# Handbook of Pediatric Eye and Systemic Disease

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# Preface

Pediatric ophthalmology is a broad field encompassing many diverse topics including embryology, chromosomal abnormalities, neurology, crainio-facial abnormalities, systemic diseases, retina disease, and strabismus. This variety makes pediatric ophthalmology interesting and intellectually stimulating, but at the time somewhat daunting. The handbook series is designed to give the practitioner an easy to understand, succinct yet detailed reference on various subjects related to pediatric ophthalmology.

The *Handbook of Pediatric Eye and Systemic Disease* is a practical resource on the diagnosis and management of eye disorders associated with pediatric systemic disease. A concise but comprehensive description of ocular manifestations of pediatric systemic disease is presented. These chapters are designed to be reader-friendly. They are organized with clear sub-headings that allow the readers to quickly find their area of interest such as *systemic characteristics*, *ocular findings*, or *treatment*. Excellent color photographs and diagrams illustrate the clinical points and help with disease recognition. Extensive use of tables and information boxes simplify and summarize complex topics. Each chapter is fully referenced to provide evidence-based practice guidelines and further in-depth reading. The last chapter is a compendium of hundreds of systemic diseases and chromosomal abnormalities that affect the eye. In this compendium are thorough lists of both systemic and ocular findings for each disease. This is an excellent aid to diagnosing syndromes based on the characteristics of the eye abnormality.

Another important use of the *Handbook of Pediatric Eye and Systemic Disease* is patient and family education. Parents are rightfully concerned about the effects of systemic disease on their child's eyes. Information, including diagrams and photographs from the handbook about the eye manifestations of

systemic disease, can be shared with the families. This important information is often lacking in general texts on ophthalmology and pediatrics.

I hope you will find the *Handbook of Pediatric Eye and Systemic Disease* to be an invaluable adjunct to your pediatric practice.

*Kenneth W. Wright, MD*

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# 1

# Embryology

Cynthia S. Cook, Kathleen K. Sulik, and
Kenneth W. Wright

## DIFFERENTIATION OF GERM LAYERS AND EMBRYOGENESIS

After fertilization of the ovum within the uterine tube, cellular mitosis results in formation of a ball of 12 to 16 cells, the morula. A fluid-filled cavity within this embryonic cell mass forms, resulting in a transformation into a blastocyst that begins to penetrate the uterine mucosa on approximately the sixth day postfertilization. The cells of the blastocyst continue to divide with the cells of the future embryo proper (embryoblast) accumulating at one pole. The cells of the primitive embryoblast differentiate into two layers, the *epiblast* and the *hypoblast*. These two cellular layers bridge the central cavity of the blastocyst, thus dividing the blastocyst into the amniotic cavity and the yolk sac (Fig. 1-1).

During the third week of gestation, the two-layered embryoblast transforms into a trilaminar embryo as central epiblast cells invaginate between the epiblast and hypoblast layers. Invagination of central epiblast cells creates a longitudinal groove through the midline of the caudal half of the epiblast, the *primitive streak*. This invagination of epiblast cells is termed *gastrulation* (Fig. 1-2A,B). Invaginating epiblast cells differentiate to form the *mesodermal* germ layer, which spreads out to fill the space between the epiblast and hypoblast. Gastrulation proceeds in a cranial to caudal progression and continues through the fourth week of human gestation. These invaginating epiblast cells displace the hypoblast cells to form the *endoderm*. The epiblast cells therefore give rise to all three definitive germ layers: *ectoderm*, *mesoderm*, and *endoderm* (Fig. 1-2C).

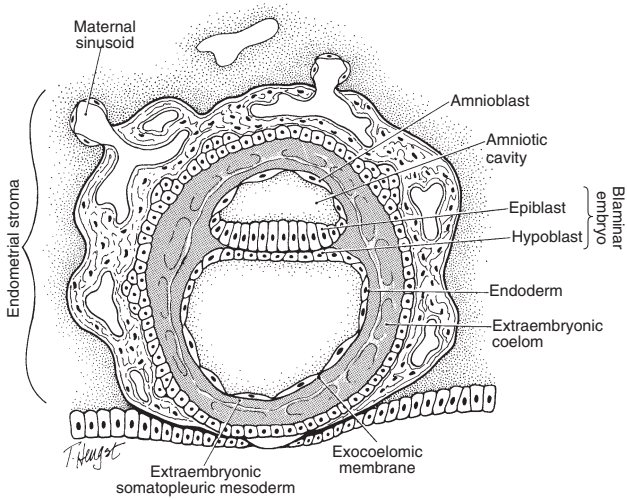



**FIGURE 1-1.** Drawing of a human blastocyst (12 days gestation) that has penetrated the maternal endometrium. An embryoblast has formed that consists of two cell layers: the epiblast above and the hypoblast below.

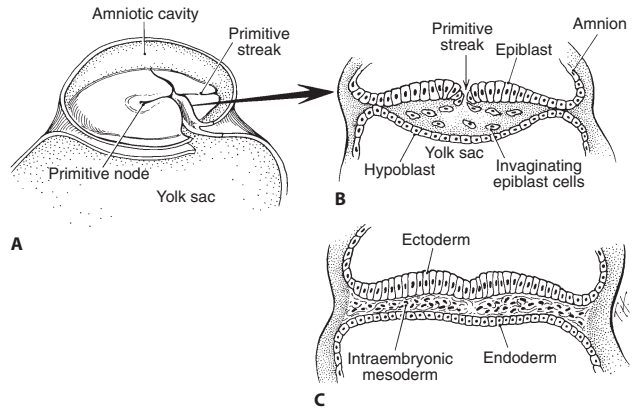



**FIGURE 1-2A–C.** **(A)** Drawing of a 17-day-old embryo in gastrulation stage (dorsal view) with the amnion removed. **(B)** Cross section of a 17-day-old embryo through the primitive streak. The primitive streak represents invagination of epiblast cells between the epiblast and hypoblast layers. Note the epiblast cells filling the middle area to form the mesodermal layer. **(C)** Cross section of the embryo at the end of the third week shows the three definitive germ layers: ectoderm, mesoderm, and endoderm.

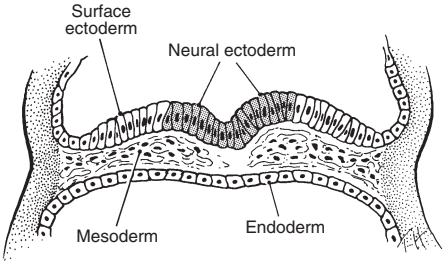



**FIGURE 1-3.** Drawing of an 18-day-old embryo sectioned through the neural plate. Note that the ectoderm in the area of the neural groove (*shaded cells*) has differentiated into neural ectoderm whereas the ectoderm on each side of the neural groove remains as surface ectoderm (*clear white cells*).

Toward the end of gastrulation, the ectoderm anterior to the primitive streak differentiates into columnar *neural ectoderm*; this expands, forming the *neural plate* from which the brain develops (Figs. 1-3, 1-4). Neural ectoderm on each side of the central neural groove expands to form bilateral elevations called the *neural folds* (Fig. 1-5). A central valley in the enlarging neural plate is called the *neural groove*. Ectoderm at the lateral margins of the neural plate has the flat, hexagonal morphology typical of *surface ectoderm* (Figs. 1-5, 1-6). By 21 days of human

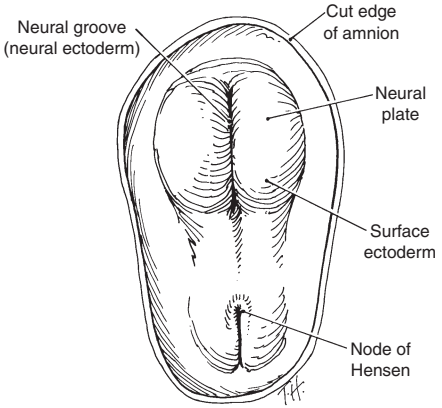



**FIGURE 1-4.** Drawing of dorsal aspect of embryo at 18 days gestation showing neural groove and enlarging neural plate.

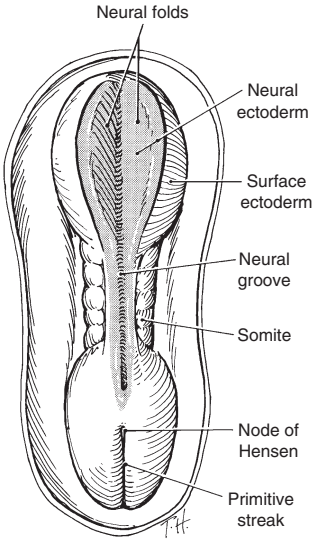



**FIGURE 1-5.** Dorsal view of a human embryo at 20 days gestation. The neural plate transforms into two neural folds on each side of the neural groove. The neural groove in the middle of the embryo is *shaded* to represent neural ectoderm; the *unshaded* surface of the embryo is surface ectoderm.

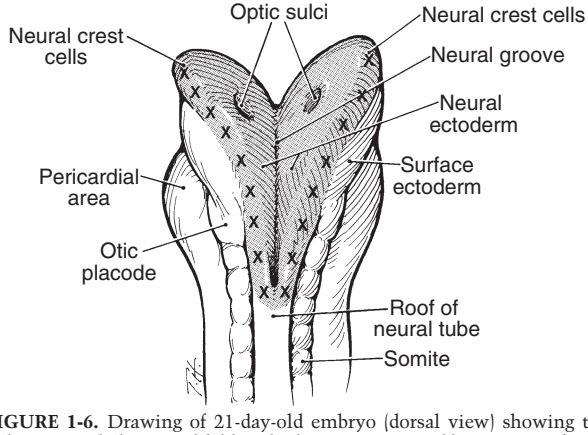



**FIGURE 1-6.** Drawing of 21-day-old embryo (dorsal view) showing the enlarging cephalic neural folds, which are separate and have not yet fused. The central neural folds have fused to form the neural tube. The neural tube, groove, and facing surfaces of the large neural folds are made up of neural ectoderm; surface ectoderm covers the rest of the embryo. Neural crest cells (*X*) are found at the junction of the neural ectoderm and surface ectoderm. Neural crest cells migrate beneath the surface ectoderm spreading throughout the embryo and specifically to the area of the optic sulci. Neural ectoderm, *dark shading*; surface ectoderm, *white*; neural crest cells, *cross-hatched area*. The neural groove is still open at this point, and somites have formed along the lateral aspect of the neural tube.

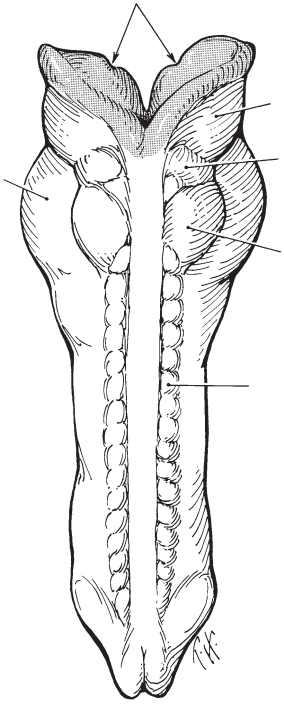


**FIGURE 1-7.** Drawing of approximately 23-day-old embryo, dorsal view, showing partial fusion of the neural folds. Brain vesicles have divided into three regions: forebrain, midbrain, and hindbrain. Note that the facing surfaces of the forebrain neural folds are lined with neural ectoderm (*shaded cells*) but the majority of the embryo is covered by surface ectoderm (*clear white*). On the inside of both forebrain vesicles is the site of the optic sulci (optic pits). The neural crest cells that will populate the region around the developing optic vesicles originate from the midbrain region.

gestation, while the neural tube is still open, the first sign of the developing eye is seen. The *optic sulci* or *optic pits* develop as invaginations on the inner surface of the anterior neural folds (Figs. 1-6, 1-7, 1-8). During expansion of the optic sulci, the central aspect of the neural folds approach each other and fuse, creating the longitudinal *neural tube.* Fusion of the neural folds

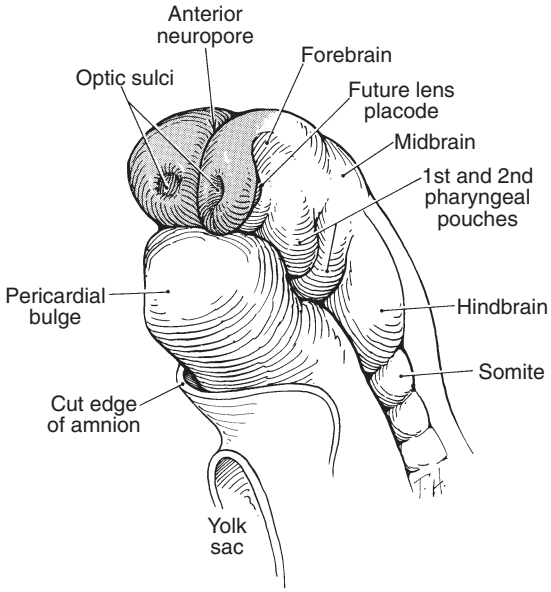



**FIGURE 1-8.** Drawing of anterior view of embryo at similar stage to Figure 1-7 (23 days) shows the optic sulci on the inside of the forebrain vesicles. *Shaded area*, neural ectoderm. The optic sulci evaginate and expand toward the surface ectoderm as the neural tube closes anteriorly. (From Webster WS, Lipson AH, Sulik KK. Am J Med Genet 1988;31:505–512, with permission.)

is initiated in the region of the future neck and proceeds along the midline in both caudal and cranial directions. Following closure of the neural tube, the neural ectoderm and optic sulci are internalized, and the embryo is then covered by surface ectoderm (Fig. 1-7).

## Neural Crest Cell Development

As the neural folds elevate and approach each other, a specialized population of mesenchymal cells, the *neural crest cells*, emigrate from the junction of the neural and surface ectoderm (see Fig. 1-6). Progenitor cells in the neural folds are multipotent, with potential to form multiple ectodermal derivatives, including epidermal, neural crest, and neural tube cells. These

cells are induced by interactions between the neural plate and epidermis. The competence of the neural plate to respond to inductive interactions changes as a function of embryonic age.[92] These stellate cells migrate peripherally beneath the surface ectoderm to spread throughout the embryo and surround the area of the developing optic sulci. Neural crest cells play an important role in eye development, as they are the precursors (anlage) to major structures, including cornea stroma, iris stroma, ciliary muscle, choroid, sclera, and orbital cartilage and bone (Table 1-1).[55,64] The patterns of neural crest emergence and emigration correlate with the segmental disposition of the developing brain.[72] Migration and differentiation of the neural crest cells are influenced by the hyaluronic acid-rich extracellular matrix and the optic vesicle basement membrane.[17] This acellular matrix is secreted by a surface epithelium as well as the crest cells and forms a space through which the crest cells migrate. Fibronectin secreted by the noncrest cells forms the limits of this mesenchymal migration.[65] Interactions between the migrating neural crest and the associated mesoderm appear to be essential for normal crest differentiation.[76,77]

**TABLE 1-1. Embryonic Origins of Ocular Tissues.**

| | |
|---|---|
| Neural ectoderm (optic cup) | Surface ectoderm (epithelium) |
| Neural retina | Corneal and conjunctival epithelium |
| Retinal pigment epithelium | Lens |
| Pupillary sphincter and dilator muscles | Lacrimal gland |
| Posterior iris epithelium | Eyelid epidermis |
| Ciliary body epithelium | Eyelid cilia |
| Optic nerve | Epithelium of adnexa glands |
| Neural crest (connective tissue) | Epithelium of nasolacrimal duct |
| Corneal endothelium | Mesoderm (muscle and vascular endothelium) |
| Trabecular meshwork | Extraocular muscle cells |
| Stroma of cornea, iris, and ciliary body | Vascular endothelia |
| Ciliary muscle | Schlemm's canal endothelium |
| Choroid and sclera | Blood |
| Perivascular connective tissue and smooth muscle cells | |
| Meninges of optic nerve | |
| Orbital cartilage and bone | |
| Connective tissue of the extrinsic ocular muscles | |
| Secondary vitreous | |
| Zonules | |

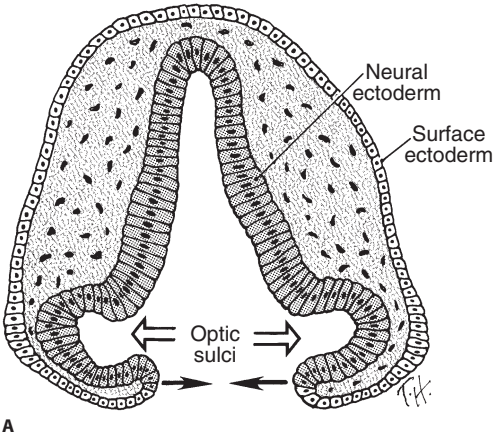
## Somite Development

During the development and closure of the neural groove, paraxial mesoderm increases in the center of the embryo to form *somites* (see Figs. 1-5, 1-6). The somites increase in number to approximately 40, and eventually this paraxial mesoderm becomes mesenchyme that, in turn, develops into connective tissue, cartilage, muscle, and bone for the trunk and extremities. The neural segmentation pattern appears to be dependent on the underlying mesoderm. In the region of the brain rostral to the developing inner ear, the mesodermal segments are called *somitomeres*, whereas segments caudal to this level are somites.[72,75] The somitomeres are mesodermal in origin and give rise to the myoblasts of the extraocular muscles and vascular endothelium in and around the eye. Unlike the trunk and extremities, orbital bone and ocular connective tissue are derived from neural crest cells, not mesoderm.

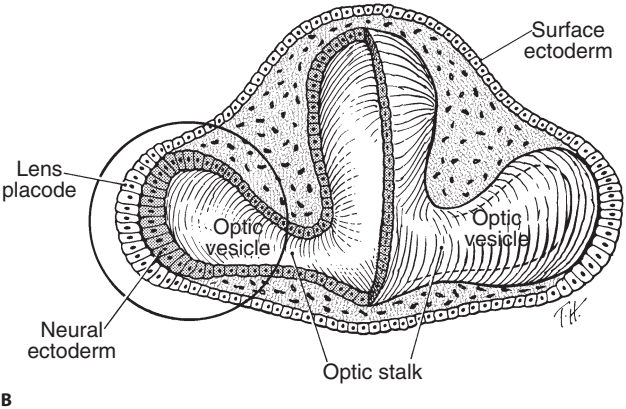
It is important to point out that *mesenchyme* is a broad term for any embryonic connective tissue, whereas mesoderm specifically relates to the middle embryonic layer. At one time the middle embryonic layer (the mesoderm) was thought to be responsible for most of the ocular and adnexal tissues. Embryologic studies have shown that mesoderm plays a relatively small role in the development of head and neck mesenchyme and is probably responsible only for the striated muscle of the extraocular muscles and vascular endothelium. With respect to the ocular development and development of the head and neck, most of the mesenchyme or connective tissue comes from the neural crest cells (see Table 1-1).

# OPTIC VESICLE AND OPTIC CUP

As the neural folds progressively fuse in a cranial direction, dilation of the closed neural tube occurs to form the "brain vesicles." By 3 weeks, these vesicles undergo neural segmentation and form the specific parts of the brain, that is, *forebrain* (prosencephalon), *midbrain* (mesencephalon), and *hindbrain* (rhombencephalon) (see Fig. 1-7). Surface ectoderm covers the outside of the forebrain, and neural ectoderm lines the inner or facing surfaces of the paired forebrain vesicles from which the eyes develop (Figs. 1-8, 1-9). The *optic sulci* develop as bilateral evaginations of neural ectoderm on the facing surfaces of the




A




B

**FIGURE 1-9A–B. (A)** Drawing of a cross section through forebrain and optic sulci of 23- to 26-day-old embryo, during the period of neural tube closure. The optic sulci are lined by neural ectoderm (*shaded cells*); the surface of the forebrain is covered with surface ectoderm (*clear white cells*). As the optic sulci (neural ectoderm) evaginate towards the surface ectoderm (hollow arrows), the edges of the brain vesicles move together to fuse, thus closing the neural tube (*solid arrows*). **(B)** Drawing of a cross section through a 26-day-old embryo at the level of the optic vesicle. The neural tube has closed, the surface ectoderm now covers the exterior of the forebrain, and the neural ectoderm is completely internalized. The surface ectoderm cells overlying the optic vesicles thicken to form the early lens placode. (From Cook CS, Sulik KK. Scanning Electron Microsc 1986;III:1215–1227, with permission).

forebrain vesicles. Expansion of the optic sulci toward the surface ectoderm and fusion of the forebrain vesicles create the *optic vesicles* (Figs. 1-9, 1-10) by approximately day 25 to 26 (embryo size, 3 mm). Closure of the neural tube and expansion of the optic vesicles occur through the mechanical influences of the cytoskeletal and extracellular matrix and localized proliferation and cell growth.[91]

The mesencephalic neural crest cells populate the region around the optic vesicle and ultimately give rise to nearly all the connective tissue structures of the avian eye, and the same can be presumed for the mammalian eye (see Table 1-1).[55,64] An external bulge indicating the presence of the invaginating optic vesicle can be seen at approximately 25 days human gestation (see Fig. 1-9). The optic vesicle appears to play a significant role in the induction and size determination of the palpebral fissure and orbital and periocular structures.[56]

At approximately 27 days gestation, the surface ectoderm that is in contact with the optic vesicle thickens to form the *lens placode* (Figs. 1-9, 1-10, 1-11). The lens placode and underlying neural ectoderm invaginate through differential growth (Fig. 1-10). The invaginating neural ectoderm folds onto itself as the optic vesicle collapses, creating a double layer of neural

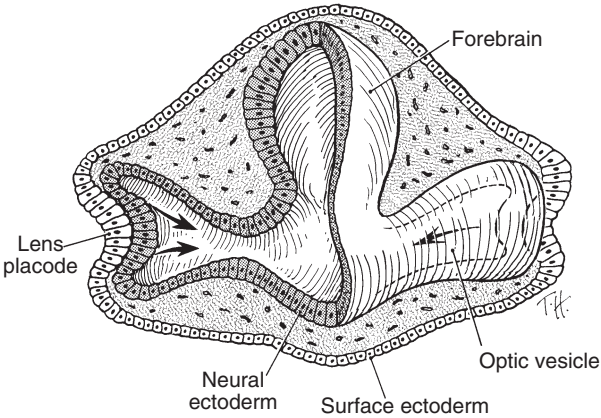



**FIGURE 1-10.** Drawing of a transection through a 28-day-old embryo shows invaginating lens placode and optic vesicle (*arrows*), thus creating the optic cup. Note the orientation of the eyes 180° from each other; this corresponds to the SEM view shown in Figure 1-12C.

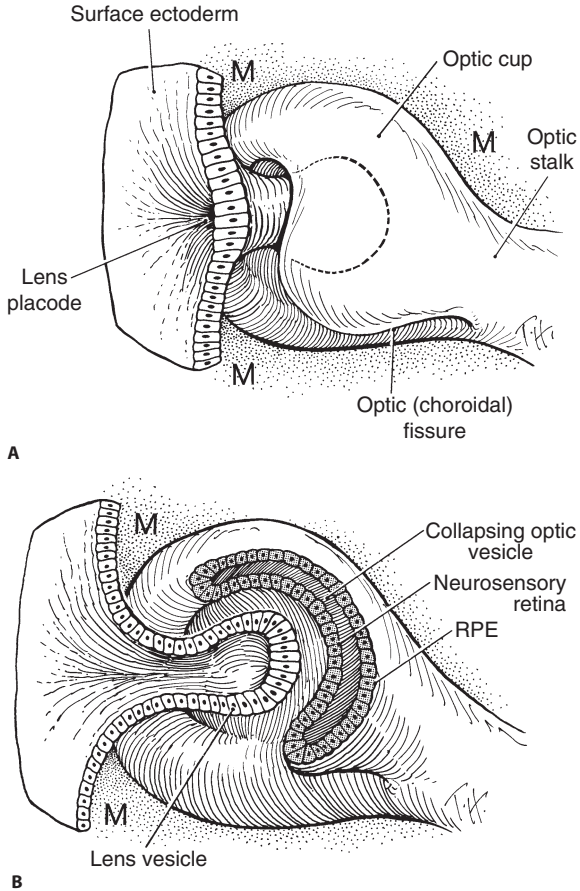



**FIGURE 1-11A,B.** Drawings show the formation of the lens vesicle and optic cup. Note that the optic fissure is present as the optic cup is not yet fused inferiorly. Mesenchyme (*M*) surrounds the invaginating lens placode. The optic stalk is continuous with the forebrain. Note that the optic cup and optic stalk are neural ectoderm. *RPE,* retinal pigment epithelium.

ectoderm, the *optic cup* (Fig. 1-11). The optic cup will eventually differentiate into *neurosensory retina* (inner layer) and *retinal pigment epithelium* (RPE) (outer layer) (Fig. 1-11). Local apical contraction[112] and physiological cell death[91] have been identified during invagination of the lens placode and formation of the optic cup. In the mouse embryo, Msx2, a homeobox-containing transcription factor, is expressed only in the cells of the optic cup that are destined to become neural retina. In vitro Msx2 has been shown to suppress RPE differentiation and may be involved in the initial patterning of the optic cup.[48] Abnormal differentiation of the outer layer of the optic cup to form aberrant neural retina has been demonstrated in several mutant mouse strains.[21,26,109] The area of future retinal differentiation demonstrates the greatest concentration of vimentin (a cytoskeletal protein) in the optic cup.[53] Regionally, within the optic cup, spatial orientation is predicted by expression of the transcription factor, vax2, which defines the ventral region (area of the optic fissure).[10] The PAX6 gene has been demonstrated within cells of neural ectodermal origin (optic cup and, later, in the ciliary body and retina), surface ectoderm (lens), and neural crest (cornea).[74] The widespread distribution of this gene supports its involvement in many stages of ocular morphogenesis.

## The Optic Fissure

Invagination of the optic cup occurs in an eccentric manner with formation of a seam, the *optic fissure*, inferiorly (Figs. 1-11, 1-12). The optic fissure is also known as the *embryonic fissure* or *choroidal fissure*. Mesenchymal tissue (of primarily neural crest origin) surrounds and is within the optic fissure and optic cup, and at 5 weeks the *hyaloid artery* develops from mesenchyme in the optic fissure. This artery courses from the *optic stalk* (precursor to the optic nerve) through the optic fissure to the developing lens (Fig. 1-12). The lens vesicle separates from the surface ectoderm at approximately 6 weeks, the same time as closure of the optic fissure. Closure of the optic cup occurs initially at the equator with progression anteriorly and posteriorly.

Once the fissure has closed, secretion of primitive aqueous fluid by the primitive ciliary epithelium establishes intraocular pressure (IOP), which contributes to expansion of the optic cup.[15,29] Experimental studies have shown that placement of a capillary tube into the vitreous cavity of a chick eye reduces the IOP and markedly slows growth of the eye.[29] Histological

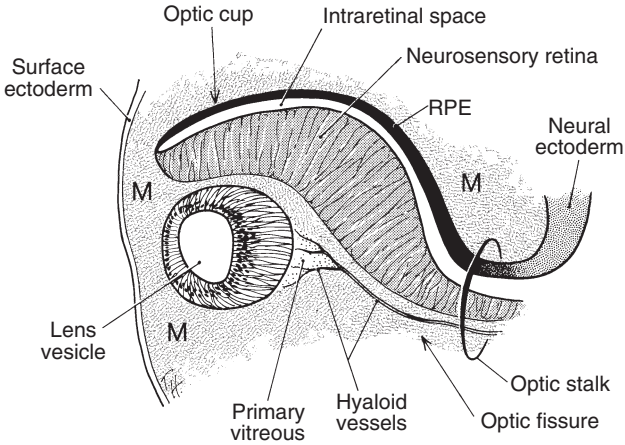



**FIGURE 1-12.** Drawing of cross section at approximately 5 weeks gestation through optic cup and optic fissure. The lens vesicle is separated from the surface ectoderm. Mesenchyme (*M*) surrounds the developing lens vesicle; the hyaloid artery is seen within the optic fissure. (From Cook CS, Sulik KK. Scanning Electron Microsc 1986;III:1215–1227, with permission.)

examination of these intubated eyes demonstrated proportional reduction in size of all the ocular tissues except the neural retina and the lens, which were normal in size for the age of the eye. The retina in these eyes was highly convoluted and filled the small posterior segment. Thus, it may be concluded that growth of the neural retina occurs independently of that of the other ocular tissues. Experimental removal of the lens in the eye does not alter retinal growth.[30] Growth of the choroid and sclera appear to be dependent upon IOP, as is folding of the ciliary epithelium.[12] Failure or late closure of the optic fissure prevents the establishment of normal fetal IOP and can therefore result in *microphthalmia* associated with *colobomas*, that is, colobomatous microphthalmia (see Ocular Dysgenesis later in this chapter).

Figure 1-13 shows a diagram of the eye at the end of the seventh week and after optic fissure closure. At this stage, the neurosensory retina and pigment epithelium are in apposition, the optic nerve is developing, and the lens has separated from the cornea, thus forming the anterior chamber. Mesenchymal tissue

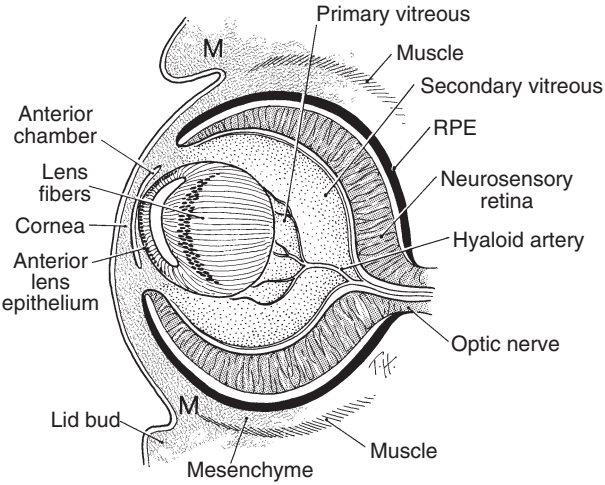




**FIGURE 1-13.** Overview at the 7th week of gestation. The developing eye is surrounded by mesenchyme of neural crest origin. (From Sulik KK, Schoenwolf GC. Scanning Electron Microsc 1985;IV:1735–1752, with permission.)

(neural crest cell origin) around the primitive retina develops into the choroid and sclera. Peripheral to the developing globe are linear accumulations of myoblasts (mesodermal origin) that are anlagen of the extraocular muscles. The eyelids are small buds above and below the developing eye. The hyaloid vasculature courses from the primitive optic nerve to the posterior lens capsule.

## LENS

Thickening of the lens placode can be seen on gestational day 27 in the human (see Fig. 1-10). Before its contact with the optic vesicle, the surface ectoderm must become competent to respond to lens inducers. It then receives inductive signals from the anterior neural plate, so that it gains a "lens-forming bias" specified for lens formation. Complete lens differentiation requires both inductive signals from the optic vesicle and an inhibitory signal from head neural crest to suppress any residual lens-forming bias in head ectoderm adjacent to the lens.[38] In the chick, a tight extracellular matrix-mediated adhesion between the optic vesicle and the surface ectoderm has been described.[47,57,69] This anchoring of the mitotically active surface ectoderm results in cell crowding, cell elongation, and formation of the thickened placode.[119] Adhesion between the optic vesicle and the lens placode is thought to ensure alignment of the lens in the visual axis.[15] Although adhesion between the optic vesicle and surface ectoderm exists, electron microscopic studies have demonstrated that there is no direct cell contact.[22,49,108] The basement membranes of the optic vesicle and the surface ectoderm remain separate and intact throughout the contact period. Experimental studies have demonstrated a requirement for functional PAX6 gene in both the optic vesicle and surface ectoderm to mediate lens placode induction.[23] The BMP4 gene, which is present only in the optic vesicle, is also required for lens induction.[35]

The lens placode invaginates forming the hollow lens vesicle (Figs. 1-11, 1-12). The size of the lens vesicle is determined by the area of contact of the optic vesicle and the surface ectoderm. Lens vesicle detachment from the surface ectoderm occurs on day 33 (7–9 mm) and is the initial event leading to the formation of the chambers of the eye. This process of separation is accompanied by active migration of epithelial cells out of the keratolenticular stalk or junction,[37] cellular necrosis, and base-

ment membrane breakdown.[36] Although apoptosis (programmed cell death) is a normal feature of lens vesicle separation, excessive and persistent cell death is associated with aphakia in the lap mouse mutant.[8]

Induction of a small lens vesicle that fails to undergo normal separation from the surface ectoderm is one of the characteristics of teratogen-induced anterior segment malformations described in animal models.[24,28,81,102] In the mouse mutant (dyl), this failure of lens vesicle separation is caused by a mutation in the FoxE3 gene that promotes survival and proliferation while preventing differentiation of the lens epithelium.[18] AP-2 transcription factors also influence lens vesicle separation as well as causing mis-expression of PAX6 and MIP26 genes.[109] Anterior lenticonus, anterior capsular cataracts, and anterior segment dysgenesis with keratolenticular adhesions (Peters' anomaly) may result from faulty keratolenticular separation. Further discussion of anterior segment dysgenesis follows. Arrest of lens development at the lens stalk stage results in aphakia in mutant mice (*ak* mutation). In addition to aphakia, affected eyes exhibit absence of a pupil and abnormalities in the iris, ciliary body, and vitreous.[40,41]

The hollow lens vesicle consists of a single layer of epithelial cells with cell apices directed toward the center of the sphere. Following detachment from the surface ectoderm, the lens vesicle is surrounded by a basal lamina, the future *lens capsule*. Abnormalities in this basement membrane may result in involution of the lens vesicle, resulting in later aphakia.[8] At approximately 37 days gestation, *primary lens fibers* form from elongation of the posterior lens epithelium of the lens vesicle (Fig. 1-14).[51] The retinal anlage promotes primary lens fiber formation in the adjacent lens epithelial cells. Experimental in vivo rotation of the lens vesicle in the chick eye by 180° results in elongation of the lens epithelial cells nearest the presumptive retina, regardless of the orientation of the transplanted lens.[31] Thus, the retina develops independently from the lens although the lens appears to rely upon the retina for cytodifferentiation. In the mouse, the Prox1 and Maf genes have been demonstrated to mediate lens fiber elongation.[88,110] As these posterior epithelial cells lengthen to fill the lumen of the lens vesicle, they lose their nucleus and most organelles.[14] Upregulation of lens-specific proteins, CP49 and CP95, is demonstrated after closure of the lens stalk.[51] The primitive lens filled with primary lens fibers is the *embryonic lens nucleus*. After the epithelial cells

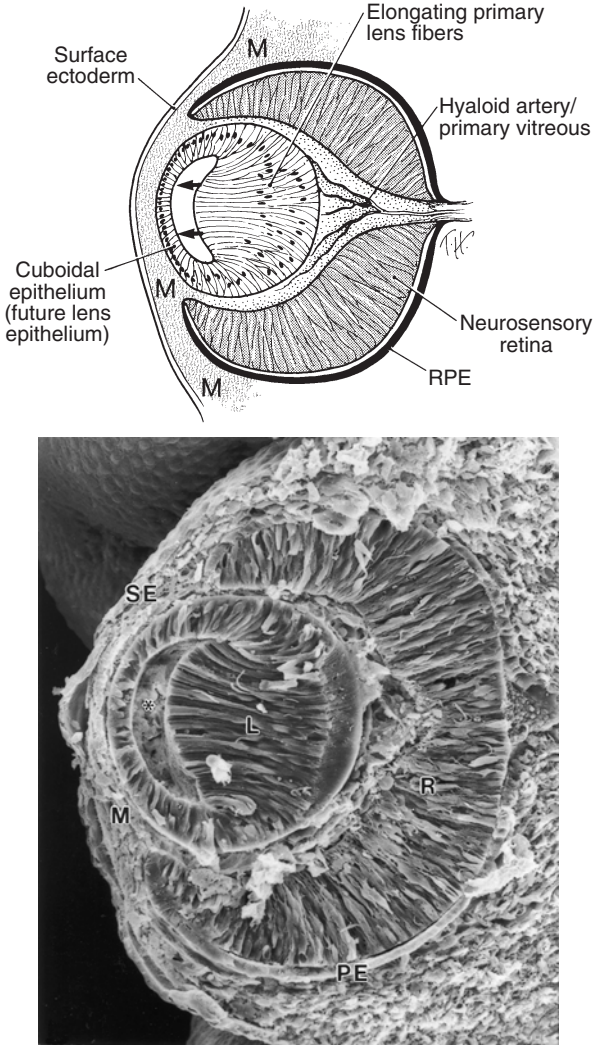



**FIGURE 1-14.** Formation of the embryonic lens nucleus and primary lens fibers at approximately 7 weeks. Note that mesenchyme (*M*) of neural crest origin surrounds the optic cup. The posterior lens epithelial cells (located nearest the developing retina, *R*) elongate, forming the primary lens fibers (*L*). The anterior epithelium remains cuboidal and becomes the anterior epithelium in the adult. The optic fissure is now closed.

of the posterior lens elongate to form the fibers of the embyronal nucleus, they eventually separate from the posterior capsule; therefore, there is an absence of epithelial cells on the posterior capsule. In the adult, the embryonic nucleus is the central round, slightly dark sphere inside the Y sutures. There are no sutures within the embryonal nucleus. The lens fibers have extensive interdigitations with a relative absence of extracellular space. Anterior lens epithelial cells (nearest the corneal anlage) remain cuboidal and become the permanent lens epithelium, which is mitotic throughout life, giving rise to future secondary fetal and adult cortical lens fibers.

After the embryonic nucleus is formed, *secondary lens fibers* develop from anterior epithelial cells to form the fetal nucleus. The anterior epithelial cells migrate to the periphery of the lens (lens equator), where they elongate and differentiate into lens fibers. This region of the lens is called the *lens bow*. These secondary lens fibers elongate anteriorly and posteriorly around the embryonic nucleus to meet at the anterior and posterior poles of the lens (Fig. 1-15). The lens fibers exhibit surface interdigitations with relative lack of extracellular space. Unlike more mature cortical lens fibers that have tapered ends, these fetal lens fibers (secondary lens fibers) have blunt tips, so when they meet they form a faint adherence or "suture." This meeting of the secondary lens fiber ends results in two Y sutures, the anterior upright Y suture and the posterior inverted Y suture

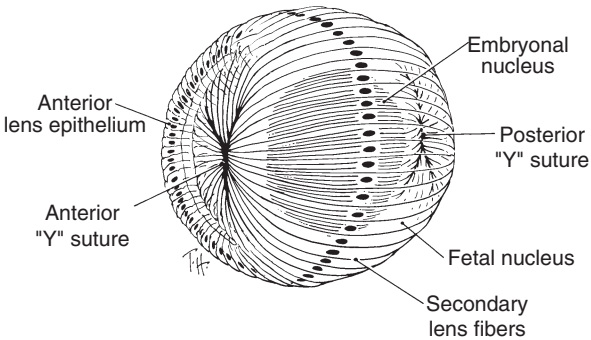



**FIGURE 1-15.** Diagram of secondary lens fibers and Y sutures. Secondary lens fibers elongate at the equator to span the entire lens, from the anterior Y suture to the posterior Y suture. The anterior Y suture is upright and the posterior Y suture is inverted.

(Fig. 1-15). The fetal nucleus consists of the secondary lens fibers and can be clinically identified as that part of the central lens that is inside the Y sutures but outside the embryonic nucleus. The lens differentiates under the influence of many growth factors, including FGF, IGF, PDGF, and TGF, and genes become active encoding cytoskeletal proteins (filensin, phakinin, vimentin, nestin), structural proteins (crystallins), and membrane proteins.[39,118] Abnormal initiation and differentiation of secondary lens fibers have been demonstrated in the Cat2 and Cat3 mutant mouse strains. These eyes exhibit abnormalities limited to the lens, unlike the aphakia mutant eyes, which have malformations of the anterior segment and vitreous and folding of the retina.[40]

At birth, the lens is almost entirely made up of lens nucleus with minimal lens cortex. Lens cortex continues to develop from the anterior epithelial cells postnatally and throughout life. Congenital cataracts that occur as a result of abnormal formation of primary or secondary lens fibers would be expected to be localized in the nuclear region between the Y sutures. Abnormal lens vesicle separation from the surface ectoderm would be associated with defects in anterior epithelium or lens capsule and may cause anterior polar cataracts. Incomplete regression of the pupillary membrane can be associated with (secondary) anterior lens opacities. A defect of the surface ectoderm or basement membrane could result in cataracts associated with anterior or posterior lenticonus.

## Tunica Vasculosa Lentis

The lens receives nutrition and blood supply from the *hyaloid artery*, a branch of the primitive ophthalmic artery. The hyaloid artery first enters the eye through the optic fissure (see Fig. 1-12) and then becomes incorporated into the center of the optic nerve as the optic fissure closes. The hyaloid vessels form a network around the posterior lens capsule and then anastomose anteriorly with the network of vessels in the pupillary membrane (Fig. 1-16). The pupillary membrane consists of vessels and mesenchyme that overlie the anterior lens capsule (see Development of Anterior Segment). This hyaloid vascular network that forms around the lens is called the *tunica vasculosa lentis*. The hyaloid vasculature reaches its greatest development at approximately 10 weeks gestation. The tunica vasculosa lentis and hyaloid artery regress during the end of the fourth month of

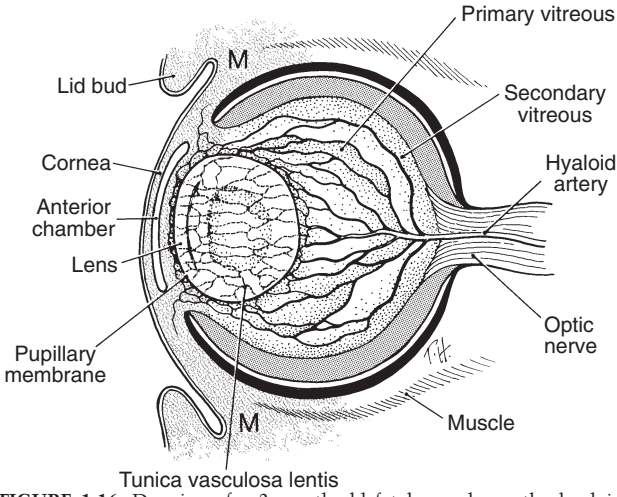



**FIGURE 1-16.** Drawing of a 2-month-old fetal eye shows the hyaloid vascular system and tunica vasculosa lentis.

gestation. The clinical lens anomaly, *Mittendorf's dot*, is a small (1–2 mm) area of fibrosis on the posterior capsule and is probably a manifestation of incomplete regression of the hyaloid artery where it attaches to the posterior capsule. The regression of the pupillary membrane begins during the sixth month and is usually complete by the eighth month. *Persistent pupillary membranes* result from incomplete regression. These iris strands may connect to an anterior polar cataract (Fig. 1-17) or area of corneal endothelial fibrosis.

## CORNEA AND ANTERIOR CHAMBER

The anterior margins of the optic cup advance beneath the surface ectoderm and its subjacent mesenchyme following lens vesicle detachment at approximately day 33 of gestation. The surface ectoderm overlying the optic cup and lens represents the presumptive *corneal epithelium*; it secretes a thick matrix producing the *primary cornea stroma*.[43] This acellular material consists of collagen fibers, hyaluronic acid, and glycosaminoglycans. Neural crest cells migrate between the surface ectoderm and

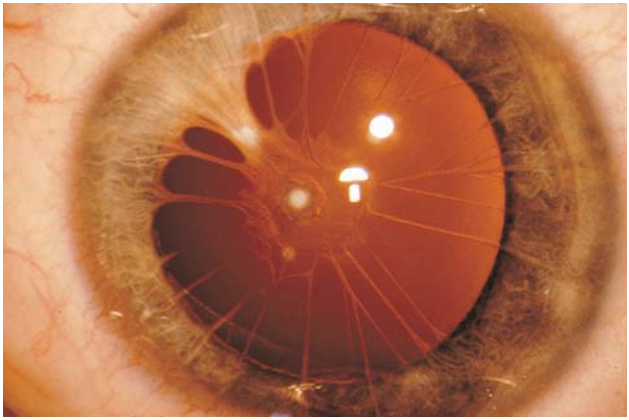


**FIGURE 1-17.** Photograph of persistent pupillary membrane with small central anterior polar cataract.

optic cup using the basal lamina of the lens vesicle as a substrate or scaffold.[11] Hydration of hyaluronic acid helps to create the space for cellular migration.[105] This loosely arranged neural crest cell-derived mesenchyme initially fills the future anterior chamber and gives rise to the corneal stroma, corneal endothelium, the anterior iris stroma, the ciliary muscle, and most of the structures of the iridocorneal angle. Separation of the corneal mesenchyme (neural crest cell origin) from the lens (surface ectoderm origin) results in formation of the anterior chamber. Mesenchymal tissue surrounds the lens and forms the tunica vasculosa lentis and is continuous anteriorly with the pupillary membrane. Capillaries within the tunica vasculosa lentis anastomose with the hyaloid vascular system. The vascular endothelium appears to be the only component of the anterior segment that is of mesodermal origin, as even the vascular smooth muscle cells and pericytes are of neural crest origin.[55,64]

The anterior corneal stroma remains acellular and gives rise to *Bowman's membrane*, which underlies the corneal epithelium. Although the corneal epithelium is of surface ectodermal origin, Bowman's membrane is a condensation of anterior corneal stroma that is of neural crest cell origin. Type I collagen fibrils and fibronectin secreted by the developing keratocytes (neural crest cell origin) form the secondary corneal stroma. Subsequent dehydration of the corneal stroma results in loss of much of the

fibronectin and a 50% reduction in thickness of the stroma.[44,65] The endothelium plays an important role in the dehydration of the stroma. Patches of endothelium become confluent during the early part of the fourth month of gestation and develop zonulae occludentes at their apices by the middle of the fourth month of gestation.[115] By the sixth month of gestation, *Descemet's membrane* and *endothelium* are structurally and functionally present and, at this time, the cornea achieves relative transparency. Proteoglycans containing keratan sulfate chains play a role in generating and maintaining corneal transparency.[34]

## IRIS AND CILIARY BODY

The two layers of the optic cup (neural ectoderm origin) consist of an inner nonpigmented layer and an outer pigmented layer. Both the pigmented and nonpigmented epithelia of the iris and ciliary body develop from the anterior aspect of the optic cup whereas the retina develops from the posterior optic cup. The optic vesicle is organized with all cell apices directed to the center of the vesicle (see Figs. 1-10, 1-11). During optic cup invagination, the apices of the inner and outer epithelial layers become adjacent. Thus, the cells of the optic cup are oriented apex to apex.

A thin periodic acid–Schiff-(PAS) positive basal lamina lines the inner aspect (vitreous side) of the nonpigmented epithelium and retina (inner limiting membrane). At approximately 4.5 months, both the pigmented and nonpigmented epithelial cells show apical cilia that project into the intercellular space. There is also increased prominence of Golgi complexes and associated vesicles within the ciliary epithelial cells.[12] These changes and the presence of "ciliary channels" between apical surfaces probably represent the first production of aqueous humor.[113]

The iris develops by an anterior growth of the optic cup. The iris stroma develops from the anterior segment mesenchymal tissue of neural crest cell origin. The iris epithelium, including the pupillary sphincter and dilator muscles, originates from the neural ectoderm of the optic cup.[51,62,63,104] The smooth muscles of the pupillary sphincter and dilator muscles represent the only muscles in the body of neural ectodermal origin. In avian species, however, the pupillary muscles are striated and originate from stromal mesenchymal (neural crest) cells that migrate into the muscle bundles to become skeletal muscle cells.[116,117]