Overview of Retinal Prosthesis Lecture

- Eye structure and function, emphasis on the retina
- Eye disease
- Retinal prostheses as a potential solution
Outside the Eye

Fig. 6.20. Drawing of the posterior aspect of the eye. The optic nerve (A) with its central vessels and surrounding meningeal sheaths is seen. Its center is located 3 mm nasal and 1 mm inferior to the posterior pole of the eye. Surrounding it are the short posterior ciliary arteries and nerves. The approximate position of the macula is at (X). Along the horizontal meridian which bisects the eye are the long posterior ciliary arteries and nerves (B). The axes of four vortex veins are shown, one for each quadrant (C). The curved, oblique insertions of the superior oblique (D) and inferior oblique (E) muscles are seen. The cut ends of the four rectus muscles are at (F). T = Temporal; N = nasal. (From Hogan, M.J.; Alvarado, J.A., and Weddell, J.E. (1971) Histology of the Human Eye, published by W.B. Saunders.)

Fig. 6.25. Drawing of the upper half of the eye. The contrasting degree of curvature of the cornea (A) and sclera (B) are evident. At the limbus (C), where they join, is the external scleral sulcus. The relation of the ora serrata (D) to the surface is shown. The nasal displacement of the optic nerve (E) with respect to the posterior pole of the eye makes the three layers of the temporal eye longer than those on the nasal side. The slightly curved oblique insertion of the superior rectus muscle is at (F), and the tendinous oblique insertion of the superior oblique muscle is at (G). Two vortex veins are seen (H), and the long posterior ciliary arteries and nerves are at (I). T = Temporal; N = nasal. (From Hogan, M.J., Alvarado, J.A., and Weddell, J.E. (1971) Histology of the Human Eye, published by W.B. Saunders.)
Layers of the Eyeball

Fig. 6.5 Preparation to show the coats and contents of the eye. Parts of the sclera, cornea, choroid, ciliary body, iris and retina have been removed.
Eye as 2 spheres

Fig. 6.3 Sagittal section of the globe.

Fig. 6.4 Anterior aspect of the eye. Parts of the cornea, sclera and iris have been removed to show the internal structures.
Optical Pathway
Accommodation: How the eye focuses near

- Accommodative triad: pupil dilation, eye convergence, lens shape change.
- Focal Length changes through relaxation of ciliary muscles, change in lens shape
The superimposed binocular fields of a normal adult male, to demonstrate the central region of binocular overlap and lateral, monocular crescents.
Topography of Retina
Topography of the Retina (fovea view)

Fig. 14.6 The ora serrata, showing its greater width temporally than on the nasal aspect. The serrations are also less developed temporally where cystic degeneration (depicted by the mottled appearance) is most evident.
Blind Spot
Layers of the retina

Fig. 14.1 Morphological organization of the retina. (A) Transverse section of retina showing pigmented epithelium (1) attached to the sensory retina that consists of photoreceptor layer (2); external limiting membrane (3); outer nuclear layer (4); outer plexiform layer (5); inner nuclear layer (6); inner plexiform layer (7); ganglion cell layer (8); nerve fibre layer (9); and internal limiting membrane (10). Ch = Choroid. Photomicrograph, original magnification × 245.

(B) Diagrammatic representation of the elements that comprise the retina. 1 = Pigment epithelium; 2 = photoreceptor layer consisting of rods (R) and cones (C); 3 = external limiting membrane; 4 = outer nuclear layer; 5 = outer plexiform layer; 6 = inner nuclear layer; 7 = inner plexiform layer; 8 = ganglion cell layer; 9 = nerve fibre layer; 10 = internal limiting membrane. (From Tripathi, R. C. and Tripathi, B. J. in Davson, H. (ed.) (1984) The Eye, published by Academic Press.)
Photoreceptors
Rods and Cones

- S-cone is morphologically distinct from others
- Cones bright light vision
- Rods low light vision
Distribution of rods and cones

- 100 million rods
- 5 million cones
  - Cones high acuity vision
  - Rods peripheral vision, low light vision
**Horizontal Cells**

Fig. 14.31 Whole mount views of horizontal cells in a Golgi-impregnated preparation of the human retina. The cells at the fovea (0.5 mm, top) are small and difficult to distinguish into the three types. By 2.5 mm eccentricity, HI, HII and HIII types are more discernible. In the peripheral retina (16 mm) the HIII cell is clearly larger than HI and has an asymmetric dendritic field. HII cells have a woolly appearance, which distinguishes them from the HI and HIII types. The short curled axon of the HII cell gives rise to occasional terminals (arrow). The HI axon terminal ends as a fan-shaped structure with many 'lollipop' terminals (HIAT), while a finer, more loosely clustered terminal (HIIAT?) is assigned putatively to the HIII horizontal cell. Scale bar = 10 μm. (From Kolb, H. et al. (1992), *J. Comp. Neurol.*, 316, 147.)
Bipolar Cells

Bipolar cell types in the primate retina:
- DB - diffuse types
- MB - midget types
- BB - blue cone type
- GBB - giant bistriated type
- RB - rod bipolar
Amacrine Cells
Ganglion cells

Fig. 14.38 Whole mount views of ganglion cells in a Golgi-impregnated preparation of the human retina. (a) P1, P2 and M cells of the fovea and central retina. The three types can be distinguished by the size of their dendritic trees when they occur adjacent to each other: P1 ganglion cells have minute dendritic trees at the fovea, which expand to be no more than a small bouquet of varicosities that measure 9–12 μm in diameter at 3 mm eccentricity; P2 cells have dendritic trees that are about the size of P1 cells; M cells are, on average, three times the size of P2 cells in the extent of their dendritic trees. All three types occur as a and b subtypes depending on the level of their dendritic trees in sublamina a or b of the inner plexiform layer. (b) Ganglion cells of the mid- and far periphery of the retina. All three cell types show a continuation from (a) of increasing size of their dendritic trees at greater eccentricities. P1 cells are rarely encountered past the mid-periphery (10 mm); many in this region have two dendritic heads (circled), others have the normal single head. P1 cells reach a maximum dendritic tree size of 25 μm; P2 and M cells occur at the far periphery and are clearly distinguishable on the size of their bodies and dendritic trees. Scale bar = 25 μm. (From Kolb, H. et al. (1992); J. Comp. Neurol., 318, 147.)
Mueller Cells
Retinal Pigment Epithelium

**Figure 11.1** Diagram of the subretinal space showing the relationship between the retinal pigment epithelium (RPE), the outer and inner segments of the photoreceptors, the outer limiting membrane (OLM), Bruch's membrane, and the choriocapillaries. The asterisk denotes the subretinal space. (From Steinberg RH, Linsenmeier RA, Griff ER. *Vision Res* 23:1315, 1983.)

**Figure 11.4** Model of mammalian retinal pigment epithelium (RPE) ion transport mechanisms. The retinal membrane incorporates an active Na⁺/K⁺ pump, a K⁺ channel, Na⁺/2HCO₃⁻ cotransport system, an Na⁺/K⁺/2Cl⁻ cotransport system, a Cl⁻/HCO₃⁻ exchange mechanism, and an Na⁺/water/lactate cotransport mechanism. The choroidal membrane incorporates a K⁺ channel, a Cl⁻ channel, and a Cl⁻/HCO₃⁻ exchange mechanism. There are yet uncharacterized efflux mechanisms for Na⁺, HCO₃⁻, lactate, and water across the choroidal membrane. This model shows the intracellular concentrations of the major ions in mammalian RPE cells. Also shown are the transepithelial potential (TEP) and the transepithelial electrical resistance across the epithelium. (Modified from Hughes RA, Gallese RP, Miller SS. Transport mechanisms in the retinal pigment epithelium. In Marmor MF, Wolfensberger TJ [eds]: *The retinal pigment epithelium: function and disease*, New York, 1998, Oxford University Press.)
Structure of Neural retina
Summary of Retinal Processing

![Diagram of retinal processing showing voltage responses of major types of neurons in the tiger salamander retina to 500-nm light steps of dim, moderate, and high intensities. Rods are about two to three log units more sensitive to the 500-nm light than the cones are. The bipolar cells are separated into four classes: the rod-dominated depolarizing bipolar cell (DRBC), and the hyperpolarizing bipolar cell (HRBC), and the cone-dominated depolarizing bipolar cell (DBRC) and the hyperpolarizing bipolar cell (HBC). Ganglion cells are divided into three main types: the ON-center, OFF-center, and ON-OFF ganglion cells (ON GC, OFF GC, and ON-OFF GC). AC, ON-OFF amacrine cells; HC, horizontal cell.]

*Figure 15-1* Voltage responses of major types of neurons in the tiger salamander retina to 500-nm light steps of dim, moderate, and high intensities. Rods are about two to three log units more sensitive to the 500-nm light than the cones are. The bipolar cells are separated into four classes: the rod-dominated depolarizing bipolar cell (DRBC), and the hyperpolarizing bipolar cell (HRBC), and the cone-dominated depolarizing bipolar cell (DBRC) and the hyperpolarizing bipolar cell (HBC). Ganglion cells are divided into three main types: the ON-center, OFF-center, and ON-OFF ganglion cells (ON GC, OFF GC, and ON-OFF GC). AC, ON-OFF amacrine cells; HC, horizontal cell.
Luminance vs. Illuminance

<table>
<thead>
<tr>
<th>Term</th>
<th>Symbol</th>
<th>Defining Equation</th>
<th>Applications</th>
<th>SI Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminous Flux</td>
<td>( P )</td>
<td>( P = K \int F(\lambda)\lambda d\lambda )</td>
<td>Specification of the total quantity of light emitted from a source.</td>
<td>lumen (lm)</td>
</tr>
<tr>
<td>Luminous Intensity</td>
<td>( I )</td>
<td>( I = \frac{dP}{d\Omega} )</td>
<td>Specification of the total quantity of light emitted by a point source, in a given solid angle.</td>
<td>candela (cd) (lumen/steradian)</td>
</tr>
<tr>
<td>Illuminance</td>
<td>( E )</td>
<td>( E = \frac{dP}{dA} )</td>
<td>Specification of density of light incident on a surface or in a given plane.</td>
<td>lumen/m² (lux)</td>
</tr>
<tr>
<td>Luminance</td>
<td>( L_e )</td>
<td>( L_e = \frac{dI}{dA_e \cos \theta} )</td>
<td>Specification of the amount of light emitted or reflected from an extended source in a given direction.</td>
<td>cd/m² (ntl)</td>
</tr>
</tbody>
</table>

- \( K \) is the maximum spectral luminous efficacy
- \( F(\lambda) \) is the radial flux at specific wavelength
- \( d\Omega \) is the solid angle (in steradian) of the source
- \( A_e \) is the surface area of the receiving element
- \( A_s \) is the surface area of the source (in m²)
- \( \theta \) is the angle between the given direction and the normal to the emitting surface
Light Units used in Clinical Electrophysiology

- Cd/m² are used to define sources
- Retinal illuminance is then calculated
  - Troland (E) is a unit of retinal illuminance
  - 1 troland of illumination occurs when a 1 cd/m² source is incident on a 1 mm² pupil
  - \( E = L A \)
    - \( E \) – trolands (cd/m²-mm²)
    - \( L \) – luminance in cd/m²
    - \( A \) – area in mm²
Scotopic and Photopic

![Diagram showing Scotopic and Photopic visual functions and luminance levels.](image)
Temporal Resolution

• It takes 40-50 ms for a light flash to be processed by the retina (i.e. response seen in optic nerve, dependent of light intensity, object size, and image eccentricity.

• If the rate at which light changes is fast enough, we perceive it as continuous. If the rate is too slow, we see the flicker. The slowest rate at which it appears continuous is the critical flicker fusion.
Temporal Summation
Ferry-Porter Law

- \( \text{CFF} = a \log L + b \)

Fig. 7. CFF at the fovea over a range of retinal illuminance (photon = troland) of the test field, showing conformity of the Ferry-Porter Law over four logarithmic units.
FP law limits

- FP Holds for bright to moderate light intensity (cone vision) independent of wavelength
- In low light, response is variable due to scotopic wavelength

Fig. 8. CFF of 19 degree test field over a range of retinal illuminance (photon = troland) for different monochromatic lights of different wavelengths.
CFF Effect of Size
CFF effect of eccentricity
Summary of retinal function

- Eye is a sphere that rotates in a “socket” under control of the oculomotor system
- Eye gaze focuses the image of interest on the fovea, the central part of primate retina that has the highest acuity vision. The fovea is only 1 degree of visual field
- Eye gaze can be redirected by excitation of peripheral retina
- Retina varies from fovea to periphery in accordance with the function of the region
- Cones detect color vision, daytime and well lit conditions
- Rods detect low vision
- Rod system trades sensitivity for acuity
# Eye Disease Prevalence

**General Population**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>30</td>
</tr>
<tr>
<td>AMD</td>
<td>8</td>
</tr>
<tr>
<td>Glaucoma (diagnosed + suspected)</td>
<td>10</td>
</tr>
<tr>
<td>Serious Refractive Error</td>
<td>9</td>
</tr>
</tbody>
</table>

(From *Br. J. Medicine* 1998)
Cataract: A “Socioeconomic” Disease?

- Due to the high success rate and great safety of cataract surgery in developed countries, cataracts are much less of a health problem today than a few decades ago. Of course, it is still a major health problem in less developed countries.
- Much of this progress is due to advances in microsurgery.
- Because of this success though, I will not focus on further needs in this area.
10 Year Longitudinal Prevalence
65 and older

• Diabetic Retinopathy – increase from 6.9 to 17.4%
• POAG – increase from 4.6 to 13.8%
• AMD – increase from 5.0 to 27.1%
• Subjects with at least 1 of the 3 – increase from 13.4 to 45.4%
The Needs: AMD

- It is estimated that over 15 million people in the USA are affected – similar number in Europe and elsewhere.
- 6 million experience some vision loss. Another 9 million are presymptomatic but show some signs (e.g., drusen) upon careful examination.
- AMD is the leading cause of blindness for people 55 or older in industrialized countries.
- 76 million baby boomers approaching 55 will cause an AMD “epidemic” in next 25 years.

(August 13, 2003)
Age-Related Macular Degeneration

New Cases of AMD Anticipated

<table>
<thead>
<tr>
<th>TEN YEAR INTERVAL</th>
<th>Choroidal Neovascularization (millions)</th>
<th>Geographic Atrophy (millions)</th>
<th>Pre-Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2010</td>
<td>2.48</td>
<td>2.50</td>
<td>21.3</td>
</tr>
<tr>
<td>2011-2020</td>
<td>3.14</td>
<td>3.20</td>
<td>28.2</td>
</tr>
<tr>
<td>2021-2030</td>
<td>3.90</td>
<td>4.00</td>
<td>35.0</td>
</tr>
</tbody>
</table>

Based upon U.S. Census Projection Data and using an incidence rate of 0.67 new cases of CNV per 100 people per year and a similar incidence of Geographic Atrophy.
The Needs: RP and JMD

The Retinitis Pigmentosa family and Juvenile Macular Degeneration grouping of diseases are:

a. Chronic, life long disease
b. Most are early age onset (<21 yrs of age)
c. This leaves many otherwise health people visually impaired for most of their life
d. Over 200,000 affected by RP/JMD and allied diseases in the US, proportionally comparable numbers around the word

These are “Orphan Diseases” for which no effective treatments are available.
Average Age of Diagnosis for Retinitis Pigmentosa and Allied Degenerative Disease

- 0-20 years
- 21-60 years
- 61-80+ years
The Needs:
Social Considerations

• After cancer, Americans most fear blindness.
• One of the main features of the world’s population has been a considerable increase in the absolute and relative numbers of older people. This phenomenon is called “population aging”. By 2020, more than 1,000 million people over 60 will be living in the world.
• Living longer offers unprecedented opportunities for personal and socially fulfilling lives but it also presents individual and societal challenges related to quality of life in old age, including independence, social interaction and health care.

(WHO Fact Sheet # 135)
FIRST SIGNS OF AMD
Financial Considerations: The Costs of Blindness

• Over 1 million Americans are legally blind – of course, from many causes. 12 million Americans suffer from some irreversible visual impairment. There are about 100,000 blind school children.

• In the USA, blindness and irreversible sight impairment cost an estimated $22.3 billion in direct costs and an additional $16.1 billion in indirect costs/yr.

• By 2030, not only will the population rise but the elderly population is expected to more than double, adding greatly to the problem. Blind seniors: 2015: 1.6M  2030: 2.4M

(Data from the National Eye Institute and the National Alliance for Eye and Vision Research)
The Costs of Blindness

Of course, improvements in drug discovery and microtechnological applications will not help all blind people –

However, it is estimated that if only 20,000 people were helped, the cost saving would be about $4 billion over a 20 year period.
Retinitis Pigmentosa
Age-Related Macular Degeneration