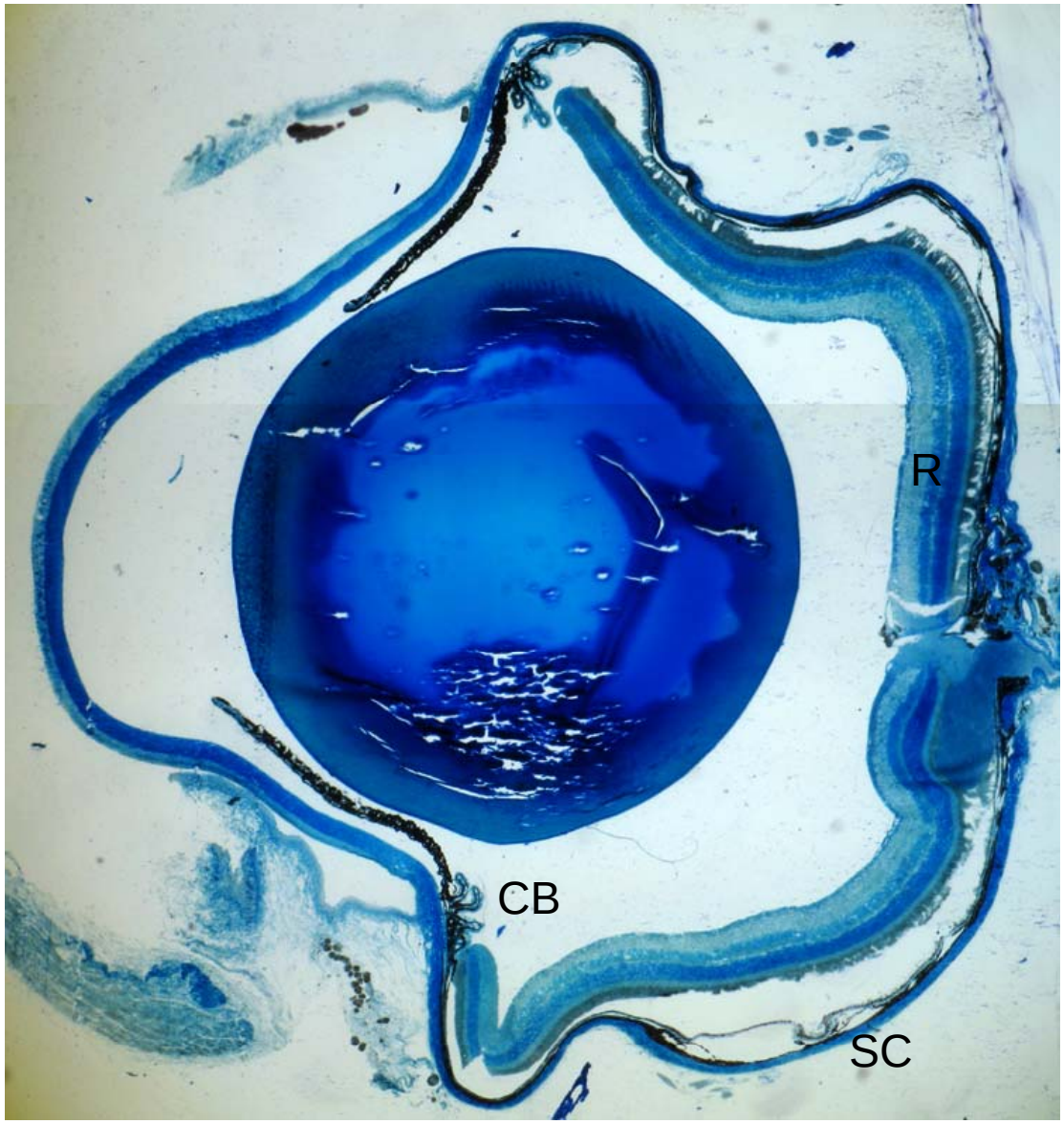
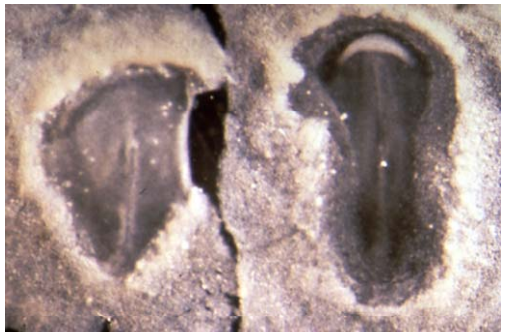
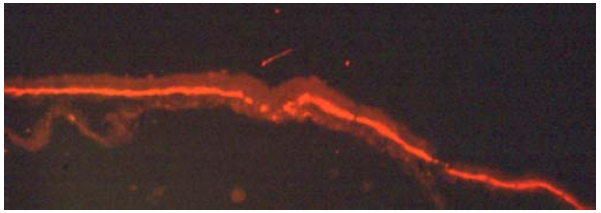
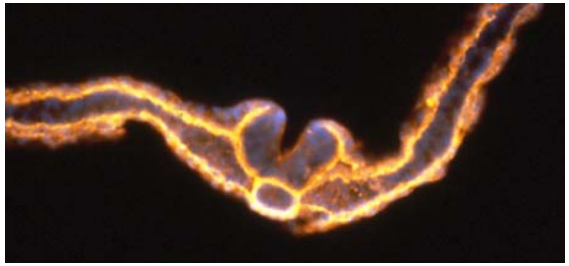
Eye histology



The 3 germ layers

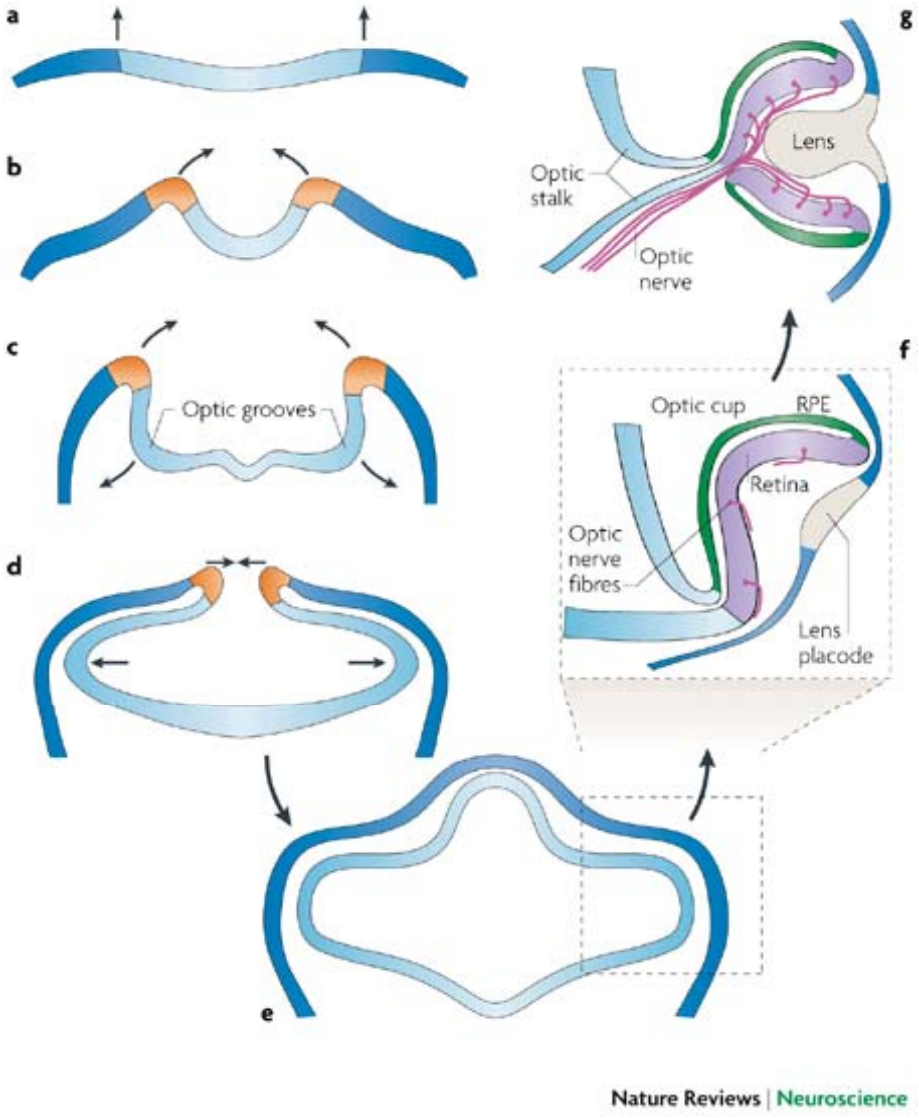
Ectoderm: epidermis, nervous system, retina, pigment epithelium, lens,
Corneal epithelium
Mesoderm: cartilage, bone, dermis; sclera, choroid, vasculature;

Endoderm: inner lining of the gut, and internal organs

Epithelium: Continuous layer of cells; cell-cell contact; no space between cells; basement membrane; retina

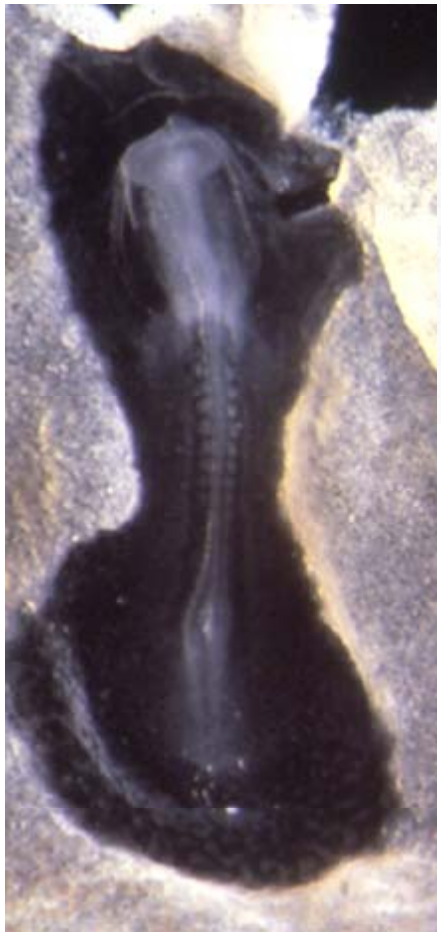
Mesenchyme: embryonic connective tissue; few cells, mostly fibroblastic
Lots of ECM, mostly collagen I; sclera

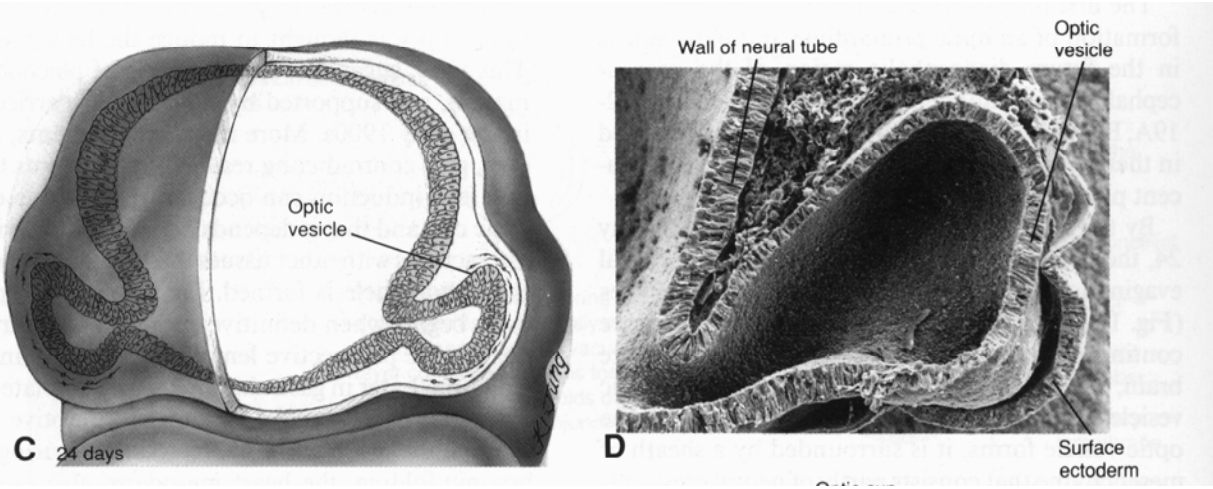
Early eye development



- **a** | The neural plate is the starting point for the development of the vertebrate eye cup. **b** | The neural plate folds upwards and inwards. **c** | The optic grooves evaginate. **d** | The lips of the neural folds approach each other and the optic vesicles bulge outwards. **e** | After the lips have sealed the neural tube is pinched off. At this stage the forebrain grows upwards and the optic vesicles continue to balloon outwards: they contact the surface ectoderm and induce the lens placode. **f** | The optic vesicle now invaginates, so that the future retina is apposed to the future retinal pigment epithelium (RPE), and the ventricular space that was between them disappears. Developing retinal ganglion cells send axons out across the retinal surface. The surface ectoderm at the lens placode begins to form the lens pit. This section is midline in the right eye, through the choroid fissure, so only the upper region of the retina and the RPE are visible. **g** | The eye cup grows circumferentially, eventually sealing over the choroidal fissure and enclosing the axons of the optic nerve (as well as the hyaloid/retinal vessels; not shown). The ectodermal tissue continues to differentiate and eventually forms the lens.

Early stages of eye formation from the fore brain





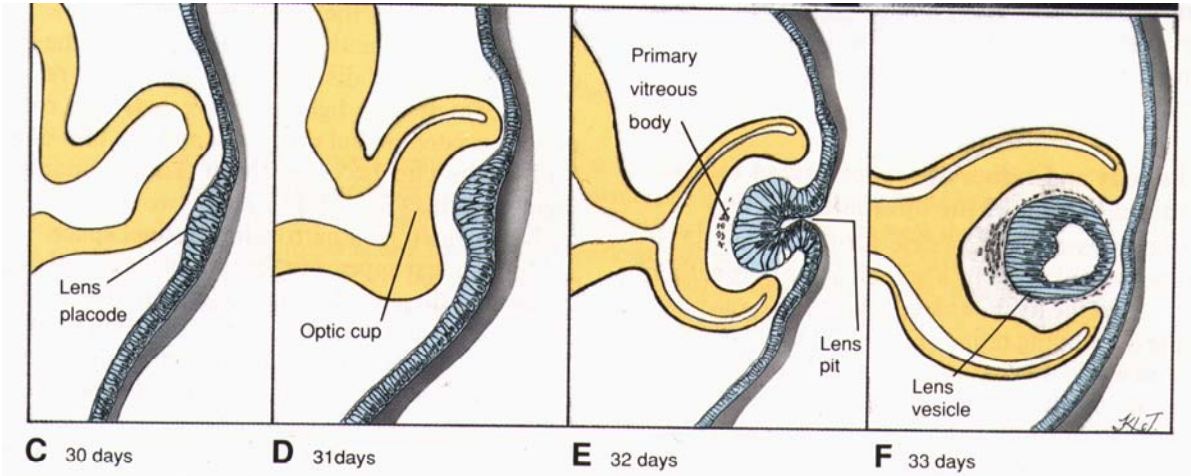
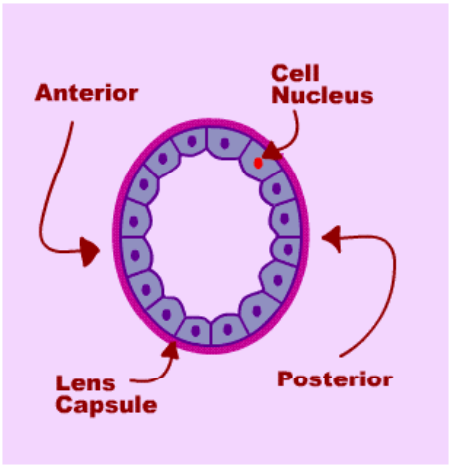
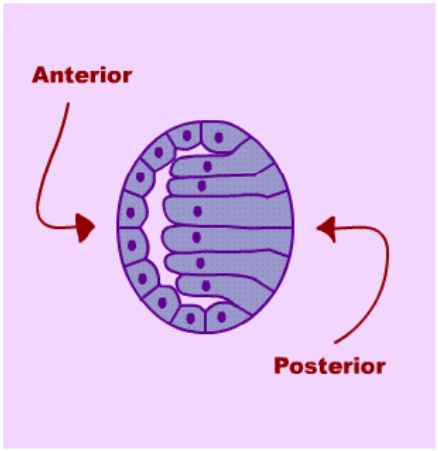
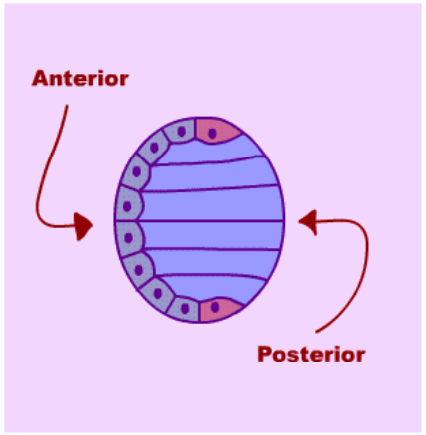
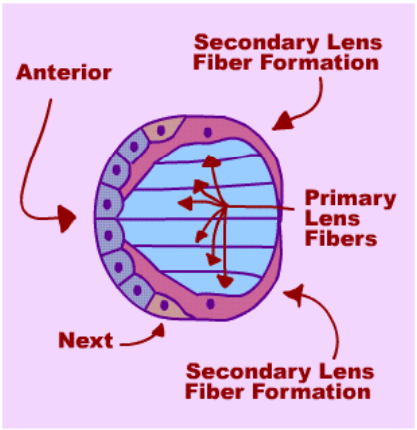


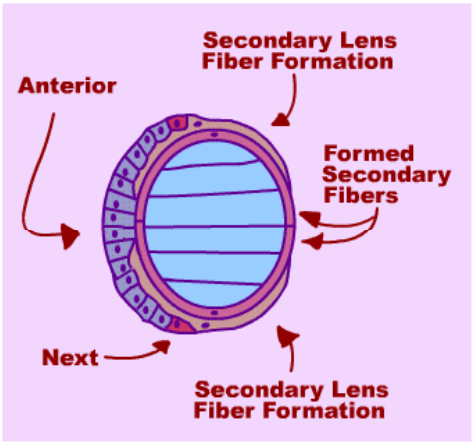
Fig. 12-20. Formation of the lens placode and lens vesicle. Contact with the optic cup is necessary for the maintenance and development of the lens placode, although other influences are apparently more important in its induction. **(A–E)** During the 5th week, the lens placode begins to invaginate to form the lens pit (arrow in Fig. B). **(E, F)** The invaginating lens placode pinches off to form a lens vesicle enclosed in the optic cup. (Fig. A photo courtesy of Dr. Arthur Tamarin.)

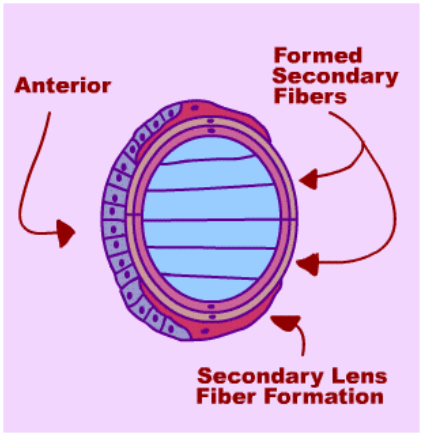

Anterior
Cell Nucleus
Lens Capsule
Posterior

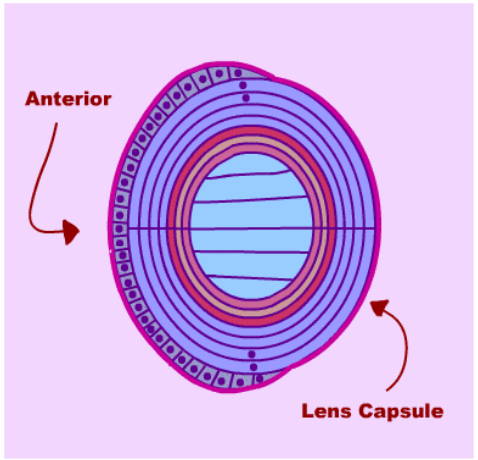

Anterior
Posterior


Anterior
Posterior

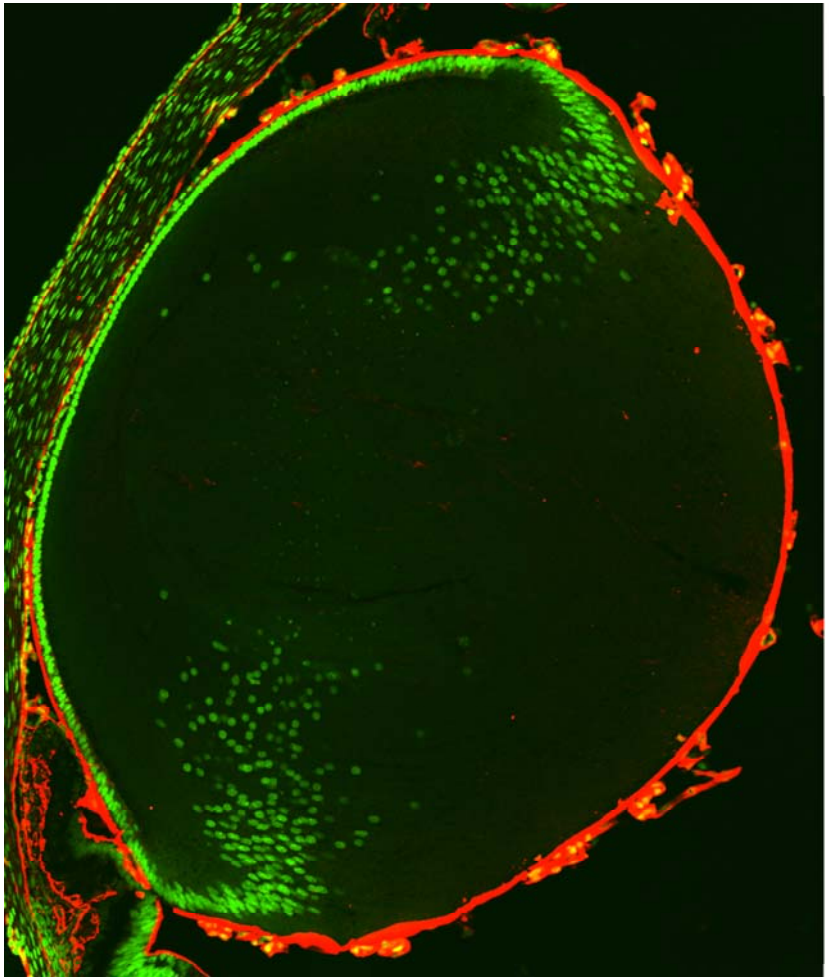

Secondary Lens Fiber Formation
Anterior
Primary Lens Fibers
Next
Secondary Lens Fiber Formation


Secondary Lens Fiber Formation
Anterior
Formed Secondary Fibers
Next
Secondary Lens Fiber Formation

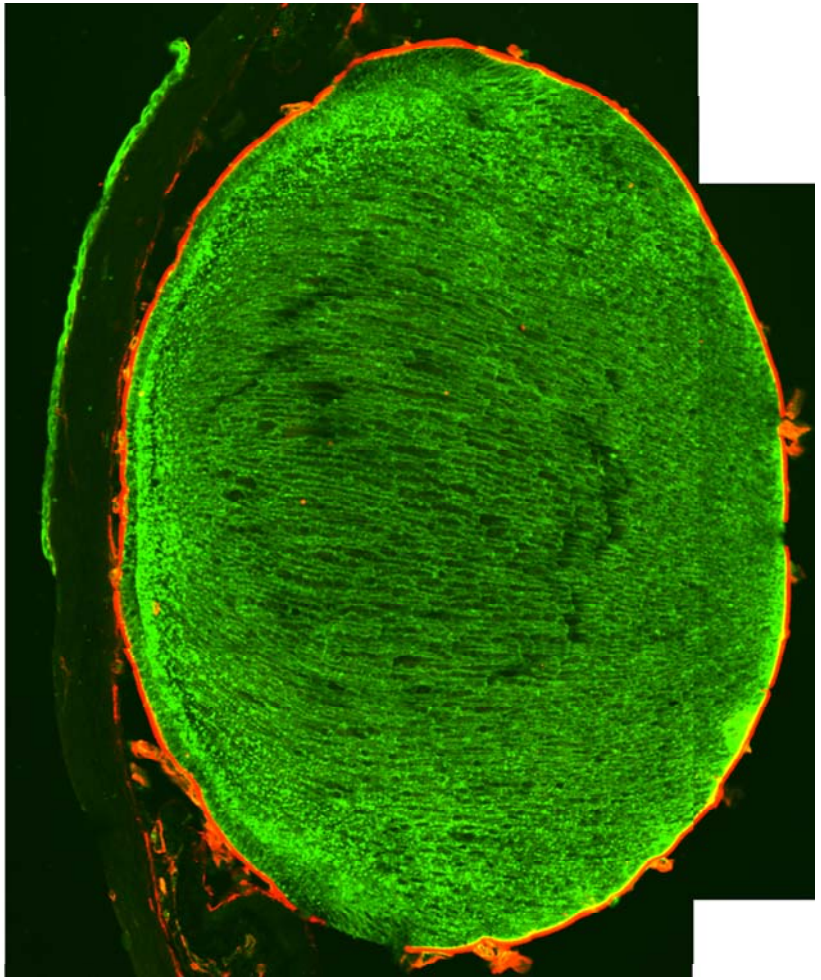

Anterior
Formed Secondary Fibers
Secondary Lens Fiber Formation


Anterior
Lens Capsule

The lens

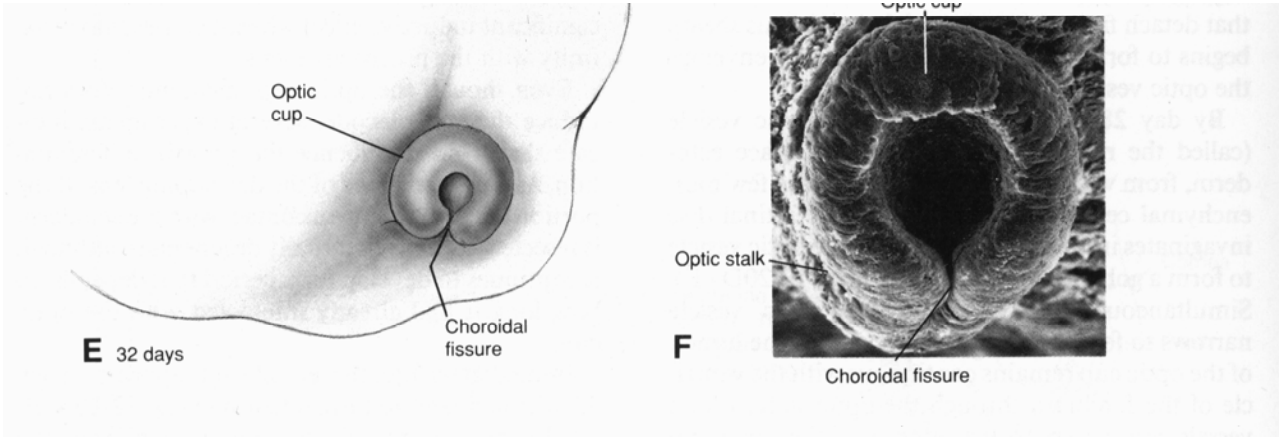


Staining for nuclei



Staining for lens fibers

Optic fissure, asymmetry of the eye cup, hyaloid vasculature



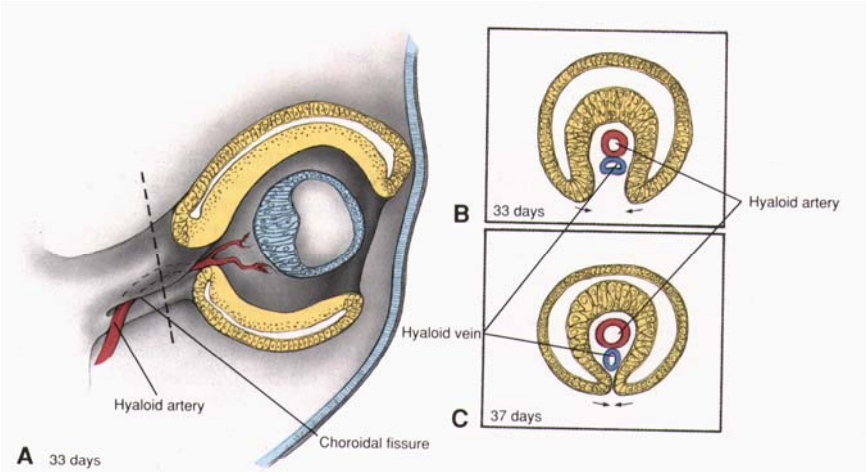
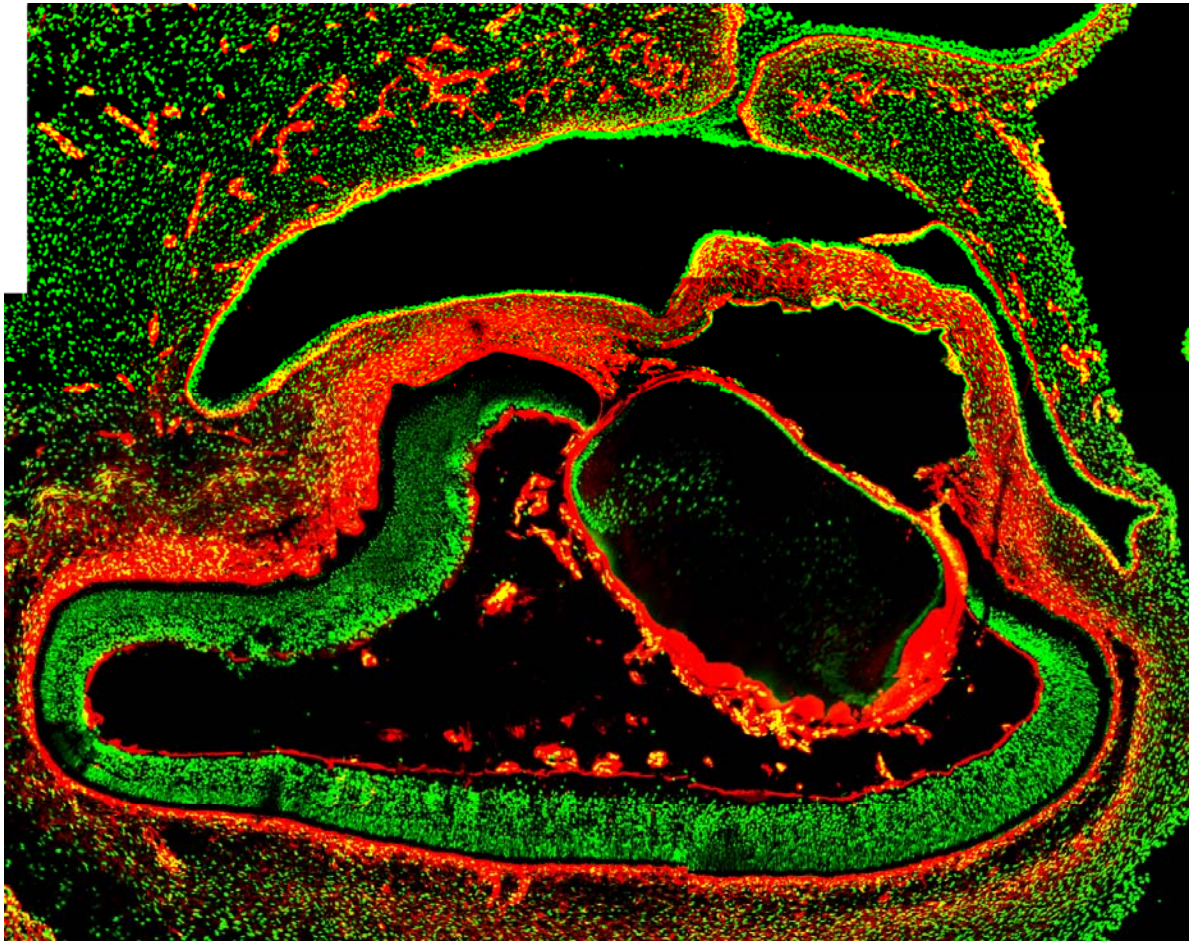
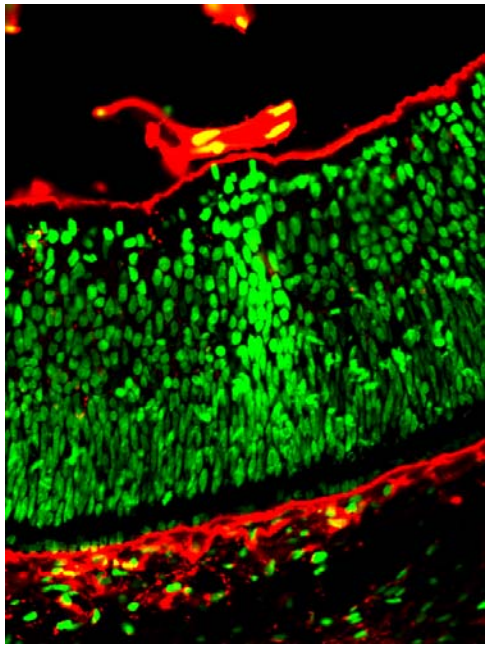


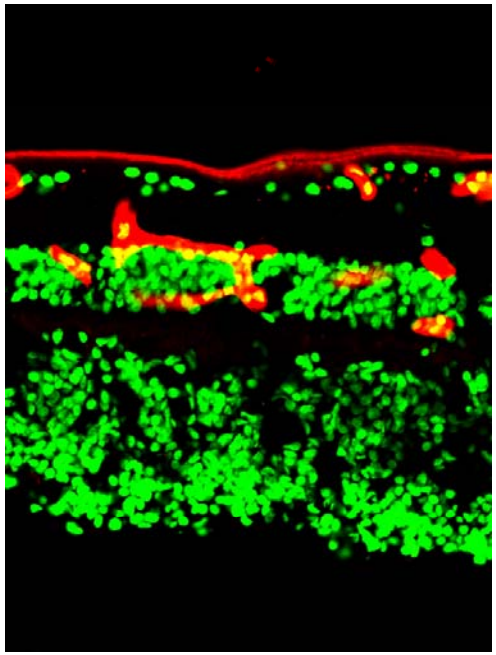
Fig. 12-22. Vascularization of the lens and retina. **(A)** As the lens vesicle detaches from the surface ectoderm, it becomes vascularized by the hyaloid vessels, which gain access to the lens through the choroidal fissure. **(B, C)** During the 7th week the edges of the choroidal fissure fuse together, enclosing the hyaloid artery and vein in the hyaloid canal. When the lens matures, the vessels serving it degenerate, and the hyaloid artery and vein become the central artery and vein of the retina.

Vasculature in the human eye

Fetal 10 weeks







adult

Regulation of eye vasculature by VEGF

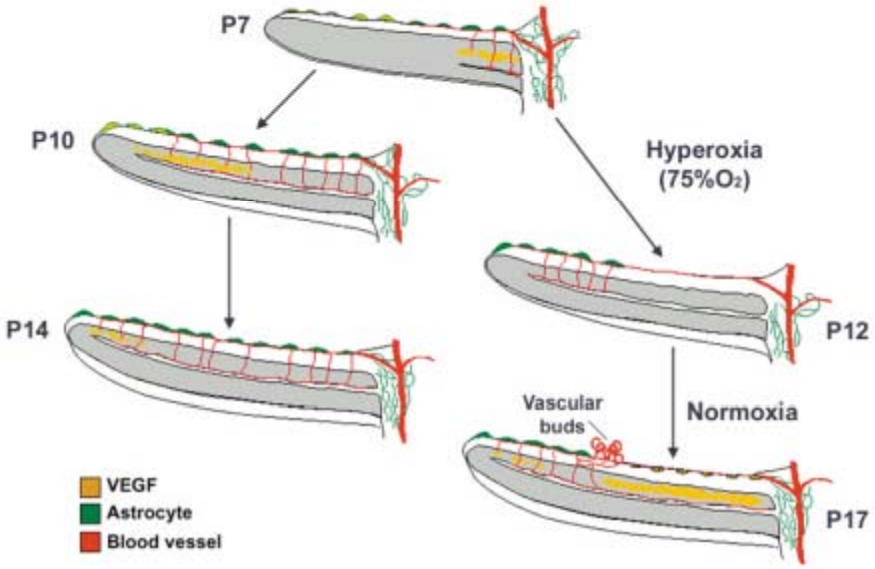


Fig. 3. Mouse model of retinal vascularization and retinopathy of prematurity (adapted from Stone et al., J. Neuroscience, 1995). **(Left)** During retinal development, maturation of the neural retina induces a "physiologic hypoxia". Astrocytes spreading from the optic nerve to the periphery respond to the hypoxia by expressing VEGF, which in turn promotes formation of the superficial vascular network. Subsequently, a second wave of neuronal activation induces VEGF secretion in the inner nuclear layer, leading to the formation of the deep vascular layers of the retina. Once the tissue is vascularized, VEGF expression decreases and the new vessels are remodeled and stabilized. **(Right)** Under hyperoxic conditions, VEGF expression is downregulated before the completion of the normal vascular development, leading to the obliteration of the central retinal vessels. Once returned to normoxia, the unperfused tissue becomes highly hypoxic, inducing a strong and uncontrolled secretion of VEGF and the formation of vascular bud invading the vitreous, characteristic of pathological neovascularization.

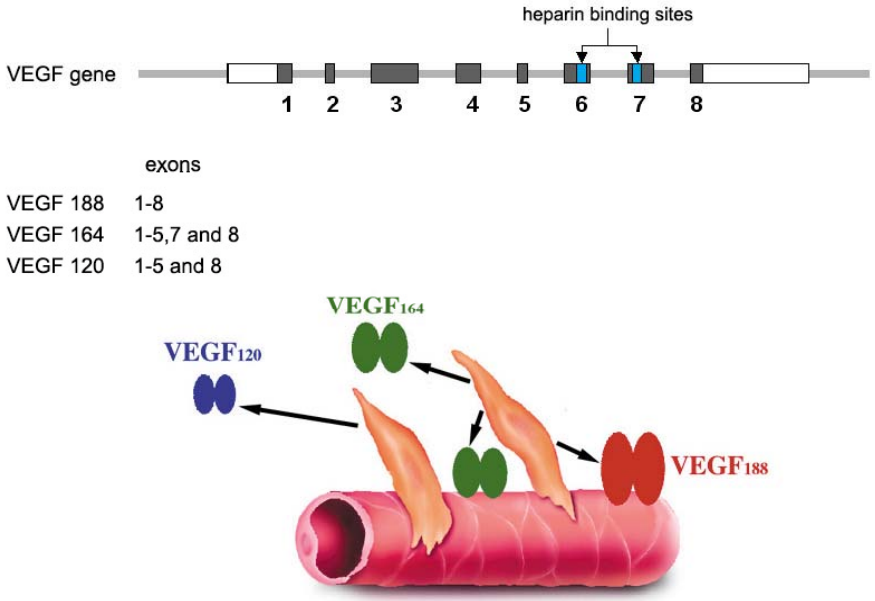
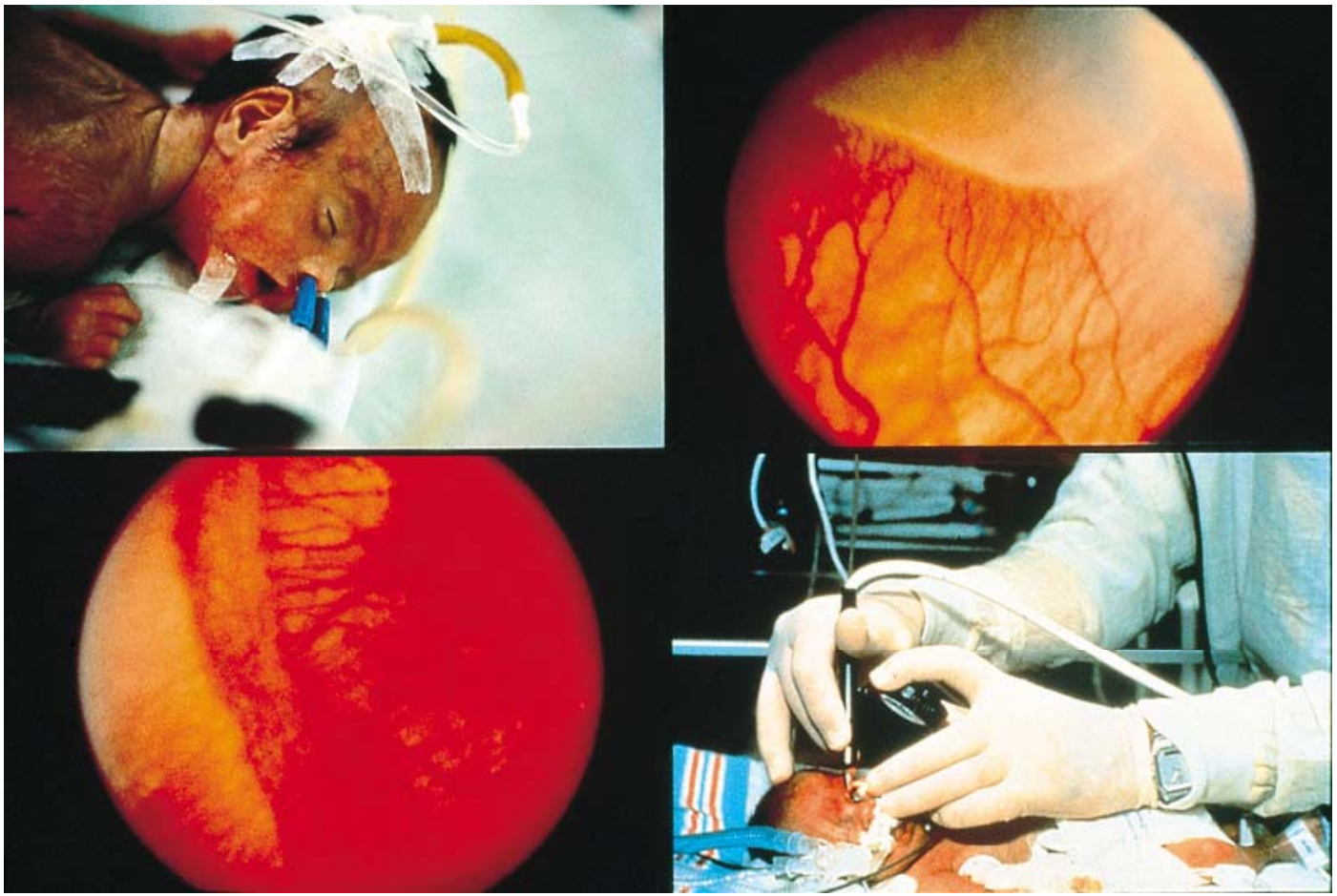
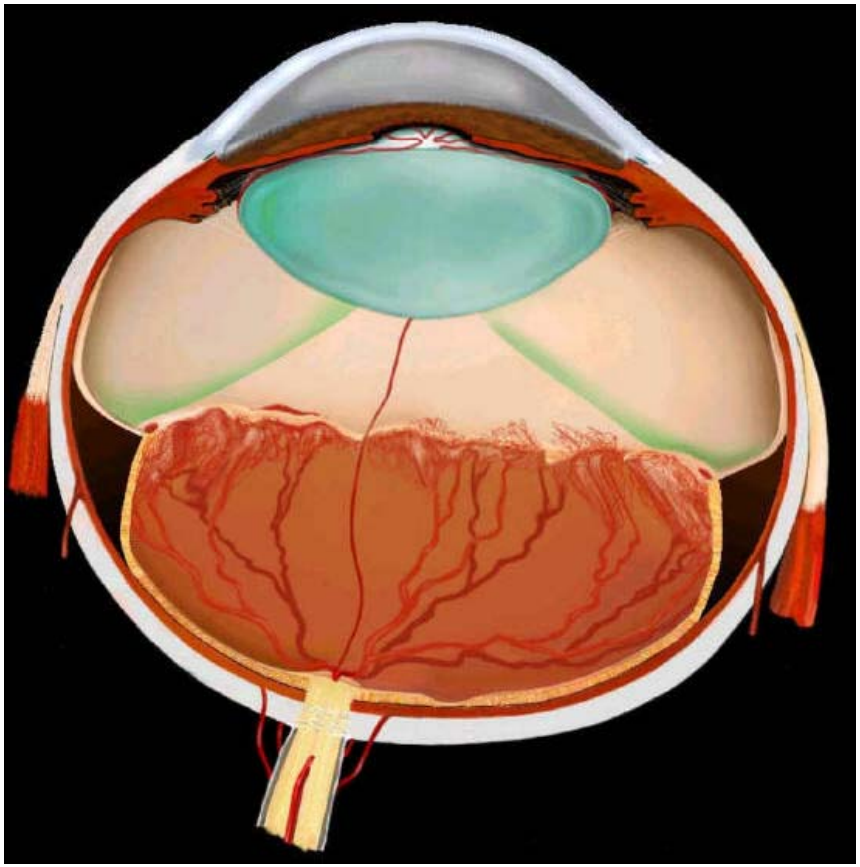


Fig. 2. Structure and extracellular localization of the VEGF isoforms. (A) In mice, as in humans, the different VEGF isoforms are generated by alternative splicing of one single gene. The isoforms differ by the presence or absence of heparin binding domains encoded by exons six and seven. **(B)** The ability of the VEGF isoforms to diffuse into the extracellular space depends on the presence of heparin binding sites. VEGF 120, which does not contain any heparin binding domains, is freely diffusible, whereas VEGF188 remains bound to the surface and/or extracellular matrix of the VEGF-producing cell.

Retinopathy of prematurity



Retinal detachment in ROP



Later eye development

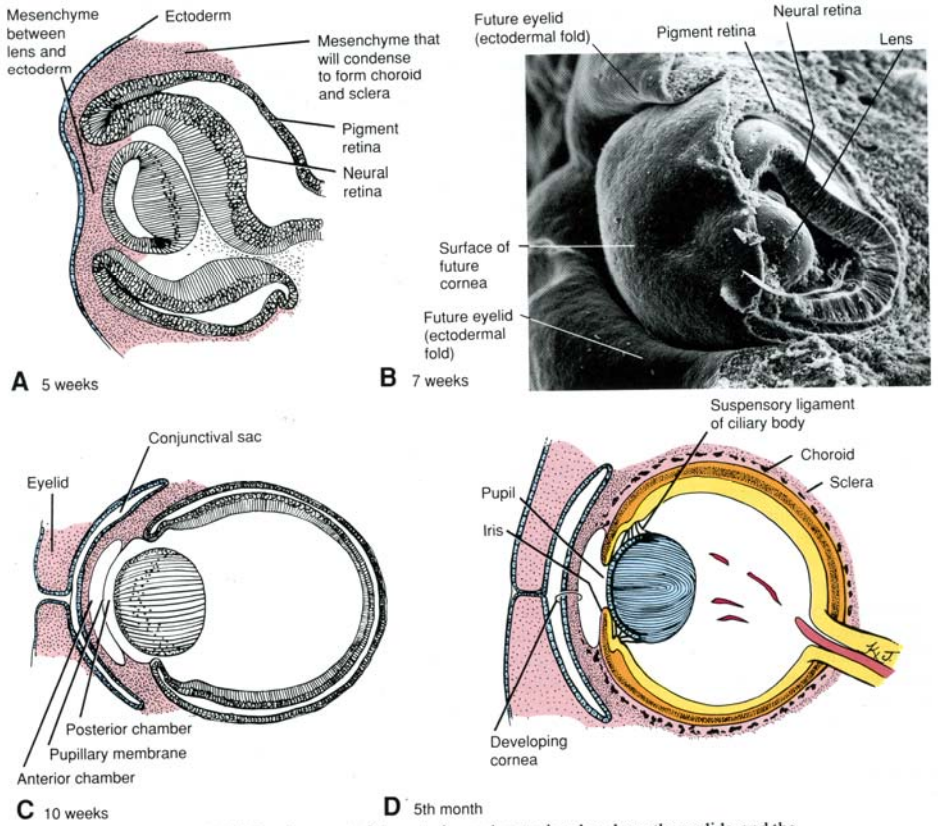
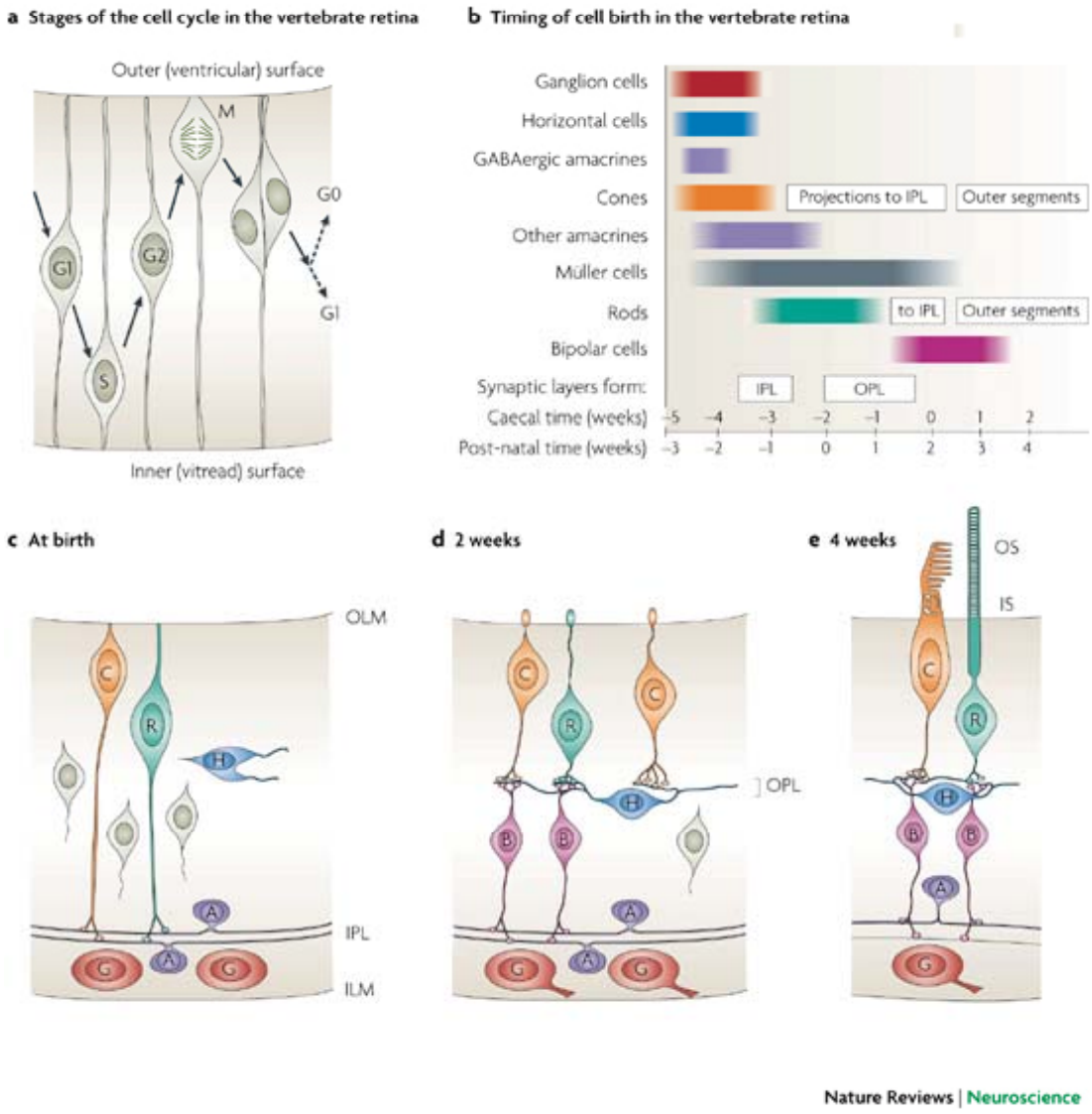


Fig. 12-24. Development of the anterior and posterior chambers, the eyelids, and the coverings of the optic globe. **(A, B)** Mesenchyme surrounds the developing eyeball (optic globe) between the 5th and 7th weeks to form the choroid and sclera. **(C, D)** Vacuolization within this mesenchyme in the 7th week forms the anterior chamber. Shortly thereafter, vacuolization in the layer of mesenchyme immediately anterior to the lens forms the posterior chamber. The pupillary membrane, which initially separates the anterior and posterior chambers, breaks down in early fetal life. The upper and lower eyelids form as folds of surface ectoderm. They fuse together by the end of the 8th week and separate again between the 5th and 7th months.

Retinal development



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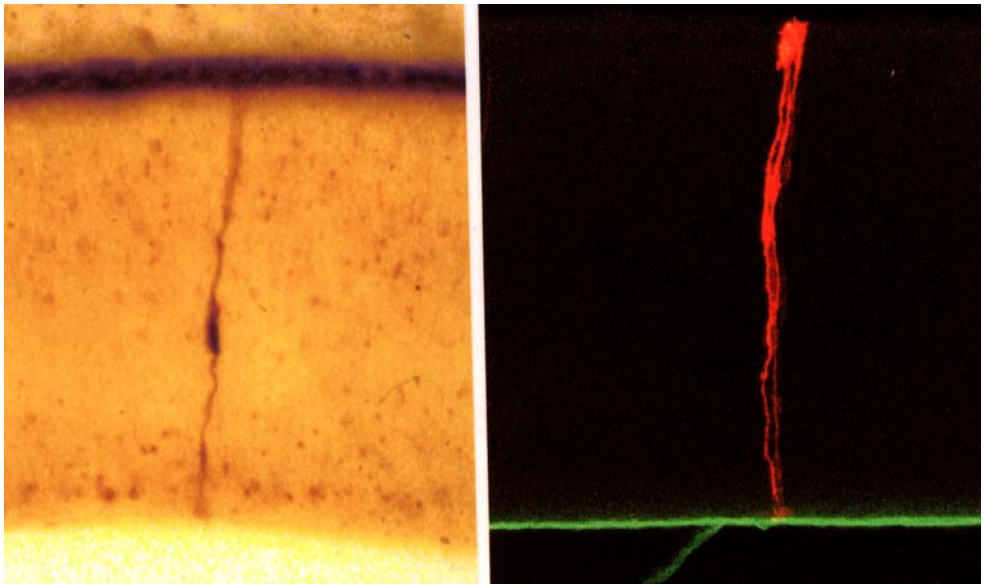
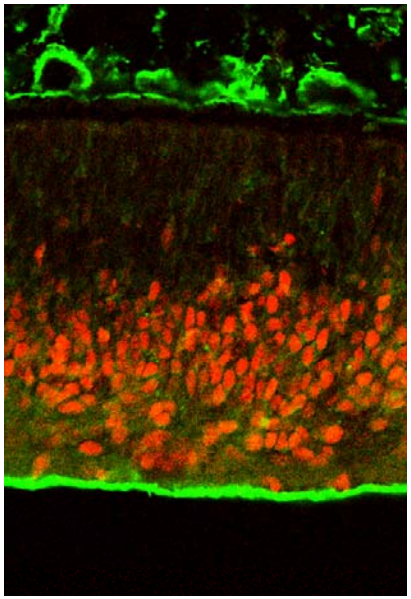
a | The cell cycle in the vertebrate retina. The soma of a replicating cell migrates between the outer (ventricular) surface, where mitosis (M) occurs, and the inner (vitread) surface. **b** | The sequential birth of cell classes in the vertebrate retina, with timings indicated for the ferret in both post-natal weeks and caecal time (that is, the time relative to eye opening), which is probably a better comparator for other species173. **c**–**e** | The maturation of neural connectivity in the retina126, 127, 174 (again, timings are for the ferret). **c** | Initially photoreceptors (which exhibit few adult morphological characteristics) send transient processes to the inner plexiform layer (IPL), where they make synaptic contacts with the two sub-laminae. **d** | Subsequently these processes retract, and developing bipolar cells insert themselves into the pathway between the photoreceptors and the inner nuclear layer (INL). **e** | At a later stage, the rod and cone photoreceptors develop inner segments (IS) and outer segments (OS). A, amacrine cell; B, bipolar cell; C, cone photoreceptor cell; G, ganglion cell; H, horizontal cell; ILM, inner limiting membrane; OLM, outer limiting membrane; OPL, outer plexiform layer; R, rod photoreceptor cell.

Retinal histogenesis



Neuroepithelial cells

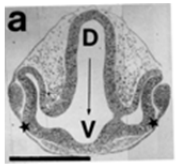


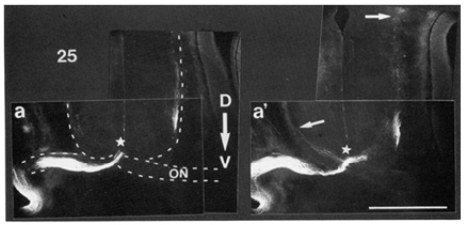
Ganglion cells

Ganglion cell axon navigation in the retina and optic nerve

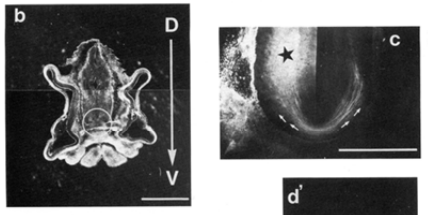
Retina

Optic chiasm

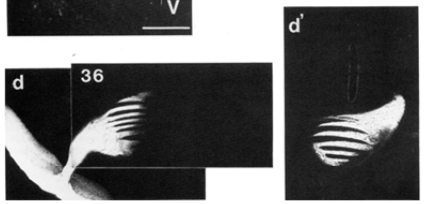




Chick, E4, 5



Chick, E4.5



Chick E8

Stem cells and postnatal growth of eyes

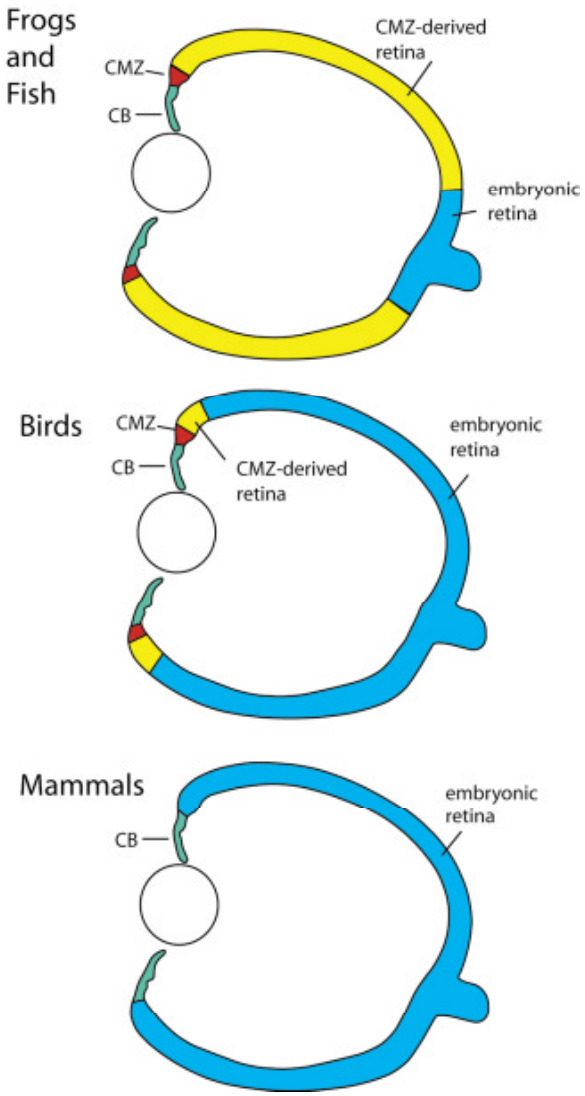
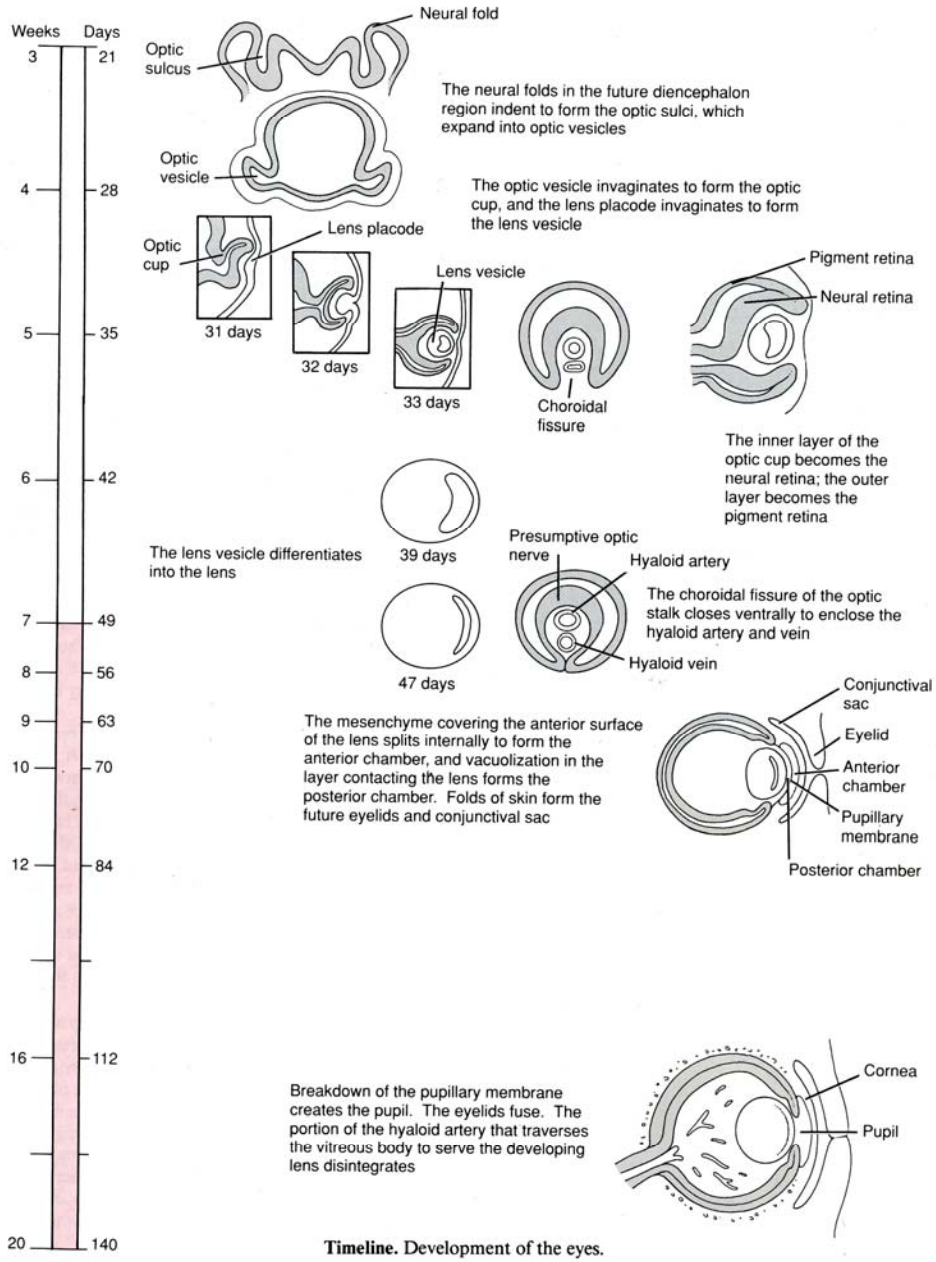


Fig. 4. The relative contribution of the CMZ to retinal growth has been progressively reduced in homeothermic vertebrates and is shown in drawings of adult eyes. The region of retina generated in the embryonic/ neonatal period is shown in blue, while that generated by the CMZ is shown in yellow for the various vertebrate classes. The CMZ itself is indicated in red to show the relationship to the ciliary body (CB) colored green.



Timeline. Development of the eyes.

Induction of the lens by the optic vesicle

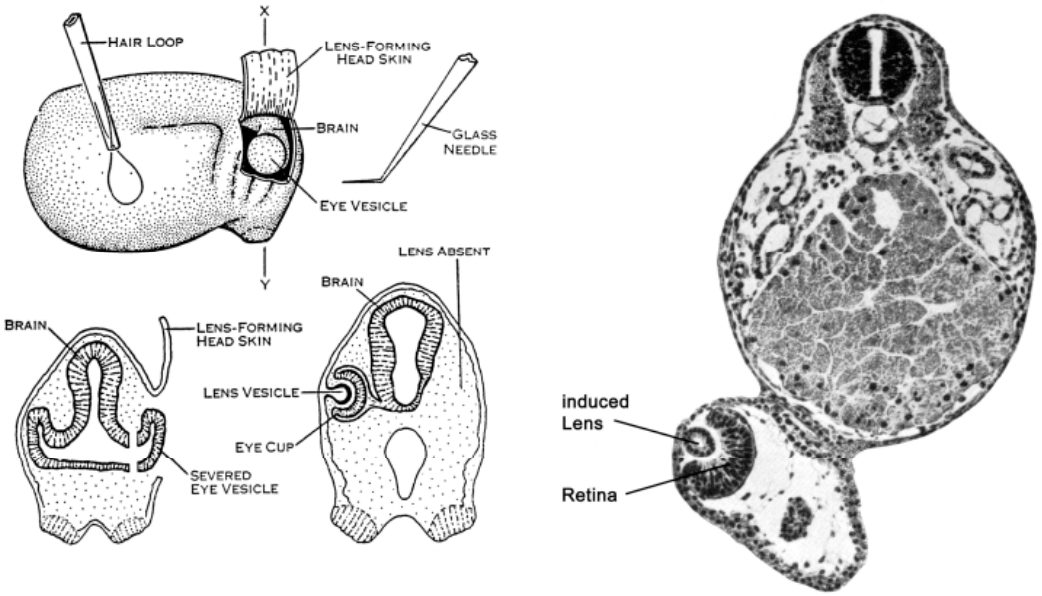
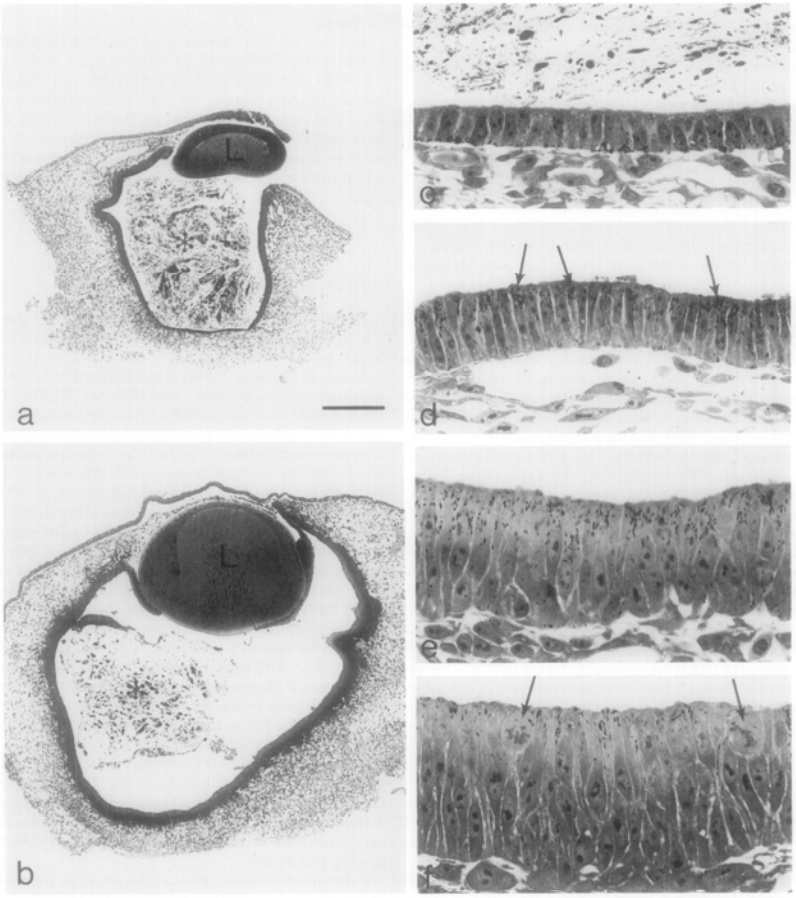
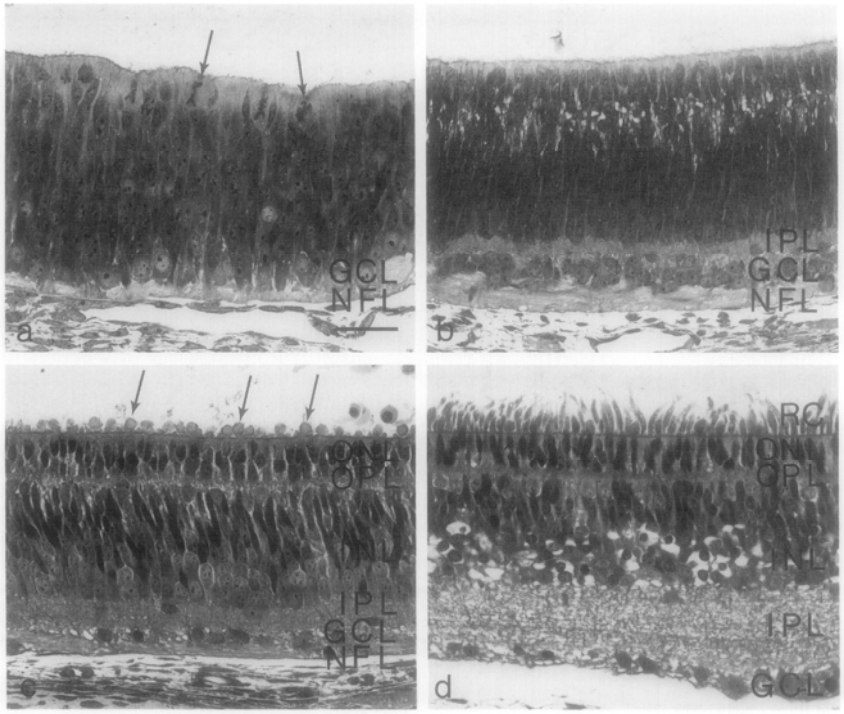


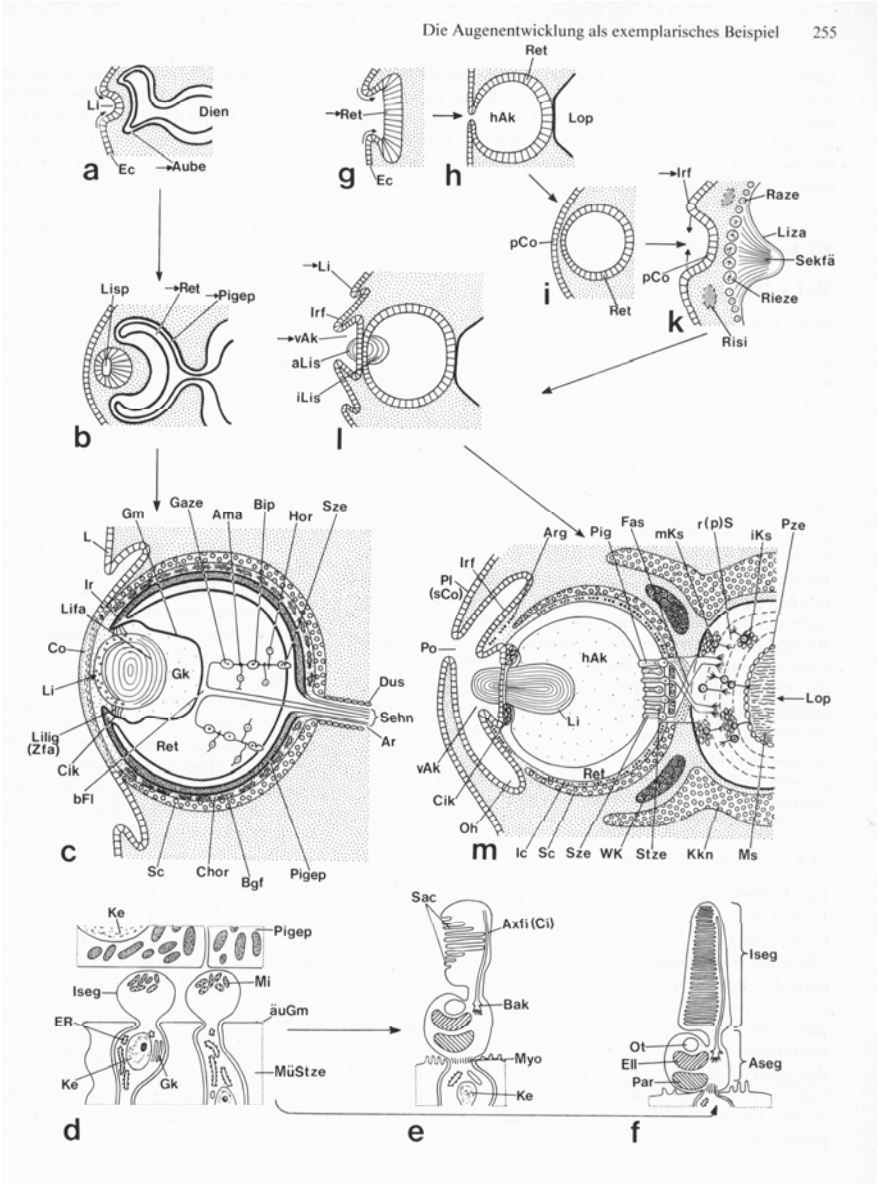
Fig. 1. (A) Exstirpation of the eye vesicle in an amphibian embryo leading to the absence of both the eye cup and the lens (after Hamburger, 1988). **(B)** Section across a Triturus taeniatus larva with a transplanted eye cup, which has induced an ectopic lens in the flank of the larva (after Spemann, 1936).

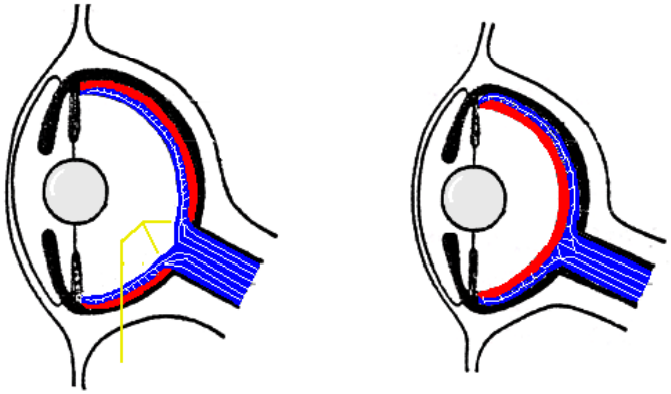
Transdifferentiation of the pigment epithelium into neural retina



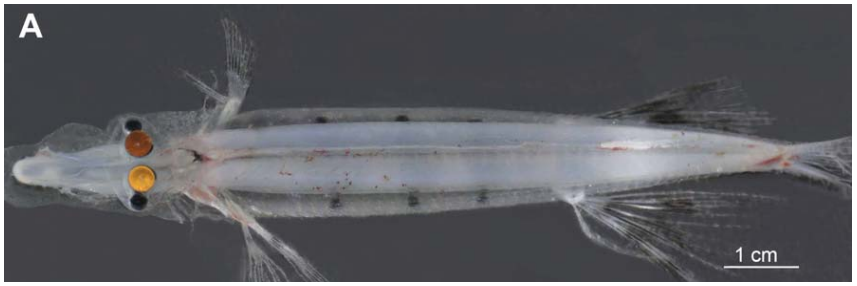


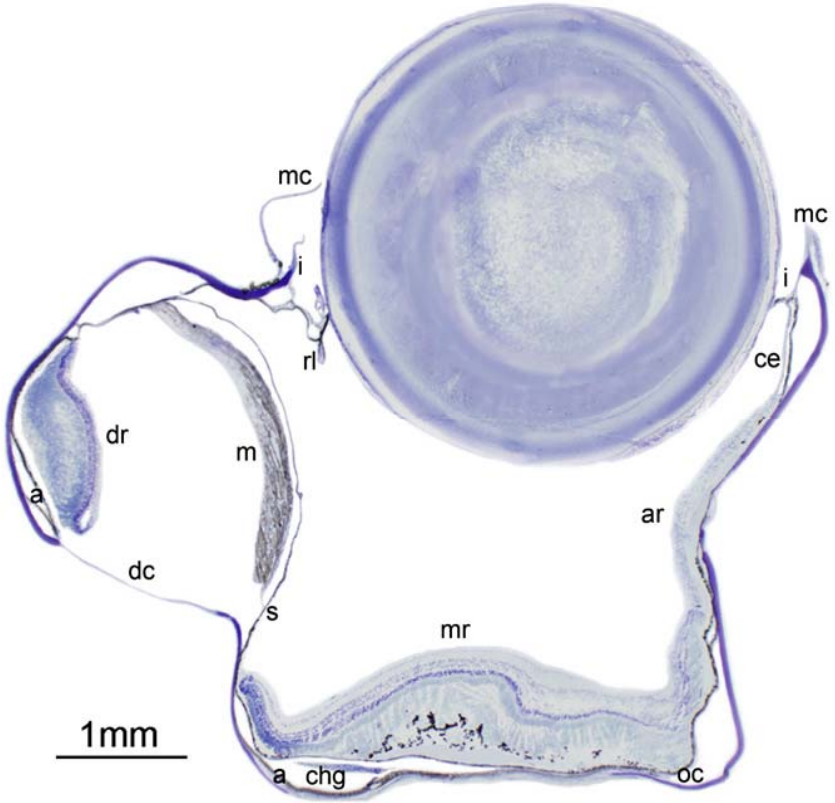
Eye formation in vertebrates and cephalopodes (squid, octopus)

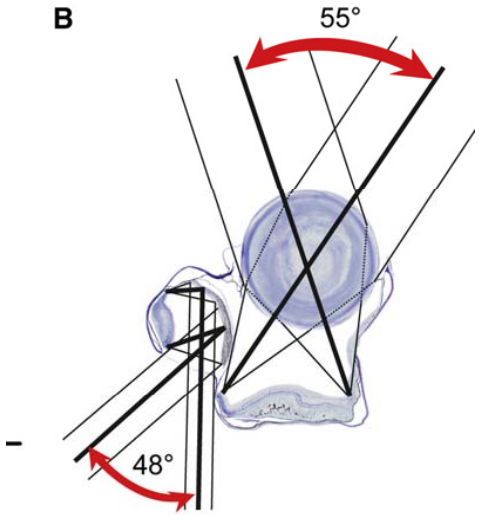


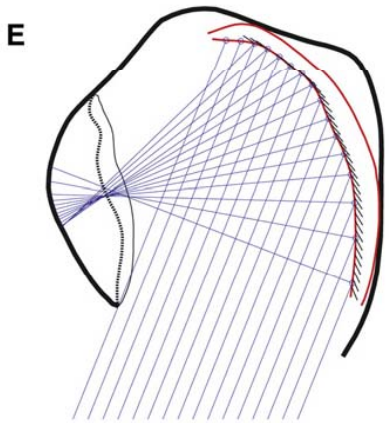


A strange eye from a fish



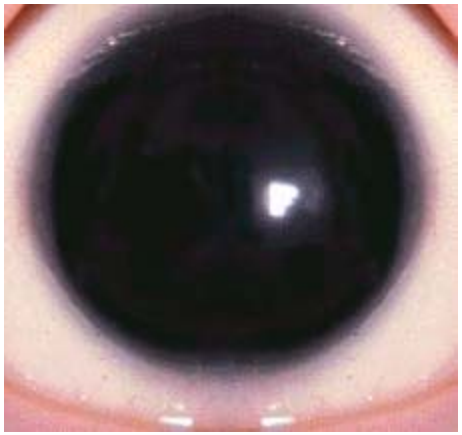




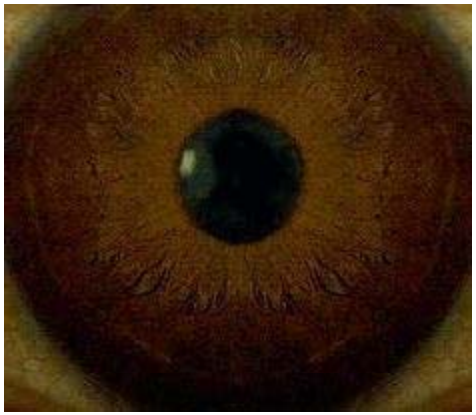


Identification of Pax6 as a gene important for eye development

Aniridia

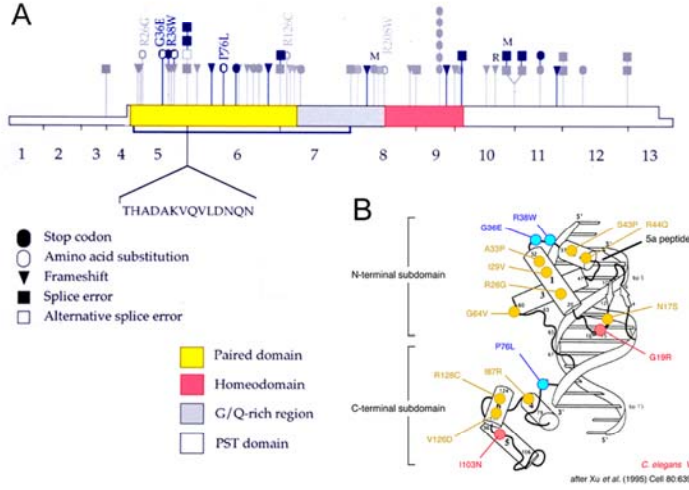


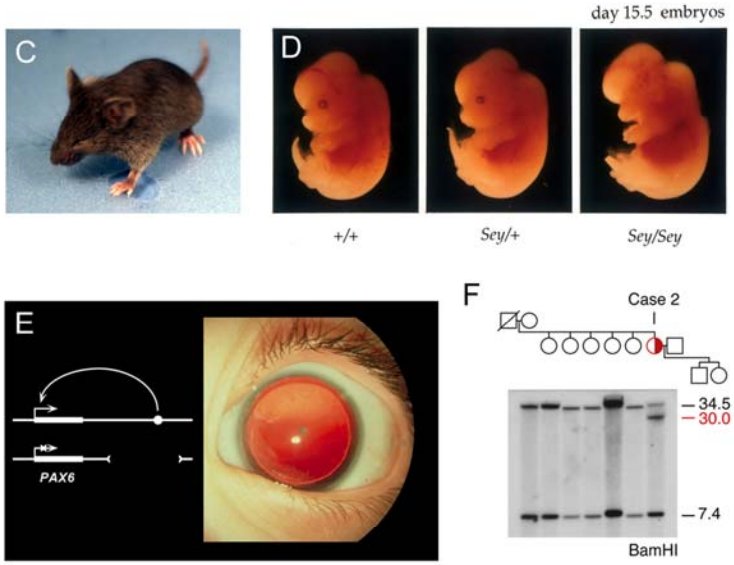
Control



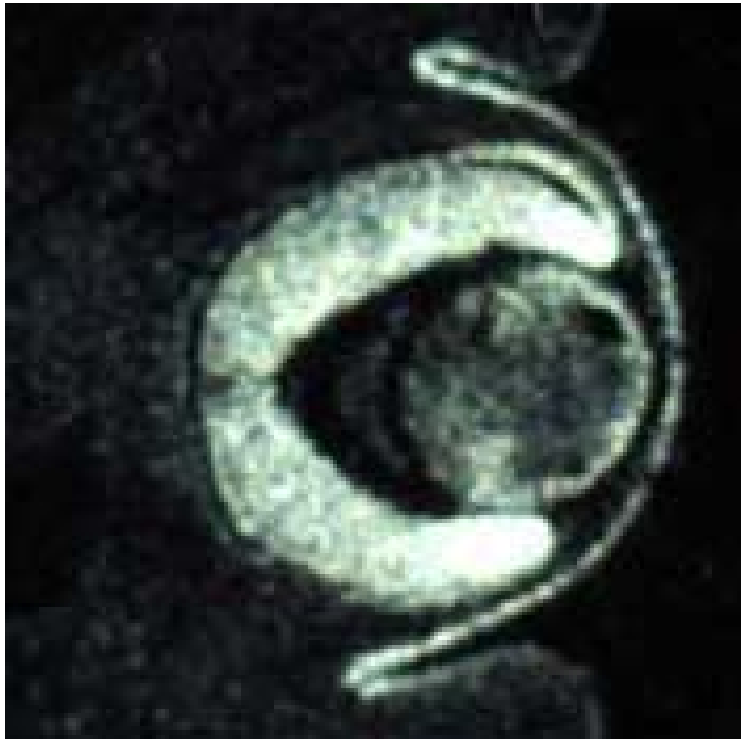
Pax6

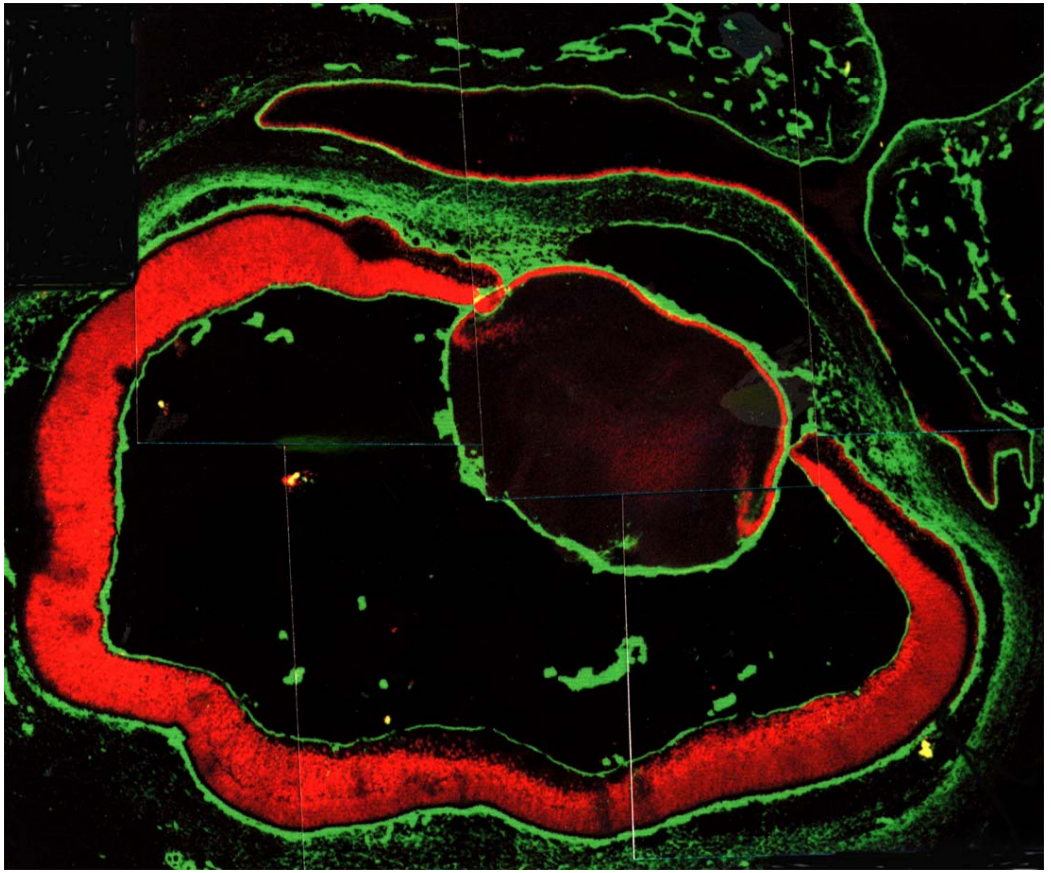
sey



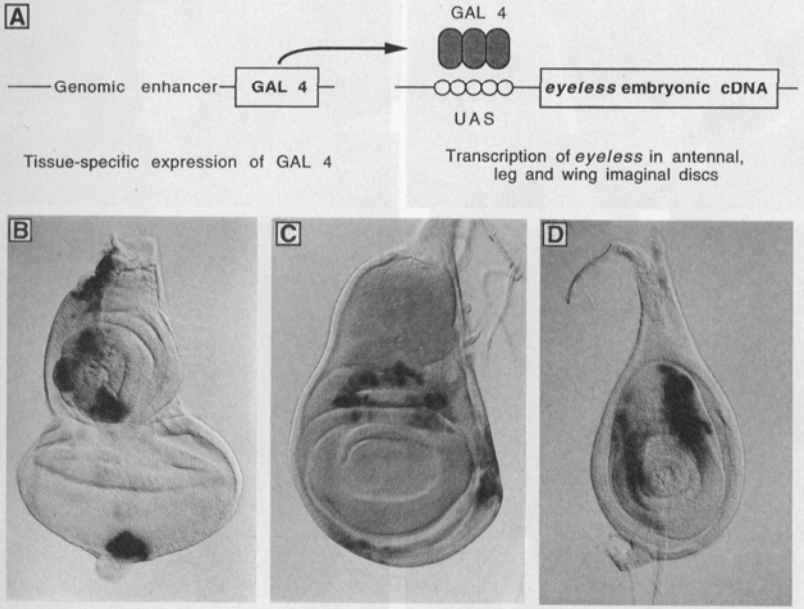


Distribution of Pax6 mRNA and protein in developing eyes

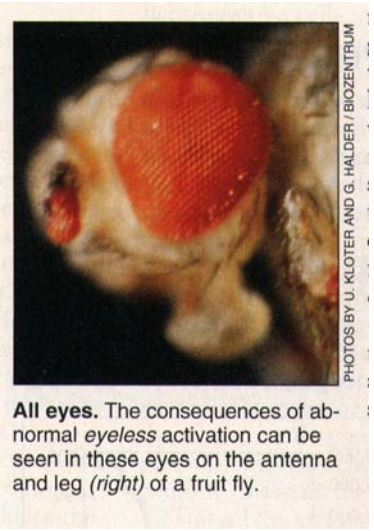




Induction of ectopic eyes by Pax6 mis-expression



g. 1. Targeted expression of *ey*. (**A**) Schematic representation of the ectopic induction of *ey* by means of e GAL4 system. In (B) through (D), β-galactosidase staining of third instar imaginal discs (*28*) shows the tivation of a UAS-*lacZ* reporter construct by the GAL4 enhancer-trap line E132. (**B**) Eye-antennal disc. e antennal portion of the disc is on the top and the eye portion is on the bottom. β-Galactosidase activity detected in parts of the antennal disc corresponding to several antennal segments and in the periphery the disc; which will give rise to head cuticle. The staining observed at the most posterior part of the eye c derives from the optic nerve. (**C**) Wing imaginal disc. β-Galactosidase activity is detected in proximal gions of the future wing blade, and in portions corresponding to the hinge regions and ventral pleura. (**D**) g imaginal disc with *lacZ* expression in portions that correspond to the tibia and femur.



All eyes. The consequences of abnormal *eyeless* activation can be seen in these eyes on the antenna and leg *(right)* of a fruit fly.

Pax6 as a master control gene for eye formation

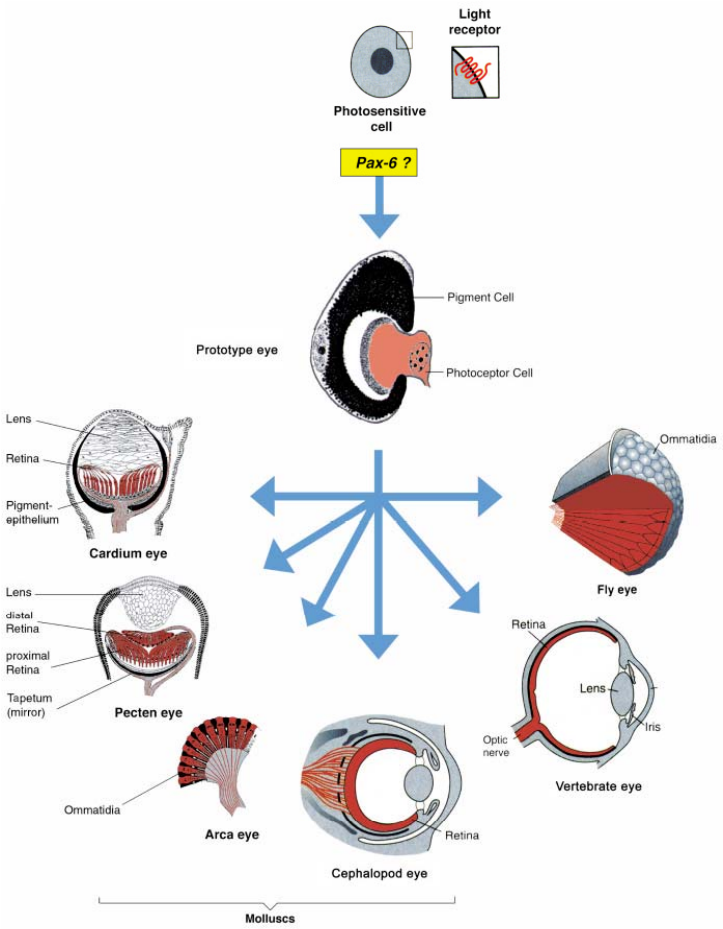
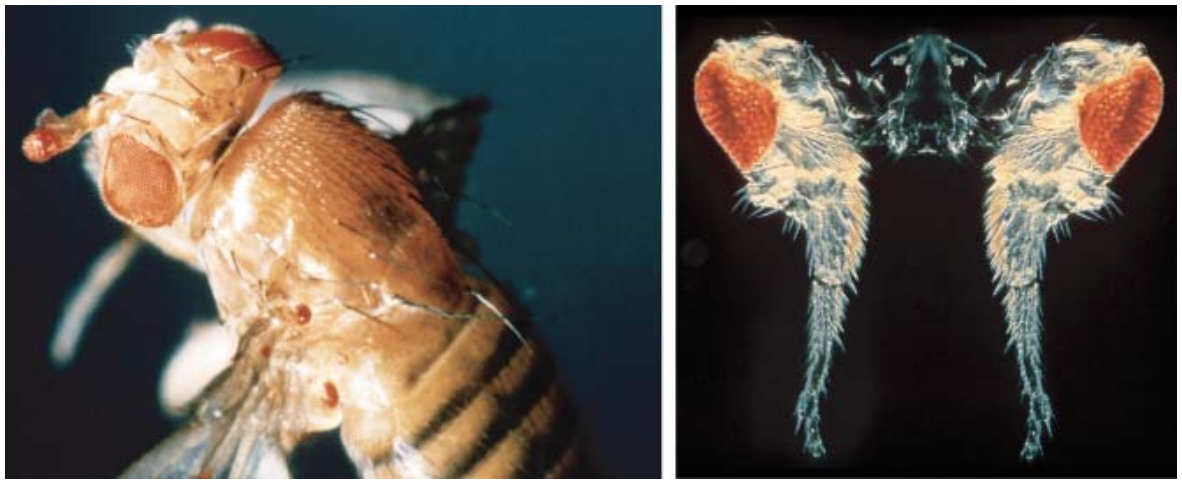


Fig. 5. Hypothetical evolution of photosensitive cells containing rhodopsin as a light receptor and monophyletic evolution of the various eye-types starting from a Darwinian prototype eye consisting of a single photoreceptor cell and a pigment cell assembled under the control of Pax 6 (after Gehring and Ikeo, 1999).

Other genes capable of inducing ectopic eyes



Twin of eyeless, toy

Fig. 2. (A) Induction of ectopic eyes by targeted expression of the eyeless gene on the antenna and wing of Drosophila . **(B)** Induction of ectopic eyes on the legs of Drosophila by targeted expression of the twin of eyeless gene.

Gene family	*Drosophila* genes	Human genes
PAX6	*eyeless, twin of eyeless* *eyegone, twin of eyegone*	*PAX6*
SIX	*sine oculis* *Optix* *Dsix4*	*SIX1, SIX2* *SIX3, SIX6* *SIX4, SIX5*
EYA	*eyes absent*	*EYA1-4*
DACH	*dachshund*	*DACH1-3*