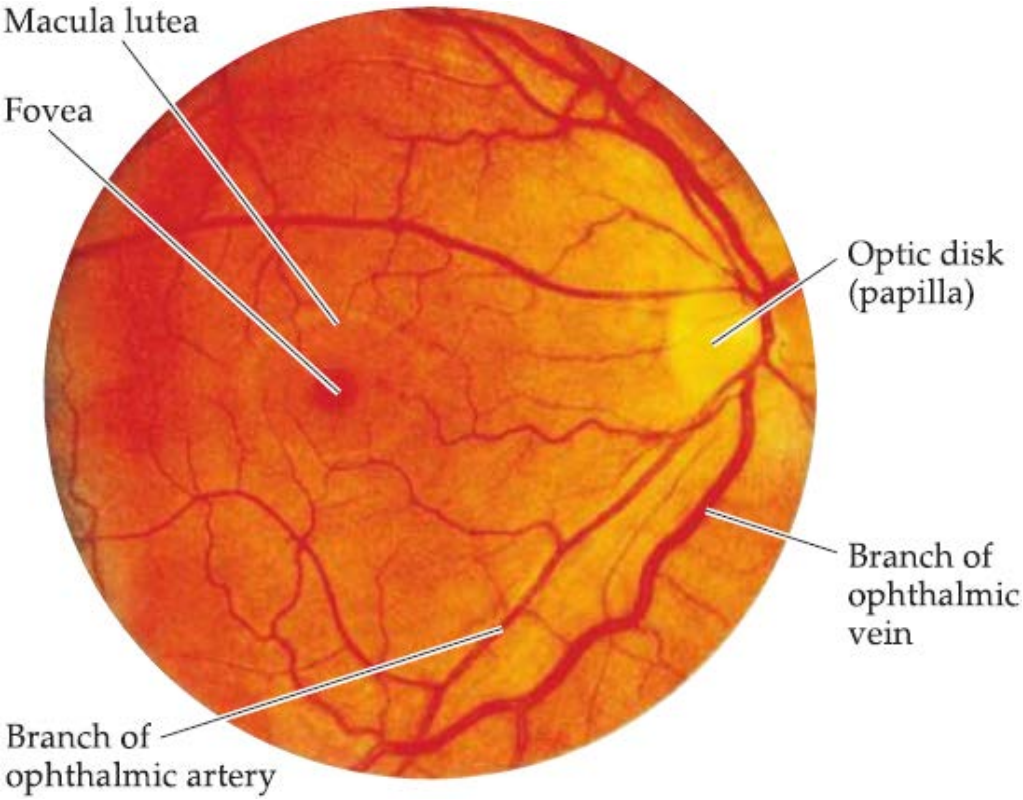
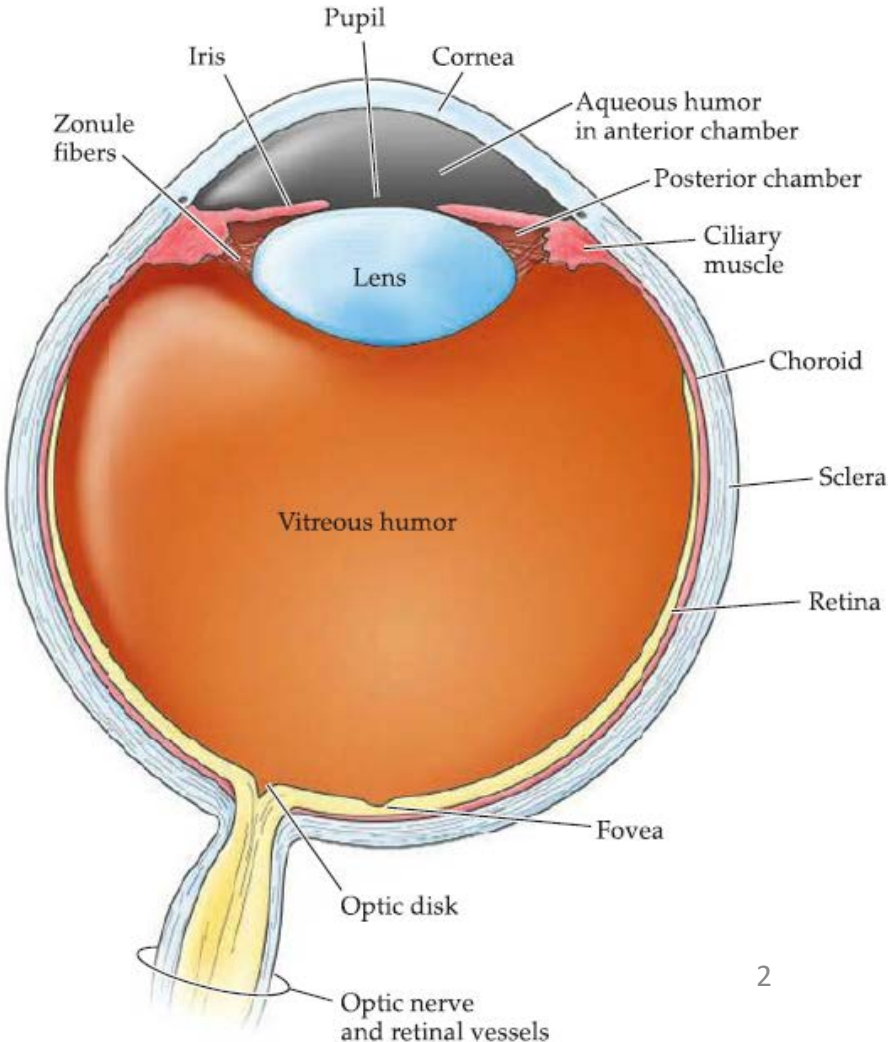
Part 4, Sensory and Motor Systems

4.3. Vision: The Eye

Retina

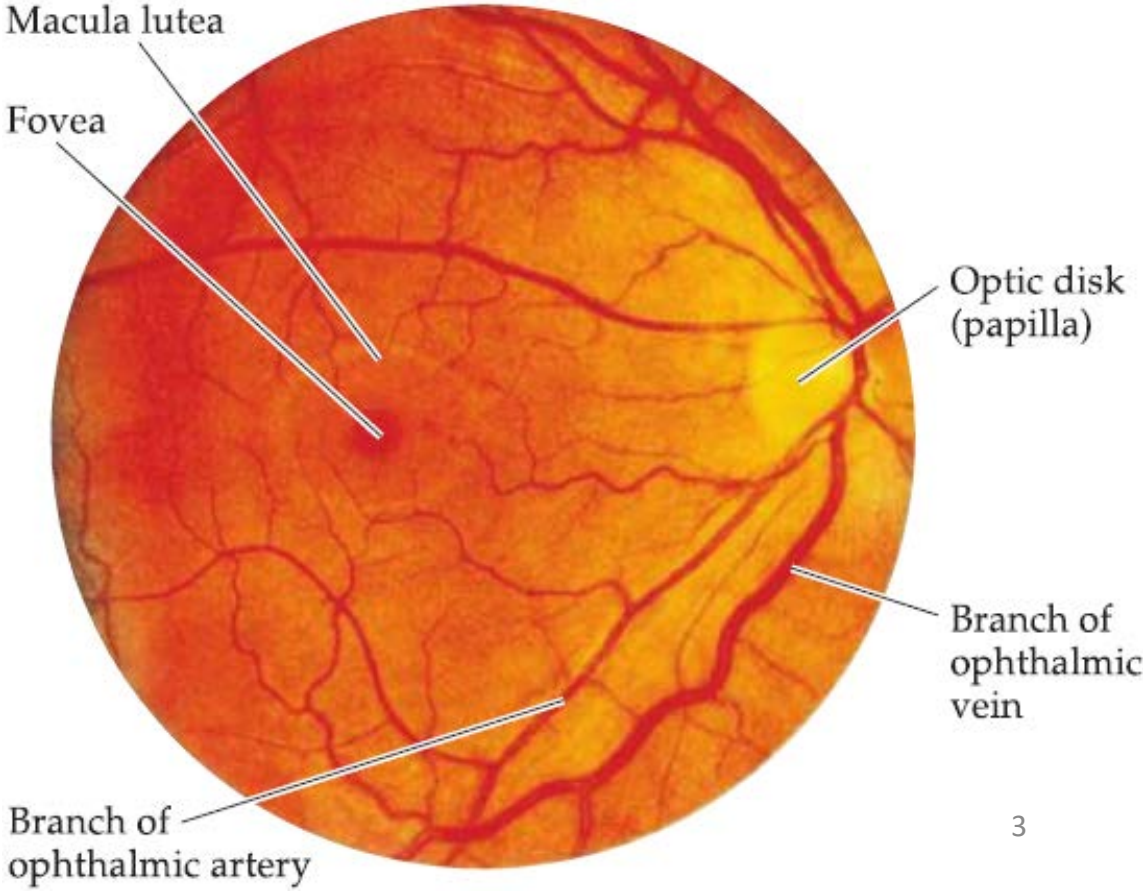
- Only the innermost layer of the eye, the **retina**, contains neurons that are sensitive to light and can transmit visual signals to central targets.
- Using an ophthalmoscope, the inner surface of the retina or **fundus**, can be visualized through the pupil.
- Numerous blood vessels, both arteries and veins, fan out over the inner surface of the retina.





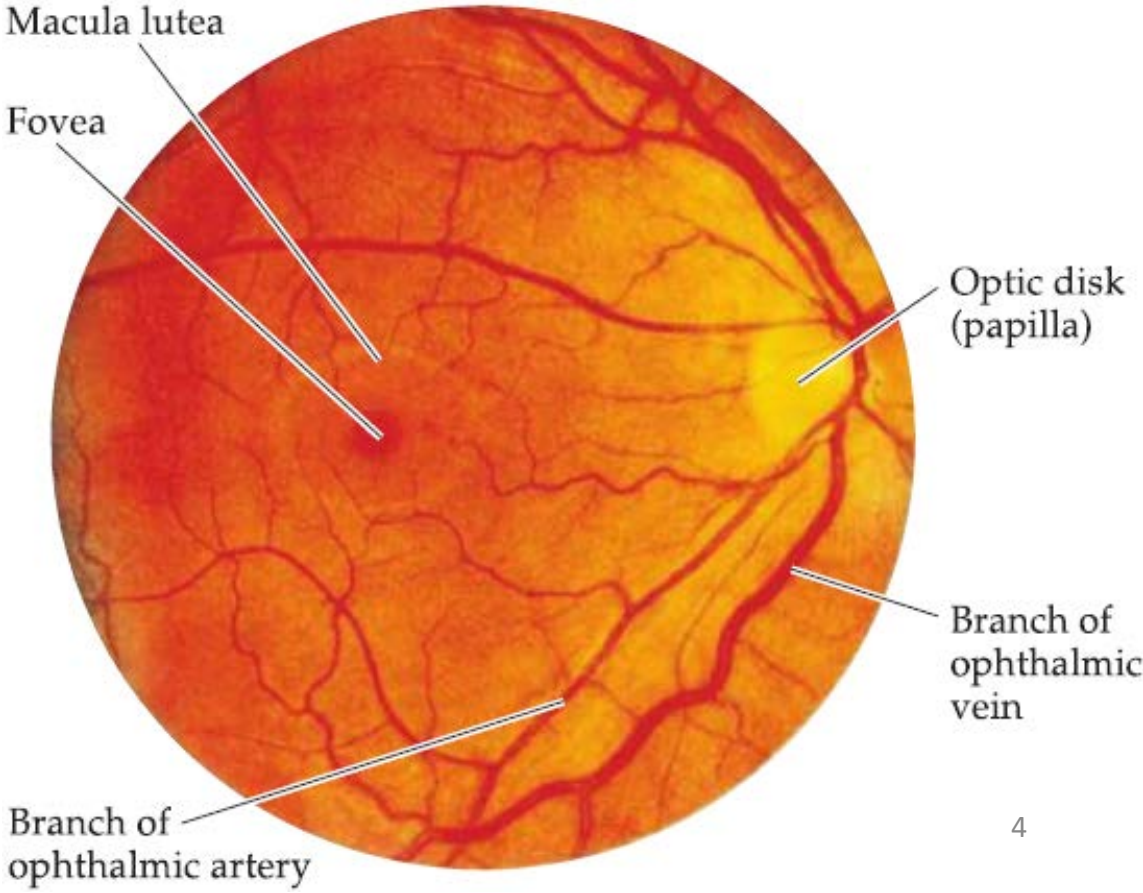
Retina

- The blood vessels arise from the ophthalmic artery and vein, which enter the eye through a whitish circular area known as the **optic disk**, or **papilla**.
  - The optic disk is also the site where retinal axons leave the eye and travel through the optic nerve to reach target structures in the thalamus and midbrain.
  - This region of the retina contains no photoreceptors and, because it is insensitive to light, produces the perceptual phenomena known as blind spot.



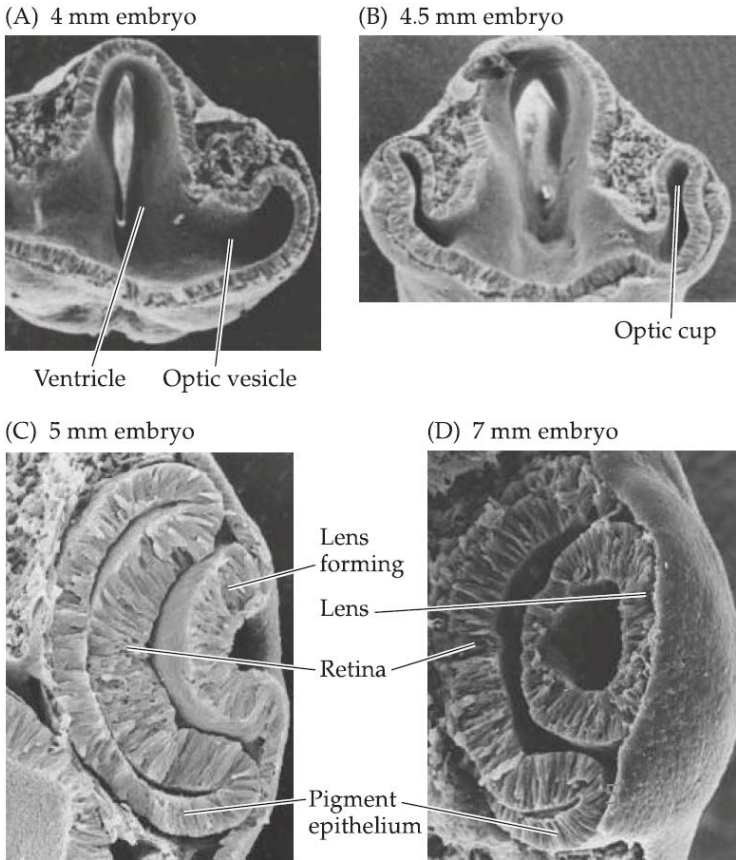
Retina

- Another prominent feature of the fundus is the **macula lutea**, an oval spot containing yellow pigment (xanthophyll), roughly 3 millimeters in diameter and located near the center of the retina.
  - The macula is the region of the retina that supports high visual acuity (the ability to resolve fine details).
  - Acuity is greatest at the center of the macula, a small depression or pit in the retina called the **fovea**.
  - The pigment xanthophyll has a protective role, filtering ultraviolet wavelengths that could be harmful to the photoreceptors.



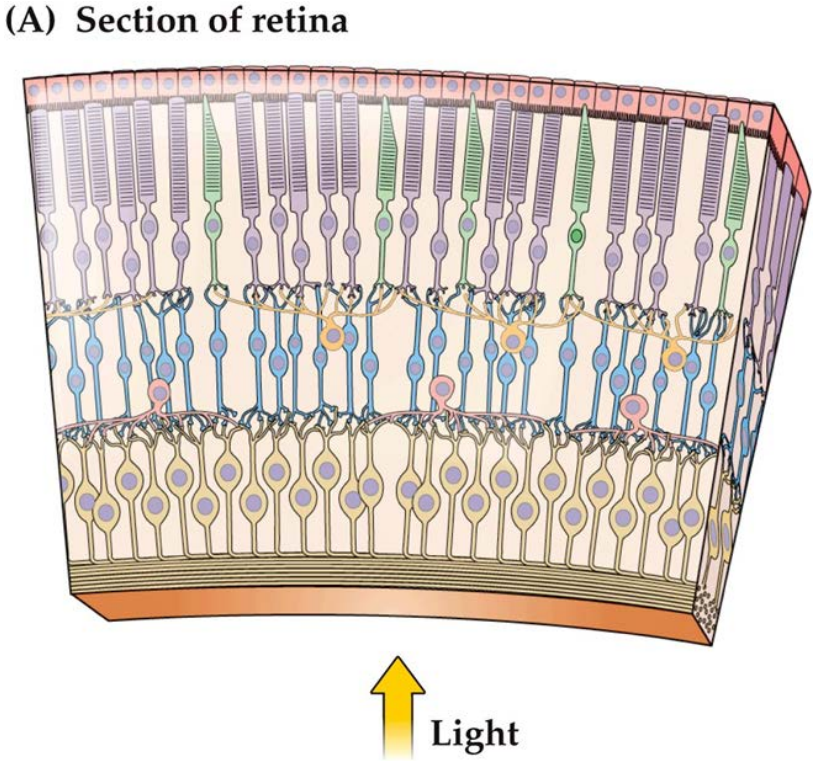
Retinal circuitry

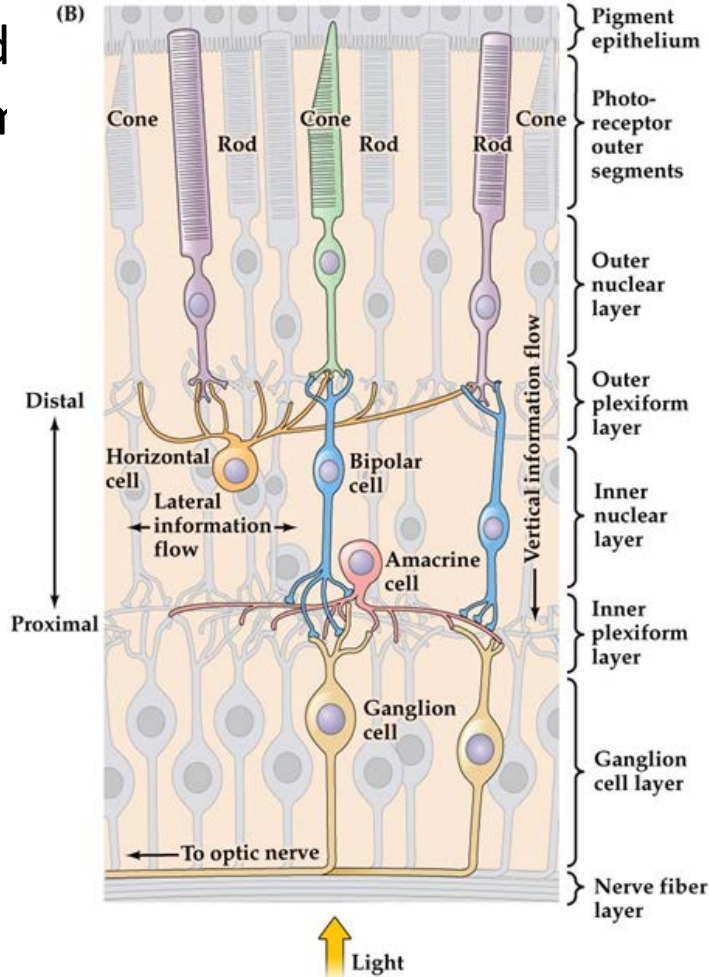
- Despite its peripheral location, the retina, which is the neural portion of the eye, is actually part of the central nervous system.
- During development, the retina forms as an outpocketing of the diencephalon called the optic vesicle.
- The optic vesicle undergoes invagination to form the optic cup.
- The inner wall of the optic cup gives rise to the retina, while the outer wall gives rise to the **retinal pigment epithelium**.
- This epithelium is a thin, melanin-containing structure that reduces backscattering of the light that enters the eye and plays a critical role in maintaining the phototransduction machinery of retinal photoreceptors.
- The retina exhibits complex neural circuitry that converts the graded electrical activity of specialized photosensitive neurons--the photoreceptors--into action potentials that travel to central targets via axons in the optic nerve.



Structure of retina

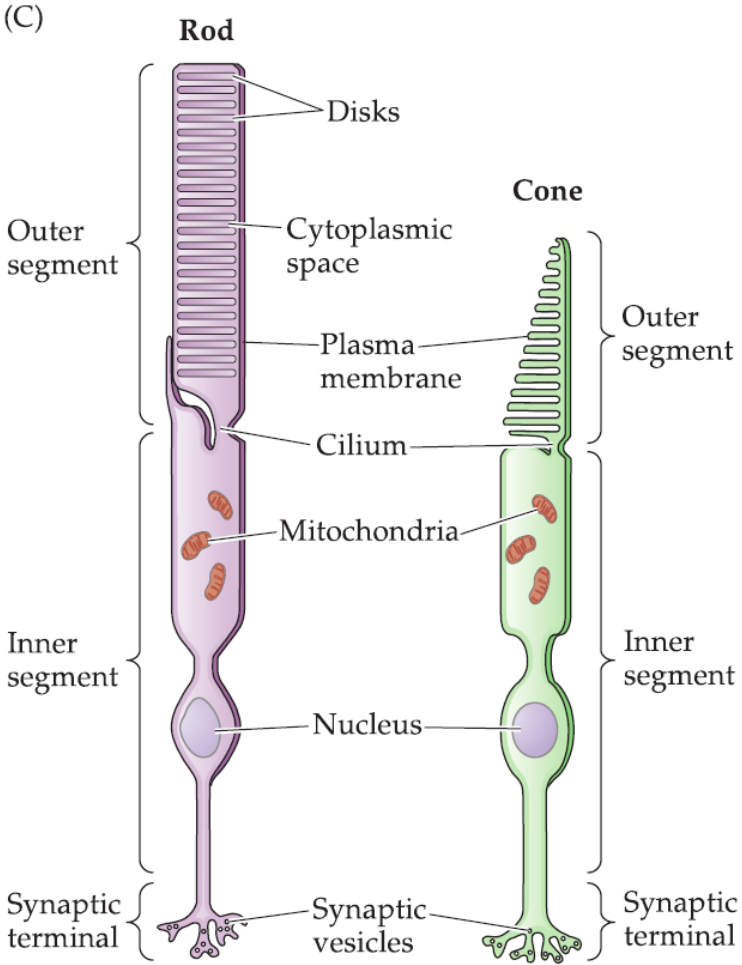
- There are five basic classes of neurons in the retina: **photoreceptors**, **bipolar cells**, **ganglion cells**, **horizontal cells**, and **amacrine** cells.
- The cell bodies and processes of these neurons are stacked in alternating layers, with the cell bodies located in the inner nuclear, outer nuclear, and ganglion cell layers, and the processes and synaptic contacts located in the inner plexiform and outer plexiform layers.

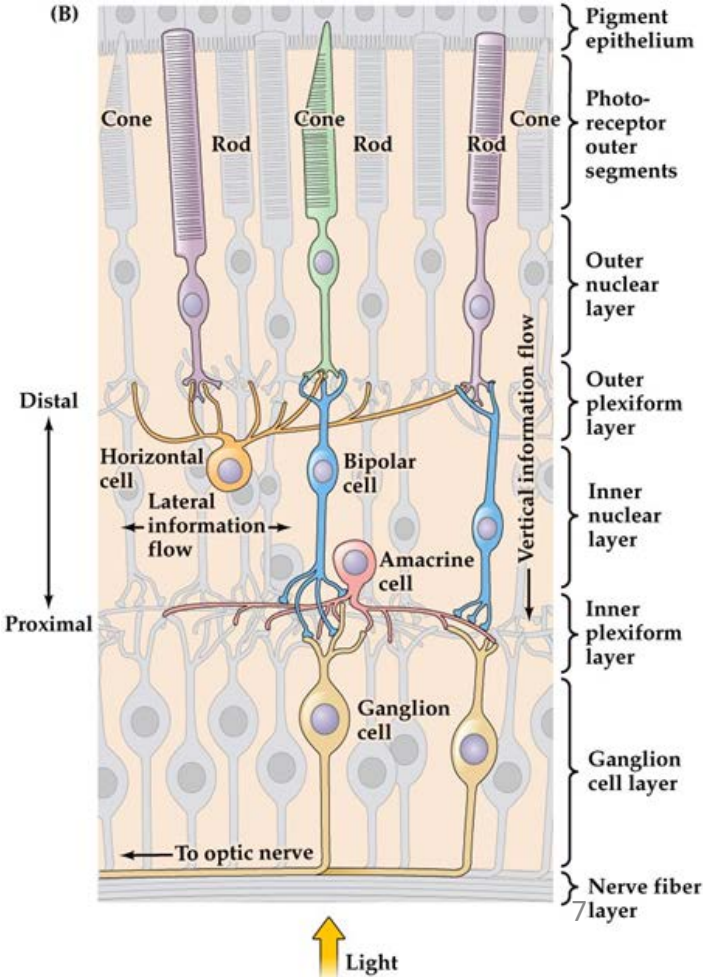




Rods and cones

- The retina contains two types of photoreceptors, **rods** and **cones**.
- Both types have an outer segment (adjacent to the pigment epithelium), composed of membranous disks containing light-sensitive photopigment, and an inner segment that contains the cell nucleus and gives rise to synaptic terminals that contact bipolar or horizontal cells.



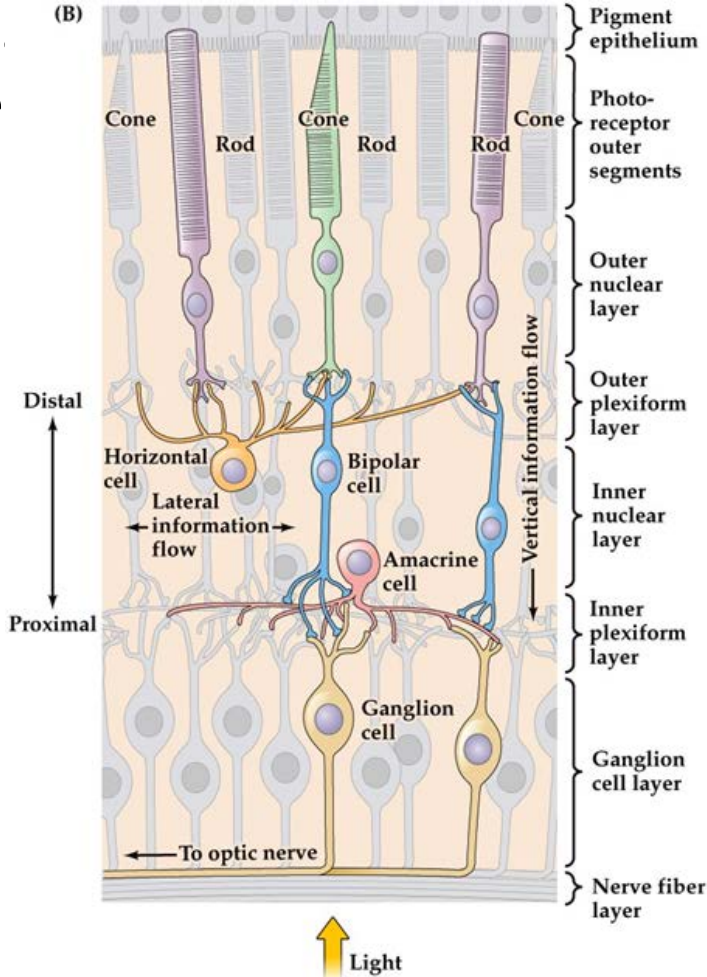


Structure of retina

- A three-neuron chain--photoreceptor cell to bipolar cell to ganglion cell--is the most direct pathway of information flow from photoreceptors to the optic nerve.

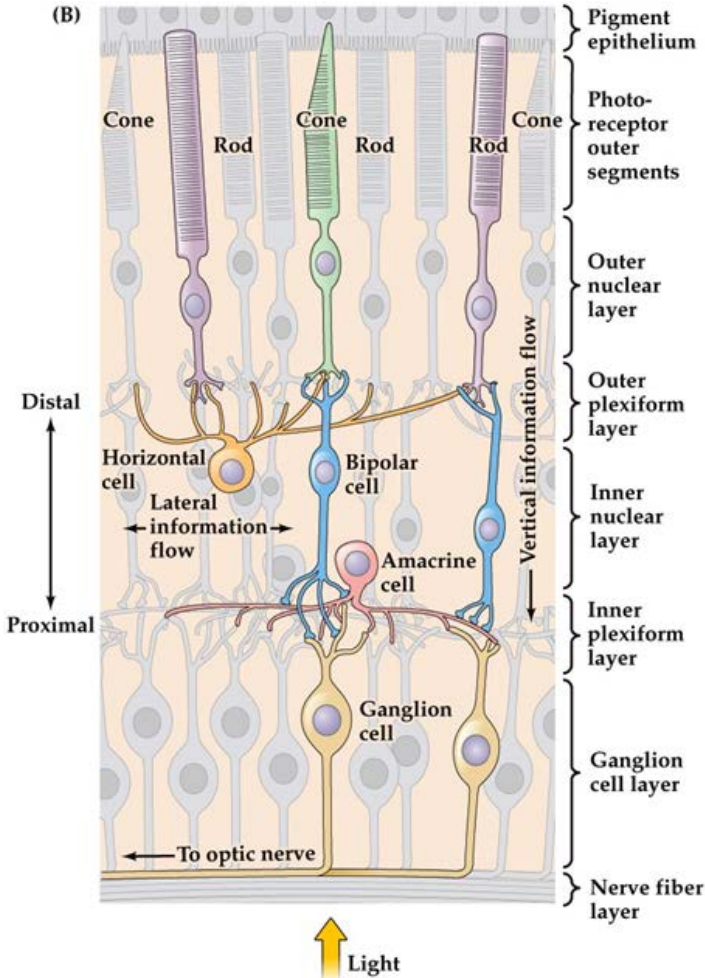
- Absorption of light by the photopigment in the outer segment of the photoreceptors initiates a cascade of events that changes the membrane potential of the receptor, and therefore the amount of neurotransmitter released by the photoreceptor terminals.

- The synapses between photoreceptor terminals and bipolar cells (and horizontal cells) occur in the outer plexiform layer; more specifically, the cell bodies of photoreceptors make up the outer nuclear layer, whereas the cell bodies of bipolar cells lie in the inner nuclear layer.



Structure of retina

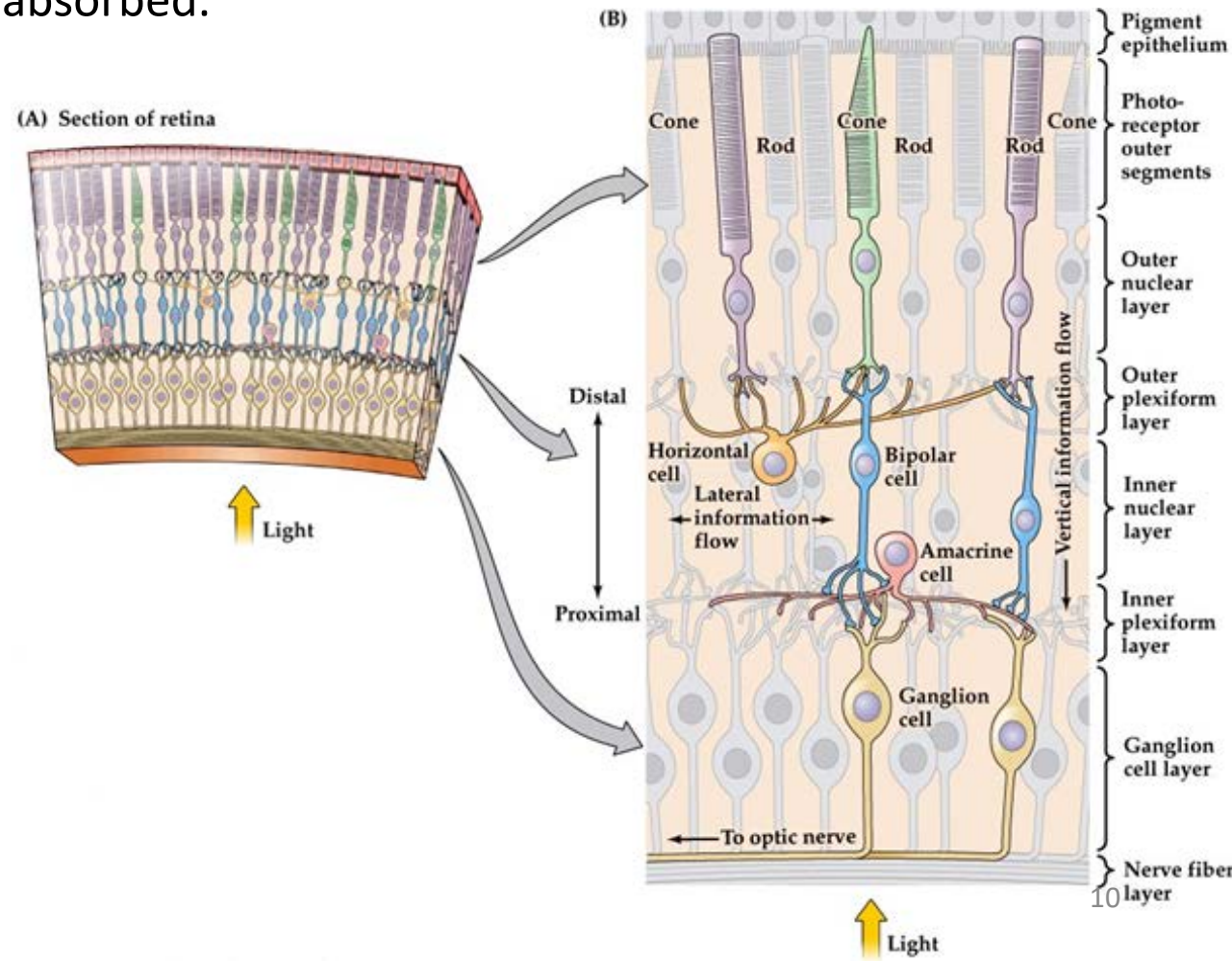
- The short axonal processes of bipolar cells make synaptic contacts in turn on the dendritic processes of ganglion cells in the inner plexiform layer.
- The much larger axons of the ganglion cells form the **optic nerve** and carry information about retinal stimulation to the rest of the central nervous system.
- The two other types of neurons in the retina, **horizontal cells** and **amacrine cells**, have their cell bodies in the inner nuclear layer and have processes that are limited to the outer and inner plexiform layers, respectively.
- The processes of horizontal cells enable lateral interactions between photoreceptors and bipolar cells that are thought to maintain the visual system's sensitivity to contrast, over a wide range of light intensities, or **luminance**.
- The processes of amacrine cells are postsynaptic to bipolar cell terminals and presynaptic to the dendrites of ganglion cells.



Retinal pigment epithelium

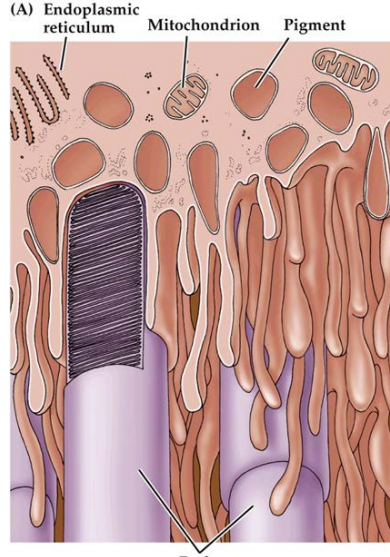
- The spatial arrangement of retinal layers at first seems counterintuitive:
  - light rays must pass through various nonlight-sensitive elements of the retina as well as the retinal vasculature (which branches extensively on the inner surface of the retina) before reaching the outer segments of the photoreceptors, which is where photons are absorbed.

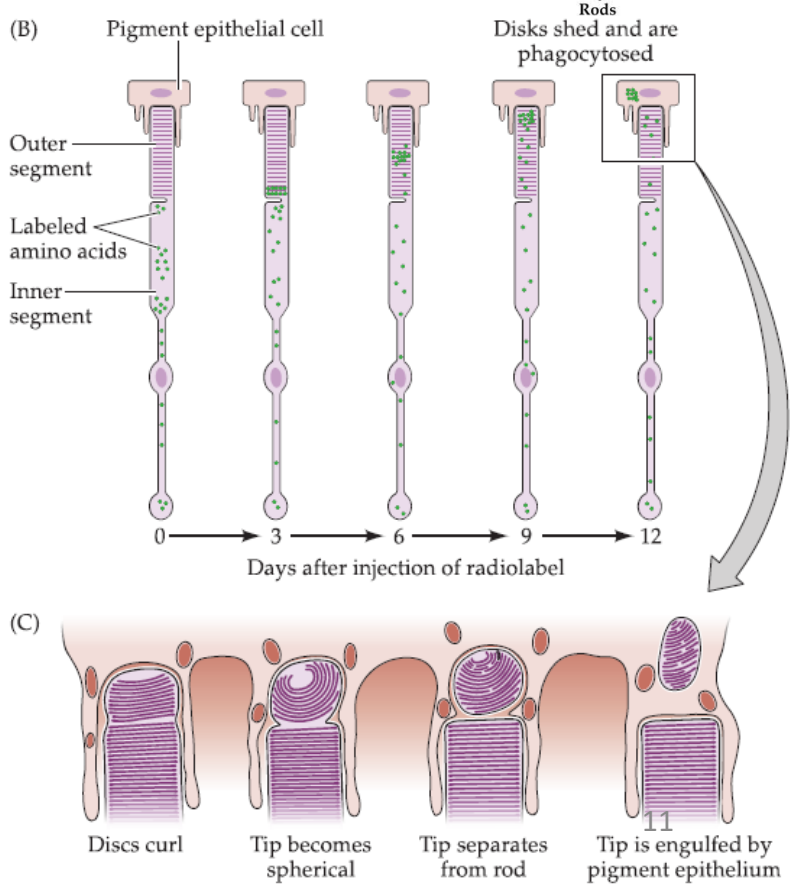
- The reason for this curious feature of retinal organization lies in the special relationship that exists among the outer segments of the photoreceptors and the pigment epithelium.



Retinal pigment epithelium

- The cells that make up the retinal pigment epithelium have long processes that extend into the photoreceptor layer, surrounding the tips of the outer segments of each photoreceptor.
- The pigment epithelium plays two roles that are critical to the function of retinal photoreceptors:
  1. The membranous disks in the outer segment, which house the light-sensitive photopigment and other proteins involved in phototransduction, have a relatively limited life span of about 12 days.
     - New outer segment disks are continuously being formed near the base of the outer segment, while the oldest disks are removed, or "shed," at the tip of the outer segment.
     - Shedding involves the ''pinching off'' of a clump of receptor disks by the outer segment membrane of the photoreceptor.
     - This enclosed clump of disks is then phagocytosed by the pigment epithelium.

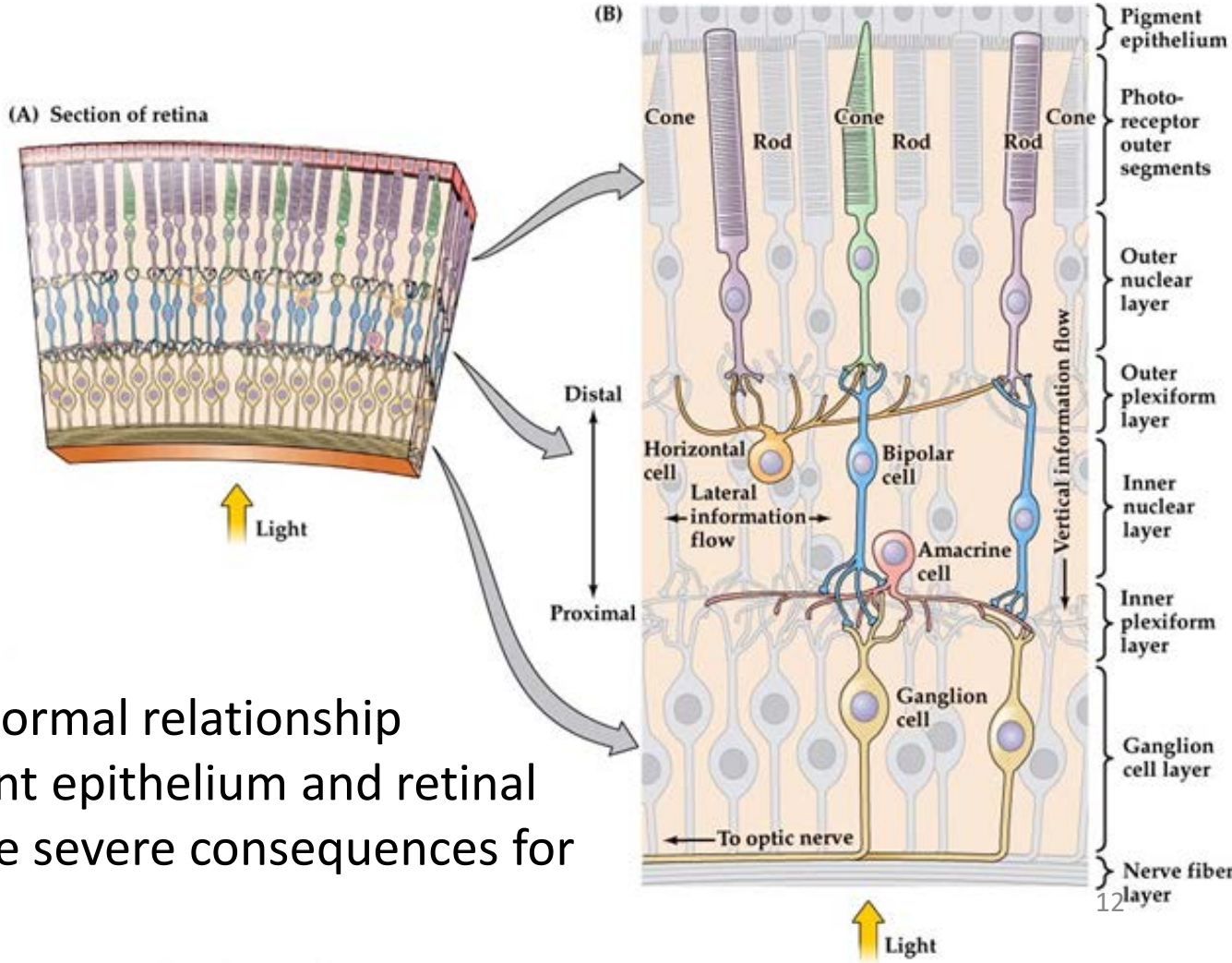




Retinal pigment epithelium

2. The epithelium's second role is to regenerate photopigment molecules after they have been exposed to light.
   - Photopigment is cycled continuously between the outer segment of the photoreceptor and the pigment epithelium.

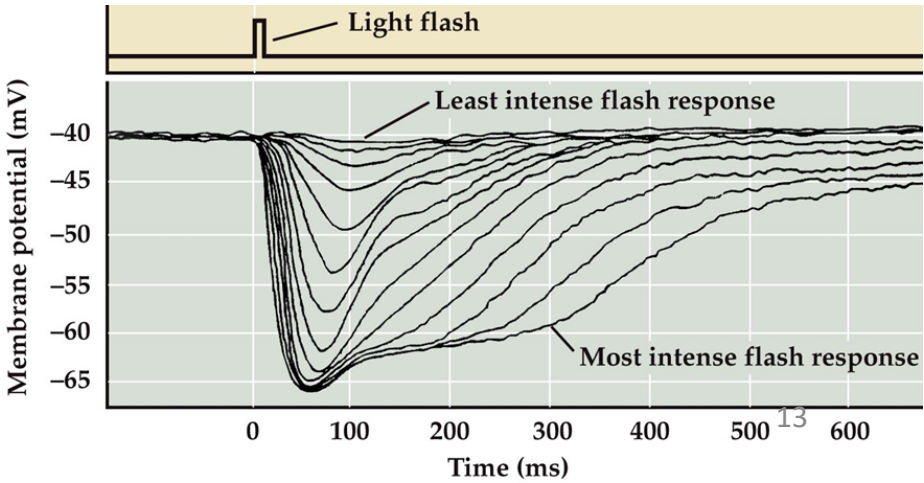
❖ These considerations explain why rods and cones are found in the outermost rather than the innermost layer of the retina.



❖ Disruptions in this normal relationship between the pigment epithelium and retinal photoreceptors have severe consequences for vision.

Phototransduction

- In most sensory systems, activation of a receptor by the appropriate stimulus causes the cell membrane to depolarize, ultimately stimulating an action potential and transmitter release onto the neurons it contacts.
- In the retina, however, photoreceptors do not exhibit action potentials; rather, light activation causes a graded change in membrane potential and a corresponding change in the rate of transmitter release onto postsynaptic neurons.
- Perhaps even more surprising is that shining light on a photoreceptor, either a rod or a cone, leads to membrane *hyperpolarization* rather than depolarization.
  - In the dark, the receptor is in a depolarized state, with a membrane potential of roughly -40 mV.
  - Progressive increases in the intensity of illumination cause the potential across the receptor membrane to become more negative, a response that saturates when the membrane potential reaches about -65 mV.

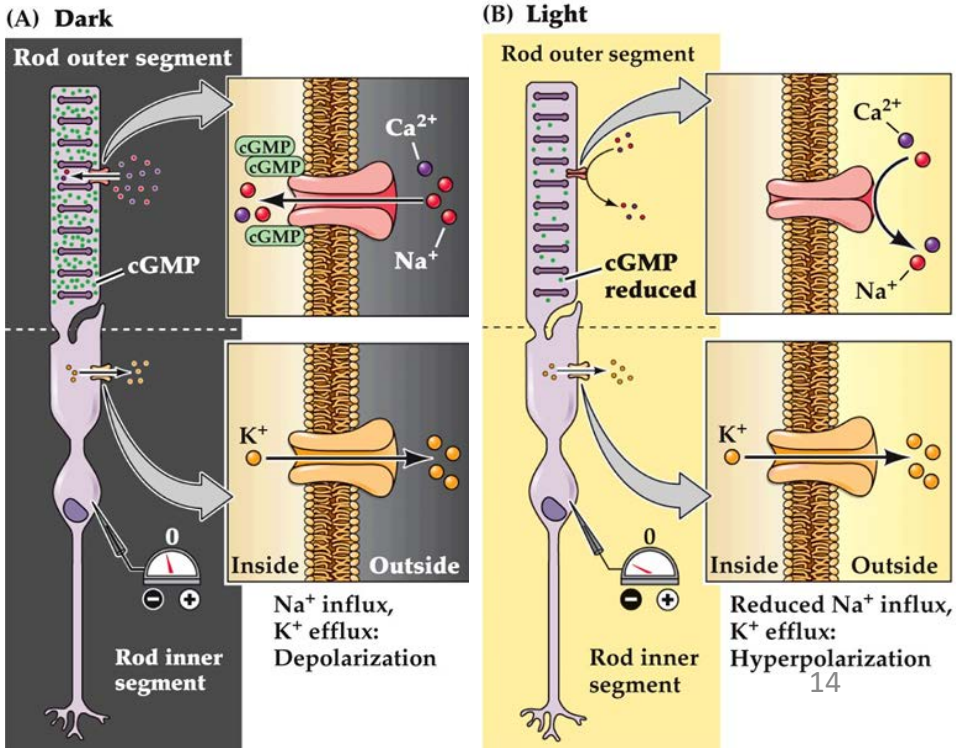


Phototransduction

- As in other nerve cells, transmitter release from the synaptic terminals of the photoreceptor is dependent on voltage-sensitive Ca^{2+} channels in the terminal membrane.
  - in the dark, when photoreceptors are relatively depolarized, the number of open Ca^{2+} channels in the synaptic terminal is high, and the rate of transmitter release is correspondingly great.
  - in the light, when receptors are hyperpolarized, the number of open Ca^{2+} channels is reduced, and the rate of transmitter release is also reduced.

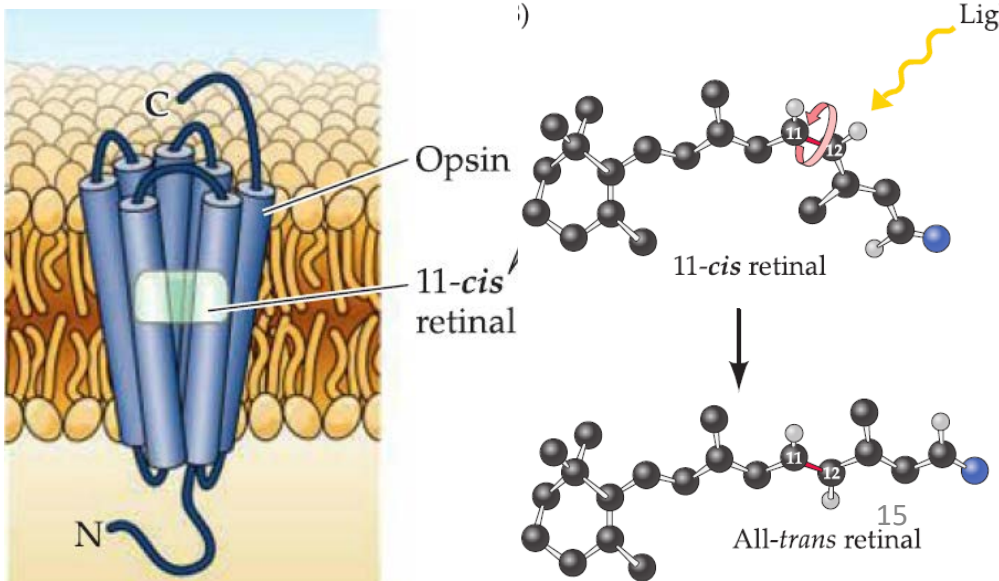
- Cyclic GMP-gated channels and light-induced changes in the electrical activity of photoreceptors:

- How does light lead to reduction of cGMP?



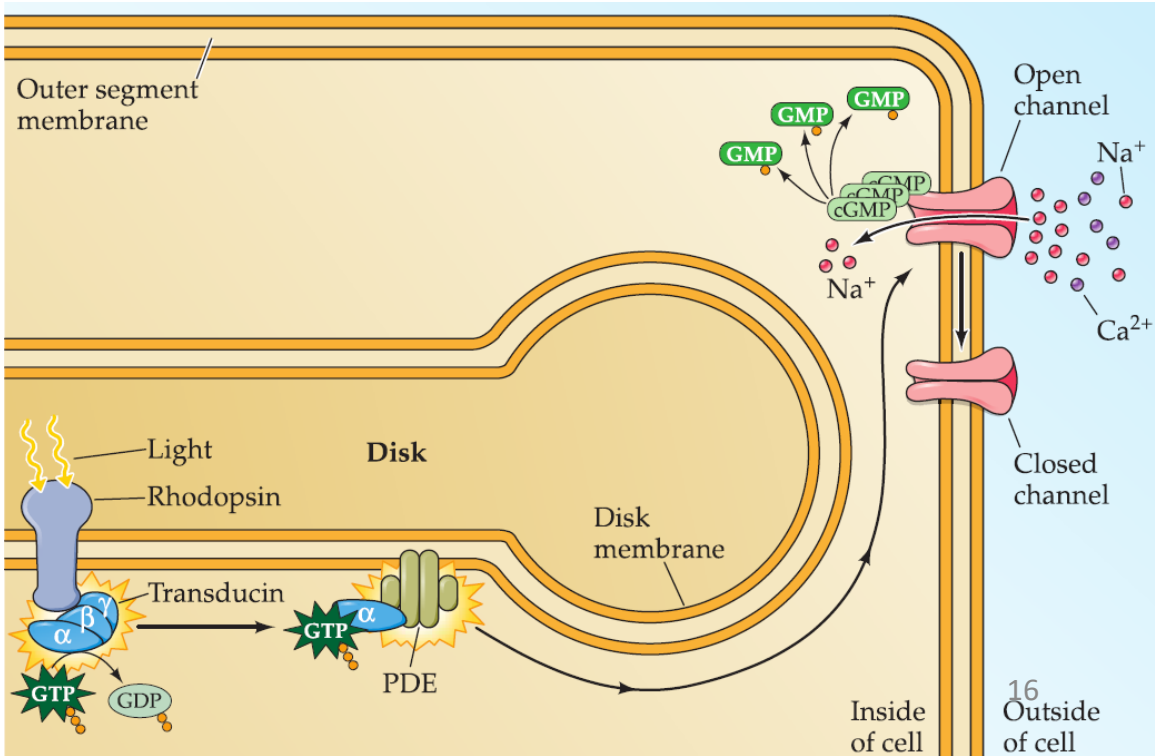
Phototransduction

- The series of biochemical changes that ultimately leads to a reduction in cGMP levels begins when a photon is absorbed by the photopigment in the receptor disks.
- The photopigment contains the light-absorbing chromophore **retinal** (an aldehyde of vitamin A) coupled to one of several possible proteins called **opsins**.
  - Most of what is known about the molecular events of phototransduction has been gleaned from experiments in rods, in which the photopigment is **rhodopsin**.
  - The seven transmembrane domains of the opsin molecule traverse the membrane of the disks in the outer segment, forming a pocket in which the retinal molecule resides.
  - When retinal absorbs a photon of light, one of the double bonds between the carbon atoms in the retinal molecule breaks, and its configuration changes from the 11-*cis* isomer to all-*trans* retinal.



Phototransduction

- The changes in opsin lead, in turn, to the activation of an intracellular messenger called **transducin**, which activates a phosphodiesterase (PDE) that hydrolyzes cGMP.
- The hydrolysis by phosphodiesterase at the disk membrane lowers cGMP concentration throughout the outer segment, thus reducing the number of cGMP molecules available to bind to the channels in the surface of the outer segment membrane and leading in turn to channel closure.

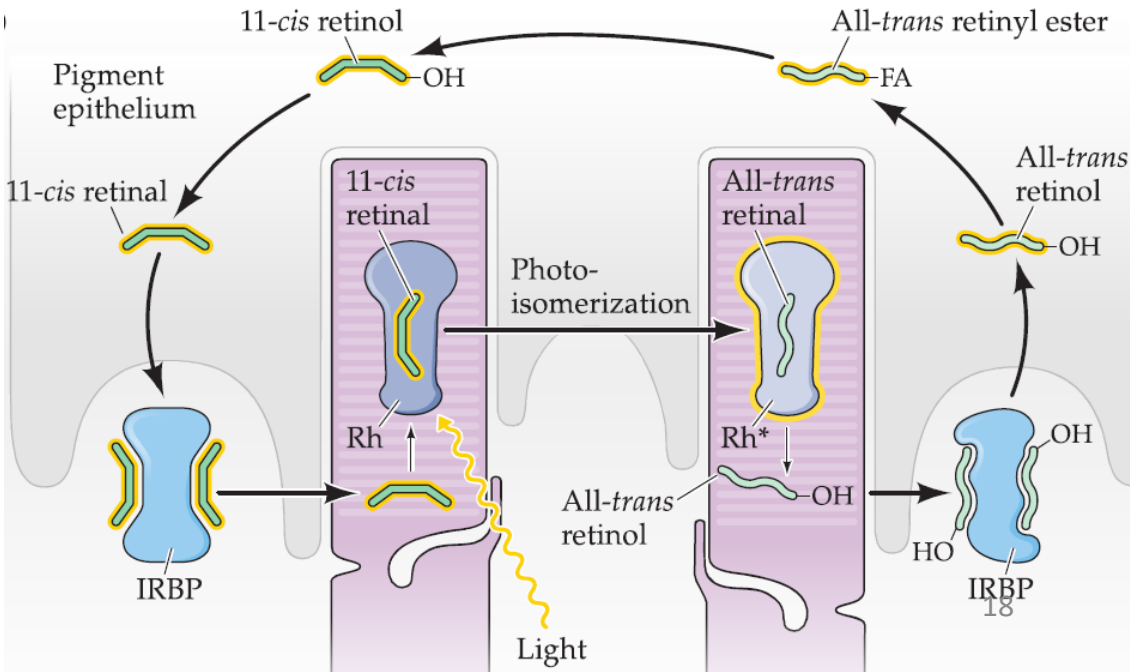


Phototransduction

- One of the important features of this complex biochemical cascade initiated by photon capture is that it provides enormous signal amplification:
  - It has been estimated that a single light-activated rhodopsin molecule can activate 800 transducin molecules--roughly 8% of the transducin molecules on the disk surface.
  - Although each transducin molecule activates only one phosphodiesterase molecule, each PDE is capable of catalyzing the breakdown of as many as 6 cGMP molecules.
  - As a result, the absorption of a single photon by a rhodopsin molecule results in the closure of approximately 200 ion channels, or about 2% of the number of channels in each rod that are open in the dark.
  - This number of channel closures causes a net change in the membrane potential of about 1 mV.
- Once initiated, additional mechanisms limit the duration of this amplifying cascade and restore the various molecules to their inactivated states.
  - Activated rhodopsin is rapidly phosphorylated by **rhodopsin kinase**, which permits the protein **arrestin** to bind to rhodopsin.
  - Bound arrestin blocks the ability of activated rhodopsin to activate transducin, thus effectively truncating the phototransduction cascade.

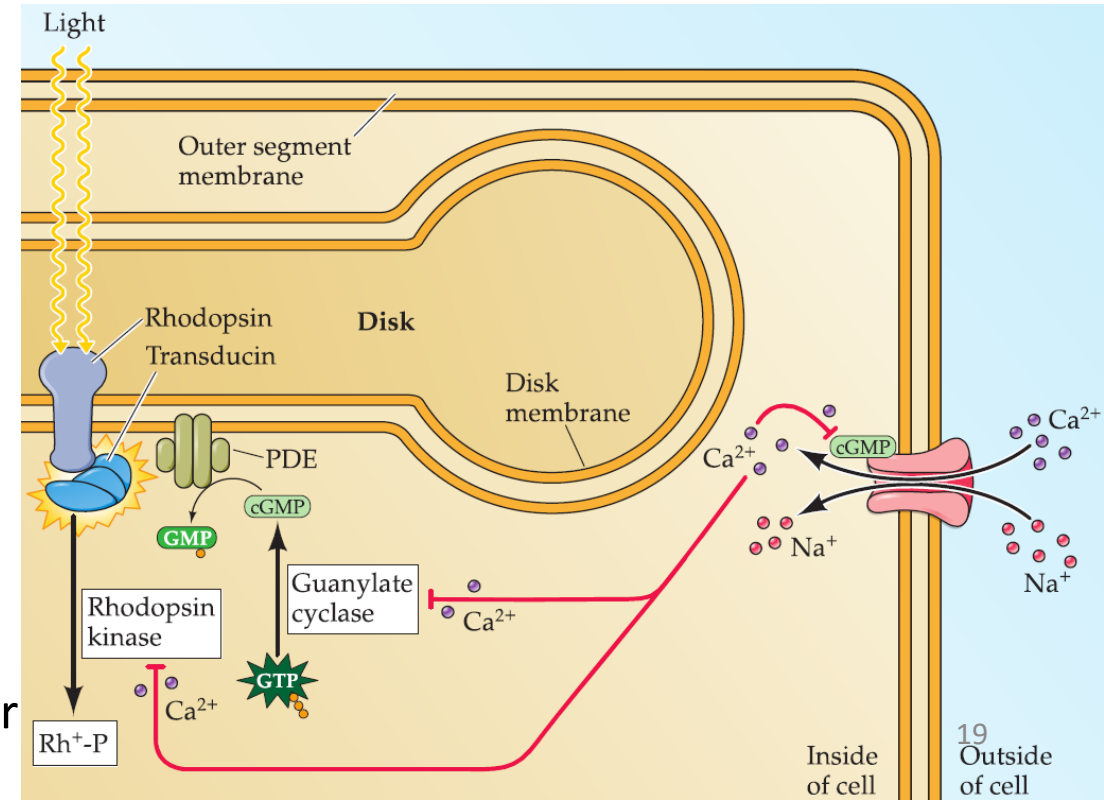
Retinoid cycle

- The restoration of retinal to a form capable of signaling photon capture is a complex process known as the **retinoid cycle**.
  - The all-*trans* retinal dissociates from opsin and diffuses into the cytosol of the outer segment, where it is converted to all-*trans* retinol.
  - All-*trans* retinol is transported into the pigment epithelium via a chaperone protein, **interphotoreceptor retinoid binding protein** (**IRBP**), where appropriate enzymes ultimately convert it to 11-*cis* retinal.
  - After being transported back into the outer segment via IRBP, 11-*cis* retinal recombines with opsin in the receptor disks.
- The retinoid cycle is critically important for maintaining the light sensitivity of photoreceptors.



Light adaptation

- The magnitude of the phototransduction amplification varies with the prevailing level of illumination, a phenomenon known as **light adaptation**.
  - Photoreceptors are most sensitive to light at low levels of illumination.
  - As levels of illumination increase, sensitivity decreases, preventing the receptors from saturating and thereby greatly extending the range of light intensities over which they operate.
- The concentration of Ca^{2+} in the outer segment appears to play a key role in the light-induced modulation of photoreceptor sensitivity.
  - The cGMP-gated channels in the outer segment are permeable to Na^{+} and Ca^{2+}.
  - Light-induced closure of these channels leads to a net decrease in the internal Ca^{2+} concentration.
  - This decrease triggers a number of changes in the phototransduction cascade, all of which tend to reduce the sensitivity of the receptor to light.

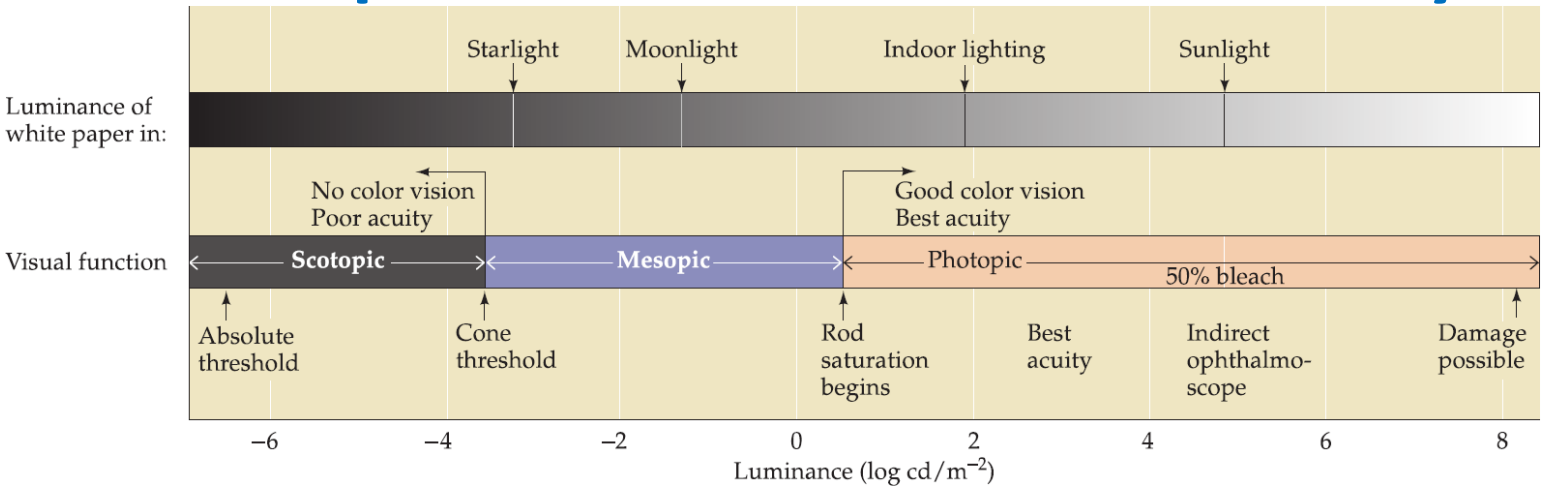


Functional specialization of rod and cone systems

- The two types of photoreceptors, rods and cones, are distinguished by shape (from which they derive their names), type of photopigment they contain, distribution across the retina, and pattern of synaptic connections.

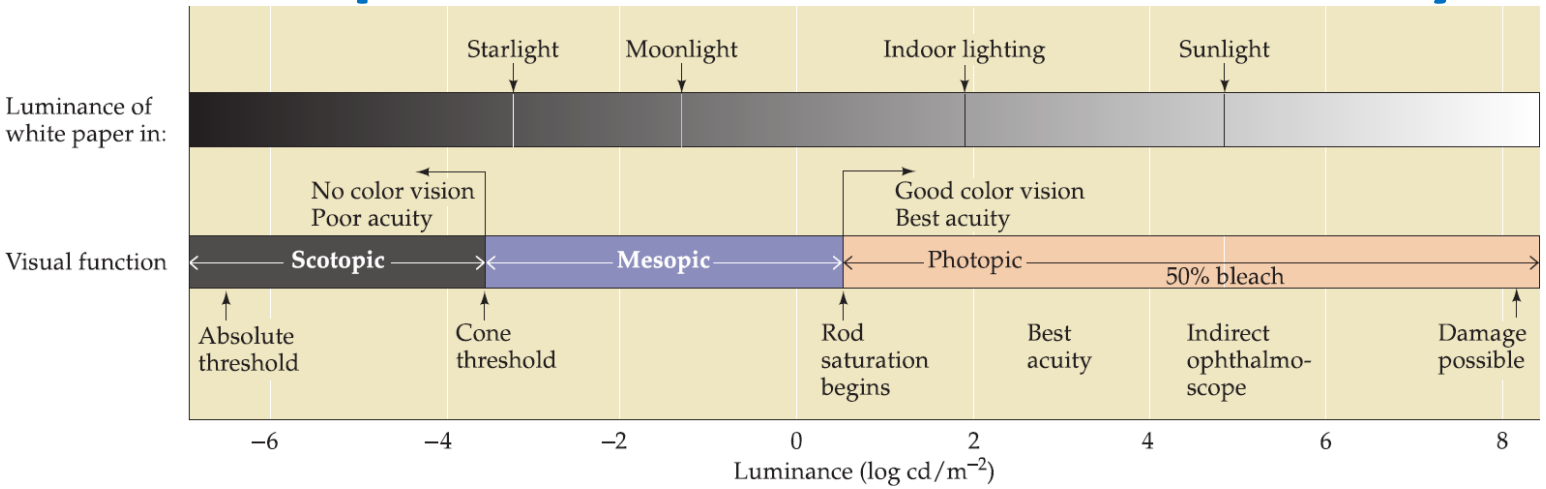
- These properties reflect the fact that the rod and cone systems (i.e., the receptor cells and their connections within the retina) are specialized for different aspects of vision.
  - The rod system has very low spatial resolution but is extremely sensitive to light; it is therefore specialized for sensitivity at the expense of resolution.
  - Conversely, the cone system has very high spatial resolution but is relatively insensitive to light; it is specialized for acuity at the expense of sensitivity.
    - The properties of the cone system also allow humans and many other animals to see color.

Functional specialization of rod and cone systems



- At the lowest levels of illumination, only the rods are activated. Such rod-mediated perception is called **scotopic vision**.
  - The difficulty of making fine visual discriminations under very low light conditions where only the rod system is active is a common experience.
  - The problem is primarily the poor resolution of the rod system (and, to a lesser extent, the fact that there is no perception of color because in dim light there is no significant involvement of the cones).
- Although cones begin to contribute to visual perception at about the level of starlight, spatial discrimination at this light level is still very poor.
- As illumination level increases, cones become more and more dominant in determining what is seen, and they are the major determinant of perception under conditions such as normal indoor lighting or sunlight.

Functional specialization of rod and cone systems



- The contributions of rods to vision drops out nearly entirely in **photopic vision** because their response to light saturates--that is, the membrane potential of individual rods no longer varies as a function of illumination because all of the membrane channels are closed.
- **Mesopic vision** occurs in levels of light at which both rods and cones contribute--at twilight, for example.

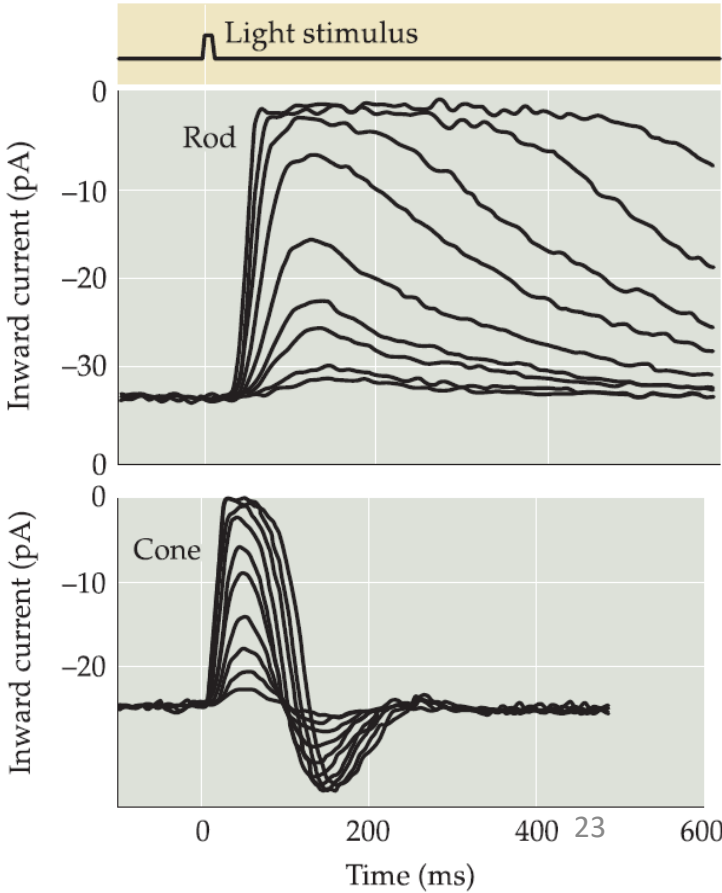
❖ From these considerations it should be clear that most of what we think of as normal "seeing" is mediated by the cone system and that loss of cone function is devastating, as occurs in individuals suffering from macular degeneration.

❖ People who have lost cone function are legally blind, whereas those who have lost rod function only experience difficulty seeing at low levels of illumination (night blindness).

Differences in transduction mechanisms of rod and cone

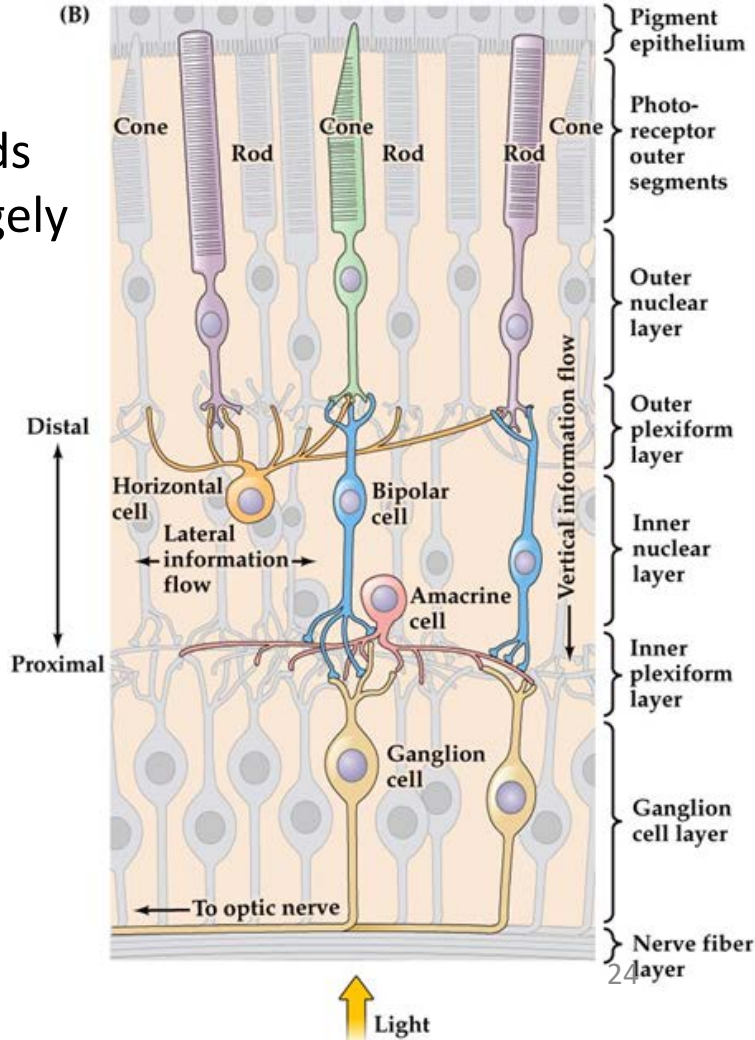
- Ability of rods and cones to respond to different ranges of light intensity:
  - Rods produce a reliable response to a single photon of light, whereas more than 100 photons are required to produce a comparable response in a cone.
    - The change in current produced by single photon capture in cones is comparatively small and difficult to distinguish from background noise.

- Response of an individual cone does not saturate at high levels of steady illumination, as the rod response does.
  - The adaptation mechanisms of the cones are more effective, which is apparent in the time course of the response of rods and cones to light flashes.
    - The response of a cone, even to a bright light flash that produces the maximum change in photoreceptor current, recovers in about 200 milliseconds, more than four times faster than rod recovery.



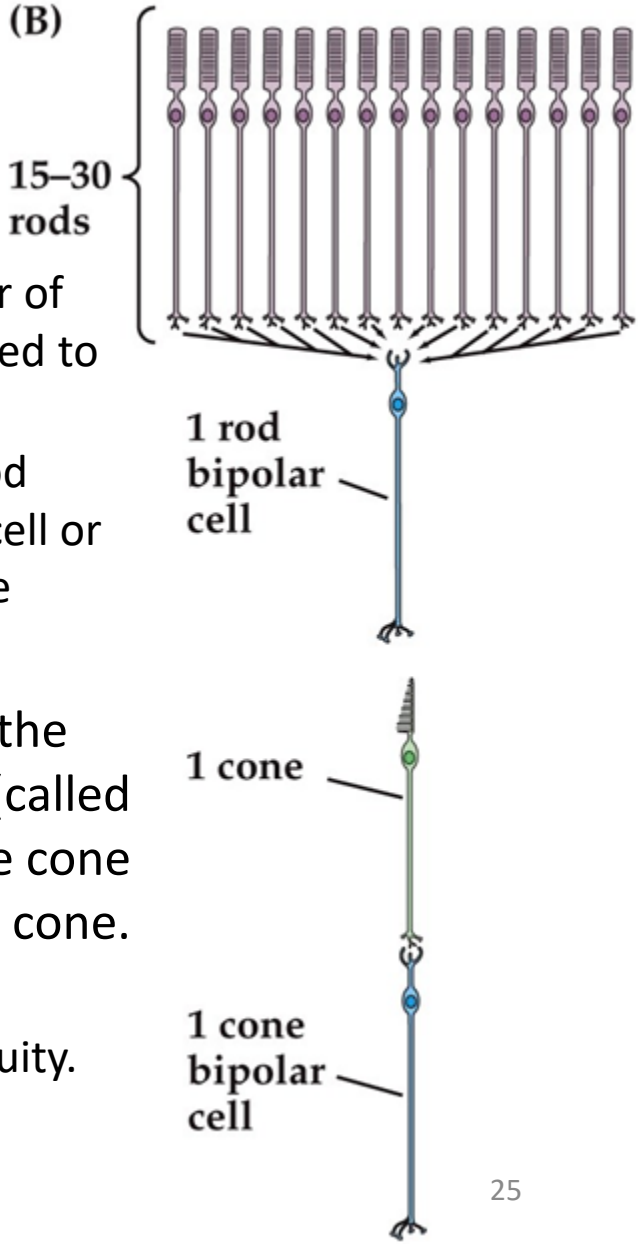
Differences in transduction mechanisms of rod and cone

- Arrangement of the circuits that transmit rod and cone information to retinal ganglion cells.
  - In most parts of the retina, individual ganglion cells respond to both rod and cone inputs, depending on the level of illumination.
  - The early stages of the pathways that link rods and cones to ganglion cells, however, are largely independent.
    - the pathway from rods to ganglion cells involves a distinct class of rod bipolar cells that, unlike cone bipolar cells, do not contact retinal ganglion cells.
    - rod bipolar cells synapse with the dendritic processes of a specific class of amacrine cells that makes gap junctions and chemical synapses with the terminals of cone bipolars; these processes, in turn, make synaptic contacts on the dendrites of ganglion cells in the inner plexiform layer.



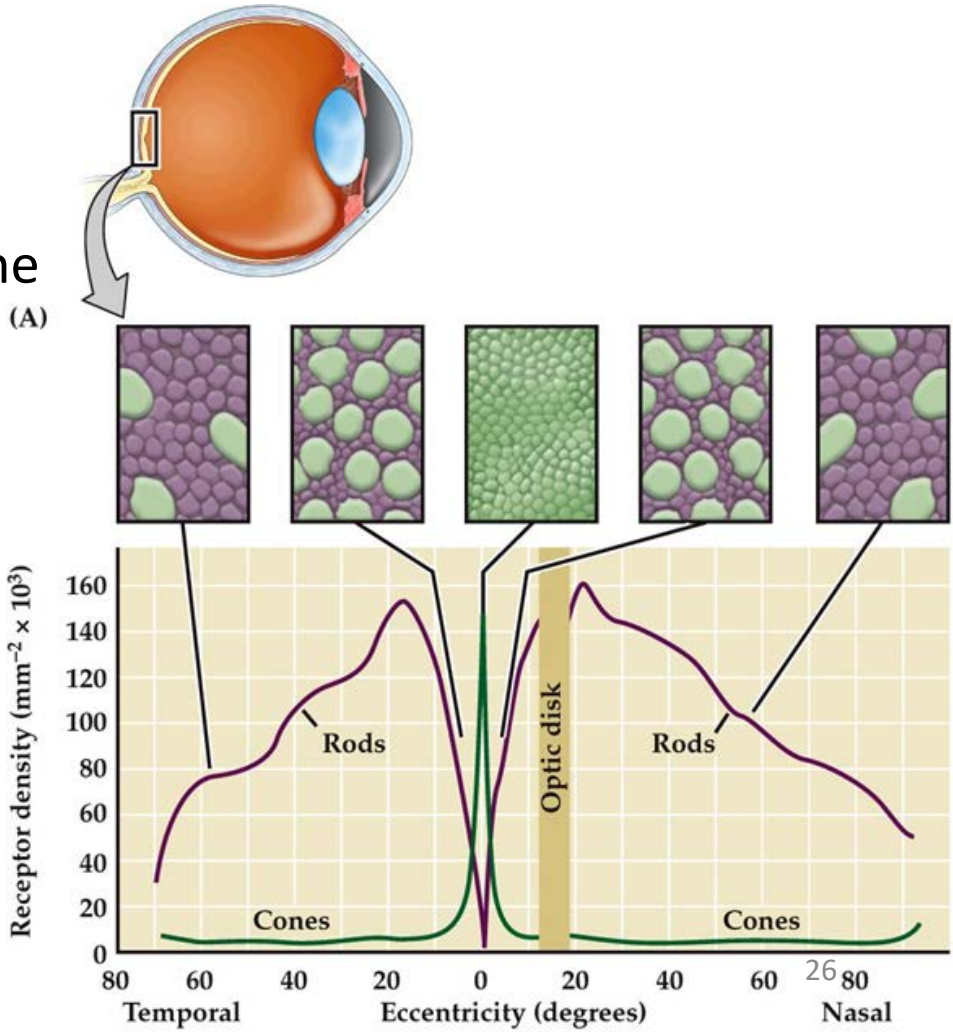
Differences in transduction mechanisms of rod and cone

- Degree of convergence:
  - Each rod bipolar cell is contacted by a number of rods, and many rod bipolar cells contact a given amacrine cell.
    - Convergence makes the rod system a better detector of light, because small signals from many rods are pooled to generate a large response in the bipolar cell.
    - Convergence reduces the spatial resolution of the rod system, since the source of a signal in a rod bipolar cell or retinal ganglion cell could have come from anywhere within a relatively large area of the retinal surface.
  - The cone system is much less convergent: each of the retinal ganglion cells that dominate central vision (called midget ganglion cells) receives input from only one cone bipolar cell, which, in turn, is contacted by a single cone.
    - The one-to-one relationship of cones to bipolar and ganglion cells is just what is required to maximize acuity.



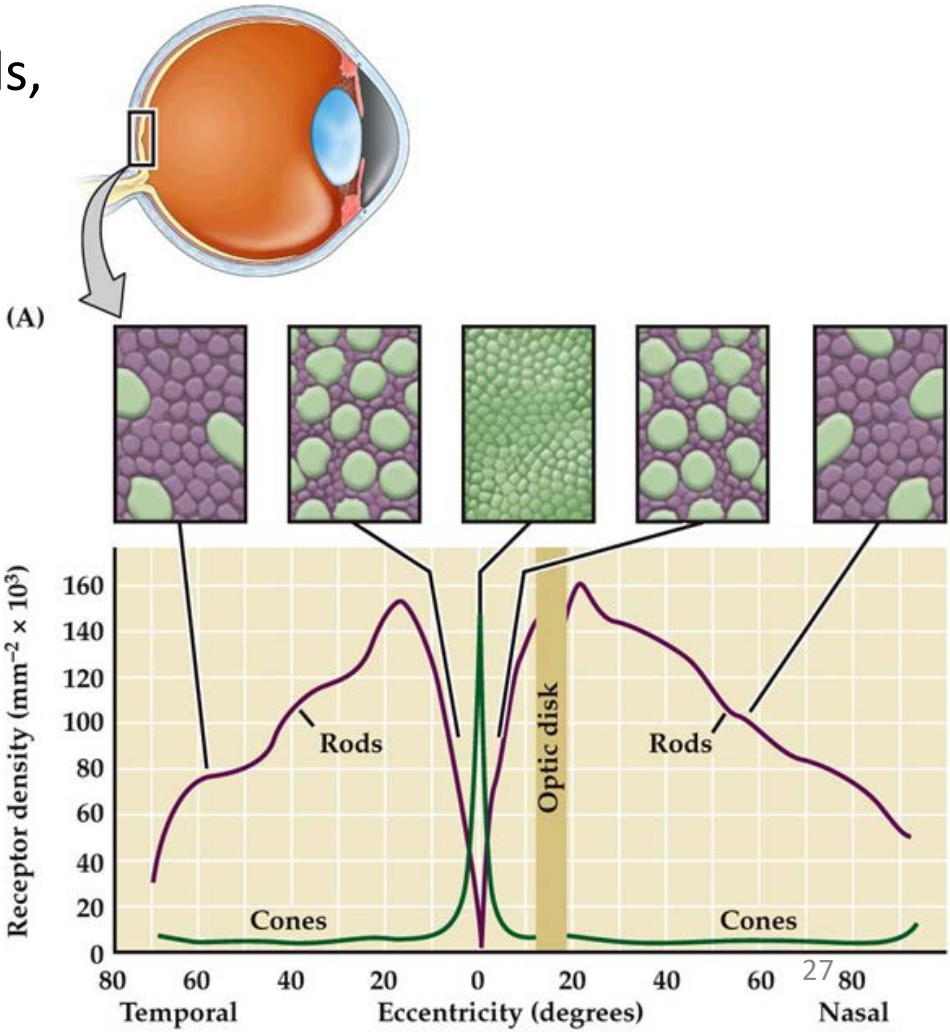
Anatomical distribution of rods and cones

- Despite the fact that perception in typical daytime light levels is dominated by cone-mediated vision, the total number of rods in the human retina (about 90 million) far exceeds the number of cones (roughly 4.5 million).
- As a result, the density of rods is much greater than that of cones throughout most of the retina.
- However, this relationship changes dramatically in the fovea, the highly specialized region in the center of the macula that measures about 1.2 millimeters in diameter.
- In the fovea (which literally means "pit"), cone density increases almost 200-fold, reaching, at its center, the highest receptor packing density anywhere in the retina.
- The increased density of cones in the fovea is accompanied by a sharp decline in the density of rods.



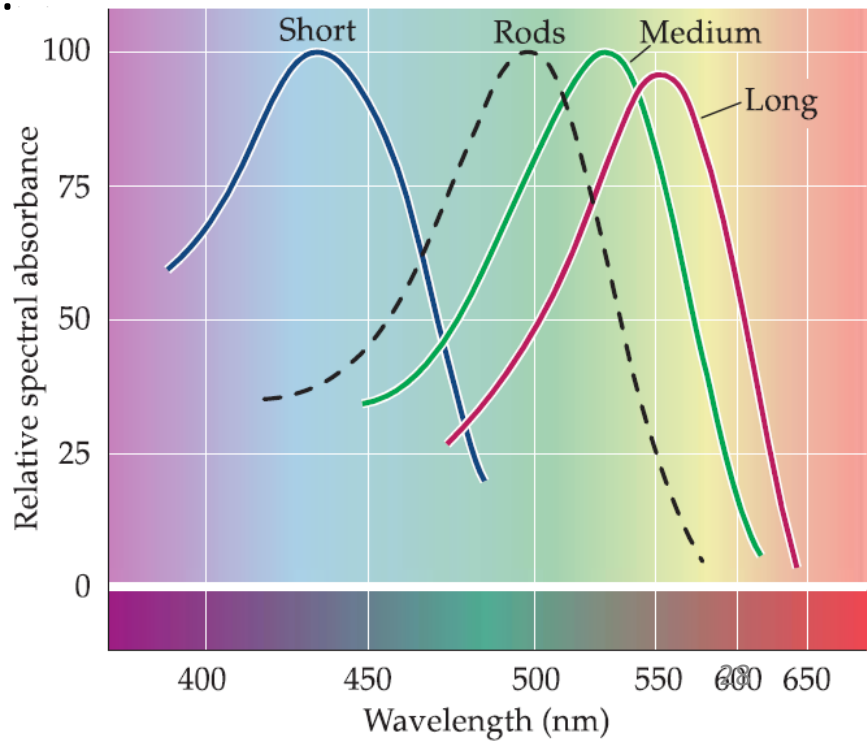
Anatomical distribution of rods and cones

- The central 300 μm of the fovea, called the **foveola**, is totally rod-free.
- The extremely high density of cone receptors in the fovea, coupled with the one-to-one relationship with bipolar cells and retinal ganglion cells, endows this component of the cone system with the capacity to mediate the highest levels of visual acuity.
- The restriction of highest acuity vision to such a small region of the retina is the main reason humans spend so much time moving their eyes (and heads) around--in effect directing the foveas of the two eyes to objects of interest.



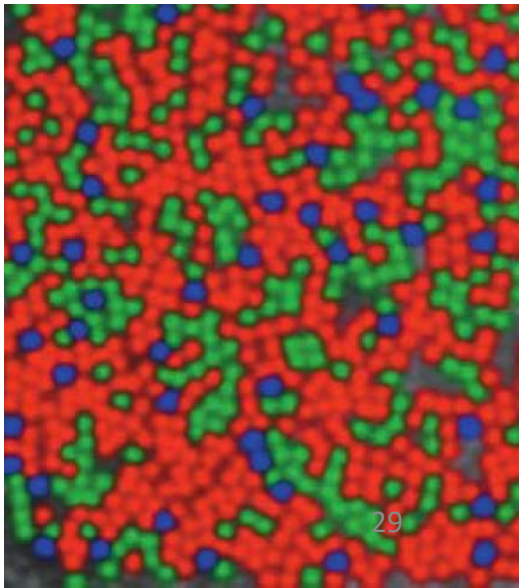
Cones and color vision

- Perceiving color allows humans and many other animals to discriminate objects on the basis of the distribution of the wavelengths of light that they reflect to the eye.
- Color obviously gives us a quite different way of perceiving and describing the world we live in, and our color vision is the result of special properties of the cone system.
- Unlike rods, which contain a single photopigment, the three types of cones differ in the photopigment they contain.
- Each photopigment is differentially sensitive to light of different wavelengths, and for this reason cones are referred to as “blue”, “green” and "red”, or, more appropriately, as short (S), medium (M), and long (L) wavelength cones--terms that more or less describe their spectral sensitivities.



Cones and color vision

- While it might seem natural to assume that the three cone types are present in roughly the same number, this is clearly not the case:
  - S cones make up only about 5-10% of the cones in the retina, and they are virtually absent from the center of the fovea.
  - Although the M and L types are the predominant retinal cones, the ratio of M to L varies considerably from individual to individual.
- Normal human color vision is fundamentally **trichromatic**, based on the relative levels of activity in three sets of cones that have different absorption spectra.
- About 8% of the male population in the United States (and a much smaller percentage of the female population) have a deficiency in color vision (commonly referred to as color blindness).
- For some of these individuals, color vision is **dichromatic**: only two bandwidths of light are needed to match all the colors that can be perceived.



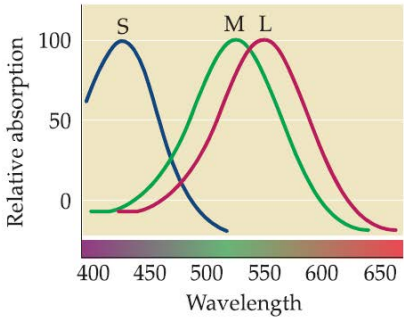
Abnormalities of color vision

- The two most prevalent forms of dichromacy are:
  - *Protanopia*: characterized by impairment in perception of long wavelengths.
  - *Deuteranopia*: impairment in the perception of medium wavelengths.

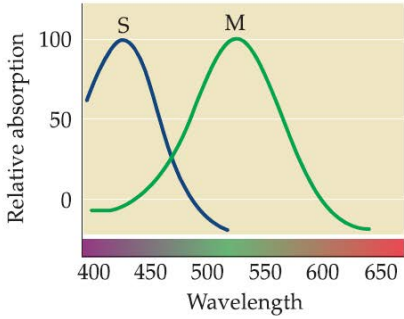
- Both have difficulties with the discrimination of red and green, and for this reason dichromacy is commonly called red-green color blindness.

- Color vision deficiencies result either from the inherited failure to make one or more of the cone pigments, or from an alteration in the absorption spectra of cone pigments.

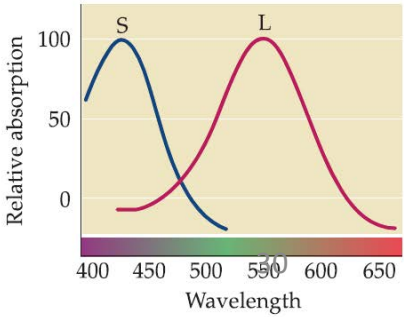
(A) Normal (trichromat)



(B) Protanopia

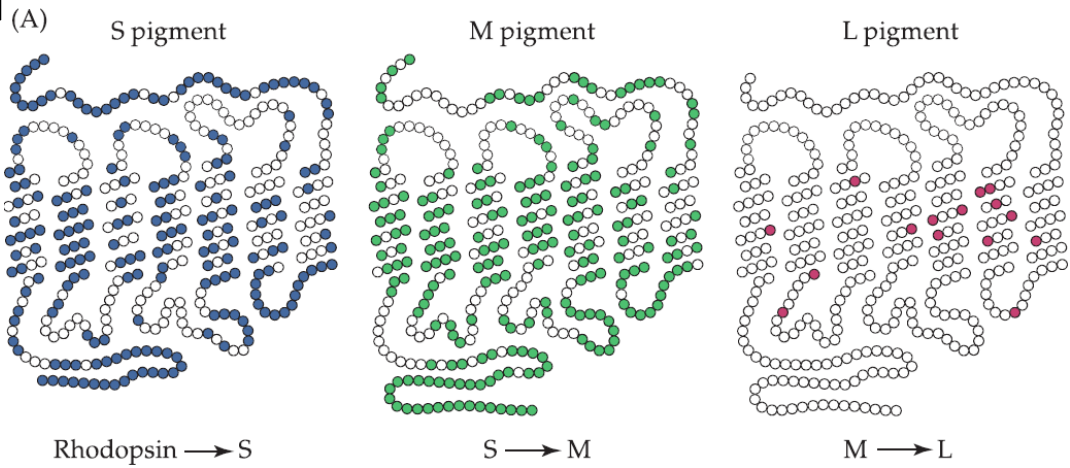


(C) Deuteranopia



Genetics of the cone pigments

- Jeremy Nathans and his colleagues at Johns Hopkins University have provided a deeper understanding of color vision deficiencies by identifying and sequencing the genes that encode the three human cone pigments.
  - The genes that encode the red and green pigments show a high degree of sequence homology and lie adjacent to each other on the X chromosome, thus explaining the prevalence of red-green color blindness in males.



  - Normal trichromats have one gene for the red pigments and can have anywhere from one to five genes for green pigments.
  - In contrast, the blue-sensitive pigment gene, found on chromosome 7, is quite different in its amino acid sequence.
- These facts suggest that the red and green pigment genes evolved relatively recently, perhaps as a result of the duplication of a single ancestral gene; they also explain why most color vision abnormalities involve the red and green cone pigments.