Embryogenesis: fertilized ovum, morula, blastula. Trophoblast forms placenta. Epi and hypoblast form the three primary germ layers during the phase of gastrulation day 14: The embryonic mesoblast consists of neuroectoderm, mesoderm and endoderm. The neural plate is composed of neuroectoderm and faces the amniotic cavity. The mesoderm is interposed between ectoderm and endoderm. The endoderm faces the yolk sac.

The neural plate shows axial folds separated by a groove on day 17 after conception parallel to the primitive axial skeleton (notochord) which for the first time gives the embryo a head to tail orientation. The neuroepithelium shows polarity, i.e., the apex is up and the cell base is down. The neural folds become further elevated until they fuse to form the neural tube on day 22. This fusion results in a polar orientation of the neuroepithelium which has the cell apex in and the cell base out.

Organogenesis of the eye: Optic pits first appear as evaginations of the forebrain (prosencephalon) on day 23. The optic vesicle is fully developed on day 25 (3mm stage). In the optic vesicle the cell apices point toward the lumen of the vesicle and the cell bases point to the outside towards the surface ectoderm.

As the optic cup forms on day 27 (5-7mm stage) related to invagination and obliteration of the vesicle cavity an apex to apex arrangement appears at the margin of the cup for the first time. The invagination is eccentric, i.e. it forms the embryonic fissure. The embryonic fissure is required for the hyaloid artery to gain access to the inner eye and for the axons of the ganglion cells to get out of the eye. One might say that as the optic cup moves away from the brain, the axons have to find a short way back to the brain. The embryonic fissure closes on day 33 (12-13mm stage).

The embryonic fissure is located inferonasally and closes at the anterior margin (the future equator) first. With the closure of the embryonic fissure the basic structure of the eye is established.

Faulty closure results in:

Coloboma

Three facts are required to understand the formation of colobomas:

1) The lips of the optic cup at the embryonic fissure consist of both inner and outer neuroepithelium. One is destined to become retina and the other destined to become pigment epithelium. If the border of these tissues is not exactly at the margin of the closing fissure and an "eversion" of the inner neuroepithelium exists, then the pigment epithelium is not going to fuse (since laterally displaced) and a pigment epithelial dehiscence will result.

2) The inner neuroepithelium fuses, however it is only the inner neuroblastic layer of the inner neuroepithelium that stays fused and bridges the coloboma.

3) Since choroidal development depends on induction by pigment epithelium, the defect is going to be pigment epithelial and choroidal. The outer retina depends on nutrition by both pigment epithelium and choroid. The neuroepithelium bridging such colobomas is going to be more atrophic and gliotic because it has the retinal vascular supply as only source of nutrition. As the malformation ages malnutrition and mechanical stretch set
the stage for hole formation in the intercalary membrane and point of reversal and related schisis-like rhegmatogenous retinal detachment.

**Development of Selected Ocular Tissues:**

**Neurosensory retina:**
4th week: inner marginal and outer primitive neuroectoderm
6th week: inner and outer neuroblastic layer separated by transient layer of Chievitz
6th week: Ganglion cell processes
3rd month: **inner neuroblastic layer** forms ganglion cells, amacrine cells, Muellerian nuclei.
  **outer neuroblastic layer** forms bipolar cells, horizontal cells, nuclei of rods and cones.

**Macular development**
3-8 months: widening of the layer of Chievitz
6th month: thickening of the fovea
At term: foveal depression, ganglion cells in center form one layer
4 months after birth: lateral displacement of 1st and 2nd neuron(and Muellerian glia), central increase in cones

**Retinal pigment epithelium:**
5th week: melanization starts at posterior pole. Complete in one week.

**Optic nerve**
7th week: hyaloid artery in, axons out of optic cup, through the primitive papilla

**Lens**
Derived from surface ectoderm at the 7 mm stage: pit, cup, vesicle.
If separation fails at the 10mm stage or is incomplete it represents Peter’s Anomaly

**Peter’s Anomaly**
Lens is adherent to cornea, there is a posterior corneal defect (endothelium, corneal stroma, Bowman’s) with termination of Descemet’s membrane where the lens is adherent to cornea (Internal ulcer of von Hippel). A central corneal opacity=leukoma, lens stalk and “top hat” lens shape may be present.

**Vitreous**
Vitreous components, 3-fold origin:
Lens (surface ectoderm), retina (neuroectoderm) and vascular endothelium (mesoderm).
**Primary** vitreous <6 weeks (<13mm): "Cellular"
**Secondary** vitreous <8 weeks (13-65mm): "Vascular"
Hyaloid vessels, collagen fibrils (Mueller cell footplates) and hyaluronic acid (neuroectodermal). More fibrils and hyaluronic acid.
**Tertiary** vitreous at >12 weeks (>65mm): Zonules and Marginal Bundle of Druault=future vitreous base.

**Persistent Hyperplastic Primary Vitreous (PHPV)**
Fetal Vasculature persists anteriorly: tunica vasculosa lenti, exaggerated Mittendorf’s dot and posteriorly: Cloquet’s canal, Bergmeister’s papilla. Retinal vascularization may
be deficient. Vascularization proceeds from the disc and, where absent, determines the 
zone of involvement
The tertiary vitreous (zonules) does not form properly, therefore the pars plicata does not 
separate from the lens equator resulting in so called “traction” on or elongation of the 
ciliary processes.

Developing Bloodvessels
The dorsal ophthalmic artery gives off the ventral ophthalmic artery, hyaloid artery, 
annular vessel and tunica vasculosa lentis. In adulthood, ophthalmic artery, temporal 
long posterior ciliary artery (T) short posterior ciliary arteries and central retinal artery 
can be traced to the dorsal ophthalmic artery.
The ventral ophthalmic artery develops into the nasal long posterior ciliary artery 
(N). 
Retinal vascular system: Formation of branch retinal arteries from the papilla at 4 
months. Completion of retinal vascularization at 8 months.

Uvea
1-2 months: capillary channels, "primitive" choroid=surface vascularization of the CNS. 
3 months: choriocapillaris forms from posterior to anterior. 
5 months: posteriorly: large, medium, choriocapillaris and anteriorly: medium vessels, 
choriocapillaris. 
Major circle of the iris sends recurrent branches at term. 
Uveal melanization 6-7 months: melanization starts at disc, and continues until after 
birth. (RPE: Melanization 5th week)

Iris
Anterior growth of the neuroepithelium in the third month. The anterior margin of the 
optic cup is called the “ Marginal sinus of von Szily”. It advances on the posterior 
surface of the iris stroma. Pupillary ruff: Marginal sinus of von Szily reaches pupil in the 
4th month and forms the iris sphincter and dilator. 
If it fails to do so, the condition is called Aniridia.

Aniridia
The iris stroma, which preexists and is neural crest derived is variably preserved (iris 
hypoplasia). The iris pigmentepithelium, sphincter and dilator are neuroectodermally 
derived and are absent. This may be shown on transillumination. The angle may close, 
resulting in glaucoma. There is an association with Wilms tumor. 
Oculocerebrorenal syndrome of Miller: nonfamilial aniridia, Wilms tumor, microcephaly, 
genitourinary anomalies. 
Neural Crest Cells: arise from neuroectoderm at the CREST of the neural folds of 
diencephalic, mesencephalic and rhombencephalic regions (not the forebrain) at the time 
of tube closure. 
Cells migrate cephalad along the dorsum of the embryo to populate the cranial region.

Neuralcrest Migration:
Posterior midbrain, ventral migration: maxillary processes 
Hindbrain, rostral migration: frontal nasal processes.

Neuralcrest derived:
corneal stroma,
endothelium,
sclera,(except superotemporally),
nerve sheath,
uveal stroma,
uveal melanocytes,
ciliary muscle,
orbital bones,
orbital fat,
muscles,
connective tissue.

**Cornea**
6 weeks (18mm stage): epithelium and acellular zones separate from lens vesicle (surface ectoderm). If not, Peter’s anomaly (see above).
Three waves of limbal (neural crest) migration occur directed to the center: endothelium, corneal stroma, iris stroma. If endothelial(Descemets) defect occurs related to incomplete separation of lens: Internal ulcer of von Hippel.

**Sclera:**
condenses anterior to posterior and is formed by neural crest except for superotemporally where it is derived from mesoderm.

**Mesoderm:**
Forms striated muscle fibers,
endothelium of blood vessels,
connective tissue superotemporally.

**Surface ectoderm:**
Forms lacrimal glands,
drainage apparatus,
glands: Moll, Zeis Meibom,
cilia,
surface epithelium,
corneal epithelium,
conjunctival epithelium,
caruncle,
lids.

**Homologues**
Retina = brain
Choroid = leptomeninges
Sclera = dura

**Derivations:**
Retina = neuroectoderm
Choroid = neuralcrest
Sclera = neuralcrest (and mesoderm superotemporally)
Neuroectoderm: iris sphincter and iris dilator.

**Ocular development**
Optic vesicle: Day 25 (5mm)
Invagination: Day 27 (7mm)
Closure of fetal fissure: Day 33 (13mm)
**Age - length (of the embryo) relationships**

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