UNIT 20 PATHOLOGY OF LID, ADNEXA, ORBIT, OPTIC NERVE, UVEA AND RETINA

Structure

20.0 OBJECTIVES

After going through this unit, you will bc able to understand:

- various diseases of lid and adnexa;
- the pathology of the common disorders of orbit and optic nerve; and
- the pathological diseases affecting uven and retina.

20.1 INTRODUCTION

The previous unit has briefly explained to you, the different diseases of the anterior segment and their pathology, This unit will describe the pathologies affecting the rest of the ocular and adnexal structures. The description is restricted to pathology and the relevant clinical findings of the disorders only.

20.2 PATHOLOGY OF LID AND ADNEXA

The eyelid is a multilayered structure which serves to protect and help lubricate the globe. Anteriorly, the lid is covered by a thin, stratified squamous, keratinized epithelium with minimal subcutaneous tissue. The muscular layer of the lid liesdeep to the skin and is composed predominantly of the orbicularis oculi muscle (Fig. 20.1). The inner layer of the lid is made up primarily of the dense, fibrous tarsal plate which contains the meibomian glands.

Finally, the innermost aspect of the lid is lined by the palpebral conjunctiva. In addition to these structures, the lid also contains cilia, eccrine sweat glands, sebaceous glands of Zeis, apocrine glands of Moll, and accessory lacrimal glands.

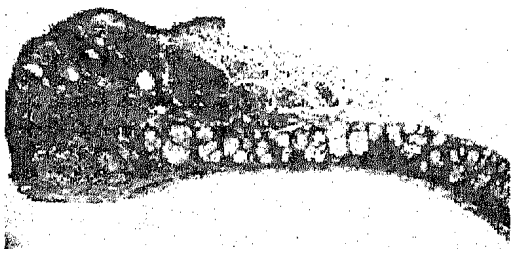

Fig. 20.1: Layers of the eyelid

The pathology of the common lid disorders is given below:

a) **Chalazion**

The extravasation of lipid material from either blocked meibomian glands of the tarsus or the glands of Zeis may incite a sterile foreign body granulomatous reaction. This often presents clinically as a painless, focal swelling in the eyelid. The pathologic change is described as a lipogranuloma. Within the granuloma, clear spaces may be seen corresponding to the location of lipid which is dissolved during histopathologic processing. Foreign body giant cells, lymphocytes, plasma cells, and PMNs may also be prominent within the lesion. Various eyelid tumors (especially sebaceous gland carcinomas) may mimic chalazia. A biopsy should be performed on all recurrent or persistent chalazia to rule out one of these lesions.

b) **Epithelial Inclusion** Cyst

Epithelial cysts (Epidermoid Cyst) may be derived from plugged hair follicles or from inclusions of squamous epithelial cells that have penetrated deep into the dermis (i.e. Following trauma or congenitally). These cysts are filled with keratin from desquamation of the hyperkeratotic, stratified squamous epithelial cells which line the cysts. In contrast to dermoid cysts, these lesions do not have any dermal appendages in the cyst wall. They are often incorrectly referred to as "sebaceous" cysts which are rare on the lids. Rupture of these cysts may cause foreign body granulomatous reaction.

c) **Actinic Keratosis**

Clinically, these lesions may appear as irregularly thickened or elevated skin which may have a brown or reddish discoloration with thickening of the epithelium. Histologically, the epithelium may show signs of acanthosis and hyperkeratosis. In addition, cellular atypia of the innermost layers of the squamous epithelium is common; however, normal polarity and maturation are preserved. The superficial dermal tissue shows a characteristic basophilic degeneration of collagen.

d) **Basal** Cell **Carcinoma** (BCC)

Basal cell carcinoma is the most common malignant tumor of the eyelids, usually involving 'the lower lid and medial canthal area. Exposure to sunlight is thought to be an impo tant causative factor. The classic description is of a rodent ulcer, which is a slowly enlarging ulcer with a pearly raised and rolled margin. Clinically, several variants may be seen: nodular or nodular-ulcerative, cystic, multicentric, and inorphea form. Histologically, the nodular and the nodular-ulcerative types are composed of anastomosing nests and cords of proliferative epidermal basilar cells. The cells have a darkly staining nucleus with minimal cytoplasm. A palisading of nuclei at the edge of the invasive tumor nests is distinctive. The cystic type of BCC is similar histologically to the nodular type, with the exception of central necrosis with cystic spaces. In the morphea form BCC, the tumor cells tend to penetrate into the dermis diffusely as branching cords of cells within a dense connective tissue matrix. It may be very difficult to clinically estimate the margins of morphea form BCC because of the diffuse infiltration of the skin.

e) **Malignant Melanoma**

Malignant melanomas of the lid, although uncommon, may occur spontaneously or secondary to malignant transformation of a preexisting nevus. Histopathologically (Fig. 20.2), the tumor cell type is similar to that seen in malignant melanoma of the skin rather than that of the globe. The cells may show a spindle-type configuration or an epithelioid-type of configuration with marked cellular dysplasia and invasion into the dermis of the lid.

Fig. 20.2: Histological section of malignant melanoma

Check Your Progress 1

1) Describe the different layers of the eyelid.

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2) List the common disorders of the lid.

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3) Discuss the Basal Cell Carcinoma of the lid.

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20.3 PATHOLOGY OF ORBIT AND OPTIC NERVE

Orbits and optic nerves are involved in various types of pathologies, some of which are malignant.

20.3.1 Orbit

You have already read the anatomy of the orbit in the previous sections. Orbit has fat, extra ocular muscles and several fascias dividing it into compartments. Hence orbit is commonly invaded by soft tissue tumors. The pathology of few common diseases of the orbit is described below:

a) Orbital Cavernous Hemangioma

Orbital cavernous hemangiornas present most commonly in young adults in the retsobulbar space. These lesions arc well encapsulated, are benign and slowly progressive, and may cause chorioretinal stria or folds. They are distinguished by the formation of large cavernous vascular channels or spaces which are considerably larger than those of capillary hemangiomas. Histologically, the mass is sharply defined and encapsulated (Fig. 20.3). These lesions are made up of large cavernous vascular spaces separated by a scant connective stroma. The spaces are lined by a flattened monolnyer of endothelial cells with variable amounts of smooth muscle in the walls. These spaces are filled with red blood cells which may layer out from the serum due to the slow flow through the lesions.

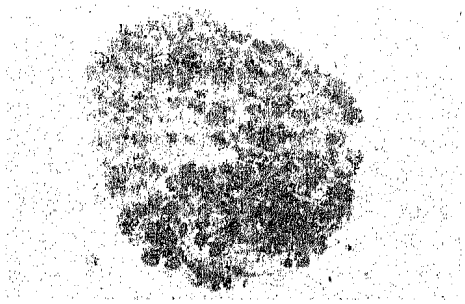


Fig. 20.3: Histological section of cavernous hemangioma

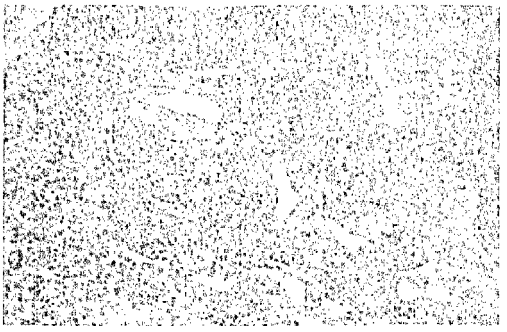


Fig. 20.4: Capillary Hemangioma

b) **Capillary Hemangioma**

These are seen in children,'are un-encapsulated, more cellular and composed of capillary sized vessels (Fig. 20.4).

c) **Orbital Lymphangioma**

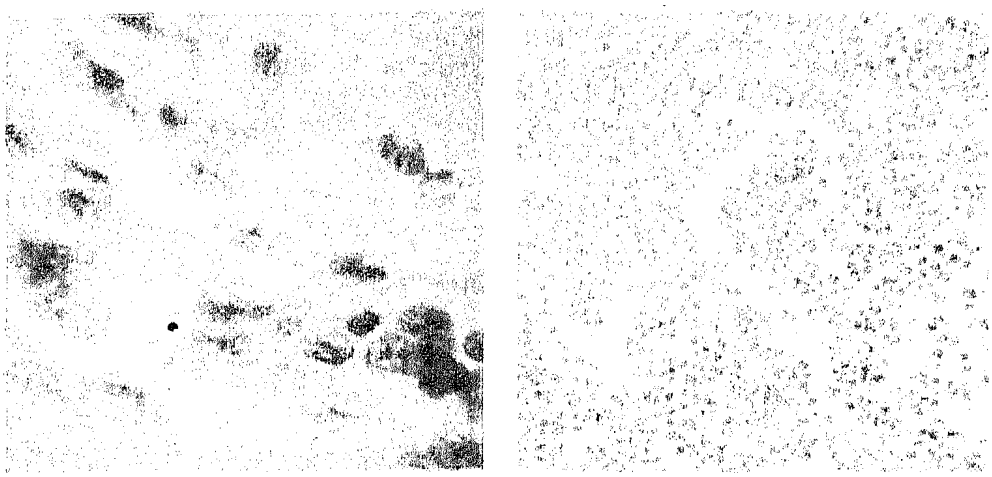
This lesion is seen most frequently in young children. The tumor tends to be diffuse and poorly outlined in the orbit. This lesion may wax and wane in size, especially when the child has an upper respiratory infection. Occasionally these tumors may undergo a rapid expansion in size when there is an acute hemorrhage in one of the tumor spaces forming a large, chocolate cyst. Histopathologically, the lesion is composed of multiple, irregular-shaped lymphatic channels which are lined by flatten endothelial cells. These lesions may also have large follicles or collections of lymphoid cells located within the walls of the lesion.

d) **Lymphoma**

Lymphomas of the orbit may arise spontaneously, or may be associated with the development of systemic lymphoma. These lesions may cause a painless, unilateral proptosis or may manifest as a salmon patch-like thickening protruding into the conjunctiva. Histopathologically, it may be difficult to differentiate malignant lymphoma from a lymphoid hyperplasia. Lymphomas characteristically show a diffuse monotonous infiltrate of atypical lymphocytes. There is minimal vasculature, no follicles, and no mixture of other cell types such as plasma cells. Benign lesions tend to show a mixture of cells, increased vascularity, and formation of follicles or germinal centers. The definitive diagnosis histopathologically often requires fresh tissue for surface staining. Lymphomas show monoclonal staining and are predominantly B cells. A typical lymphoid hyperplasia will show a mixture of B and T cells and will be polyclonal.

e) **Orbital Rhabdomyosarcoma** .

This is the most common primary mesenchymal orbital neoplasm' of childhood, with average age of onset 7-10 years. Clinically, patients often have a rapid onset of unilateral proptosis with chemosis and redness. This tumpr does not arise from differentiated muscle, but rather arises from primitive undifferentiated mesenchyme which may be located anywhere in the orbit. The neoplastic cells tend to differentiate toward cells resembling those of the rhabdomyoblast of a seven to ten week old fetus. Three cytologic variances are recognized—embryonal, alveolar and pleomorphic. The most common variant in the orbit is the "embryonal" type in which the cells are elongated with an abundant eosinophilic cytoplasm assuming a racquet or strap shape, with occasional tadpole-shaped cells. The cells are arranged in a loose syncytium. Mitotic figures are frequent. Characteristic cross-striations representing Z-bands in the cytoplasm are often not present and special stains (trichrome) or EM studies may be necessary to make the diagnosis. The "alveolar variant" shows fibrovascular septae or trabeculae dividing the neoplastic cells into clusters resembling lung alveoli and tends to be more aggressive. The "adult pleomorphic variant" is the least common and consists of more differentiated cells with obvious cross-striations (Fig. 20.5).



(a) Embryonal **Type** (b) Alveolar **Type**

Fig. 20.5: Orbital Rhabdomyosarcoma

20.3.2 Optic Nerve

The optic nerve is composed primarily of axons from the retinal ganglion cells. In addition, there are multiple glial support cells and tissue in the nerve itself. The optic nerve begins at the optic nerve head or disc and passes through the sclera in the area of the lamina cribrosa and then extends through the orbit and optic canal to the chiasma. Myelination begins posterior to the lamina cribrosa, where the optic nerve is surrounded by a three-layered meningeal sheath similar to the central nervous system which consists of a dura (optic nerve sheath), arachnoid, and pia. Oligodendrocytes, astrocytes and microglial cells are the glial cells. Oligodendrocytes produce and maintains the myelin; that sheaths the optic nerve. The subarachnoid space is in direct communication with the subarachnoid space of the central nervous system. The central retinal artery and vein penetrate the optic nerve and enter the eye from the center of the disc. The optic nerve receives its blood supply mainly from vessels that originate in the ophthalmic artery.

a) **Colobomas/Congenital Anomalies:** Minor congenital anomalies of the optic nerve may lead to an oblique, horizontal, or tilted disc, often with the appearance of inferior conus. **A** more serious congenital defect of the optic nerve is an optic nerve coloboma. A coloboma is a unilateral abnormality of the optic nerve head thought to be secondaiy to a failure of fusion of the posterior part of the embryonic fissure. A complete optic nerve coloboma may form a large hole or posterior protrusion in the area of the optic nerve. Histopathologically, a coloboma is seen as a large defect with mostly bare sclera and a small amount of fibrous tissue or gliosis lining the defect. The retina and choroid along the edges of the coloboma may also be involved. Another form of an optic nerve coloboma is the so-called morning glory syndrome which is characterized by a large excavation of the optic nerve head that resembles the morning glory flower.

b) **Optic Atrophy**

Simply defined, this is a loss of function of the optic nerve with resulting gliosis and a decrease or loss of capillaries and axonal tissue within the nerve. The type of optic alrophy depends on the pathogenetic Factors involved:

i) ascending atrophy—damage from within the eye (glaucoma, optic neuritis, papilledema, and many primary lesions of the retina-choroid)

ii) descending atrophy—from damage to the optic nerve or bruin (trauma, hydrocephalus, neoplasm, demyelinating diseases),

iii) or due to congenital defect (Leber's optic atrophy).

Clinically, the atrophic disc appears white and pale diffusely. Histologically, the myelin sheaths and axons degenerate, resulting in loss of substance of the

optic nerve, causing expansion of the subarachnoid space (and causing the dura to appear redundant). The pial septa thicken:; within the optic nerve due to proliferation of the glial, meningeal, and connective tissue elements. Gliosis is also seen randomly within the nerve parenchyma. Within the retina there is a corresponding loss of ganglion cells and nerve fiber layer. Other clue:; such as loss of the inner nuclear layer (central retinal artery occlusion) or posterior bowing of the lamina cribrosa with cupping (glaucoma) may give clues to the origin of the atrophic process.

c) **Drusen**

Drusen of the optic disc consists of hyaline like calcified material within the nerve substance. They are usually bilateral and thought to result from intracellular mitrochondrial calcification within the axons. Optic nerve head drusen are seen clinically as whitish-yellow irregularities on the surface of the optic disc or deeper within the disc tissue causing an irregularity to the disc, which may be mistaken **for** papilledema. Histopathologically, drusen are seen as dark collections of material in the optic nerve head anterior to the lamina cribosa. This material is acellular and stains darkly basophilic. In addition, these lesions may also be calcified. Drusen also stain positive for acid mucopolysaccharides.

d) **Papilloedema**

Papilloedema is a bilateral swelling or edema of the optic disc secondary to any factor which may increase cerebral spinal fluid pressure. Fundus examination reveals a swollen optic nerve head with elevation, edema and narrowing of the physiological cup, vascular congestion with small areas of flame-shaped hemorrhage and exudates. and possible surrounding retinal edema. Histopathologically, the axons in the optic disc are markedly edematous and swollen with surrounding tissue edema and also increased vascular congestion.

e) **Optic Nerve Glioma**

Optic nerve gliomas are tumors derived from neuroglial astrocyte elements. These tumors occur most commonly in children with a median age at time of diagnosis of five years. Common presenting signs include unilateral proptosis, decreased acuity, strabismus, papilledema leading to optic atrophy, arid occasional CRV occlusion, These is an increased association with von Recklinghausen's disease or neurofibromatosis. On gross pathologic exam, one would see a smooth fusiform enlargement of the optic nerve. The tumor often extends into meninges causing meningeal hyperplasia which may make differentiation from an meningioma difficult on a superficial optic nerve biopsy. Histopathologically, most optic nerve-gliomas are Grade I or juvenile pilocytic (hair-like) astrocytomas. These tumors consist of benign-appearing, round to spindle-shaped astrocytic nuclei with dendrite-like cytoplasmic processes. Rosenthal fibers are a characteristic but not a diagnostic degenerative change. These are fusiform, cigar-shaped, eosinophilic structures within the astrocyte cytoplasmic processes. Some lesions may also show small areas of necrosis within the tumors which show myxomatous cystic spaces.

f) **Optic Nerve Meningioma**

The most common primary site of this tumor is intracranial, and it invades the orbit secondarily. Less commonly, it arises intraorbitally around the optic nerve. Orbital meningiomas are more common in middle-aged females. They tend to he more aggressive in children. Clinically, these lesions commonly present with a painless decrease in visual acuity arid progressive exophthalmos. They present less commonly with visual field loss, optic atrophy, optociliary shunt vessels, lid edema, muscle palsies, retinal striae, hypertrophy or hyperostosis of the bony orbit. There is also a small increased

incidence in von Recklinghausen's disease. Clinically, an optic disc exam may reveal disc edema, or disc atrophy with optociliary shunt vessels. Pathologically, these tumors may show several histologic patterns including meningotheliomatous or syncytial (large, uniform cells with indistinct boundaries forming solid sheets) and psammomatous (whorled pattern of concentric cell layers). The central core of some nests become hyalinized and calcified forming psammona bodies.

g) **Temporal Arteritis**

Diffuse inflammation of the arteries may lead to the condition of temporal arteritis. Clinically, the patient may note a sudden painless loss of vision in one eye with characteristic altitudinal type of visual field loss. In addition, the patient may have generalized symptoms of polymyalgia rheumatica such a:; low grade fever, loss of appetite, generalized weakness, and jaw claudication. Optic disc examination in the acute stage reveals a small amount of swelling and irregclarity of the disc with normal vascularity. The lesion causing the visual loss is thought to involve obstruction of a posterior ciliary artery. The diagnosis of this entity is confirmed by taking a biopsy of the temporal artery. The histo-pathologic examination of the temporal artery reveals a granulomatous inflammation of the wall of the artery characterized by epithelioid cells and giant cells. In addition, the internal elastic lamina is often discontinuous and fragmented. These arteries also characteristically show moderately severe arterial sclerotic changes.

Check Your Progress 2

1) List few common orbital tumors.

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2) Describe the, pathology of the orbital rhabdomyosarcoma.

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3) Discuss the histo-pathogenesis of optic atrophy.

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4) Describe the clinical signs of papilloedoma.

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20.4 PATHOLOGY OF UVEA AND RETINA

Uveal tract and retina constitute the middle and the inner layer of the eyeball. Their pathologies have early effect on visions.

20.4.1 Pathology of Uvea

As you must have read in the section describing anatomy of the uvea, the uvea has 3 parts: iris, ciliary body and the choroid. The uvea can be affected either by inflammatory disorders of immunological and infective etiology or by neoplastic disorders. Pathology of few common disorders is discussed below.

a) **Iris Pigment Epithelial Cyst**

Pigmented iris epithelial cysts may arise from the posterior pigment epithelium of the iris, on the posterior surface, or at the pupillary margin. These cysts are usually benign and attached to the iris, although on occasion

a 'cyst may break loose and become free-floating, possibly causing pupil obstruction or secondary angle closure glaucoma. These cysts are often pigmented and may give the appearance of a malignant melanoma of the iris. Histopathologically, these cysts are lined by epithelial cells from the posterior pigment epithelial layer of the iris.

b) Sympathetic **Ophthalmia**

Sympathetic ophthalmia or sympathetic uveitis is an inflammatory condition seen after severe perforating or penetrating ocular injury, usually associated with loss of uveal tissue or uveal prolapse. This condition is characterized by a diffuse bilateral granulomatous panuveitis, which can occur anywhere from several weeks to several years following injury to one of the eyes (exciting eye). Removal of a severely traumatized eye prior to development of this inflammation will protect the other eye from sympathetic ophthalmia. This condition is thought to be an auto-immune reaction of the delayed hypersensitivity type, possibly to uveal or retinal antigens. Clinically, this condition is characterized by a granulomatous inflammation with large "mutton-fat" keratic precipitates and a diffuse uveitis. This inflammation classically spares the chorio-capillaris. The inflammation is a granulomatops inflammation composed predominantly of epithelioid cells which may form multi-nucleated giant cells, as well as lymphocytes. Another characteristic feature of this inflammation is the formation of "Dalen-Fuchs'" nodules. These nodules are comprised of epithelioid cells which are felt to be derived from either the monocyte/macrophage cell line or possibly from retinal pigment epithelial cells. These nodules are located between Bruch's membrane and the retinal pi'gment epithelium.

c) Phthisis **Bulbi**

Phthisis bulbi is an end-stage ocular response to sever ocular disease, inflammation, or insult. Clinically, the globe will be soft and hypotonus with minimal or no vision and loss of much of the normal architecture of the eye. Histopathologically, the globe is small and shrunken with marked thickening of the sclera, as well as disorganization and atrophy of much of the intraocular contents. The intraocular contents are markedly disrupted and difficult to recognize. Commonly, the retinal pigment epithelium may undergo a metaplasia leading to intraocular ossification or bone formation in the end-stage of phthisis bulbi.

d) Melanocytic **Tumors of Uvea**

Malignant melanomas of the uvea are the most common intraocular malignancy in adults. These tumors may arise from the iris, ciliary body, or choroid. These tumors arise de-novo or also arise from pre-existing nevi. Iris melanomas arise from the anterior layer of iris stromal tissue. These tend to appear as a variably pigmented mass on the iris but may also diffusely involve anterior chamber structures causing glaucoma or uveitis.

Histopathologically, the vast majority of malignant melanomas of the iris are composed of spindle cells. These tumors are more benign than melanomas of the ciliary body or choroid and only rarely metastasize. Malignant melanomas most commonly arise from the posterior uveal structures, the choroid and ciliary body. The presenting symptoms depend on the location of the lesion. If the lesion is located posteriorly, the patient will note blurred vision. Often, the mass is found on routine ocular examination. Histologically, in the absence of extraocular extension, the major determinants of prognosis are cell type, tumor size, and location. Cell type is generally categorized under the Callender classification system.

Spindle-A cells have slender nuclei with delicate chromatin, ill-defined or absent nucleoli, and no mitotic activity. Often a longitudinal fold of the nuclear membrane accounts for a prominent streak of chromatin.

Spindle-B cells have more plump nuclei containing small but prominent nucleoli and coarse chromatin. Mitotic figures are common.

Epithelioid cells are variable in size but are usually larger and pleomorphic or polygonal. They exhibit variations in size and shape of their nuclei and may be multinucleated. 'Chromatin shows coarse clamping. Mitotic figures are abundant. Cells show loss of intercellular cohesiveness. Lesions composed of exclusively spindle-A cells are now regarded to behave almost like nevi.

The designation of **"mixed"** cell type implies the presence of a mixture of spindle and epithelioid melanoma cells. Spindle-B tumors inay also form a fascicular pattern with palisading of the cells.

A final classification is that of a necrotic tumor in which necrosis precludes identification of **a** cell type. Other histologic findings may include rupture of Bruch's membrane with a mushroom-like out-pouching of the tumor underneath the retina. In addition, there may be an associated exudative retinal detachment **and** also a cystic degeneration of the retina overlying the tumor, These tumors may extend from the eye by invasion of scleral emissarial channels or vortex veins. Direct invasion of the sclera or optic nerve is much less common. The tumor may extend into the orbit and may matastasize distantly. The most common site of the metastasis is the liver.

20.4.2 Pathology of Retina

The retina is a multilayered neural ectoderm structure which lines the inside surface of the eye posterior to the ora serrata. The retina has three cellular layers (Fig. 20.6) which are classified as the ganglion cell layer, the inner nuclear' layer, and the outer nuclear layer. The connections between the cellular layers are found in the inner plexiform layer and the outer plexiform layer. The rods and cones are the outermost layer of the retina and are in direct approximation to the retinal pigment epithelium. The choroid underlies the retina and is responsible for providing nourishment to the outer one-third of the retina, The fovea in the center of the macula is that area of the retina where the most acute vision is, obtained.

The arrangement of the retina (histologically) is vertical from outer to inner layers, except for the nerve fibre layer, where the axons run horizontally towards the optic nerve head.

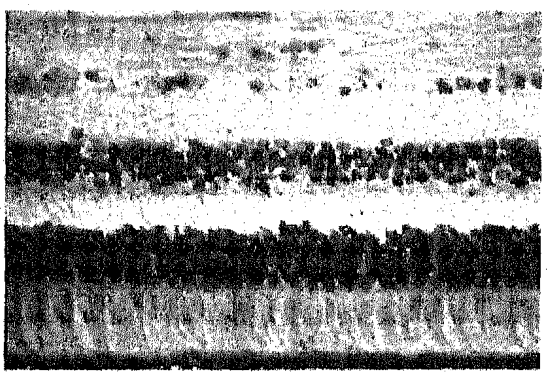

Fig. 29.6: Layers of the retina

The common retinal disorders are discussed below:

a) **Diabetic Retinopathy**

Although diabetes may affect multiple parts of the eye, the most common area affected is the retina. Diabetic retinopathy is divided into three classifications—background retinopathy, pre-proliferative retinopathy, and proliferative retinopathy.

Background Diabetic Retinopathy

Background diabetic retinopathy is characterized by retinal capillary microaneurysms, some venous abnormalities, hemorrhages, exudates, and edema.

i) *Capillary Microangiopathy*

Histopathologically the earliest change is in the retinal micro-circulation. There are a) microvascular obstructions and permeability changes non-perfusion of capillaries. The earliest changes occur in the capillary beds, then subsequently in larger pse-capillary arterioles (leading lo cotton-wool spots which result from acute micro-infarctions) and arc: caused by deposition **of** PAS positive plasma derivatives in the defective endothelium. b) Retinocapillary microaneurysms. These develop adjacent to areas of capillary non-perfusion. c) Basement membrane thickening. This also contributes to gradual closure of small arterioles. d) Loss of pericytes. Ratio of pericytes to cndothelial cells is reversed in diabetics. This loss of pericytes creates a weaker vessel wall partially explaining aneurysm formation.

ii) *Intraretinal Hemorrhages*

a) Flame-shaped—blood deposited superficially between fibers of nerve fiber layer. b) Dot and blot—focal deposits in deeper inner nuclear and outer plexiform layers [Fig. 20.7 **(a)].**

iii) *Exudates*

Hard, yellow, waxy protein and lipid from serum exudate or from degenerating neural eleincnts. These are deposited in the outer plexiform layer seen as an eosinophilic material on histologic sections. They can sometimes form a circinate pattern around the macula [Fig. 20.7 (b)].

Macular Changes

a) Due to vascular permeability Macular edema (which can progress to macular retinoschisis and hole formation) and hard exudates are seen. (b) Due to retinal vascular occlusion-Cotton wool spots and fluorescein angiography showing focal capillary dropout or enlargement of foveal avascular zone with subsequent ischaemia are noted.

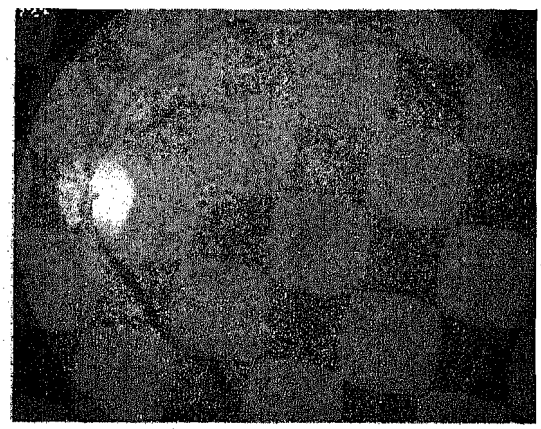

Fig. 20.7(a): Intraratinal hemorrhages

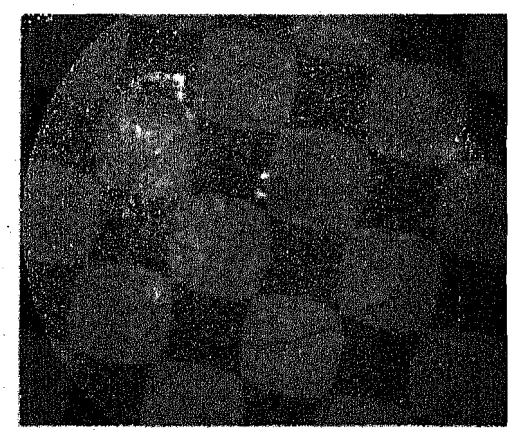

Fig. 20.7(b): Exudates

Pre Proliferative Diabetic Retinopathy

This consists of any or all of the changes of background diabetic retinopathy with **the** addition of significant venous beading, cotton wool spots, extensive formation of IRMA, extensive ischemia.

i) *Significant Venous Beading*

Initially, venules may show focal areas of dilation which may progress to significant venous beading and formation of venous loops as the diabetic retinopathy progresses.

ii) *Cotton Wool Spots* (cystoid bodies or soft exudates)

Actually not an exudate, but produced by clusters of focal ischaemic infarcts in nerve fiber layer. Histologically, cystoid bodies which are clusters of degenerated and swollen ganglion cells axons which resemble round or fusiform cells are seen.

iii) *Intraretinal Microvascular Abnormalities (IRMA)*

To compensate for hypoxic conditions, non-leaking intraretinal vascular shunts may develop (IRMA). These indicate a progression toward the pre-proliferative phase.

iv) *Extensive Retina Ischaemia*

Proliferative Diabetic Retinopathy: Changes may occur in the presence or absence of clinically visible background diabetic retinopathy. Neovascularizatiou and fibrous tissue proliferation occur in response to hypoxia and may arise on the optic disc (NVD) or elsewhere (NVE). New vessels arise from primitive mesenchymal elements which can then undergo fibrous metaplasia. Associated changes include retinal wrinkling, macular heterotropia, thickening and detachment of the posterior hyaloid membrane. Ultimately, one may get traction from the contracting vitreous body which has become adherent to the retina via a pre-retinal fibrovascular membrane, thus producing vitreous hemorrhage (which may fill the vitreous, directly overlie the macula, or promote formation of a dense posterior hyaloid membrane over the macula) and/or retinal detachment.

Diabetes may also cause changes in other areas of the eye. Ischaemia may lead to the formation of neovascularization on the iris which is also called rubeosis iridis. Pathologically, this is characterized by proliferation of fibrovascular tissue on the anterior-most surface of the iris. As this tissue contracts, it may cause eversion of the iris pigment epithelium rind sphincter muscle at the pupillary margin causing cctropion uvea. This fibrovascular ussue may also grow from the surface of the iris to the area of the trabecular meshwork in the anterior chamber angle causing a peripheral anterior synechiae (PAS) and neovascular glaucoma. In addition, the iris pigment epithelium may show small empty spaces or lacy vacuolization. Histopathologic examination of the ciliary body reveals a characteristic diffuse thickening of the basement membrane of the innermost pigmented ciliary epithelium. In addition, choroidal vessels may also show a diffuse thickening of their walls. The periodic acid-Schiff (PAS) stain is an excellent way to look for thickened basement membranes and vessels.

b) **Central Retinal Artery Occlusion (CRAO)**

Occlusion of the central retinal artery clinically leads to a sudden, painless loss of vision in the involved eye **As** the retina becomes ischaemic, it swells and looses it's vascularity. Histopathologically the nerve fibre layer and the ganglion cell layer are the thickest and because they are absent in the fovea, the normal colour of the choroid shows through and produces a "cherry red spot" at the fovea. Examination of the ocular fundus reveals diffuse ischaemia of the retina with a pale whitening as well as swelling or edema of the retina with marked decreased vascularity. The central fovea shows a classic "cherry red spot" which is secondary to ischaemic white retina surrounding the normal choroidal blood flow to the area of the fovea. CRAO usually results from an embolic event, localised arterial sclerosis or rarely vasculitis, which occurs at the level anterior to the optic canal. The retina itself will show marked ischaemia of the innermost layers during the early stages of occlusion. Late stages show atrophy of the innermost layers of the retina with gliosis. A similar occlusion of one of the branch retinal arteries usually secondary to an embolic phenomenon will lead to a sector-shaped arc of retinal ischaemia and pallor.

c) Central Retinal Vein Occlusion (CRVO)

Clinically, occlusion of the central retinal vein is manifest by a painless decrease in vision which is usually not as severe as that seen in arterial occlusion. It occurs at the level of the lamina cribrosa and develops due to structural changes (which occur in conditions like arterial sclerosis, diabetes, hypertension and glaucoma) in the CRA and lamina cribrosa which lead to compression of central retinal vein or CRV. This causes a turbulant flow in the CRV and predisposes it to thrombosis. Fundus examination reveals wide-spread hemorrhages throughout the retina with swelling and edema. The degree of retinal involvement depends on whether the venous occlusion is a partial or incomplete occlusion (venous stasis retinopathy—non-ischeamic) or a more complete central retinal vein occlusion (hemorrhagic retinopathy—ischenmic). Gross histopathologic examination reveals wide-spread hemorrhages throughout the entire retina. Histopathologic examination reveals hemorrhages throughout all layers of the retina with diffuse areas of hemorrhagic infarct and ischearnia.

d) Lattice Degeneration

Lattice peripheral degeneration of the retina is a bilateral condition which involves the retina peripherally between the areas of the ora sen-ata and the equator. Examination of the fundus reveals a circumferential area of involvement characterized by small criss-crossing white lattice lines which represent thickened, hyalinized blood vessels. There may be areas of hyperpigmentation associated with the areas of lattice degeneration. There is often a pocket of liquified overlying vitreous with condensed vitreous forming adhesions to the margins of the lattice degeneration which may lead to subsequent retinal detachment. Histopathologically, the retina shows signs of atrophy and thinning with a small amount of gliosis superficially. The retinal vessels are thickened and hyalinized. The overlying vitreous shows liquefaction centrally with areas of vitreoretinal adhesions seen at the edge of the lattice lesion.

e) Hetinitis Pigmentosa

Retinitis pigmentosa is a hereditary degenerative disorder which is characterized by bilateral progressive loss of peripheral vision, night blindness, and marked ring-like constriction of visual field. Fundus examination reveals an atrophic, waxy pallor to the optic disc with marked attenuation of retinal arterials. The retina itself shows a charactelistic bony spicule-shaped disruption of pigmentation. Histopathologically, this lesion is characterized by migration of macrophages and RPE cells filled with melanin into the retina, especially around blood vessels. This is thought to explain the bony spicule pattern of pigmentation seen on fundus examination. In addition, there is an atrophy of the photoreceptors of the retina as well as the choriocapillaris.

f) Rhegmatogenous Retinal Detachment

A rhegmatogenous retinal detachment may form due to a hole or a tear in the retina secondary to traction or degeneration. This allows fluid into the space between the retina and the RPE and may cause a retinal detachment. Fundus examination often reveals a small hole or a horseshoe type tear in the retina with an elevated, translucent, and irregular detachment of the retina. Gross pathologic examination of a long-standing retinal detachment often reveals the classic funnel shape of the detachment. The retina remains attached in the area of the optic nerve as well as the ora serrata but is detached in the other areas. Histopathologically, in the early stages a retinal detachment will show degeneration of the outer retinal layers and

photoreceptors with subretinal exudate present. Long-standing detachments can show disruption and atrophy of normal retinal architecture with extensive gliosis or proliferative vitreoretinopathy.

g) **Retinoblastoma**

Retinoblastoma is the most common intra-ocular tumor of childhood affecting approximately one in twenty thousand live births. It may be inherited as an autosomal dominant trait with incomplete penetrance (possibly a deletion in the area of 'chromosome 13q14) or may arise as a sporadic form. The tumor may present clinically as leulcocoria, strabismus, red eye, change in colour of iris, spontaneous hyphaema, pseudohypopyon, and ocular enlargement because of glaucoma. Retinoblastoma is thought to arise from primitive neural elements of the retina rather than the glial elements. Histopathologically, this tumor may have one of several growth patterns: **exophytic** (tumor grows into subretinal space), **endophytic** (toward the vitreous or as a mixture of both patterns). Dystrophic calcification and necrosis are common. The tumor cells have large basophilic nuclei with scant cytoplasm. Well differentiated tumors have Flexner-Wintersteiner rosettes which consist of a row of photoreceptor-like tumor cells arranged into a circular pattern. The outer segments of primitive rods and cones point toward the lumen. The outer nuclear layer forms the cellular lining of the rosette. These are essentially pathognomonic of retinoblastoma. Fleurettes are tumor cells which show a great deal of differentiation toward photoreceptors, but are arranged side-by-side. Pseudo rosettes are circumferential arrangements of viable basophilic tumor cells around blood vessels. Prognosis worsens with:

1) Optic nerve invasion, especially if present in the cut surface of the enucleated optic nerve;

2) Absence of Flexner-Wintersteiner rosettes indicating less differentiation;

3) Choroidal invasion; or

4) Large size, especially with vitreous seeding or extension anterior to the equator. Retinoblastomas may extend locally into the orbit and directly invade the brain and the central nervous system. In addition, these tumors may show wide-spread metastases. The treatment consists predominantly of enucleation of the involved eye and/or radiation therapy.

Check Your Progress 3

1) List the three parts of uvea.

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2) What is sympathetic ophthalmia? Discuss its pathology.

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3) Describe the pathology of uveal melanoma.

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4) List the fundus changes of Pre-proliferative Diabetic Retinopathy.

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5) Haw do you diagnose central retinal vein occlusion?

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6) What causes retinal detachment?

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20.5 LET US SUM UP

In this unit you have learnt about the pathology of orbit, uvea and retina. You have learnt that most disorders described here are blinding and some of them are life threatening also. Proper understanding of their pathology is must to comprehend their clinical features and their prompt diagnosis. You have learnt to read further about diabetic retinopathy which has become the leading cause of blindness worldwide. In next unit you will learn about pathology of conjunctiva, cornea, glaucoma and lens.

20.6 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) The eyelid is a multilayered structure which serves to protect and help lubricate the globe. Anteriorly, the lid is covered by a thin, stratified squamous, keratinized epithelium with minimal subcutaneous tissue. The muscular layer of the lid lies deep to the skin and is composed predominantly of the orbicularis oculi muscle. The inner layer of the lid is made up primarily of the dense, fibrous tarsal plate which contains the meibomian glands. Finally, the innermost aspect of the lid is lined by the palpebral conjunctiva.

2) The common disorders of this lid are given below:

a) Chalazion

b) Epithelial inclusion cyst

c) Actinic keratosis

d) Basal cell carcinoma (BCC)

e) Malignant melanoma

3) Basal cell carcinoma is the most common malignant tumor of the eyelids, usually involving the lower lid and medial canthal area. Clinically, several variants may be seen: nodular or nodular-ulcerative, cystic, multicentric, and morpheaform. Histologically, the nodular and the nodular-ulcerative types are composed of anastornosing nests and cords of proliferative epidermal basilar cells. The cells have a darkly staining nucleus with minimal cytoplasm. A palisading of nuclei at the edge of the invasive tumor nests is distinctive. The cystic type of BCC is similar histologically to the nodular type, with the exception of central necrosis with cystic spaces. In the morpheaform BCC, the tumor cells tend to penetrate into the dermis diffusely as branching cords of cells within a dense connective tissue matrix.

Check Your Progress 2

1) Few pathologically important common diseases of the orbit are as below:

   a) Orbital cavernous hemangioma

   b) Capillary hemangioma

   c) Orbital lymphangioma

   d) Lymphoma

   e) Orbital Rhabdomyosarcoma

2) The tumor does not arise from differentiated muscle, but rather arises from primitive undifferentiated mesenchyme which may be located anywhere in the orbit. The neoplastic cells tend to differentiate toward cells resembling those of the rhabdoinyoblast of a seven to ten week old fetus. Three cytologic variances are recognized. The most common variant in the orbit is the "embryonal" type in which the cells are elongated with an abundant eosinophilic cytoplasm assuming a racquet or strap shape, with occasional tadpole-shaped cells. The cells are arranged in a loose syncytiuin. Mitotic figures are frequent. Characteristic cross-sttiations representing Z-bands in the cytoplasm are often not present and special stains (trichrome) or EM studies may be necessary to make the diagnosis.

3) Histologically, the myelin sheaths and axons degenerate, resulting in loss of substance of the optic nerve, causing expansion of the subarachnoid space (and causing the dura to appear redundant). The pial septa thickens within the optic nerve due to proliferation of the glial, meningeal, and connective tissue elements. Gliosis is also seen randomly within the nerve parenchyma. Within the retina there is a corresponding loss of ganglion cells and nerve fiber layer.

4) Fundus examination reveals a swollen optic nerve head with elevation, edema and narrowing of the physiological cup, vascular congestion with small areas of flame-shaped hemorrhage and exudates, and possible surrounding retinal edema.

Check Your Progress 3

1) The three parts of the uvea are iris, ciliary body and choroid.

2) Sympathetic ophthalmia or sympathetic uveitis is an inflammatory condition seen after severe perforating or penetrating ocular injury, usually associated with loss of uveal tissue or uveal prolapse. This condition is characterized by a diffuse bilateral granulomatous uveitis which can occur anywhere from several weeks to several years following injury of one of the eyes. This condition is felt to be an auto-immune reaction of the delayed hypersensitivity type, possibly to uveal or retinal antigens. Histopathologically, sympathetic ophthalrnia is characterized by a diffuse, granulomatous inflammation of the uvea. This inflammation classically spares the choriocapillaris.

3) Malignant Melanoma: Histopathologically, the vast majority of malignant melanomas of the iris are composed of spindle cells. The major determinants of prognosis are cell type, tumor size, and location. Cell type is generally categorized under the Callender classification system.

   a) Spindle-A cells

   b) Spindle-B cells

   c) Epithelioid cells

   d) Mixed cell type

4) Pre-proliferative retinopathy consists of any or all of the changes of background diabetic retinopathy with the addition of significant venous beading, cotton wool spots, extensive formation of IRMA, extensive ischeamia.

5) Clinically, occlusion of the central retinal vein is manifest by a painless decrease in vision which is usually not as severe as that seen in arterial occlusion. Fundus examination reveals wide-spread hemorrhages throughout the retina with swelling and edema.

6) A rhegmatogenous retinal detachment may form due to a hole or a tear in the retina secondary to traction or degeneration. This allows fluid into the space between the retina and the RPE and may cause a retinal detachment.