CHAPTER 1

Ocular Structures and their Development

OCULAR STRUCTURES

- Eyeball
- Visual pathway
- Orbit, extraocular muscles and appendages of the eye

DEVELOPMENT OF THE EYE

Formation of primordia giving rise to ocular structures

- Formation of optic vesicle and optic stalk
- Formation of lens vesicle
- Formation of optic cup

Changes in the associated mesenchyme

Development of various structures of eyeball, orbit and ocular adnexa

- Formation of structures of eyeball
- Development of ocular vessels
- Development of accessory ocular structures
- Development of extraocular muscles
- Development of orbit

Summary and milestones of development of ocular structures

Structures derived from embryonic layers

Important milestones in the development of ocular structures

- Pre-embryonic period to end of third week
- Embryonic period
- Fetal period
- Postnatal period

OCULAR STRUCTURES

This chapter gives only a brief account of the anatomy of eyeball and its related structures. The detailed anatomy of different structures is described in the relevant chapters.

EYEBALL

Each eyeball (Fig. 1.1) is a cystic structure kept distended by the pressure inside it. Although, generally referred to as a globe, the eyeball is not a sphere but an oblate spheroid, consisting of two modified spheres fused together. Cornea is a part of the anterior smaller sphere with a radius of 7.8 mm and sclera is part of the posterior larger sphere with a radius of about 12 mm.

Dimensions of an adult eyeball

Dimensions of an adult eyeball are as below (Fig. 1.2):

- Anteroposterior diameter 24 mm
- Horizontal (lateral) diameter 23.5 mm
- Vertical diameter 23 mm
- Circumference 75 mm
- Volume 6.5 ml
- Weight 7 g

Poles and equators of the eyeball

■ ***Poles*** The central point on the maximal convexities of the anterior and posterior curvatures of the eyeball is called the *anterior pole* and *posterior pole*, respectively (Fig. 1.3).

■ ***Equators*** of eyeball are:

- G*eometric equator* of the eyeball lies at the midplane between the two poles.
- A*natomical equator* of the eyeball is tilted slightly backward on the temporal side (due to bulge of the sclera on this side) and slightly forward on the nasal side.
- S*urgical equator* refers to the greatest circumference of the globe approximately in the coronal plane.

Axes and angles of the eyeball

The eye has three principal axes and three visual angles (Fig. 1.4).

Axes of the eye

1. *Optical axis* is the line passing through the centre of the cornea (P), centre of the lens (N) and meets the retina (R) on the nasal side of the fovea.

In practice, it is impossible to determine accurately the optic axis, since we cannot know the exact centre of cornea. However, it is much easier to estimate centre of pupil, for example by the image of point light on the cornea. Therefore, in practice, we substitute the optic axis by a line perpendicular to the cornea at the point coinciding to the centre of pupil. This line (AP) is called *pupillary line*.

2. *Visual axis* is the line joining the fixation point (O), nodal point (N), and the fovea (F).

3. *Fixation axis* is the line joining the fixation point (O) and the centre of rotation (C).

Visual angles

Visual angles include (Fig. 1.4):

1. *Angle alpha.* It is the angle (ONA) formed between the optical axis (AR) and visual axis (OF) at the nodal point (N).

2. *Angle gamma.* It is the angle (OCA) between the optical axis (AR) and fixation axis (OC) at the centre of rotation of the eyeball (C).

3. *Angle kappa.* It is the angle (OPA) formed between the visual axis (OF) and pupillary line (AP). The point P on the centre of cornea is considered equivalent to the centre of pupil.

Note. Practically, only the angle kappa can be measured and is of clinical significance. A positive angle kappa results in pseudoexotropia and a negative angle kappa in pseudoesotropia.

Coats of the eyeball

The eyeball comprises of three coats: Outer (fibrous coat), middle (vascular coat) and inner (nervous coat).

1. *Fibrous coat (cornea and sclera).* It is a dense strong wall which protects the intraocular contents.

- *Cornea*, the anterior 1/6th of this fibrous coat is transparent forms.
- *Sclera*, posterior 5/6th opaque part.
- *Limbus*. Cornea is set into sclera like a watch glass. Junction of the cornea and sclera called limbus. It is marked at the surface by the external

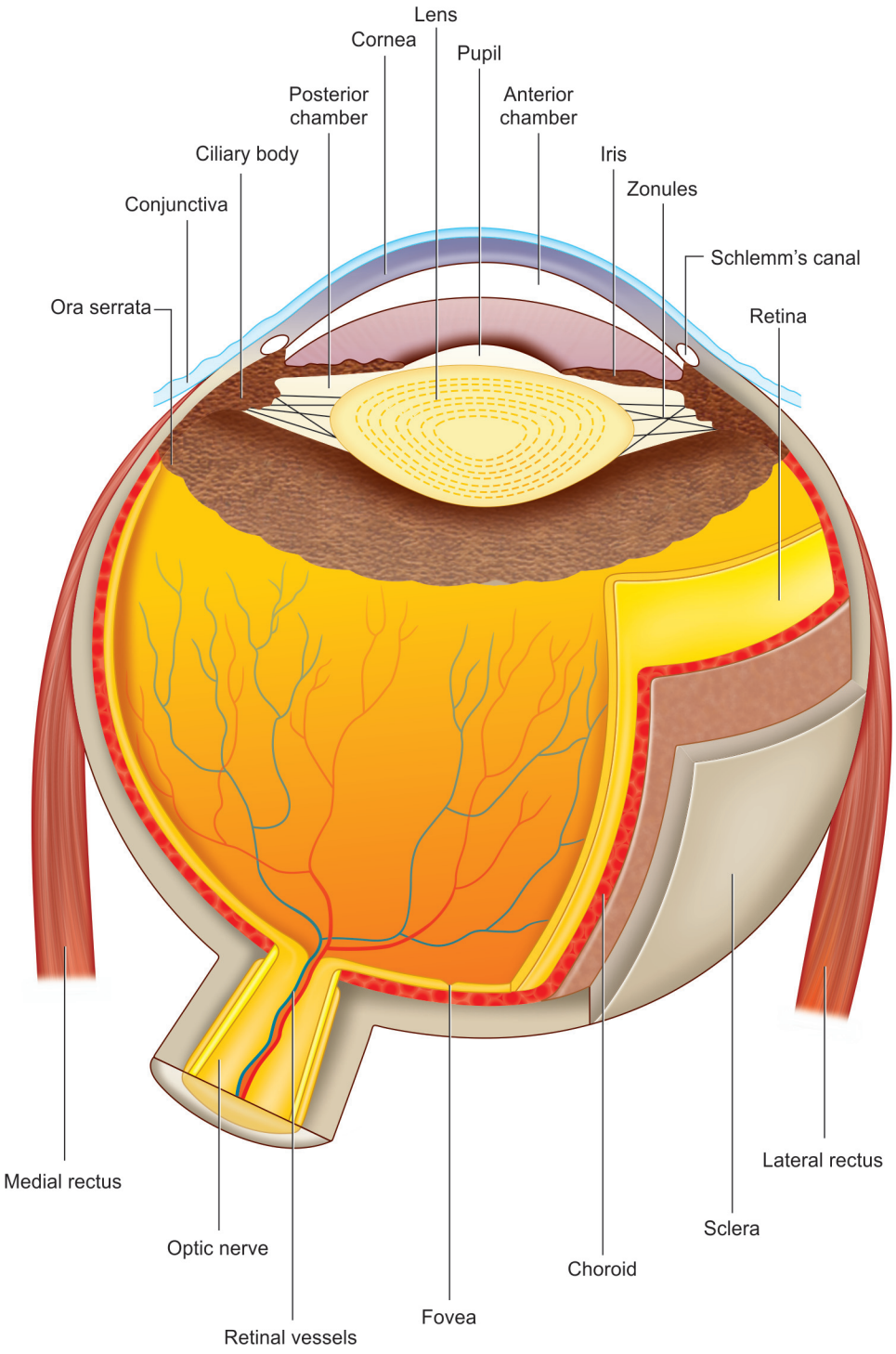

Fig. 1.1. *Gross anatomy of the eyeball.*

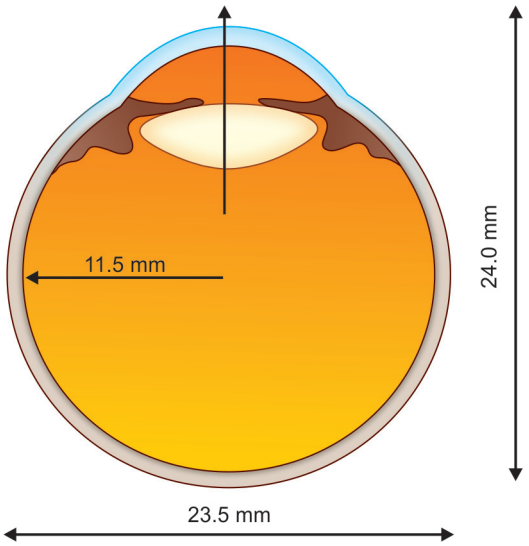

Fig. 1.2. *Dimensions of an adult eyeball.*

scleral sulcus (Fig. 1.3). Conjunctiva is firmly attached at the limbus.

2. *Vascular coat (uveal tissue).* It supplies nutrition to the various structures of the eyeball. *It consists of three parts:*

- *Iris* is the anterior most part of uveal tract. It is a thin circular disc like structure with a central hole called pupil of 3–4 mm in size.
- *Ciliary body* is forward continuation of choroid and extends from the ora serrata to iris.
- *Choroid* is the posterior most part of uveal tract which extends from optic disc margin to ora serrata.

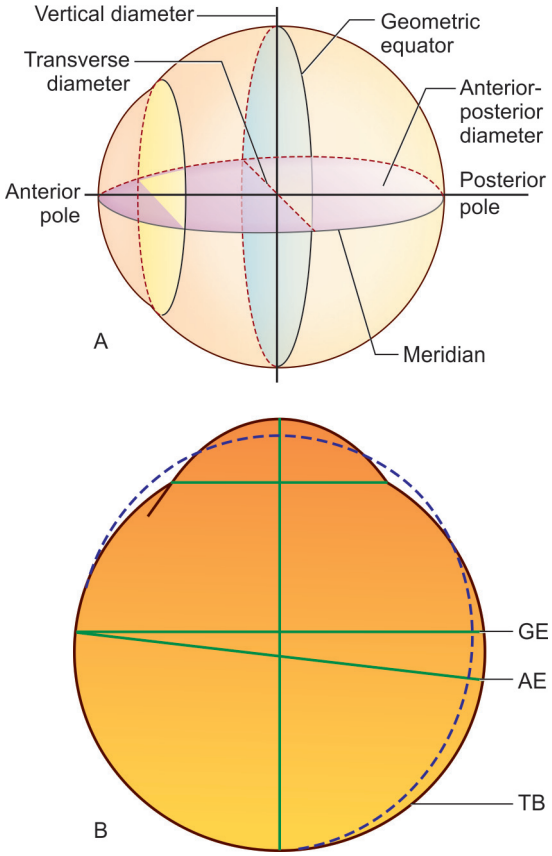

Fig. 1.3. *A, Poles and equators of the eyeball; B, Anatomical equator is tilted backward temporally due to bulge of the sclera. (GE: Geometric equator; AE: Anatomic equator; TB: Temporal bulge).*

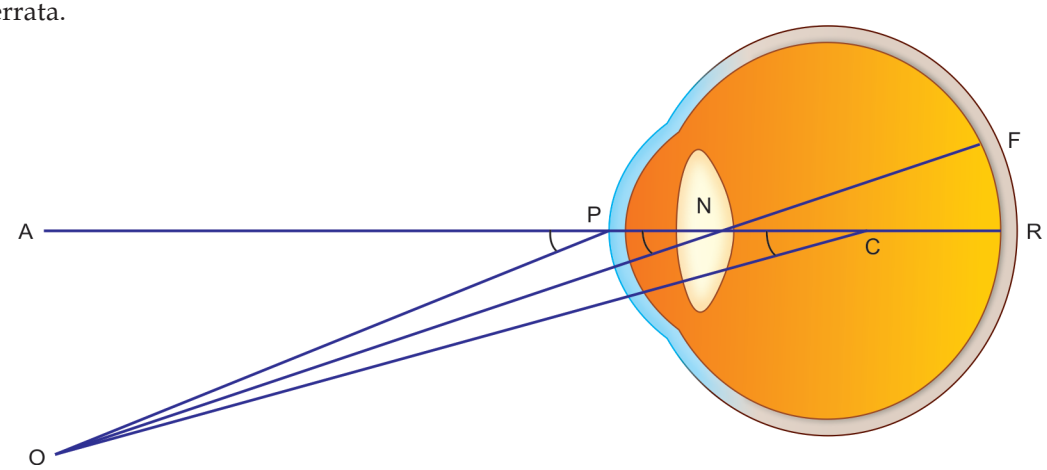

Fig. 1.4. *Axes of the eye: Optical axis (AR); visual axis (OF); fixation axis (OC) and visual angles: angle alpha (ONA, between optical axis and visual axis at nodal point N); angle kappa (OPA, between optical axis and papillary line—OP); angle gamma (OCA, between optical axis and fixation axis).*

3. ***Nervous coat (retina).*** It is concerned with visual functions, and projects to the visual cortex through visual pathway.

Segments and chambers of the eyeball

The eyeball can be divided into two segments—anterior and posterior:

1. ***Anterior segment.*** It includes crystalline lens (which is suspended from the ciliary body by zonules), and structures anterior to it, viz. iris, cornea and two aqueous humour-filled spaces, anterior and posterior chambers.

Anterior chamber.

- *Bounded* anteriorly by the back of cornea, and posteriorly by the iris and part of ciliary body.
- *Depth.* The anterior chamber is about 30 mm deep (range 2.5–4.4 mm) in the centre in normal adults. It is shallower in hypermetropes and deeper in myopes, but is almost equal in the two eyes of the same individual.
- *Content:* It contains about 0.25 ml of the aqueous humour.
- *Communicates* with the posterior chamber through the pupil.

Posterior chamber. It is a triangular space containing 0.06 ml of aqueous humour. It is bounded anteriorly by the posterior surface of iris and part of ciliary body, posteriorly by the crystalline lens and its zonules, and laterally by the ciliary body.

2. ***Posterior segment.*** It includes the structures posterior to lens, viz. vitreous humour, retina, choroid and optic disc.

VISUAL PATHWAY

Each eyeball acts as a camera; it perceives the images and relays the sensations to the brain (occipital cortex) via visual pathway which comprise optic nerve, optic chiasma, optic tract, lateral geniculate body and optic radiations (Fig. 1.5).

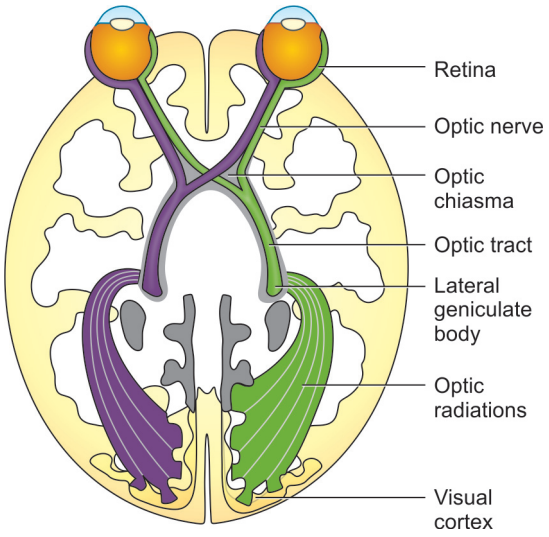

Fig. 1.5. *Gross anatomy of the visual pathways.*

ORBIT, EXTRAOCULAR MUSCLES AND APPENDAGES OF THE EYE

Each eyeball is suspended by extraocular muscles and fascial sheaths in a quadrilateral pyramid-shaped bony cavity called *orbit* (Fig. 1.6). Each eyeball is located in the anterior orbit, nearer to the roof and lateral wall than to the floor and medial wall. Each eye is protected anteriorly by two shutters called the *eyelids.* The anterior part of the sclera and posterior surface of lids are lined by a thin membrane called *conjunctiva.* For smooth functioning, the cornea and conjunctiva are to be kept moist by tears which are produced by lacrimal gland and drained by the lacrimal passages. These structures (eyelids, eyebrows, conjunctiva and lacrimal apparatus) are collectively called *the appendages of the eye.*

DEVELOPMENT OF THE EYE

The development of the eyeball can be considered to commence around day 22 when the embryo has eight pairs of somites and is around 2 mm in length.

FORMATION OF PRIMORDIA GIVING RISE TO OCULAR STRUCTURES

The eyeball and its related structures are derived from the following primordia:

- *Optic vesicle,* an outgrowth from prosencephalon (neuroectodermal structure).
- *Lens placode,* a specialised area of surface ectoderm called and the surrounding surface ectoderm.

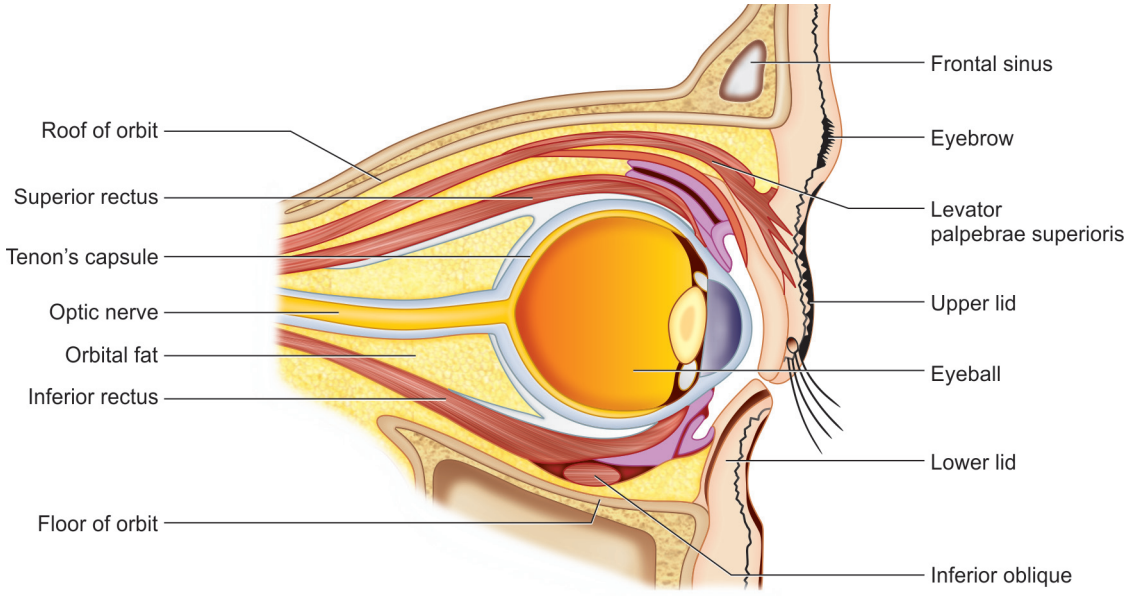

Fig. 1.6. *Section of the orbital cavity to demonstrate eyeball and its accessory structures.*

- *Mesenchyme* surrounding the optic vesicle.
- *Visceral mesoderm* of maxillary process.

Before going into the development of individual structures, it will be helpful to understand the formation of optic vesicle, lens placode, optic cup and changes in the surrounding mesenchyme, which play a major role in the development of the eye and its related structures.

FORMATION OF OPTIC VESICLE AND OPTIC STALK

The first evidence of primitive eye formation occurs during the third week of gestation. The brain and eye develop from the most anterior region of neural plate. The neuroectodermal cells at the apex of neural folds proliferate and produce a population of neural crest cells (Fig. 1.7A), which contribute extensively to the tissues of eye. The region of neural plate (Fig. 1.7A), which is destined to form the prosencephalon shows a linear thickened area on either side (Fig. 1.7B), which soon becomes depressed to form the optic sulcus (Fig. 1.7C). Meanwhile the neural plate becomes converted into prosencephalic vesicle. As the optic sulcus deepens, the walls of the prosencephalon overlying the sulcus bulge out to form the *optic vesicle* (Fig. 1.7D, E). The proximal part of the optic vesicle becomes constricted and elongated to form the *optic stalk* (Fig. 1.7F, G, H).

FORMATION OF LENS VESICLE

As the optic vesicle grows laterally (during the third week of gestation), it comes in relation with the surface ectoderm. At about 27 days of gestation (embryo 4.0–4.5 mm), the area of the surface ectoderm overlying the optic vesicle becomes thickened to form the *lens placode* (Fig. 1.8A) which sinks below the surface and is gradually converted into *the lens vesicle* (Fig. 1.8B, C). It is soon separated from the surface ectoderm at 33rd day of gestation (Fig. 1.8D).

FORMATION OF OPTIC CUP

During the fourth week of gestation (embryo 7.6–7.8 mm), while the lens vesicle is forming (from the surface ectoderm), simultaneously the optic vesicle is converted into a double-layered *optic cup.* It appears from Fig. 1.8 that this has happened because the developing lens has invaginated itself into the optic vesicle. However, this is not so. The conversion of the optic vesicle to the optic cup is due to differential growth of the walls of the vesicle. The margins of optic cup grow over the upper and lateral

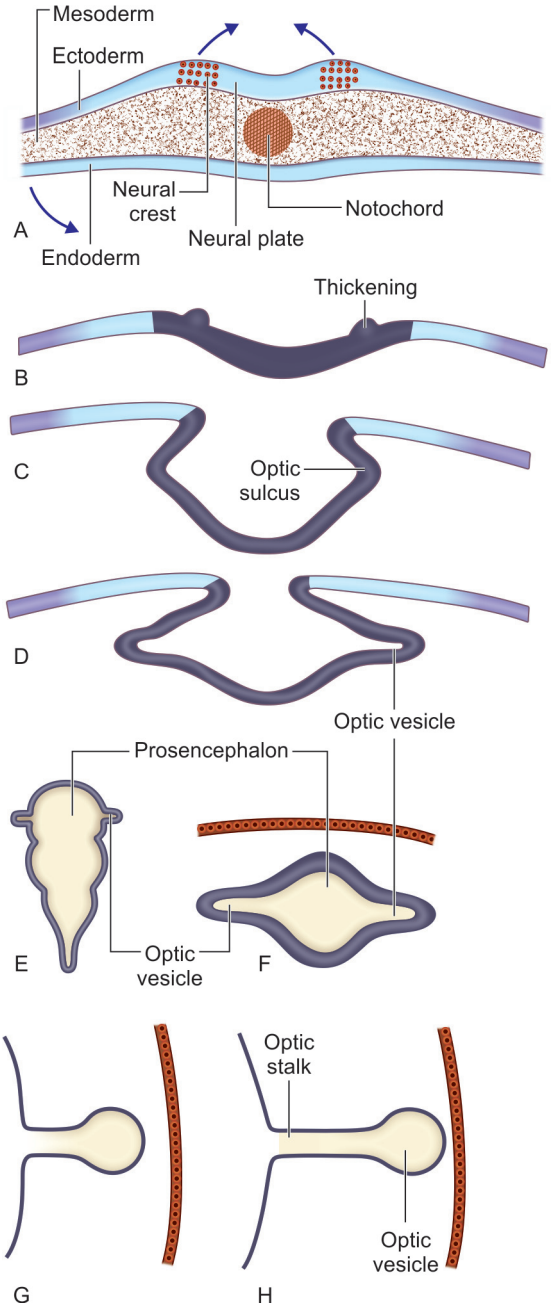

Fig. 1.7. *Formation of the optic vesicle and optic stalk.*

sides of the lens to enclose it. However, such a growth does not take place over the inferior part of the lens, and therefore, walls of the cup show deficiency in this part. This deficiency extends to some distance along the inferior surface of the optic stalk and is called the *choroidal* or *fetal fissure* (Fig. 1.9). This embryonic ocular fissure closes by 6th week of gestation. When the lips of the fissure fail to fuse by 6th or 7th week, typical colobomas result (Box 1.1 and Box 1.2). By the end of 7th week of gestation, most of the basic structures of the eye are present. Thereafter, ocular development is mainly a process of differentiation and modification of various parts of the globe.

CHANGES IN THE ASSOCIATED MESENCHYME

The developing neural tube (from which central nervous system develops) is surrounded by mesenchyme. Mesenchyme is a loose tissue consisting of stellate, amoeboid mesenchymal cells embedded in a matrix rich in glycosaminoglycans.

Mesenchymal cells may be derived from serosal sources, namely mesoderm (dermatome or sclerotome component of the somite or lateral plate mesoderm) or neural crest. Thus this descriptive term mesenchyme does not imply an origin from any particular embryonic germ layer. The mesenchyme surrounding the neural tube subsequently condenses to form meninges. An extension of this mesenchyme also surrounds the optic vesicle, except at its apex, which is closely apposed to the surface ectoderm on the lateral side of the developing head. This

Box 1.1 ***Clinical pearls: Coloboma***

Incomplete closure of the optic fissure may affect the developing optic cup or stalk and the adult derivations of these structures, resulting in an inferior nasal defect in the optic disc, retina, ciliary body, or iris. This defect is called a coloboma and can vary from a slight notch to a large wedge-like defect. A large iris coloboma produces a keyhole-shaped pupil, although the remainder of the iris develops normally. When the coloboma is unilateral, the affected iris may have denser pigmentation than the opposite normal iris. Colobomas affecting the sensory retina and RPE also involve the choroid because its differentiation depends on an intact RPE layer. Bare sclera is seen in the area affected, with retinal vessels passing over the defect.

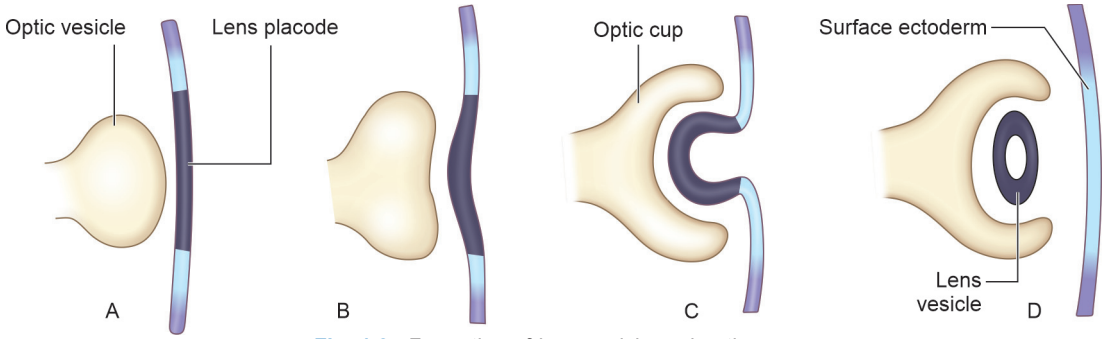

Fig. 1.8. *Formation of lens vesicle and optic cup.*

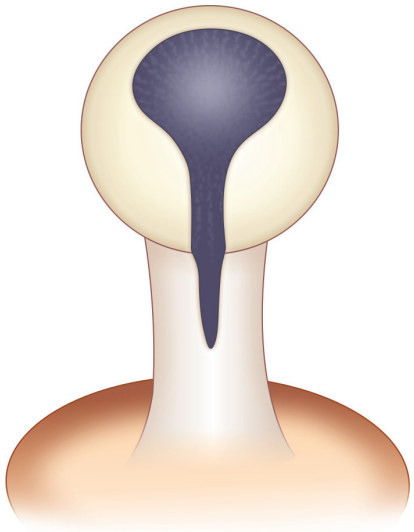

Fig. 1.9. *Optic cup and stalk seen from below to show the choroidal fissure.*

mesenchyme may be derived from the cephalic neural crest and indeed from crest cells detaching from the outer surface of the optic vesicle itself. Later, this mesenchyme differentiates to form a superficial fibrous layer (corresponding to dura), which will form the sclera and cornea and a deeper vascular layer (corresponding to pia arachnoid) which will form stroma of uveal tissue (Fig. 1.10).

With the formation of optic cup, part of the inner vascular layer of mesenchyme is carried into the cup through the choroidal fissure. With the closure of this fissure, the portion of mesenchyme which has made its way into the eye through the fissure is cut off from the surrounding mesenchyme and gives rise to hyaloid system of the vessels (Fig. 1.11). The fibrous layer of mesenchyme surrounding anterior part of optic cup forms the cornea. The corresponding vascular layer of mesenchyme becomes iridopupillary membrane, which, in the peripheral region, attaches to the anterior part of the optic cup to form iris. The central

Box 1.2 ***Clinical pearls: Malformations of the neural tube and optic vesicle***

These occur in the 1st month of embryonic life and include:

- *Anophthalmia*, which is extremely rare, and is due to a failure of formation of the optic vesicle. The orbits do not contain ocular tissue, but the extraocular muscles (mesoderm) and lacrimal gland (ectoderm) are present.
- *Nanophthalmia and microphthalmia*. Farmation of the optic vesicle without proper subsequent development produces a rudimentary eye in the orbit nanophthalmia (or dwarf eye).
  In microphthalmia, there is a small but recognizable eye that contains recognizable elements, e.g. lens, choroid, and retina.
- *Synophthalmia*. Fusion of the two eyes may result from a malformation of the mesodermal tissue between the optic vesicles or faulty inductive processes. Only rarely is a single eye (cyclops) formed by this mechanism and in most cases there are two recognizable corneas and lenses, and identifiable ports of the iris and ciliary body. The midline scleral and uveal tissue may be absent and the optic nerve may be single or duplicate. This malformation may be associated with a deletion of chromosome 18.
- *Congenital cystic eye*. A disorganized cystic structure may arise owing to disturbances in the process of invagination of the retinal disc.

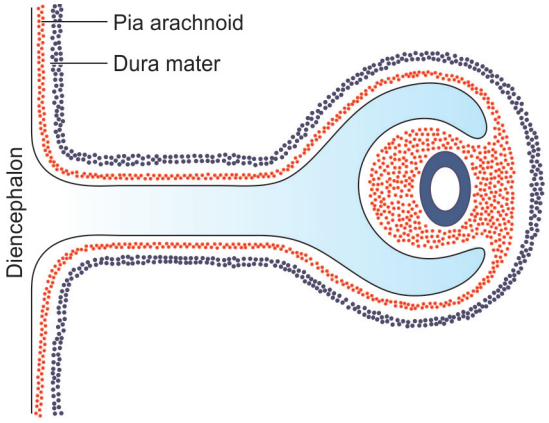

Fig. 1.10. *Developing optic cup surrounded by mesoderm.*

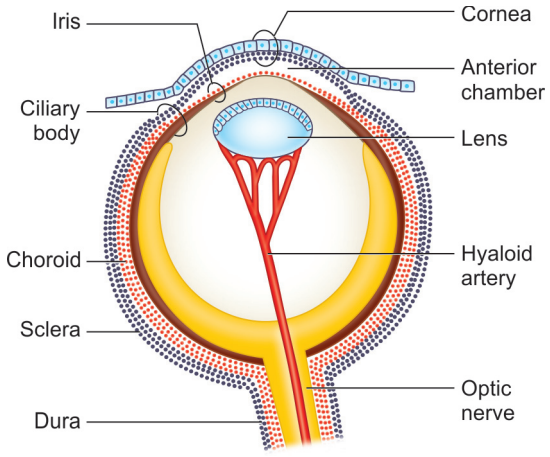

Fig. 1.11. *Derivation of various structures of the eyeball.*

part of this lamina is pupillary membrane and also forms the tunica vasculosa lentis (Fig. 1.11).

In the posterior part of optic cup, the surrounding fibrous mesenchyme forms sclera and extraocular muscles, while the vascular layer forms the choroid and ciliary body.

DEVELOPMENT OF VARIOUS STRUCTURES OF EYEBALL, ORBIT AND OCULAR ADNEXA

DEVELOPMENT OF STRUCTURES OF EYEBALL

RETINA

Retina is developed from the two parts of the optic cup (Fig. 1.12):

- *Neurosensory retina* from the inner wall and
- *Retinal pigment epithelium* from the outer wall.

Neurosensory retina

The neurosensory retina develops by differentiation from the inner wall of the optic cup by the following stages:

1. *Formation of primitive and marginal zone.* Inner wall of the optic cup is a single-layered epithelium with an internal and an external basement membrane. As the development proceeds, this layer proliferates and during 4th–5th week of gestation, the primitive retina formed is arranged in two zones:

- *Outer primitive zone* (nuclear zone or germinal epithelium) filled with eight to nine rows of nuclei and
- *Inner marginal zone* (layer of His) devoid of nuclei (Fig. 1.13A).

2. *Formation of inner and outer neuroblastic layers.* The neuroepithelial cells actively divide by mitosis and by 6th to 7th week of gestation are differentiated into two layers, the *inner* and *outer neuroblastic layers.* These layers are separated by the *transient fibre layer of Chievitz,* which disappears subsequently (Fig. 1.13B).

- *Inner neuroblastic layer* differentiates to form ganglion cells (the cells which develop first of all), Muller's cells and the amacrine cells.
- *Outer neuroblastic layer* differentiates to form rods and cones, the bipolar cells and the horizontal cells.

3. *Development of various layers of sensory retina.*

- *Nerve fibre layer* becomes identifiable on the inner aspect of the inner neuroblastic layer owing to the growth of ganglion cell axons that converge towards the optic stalk.

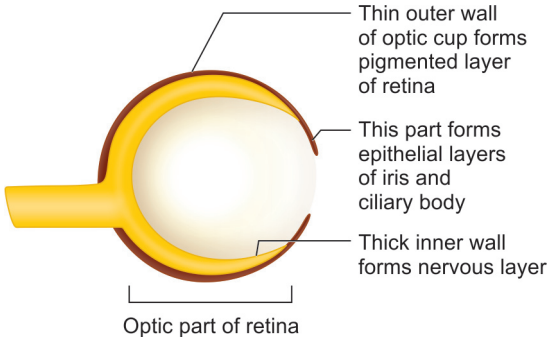

Fig. 1.12. *Development of the retina.*

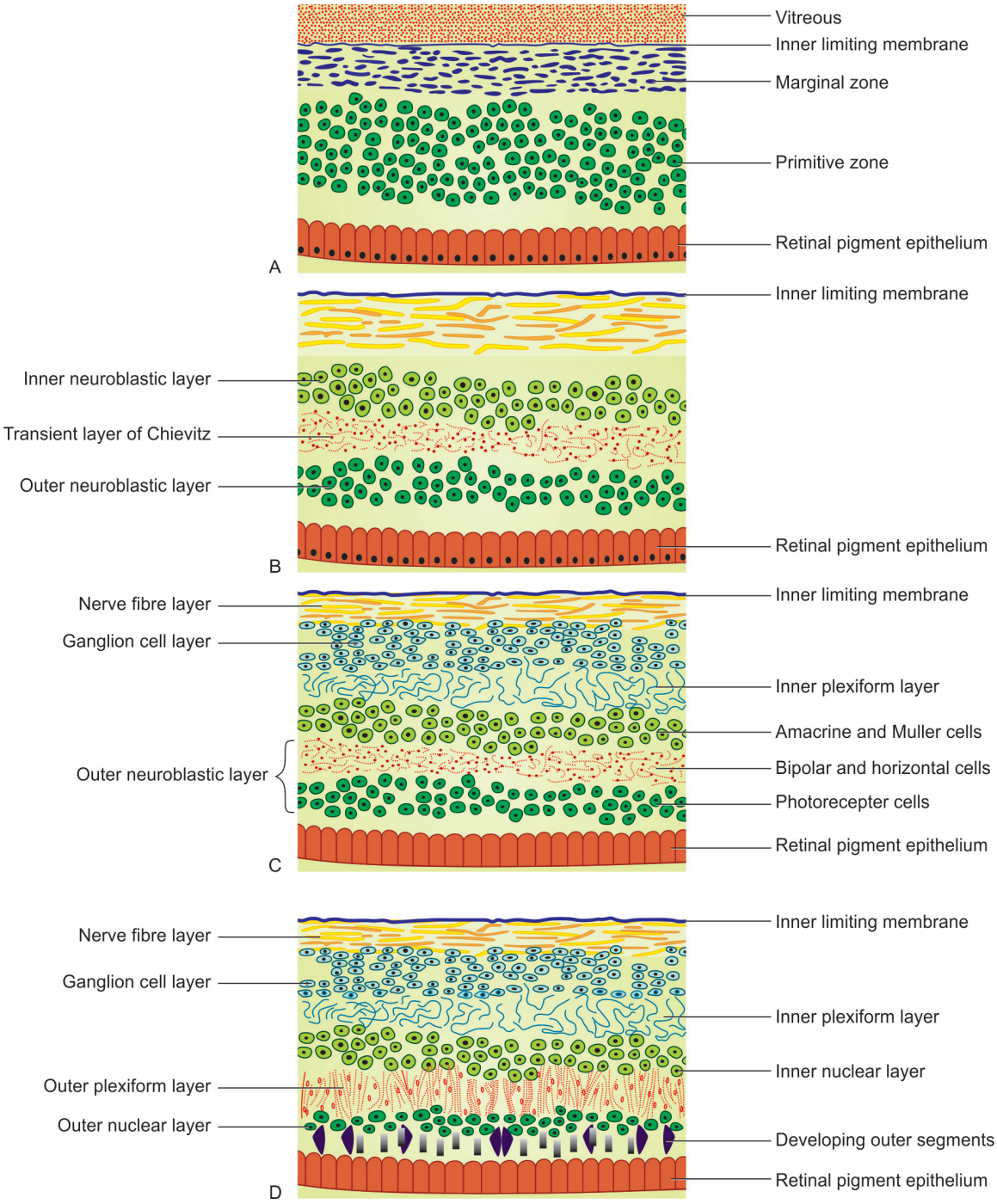

Fig. 1.13. *Zones of primitive retina during: A, 4th–5th week of gestation; B, 6th–8th week of gestation; C, 10th–12th week of gestation; and D, 4th month of gestation.*

- *Inner plexiform layer*, a zone where the processes of cells from the inner neuroblastic layer intermingle, becomes identifiable at approximately 10.5 weeks, thereby obliterating the transient layer of Chievitz (Fig. 1.13C).
- *Inner nuclear layer.* A new intermediate nuclear layer, becomes identifiable in the posterior pole of retina and already contains the amacrine and Muller cell bodies and shortly afterwards the bipolar and the horizontal cells differentiate from the outer neuroblastic layer and migrate into this new nucleated layer (Fig. 1.13C).
- *Outer nuclear layer* is formed by the remaining components of the outer neuroblastic layer containing the cell bodies of photoreceptors (rods and cones).
- *Outer plexiform layer* (Fig. 1.13D) is constituted by zone where fibres from this layer intermingle with those of the inner nuclear layer.
- *External limiting membrane* (not a membrane per se) of the retina is identifiable in the early stages as rows of tight junctions between, adjacent neuroblasts.

4. Differentiation of the retinal layer thus starts during 6th week of gestation and by 5½ months of gestation, all the layers of the adult retina are recognizable. In the macular area, the development is delayed up to 8th month of gestation. Further differentiation of the retina and specialization of the macular region continues until several months after birth.

Some important landmarks in retinal development include:

- *Synaptogenesis in cone pedicles* occurs at approximately 4 months and in rod spherules around 5 months.
- *Photoreceptor outer segment formation* commences around the 5th month.
- *Horizontal cells become distinguishable* around the 5th month.
- *Microglia* (resident tissue macrophages) invade the retina via the retinal vasculature (4 months) and peripheral subretinal space (10 weeks onwards).
- *Terminal expansions of Muller cells* beneath the inner limiting membrane mature around 4.5 months, at around the same time as their processes can be identified between the rods and cones.

Retinal pigment epithelium

Cells of the outer wall of the optic cup become pigmented around 6th week of gestation. Its posterior part forms the retinal pigment epithelium (RPE) of the retina and the anterior part continues forward in ciliary body and iris as their pigmented epithelium. Initially, the RPE comprises a mitotically active pseudostratified columnar ciliated epithelium. The cilia disappear as melanogenesis commences. The mitotic activity ceases by birth, thereafter growth of eye and consequently of the RPE itself is accommodated by hypertrophy or enlargement of existing cells. The mature RPE cells are hexagonal in shape, homogenous in size and in section appear as simple cuboidal epithelium. Melanin production in the pigment epithelial cells is gene-regulated and may be defective in albinism (Box 1.3).

Brief summary of scheme of the general development of the retina and the pathway that the various cellular layers and membranes take in their formation is illustrated in Fig. 1.14.

RETINAL VESSELS

The fetal fissure along the optic stalk closes around the hyaloid artery, and the portions of the vessel within the stalk become the central retinal artery. A branch of the primitive maxillary vein located within the optic stalk is the likely precursor of the central retinal vein. Early in the fourth month of development, primitive retinal vessels emerge from the hyaloid artery near the optic disc and enter the developing nerve fibre layer.

Signals from biomolecular agents guide the growth and pathway of neurons and likely also guide the growth of these retinal vessels.

The vessels of the retina continue to develop, gradually forming the arterioles, venules, and capillary beds, but all vessel structure is not completed until approximately 3 months after birth, with the vessels to the nasal periphery completed before those to the temporal

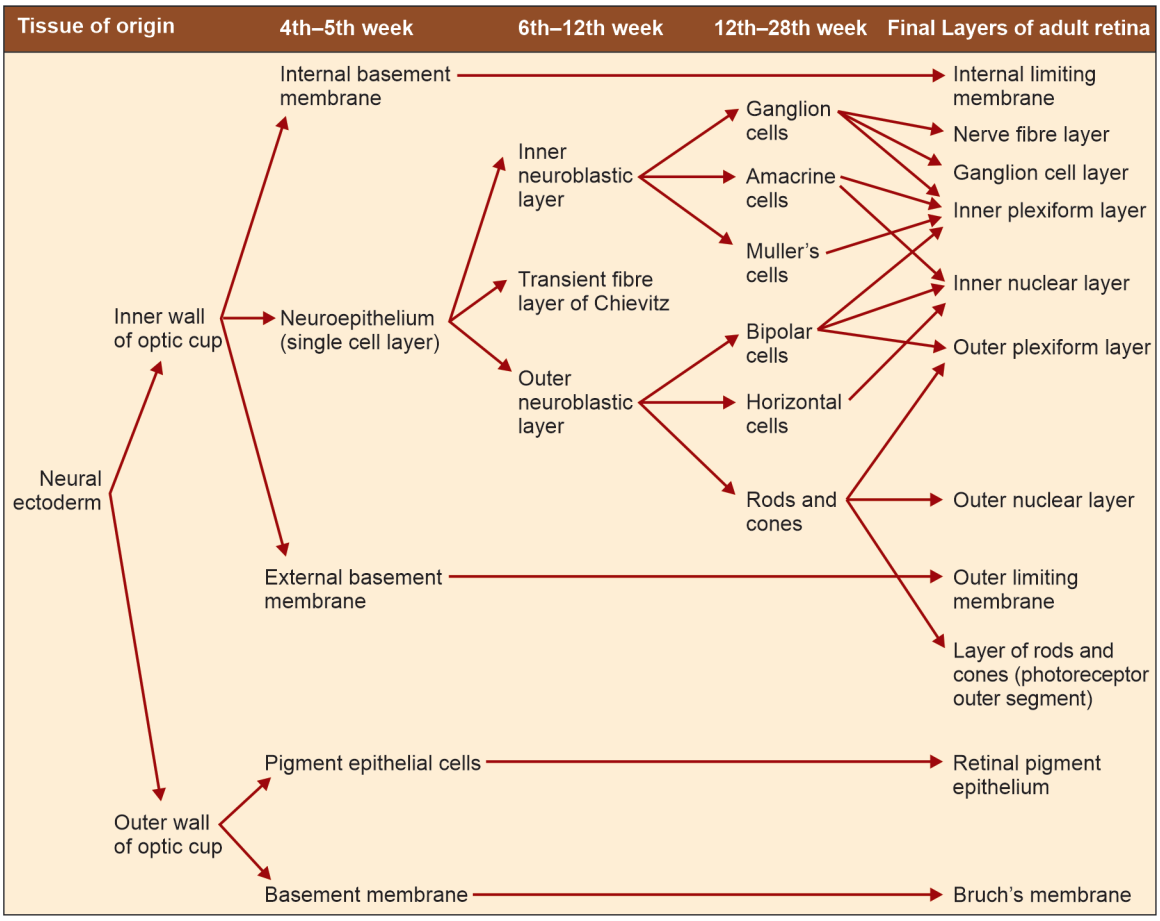

Fig. 1.14. *A schematic flowchart showing the cellular origin of the various layers of the retina during embryogenesis.*

Box 1.3 ***Clinical pearls: Ocular albinism***

Melanocytes that derive their pigment from neural crest (i.e. those located in the choroid, skin, and hair) show a variance that is related to race. Melanocytes that are neuroectodermal in derivation (i.e. retinal pigment, iris, and ciliary body epithelia) are densely pigmented in all races. Melanin production is gene-regulated, and in an individual with albinism either or both types of melanocytes can be affected. Because normal development of sensory retina is influenced by a melanin-related agent produced in the RPE, when pigment is absent from this layer, as occurs in ocular albinism, a number of retinal abnormalities are present at birth in addition to the absence of pigmentation. The macula is underdeveloped and the fovea may be absent. The number of rods may be decreased. Abnormal optic nerve projection to the lateral geniculate nucleus occurs, with more crossed fibres than normal, often resulting in binocular problems.

periphery. Therefore, premature infants are at high risk of developing retinopathy of prematurity, i.e. ROP (Box 1.4).

OPTIC NERVE

It develops in the framework of optic stalk as follows (Fig. 1.11):

- *Optic nerve fibres* develop from the nerve fibre layer of retina which grow into the optic stalk by passing through the choroidal fissure (by 6th week of gestation) and pass posteriorly to the brain.

Box 1.4 ***Clinical pearls: ROP***

Premature infants can develop retinopathy of prematurity (also called retrolental fibroplasia). The immature retinal blood vessels undergo vasoconstriction and cease to develop. Later vasoproliferation occurs; however, the new vessel growth is composed of "leaky" vessels with poorly formed endothelial tight junctions. Potential serious complications include neovascular invasion of the vitreous and development of vitreoretinal adhesions, which may be followed by haemorrhage and retinal detachment.

- *Glial system of the nerve* develops from the neuroectodermal cells forming the outer wall of the optic stalk.
- *The glial septa* surrounding the nerve bundles are composed of astroglia that differentiate from the cells of the inner wall of the optic stalk.
- *Sheaths of the optic nerve* are formed from the layer of mesenchyme which surrounds the optic stalk (like meninges of other parts of central nervous system), between the 3rd and 7th month of gestation.
- *Myelination of the nerve fibres* begins from the chiasma at about 7th month, proceeds distally and reaches the lamina cribrosa just before birth and stops there. In some cases, this extends up to around the optic disc and presents as congenital opaque nerve fibres. These develop after birth.

Note. Malformations of optic nerve head may occur due to faulty closure of posterior part of optic fissure (Box 1.5).

CRYSTALLINE LENS

Lens placode and vesicle

Lens placode, the thickened area of surface ectoderm from which the lens develops, is identifiable by 27 days of gestation (embryo 4–4.5 mm) (Fig. 1.7A). The lens placode invaginates the sinus below the surface ectoderm to form a lens vesicle, which consists of a single layer of cells covered by a basal lamina (Figs 1.8B and C and 1.15).

Box 1.5 ***Clinical pearls: Malformations of the optic nerve head***

Disc coloboma. When there is a failure of closure of the posterior part of the optic fissure, the optic nerve head is deformed by a coloboma, located inferonasally and associated with bulging of the sclera . The coloboma may take the form of a small recess (*optic pit*) at the rim of the disc: this is a herniation of the retina into the meninges and adjacent optic nerve. The clinical importance of an optic pit lies in its association with visual loss due to leakage from the pit and exudation of fluid beneath the *macula. Axial coloboma or 'morning glory* syndrome': The most extreme axial malformation is the 'maming glory syndrome', so-called because of the similarity to the American flower of the same name. This malformation is complicated by severe visual dysfunction and characterized by retrodisplacement of the optic disc into the meninges of the optic nerve. The abnormality is due to a defect in mesodermal organization in the disc; the lamina cribrosa is not formed and there is fat and smooth muscle in the meninges.

Formation of primary lens fibres

The cells of the posterior wall of the lens vesicle rapidly elongate and get filled with proteins called crystallines, which make them transparent. The bases of these densely packed cells remain anchored to the basal laminae posteriorly and their apices grow towards the anterior lens epithelium obliterating the lumen of lens vesicle (Fig. 1.15). These elongated transparent cells are known as primary lens fibres. The nuclei of the lens fibres are present more anteriorly within the cells to form a line convex forward called the nuclear bow. The primary lens fibres now become attached to the apical surface of anterior lens epithelium and their nuclei disappear. The primary lens fibres are formed up to the 3rd month of gestation and are preserved as the compact core of the lens, known as ***embryonic nucleus***. The posterior aspect of the lens, therefore, becomes devoid of epithelium.

Formation of secondary lens fibres

The equatorial cells of the anterior epithelium remain active throughout the life and form the

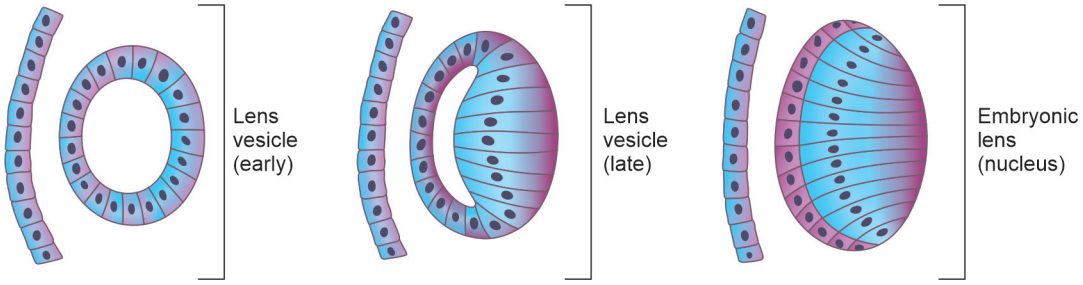

Fig. 1.15. *Development of the crystalline lens.*

so-called secondary lens fibres (Fig. 1.16). Since the secondary lens fibres are laid down concentrically, the lens on section has a laminated appearance. Depending upon the period of development, the secondary lens fibres are named as below:

Fetal nucleus refers to the secondary lens fibres formed from 3rd to 8th month of gestation. The initial lens fibres of fetal nucleus reach both the anterior and posterior poles and they surround the embryonic nucleus. This process mandates that the primary lens fibres (embryonic nucleus) lose their original attachments with the lens epithelium anteriorly and their basal laminae posteriorly. The subsequently formed fibres of fetal nucleus can no longer extend from one pole to the other. Instead they meet at radiating lines or sutures that appear as an erect Y anteriorly and an inverted Y posteriorly (Fig. 1.17). Later in gestation and following birth, the growth of the lens fibres is asymmetric. Therefore, instead of simple Y sutures, a more complicated dendritic pattern is observed in infantile and adult nucleus.

- ***Infantile nucleus*** refers to the secondary lens fibres formed during the last weeks of fetal life to puberty.
- ***Adult nucleus*** is formed by the secondary lens fibres formed after the puberty.
- ***Cortex*** consists of the recently formed superficial secondary lens fibres.

Note. Congenital cataract may develop due to faulty development of lens fibres (Box 1.6).

Formation of lens capsule

The true lens capsule is a membranous noncellular envelope that surrounds the lens. It is a true basement membrane produced as a result of basal laminae material deposited by the lens epithelium on its external aspect.

Tunica vasculosa lentis

During embryonic and fetal development, the lens receives nourishment via an intricate vascular capsule, the tunica vasculosa lentis, that completely encompasses the lens by approximately 9 weeks. It is formed from the mesenchyme

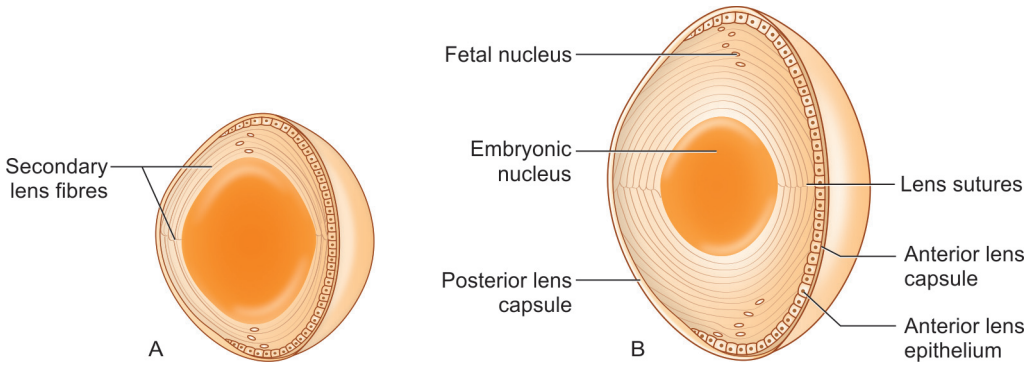

Fig. 1.16. *Formation of: A, Secondary lens fibres 7 weeks; and B, Fetal nucleus.*

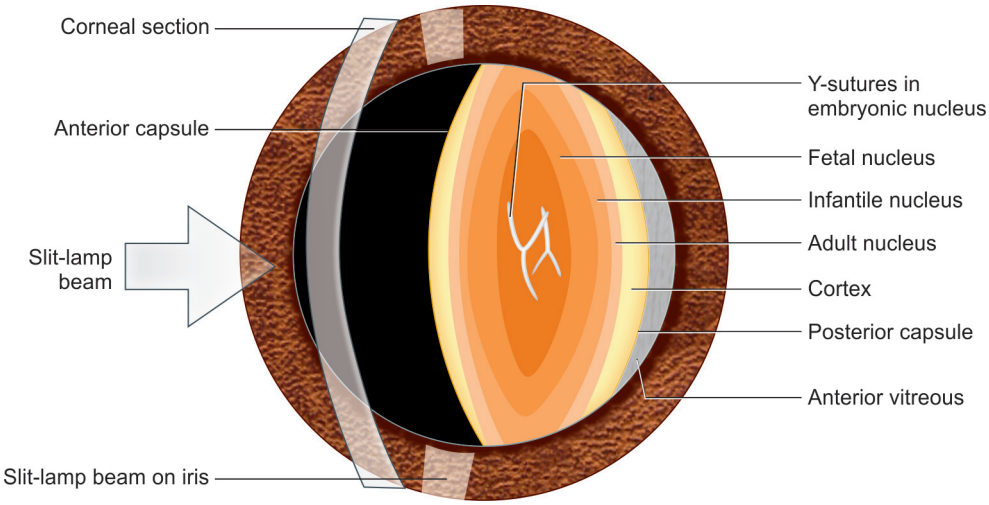

Fig. 1.17. *Y-shaped sutures around the embryonic nucleus can be seen on slit-lamp examination.*

Box 1.6 ***Clinical pearls: Congenital cataract***

The spectrum of lens opacities that results from abnormalities during lens development ranges from pinpoint densities having no effect on vision to significant opacities causing extensive loss of vision. If the tissue near the developing lens fails to induce the lens fibres to elongate and pack together in an orderly way, the lens fibres will be misaligned, forming a cataract of the primary fibres. Interference with secondary lens fibres can lead to sutural cataracts. Viral infection affecting the mother during the first trimester often causes congenital malformations, including a cataract. The developing lens is vulnerable to the rubella virus (German measles) between the fourth and seventh week of development, when the primary fibres are forming. After this period, the virus cannot penetrate the lens capsule and thus will not affect the lens. The cataract usually is present at birth but may develop weeks to months later because the virus can persist within the lens for up to 3 years. The opacity may be dense and opaque or it may be diffuse; the cataract may affect the nucleus only or may involve most of the lens.

that surrounds the lens. Three components of tunica vasculosa are anterior pupillary membrane, capsulopupillary membrane and posterior pupillary membrane (Fig. 1.18). In the earliest stages of development, tunica vasculosa lentis receives an abundant arterial supply from the hyaloid artery. Later, this blood supply regresses, and the vascular capsule disappears before birth. For its nutrition, the lens now depends on diffusion from the aqueous and vitreous.

Formation of lens zonules

They develop from the neuroectoderm in the ciliary region. The earliest fibres of the zonular apparatus are a continuation of the internal limiting membrane that thickens over the nonpigmented epithelium of the developing ciliary processes. They begin to develop at about the 10th week of gestation (45 mm stage). Later, zonular fibres are synthesized by the ciliary epithelial cells, and the zonules increase in number, strength and coarseness. By the 5th month of gestation, the zonules have reached the lens and merge with both the anterior and posterior capsules.

Changes in the developing lens shape

The lens undergoes the following changes in shape during development:

- During initial development, the lens is elongated anteroposteriorly.
- It is nearly spherical, soft and reddish in tint at the 18–24 mm stage.
- As more and more secondary lens fibres are added to the equator, the lens becomes ellipsoid, a trend that continues till birth.

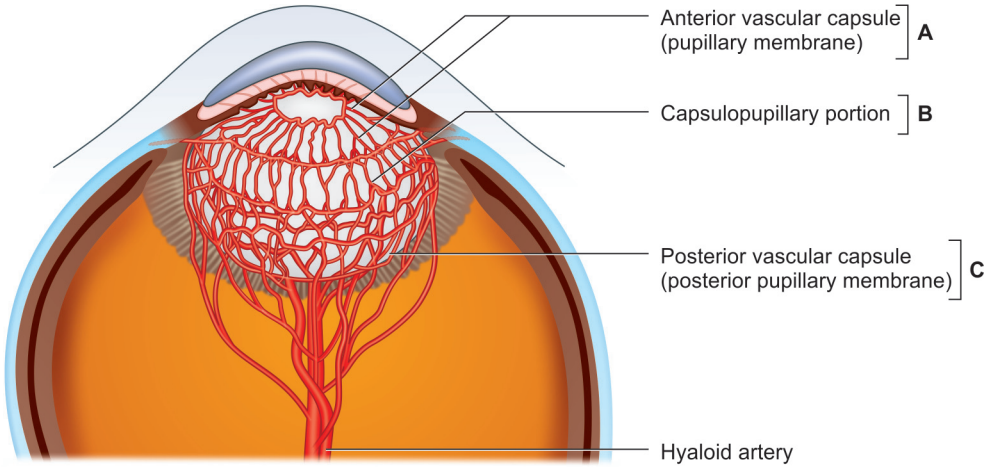

Fig. 1.18. *Three components of tunica vasculosa: A, Anterior pupillary membrane; B, Capsulo pupillary membrane; and C, Posterior pupillary membrane.*

- At birth, the lens is almost spheroidal, being slightly wider in the equatorial plane. The anteroposterior diameter of lens at birth is nearly that of an adult, but its equatorial diameter is about two-thirds of that reached in the adult.

ANTERIOR AND POSTERIOR CHAMBERS, AQUEOUS OUTFLOW PATHWAY AND CORNEA

Mesenchymal mass of neural crest origin is now considered to give rise to the cornea, iris and anterior chamber angle (rather than that of mesodermal origin as thought originally).

Three waves of tissue come forward, between the surface ectoderm and developing lens, from the undifferentiated mesenchymal mass of neural crest cell origin and contribute to formation of structures of anterior segments of eyeball as below:

- *First wave* (Fig. 1.19) differentiates into primordial corneal endothelium by 8th week and subsequently produces Descemet's membrane as well.
- *Second wave* (Fig. 1.19) grows between the corneal epithelium and endothelium and produces corneal stroma.
- *Third wave* (Fig. 1.19) insinuates between the developing cornea and lens and gives rise to the pupillary membrane and stroma of iris (Fig. 1.19).

Anterior chamber cavity is formed as a slit in the mesenchyme between the surface ectoderm and developing iris. The mesenchyme anterior to the slit forms the corneal endothelium and that posterior to the slit forms the primary pupillary membrane.

Angle of the anterior chamber is occupied by a nest of loosely organized undifferentiated neural crest derived mesenchymal cells that are destined to develop into the trabecular meshwork. Thus, development of trabecular meshwork occurs by a simple process of growth and differentiation from the mass of the mesenchymal cells of neural crest cell origin forming angle of developing anterior chamber.

■ ***Concept of anterior chamber angle development*** proposed by Shields MB (published in Trans Am Ophthalmol Soc. 1983;81:736) is as below (Fig. 1.20A to D):

- *Closed cavity of anterior chamber* is created by a continuous layer of endothelial cells (derived from neural crest cells) at 5th month of gestation (Fig. 1.20A).
- *Anterior surface of iris (i)* at this stage is inserted in front of the primordial trabecular meshwork (TM) (Fig. 1.20A).
- *Endothelial layer progressively disappears* in the third trimester, from the pupillary membrane (PM) and iris and cavities over the anterior chamber angle (ACA), possibly becoming incorporated in the trabecular meshwork. At the same time, peripheral uveal tissue begins to slide posteriorly in relation to the chamber angle structure (arrow) (Fig. 1.20B).

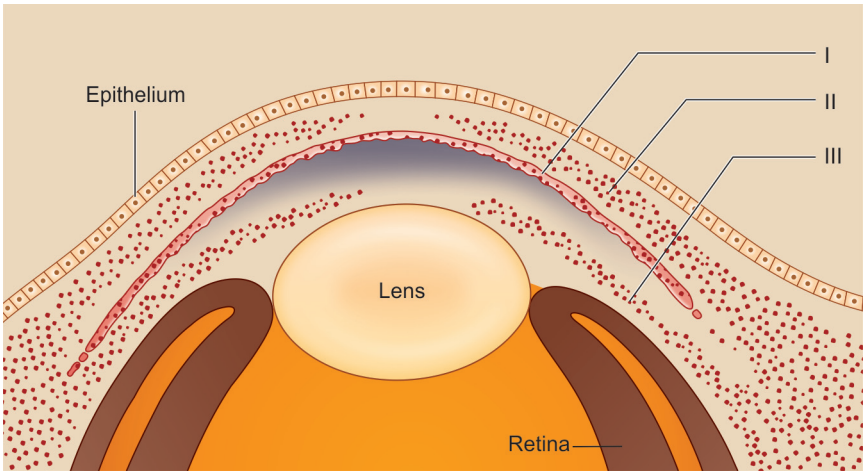

Fig. 1.19. *Three successive waves of ingrowth of neural crest cells contributing to formation of structures of anterior segment: I, First wave forms the corneal endothelium; II, Second wave forms corneal stroma III, Third wave forms the iris and part of the pupillary membrane (from: Tripathi BJ, Tripathi RC, Wisdom J. Embryology of the anterior segment. Elds MB, Krupin T, eds. The Glucomas. 2nd ed. St Louis: Mosby: 1996).*

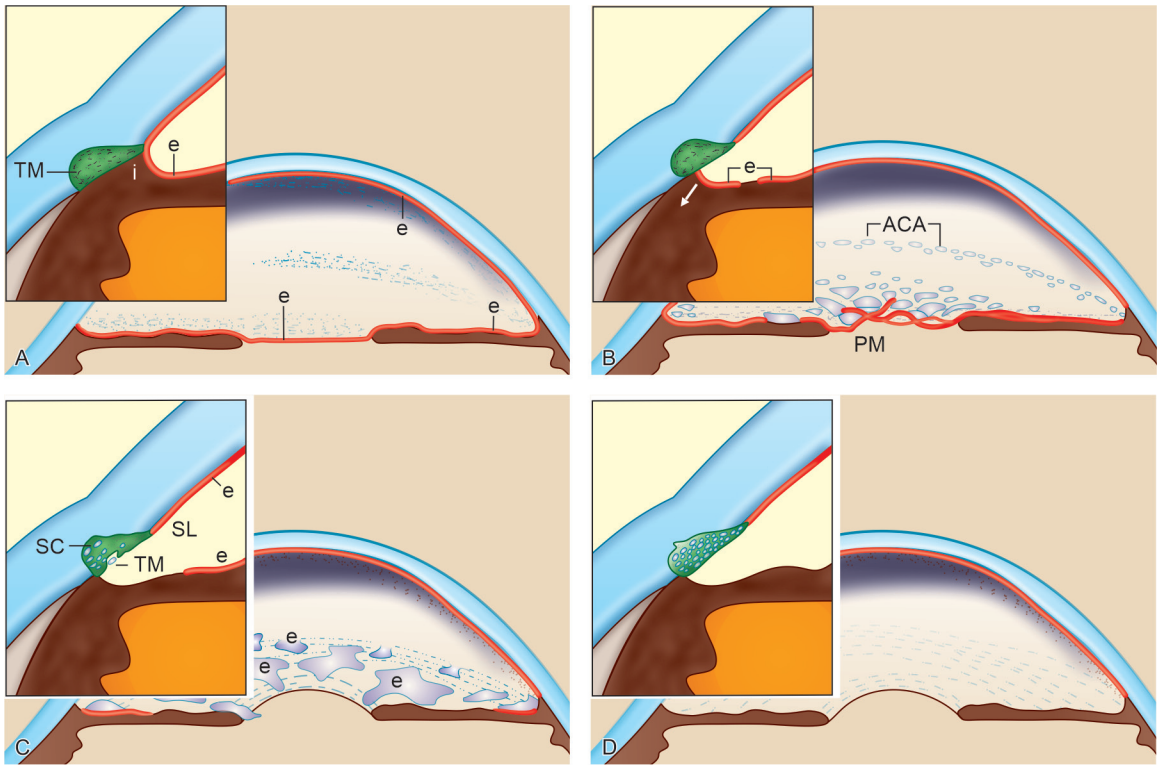

Fig. 1.20. *Development of anterior chamber angle: A, At 5 months, a continuous layer of endothelium (e) creates a closed cavity of anterior chamber and anterior surface of iris (i) inserts in front of primordial; trabecular meshwork (TM); B, In third trimester, endothelial layer progressively disappears from pupillary membrane and iris cavitates over the anterior chamber angle (ACA); C, Development of trabecular lamellae and intertrabecular spaces progressing towards Schlemm's canal (SC) and Schwalbe's line (SL); D, Normal anterior chamber angle is not developed until 1 year of age. (Source: Redrawn from Shields MB; Published in Trans Am Ophthalmol Soc 1983;81:736).*

- *Development of the trabecular lamellar* and intratrabecular spaces begins in the inner posterior aspect of the primordial tissue and progresses towards the developing Schlemm canal (SC), and Schwalbe line (SL) (Fig. 1.20C).
- *Normal anterior chamber angle*, as shown in Fig. 1.20D, is not fully developed until 1 year of age.

Schlemm's canal develops by the end of third month of gestation from the channels derived from mesodermal mesenchyme. Thus, the embryological origin of trabecular cells (neural crest derived mesenchyme) is different from that of vascular endothelial cells of Schlemm's canal (mesodermal mesenchyme).

Posterior chamber develops as a split in the mesenchyme posterior to the developing iris and anterior to the developing lens (Fig. 1.11). The anterior and posterior chambers communicate when the pupillary membrane disappears and the pupil is formed.

CORNEA

Development of various layers of cornea is summarized below (Figs 1.11, 1.19 and 1.21):

1. *Epithelium* is formed from the surface ectoderm. At about 40 days of gestation (embryo 17–18 mm), corneal epithelium consists of a superficial squamous cell layer and a basal cuboidal epithelial cell layer (Fig. 1.21A). By 3 months of gestation, epithelium is 3-layered (Fig. 1.21D) and by the time the eyelids open at 5–6 months of gestation, the corneal epithelium attains an almost adult appearance.

2, 3. *Stroma and Bowman's layers* are derived from the mesenchymal cells that insinuate between the surface ectoderm and the developing lens.

- *Primary corneal storma* is secreted by basal layer of epithelium and consists of fine filaments, amorphous material and only a few collagen fibrils.
- *At about 22–24 mm stage* (7th–8th week), the mesenchymal cells migrate into the primary

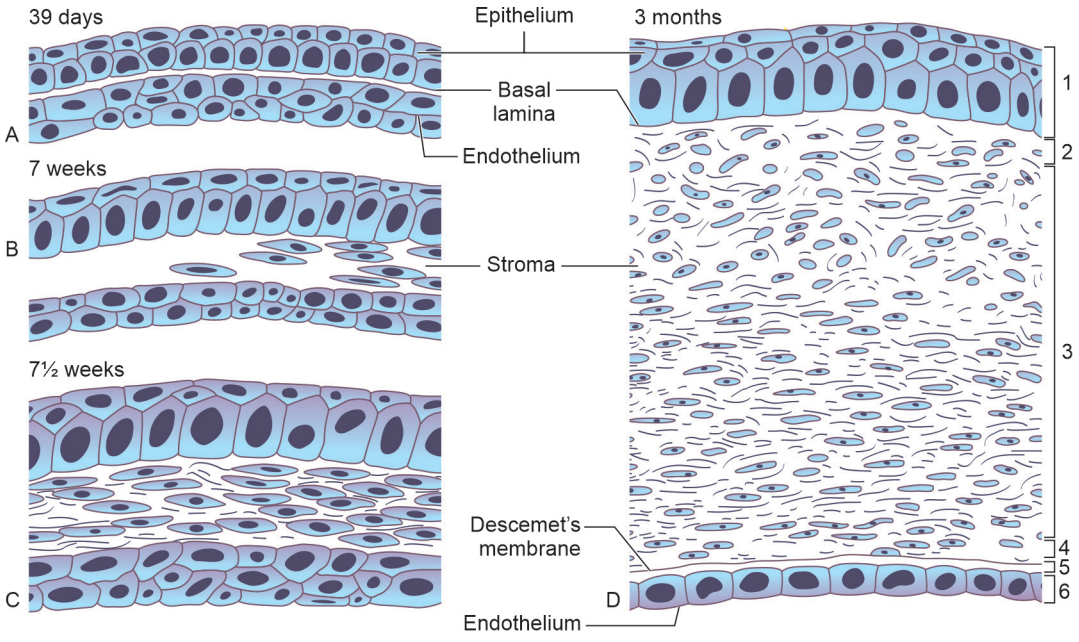

Fig. 1.21. *Development of the cornea in the central region. A, At day 39, 2-layered epithelium rests on the basal lamina and is separated from the endothelium (2–3 layers) by a narrow acellular space. B, At week 7, mesenchymal cells from the periphery migrate into the space between the epithelium. C, Mesenchymal cells (future keratocytes) are arranged in 4–5 incomplete layers by 7½ weeks; a few collagen fibrils are present among the cells. D, By 3 months, the epithelium has 2–3 layers of cells, and the stroma has about 25–30 layers of keratocytes that are arranged more regularly in the posterior half.*

corneal stroma (between epithelium and endothelium) and contribute to the further development of corneal stroma (Fig. 1.21B).

- *The invading mesenchymal cells differentiate into stromal fibroblasts* or keratocytes that actively secrete the type I collagen fibrils and the matrix of mature (secondary) corneal stroma.
- *Bowman's layer* starts forming by condensation of most superficial acellular part of corneal stroma after 4 months of gestation and is fully developed at birth.
- *By 5 months*, corneal nerves are present. It is important to note that the fetal cornea is very hydrated compared to the adult form and is, therefore, translucent rather than transparent.

4, 5, 6. *Endothelium, pre-Descemet's membrane and Descemet's membrane* are formed from mesenchymal cells derived from neural crest, which are situated at the margins of the rim of the optic cup. These cells migrate into the developing eye beneath the basal lamina of the corneal epithelium and form the primordial corneal endothelium.

- *At about 40 days of gestation* (17–18 mm embryo), the corneal endothelium consists of two layers of flattened cells (Fig. 1.21A).
- *By the third month* (embryo 63 mm), the endothelium in the central region of cornea becomes a single layer of flattened cells that rest on their interrupted basal lamina—the future Descemet's membrane (Fig. 1.21D).
- *Apices of the endothelial cells* are joined by zonulae occludentes in the middle of the 4th month, which corresponds to the production of aqueous humour by the ciliary processes.
- *At the 6th month of gestation*, Descemet's membrane is demarcated clearly.

Malformations of cornea

A few corneal malformations are highlighted in Box 1.7.

Box 1.7 *Clinical pearls: Corneal malformations*

Corneal leucoma: Corneal opacification may be due to a failure of the keratocytes to produce collagen fibres arranged in a lamellar structure, instead the pattern resembles sclera (scleralization of the cornea).

Peter's anomaly is a term used to describe a posterior axial stromal defect associated with incarceration of the pupillary part of the iris at the edge of the defect.

Embryotoxon. A mild form of malformation is the presence of thickening at the periphery of Descemet's membrane (Schwalbe's line). When this is visible clinically it takes the form of a bow, hence the term *embryotoxon*.

Broad strands of tissue derived from the iris are sometimes seen in the chamber angle. In *Axenfeld's anomaly*, iridocorneal strands are localized to Schwalbe's line. When 'iris hypoplasia' is present, the malformation is known as *Rieger's anomaly*.

SCLERA

Sclera (Fig. 1.11) is developed from the mesenchymal cells surrounding the optic cup (corresponding to dura of CNS). Most of the mesenchymal cells are derived mainly from the neural crest. However, those in the caudal region of the sclera are probably derived from the paraxial mesoderm that lies juxtaposed to the caudomedial surface of the optic cup throughout the period of crest cells migration. The process starts at the limbal-equatorial region (future site of extraocular muscle insertion), around 7th week of gestation and is completed by 5th month. Deposition of elastin and glycosa aminoglycans are added to extracellular matrix at a later date.

UVEAL TISSUE

Choroid

It is mainly derived from the inner vascular layer of the mesenchyme that surrounds the optic cup (Fig. 1.11). Melanocytes of choroid originate from the neural crest.

Ciliary body

- *Both epithelial layers of ciliary body* develop from the anterior part of two layers of optic cup (neuroectoderm) (Fig. 1.11). The ciliary epithelium undergoes a convulating or folding movements to form about 70–75 ciliary processes.

- *Stromas of ciliary body*, ciliary muscle and blood vessels are developed from the vascular layer of mesenchyme surrounding the optic cup.

Iris

- *Both layers of epithelium* are derived from the marginal region of optic cup (neuroectodermal) (Figs 1.11 and 1.19).
- *Sphincter and dilator pupillae* muscles are derived from the anterior epithelium (neuroectodermal).
- *Stroma and blood vessels* develop from vascular layer of mesenchyme present anterior to the optic cup. Towards the end of gestation, the central iris stroma (pupillary membrane) disappears forming the pupil. Sometimes a few strands of this tissue are left as *persistent pupillary membrane.*

Aniridia, i.e. developmental absence of iris may occur in some cases (Box 1.8).

VITREOUS

1. *Primary or primitive vitreous* is mesenchymal in origin and is a vascular structure having the hyaloid system of vessels. It is present in between the 4th and 5th weeks of gestation (Fig. 1.11). Surface ectodermally derived elements that surround the lens during invagination are also thought to contribute to the primary vitreous. Thus the primary vitreous may be of mixed ectodermal and mesenchymal origin.

It is composed of cytoplasmic processes derived from ectoderm of lens and neuroectoderm of optic cup, which is joined by mesenchymal vascular structures called the hyaloid system.

2. *Definitive or secondary or vitreous proper* is secreted by neuroectoderm of optic cup from 2nd month of gestation onwards. This is an avascular structure, basically an extracellular matrix, consisting mainly of a compact network of type II collagen fibrils and primitive hyalocytes. The precise origin of hyalocytes is presumed to be from the phagocytic monocytes of the primary vitreous which are derived from mesenchymal cells. The content of hyaluronic acid is very low during the prenatal period, but increases after birth. When this vitreous fills the cavity by 5th to 6th months of gestation, primitive vitreous is reduced to a small central space, *Cloquet's canal*, which courses between the optic nerve head and the posterior surface of the lens.

Note. Sometimes the hyaloid system persists as malformations (Box 1.9).

3. *Tertiary vitreous* is developed from neuroectoderm in the ciliary region during 4th month of gestation and is represented by the vitreous base and ciliary zonules.

Box 1.8 *Clinical pearls: Aniridia*

Aniridia is a rare autosomal dominant bilateral disease in which there is an apparent absence of the iris. The term is a misnomer, because histologically the abnormal iris is seen as a stump of hypercellular stroma often with an abnormal proliferation of the pigment epithelium. Malformation or hypoplasia of the outflow system occurs in aniridia, as do anterior and posterior cortical lens opacities. The lens may dislocate (ectopia lentis) and the optic nerve may be hypoplastic. It is now well known that aniridia is coused by mutations of the pox-6 gene. Other mutations have been identified in Peter's anomaly and corneal dystrophy, supporting the suggestion that this gene is a crucial transcription factor gene for ocular development.

Box 1.9 *Clinical pearls: Malformations of the vitreous and hyaloid artery system*

Normally, the hyaloid system of vessels vanishes completely, but in some disorders regression does not occur and dense vascularized collagenous tissue contracts and deforms the normal tissues of the anterior and posterior segment. Persistent tunica vasculosa lentis. Persistence of the anterior port of the tunica vasculosa lentis or the pupillary membrane causes deformation of the iris.

Persistent hyperplastic (anterior) primary vitreous. If the embryonic fibrovascular tissue in the anterior vitreous face persists, the ciliary processes are drawn internally. The lens is opaque in persistent hyperplastic anterior primary vitreous, because a retrolental fibrovascular mass erodes the posterior lens capsule and penetrates the lens cortex.

DEVELOPMENT OF OCULAR VESSELS

- ***Primitive dorsal and ventral ophthalmic arteries*** bud inward from the internal carotid artery in the mesenchyme surrounding the optic vesicle late in the fourth week and join a loose reticulum of capillaries around the optic vesicle.

- ***Hyaloid artery*** develops as a branch of primitive dorsal ophthalmic artery. After getting incorporated in the optic cup, the hyaloid system extends up to the lens and joins the tunica vasculosa lentis (Fig. 1.18). These vessels nourish the developing eye and disappear in the third trimester.

- ***Stapedial artery***, a transient vessel, arises from the carotid to supply the expanding orbit. Later, the distal part of stapedial artery is annexed to the ophthalmic artery.

- ***Definitive ophthalmic artery*** is developed from the primitive dorsal ophthalmic artery at the sixth week of gestation, while the primitive ventral ophthalmic artery almost disappears, only a portion of it remains as the nasal long posterior ciliary artery.

- ***Temporal long posterior ciliary artery, short posterior ciliary arteries and central retinal artery*** grow as buds from the ophthalmic artery.

- ***Major arterial circle of iris*** is formed by a coalescence of branches from the long ciliary arteries in the mesenchyme that surrounds the optic cup.

- ***Minor arterial circle of iris*** remains peripherally after the disappearance of pupillary membrane.

DEVELOPMENT OF ACCESSORY OCULAR STRUCTURES

EYELIDS

Eyelids are formed by reduplication of surface ectoderm above and below the cornea during 2nd month of gestation (Fig. 1.22). The folds enlarge and their margins meet and fuse with each other. The lids cut off a space called conjunctival sac. The folds thus formed contain some mesoderm which would form the muscles of the lid and the tarsal plate. The lids separate after seventh month of intrauterine life.

- *Tarsal glands* are formed by ingrowth of a regular row of solid columns of ectodermal cells from the lid margins.
- *Ciliary glands* are outgrowths from the ciliary follicles.
- Cilia develop as epithelial buds from lid margins.

CONJUNCTIVA

It develops from the ectoderm lining of the lids and covering the globe (Fig. 1.22).

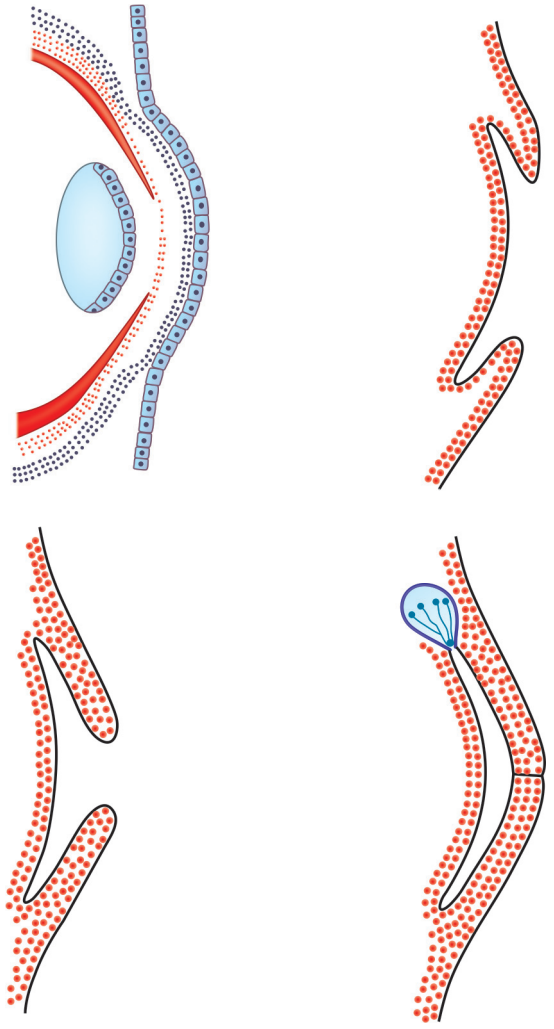

Fig. 1.22. *Development of the eyelids, conjunctiva and lacrimal gland.*

- *Conjunctival glands* develop as growth of the basal cells of upper conjunctival fornix. Fewer glands develop from the lower fornix.

LACRIMAL APPARATUS

Lacrimal gland

Lacrimal gland develops by epithelial-mesenchymal interaction.

Epithelial buds, about 8 in number and cuneiform in shape grow from the superolateral side of the conjunctivals by the end of second month of fatal life (Figs 1.22 and 1.23).

Mesenchymal cells, derived from the neural crest, aggregate at the tips of epithelial buds.

Acini, develop from the differentiation of mesenchymal cells aggregated at the tips of epithelial buds.

Formation of lacrimal glands structure is as below (Fig. 1.23)

- *Acini.* Neural crest derived mesenchymal cells aggregate at the tips of the buds and differentiate into acini.
- *Ducts* of the glands are formed by vaculation and development of lumen in the cord cells.
- *Gland becomes divided into orbital and palpebral parts* with development of levator palpebrae superioris (LPS) muscle.
- *Reflex tear production* from the lacrimal glands occurs after 20 days of birth, that is why the infant cries with tears.

Lacrimal sac, nasolacrimal duct and canaliculi

These structures develop from the ectoderm of nasolacrimal furrow which extends from the medial angle of eye to the region of developing mouth. The ectoderm gets burried to form a solid cord which is later canalised. The upper part forms the *lacrimal sac*. The *nasolacrimal duct* is derived from the lower part as it forms a secondary connection with the nasal cavity. Some newborns may have congenital nasolacrimal duct (NLD) blockage (Box 1.10).

Some ectodermal buds arise from the medial margins of eyelids. These buds later canalise to form the *canaliculi*. The lower lacrimal canaliculus, as it extends laterally, cuts off a part of the eyelid with its components which forms *caruncle* and *plica semilunaris.*

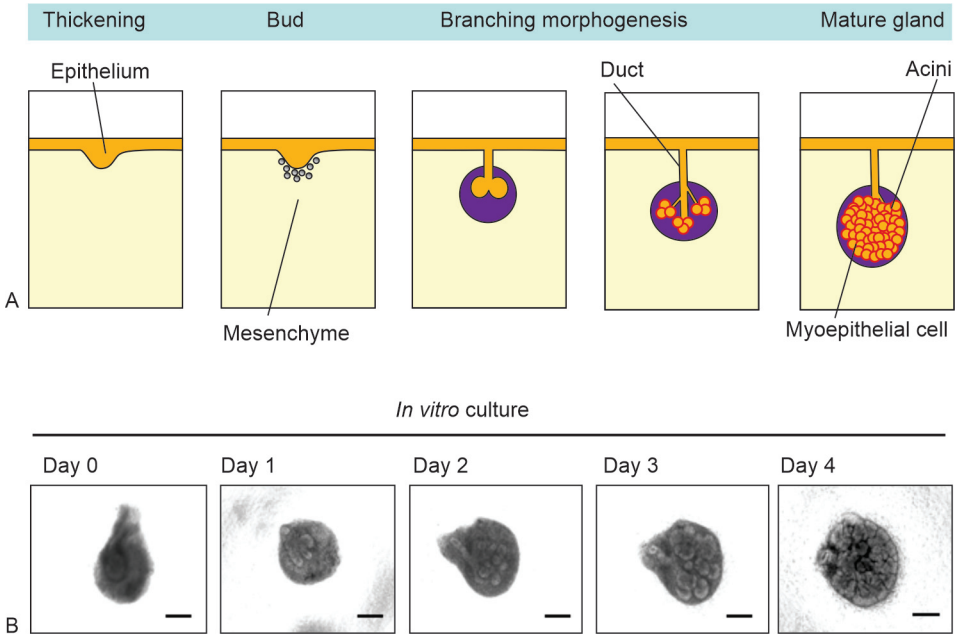

Fig. 1.23. A, Development of lacrimal gland by interaction of epithelial cells with mesenchymal cells (derived from neural crest); B, In vitro culture of mouse lacrimal gland

Box 1.10 ***Clinical pearls: Developmental anomalies of the nasolacrimal duct***

Disturbances in morphogenetic processes may lead to multiple canaliculi and punctae, abnormal diverticulae, and blockage of the nasolacrimal duct, possibly because of debris from the degenerating central cells producing a mucocoele (not uncommon in the first few weeks after birth).

DEVELOPMENT OF EXTRAOCULAR MUSCLES

The extraocular muscles are some of the few periocular tissues that have been shown not to be of neural crest origin. Recently, they are thought to differentiate *in situ* from the mesodermal derived mesenchymal tissue which constitutes the myotomic cells of the preotic mesodermal somites that have shifted cranially.

Interaction between neural crest, mesenchymal tissue (from which extraocular muscles develop) and the neural ectoderm from which the various structures of eye develops (Fig. 1.24).

- The four rectus muscles and the superior and inferior oblique muscles differentiate from the mesenchyme in the region of developing eyeball *(prechordal mesenchyme).*
- Originally represented as a single mass of mesenchyme, they later separate into distinct muscles, first at their insertions and later still at their origins.
- *Myoblasts* with myofibrills and immature Z bands are distinguishable by the 5th week of gestation.
- *The extraocular muscles appear in approximately the following sequences:* lateral rectus, superior rectus and levator palpebral superioris (week 5), superior oblique and medial rectus (week 6), followed by inferior oblique and inferior rectus (common primordium).
- *During development, the extraocular muscles become associated with* the axons of the general somatic efferent neurons of cranial nerves III, IV and VI, which innervate these muscles.

DEVELOPMENT OF ORBIT

The orbit develops around the eyeball. It is derived above from the mesenchyme that encircles the optic vesicle and mesenchymal capsule of forebrain, below and laterally from the maxillary processes, medially by the frontonasal process and behind by the pre- and orbitosphenoid. The orbital bones are formed in the membrane except those belonging to the base of skull, which develop in the cartilage. These bones differentiate during the 3rd month and later undergo ossification. Initially, the optic axes are directed laterally toward the side of head; only later are they directed anteriorly. At birth, orbit is hemispherical. Its growth corresponds with the growth of the eyeball. Although, the eyeball reaches the adult size by 3 years of age, the orbit undergoes considerable alterations in shape and grows progressively until puberty.

■ ***Craniofacial abnormalities*** involving orbit may occur due to deficts in neural crest cell migration and differentiation (Box 1.11).

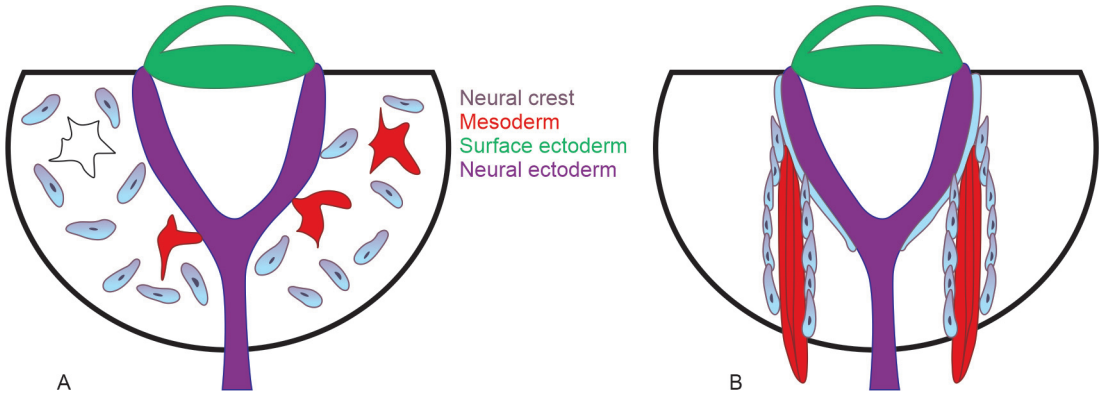

Fig. 1.24. A, Interaction between neural crest and mesenchymal tissue (mesoderm); B, Normal development of extraocular muscles

Box 1.11 ***Clinical pearls: Craniofacial abnormalities***

It is now recognized that a group of craniofacial abnormalities, the mandibulofacial dysostoses, including Treacher-Collins and Hallerman-Streif syndromes, are most likely caused by deficits in neural crest cell migration and differentiation in the first and second pharyngeal arches. These manifest as abnormal ear development, hypoplasia of the maxilla and mandible, and lower lid defects. These and more generalized disturbances of neural crest migration, e.g. Rieger's syndrome, Pierre Robin syndrome, and conditions affecting primarily the periocular region such as Peter's anomaly, are increasingly being classified as neurocristopathies because of their proposed link to disturbances in neural crest cell migration, proliferation, and differentiation.

SUMMARY AND MILESTONES OF DEVELOPMENT OF OCULAR STRUCTURES

STRUCTURES DERIVED FROM THE EMBRYONIC LAYERS

Based on the above description, the various structures derived from the different embryonic layers can be summarized as below:

1. Surface, ectoderm
- The crystalline lens
- Epithelium of the cornea
- Epithelium of the conjunctiva
- Lacrimal gland
- Epithelium lining the lacrimal apparatus
- Skin of eyelids and its derivatives, viz. cilia, tarsal glands and conjunctival glands.

2. Neuroectoderm
- Retina with its pigment epithelium
- Epithelial layers of ciliary body
- Epithelial layers of iris
- Sphincter and dilator pupillae muscles
- Optic nerve (neuroglia and nervous elements only).

3. Periocular mesenchyme derived from the neural crest and associated paraxial mesoderm
- Blood vessels of iris, choroid, ciliary vessels, central retinal artery and other ocular vessels
- Substantia propria, Descemet's membrane and endothelium of cornea
- Sclera
- Stroma of iris
- Ciliary muscle and stroma of ciliary body
- Sheaths of optic nerve
- Extraocular muscles
- Fat, ligaments and other connective tissue structures of the orbit
- Superior and medial walls of the orbit
- Connective tissue of the upper eyelid.

4. Visceral mesoderm of maxillary process below the eye
- Inferior and lateral walls of orbit
- Connective tissue of the lower eyelid.

MILESTONES IN THE DEVELOPMENT OF OCULAR STRUCTURES

PRE-EMBRYONIC PERIOD (FERTILIZATION TO END OF THIRD WEEK)
- Formation of the principal germinal layers
- Formation of the neural plate and neural groove.

EMBRYONIC PERIOD (BEGINNING OF 4TH TO END OF 8TH WEEK)

22 days (2.6 mm stage)

Appearance of the optic pits in neural folds.

25 to 28 days (3.2 mm stage)
- Invagination of primary optic vesicle
- Beginning of lens placode formation
- Condensation of mesoderm determining extraocular muscles.

5th week (4–8 mm stage)

4 to 4.2 mm stage
- Full development of primary optic vesicle
- Earliest appearance of the primitive and marginal zones of the presumptive retina.

4.5 to 5 mm stage

- Beginning of invagination of optic vesicle to form optic cup
- Formation of the lens pit
- Ophthalmic artery emerges from the internal carotid.

5.5 to 6 mm stage

- Development of embryonic fissure
- Hyaloid artery emerges from the primitive dorsal ophthalmic artery.

7 mm stage

- Lens pit has developed into a closed vesicle in contact with the surface ectoderm.
- Hyaloid artery enters the embryonic fissure and reaches up to posterior pole of the lens vesicle.

6th week (8–15 mm stage)

8 to 9 mm stage

- Lens vesicle becomes hollow sphere detached from the ectoderm.
- Hyaloid artery takes part in the formation of the posterior part of the tunica vasculosa lentis.

11 to 12 mm stage

- Beginning of closure of embryonic cleft in its mid-portion.
- Second stage of retinal differentiation with formation of primitive inner nuclear layer.
- Formation of lens fibres from posterior epithelial cells of lens vesicle.

13 to 14 mm stage

- Almost complete closure of embryonic fissure except at anterior and posterior extents.
- Optic nerve fibres travelling proximally into optic nerve.
- Beginning of development of secondary vitreous.
- Choriocapillaris is completely formed.
- Double layer of cells at the surface ectoderm forms the corneal epithelium.
- Orbital mesoderm begins to differentiate into extraocular muscles.

7th week (15–22 mm stage)

15 to 16 mm stage

- Distal end of embryonic fissure is completely closed.
- Differentiation of inner and outer neuroblastic layers of retina affected by appearance of transient fibre layer of Chievitz at posterior pole.
- Rudiments of lids have developed into definite folds and the fibres of the orbicularis oculi muscle begin to surround the eye.

17 to 18 mm stage

- Formation of anterior portion of tunica vasculosa lentis.

20 to 21 mm stage

- Proximal remnant of embryonic fissure closed.
- Beginning of nerve fibre crossing to form the optic chiasma.
- Separation of corneal epithelium and endothelium by acellular layer.
- Nuclei of primary lens fibres disappear.
- Lid folds gradually cover the eyes.
- Canaliculi are present.

8th week (22–30 mm stage)

- Optic chiasma is fully formed.
- Penetration of acellular layer of cornea by mesoderm to form the corneal stroma.
- Pupillary membrane is completely formed.
- Beginning of anterior chamber can be discerned.
- All the motor nerves of the eye have reached the extraocular muscles.

FETAL PERIOD (BEGINNING OF 3RD MONTH TO BIRTH)

9th week (30–40 mm stage)

- Ciliary body begins to appear.
- Secondary vitreous is fully evident.
- Y-sutures are now apparent in the embryonic nucleus of the lens.

10th week (40–50 mm stage)

- Zonule makes its appearance.
- Bowman's membrane is forming.

- Tenon's capsule begins to form in the equatorial region.
- Fibres of the orbicularis oculi are forming.
- At the end of this period, optic tracts have formed.

11th week (50–60 mm stage)

- Macula begins to differentiate.
- Differentiation of the occipital cortex occurs.
- The hyaloid system is maximally developed.
- Rectus muscles are well differentiated.
- Levator separates from the superior rectus.

12th week (60–70 mm stage)

- Sphincter pupillae appear.
- The limbus is well demarcated and the canal of Schlemm emerges.
- Hyaloid system begins to atrophy.
- Orbicularis is well developed.

4th month (70–110 mm stage)

- Ciliary processes are fully formed.
- Secondary vitreous develops considerably.
- Lashes and glands of the lids appear and the plica is well formed.
- Tenon's capsule is fully formed.
- Orbital walls are well developed.

5th month (110–150 mm stage)

- Myelination in the geniculate body is evident.
- All layers of the choroid are now visible and melanoblasts appear in its external portion.
- Iris is fully developed.
- Extraocular muscles have differentiated their tendinous insertions.
- Dural sheath of the optic nerve can be distinguished.

6th month (150–200 mm stage)

- Dilator pupillae begin to form.
- Sphincter muscle of the pupil is fully differentiated.
- Descemet's membrane has appeared.
- Anterior chamber angle is forming peripherally.

7th month (200–230 mm stage)

- Rods are differentiated in the retina.
- Fovea becomes obvious.
- Bergmeister's papilla begins to atrophy.
- Lacrimal canaliculi have opened on to the lid margins and the tarsus is well formed in the upper lids.

8th month (230–265 mm stage)

- All layers of the retina are extensively developed throughout.
- Retinal vessels have reached the ora.
- Fetal nucleus of the lens is complete.
- Circulation of the anterior segment is complete
- Angle of anterior chamber is formed completely.

9th month (265–300 mm stage)

- Diameter of the globe increases to 16 to 17 mm.
- Except macula, general development of the retina is now complete.
- Retinal vessels reach the periphery.
- Infantile nucleus of the lens begins to appear.
- Pupillary membrane and hyaloid vessels have disappeared.
- Formation of the physiologic cup of the disc begins.

At term

- Apart from the fovea, the retina is fully differentiated
- Myelination of optic nerve fibres has reached the lamina cribrosa.
- Coiled remnants of the hyaloid artery have attached anteriorly up to the posterior lens capsule and float freely in Cloquet's canal.
- Lacrimal gland is still undeveloped and tears are not secreted.
- Nasolacrimal duct has reached the nasal cavity but is frequently separated from the inferior meatus by a membrane.

POSTNATAL PERIOD

ORBIT

Changes in the orbital anatomy parallel that of the development of the skull and facial bones.

■ ***Angle between the orbital axes.*** At first the angle between the orbital axes is nearly 180° in

intrauterine life with continuous growth and middle structural changes of face, the wyes become gradually oriented more frontally. At birth, the angle is reduced to about 71°. The adult condition of 68° is not achieved until adolescence.

■ ***Orbital opening*** is almost circular in outline at birth, the vertical diameter being about the same as the horizontal diameter: but in adults, the latter increases giving a horizontally oval configuration.

■ ***Volume of the orbit*** at birth is 10.3 ml, doubling by 1 year to 22.3 ml, and reaching the adult volume of 30 ml by 6–8 years. Orbital volume at various ages is as below:

- Birth: 10.3 mm^3
- 1 yr: 22.3 mm^3
- 6–8 yr: 39.1 mm^3
- Adult: Males 59.2 mm^3
  Females 52.4 mm^3

■ ***Bony interorbital distance*** in children is small and narrow (relatively hypoteloric) because of the absence of ethmoidal and frontal air cells. This may per se give the impression of pseudostrabismus since the eyes look too close together, but with the growth of ethmoidal and frontal sinuses later on, the distance increases and the pseudostrabismic look disappears. On the other hand, excess soft tissue changes over the bridge of the nose will produce apparent telecanthus in children which will disappear with age. This picture may also produce the impression of apparent hypertelorism which is really not present.

Any alterations in the intercanthal/orbital distances and orbital volume changes (shallow orbit with exorbitism) will produce *craniofacial dysmorphias*. In long headed skulls (scaphocephaly), the orbits may tend to look more laterally than in the short headed skulls (brachycephaly).

■ ***Infraorbital foramen*** is present at birth but it is a terminal notch of the infraorbital groove whose roof has not yet grown to form a canal.

■ ***Optic canal*** at birth is actually a foramen but later becomes canal, and at 1 year its length is 4 mm.

■ ***Periorbita*** is much thicker, stronger, and also more firmly adherent in neonates then in the adult, and these facts have to be borne in mind while carrying our orbital exenteration in children. The higher incidence of failure in paediatric DCR is because the cut edges of the bony ostium grow actively and may occlude the opening. Also, collapse of the nasal bridge may lead to a deformity. This is why DCR in children is usually delayed till preferably 4–5 years of age (the earliest may be 3 years).

LIDS AND LACRIMAL APPARATUS

Palpebral fissure

Vertical dimensions

- <1 year: 8–8.5 mm
- 1–10 year: 9 mm

Horizontal dimensions

- Birth: 18 mm
- 1st year: Little change
- 1–10 year: Rapid increase to adult level of 30 mm

Lacrimal system

- *Excretory and secretory functions* of the lacrimal apparatus are operational in most normal infants at birth.
- *Basal and reflex tear secretions* are also demonstrated in more than 80% of infants, at birth. Though psychic and emotional tearing occurs several months after life.
- *Development of the nasolacrimal duct* or NLD for the most part is complete at birth. However, congenital impotency of NLD occurs in some infants. The incidence varies, but early conservative management with hydrostatic sac massage has a definitive role in its cure in almost 90% of them.

EXTRAOCULAR MUSCLES

Rectus muscles

- *Thinner* at birth.
- *Width of insertion* is 6.8–7.6 mm at birth, which is 2.5–3 mm less than in adult. Adult level is reached by 20 months of age.

- *Distance from insertion to limbus*
  - At birth 2 mm less than in adult
  - 6–9 months 1 mm less than in adult
  - 20 months Adult-like
  - Insertion of lateral rectus is at 1–2 mm in front of equator, at birth.
  - Insertion of medial rectus is at 1–2 mm in front of equator, at birth.

EYEBALL

Size of eyeball

- Birth: 70% of its adult size
- By 3 years: 90% of its adult size
- Anterior segment at birth = 75.80% of adult size
- Posterior segment at birth = <50% of adult size

Axial length

- Birth 16.00 mm
- 18 months 20.3 mm
- 5 years 21.4 mm
- 13 years 21.4 mm
- Adults 23.6 mm

Sclera and cornea

Scleral thickness at equator

- At birth 0.45 mm
- Adult 1.09 mm
- Birth 80% of adult diameter
- 1 year 95% adult diameter

Changes in cornea with age

- *Enlarges in diameter:* Horizontal diameter increases to 11–12 mm by 1 year from 9.8 mm (9.0–10.5 mm) at birth
  Vertical diameter 10.4 mm
- *Curvature flattens as below:*
  - At birth 51.2 D
  - 6 month 45.2 D
  - Adult 43.5 D
- *Central corneal thickenss decreases:*
  - At birth 0.96 mm
  - 6 month 0.52 mm

Anterior chamber and intraocular pressure

Depth of anterior chamber

- Birth 2.6 mm (2.4–2.9 mm) at birth
- Width Changes little

Anterior chamber morphology at birth

- Anterior insertion of iris (to just behind scleral spur).
- More translucent appearance of the trabecular meshwork.
- Trabecular meshwork is less pigmented.
- Attains adult-like morphology by 1 year of age.

Intraocular pressure

- Low at birth 7.8 ±0.4 mm Hg (under Flourthane anaesthesia)
- It increases by 1 mm per year up to 5 years to reach the adult levels.

Uveal tract and pupil

It undergoes considerable alterations after birth:

- *Dilator pupillae* is poorly developed and does not reach adult proportions until about the 5th year.
- *Iris stromal pigment* develops after birth; so in white races this tissue is initially light blue in colour for some time.
- *Mean pupillary diameter* (birth is 3.6 ±0.9 mm
  - It changes little with age (2.5–4.0 mm in adults)
  - Pupillary light reaction is normal at birth
- *Pars plana zone* at birth is underdeveloped and the pars plicata is within just 2 mm behind limbus (the surgical incision is through this site in lensectomy or vitrectomy procedures).
- *Ora serrata* recedes by the age of 7 years.

Lens

Lens capsule increases in thickness especially anteriorly. Hyaloid remnants at the posterior capsule gradually atrophy through childhood.

Nucleus. Although, the infantile nucleus is present at birth it continues to grow by accumulation of new fibres up to puberty.

Cortex. The accretion of new fibres forms cortex, which continues throughout life. The recently formed fibres are present in the most superficial part of cortex.

Dimensions of crystalline lens

Thickness

- Birth 3.4–4 mm
- 50 years 4 mm
- >50 years 4.75–5.0 mm

Equatorial diameter

- Birth 6.0–6.5 mm
- Adult 9.10 mm (reached by 2nd decade)

Retina

Postnatal changes in retina can be described separately in the macular (where most notable changes are seen) optic disc and the peripheral fundus.

Macula

Development of the macula lags behind rest of the retina and thus considerable changes occur after birth. Differentiation of all layers proceeds during the first 4 months, at the end of which period the characteristic foveal reflex is present on ophthalmoscopy.

- Macule is barely functional at birth. Histologically and functionally mature by 4 years.

Histologic maturity

- Foveolar diameter (rod-free zone)
  Birth: 1100 μm
  15–45 months: 700–750
- Foveal cone maturation is completed by 15 months

Foveal cone density

- Birth 18 cones/100
- 45 m 31 cones
- Adult 42

Functional maturity

- *Visual fixation* is present at birth and is well developed by 2 months.
- *Visual following* is well developed by 3 months.
- *Differentiation of fovea* is completed by 4 months and characteristic foveal reflex is present on ophthalmoscopy.

Optic disc

- *Colour.* At birth, the disc is relatively and uniformly pale when compared to the pink colour of the older disc. This relative pallor, however, changes to the normal adult pink colour by about 6 months to 1 year of age.
- *Physiological cupping* of the disc is not seen in premature infants or underdeveloped full term infants, such that the optic disc may appear grey at birth resembling optic nerve atrophy.

Peripheral fundus

Fundus still lacks the pigmentation of the adult and the choroidal vessels are distinctly visible.

OPTIC NERVE AND UPPER VISUAL PATHWAY

- Myelination proceeds from occipital cortex downward and is not complete until the end of the fourth month.
- Myelination of the optic nerve begins during foetal life at the lateral geniculate body and reaches the optic disc around the time of birth.
- Normally, the myelin does not extend anterior to the cribriform plate, but rarely it may reach the retina producing clinically visible myelinated nerve fibres, with may be associated ocular anomalies.

REFRACTIVE STATUS, VISUAL ACUITY, VISUAL FIELDS AND STEREOPSIS

Refractive status

- Term infant: + 0.62D to 2.24 D
- Increases up to 7 years of age
- Then decreases and stabilizes by 14–15 years
- Myopic shift:
  – In hypermetropes—0.12 D/year
  – In mypose—0.55 D/year

Visual acuity

Postnatal maturation of visual pathway plays an important role in development of vision. The 1st year of life remains the dynamic and plastic period for visual development. Any pathology during this period will impair its development. The visual system remains malleable at least during first decade of life, and attention to this visual plasticity is considered for the prevention and treatment of amblyopia.

Table 1.1. *Levels of visual acuity*

Visual acuity	*1 Months*	*2 Months*	*6 Months*	*Age at which 6/6 is achieved*
i. Optokinetic nystagmus	6/120	6/60	6/30	20–30 months
ii. Preferential looking	6/120	6/60	6/30	24–36 months
iii. VEP	6/120	6/60	6/6–6/12	6–12 months

Maturation of vision

- *Optokinetic nystagmus* is well developed at birth.
- *Level of visual acuity* as measured by different methods is summarized in Table 1.1.
- Accommodation is well developed by 4 months
- In ERG studies, the 'a' wave (the major negative component) reflecting the hyperpolarization of retinal photoreceptors by incident light, is generally manifested by 1 year; whereas the 'b' wave reflecting bipolar function usually appears at 6 months and fully develops by the 1st year.
- *Ocular alignment* becomes stable by 1 month.

Stereopsis

- Development of stereopsis roughly parallels the development of visual acuity. It can be demonstrated at 3 to 6 month of age and rapidly improves thereafter.
- Stereoacuity (titmus) at adult level is achieved by 7 yrs.

Visual fields

- Using suitable kinetic perimetry, the monocular visual fields in newborns extend 28 degrees to left and right of the vertical meridian, and 11 degrees above and 16 degrees below the horizontal meridian.
- Rapid expansion in dimension of the visual fields follows, and at 1 year of age the superior visual field is comparable to that of adults.
- By 10 years of age, adult visual field size is attained.

EYE MOVEMENTS

- Initially, eye movements are irregular and not conjugate.
- But by 5 to 6 weeks, the eyes can follow a light over a considerable range.
- Pursuit of small objects occurs at about 3 months and transition from reflex to conscious fixation becomes apparent; but conjugate fixation is not accurate until about 6 months, when convergence is established.
- Corrective fusion reflexes are fully functional towards the end of the first year.

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