagocytosis. The melanosomes are displaced apically as the lipofuscin granules accumulate at the base. Complex granules containing both melanin and lipofuscin are called *melanolipofuscin granules*; in advanced age, these can be more numerous than the melanosomes. In the retinal periphery, this accumulation of lipofuscin and loss of melanin appears to be responsible for certain age-associated pigmentary patterns. Retinal pigment epithelial lipofuscin is also increased in recessive Stargardt's disease and in age-related maculopathies.[24,26]

Pearls

- Accumulation of lipofuscin- with loss of melanin- in pigment epithelial cells of the retinal periphery appears to be responsible for certain age-associated pigmentary patterns.

There are no structural junctions between the retinal pigment epithelial cells and the photoreceptors. This is in contrast to the numerous tight junctions present between the corresponding two neuroepithelial layers of the ciliary body and the iris.[1] Instead, the epithelioretinal interspace contains a glycosaminoglycan matrix. Further, the retinal pigment epithelium constantly pumps fluid out of this space, creating a net negative pressure, to maintain photoreceptor apposition. This active transport accounts for about 70% of the total forces responsible for retinal apposition.[13,24]

In addition, interphotoreceptor matrix proteins act as a glue to keep the cells apposed. These protein adhesions are surprisingly strong in the freshly enucleated, and presumably in the living, eye. In experimental studies, the sensory retina was peeled from underlying pigment epithelium in freshly enucleated human and monkey eyes. If done within 1 minute of enucleation, the cone photoreceptor sheaths- components of the interphotoreceptor matrix- stretched to twice their normal size before their attachment to the pigment epithelium broke.[27]

1.3.2 Sensory Retina

The sensory retina is distinctive for its highly ordered architecture, seen by light microscopy and optical coherence tomography (▶ Fig. 1.3). Even at low microscopy power, three distinct bands of nuclei are readily evident, separated by tissue containing few or no cell nuclei.

Photoreceptor cells, both rods and cones, are unique, elongated cells; their nuclei comprise the outer nuclear layer of the retina. There are approximately 120 million rods and 6 million cones in the human retina.[28] Both rods and cones have specialized light-gathering ends- the outer segments- which represent specialized sensory cilia.

The rods are so named because the outer segment is cylindrical in shape. The stacked discs of the rods contain rhodopsin, the visual pigment for scotopic vision. The discs are separated

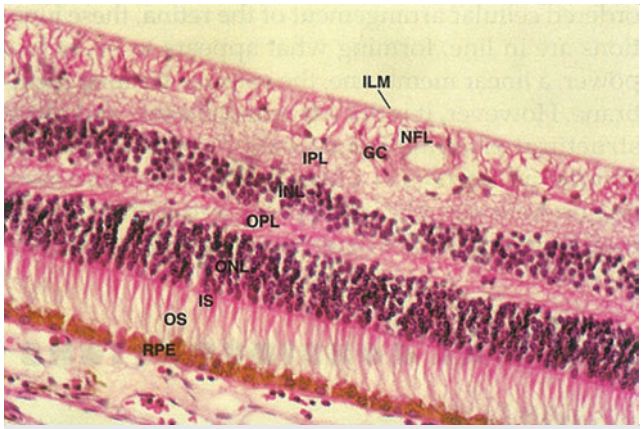

Fig. 1.3 The sensory retina and retinal pigment epithelium (RPE). The photoreceptor outer segments (OS) and inner segments (IS) have their cell nuclei within the outer nuclear layer (ONL). They synapse with the neurons of the inner nuclear layer (INL) in the outer plexiform layer (OPL). These neurons, in turn, synapse with the ganglion cells (GC) in the inner plexiform layer (IPL). Axons from the ganglion cells form the nerve fiber layer (NFL). The internal limiting membrane (ILM) is the inner margin of the sensory retina. Hematoxylin and eosin, ×156.

from the surrounding unit membrane of the cell. The outer ends of the outer segments are constantly shed, taken up by the retinal pigment epithelium, and regenerated at the proximal end.[29]

The cone outer segments are shorter than those of the rods, and thus they do not extend as closely to the pigment epithelial layer. The outer segment is tapered, giving the cone its name. However, in the fovea, the cones are not tapered, but instead are long, slender, and cylindrical in shape, allowing for tight packing. The stacked discs in cone photoreceptors generally remain continuous with the cell membrane. Cone discs are also shed and regenerated.

There are three types of cones, each type with its own spectral sensitivity; the light-sensitive proteins for these likewise reside in the stacked membranes of the outer segments. The proteins are chemically similar to opsin, the rod visual protein.

Connecting each outer segment to the inner segments is a nonmotile cilium. The inner segments, which connect the outer segments with their discs to the cell bodies, are filled with numerous mitochondria and other organelles of synthesis and transport.[29] The outer portion of the inner segment, containing the mitochondria, is called the *ellipsoid*. The inner portion of the inner segment is called the *myoid*. It contains smooth and rough endoplasmic reticulum and many microtubules. The inner segments of the cones are similar to those of the rods, but the ellipsoids are much larger and the mitochondria are several times more numerous. The presence of these organelles demonstrates the high metabolic activity and oxygen requirements of these cells.[1]

The photoreceptor cells and adjacent Müller's cells form tight junctions with each other. Because of the ordered cellular arrangement of the retina, these junctions are in line, forming what appears to be- at low power or on optical coherence tomography- a linear membrane, the external limiting membrane. However, it is not a true membrane, and ultrastructural examination reveals it to be a series of zonulae adherentes in a linear array. This close association between photoreceptors and Müller's cells may be important for inner-segment metabolism.[1]

Special Considerations

- The external limiting membrane of the retina is not a true membrane. It represents a linear array of tight junctions (zonulae adherentes) located between the photoreceptor cells and adjacent Müller's cells.

Synapses between photoreceptors and the cells of the inner nuclear layer occur in the outer plexiform layer. The synapsing end of the rod is called the *spherule*, and the much larger, broader end of the cone is called the *pedicle*. In addition, both cones and rods have lateral extensions near their synapsing ends; these extensions connect with adjacent rods and cones, but apparently without synaptic vesicles.[1]

The inner nuclear layer is populated by the cell bodies of horizontal, bipolar, interplexiform, and amacrine cells. Horizontal cells tend to be located at the outer margin of the inner nuclear layer. Bipolar cells stretch along the thickness of the inner nuclear layer, forming synapses with both the photoreceptors and the ganglion cells. Amacrine and interplexiform cells align along the inner margin of the inner nuclear layer. Interplexiform cells also have processes within both plexiform layers.[8]

Synapses with the next order of neurons, the ganglion cells, occur in the inner plexiform layer. However, in addition to centripetal synapses- from photoreceptors to occipital cortex- it is also evident that synapses occur between different cells within the inner nuclear layer.[8]

The ganglion cell layer is the innermost layer of cell nuclei. These cells are generally relatively large, with abundant cytoplasm. In the peripheral retina, this layer consists of only a single layer of cells. The anatomic macula is defined as the circular area where the ganglion cell layer consists of two or more layers of cells; more centrally at the foveal margin, it thickens to comprise up to seven or eight layers of cells. Ganglion cells have from one to several dendrites and have been classified into several different functional types.[1]

Pearls

- In conditions that result in swelling and opacification of the ganglion cell layer, such as storage disorders and central retinal artery occlusions, retinal opacification is most prominent in the macular region because the ganglion cell layer is thickest in the macula but not in the foveola where the ganglion cell layer is discontinuous—hence the "cherry red spot" appearance in the central macula in such conditions.

The ganglion cells each send a single axon through the nerve fiber layer to the optic nerve. Thus, this is the only retinal layer that is not discontinuous across the optic nerve head. As one would expect, the nerve fiber layer is thickest adjacent to the disc and thinnest at the ora serrata. As measured in quadrants adjacent to the nerve, the nerve fiber layer is thickest superiorly and thinnest in the papillomacular bundle, temporal to the disc.[30]

The axons synapse at the lateral geniculate body. Those originating in the temporal half of the retina remain ipsilateral, while those from the nasal half cross at the optic chiasm. However, there appears to be some intermingling along this vertical dividing line, so that some temporal fibers cross and some nasal fibers do not; this may explain evidence of macular sparing in unilateral occipital cortical disease.[31]

Controversial Points

- "Macular sparing" in unilateral occipital cortical infarct may be, at least in part, explained by the finding that not all ganglion cell axons from the temporal retina remain uncrossed at the optic chiasm and not all axons from the nasal retina cross at the chiasm.

Müller's cells extend virtually the entire thickness of the retina. The outermost apical portion of the cells is bound by zonulae adherentes to the photoreceptors, and the cells have delicate processes- fiber baskets- that extend even further outward, reaching the interphotoreceptor matrix. Müller's cells extend inward to the inner limiting membrane. They have lateral

processes that surround adjacent cells in the nuclear and plexiform layers, acting as a support. Their nuclei reside in the inner nuclear layer and processes surround the retinal capillary plexus in a so-called bipolar arrangement, nourishing neurons. Müller's cells spread out laterally and help to form the internal limiting membrane, which is a true basement membrane. The internal limiting membrane is attenuated in areas where large blood vessels in the nerve fiber layer displace these cells.[1] Other types of glial cells, including microglia and astrocytes, are also present in the retina.[8]

1.3.3 Retinal Circulation

The retina receives a dual circulation of blood. The inner half of the sensory retina, extending outward to include approximately the inner third of the inner nuclear layer, is supplied by the retinal vasculature. The outer half receives its nourishment by diffusion from the choroidal circulation.

The retinal vessels, like those of the brain, are end vessels and do not anastomose except under pathologic circumstances. Also, like those of the brain, and unlike those elsewhere in the body, the retinal capillaries are impermeable to relatively small molecules, such as fluorescein.

Pearls

- The retinal vessels, like those of the central nervous system, are end vessels and do not normally anastomose. Similar to those of the brain, the retinal capillary endothelial cells have tight junctions, which make the vessels impermeable to relatively small molecules, such as fluorescein.

Vascularization of the retina begins during the 16th week of gestation at the optic nerve head,[32] and normally reaches the ora serrata nasally at the time of birth. It is not quite complete temporally at term because the distance from the optic nerve head to the ora is greater.

The vessels of the retinal circulation emerge at the optic disc and almost immediately divide to form four branches. The two temporal vessels run superiorly and inferiorly to the macula in an arcuate configuration, whereas the superonasal and inferonasal vessels run more directly peripherally. As the vessels proceed peripherally, they further branch and taper in size. The specific pattern of the retinal vessels is unique to each individual.

The large arterioles and venules travel in the nerve fiber layer and ganglion cell layer. (Despite the fact that the central retinal vessels remain histologically arteries and veins for only a short distance from the optic disc, peripherally becoming arterioles and venules, respectively, the terms *artery* and *vein* are used clinically and histologically to designate the respective vessels and their diseases.) The veins accompany the arteries, and the vessels may cross each other multiple times as they proceed peripherally. Where they cross, they share a common adventitial sheath. With increasing age and the development of arteriosclerosis, the crossings can become accentuated, with compression of the less resilient vein. Branch retinal vein occlusions typically occur at crossings where the artery crosses over the vein.[33]

Pearls

- Retinal arteries and veins share a common adventitial sheath where they cross. Increasing atherosclerosis can cause the artery to impinge on the underlying, less resilient vein, and this appears to explain why branch retinal vein occlusions tend to occur where the artery crosses over the vein.

The smaller vessels, including the capillaries, extend outward at the level of the nerve fiber layer and the inner nuclear layer. Close to the foveal avascular zone, the capillaries form a single layer, but elsewhere the capillaries are present in two or more distinct layers.[34] The most peripheral millimeter or so of the sensory retina is avascular.

Frequently, the retina receives some blood supply from an artery originating in the choroid that travels around the margin of Bruch's membrane at the margin of the optic nerve head (▶ Fig. 1.4). In one clinical study, about half of all the patients studied had at least one cilioretinal artery in one eye, and about a third had such vessels bilaterally.[35] Most were seen at the temporal margin of the disc, and many such vessels supplied at least a portion of the macular circulation. Such vessels are supplied by the short posterior ciliary arteries, like the choroidal vessels. Thus, they fill before the central retinal artery and can be recognized on fluorescein angiography.[35]

As noted earlier, the retinal capillaries, including those of any cilioretinal vessels, are impermeable to relatively small molecules. This so-called inner blood–retinal barrier is the vascular endothelium. The site of the barrier is the specialized tight junctions (zonulae occludentes) between individual endothelial cells. Also, in contrast to that of the choriocapillaris, the capillary endothelium of the retina does not have pores.[15]

The sympathetic nervous system is responsible in most parts of the body for regulation of vascular tone. However, the retinal vessels are an exception; regulation is mediated by a number of vasoactive substances secreted by the vascular endothelium.[36]

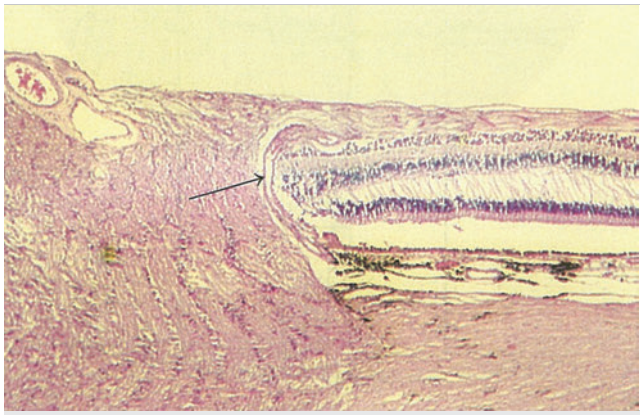

Fig. 1.4 A cilioretinal artery (arrow) originates from the choroid and proceeds inward around Bruch's membrane, retinal pigment epithelium, and outer retina to enter the nerve fiber layer. Hematoxylin and eosin, ×62.

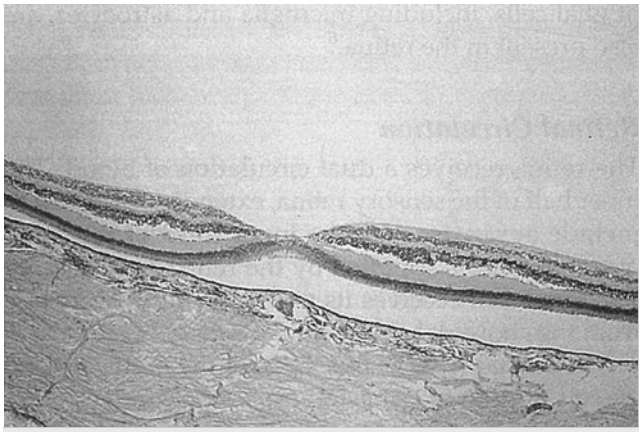

Fig. 1.5 Low-power view of the macula. Even at this magnification, the thickness of the ganglion cell layer is clearly visible. The sensory retinal detachment is an artifact. Hematoxylin and eosin, × 16.

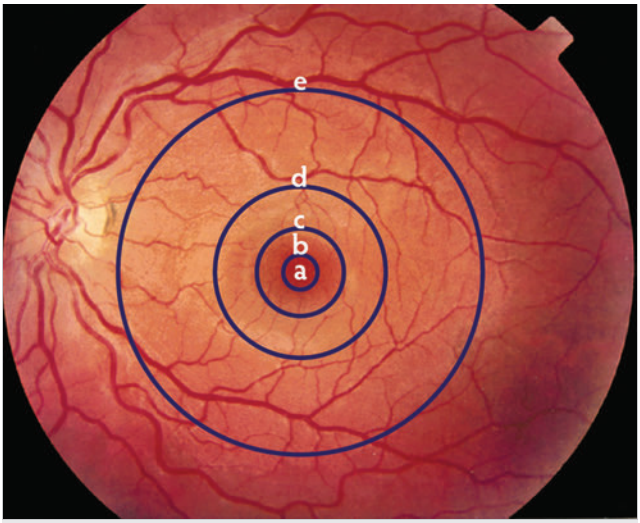

Fig. 1.6 Terms for central area of the posterior pole with approximate sizes. (**a**) Foveola: 0.35 mm diameter; (**b**) fovea: 1.5 mm diameter; (**c**) parafovea: 0.5 mm ring; (**d**) perifovea; 1.5 mm ring. The area centralis thus has a diameter of 5.5 mm: 1.5 + 2 × 0.5 + 2 × 1.5 = 5.5 mm.

1.3.4 Macula

The macula, or area centralis, is a specialized region of the retina.[37] The terms *macula* and *fovea* are used in different ways by the anatomist and the clinician because clinical landmarks have no precise anatomic counterpart, and vice versa. Anatomically, the macula includes the entire area of the retina where the ganglion cell layer is more than a single cell layer in thickness (▶ Fig. 1.5). It corresponds to the clinician's posterior pole and is about 5.5 mm in diameter, approximately bounded by the superior and inferior temporal vascular arcades (▶ Fig. 1.6). Superficial capillaries supplying the nerve fiber layer are oriented radially and are called the radial peripapillary capillary net.[38] They do not extend beyond the near periphery or fovea and cause cotton wool spots when occluded. These radial capillaries are angiographically distinct from the deeper two plexuses, the superficial one on the inner aspect of the inner nuclear layer and the deep capillary plexus on the outside. Radicular vessels- some right angled- dip deep down into the retina to supply these plexus.[39] Focal intraretinal periarteriolar transudates or paracentral acute middle maculopathies may result from deeper intraretinal (pre)capillary leakage or occlusion.[40,41]

What is clinically referred to as the fovea[42] is a central depression about 1.5 mm in diameter, approximately the size of the optic disc. In younger people, the boundary of this central depression- the margo foveae- often produces a horizontally oriented, slightly oval light reflex. With age, this reflection dims. More centrally from this boundary is the limit of the capillary network, or the foveal avascular zone, about 500 to 600 µm (0.5–0.6 mm) in diameter. The foveola measures about 350 µm (0.35 mm) in diameter and is the floor of the anatomic fovea. Particularly in younger people, a tiny bright dot of light overlying the center of this pit can sometimes be seen. This is a virtual image formed by the configuration of the retina in this region. The foveola and the foveal clivus act as a minute parabolic mirror, reflecting the incident light.

The *foveola* is populated with specialized cones, and rods are entirely absent.[1] Morphologically, the cones are long, slender, and rodlike, allowing tighter packing, particularly in the central 200-µm area, the umbo. The floor of the foveola consists only of the cones and Müllerian glial cell processes, the remaining layers of the sensory retina having been displaced peripherally (▶ Fig. 1.7). To synapse with the next order of neurons, the inner fibers of the cones in the foveola must be oriented obliquely, forming *Henle's fiber layer*. Fluids collect more easily in the outer plexiform layer around the foveola because of the oblique orientation of the photoreceptor fibers here compared to their more vertical orientation peripherally.

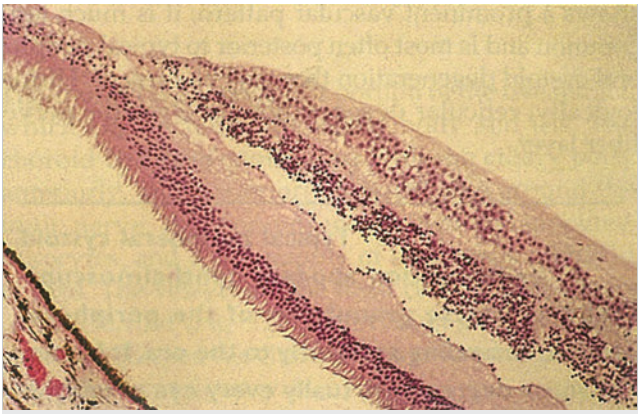

Fig. 1.7 Medium power view of the macula shows the foveola at the upper right, populated only by cone photoreceptors. Immediately adjacent, all nuclear layers are about equally thick. The split between the outer plexiform layer and the inner nuclear layer is an artifact. Hematoxylin and eosin, × 62.

A yellow coloration gives the *macula lutea* its name. This pigment is not well seen with white light, but with red-free light or with blue light photography, it is more obvious. It is present in all the retinal layers inward to the outer nuclear layer, especially in both plexiform layers.[43] Its highest concentration is in the foveola, where it is theorized to function as an optical filter. The pigment is dissolved out with routine histologic fixation, but its location has been analyzed in fresh-frozen sections and with specialized fixatives. Chemically, it is a carotenoid called *lutein*.[44]

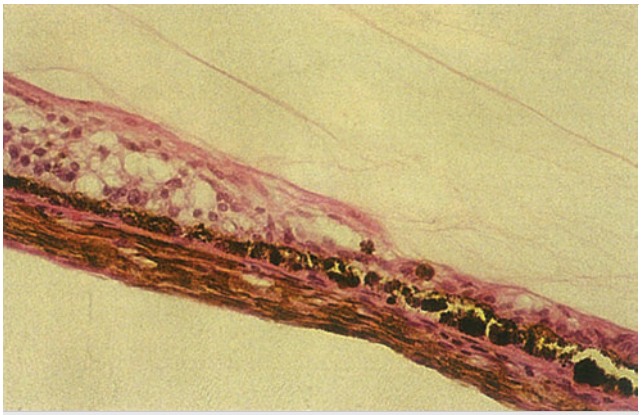

Fig. 1.8 The ora serrata region shows relatively disorganized layers in the sensory retina, to the left. There is an abrupt transition to nonpigmented ciliary epithelium, to the right. There are strands of vitreous visible overlying this region, the vitreous base. Hematoxylin and eosin, ×156.

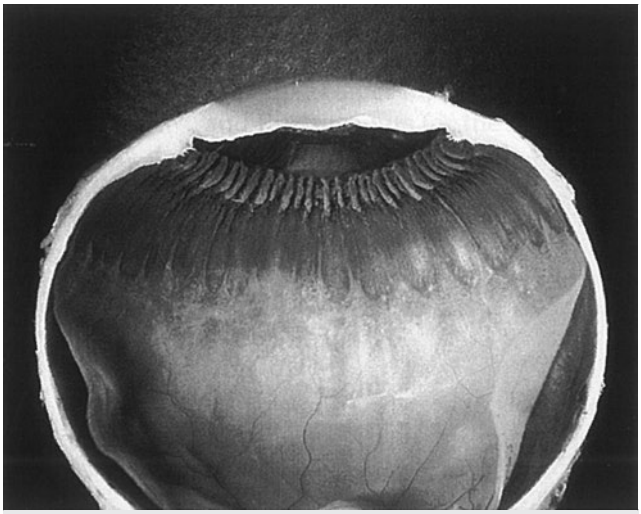

Fig. 1.9 The teeth and bays of the ora serrata are readily seen in the nasal portion of the eye.

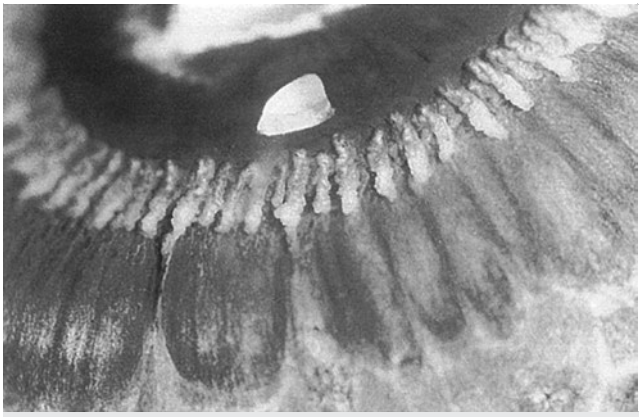

Fig. 1.10 Two meridional complexes.

Pearls

- Fluids collect more easily in the outer plexiform layer around the foveola because of the oblique orientation of the photoreceptor fibers here compared to their more vertical orientation peripherally.

1.3.5 Retinal Periphery

Anatomically, the retinal periphery includes all portions of the retina that are not part of the anatomic macula, or, otherwise stated, that part of the retina where the ganglion cell layer is a single cell layer thick. The ora serrata is the junction between the sensory retina and the nonpigmented ciliary epithelium (▶ Fig. 1.8). The ora serrata is, as the name implies, serrated in configuration. This serration is most obvious, with deep bays and more pronounced teeth, in the superonasal region (▶ Fig. 1.9).[45] Elsewhere, the teeth and bays are less distinct.

The preequatorial retina has particular anatomic structures and variations. *Meridional folds* are linear elevations in the peripheral retina that appear as tented-up ridges, with the folds arranged meridionally. They can occur anywhere from the ora- within a tooth or bay- to a region about 6 mm posterior to the ora. About four-fifths arise in a tooth. If folds arise in a dentate process that is aligned so that it meets with a ciliary process anteriorly, the structure is called a *meridional complex* (▶ Fig. 1.10). In a large autopsy study, meridional folds and complexes occurred with equal frequency in all decades of life; thus, they are congenital, not degenerative, lesions. Racial prevalence was equal, but they were more frequent in men.[45]

Ora serrata pearls are small, spherical, glistening bodies seen within retinal teeth, or just posterior to them, in aging eyes. They may appear opalescent, giving them their name. Sometimes they are brown to black. They may be multiple, extending in a line along the tooth. They are formed beneath the retinal pigment epithelium and may thus be a type of druse. Subsequently, they work their way to the retinal surface and may even end up within overlying vitreous.[46]

An oral bay may extend posteriorly to be unusually deep. Typically, such a bay is bounded by two unusually large teeth, called *giant teeth*. If the bay is closed by the fusion of two adjacent teeth, it is called an *enclosed oral bay* (▶ Fig. 1.11). The enclosed area appears clinically and histologically as an "island" of pars plana with retinal tissue both anterior and posterior to the island. These findings occur independently of age and appear to be congenital variations.[45]

With increasing age, *cystoid degeneration* occurs at the ora serrata, particularly in the temporal region. Typical peripheral cystoid degeneration involves the outer plexiform layer, resulting in spaces that contain an acid mucopolysaccharide. Clinically, it appears as a coarsely granular change in the peripheral retina, extending anteriorly to the ora serrata. Posteriorly, there is an abrupt boundary with normal-appearing peripheral retina. Typical peripheral cystoid degeneration is seen to some degree in virtually every eye of individuals older than 20 years. Reticular degeneration, in contrast, appears more finely

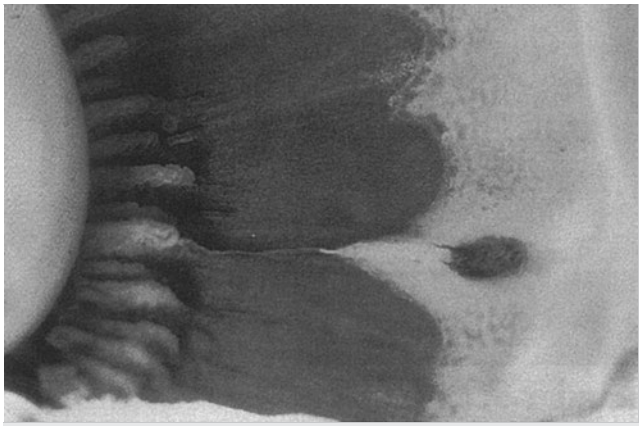

Fig. 1.11 Enclosed oral bay. Two retinal teeth enclose an island of ciliary body epithelium.

granular and shows a prominent vascular pattern; it is much less common and is most often posterior to typical peripheral cystoid degeneration that may be present. Histologically, reticular degeneration involves the nerve fiber layer.

Pearls

- Typical peripheral cystoid degeneration appears ophthalmoscopically as coarse granularity of the peripheral retina, extending anteriorly to the ora. It is seen to some degree in virtually every eye of individuals older than 20 years.

Both types of peripheral cystoid degeneration may progress to degenerative schisis, arbitrarily defined as spaces that extend radially for 1.5 mm or more. Typical degenerative retinoschisis tends to remain flat and be nonprogressive, whereas reticular degenerative retinoschisis shows a bullous elevation of the inner aspect of the split and has a tendency to extend posteriorly.[47]

Several types of focal elevations of retinal tissue, called *retinal tufts*, have been identified. Noncystic retinal tufts occur at the vitreous base and- by virtue of their location- do not lead to retinal detachment. Cystic retinal tufts are more posterior, and appear as 0.1- to 1.0-mm whitish elevations. They are present in all age groups and in all quadrants of the retina. There can be associated pigment changes at the base of the tuft, as well as small holes or tractional tears. Histologically, there is microcystic change within and around the tuft, and frequently vitreous condensations are present on the surface.[48]

Zonular traction tufts can also lead to retinal detachment. These are congenital lesions that extend over the pars plana from the peripheral retina and become continuous with a zonular fiber. The retina at the base of the tuft is tented up and tends to show cystoid degeneration. The tuft is composed of a thin glial strand, and rarely embryonal epithelium. For unexplained reasons, about 80% are nasal, and three-quarters occur in male subjects.[49]

Because the nonpigmented ciliary epithelium is attached to the pigmented ciliary epithelium by tight junctions between

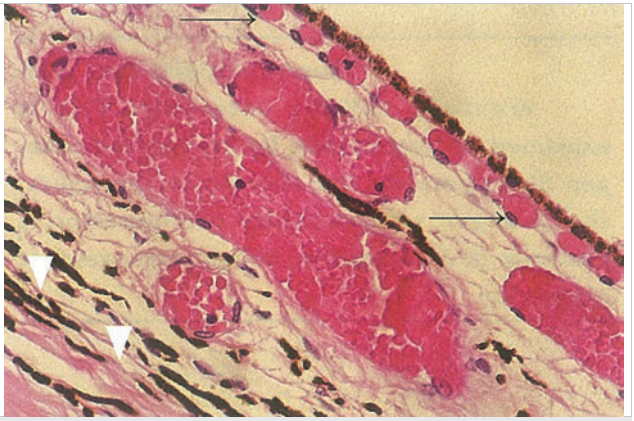

Fig. 1.12 The choroidal vasculature. Beneath the retinal pigment epithelium and Bruch's membrane (inconspicuous in this infant eye) is the choriocapillaris (arrows). There is increased pigmentation in the region of the lamina fusca (arrowheads) where choroid joins sclera. Hematoxylin and eosin, ×125.

cells, sensory retinal detachment does not usually progress anteriorly to the ora. However, tears may occur at the anterior vitreous base, perhaps triggered by iatrogenic pars plana penetration.

Pearls

- Sensory retinal detachments do not usually progress anteriorly to the ora because in the pars plana the nonpigmented ciliary epithelium is attached to the pigmented ciliary epithelium by tight junctions.

1.4 Choroid

The choroid is the posterior portion of the uveal tract, which also includes the ciliary body and iris. Anteriorly, the choroid is continuous with the ciliary body, and posteriorly it terminates at the glial border tissue of Jacoby around the optic nerve. It is composed of uveal melanocytes, fibrocytes, and a rich supply of anastomosing blood vessels. The vessels are the most conspicuous aspect of the choroid (▶ Fig. 1.12). When congested, they substantially thicken the choroidal parenchyma and give it a spongy consistency.

The blood supply of the uveal tract comes from several sources, although all are ultimately derived from the ophthalmic artery. Some 15 to 20 short posterior ciliary arteries enter perpendicularly through the peripapillary sclera and supply prelaminar the optic nerve and the choroid. Vessels traverse the suprachoroidal space, then branch in the choroid and extend anteriorly beyond the equator.

The two long posterior ciliary arteries enter the sclera obliquely at the foveal horizontal meridian posteriorly, proceeding anteriorly in the suprachoroidal space to the supraciliary space (▶ Fig. 1.13). They branch at about the level of the ora serrata to join the major iridal circle and supply much of the

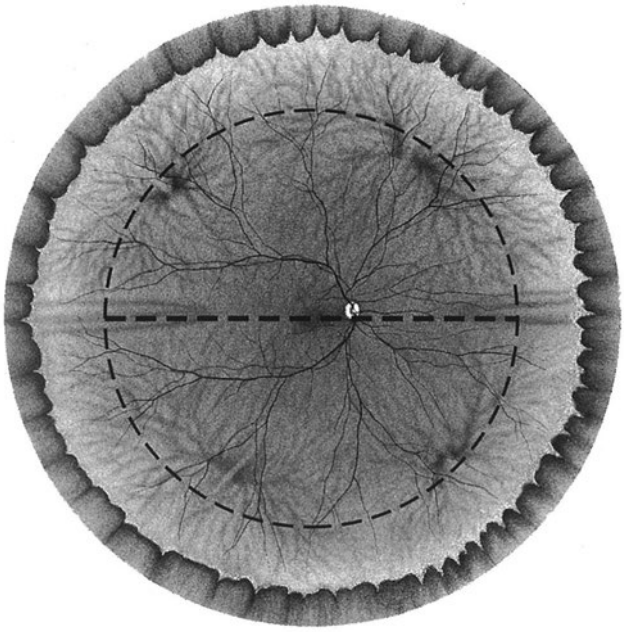

Fig. 1.13 Landmarks of the peripheral retina. The vortex vein ampullae lie just posterior to the equator (dotted circle), and the long posterior ciliary arteries and nerves mark the location of the foveal horizontal meridians (dashed line).

anterior uveal circulation, but some branches also loop back into the anterior choroid. In addition, a total of seven anterior ciliary arteries travel within the four rectus muscles, entering the sclera as major perforating branches at the rectus muscle attachments anterior to the equator. Each rectus muscle has two anterior ciliary arteries- except for the lateral rectus, which has one- derived from the lacrimal artery. In addition to supplying the iris and ciliary body via anastomoses with the major iridal circle, these vessels make contributions to the limbus and palisades of Vogt. Episcleral branches form the superficial marginal plexus and the peripheral corneal arcades. Both are prominent and hyperemic in iritis.

The choroid is drained by vortex veins. These vessels are clinically visible, particularly in blond fundi, as irregular, star-shaped, sometimes protruding structures (▶ Fig. 1.13). Venules come together and drain into a dilated structure- the vortex ampulla- from which the vortex vein pierces the sclera and exits the eye. Although schematic drawings like ▶ Fig. 1.13 show four of these vortex vein ampullae, just posterior to the equator superonasally, superotemporally, inferotemporally, and inferonasally, the number actually varies in different eyes, averaging about seven per eye; they are more numerous nasally.[1]

Pearls

- The vortex vein ampullae and the long posterior ciliary artery–nerve complexes are good clinical fundus landmarks. There are one or more vortex vein ampullae in each quadrant, all in a location just posterior to the equator. There are two long posterior ciliary artery–nerve complexes, and they are consistently located in the foveal horizontal meridians.

Within the choroid itself, the largest vessels are closest to the sclera, and the choriocapillaris is the innermost layer. The outermost layer is called *Haller's layer*, and the middle layer, consisting of medium-sized pre- and postcapillary vessels, is *Sattler's layer*. The choriocapillaris is a monolayer of interlacing capillaries and is distinctive for consisting of the largest capillaries in the body, measuring up to 20 µm in diameter in the macula and up to 50 µm peripherally.[1] The density of the choriocapillaris decreases with age.[18]

Although it appears anatomically that the capillaries of the choriocapillaris form a diffuse network throughout the choroid, evidence from postmortem studies and fluorescein angiography indicates that in the posterior pole the capillaries are arranged in a lobular pattern, with a feeding precapillary arteriole in the center of each lobule and several postcapillary venules draining the lobule peripherally.[50] The arterioles taper rapidly to form multiple capillaries, and this accounts for the high rate of blood flow through the capillary bed. This high flow rate appears to function at least in part as a heat-dissipating mechanism.[51] There are also numerous arteriole–arteriole anastomoses, particularly in the posterior pole.[52]

In the far periphery, the choroidal vessels are arranged more meridionally, so that the arteries and veins are more parallel, connected by capillaries in a manner suggesting a ladder. At the equator, the configuration is a transition between these two arrangements, a spindle configuration.[53] In this region, the venules tend to be more central and the arterioles more peripheral.[54]

The capillaries have fenestrations, or pores, which are most numerous on their inner aspect, toward the pigment epithelium. This allows diffusion of metabolites to and from the pigment epithelium and outer aspect of sensory retina. Ultrastructurally, these fenestrations consist of small, circular areas 60 nm in diameter in the unit membrane of the capillary endothelium. Like capillaries elsewhere, individual endothelial cells are joined together by zonulae occludentes.[55]

The retinal pigment epithelium and the outer half of sensory retina are nourished through diffusion from the choroidal circulation. Occlusion of the choroidal circulation occurs commonly in the far periphery, resulting in focal loss of pigment epithelium and outer retinal layers. Clinically, this is termed *cobblestone degeneration*.

The choroid is innervated by the short posterior ciliary nerves. These enter and travel with the short posterior ciliary arteries. They remain myelinated for a short distance within the eye, and then become unmyelinated. They appear to supply sympathetic innervation to the blood vessels.[1]

The long posterior ciliary nerves enter the peripapillary sclera obliquely at the foveal horizontal meridians, along with the long posterior ciliary arteries. The nerves travel in the suprachoroidal space, between choroid and sclera, and remain myelinated until arriving in the ciliary body.[1]

The choroidal melanocytes, like those of the rest of the uveal tract, skin, and hair, are derived from neural crest. They are star-shaped and have many long, delicate processes. They contain numerous small, round-to-oval melanosomes[1] and retain the ability to synthesize melanin throughout life. It is hypothesized that the melanin of both the choroid and pigment epithelium serve to absorb excessive light.[20] Other cells present in the choroid include scattered fibrocytes.

The choroid is attached to the sclera by means of long, interconnecting collagen fibers called lamina fusca. Within this suprachoroidea are melanocytes and nerve plexuses.[1] The attachments between choroid and sclera are essentially perpendicular posteriorly, keeping the choroid relatively tightly bound, but they become more obliquely oriented anteriorly. Thus, suprachoroidal fluid preferentially collects anteriorly.

Pearls

- Suprachoroidal fluid preferentially collects anteriorly. This is explained, at least in part, by the way the collagen fibers connect the choroid to the sclera; the stronger, perpendicular configuration is posterior and the weaker, oblique arrangement is anterior.

1.5 Acknowledgment

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2 Retinal and Retinal Pigment Epithelial Physiology

Michael F. Marmor and Loh-Shan B. Leung

2.1 Introduction

Many retinal disorders have a selective effect on particular cells or metabolic systems within the retina and retinal pigment epithelium (RPE). Effective management of these disorders, which include conditions as diverse as retinitis pigmentosa (RP), central serous chorioretinopathy (CSC), and congenital color blindness, requires an understanding of retinal physiology and of the interaction between the retina and RPE. The physiology of the retina cannot be separated from that of the RPE, especially in a clinical context, because the RPE actively supports and facilitates retinal function and is also a frequent site of damage in disorders of the ocular fundus.[1]

2.2 Retinal Pigment Epithelium

Although the RPE is derived embryologically from the same neural tube tissue as the neurosensory retina, the RPE cells differentiate into a monolayer epithelium that behaves functionally more like the lining of the gallbladder than like central nervous system tissue. The cells are linked by tight junctions and show anatomic and physiologic membrane specializations on the apical and basal surfaces (▶ Fig. 2.1). These enable the RPE to control water and nutrient access to the subretinal space, which is critical to the viability of the photoreceptors. Major functions of the RPE are outlined in the following text box.

Selected Functions of the Retinal Pigment Epithelium

- Pigment functions
  - Light adaptation and screening
  - Detoxification and binding
  - Lipofuscin accumulation
  - Antigenic properties
- Environment and metabolic control
  - Blood–retinal barrier
  - Transport of nutrients and ions
  - Dehydration of subretinal space
  - Synthesis of enzymes, growth factors, and pigments
  - Interaction with endocrine, vascular, and proliferative factors
- Visual pigment cycle
  - Capture and storage of vitamin A
  - Isomerization of all-*trans* to 11-*cis* vitamin A
- Retinal adhesion and interphotoreceptor matrix (IPM)
  - Matrix domains surrounding rods and cones
  - Metabolic control of adhesiveness
- Photoreceptor phagocytosis and aging
  - Phagocytosis of outer segment tips
  - Digestion and recycling of membrane material
  - Aging effects: lipofuscin, drusen
  - Deposits and alterations in Bruch's membrane
- Electrical activity
  - Response to light-induced ionic changes: c-wave, fast oscillation
  - Response to light-induced chemical signals: electro-oculogram (EOG)
  - Nonphotic responses to chemical agents
- Repair and reactivity
  - Repair and regeneration
  - Immunologic interactions
  - Scarring and pigment migration
  - Role in modulating fibrovascular proliferation

2.2.1 Pigments and Optical Functions of the Retinal Pigment Epithelium

The RPE is so named because of its content of *melanin*, a large polymeric molecule synthesized in cytoplasmic granules called *melanosomes*. The RPE is the first tissue in the body to become pigmented, and some degree of melanogenesis continues throughout life. However, in older eyes, many melanin granules fuse with lysosomes and break down, and the elderly fundus typically appears rather depigmented. It has long been assumed that a major function of melanin was the absorption of stray light, to minimize scatter within the eye. This is understandably true in animals such as the frog, in which long pigment-containing processes extend up between the photoreceptors. However, the RPE processes around rods are rather short in humans, and in general the RPE is less pigmented than the choroid (most racial differences in fundus appearance reflect pigmentation of the choroid rather than of the RPE). There is no difference in visual acuity between blond and heavily pigmented fundi. The loss of acuity in albinism is a result of poor foveal cone organization rather than of light scatter.

Melanin may also serve a protective function in the eye, as a free radical scavenger and as an agent that can bind toxins. This latter role is controversial, however, because it is not clear whether the binding of certain retinotoxic drugs, such as chloroquine and thioridazine, protects the retina by removing the toxic agents from the cytoplasm or enhances their toxicity by concentrating the agents near the retina.

As the eye ages, there is accumulation of another RPE pigment, *lipofuscin*. This is an aging pigment, present throughout the nervous system, but it may have special significance within the eye. Lipofuscin in the RPE is thought to be derived from lipids of the photoreceptor outer segments and metabolic by-products of the visual pigment regeneration cycle that have been ingested and digested by the RPE through the process of outer segment renewal (see later), including membrane fragments that may have been damaged by light absorption or oxidation. A major component is *N*-retinylidene-*N*-retinyl-ethanolamine, or A2E, a toxic by-product of all-*trans*-retinal binding that is controlled in part by the *ABCA4* (Stargardt's disease) gene.[2,3] Lipofuscin can be identified even in the RPE of children, but it does not become prominent until adulthood. With aging,

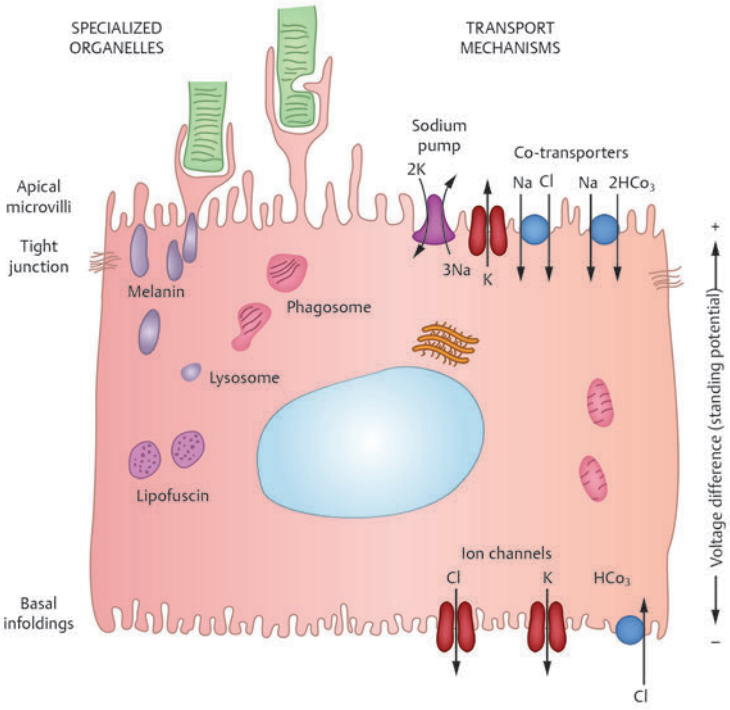

Fig. 2.1 RPE cell showing the major anatomic specializations and some of the membrane transport mechanisms. The apical region (with long microvilli ensheathing the photoreceptors) is separated by tight junctions from the basal region (with small but numerous infoldings). Lysosomes can merge with other granules to form phagolysosomes or melanolysosomes. Different ion channels and cotransporter systems are found in the apical and basal membranes, and the electrogenic sodium pump is on the apical membrane. These transport systems generate a voltage (standing potential) across the cell.

the RPE cells are often clogged massively with the golden autofluorescent pigment.

Controversial Points

- Melanin in the RPE may have a protective function in scavenging free radicals and binding toxins. However, this latter role is controversial, as it is not clear whether binding of certain drugs, such as chloroquine and thioridazine, protects the retina or enhances toxicity by concentrating the agents near the retina.

A2E is a component of the lipofuscin-like material that accumulates in the RPE of eyes with Stargardt's disease, fundus flavimaculatus, and Best's disease (vitelliform dystrophy).[4] The autofluorescent pigment in these disorders clogs cells throughout the retina, even at younger ages, and not just in the macular region, where fundus pathology of these disorders is most prominent clinically. However, we still have much to learn about these disorders. For example, although a Stargardt's disease phenotype can by caused by *ABCA4* mutations, defects in the same gene can also cause cone dystrophy or even retinitis pigmentosa. Furthermore, there can be phenotypic variations within a family, and the relationship to A2E is not always clear.

2.2.2 Control of the Subretinal Space

The neurosensory retina is embryologic brain tissue, and as such it requires the same environmental protection as tissue in the brain. A blood–brain or *blood–retinal barrier* is provided in part by the intrinsic retinal blood vessels, which have tight junctions like cerebral vessels (*inner* blood–retinal barrier). However, the choroidal vessels, which provide nutrition to the outer retina, are leaky, and the other part of the blood–retinal barrier is provided by the tight junctions of the RPE (*outer* blood–retinal barrier). Secreted factors, such as vascular endothelial growth factor (VEGF), play an important role in fluid homeostasis in the subretinal space and maintenance of this outer blood–retinal barrier (see later). The apical and basal RPE membranes contain a variety of selective ion channels and a variety of active and facilitative transport systems that control the movement of ions and water and the transport of metabolites, such as glucose and amino acids.[5] The amino acid taurine, for example, is essential for photoreceptor function and is concentrated by the RPE; D-glucose but not L-glucose is transported into the subretinal space. There are different channels and transporters on the apical and basal surfaces, such as an electrogenic sodium–potassium pump on the apical membrane and a chloride–bicarbonate exchange transporter on the basal membrane. The asymmetry between the apical and basal membranes accounts for the development of a voltage (called the *standing potential*) across the RPE, and it also results in a net movement of ions away from the subretinal space that drives the transport of water.

Special Considerations

- The blood–retinal barrier is provided by the tight junctions of the retinal blood vessels (inner barrier) and the tight junctions of the RPE (outer barrier). For proper protection and function of the neurosensory retina, the barrier needs to be intact at both levels.

The RPE active transport mechanisms for water are very powerful. If a large retinal detachment is buckled without drainage, fluid can clear within 24 hours. The RPE can remove water from

the subretinal space against a substantial gradient of hydrostatic or osmotic pressure, even when the subretinal fluid contains protein.[6] It is important to recognize that it is the presence of tight junctions between the RPE cells that necessitates this active transport. Passive transport mechanisms, such as intraocular pressure against the retina and osmotic pressure from the choroid, also tend to drive fluid *out* of the subretinal space—but water movement is normally restricted by the RPE barrier. When the RPE barrier is damaged, fluid actually leaves the subretinal space *faster* than under normal conditions. In other words, a normal eye will not accumulate fluid in the subretinal space just because the RPE barrier is disrupted.

These observations have relevance for clinical disorders such as serous detachments. They show that the presence of a defect in the RPE is not by itself sufficient to cause serous detachment, even though it may be necessary.[7] There must be a pressure head within the choroid, such as a neovascular membrane or an area of ischemic or inflammatory injury, to drive fluid in the retinal direction. This explains the fluid that accumulates over areas of inflammation and RPE damage in Harada's disease or over regions of choroidal ischemia in accelerated hypertension or preeclampsia, or the local fluid that accumulates over choroidal neovascularization in age-related macular degeneration. However, this does not explain why fluid spreads far beyond a small focal leak in disorders such as idiopathic CSC (▶ Fig. 2.2), as one would expect the RPE to remove such fluid rapidly. These conditions probably involve a diffuse impairment of fluid transport across larger regions of RPE, which prevents rapid absorption. This could result from RPE disease, but may more often be a result of choroidal disease. For example, indocyanine green angiography of eyes with CSC typically shows broad areas of choroidal hyperperfusion and hyperpermeability, and high-resolution optical coherence tomography shows choroidal thickening in the central macula. The leak itself may be something of an epiphenomenon—but when a leak develops in a susceptible eye, fluid can accumulate and the disease becomes symptomatic (see Chapter 16).

2.2.3 Visual Pigment Regeneration

Another critical metabolic interaction between the retina and RPE is the visual pigment cycle. The RPE serves to capture vitamin A from the bloodstream, and it stores esterified vitamin A within its cytoplasm. Specific binding proteins (e.g., *interphotoreceptor retinoid-binding protein, IRBP*) serve to transport vitamin A across the subretinal space to be incorporated into rhodopsin in the photoreceptors. After rhodopsin is activated by light, the desensitized (*all-trans*) vitamin A is transported back to the RPE to be stored and isomerized to the 11-*cis* conformation (▶ Fig. 2.3). Many of the enzymes involved in this process have been found to cause human disease when missing or abnormal.[8]

This cycle of rhodopsin regeneration can take upward of a half-hour in a normal eye and is a basis of the clinical test of dark adaptometry. After an extensive exposure to bright light, the cones recover to maximum sensitivity in 6 to 8 minutes in the dark, whereas the rods require close to 30 minutes. The significance of this regenerative process is apparent to all of us as the time it takes to adjust to the darkness inside a movie theater or on a moonlight walk.

The *RDH5* gene in RPE causes a disorder called *fundus albipunctatus*,[9,10] which shows white dots throughout the posterior fundus associated with a curious form of night blindness. Affected individuals cannot find their seats going into a movie theater but may see well by the end of a double feature. The problem is not a *lack* of rod function but a striking *delay* in dark adaptation. After 4 hours in the dark, patients with fundus albipunctatus can have normal sensitivity and a normal rod

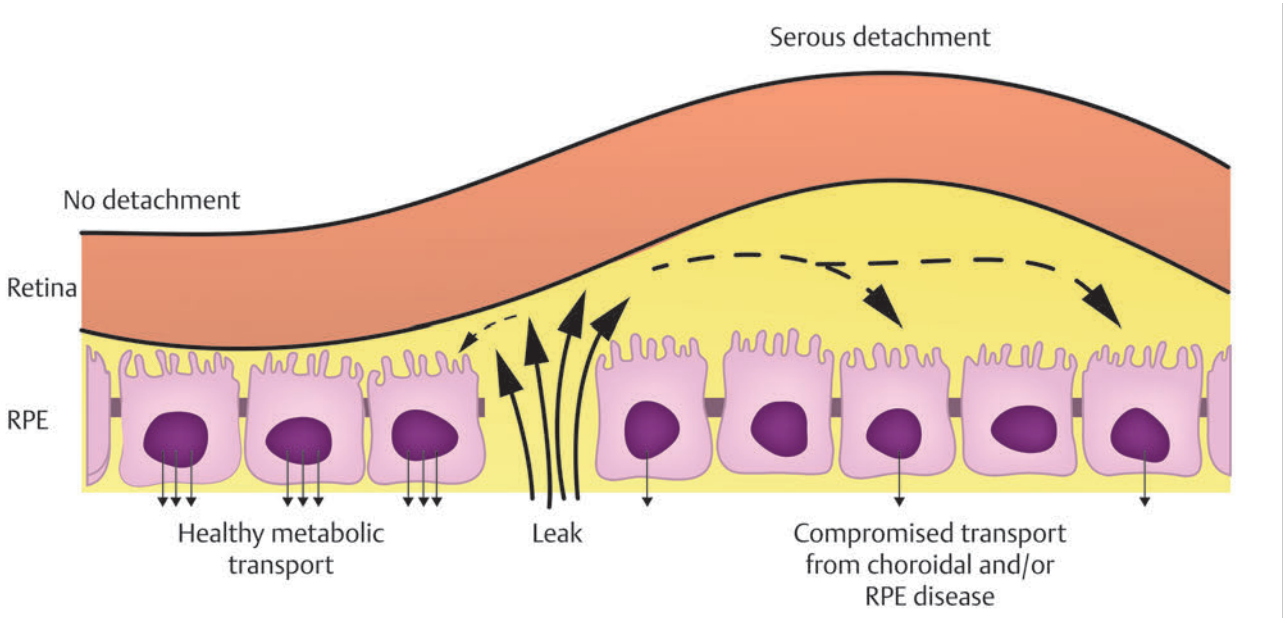

Fig. 2.2 A small site of RPE leakage. To the left, where the choroid and RPE are healthy and water transport is normal, there is no detachment. To the right, where vascular and/or RPE dysfunction compromises transport (and retinal adhesiveness as well), a serous detachment has developed beyond the site of leakage. (Modified from Marmor.[13])

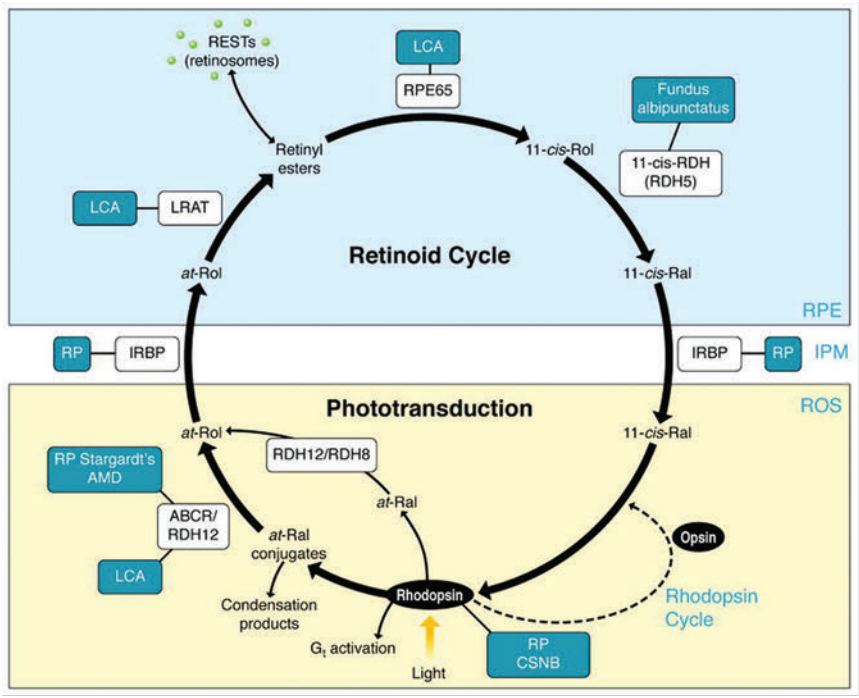

Fig. 2.3 Visual pigment regeneration cycle. The absorption of a photon by rhodopsin changes the coupled 11-*cis*-retinal to all-*trans*-retinal. This chromophore releases from the opsin and must be bound for transport to the RPE where it is esterified, stored, and then reisomerized to 11-*cis* before transported back to the outer segment where it couples again with opsin to make rhodopsin. The diagram shows some of the critical enzymes that control different phases of this cycle and that are known to cause human disease. (Reprinted with permission by Elsevier from von Lintig J et al.[8])

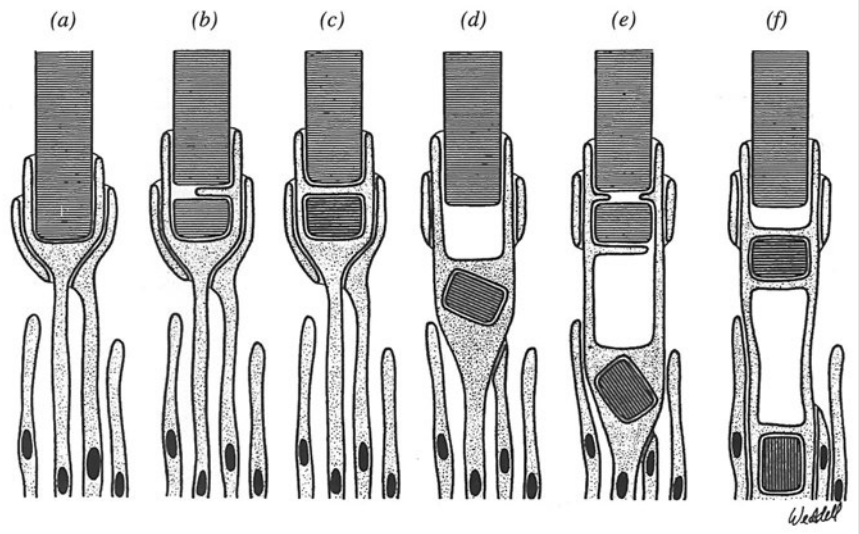

Fig. 2.4 Phagocytosis of outer segment tips by the microvilli of the RPE. (Reprinted with permission from Steinberg RH, Wood I, Hogan MJ. Pigment epithelial ensheathment and phagocytosis of extrafoveal cones in human retina. Philos Trans R Soc Lond B Biol Sci. 1977; 277(958): 459–474)

electroretinography (ERG). Loss of the RPE genes *LRAT* or *RPE65* will disrupt rod function severely and cause a form of Leber's amaurosis (essentially an early-onset severe RP).

2.2.4 Photoreceptor Regeneration and Phagocytosis of Outer Segments

The photoreceptor outer segments are exposed to radiant energy on a regular basis, and they exist in a high-oxygen environment by proximity to the choriocapillaris. Both light absorption and oxygen facilitate the production of free radicals, which damage lipid membranes. Cells in the skin would not last a lifetime without renewal, and the same is true for the photoreceptor outer segments. Thus, every day more than 100 discs at the distal end of each photoreceptor outer segment are phagocytosed by the RPE (▶ Fig. 2.4), and new discs are synthesized continually to replace them.[11] The cones tend to shed more vigorously at the onset of darkness and the rods at the onset of morning light, but some phagocytosis takes place continually. The phagocytosed disc material becomes encapsulated in bodies called *phagosomes*, which merge with lysosomes to facilitate digestion. Residual material is eventually egested across the basal RPE membrane. Some necessary fatty acids are retained and recycled back into the synthetic process. The metabolic demands of this process are impressive; each RPE cell ingests and digests upward of 4,000 discs daily. The *ABCA4* protein is believed to be a transporter within the photoreceptor disc membrane involved in the recycling process of all-*trans*-retinal. Defects lead to accumulation of A2E (discussed earlier) within the discs and subsequently within the RPE cells that phagocytose them.

A form of RP has been identified which depends on this process. Defects in the *MERTK* gene leads to a failure of RPE phagocytosis, followed by degeneration of the overlying rods and cones.[12] Pathology of the phagocytic process could, in theory, be relevant to excessive lipofuscin formation or to other aspects of aging and age-related macular degeneration.

2.2.5 Retinal Adhesion and the Interphotoreceptor Matrix

The RPE contributes to the formation of the IPM and to its effectiveness as a bond between the retina and RPE. It is important to recognize that the IPM is not just a viscous "goo" but has an elaborate structure based on segregated chemical domains that contain different glycosaminoglycans and related molecules. By binding fluorescent lectins to these molecules, one can identify discrete matrix sheaths that surround the cones and rods independently and bond to both RPE and outer segment membranes.

Adhesion of the retina to the RPE is a complex physiologic function; it appears to involve several complementary systems that keep the retina firmly in place unless a positive force (such as vitreous traction) pulls it off.[13] Retinal apposition is facilitated by intraocular pressure on the retina, by the draw of choroidal osmotic pressure, and by the presence of a formed vitreous gel. The RPE microvilli also wrap tightly around the tips of the outer segments for the purpose of phagocytosis, but there are no anatomic connections between the RPE microvilli and the outer segments. The IPM forms a viscous bond between the two layers, but this fluid connection is probably of lesser importance than the structural and chemical bond that is formed by the IPM by means of specific receptors where the matrix is in contact with the outer segment and RPE membranes. For example, these matrix domains can be seen to stretch dramatically when the retina is peeled away from the RPE (▶ Fig. 2.5), which demonstrates the firm attachment of the IPM to both the retinal and RPE surfaces.[14]

The structural and bonding characteristics of the IPM are affected by its degree of hydration and its ionic content, both of which are controlled by the transport characteristics of the RPE. Thus, the strength of retinal adhesion is highly dependent on metabolic activity, which governs RPE ion and water transport.[13] For example, retinal adhesive strength drops within minutes after death or after occlusion of the ocular circulation. This metabolic dependence of retinal adhesion may explain, in part, the greater susceptibility to detachment in older eyes (or perhaps highly myopic eyes), in which the vascular supply may be less functional as a result of age (or ocular expansion).

Retinal adhesive strength can be modulated osmotically and metabolically in experimental models. Systemic osmotic agents dehydrate the subretinal space and IPM and increase retinal adhesion to a modest degree, and a similar increase in adhesive strength can be produced by acetazolamide and other carbonic anhydrase inhibitors because they increase the rate at which fluid is transported out of the subretinal space. These agents could, in theory, prove helpful in the management of detachment disorders, but to date no such applications have been demonstrated.

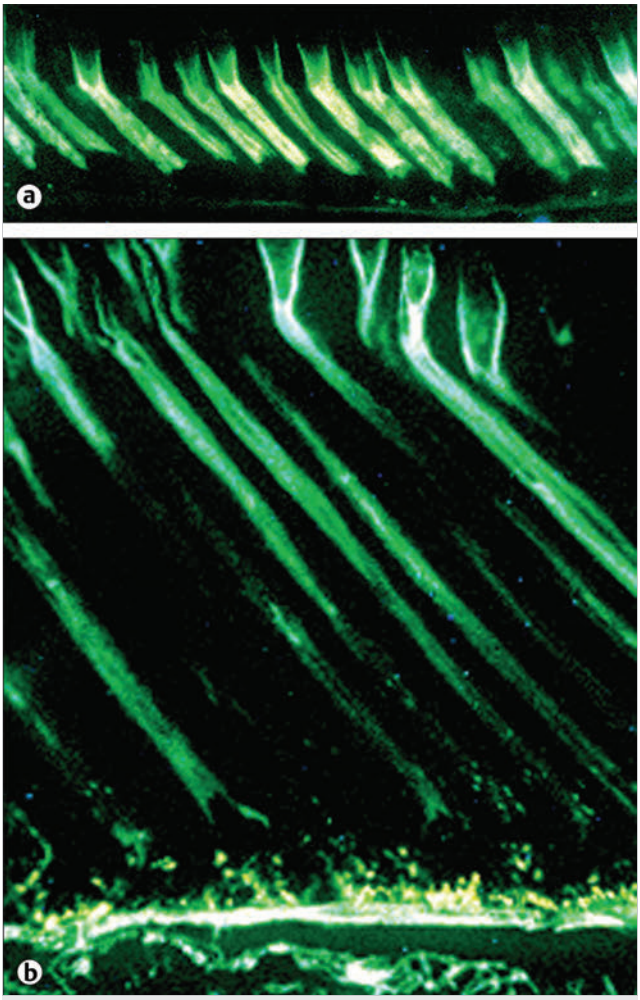

Fig. 2.5 Cone matrix sheaths of the interphotoreceptor matrix in rabbit (labeled with fluorescent peanut agglutinin). The retina is above and the RPE below. (**a**) Normal tissue with compact sheaths. (**b**) Tissue in which the retina is partially pulled away from the RPE. The cone matrix sheaths are stretched enormously, indicating strong attachment to both sides of the subretinal space. (Reprinted with permission from Hageman GS, Marmor MF, Yao X-Y, Johnson LV. The interphotoreceptor matrix mediates primate retinal adhesion. Arch Ophthalmol. 1995; 113 (5):655–660)

Pearls

- The IPM plays a significant role in the normal adhesion of the neurosensory retina to the RPE. The structural and bonding characteristics of the IPM are affected by its degree of hydration and its ionic content, both of which are controlled by the RPE. Therefore, conditions that affect the metabolic activity of the RPE can, in turn, affect the strength of retinal adhesion.

Carbonic anhydrase inhibitors might also seem relevant to the absorption of fluid in serous detachments, although anecdotally they seem to have little effect. The reason may lie with the fact that carbonic anhydrase inhibitors must act on RPE transport systems to be effective, and if the RPE is damaged by

detachment, ischemia, inflammation, or disease such as CSC, there may not be a substrate on which the drug can work. Carbonic anhydrase inhibitors have been shown to reduce cystoid macular edema in some patients with conditions such as aphakia/pseudophakia and RP.[15] Significant benefits have not been found in diabetic retinopathy or other types of retinal edema.

2.2.6 Electrical Activity of the Retinal Pigment Epithelium

The RPE interacts electrically with the retina. The RPE is not a photoreceptive tissue and generates no direct response to light, but RPE cells respond electrically to ionic changes in the subretinal space or to chemical substances released as a result of photoreception. There are three basic light-induced responses of the RPE membranes.[16] As a result of photoreception, there is, for a few seconds, a drop in the potassium concentration of the subretinal space; an effect that is recordable as the *c-wave* of the ERG. This potassium change is then transmitted slowly through the RPE cell, and roughly 1 minute later the basal membrane of the RPE hyperpolarizes and produces a small negative dip in the standing potential that is called the *fast oscillation*. This response involves basal chloride channels and can be abnormal in some patients with cystic fibrosis. Light activation of the photoreceptors also causes the release of a messenger substance (as yet unknown, but possibly dopaminergic) to produce a slow basal depolarization of the RPE that does not reach its peak until 5 to 10 minutes after the onset of light. This voltage, called the *light response of the standing potential*, is the physiologic basis of the clinical EOG.

The bestrophin-1 protein, encoded by the *BEST1 (VMD2)* gene responsible for Best's vitelliform macular dystrophy, regulates a basal calcium and chloride channel in the RPE that seems responsible for the light response.[17,18] However, the visual role of these bestrophin channels is unclear, and Best's disease patients have a normal ERG. Thus, the clinical EOG is derived from the RPE, but is not necessarily a broad measure of RPE function.

Interestingly, basal RPE membrane polarization can also be induced pharmacologically by the intravenous injection of hyperosmolar agents, acetazolamide, or sodium bicarbonate. These "nonphotic" responses are specific for the RPE because they can be induced exclusive of retinal function, but their clinical significance remains to be determined.

2.2.7 Secretion

PEDF and VEGF

The RPE secretes a number of growth factors in both physiologic and pathologic states. Among the most important are pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF). Despite its name, PEDF is found in many different types of tissues and is widely conserved across species.[19] It acts as a cell cycle regulator, has antiapoptotic effects, and is likely a protective factor against agents of cellular and oxidative stress such as peroxide and glutamate. Additionally, PEDF serves as a potent inhibitor of angiogenesis, and is secreted preferentially at the RPE cell apical surface into the IPM.[20]

In contrast, the role of VEGF as an angiogenic agent is well known; initially described in the context of tumor growth, VEGF is upregulated in a variety of disease states. VEGF acts in opposition to PEDF, and the VEGF/PEDF ratio in a tissue determines whether angiogenesis takes place.[21] Its primary actions are to stimulate vascular endothelium to form new capillaries, and to increase vascular permeability. While these functions are particularly relevant to diseases such as diabetic retinopathy, macular edema, and age-related macular degeneration, VEGF also has an important physiologic role. Secreted constitutively by the RPE at the basolateral surface, VEGF maintains the fenestrations in the choriocapillaris and helps the RPE to regulate fluid resorption and serve as an outer blood–retinal barrier. VEGF activity rises when PEDF activity is depressed, which may occur with oxidative stress and complement activation and be relevant for age-related macular degeneration.[22]

2.3 Retina

Some aspects of retinal physiology are outlined in the following text box.

Selected Functions of the Retina

- Transduction
  - Rhodopsin activation
  - G-protein amplification cascade
  - Cyclic guanosine monophosphate (cGMP) control of sodium channels
  - Receptor potential generation
  - Recovery mechanisms
- Retinal integration
  - Horizontal and bipolar cell interactions
  - Center-surround receptive fields
  - Sensitivity to contrast more than brightness
  - On- and off-pathways
  - Parallel neural pathways for resolution, color and, motion/spatial orientation
- Adaptation
  - Chemical—pigment regeneration cycle
  - Neural—photoreceptors and neural adjustments
  - Increment threshold sensitivity
- Color vision
  - Trichromacy—cone photoreceptor pigments
  - Color opponency—center-surround organization (red vs. green, blue vs. yellow)
  - Special characteristics of blue-sensitive cones
- Electrical responses
  - Early receptor potential
  - Receptor potential—ERG a-wave
  - Bipolar and Müller cells responses—ERG b-wave
  - Integrative neurons—ERG oscillatory potentials
  - Ganglion cells—pattern ERG wave
  - Macular cones—multifocal ERG

2.3.1 Photoreception and Transduction

Vision takes place because of the existence of photopigments and photoreceptive cells that can transform (transduce) radiant

energy (light) into a neural response. The earliest animal photoreception occurs in one-celled organisms such as *Euglena*, which have photopigments at the base of the flagellum; the absorption of light modifies swimming behavior and the organisms can move toward or away from light. With evolution, entire cells became specialized as photoreceptors and gradually evolved into a photosensitive tissue (retina) within an optical framework (eye).

The human photoreceptor is a specialized cilium in which the inner segment of the cell contains metabolic machinery to synthesize protein and maintain ionic homeostasis; the outer segment is a massive collection of cell membrane that is studded with visual pigment. Both cone and rod visual pigments consist of 11-*cis* vitamin A aldehyde (*retinal*) bound to a large protein that determines the spectral sensitivity of the pigment. Rhodopsin is most sensitive to (i.e., most likely to capture a photon from) light at 500 nm (blue-green), whereas the three cone pigments peak, respectively, at about 426, 520, and 560 nm. Note that this spectral sensitivity of a photoreceptor does not mean that it can distinguish between different colors of light, but simply that it will statistically capture more photons at the wavelength of its peak sensitivity than at a different wavelength. Once captured, the effect of a photon is identical regardless of its wavelength. In other words, rods are much more sensitive to blue light than to red, but once captured, a red photon is just as effective a stimulus as a blue one.

The fundamental process of *transduction* is similar in rods and cones, although the cone pigments are able to regenerate chemically much faster than rhodopsin (discussed earlier). The electrical responses generated by cones are also faster than those in rods, and there are major differences in saturation and adaptation that will be considered later. Some of these differences may relate to the structural qualities of rods and cones. As new rod membranes are synthesized, the "discs" become internalized within the outer cell membrane. By contrast, many of the cone discs remain in continuity with the outer cell membrane.

An ideal photoreceptor should respond to a minimum amount of light with an electrical response large enough to trigger synaptic transmission. This is achieved through a chemical amplification cascade, similar to the enzymatic cascade that governs certain hormonal responses. When a photon strikes a rhodopsin molecule, the 11-*cis*-retinal is transformed to *all-trans*-retinal, which alters the stability of the rhodopsin molecule and leads to a sequence of conformational changes. Within about 1 millisecond after absorbing a photon, the rhodopsin has changed to metarhodopsin II, and the transduction cascade is activated. Further chemical changes in the rhodopsin molecule lead to the visual pigment regeneration cycle, with eventual splitting off of the vitamin A moiety and its transport to the RPE for storage and reisomerization (▶ Fig. 2.3). However, all these later chemical changes are irrelevant to the perception of that photon and may take place during many minutes after the visual event has passed.

Activated rhodopsin initiates the transduction cascade (▶ Fig. 2.6) by activating an outer segment protein called *transducin*, a type of G-protein.[23] One rhodopsin molecule activates about 500 transducin molecules, each of which in turn activates *phosphodiesterase*, which catalyzes the breakdown of thousands of molecules of cGMP within the outer segment cytoplasm. cGMP acts on the outer segment to hold open the sodium channels in the cell membrane and keep the photoreceptor

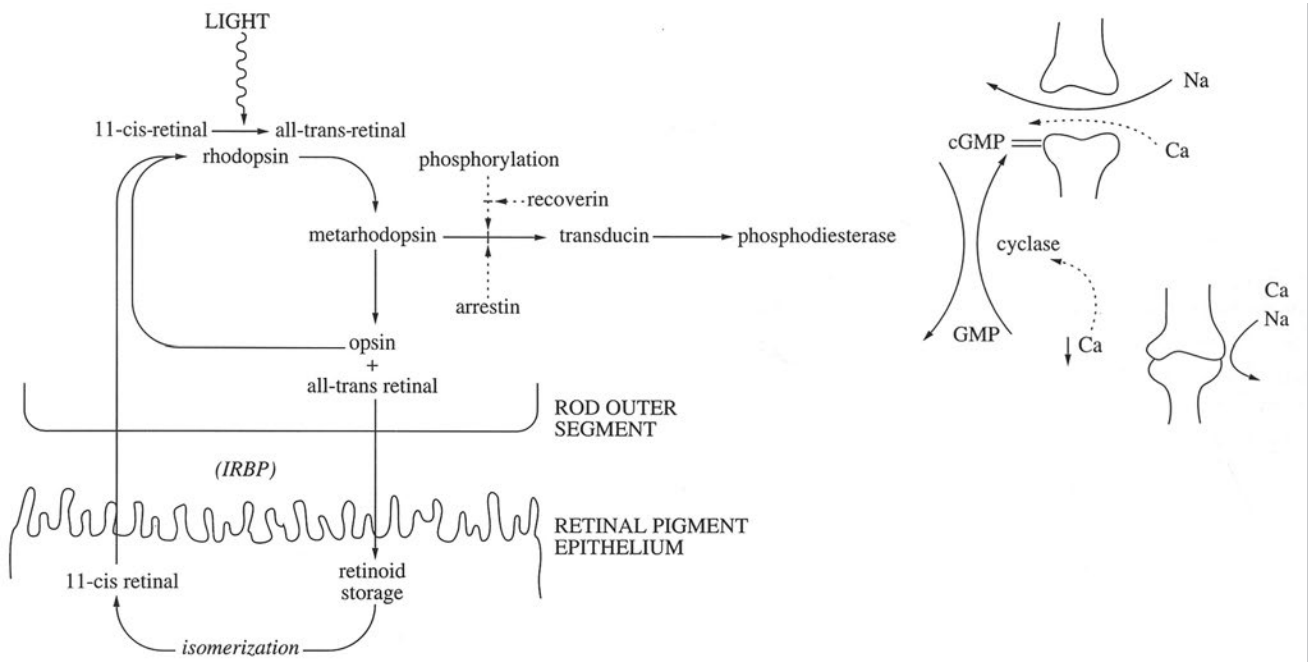

Fig. 2.6 Transduction cascade and visual pigment regeneration cycle. When light changes 11-*cis*-retinal to all-*trans*-retinal, it activates two cycles of chemical activity. The early conformational change to metarhodopsin initiates a G-protein cascade that breaks down cyclic guanosine monophosphate, closes sodium channels, and generates the receptor potential. Quite independently, the metarhodopsin continues to change chemically, eventually breaking down into retinal and opsin that recycle slowly (in part through the retinal pigment epithelium) to restore rhodopsin to the outer segments. IRBP, interphotoreceptor retinoid-binding protein.

depolarized. As light reduces the concentration of cGMP, the sodium channels close and the photoreceptor hyperpolarizes (a response called the *receptor potential*). A single photon can block the entry of more than a million sodium ions, and the resulting voltage change modulates the release of neurotransmitters at the synaptic endings of the photoreceptor to begin the neural process of vision. The receptor potential then turns off because activated rhodopsin is phosphorylated and an outer segment protein called *arrestin* binds the phosphorylated rhodopsin and prevents activation of transducin and phosphodiesterase.[24] Also, transduction causes a fall in the cytoplasmic calcium concentration that in turn activates a GMP cyclase that generates new cGMP to reopen the sodium channels.

This electrical system may seem puzzling, insofar as most nerve cells respond to stimulation by an opening of sodium channels and depolarization. The difficulty is not with the photoreceptor, however, but with our anthropomorphic notion that light must be the stimulus. If you think of a photoreceptor as a cell at rest in the light, then stimulation with a shot of darkness produces a typical depolarizing sensory response. The propensity of photoreceptors to be "stimulated" in the dark is, in fact, very important to understand their metabolism. Because the photoreceptors spend extended periods of time with open sodium channels in a state of depolarization, the cells would swell and die unless there were a means to remove the sodium as fast as it comes in. This is accomplished by an electrogenic sodium–potassium pump in the membrane of the inner segment. The energy demands of this pump give the photoreceptor one of the highest metabolic rates in the body. The choriocapillaris has one of the highest flow rates per unit area of any vascular tissue to supply a surplus of oxygen for this metabolic activity.

A number of human disorders have been recognized that involve components of the photoreceptive cascade (▶ Fig. 2.3 and ▶ Fig. 2.6).[25] A small percentage of families with RP have been found to have abnormalities in the transduction protein, *phosphodiesterase*. This leads to excess GMP within the cell and eventual photoreceptor degeneration. The most common genetic abnormality that has been identified in dominant RP is a structural change in the *rhodopsin* molecule. Well over 50 different single amino acid defects in rhodopsin have been described to date among dominant RP families, some causing very severe RP and some rather mild disease. The mechanism by which these defects lead to gradual photoreceptor decompensation remains to be shown. RP families have also been identified with defects in peripherin, an outer segment protein of uncertain role in the visual process. Abnormalities in *arrestin* have been shown to be responsible for Oguchi's disease,[26] a rare form of congenital night blindness having the curious property that patients require many hours to adapt to the dark but can lose their dark sensitivity with only a very brief exposure to light (that is insufficient to bleach most of the visual pigment). The explanation of this curious symptomatology is that without normal arrestin, the transduction process cannot be turned off quickly, and rods that are activated remain hyperpolarized with a loss of sensitivity. Another rod protein, called (somewhat inappropriately) *recoverin*, blocks rhodopsin phosphorylation in the presence of high calcium concentrations. Thus, it prevents shutoff of the cascade and may help to regulate internal calcium. Antibodies to recoverin are found in some cases of cancer-associated retinopathy.[27] The ATP-binding cassette protein, produced by the *ABCA4* gene, although not classically part of the phototransduction cascade, also plays an important role in the removal of toxic metabolites and the regeneration of retinal in the visual cycle. Its role in the context of Stargardt's macular dystrophy has been described earlier.

Pearls

Several retinal disorders are known to involve specific components of the photoreceptive cascade and visual pigment regeneration cycle. These conditions and their corresponding defective component(s) include the following:

- RP: rhodopsin, phosphodiesterase, peripherin
- Oguchi's disease: arrestin
- Cancer-associated retinopathy: recoverin
- Stargardt's disease: *ABCA4*
- Leber's amaurosis: *RPE* genes *LRAT* and *RPE65*
- Fundus albipunctatus: RDH5

2.3.2 Adaptation

Because the recovery process begins shortly after the onset of transduction, the receptor potential falls back rapidly from its peak within a period of milliseconds. In other words, the response of a photoreceptor to the onset of light is much larger than to a light that is maintained over time. This is one type of adaptation. There are other types of adaptation that occur at the photoreceptor level. At very dim light levels (scotopic illumination), only rods are functional, but as the background light gets brighter and brighter the rod response gets progressively saturated until rods can no longer respond at all. This occurs at moderate levels of light, at which we begin to see colors (mesopic illumination). Only cones are functional at higher levels of light (photopic illumination), but cones can adjust (adapt) over a large range of brightness without saturating, which is fortunate and allows us to function outside on a sunny day.

This *neural adaptation* of cones is critical to vision in the real world. The process of *chemical adaptation*, which was described earlier, is necessary to gain maximum sensitivity in a dark environment, but it would be dysfunctional in the real world if we had to wait 20 or 30 minutes every time we entered a dimly lit room. In contrast, cones can adapt to changes in ambient brightness within seconds, although we only have a limited range of black-to-white discrimination at any point in time. As the cone sensitivity shifts, what appeared white indoors will seem black in the sunlight. Thus, a tunnel seems black as we approach it on a sunny day, but when we enter, the eye resets its gray scale very quickly so that we can see the road. This adaptation to different environments also allows us to enjoy photographs and art, which cannot duplicate (on the wall of a gallery) the true brightness of either a dark room or a sunny outdoor scene. We recognize the scene because the *range* of brightness in the picture mirrors what our eyes would see in that environment

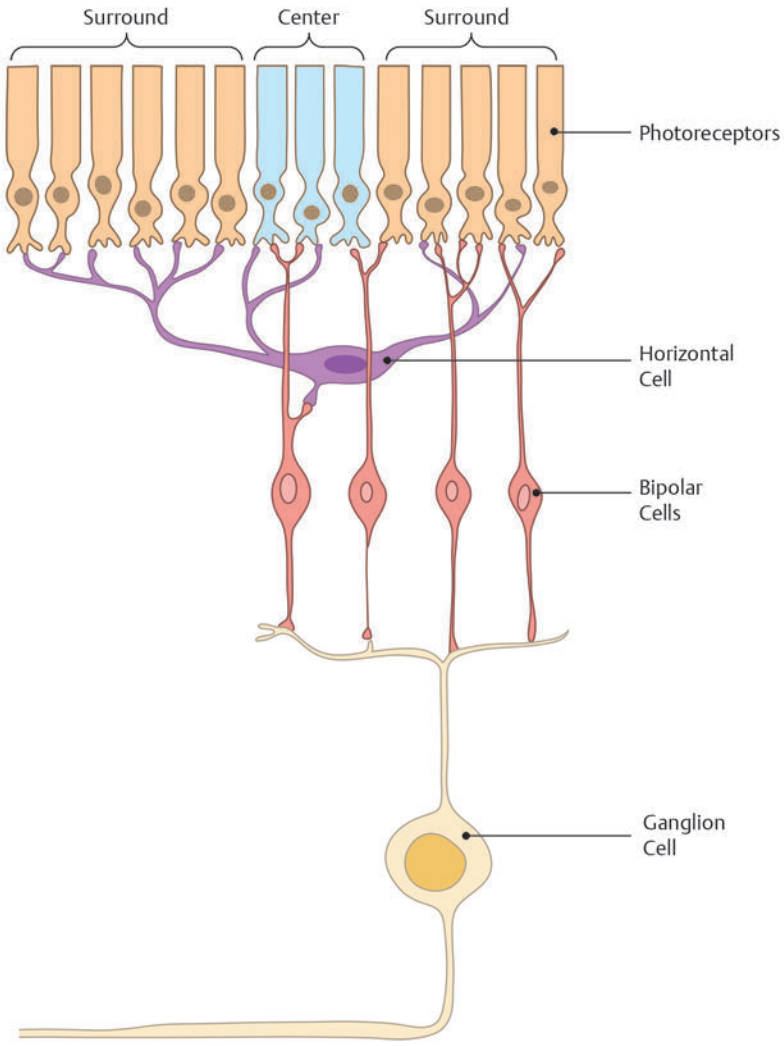

Fig. 2.7 Simplified diagram of retinal circuitry showing how center-surround (excitatory-inhibitory) receptive fields are generated in bipolar cells. The excitatory center represents direct input from overlying photoreceptors, and the surround represents inhibitory input from horizontal cells that have synaptic connections with more distant photoreceptors. (Modified from Marmor.[33])

2.3.3 Retinal Integration and the Recognition of Contrast

There are roughly 120 million rods and 6 million cones in the retina, but only 1 million optic nerve fibers. This means that it is impossible for the eye to transmit to the brain a 1:1 map of the photoreceptor image. The retina must simplify and code visual information so that all necessary spatial and color information can be transmitted through nerve fibers that are numerically less than 1% of the photoreceptive elements. The basic mechanism by which the retina accomplishes this is a neural organization that is wired to recognize contrasts and edges rather than absolutes of brightness or color.

Embryologically, retina is brain, and contains three strata of neurons that begin to process visual signals (▶ Fig. 2.7). This circuitry is very complex, as there are many different specialized types of bipolar, horizontal, amacrine, and ganglion cells (large, small, fast, slow, "on" responsive, "off" responsive, etc.) to serve different components of vision such as color, movement, depth, resolution, and so forth. This brief chapter does not allow a full description of such complexity, and what follows is merely an example of how a neural cascade can begin to code photoreceptor input into recognition of edges and contrast. It is highly simplified, and should not be construed as describing "retinal organization."

The *receptive field* of a retinal neuron is the portion of the visible world in which light can stimulate that particular cell. For each photoreceptor, this area is quite small, but the receptive fields of bipolar cells or ganglion cells can be much larger, to the extent that there is convergence of multiple photoreceptors on each bipolar cell and possibly further convergence of bipolar cells on ganglion cells. Convergence is at a minimum for the cone cells within the fovea, and close to 1:1 transmission is necessary to achieve the high resolution that we need for sharp visual acuity. However, there is considerable convergence among cones in the periphery and even more convergence within the rod system, which is designed to capture light and perceive motion rather than to resolve small objects.

The recognition of contrast begins at the bipolar cell level. The receptive fields of bipolar cells are doughnut-shaped, with an excitatory response to light in the center and an inhibitory response to light in the surround (*on-center cells*), or vice versa

(*off-center cells*). This organization results from the confluence of bipolar cell and horizontal cell synaptic processes at the base of the photoreceptor (▶ Fig. 2.7). The central portion of the receptive field is determined by the photoreceptors that feed directly onto the bipolar cell. Sensitivity to the surround is determined by horizontal cells; these cells ramify over a much larger area (corresponding to the surround), and make *inhibitory* contact with the photoreceptor–bipolar synapses in the center. Thus, light falling on the center of the receptive field of an on-center bipolar cell has a direct (e.g., excitatory) effect, whereas light falling on the surround comes through horizontal cells and has an inhibitory effect on the bipolar cell. In "off-center" bipolar cells, the effects are reversed.

How does this receptive field organization generate *contrast sensitivity*? Illumination that evenly covers both the center and surround regions of the bipolar cell receptive field is relatively ineffective as a stimulus, because the center and surround regions offset each other (▶ Fig. 2.8). An edge crossing the receptive field, however, will stimulate only part of the surround and thus create an imbalance that is a powerful stimulus to the cell. Because of adaptation, it is also necessary that these edges sweep continually across the retina to maintain activation of the neurons. Vision would fade within seconds if the eyes were held absolutely still, and thus our eyes are always jiggling very slightly with microsaccades. This center-surround, contrast-sensitive organization of the bipolar cells is passed on to the ganglion cells, and eventually to cortical neurons (which develop more sophisticated receptive fields). This organization of the retina means that our eyes are exquisitely sensitive to edges and differences in brightness but are relatively disinterested in steady illumination. We see objects by their borders, and the brain fills in the centers if there is no new pattern to create a stimulus. This is why we do not perceive our own blind spot.

The powerful sensitivity of the retina to contrast accounts for many common illusions of brightness. A gray circle on a white background appears dark, whereas the same gray on a black background will appear quite light. A related phenomenon was described by the physicist/psychologist Ernst Mach.[28] At a junction between two levels of gray, we tend to perceive an extra band of lightness on the lighter side, and a band of darkness on the darker side, of the edge. These *Mach bands* are quite

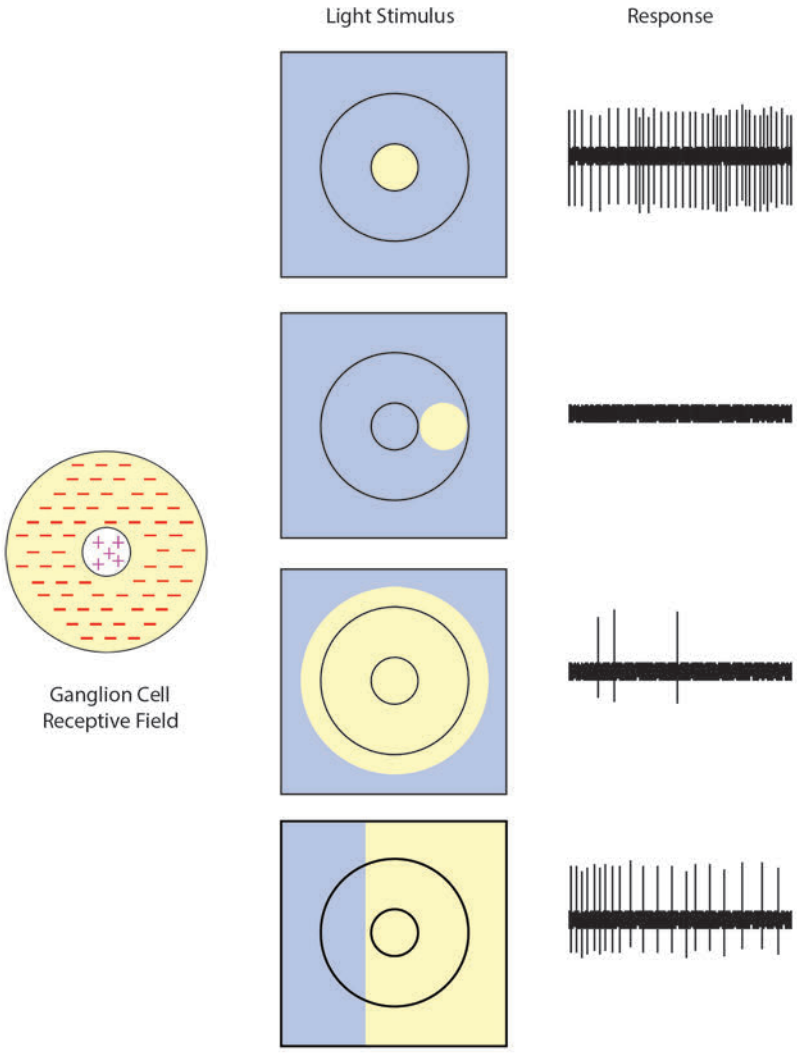

Fig. 2.8 Ganglion cell receptive fields showing why edges and contrast are critical to vision. The cell is activated by stimulation of the center area and inhibited by stimulation of the surround area, but it responds only minimally to diffuse light because the center and surround offset each other. An edge is an effective stimulus because when it covers the center, it covers only a part of the surround, and the balance of effects is excitatory. (Modified from Marmor.[33])

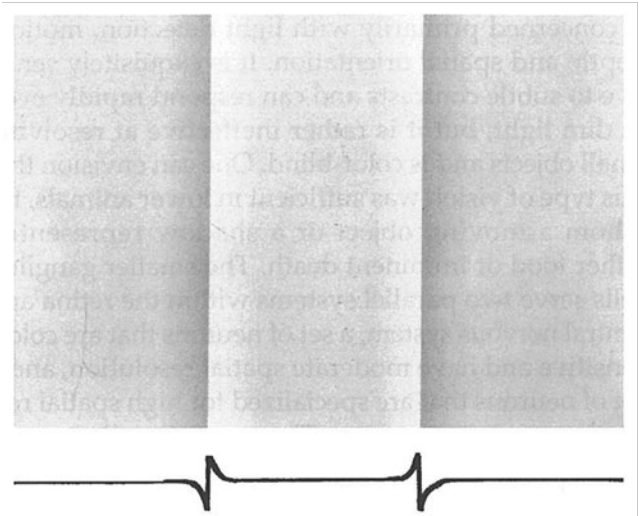

Fig. 2.9 Illusion of darkness and lightness produced by the presence of Mach bands. The line beneath the shaded figure shows the relative brightness at each point. Each of the three regions is equally bright, except at the junctions. The central area appears lighter because of a light-to-dark junction on either side of it. Holding a pencil over the junctions will show that all three regions are the same.

involuntary perceptions because they are hard-wired in the neural organization of our retina. Conversely, if one creates a light–dark junction within an evenly gray surface, our eyes and brain can be fooled into dividing the whole surface into perceived regions of light and dark (▶ Fig. 2.9). These illusions are powerful evidence that the human eye is an instrument for contrast detection rather than an instrument for the recognition of absolute levels of illumination.

It was noted earlier that bipolar cells may be on-center or off-center. Rods feed only into on-center cells, the so-called depolarizing bipolar cell pathway. Cones, however, feed into both depolarizing and hyperpolarizing bipolar cells. Because the hyperpolarizing cells depolarize to the *offset* of light, these pathways are sometimes called *on-* and *off-pathways*. The functional significance of the on- and off-pathways for visual perception is complex, but some human diseases have already been identified that involve these pathways selectively.[29] In the most common form of congenital stationary night blindness (CSNB), affected individuals are born without the ability to see in the dark and without any rod b-wave on ERG. The rod a-wave is present, however, and the disease was thought for a long time to represent a synaptic blockage between rods and bipolar cells. However, CSNB is actually a congenital lack of the on-pathway (of both rods and cones) rather than a specific rod disease. Retention of the cone off-pathway seems sufficient to allow relatively normal visual acuity and color perception in most of these patients.

The conscious perception of our world is far more complex than just the recognition of light and dark, or edge and center, as we also distinguish qualities such as motion, texture, color, shape, and depth. To some degree, these various perceptions begin with systems of distinct bipolar and ganglion cells that work parallel to one another within the visual system and feed into brain areas that perceive these qualities.[30] In general, the larger ganglion cells are concerned with light detection, motion, depth, and spatial orientation. These cells respond to brightness rather than color, but are sensitive to subtle contrasts and can respond rapidly even in dim light. The smaller ganglion cells form two additional parallel systems within the retina and central nervous system. One contains our color-sensitive neurons, which have moderate spatial resolution. The second contains neurons that are specialized for high spatial resolution and fine acuity. These small cell systems require good lighting and high degrees of contrast. Although these *parallel pathways* remain relatively independent up to the visual association areas of the cerebral cortex, interaction and crosstalk between these systems helps to produce an integrated perception of the world.

2.3.4 Color Vision

Mammals are almost universally red-green color-blind, with the exception of higher apes and humans. For example, cats and dogs have only short-wavelength-sensitive cones (S cones) and long-wavelength-sensitive cones (L cones). This permits them to distinguish between the blue and yellow ends of the spectrum. However, they cannot make the full range of color distinctions that are visible to most humans. The development of human trichromatic vision is a relatively recent phylogenetic event, when the long-wavelength pigment in some Old World apes mutated into a red-sensitive (L) and green-sensitive (M = middle) cone pigment. Whereas our S cone pigment shows only 43% homology in amino acid sequences with the long-wavelength pigments, there is 95% homology between the M and L pigments. The S cone pigment is coded on a somatic chromosome, but the M and L pigment genes are on the X chromosome.[31]

Although three cone pigments are necessary to perceive a full spectrum of colors, the bipolar and ganglion cells do not transmit spectral information directly (▶ Fig. 2.10). Rather, these cells are organized into center-surround receptive fields based on contrast between red and green, or blue and yellow. Some ganglion cells have a red excitatory center and green inhibitory surround, or vice versa, so that they recognize the relative levels of stimulation of the M and L cones. Blue- and yellow-sensitive ganglion cells recognize contrast between the S cones and the combined long-wavelength (M and L) system, which would be a phylogenetically older set of contrasts. Because of this cellular organization in the retina, we ultimately recognize colors by their relationships to each other as much or more than by the absolute wavelengths. One implication of this is that we can maintain a sense of color constancy under a variety of lighting conditions. We tend to see most colored objects as the same, for example, in bluish daylight or yellow incandescent light. However, the fact that form and depth are perceptions that depend on brightness means that we will have trouble distinguishing objects that differ in color but not in brightness. Color is essentially superimposed upon our brightness-based recognition of shapes, movement, and depth.

There are physiologic differences between the short-wavelength and long-wavelength cones. For example, the *S* cones are quite rodlike in some of their electrical and temporal characteristics. There are a much smaller number of S cones than M and L cones within the retina, and there are no S cones at all in the absolute center of the fovea. If a blue dot is tiny enough, and in

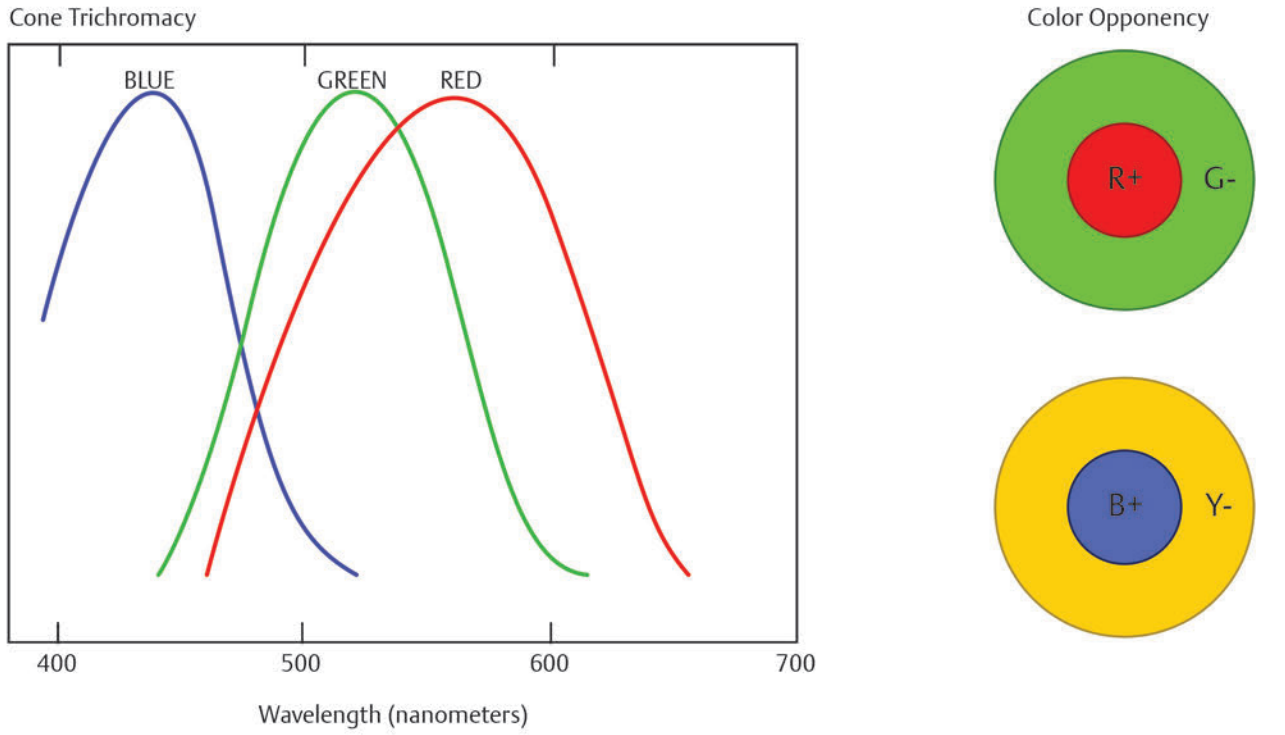

Fig. 2.10 Trichromacy and color opponency in the retina. Three cone types, with blue-, green-, and red-sensitive pigments, have the spectral sensitivities shown on the graph. However, horizontal and bipolar cell interactions lead to center-surround receptive fields at the ganglion cell level (and higher in the central nervous system) that contrast either green and red, or blue and yellow. Color perception is ultimately a matter of contrast recognition more than of absolute wavelength.

the exact center of gaze, we cannot recognize it as blue—but in reality we see blue colors just off center and our brain assumes that the color remains constant across the center of the visual field. Possibly because of their smaller numbers or because of metabolic differences, the S cones may be more susceptible to retinal disease and they can be selectively damaged in retinal degenerations and dystrophies, glaucoma, and diabetic retinopathy. Patients with all these disorders tend to have subtle deficiencies in blue-yellow discrimination.

Pearls

- The S cone system is more susceptible to retinal disease than the M or L cone system. It can be selectively damaged in retinal degenerations and dystrophies, glaucoma, and diabetic retinopathy. Therefore, patients with these disorders tend to have subtle deficiencies in blue-yellow discrimination.

2.3.5 Electrical Responses of the Retina

Clinical electrophysiologic tests are discussed in Chapter 7, but it is important to understand the cellular origin of retinal electrical signals (▶ Fig. 2.11). When a bright light is turned upon a dark-adapted eye, the eye produces a sequence of retinal and RPE voltage changes that may oscillate for hours. Within the first few milliseconds, there is a small negative wave called the early receptor potential, which is generated by conformational changes in the visual pigment molecules during transduction. A very bright flash is required to elicit this response, which seems to be dominated by cones rather than rods; although it has been recorded in humans, it is not of general use clinically. The *receptor potential*- the primary hyperpolarization of the photoreceptors in response to light- occurs within 5 to 10 milliseconds. It generates the initial negative deflection of the ERG a-wave, and the downward slope of the *a-wave* is a good measure of photoreceptor integrity. A-wave amplitude is not as precise because it also depends on the speed and magnitude with which the positive-going *b-wave* develops and cuts off the a-wave. In normal eyes, the b-wave is the largest ERG response; it peaks at 30 to 50 milliseconds and appears to be generated electrically by both Müller cells (responding passively to ionic changes in their environment) and bipolar cells. Physiologically, the b-wave represents neural activity in the inner retina. The *oscillatory potentials* on the rising phase of the b-wave are also generated in the inner retina, possibly by feedback circuits involving amacrine cells and other integrative neurons.

If electrical recording is continued after the b-wave diminishes, one observes a few *seconds* later another positive wave, called the *c-wave*. This represents a passive response by the apical membranes of the RPE and Müller cells to the fall in potassium concentration of the subretinal space that follows transduction. This ocular voltage then dips during the next *minute* to generate the *fast oscillation*, and then rises during 5 to 10 *minutes* as the *light response* of the standing potential.

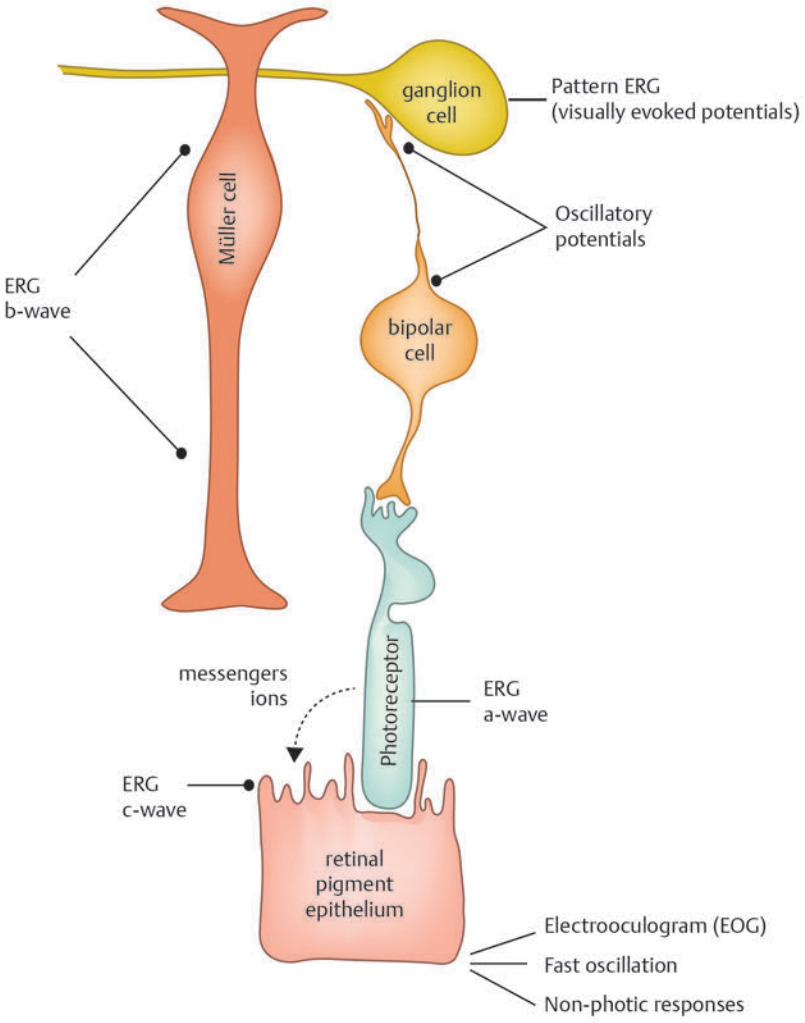

Fig. 2.11 Clinical electrical responses from the retina and retinal pigment epithelium (RPE). The RPE responses require stimulation of the photoreceptors or administration of pharmacologic agents because the RPE is not itself photosensitive. The retinal responses localize to different cellular layers as shown. ERG, electroretinogram.

These are RPE-generated responses, and their mechanism has been discussed earlier. The ocular voltage may continue to oscillate slowly during 1 to 2 hours, but these late fluctuations have not been used clinically.

All the responses noted so far come from cellular elements that are, to a large degree, oriented radially within the eye (e.g., photoreceptors, bipolar cells, RPE cells) and can summate in parallel to generate a large extraocular signal. The ganglion cells are oriented circumferentially, however, and thus produce a much smaller signal with external (corneal) recordings. Nevertheless, a small negative response arises from ganglion cells that can be elicited with strong red or yellow flashes on a blue rod-suppressing background (photopic negative response) or an alternating checkboard stimulus that minimizes luminance signals (pattern electroretinogram). These responses are reduced in glaucoma, for example, but have not yet been refined to the point that they are used much for individual patients.

The full-field ERG is dominated by the retinal periphery, even for cones (cones are most densely packed in the fovea, but 90% of cones are outside the macula). To record a macular ERG is tricky, since light scatter within the eye from a focal stimulus can overwhelm the response. A technique called multifocal ERG (mfERG) overcomes this problem by presenting a computerized stimulus of small hexagons that are scaled in size to match cone density, and that flicker on and off in a seemingly random fashion. The computer calculates how much signal correlates with each stimulus hexagon, and prints an array of small cone ERG responses from different regions of the macula. The mfERG is now widely used to assess macular pathology.

2.4 Conclusion

The primary photoreceptive tissue in the eye is the retina, which not only captures radiant energy but also codes visual input into contrast-sensitive receptive fields to maximize the visual information that can be transmitted through a limited number of optic nerve fibers. The photoreceptors are responsible for transduction, many aspects of adaptation, and the initial ability to perceive a full spectrum of colors. However, the integrative circuits of the retina, which produce contrast sensitivity, are the foundation for how objects are ultimately recognized and perceived. The retina cannot function without close apposition to the RPE and without the various support functions carried out by the RPE, which include visual pigment regeneration,

phagocytosis of outer segment material, control of the subretinal space, and the maintenance of retinal adhesion. Loss of these functions through aging may contribute to a variety of diseases. A number of ocular disorders have been discovered with genetic defects in specific aspects of the transduction or integrative pathways of the retina. Physiologic tests, such as dark adaptation, the ERG, and the EOG, reflect retinal physiology and can provide the clinician with information about the status of individual cell types within the retina or about the depth and regional distribution of retinal disease.

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