CHAPTER

1

Anatomical Development of the Eye

EMBRYOLOGY

After fertilization of the ovum, cellular mitosis results in the formation of a ball of 12–15 cells, called the *morula*. A fluid-filled cavity now forms within the morula, termed as *blastocyst*, which embeds itself in the uterine mucosa around 6th day of fertilization. The cells continue to divide and accumulate at one pole. The cells of this 'primitive embryoblast' differentiate into two layers—the 'epiblast' and the 'hypoblast'. These two cellular layers bridge the central cavity, thus dividing the blastocyst into the amniotic sac and the yolk sac.

Division and differentiation continues and the epiblast cells give rise to all three definitive germ layers, viz. 'ectoderm', 'mesoderm' and 'endoderm'. The central ectoderm differentiates to form a columnar 'neural ectoderm'. This forms the neural plate, which later develops into the head and brain.

At about 21 days of gestation, previously formed neural folds from neural groove fuse to form the 'neural tube' in the middle of the embryo. At this time, the first signs of developing eye is seen, called the 'optic pit'. The optic pits are seen as invaginations of neural ectoderm on the inner surface of the anterior neural folds.

As the neural folds elevate and approach each other, a specialized population of mesenchyme cells, the 'neural crest' cells develop. Neural crest cells play an important role in eye development because they are the precursors to major eye

structures including the corneal stroma, ciliary muscles, iris stroma, choroid, sclera, orbital cartilage and bone.

During the development and closure of the neural groove, the mesoderm develops to form 'somites'. These somites give rise to myoblasts which subsequently form the vasculature in and around the eyes.

Unlike trunk and extremities, orbital cartilage, bone and ocular connective tissue are derived from neural crest tissue, not mesoderm. It is important to remember that 'mesenchyme' is a broad term for any embryonic connective tissue, whereas 'mesoderm' specifically relates to embryonic germ layer. Recent embryologic studies have shown that mesoderm plays a relatively small role in the development of face and eyes. With respect to the eyes, most of the mesenchyme tissues come from the neural crest cells. By end of 3 weeks, neural folds progress to form brain vesicles and then segmentation occurs to form specific parts of the brain, i.e. forebrain, midbrain and hindbrain. It is from the forebrain that bilateral 'evaginations' develop to present as 'optic sulci'. Invagination of the optic sulci creates 'optic vesicles'. The transformation of optic sulci into vesicle is considered to occur concurrently with the closure of anterior neural tube, which is completed by 25th day of gestation (3 mm embryo size).

The neural crest cells populate around this vesicle and ultimately give rise to nearly all the connective tissue of the human eyes. The timing and generation of the optic vesicle has a significant role in the induction and size determination of the palpebral aperture and orbital structures.

At around 26 days of gestation, the surface ectoderm that is in contact with the optic vesicle, thickens to form the 'lens placade'. The lens placade then invaginates with the underlying neural ectoderm. The invaginating neural ectoderm folds onto itself, creating a double layer of neural ectoderm, forming the 'optic cup'. The optic cup eventually differentiates into the 'neurosensory retina' (the inner layer) and the 'pigment epithelium layer' (the outer layer).

Points to note

Local apical contraction and physiologic cell death have been observed during invagination of lens placade and formation of the optic cup. These episodes are the harbinger of many congenital malformations encountered in this area.

Invagination of the optic cup occurs in an eccentric manner progressing from inferior to superior, with ultimate formation of a seam, the 'optic fissure' or 'choroidal fissure'. Mesenchyme of neural crest origin surrounds and fills the optic fissure. At 5 weeks of gestation, the hyloid artery develops from the mesenchyme in the optic fissure and courses from the optic stalk to the lens placade anteriorly. The lens placade now separates from the surface ectoderm before the optic fissure closes.

INTRAOCULAR DEVELOPMENT

The closure of the optic fissure, at the end of 7th week, is an important milestone in the development of the eye. Abnormal or delayed closure of the optic fissure results in an inferior coloboma often with microphthalmic eyes. At this stage of 7–8 weeks, the neurosensory retina and pigment epithelium are in approximation, the optic nerve is developing, and the lens vesicle is separating from the cornea to form the anterior chamber. The mesenchyme of neural origin around the primitive retina develops into choroid and the sclera. Around this developing globe, myoblasts of mesodermal origin arrange in linear fashion and are precursors of future extraocular muscles. The eyelids emerge as small buds above and below the globe. As the lens placade invaginates, it forms a hollow center and becomes the 'lens vesicle'. Detachment of the lens placade, now lens vesicle, occurs around 5th week and is the hallmark of formation of chambers within the eye. Failure of proper separation of lens vesicle from the surface ectoderm is one of the characteristics of a teratogenic–induced 'dysgenesis' of the anterior segment of the eye.

Applied anatomy: Anterior lenticonus, anterior capsular cataract, and anterior chamber cleavage syndromes are the result of faulty keratolenticular separation.

Following separation, the lens vesicle gets surrounded by a layer of basal lamina, the lens capsule. At approximately 38–40 days of gestation (6 weeks), the cells of posterior lens vesicle lengthen to fill the vesicle, loose their nuclei and most of their intracellular organelles. It has been found that amazingly retinal anlage promotes primary lens fibre formation. The retina develops independently while the lens appears to rely on the retina for cytodifferentiation. The primitive lens, filled with the primary lens fibres, is the 'embryonic lens nucleus'. In adult, the primary embryonic nucleus is the central round, slightly dark sphere within the 'Y' sutures. Anterior lens epithelial cells remain cuboidal and are mitotic throughout life, giving rise to future fetal and adult lens fibres. The anterior lens cells gradually migrate to the lens periphery (the equator), and they elongate to form secondary lens fibres. These secondary lens fibres course anteriorly and posteriorly around the embryonic nucleus to meet at the centre of lens, the poles. These early lens fibres have blunt ends, so when they meet they form a loose adherence and produce the 'Y' sutures. At birth, the lens is entirely made of nucleus and minimal cortex. The cortex, then, continues to form from the anterior lens fibres throughout life, albeit at a very slow pace.

After separation of the lens vesicle, the overlying surface ectoderm forms the corneal epithelium and then secretes a thick matrix, producing the 'corneal stroma'. Neural crest cells then migrate between lens vesicle and corneal epithelium, filling the anterior chamber and forming the 'corneal endothelium'. The iris develops from the cells of anterior optic cup, iris stroma from the mesenchymal neural crest cells and the two layers of epithelium from the neural ectoderm. The smooth muscles of the iris develop from differentiation of neural ectoderm. The pupillary constrictor and the dilator are only muscles in the body of ectodermal origin.

Differentiation and separation continues in the cells present in the anterior chamber until a cavity, primitive anterior chamber forms. Discrepancies in the separation of this tissue are the harbinger of number of disorders belonging to the 'anterior chamber dysgenesis' syndromes.

The choroid and the sclera are derived from the mesenchymal tissue of neural crest origin. By approximately 12 weeks of gestation, the choroid and sclera have enveloped the optic stalk. The lamina cribrosa consists of cells that have penetrated the optic nerve. By 16 weeks of gestation, the vasculature of the choroid begins to take shape with the choriocapillaries forming, anastomosing with the short posterior ciliary arteries and ultimately joining in the four vortex veins.

DEVELOPMENT OF THE RETINA

Our primary focus, as regards vision, is the development of the retina and the optic nerve. As already mentioned, the retina develops from the neural ectoderm with the outer pigment epithelium (RPE) developing from the outer layer and the neurosensory retina developing from the inner layer of the optic cup. Bruch's membrane, the basal lamina of the pigment epithelium, begins to emerge by 4th week and is well developed by 6th week of gestation.

By 4 months (16 weeks) of gestation, the RPE cells take on their hexagonal shape and develop 'microvilli', which interdigitate with projections from the photoreceptor cells of the inner retina.

By about 8th week, proliferation of cells of inner neurosensory retina commences with formation of inner and outer neuroblastic layers, and consequently differentiation of the ganglion cells giving rise to primitive nerve fibre layer.

At about 6 weeks of gestation, axons from the developing ganglion cells pass through the vacuolated spaces of the inner wall of the optic stalk. Simultaneously, 'hyloid artery' develops in the centre of the primitive optic nerve. A glial sheath forms around the hyloid artery and along with the regression of hyaloid arteries the glial tissue also regresses. 'Bergmeister's papilla represents the remnants of this glial tissue. These glial cells migrate to the optic stalk, accumulate there and form the primitive 'optic disc'. These glial cells which form the glial part of the lamina cribrosa, come from the optic stalk which is of

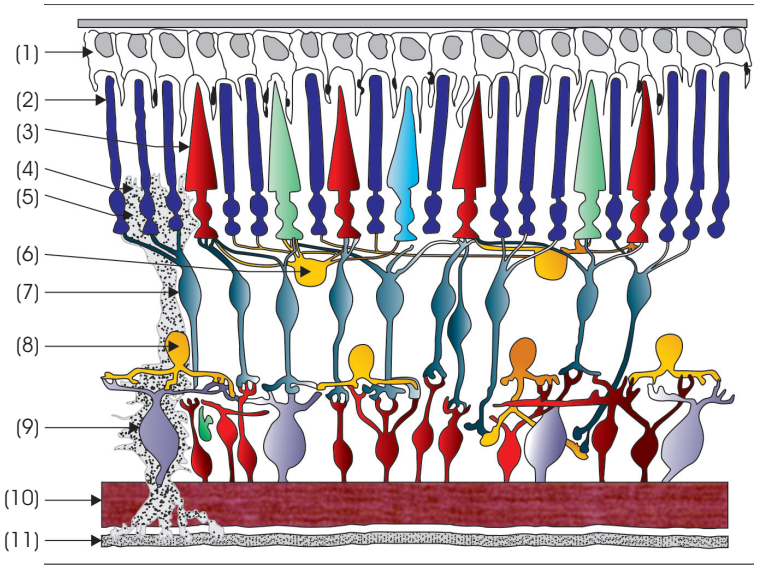
neural ectodermal in origin. Later, mesenchymal portion of the disc develops from the neural 'crest' cells.

By 3rd month of gestation, the optic nerve shifts nasally as temporal aspect of the globe enlarges.

Myelination of the optic nerve starts at the chiasma at about 7 months of gestation and progresses towards the eye. Normally, myelination stops at the optic disc, one month post natal. Myelination of retinal nerve fibres occur, if the process of myelination continues past the optic disc. Reason for 'retinal myelination' is explained as an 'ectopic' phenomenon and is associated with high myopia and amblyopia (Figs 1.1 to 1.3).

RETINAL VASCULATURE

It is important to understand the time bound development of retinal vasculature as this has bearing on the prematurity of birth. The central retinal artery grows from the optic disc to



(1) Pigment epithelium; (2) Rods; (3) Cones; (4) Outer limiting membrane; (5) Müller cells; (6) Horizontal cells; (7) Bipolar cells; (8) Amacrine cells; (9) Ganglion cells; (10) Nerve fiber layer; (11) Inner limiting membrane.

Fig. 1.1: Depiction of retinal layers.

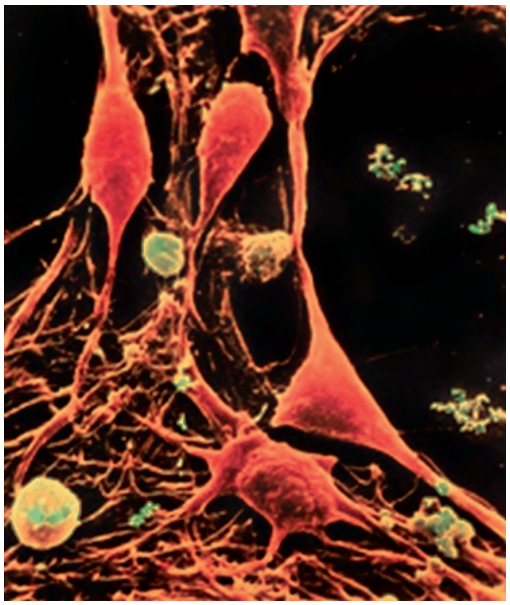


Fig. 1.2: Photomicrograph of amacrine cells of retina

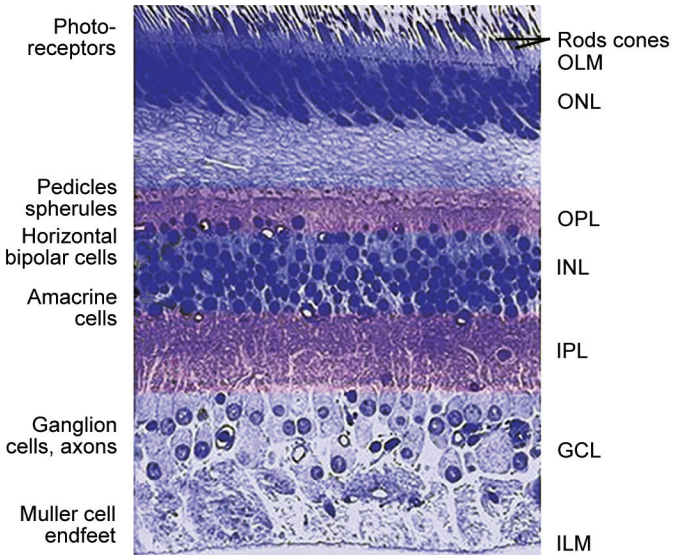


Fig. 1.3: Light micrograph of a vertical section through central human retina

the retinal periphery forming the nasal and temporal arcades. Between 5 and 6 months of gestation, the retinal arcades have progressed to the equator of the eye. By this time, the long and short posterior ciliary arteries have developed with the long ciliary supplying the anterior segment while the short ciliary supplying the choroid. The retinal vessels grow faster towards the nasal retina; even at full term birth, there is a small crescent of temporal retina devoid of vessels. The fact that a newborn infant has an immature temporal retina, may explain scattered cases of ROP even in a full term birth.

Applied anatomy: Oxygen affects 'angiogenesis' and seems to play a role in stimulating or retarding vascular growth. Vascular endothelial growth is promoted by low oxygen tension and is inhibited by high oxygen tension. These findings give rise to the hypothesis that 'retinopathy of prematurity' is secondary to an increased oxygen concentration which results in inhibition or 'retraction' of the peripheral capillary vasculature. This retraction of the vessels results in retinal 'hypoxia' and consequent secondary endothelial cell growth and 'neovascularization'.

By 6 months of gestation, all structures in and around the eye have formed including lids and orbital adnexa. The lid fissure begins to take shape with the separation of the lids. From now on, development and maturation of the structures of the eye continue till birth.

POSTNATAL DEVELOPMENT OF RETINA

Since vision is directly related to the development of retina and visual pathways, it would be relevant to follow the development of these structures in the immediate postnatal life. Of all the structures of the eye, the 'macula' is the least developed at birth. The peripheral retina is comparatively well developed histologically and functionally at birth.

After birth, the macula dramatically develops by 4 years of life, wherein the vision assumes its normal level of functioning. Most notable changes are in macular pigmentation, annular

ring development, foveal reflex and cone photoreceptor maturation.

Ophthalmoscopic studies of premature birth infants showed that macular pigmentation is not evident before 33 weeks of gestation. Between 34 and 35 weeks, pigmentation appears in the pigment epithelial cells, producing a dark red appearance, that is quite distinct from the surrounding retina. The pigment epithelial cells at macula become narrower, taller, and more tightly packed and are accountable for the dark appearance. The yellow xanthophyllic pigment usually found in adult retina is not present in neonates. This pigment originates from the 'dietary carotenoids' and appears later in life and gradually increases with age. The parafoveal capillary-free zone also contributes to the typical appearance of macula.

The 'annular ring' at macula, a prominent ophthalmoscopic finding, shows as a circular light reflex surrounding the macula. This first becomes apparent at 36 weeks of gestation and is due to changes in the ganglion cell layer. At around 28 weeks, the ganglion cells migrate to the periphery of macula, accumulate there and form a concentric mound. This forms a 'crater-like' appearance at macula, created by a thicker peripheral mound and a thinner central area.

The 'foveal reflex' is the last ophthalmoscopic finding to develop, and can be seen around birth. The explanation of this finding is thinning of inner and outer nuclear layers at fovea, creating again a crater-like formation, known as the 'foveal pit'.

Though the macula may appear ophthalmoscopically normal at birth, but histologically and functionally maturation occurs later in childhood. The most remarkable changes in histology of retina consists of cone diameter, shape of inner and outer parts of cone, and cone density.

At birth, the rod-free region of macula is approximately 1100 μ (micro mm) in size. In next few years, a decrease in the rod-free region of macula occurs due to inward migration of cone nuclei. The rod-free area reaches adult diameter of 700–750 μ by 3 years of life.

Three concomitant changes at macula are directly responsible for improvement of visual acuity with age, and that are:

(1) Differentiation of foveal cone photoreceptors; (2) reduction of rod-free zone; and (3) increase in the cone density.

At birth, the inner cone segments are round and thick, and outer segments are short. The inner and outer segments mature at different rates. By 15 months of age, the outer segments have elongated to almost half the adult size. By 4 years, the outer segments are still 30% shorter than adult size. On the other hand, the inner segments mature faster, assuming the adult architecture by 15 months of age. With thinning of cone receptors, they move closer to each other and become tightly packed. Cone density in the foveal region increases from 18 per 100 μ to 22 per 100 μ by 15 months of age, and further to 30 per 100 μ by 4 years. Adult cone density at fovea is around 42 per 100 μ. Increase in acuity, particularly resolution acuity, parallels the increase in cone density.

Applied aspect: When we discuss the higher levels of vision, we try to understand the phenomena of hypervisual acuity or vernier acuity. The 'cone spacing' in an adult fovea is 2.5 μ or 28 seconds/arc. Beyond this limit, the eye does not function. To discriminate between two fine points or lines, as in hyperacuity, the visual acuity rises to 15–20 seconds/arc, which is beyond the scope of the fovea. Therefore, in such cases, the role of 'visual cortex' comes into play.

At birth, the retinal vasculature is fully developed at the posterior pole. At fourth month of gestation, the vessels are first evident at the disc; by eighth month, the retinal vasculature is complete on the nasal side; but the temporal is fully vascularized several weeks after birth.