

# OPHTHALMIC PATHOLOGY FOR MEDICAL STUDENTS

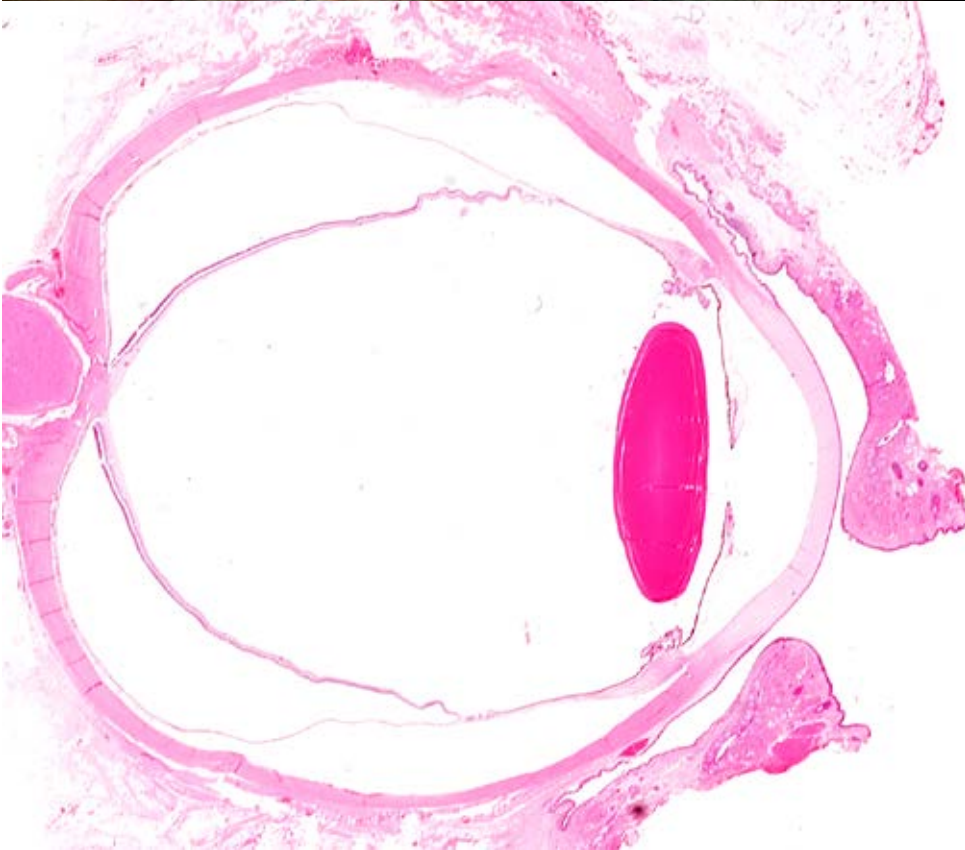
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**SUGGESTED READING:** PATHOLOGIC BASIS OF DISEASE 7<sup>th</sup> Edition, pp 1421-47.

**OBJECTIVES:** At the end of the web site review, the student should be able to:

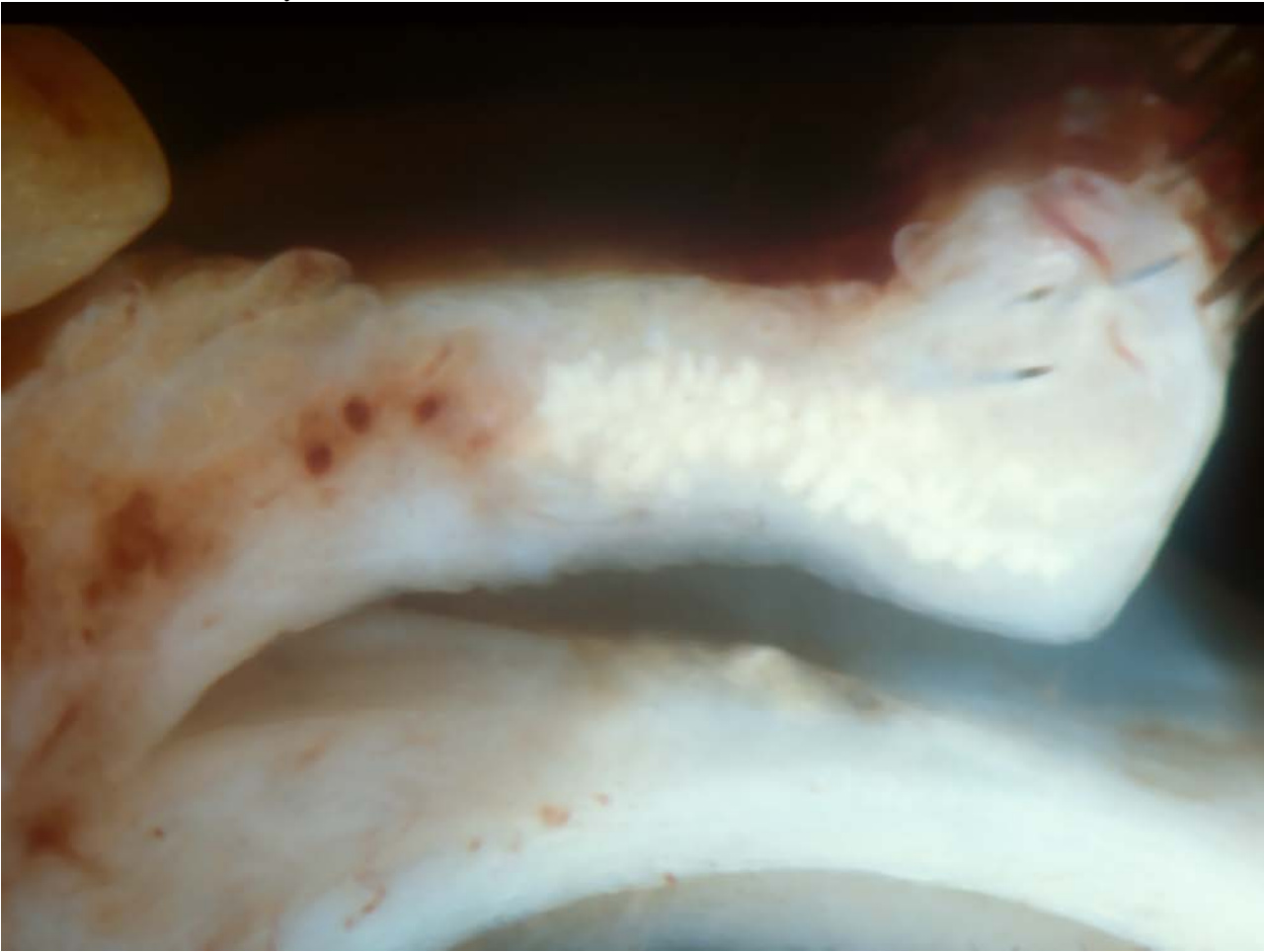
1. Describe the clinical and pathologic features of eyelid inflammation and tumors.
2. Recognize the differences between solar-induced and malignant changes of the conjunctiva.
3. Describe the differences between viral, bacterial, and fungal infections of the cornea.
4. Describe the clinical and pathologic features of patients with vascular diseases, and diabetic changes.
5. Recognize and understand the degenerative changes in age-related macular degeneration.
6. Describe differences between the pathologic changes in papilledema versus optic nerve changes in glaucoma.
7. Compare the clinical and histopathologic features of retinoblastoma versus ocular malignant melanoma.

# **I. OVERVIEW OF OCULAR AND ORBITAL ANATOMY**



## II. EYELIDS AND EXTERNAL DISEASE

### A. Anatomy



1. Skin layer – stratified squamous keratinized epithelium
2. Muscle layer – orbicularis oculi
3. Tarsus – meibomian gland layer
4. Conjunctival layer



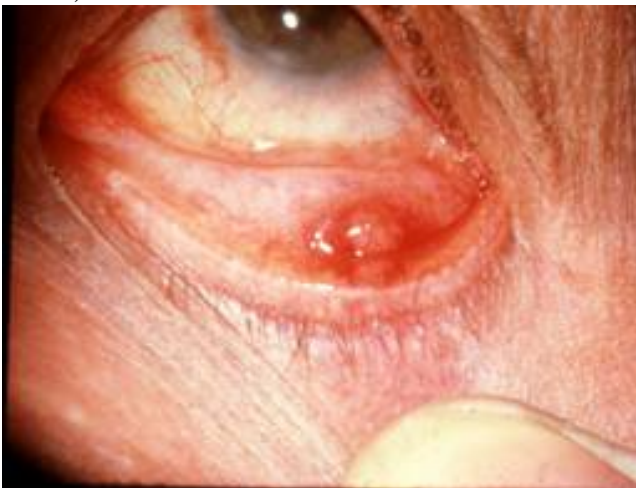
B. Infection of eyelid

1. **Sty or hordeolum** – an infection of the eccrine sweat glands or the glands of Moll. It is most often a low-grade Staph infection.

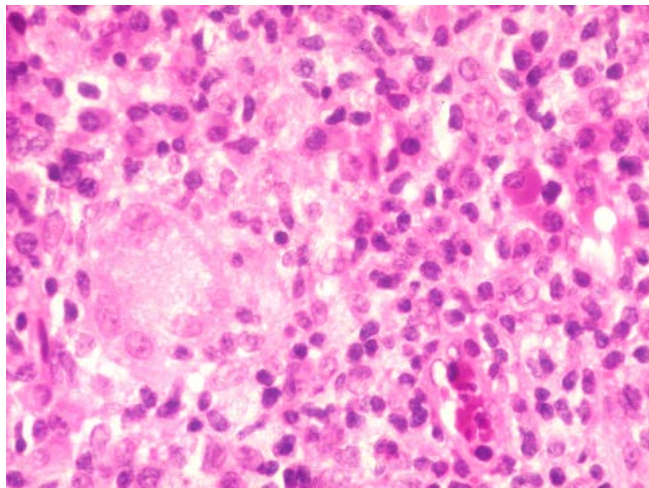


A sty (or hordeolum) is a red mass mainly on the outside (skin surface) of the eyelid.

Inflammatory lesion of eyelids - **Chalazion** – a chronic inflammatory infiltrate of the meibomian or Zeis glands. If a presumed chalazion recurs, biopsy it to be sure that it is not a neoplasm such as a sebaceous carcinoma (see tumor section below).



Grossly, a Chalazion is a red lump mainly on the inside (conjunctival surface) of the eyelid.



Chalazions have lymphocytes and epithelioid macrophages with some giant cells. Lipid droplets are present, which appear as empty areas in routine sections.

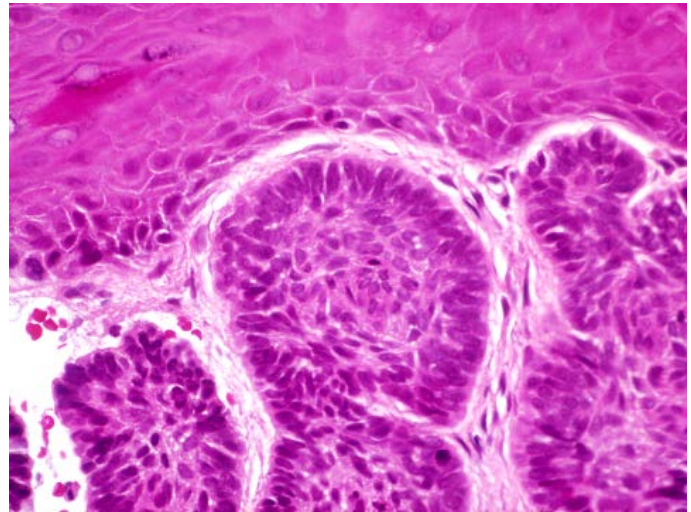


D. Tumors of the eyelids

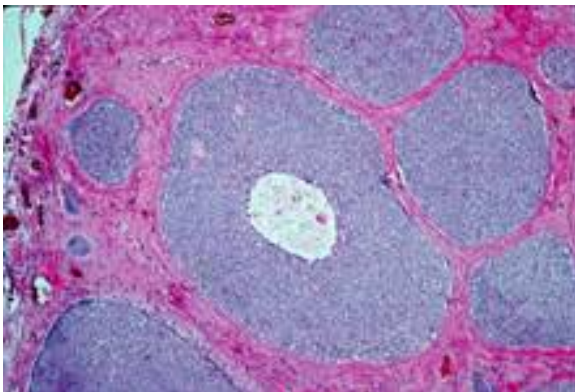
1. **Basal cell carcinoma** – the most common malignant tumor of the eyelids (and of the skin in general). It is more common on the lower lid, especially at the medial side. It is due to exposure to sunlight / UV radiation. There are three main kinds of basal cell carcinoma: Nodular – large solid nests of tumor cells, Cystic – tumor cell nests with central cysts, and Morpheaform or sclerotic – very small nests of tumor cells which invade widely. Morpheaform basal cell carcinomas are uncommon, but are important to know about since they often invade further than is grossly apparent and thus often recur.



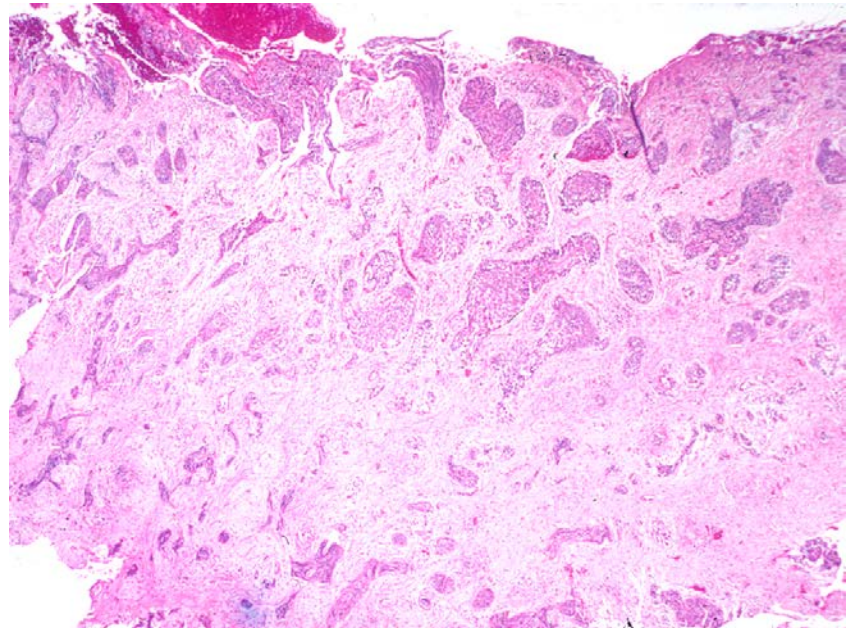
Typical basal cell carcinoma – a central ulcer with a raised, pearly border, and loss of the nearby lashes.



Nodular basal cell carcinoma (at bottom, under the epidermis at top), with nuclear palisading (the nuclei near the edge of the tumor nests line up).



Cystic basal cell carcinoma



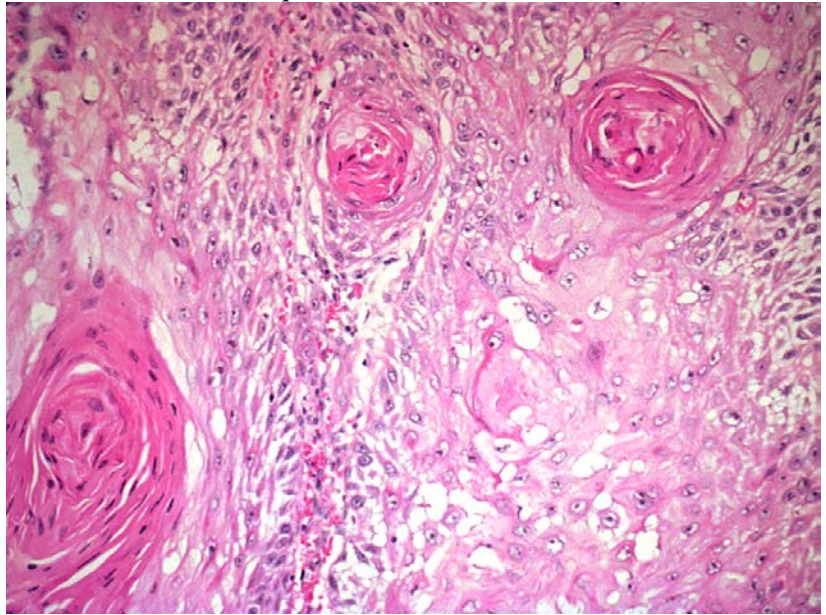
Morpheaform basal cell carcinoma – small tumor cell nests in a fibrous stroma, often extending further than is grossly evident.



2. **Squamous cell carcinoma** – usually considered the second most common kind of eyelid malignancy (in a few studies sebaceous carcinomas are more common). They often progress from a scaly noninvasive lesion (a solar or actinic keratosis, or a squamous carcinoma in situ).

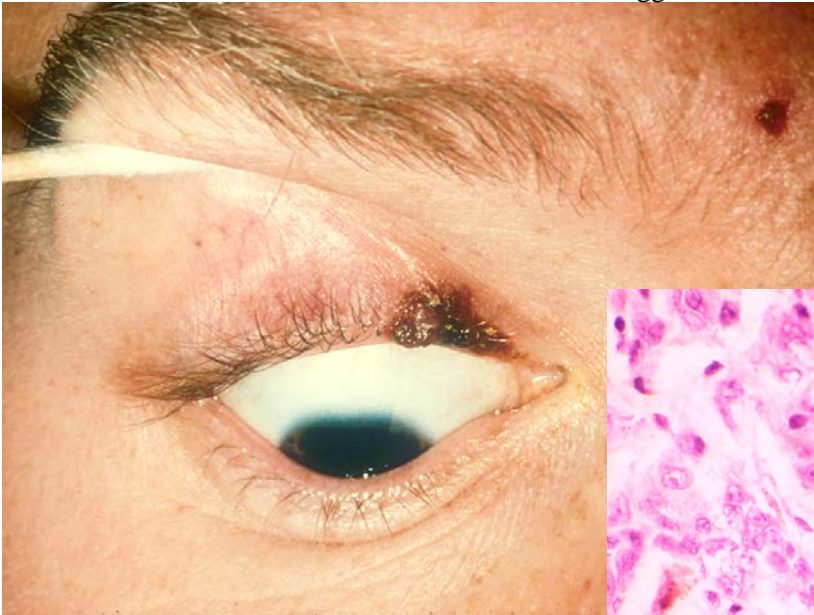


Squamous carcinoma. Sometimes has an orange gross appearance. Note the loss of lashes – an important hint of a neoplasm.

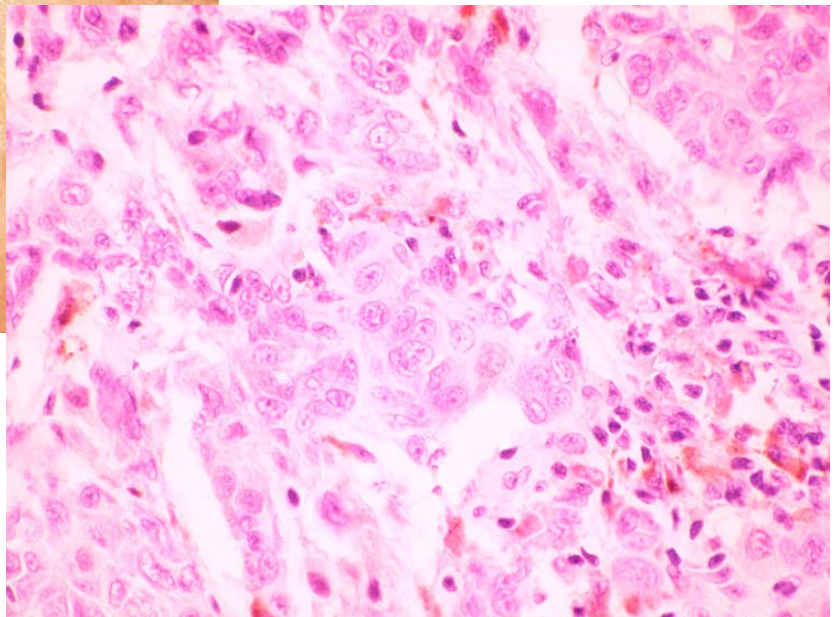


Squamous carcinomas can have cellular dysplasia, thickening of the dysplastic overlying epidermis, and squamous pearls (the eosinophilic whorls above).

3. **Malignant melanoma** - Melanomas can arise from benign nevi. They are recognized grossly by their irregular contours and colors. Many are 1 cm or more in greatest diameter (below left), while most nevi are 6 mm in diameter or smaller. Melanomas are uncommon but aggressive tumors that can metastasize.

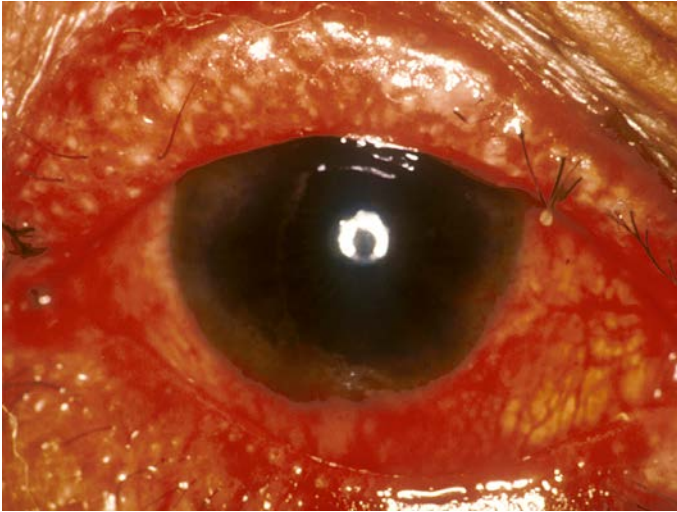


Many melanomas have dark brown pigment called melanin. Unlike nevi, melanomas are usually inflamed.

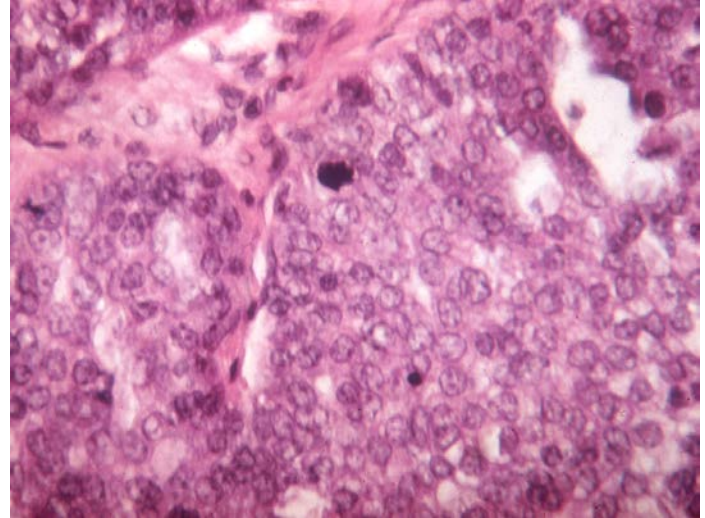




4. **Sebaceous gland carcinoma** – this is an aggressive tumor that can metastasize. It can mimic blepharoconjunctivitis or recurrent chalazion grossly (although loss of the lashes is an important hint).



Sebaceous carcinomas are often red and thus mimic inflammatory lesions. The loss of lashes is an important hint.

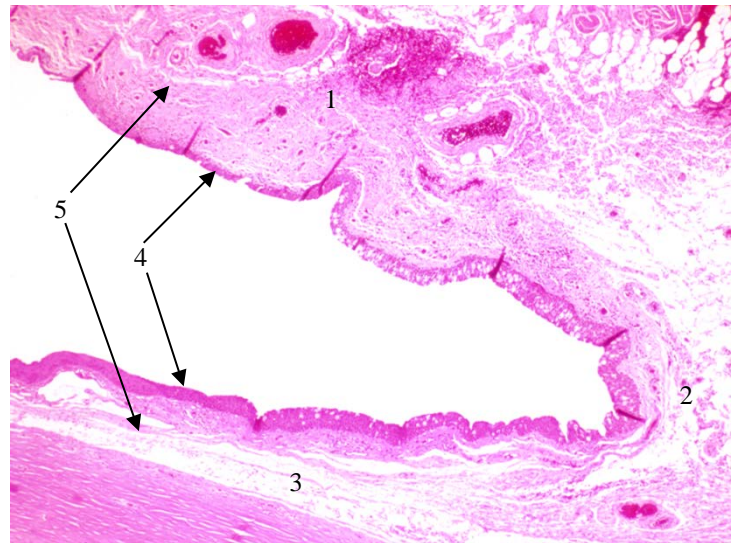


Sebaceous carcinomas have solid nests of cells, but also have small clear areas in the cytoplasm -lipid in the tumor cells.

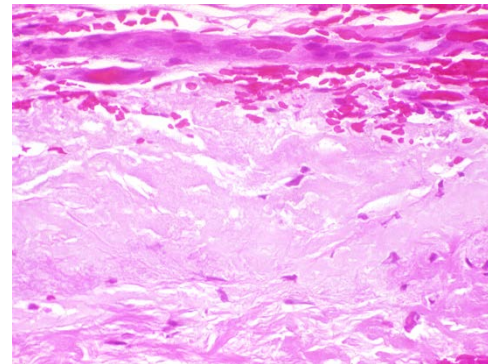
### III CONJUNCTIVA

#### A. Anatomy

1. Palpebral conjunctiva
2. Fornix conjunctiva
3. Bulbar conjunctiva
4. Epithelium – stratified squamous nonkeratinized epithelium
5. Underlying substantia propria

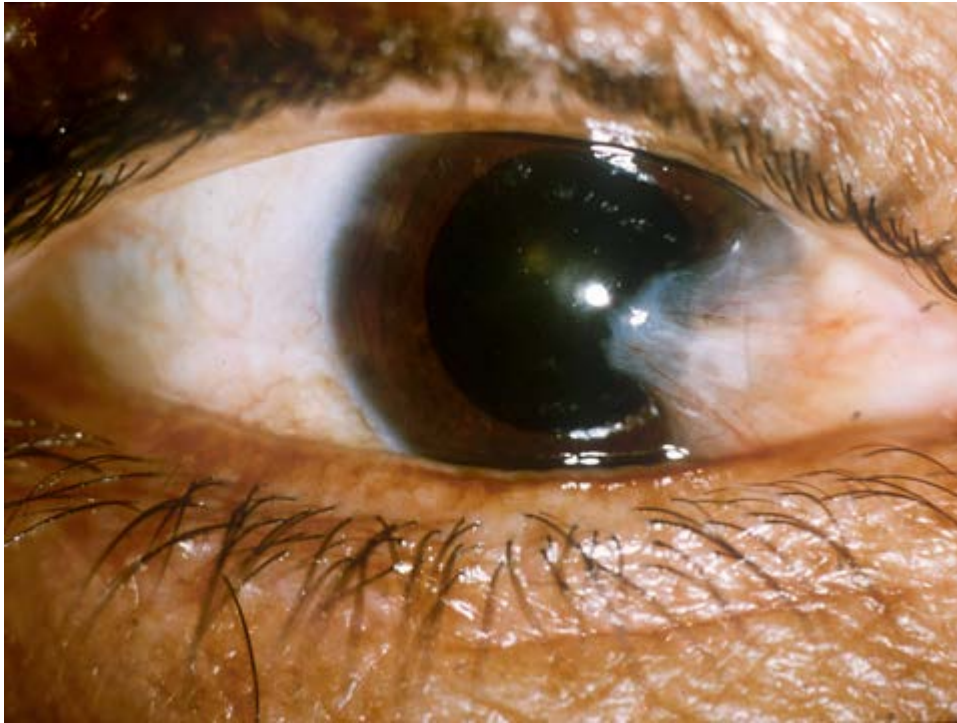


B. **Pinguecula** – a raised, yellowish-white, vascularized lesion (see arrow, below left) near the limbus (the scleral-corneal junction). It is seen in the elderly with extensive sun exposure.

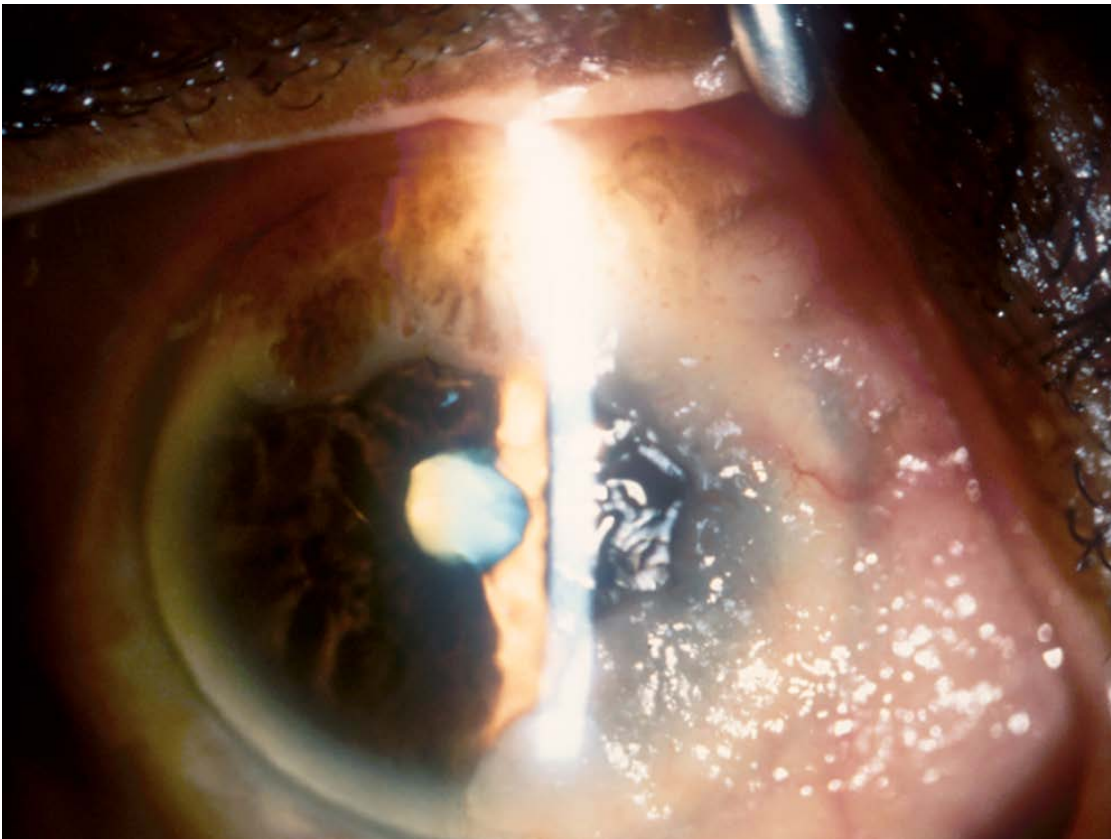


A pinguecula has solar elastosis and basophilic degeneration of the substantia propria collagen (i.e. there is pale grey-blue, UV-damaged collagen).

- C. **Pterygium** – this is basically a pinguecula extending onto the cornea, interfering with vision as seen below.

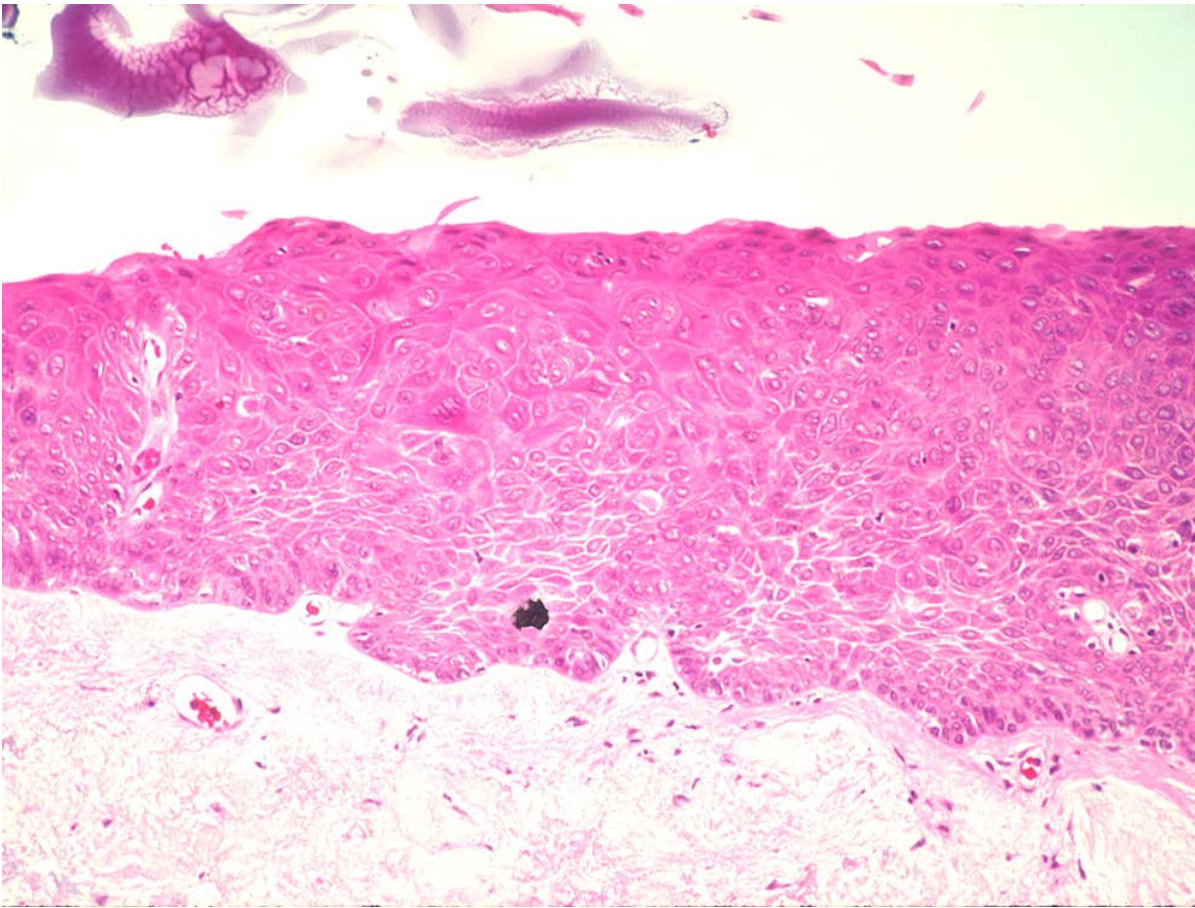


- D. **Conjunctival intraepithelial neoplasm (CIN)** – this is an in-situ squamous carcinoma. There are atypical squamous cells in the epithelium without invasion.



In CIN, there is a pale grey, cloudy, irregular discoloration of the conjunctiva with increased vascularity.



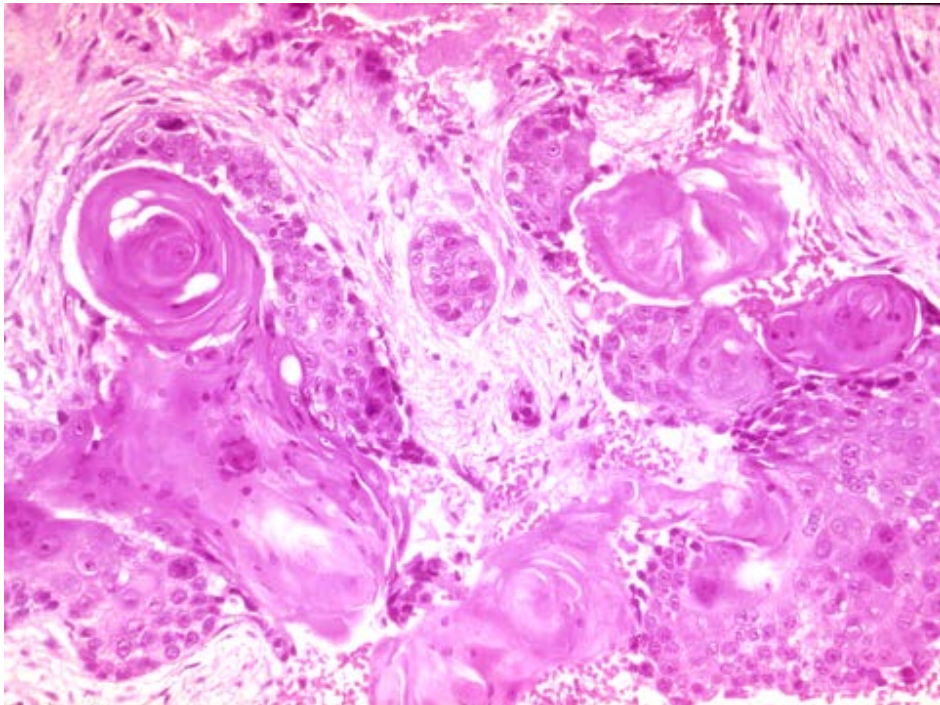


The squamous epithelium, while disorganized and atypical, does not invade the stroma underneath.

E. **Squamous carcinoma of the conjunctiva** – Like squamous carcinoma of the lid, there is invasion of the underlying stroma.



Squamous carcinoma is a red raised mass. The surface can be irregular.

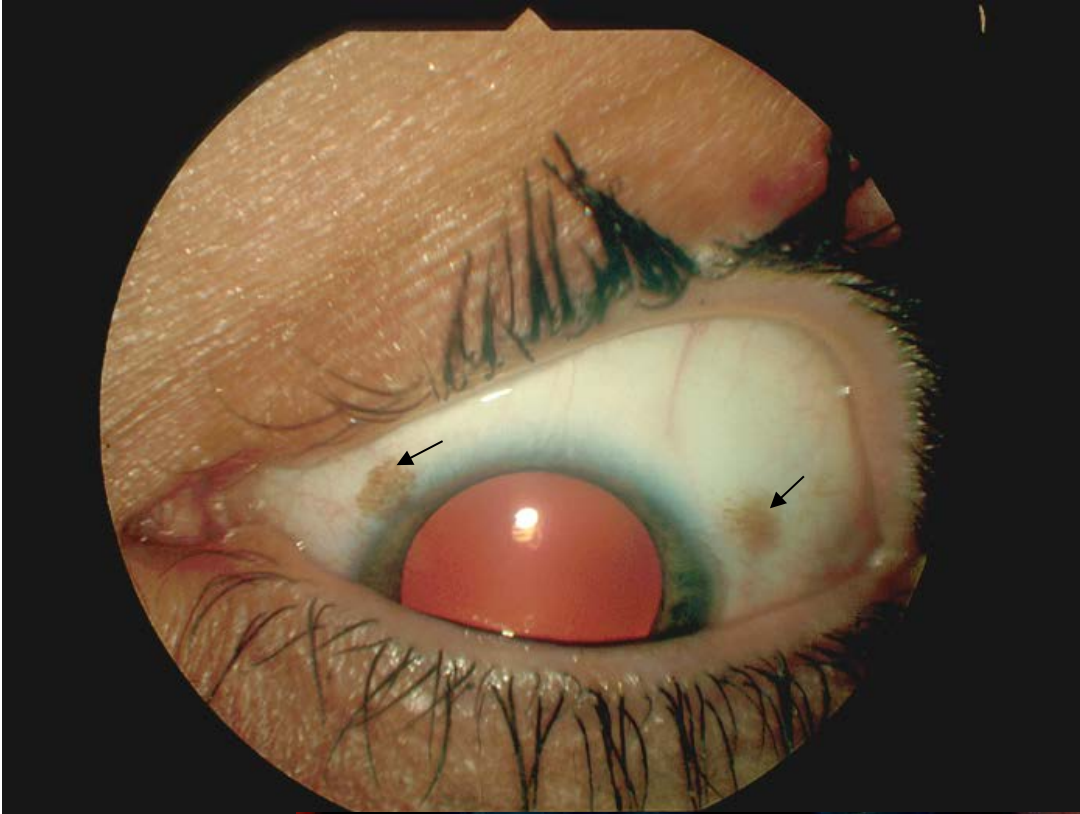


Nests of malignant squamous cells invade the stroma. They are forming squamous pearls.

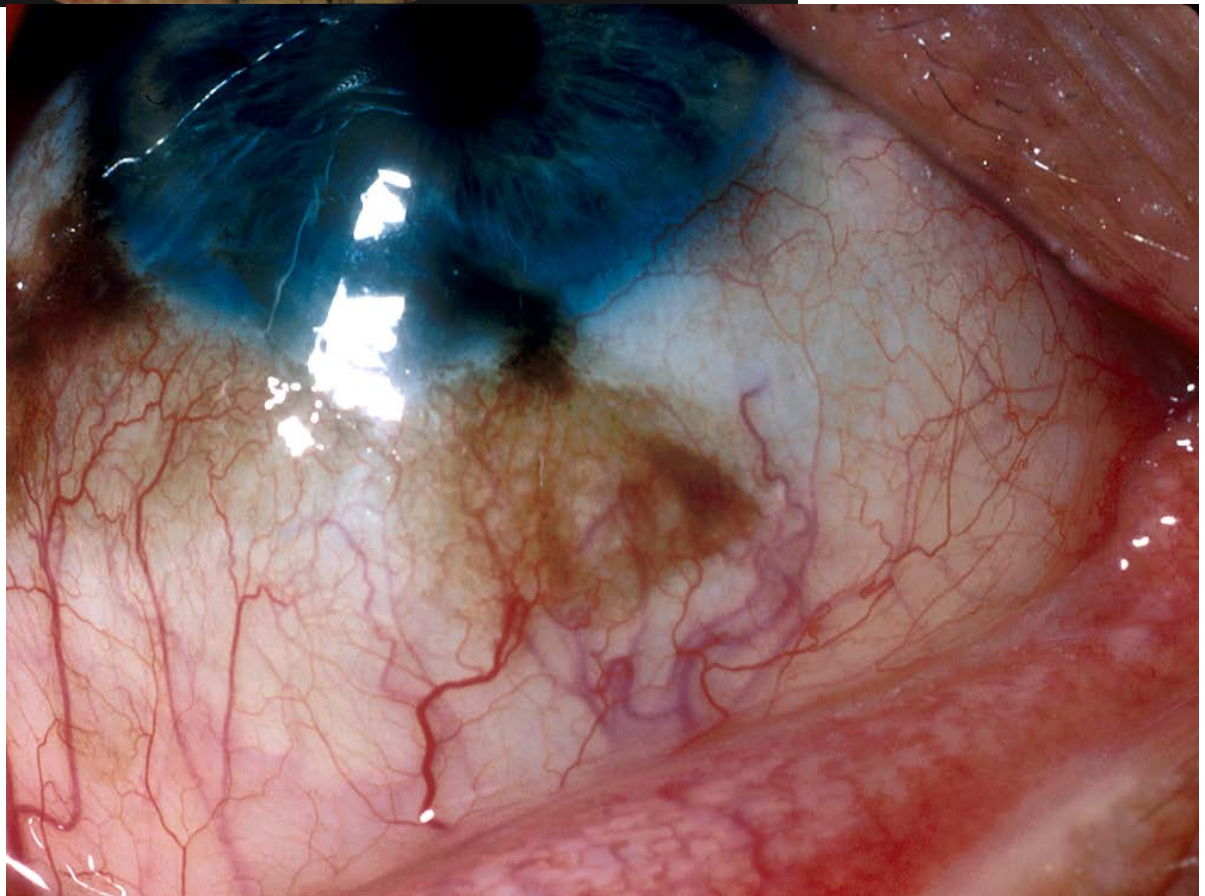


F. **Pigmented conjunctival lesions**

1. **Primary acquired melanosis (PAM)** –hyperplasia of intraepithelial lymphocytes, with or without atypia, similar to a carcinoma in situ. Grossly, this is a brown patch on the conjunctiva. It is benign, but can be a melanoma precursor.

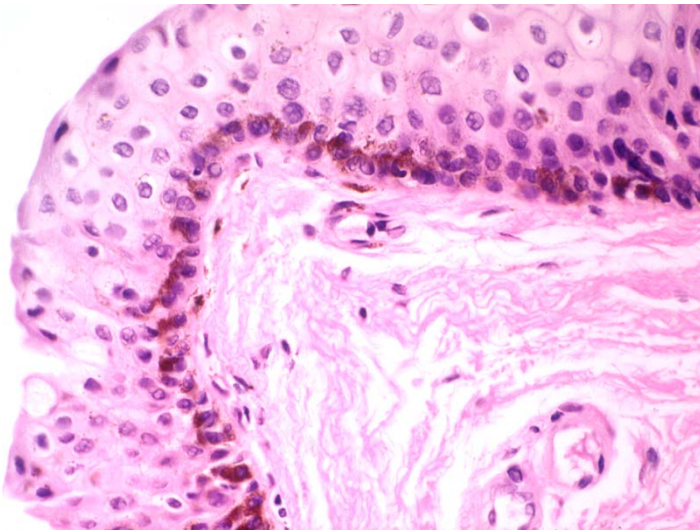


PAM without atypia –  
brown patches (arrows).

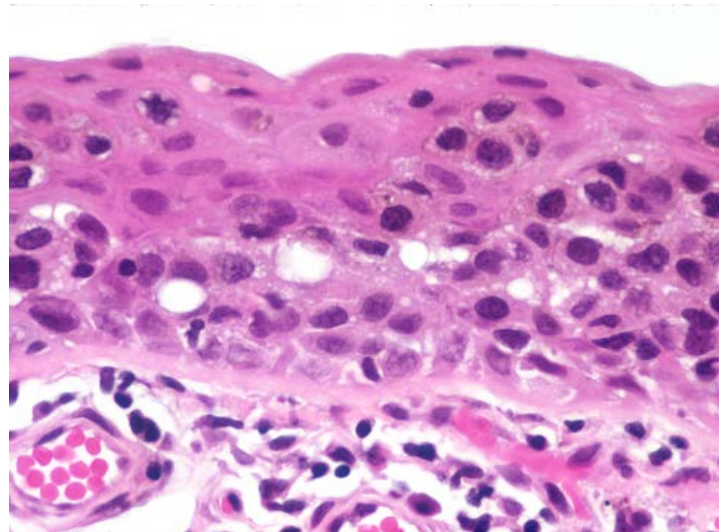


PAM with  
atypia. Note the  
irregular  
coloration and  
contours.



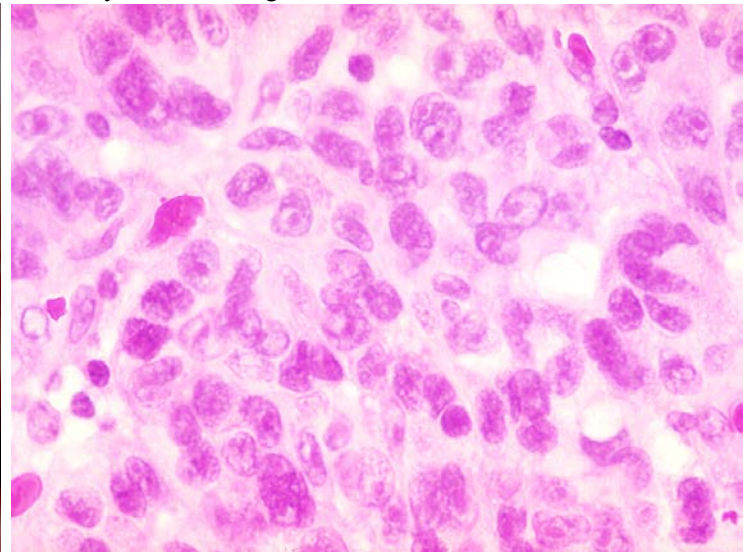


PAM without atypia – melanocyte hyperplasia and increased pigmentation at the base of the epithelium.



PAM with atypia - atypical melanocytes in the epidermis.

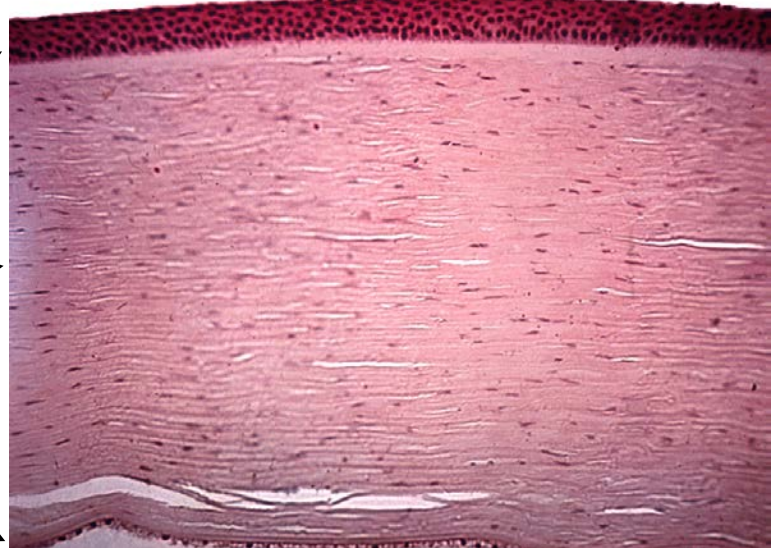
2. **Malignant melanoma** – This is a malignant neoplasm of melanocytes, often arising in PAM. See the large dark, raised lesion (below left). It is composed of invasive, highly atypical melanocytes (below right).



#### IV. CORNEA

##### A. Anatomy

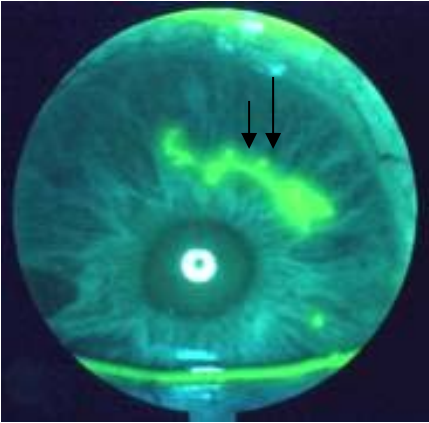
1. Epithelium
2. Stroma
3. Descemet's membrane and endothelium



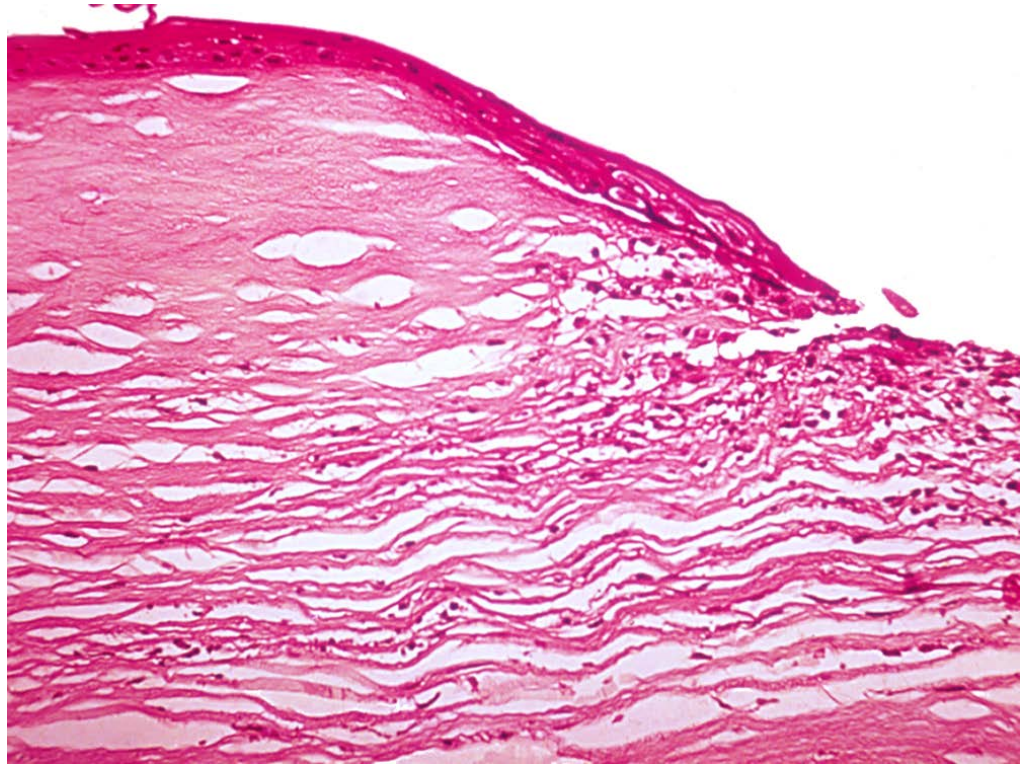


## B. Infections

**Herpes keratitis** – A herpes virus infection (almost always type 1) of the corneal squamous epithelium often causes a dendritic ulcer.

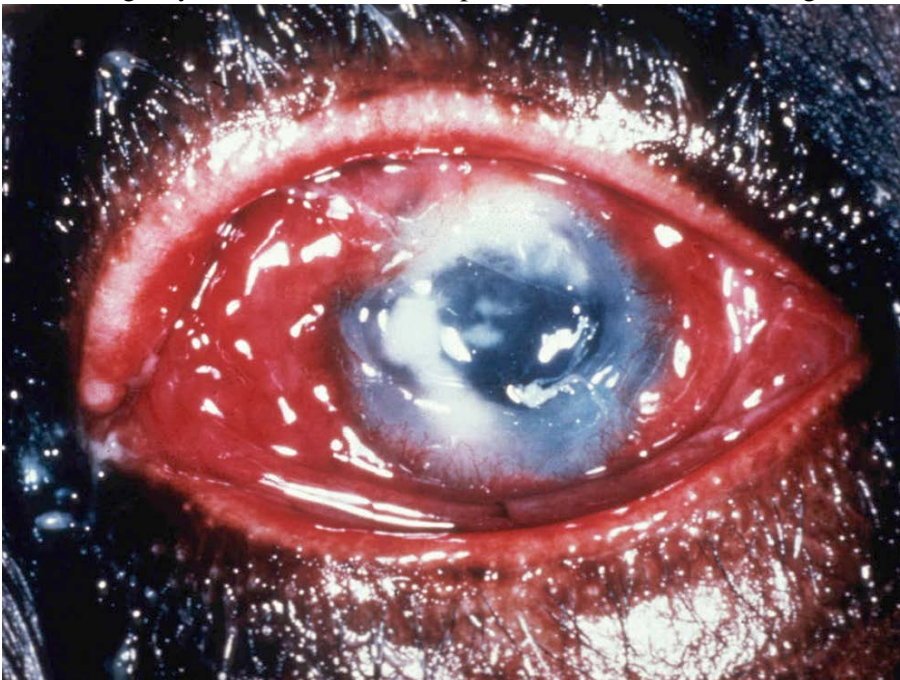


Blue light with fluorescein – showing the dendritic ulcer (arrow) typical of herpes.



Herpes causes an irregular ulcer of the epithelium, with loss of the special layer just beneath it (Bowman's layer) . There is also an infiltrate of lymphocytes and plasma cells.

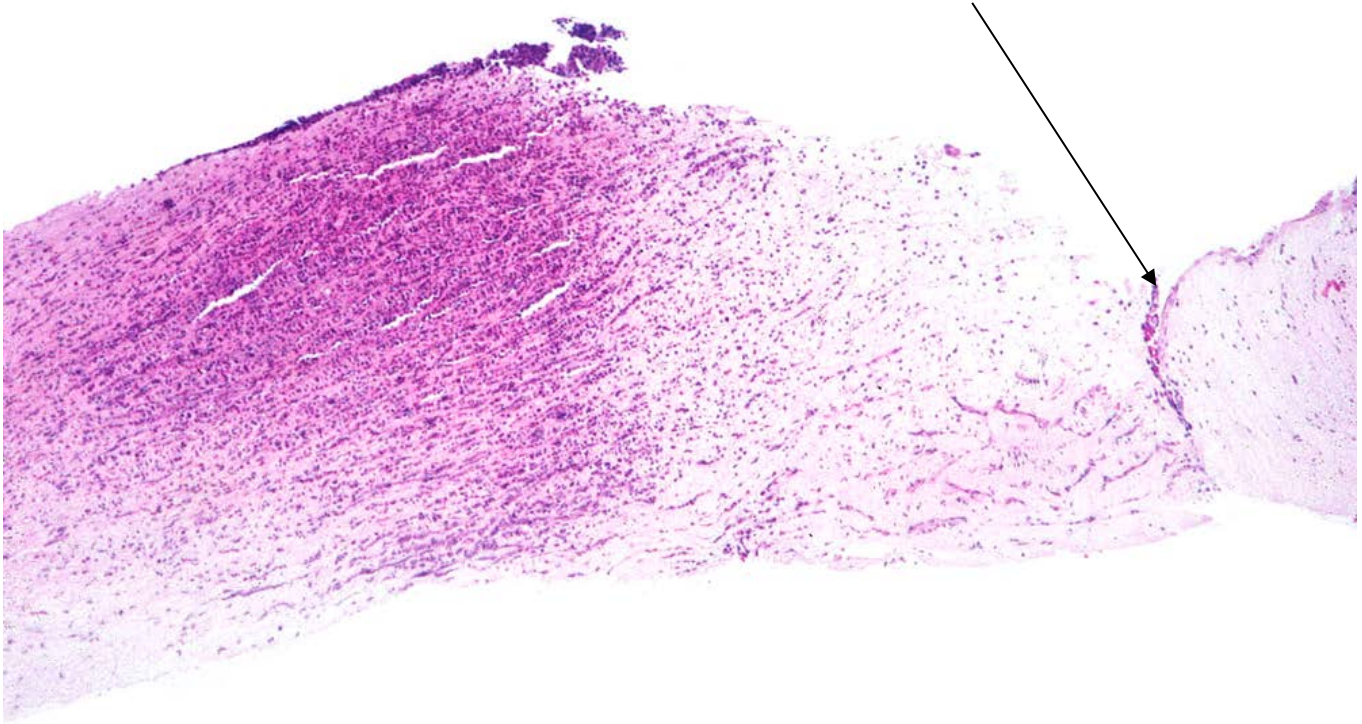
2. **Bacterial Keratitis** – This is often due to *Pseudomonas* from leaving contacts in too long, as shown below. This is an emergency – it can cause corneal perforation with severe damage.



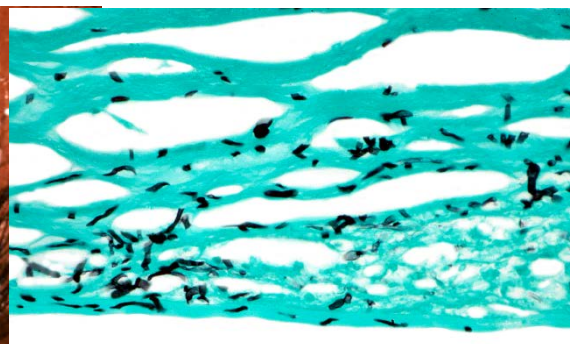
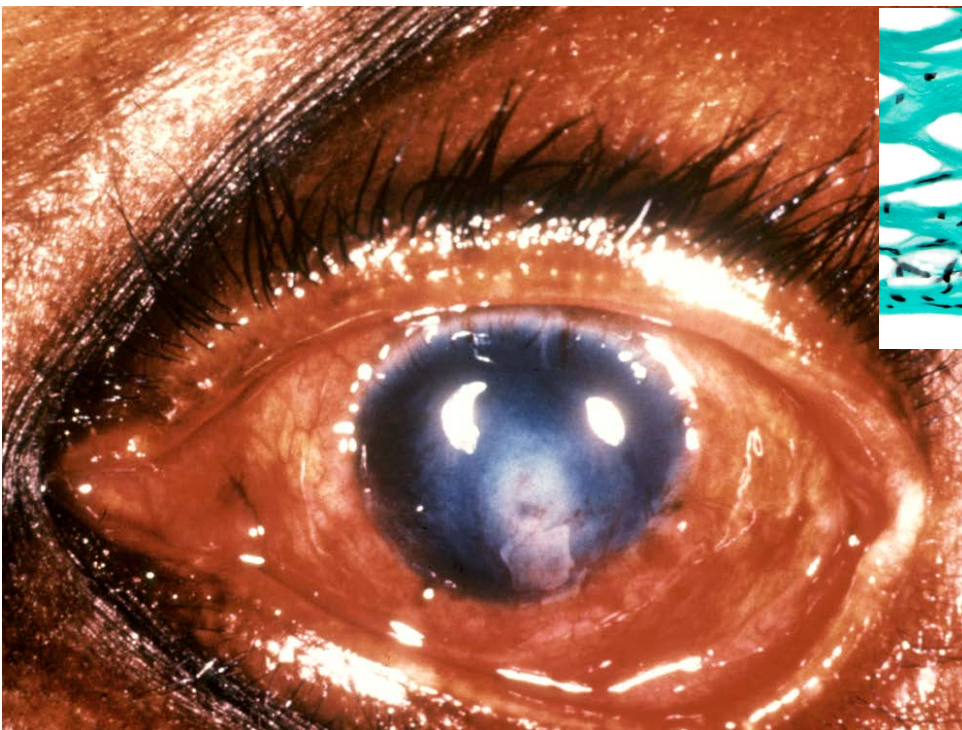
There is severe conjunctival inflammation, with deep red discoloration and a pale exudate. The cornea shows a white infiltrate in the area of the ulceration.



Bacterial Keratitis corneal perforation - the cornea has severe acute inflammation (many neutrophils), and can perforate as shown here (arrow).



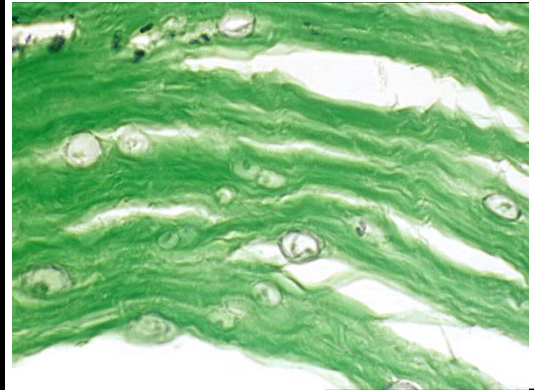
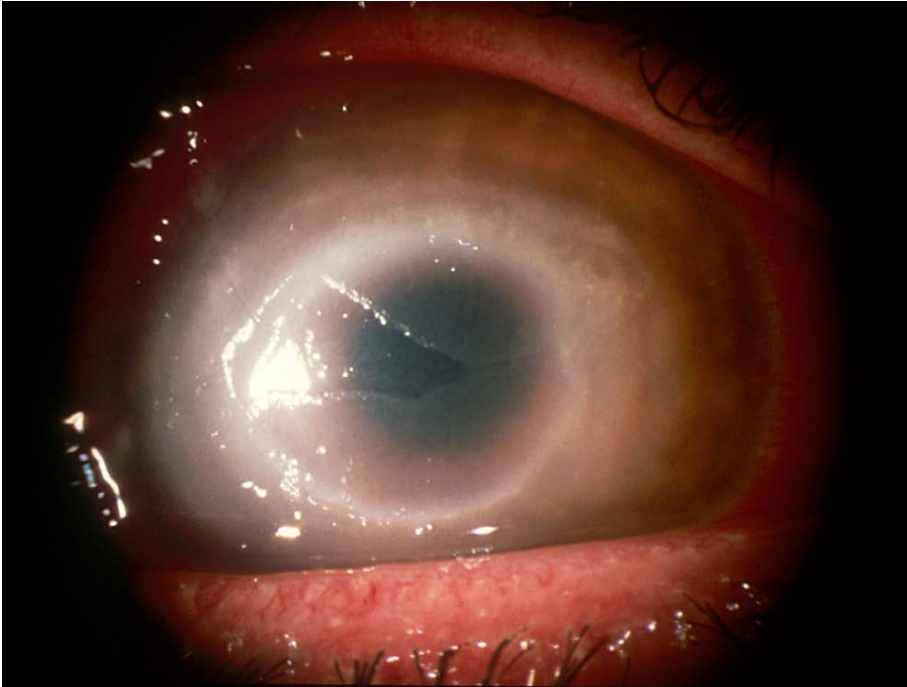
3 **Fungal conjunctivitis** – This causes conjunctival inflammation and often has an indolent course. Special stains are needed to identify the organisms.



GMS special stain for fungi (black).



4. **Acanthamoeba keratitis** – this is usually due to prolonged wearing of contact lenses, and is very difficult to treat.



Acanthamoeba organisms form the small cysts in the cornea as seen above.

**V. GLAUCOMA** – is optic nerve damage at the optic cup, usually due to increased intraocular pressure. The optic cup enlarges as there is damage to the nerve. There are two kinds of glaucoma, narrow-angle and open angle.

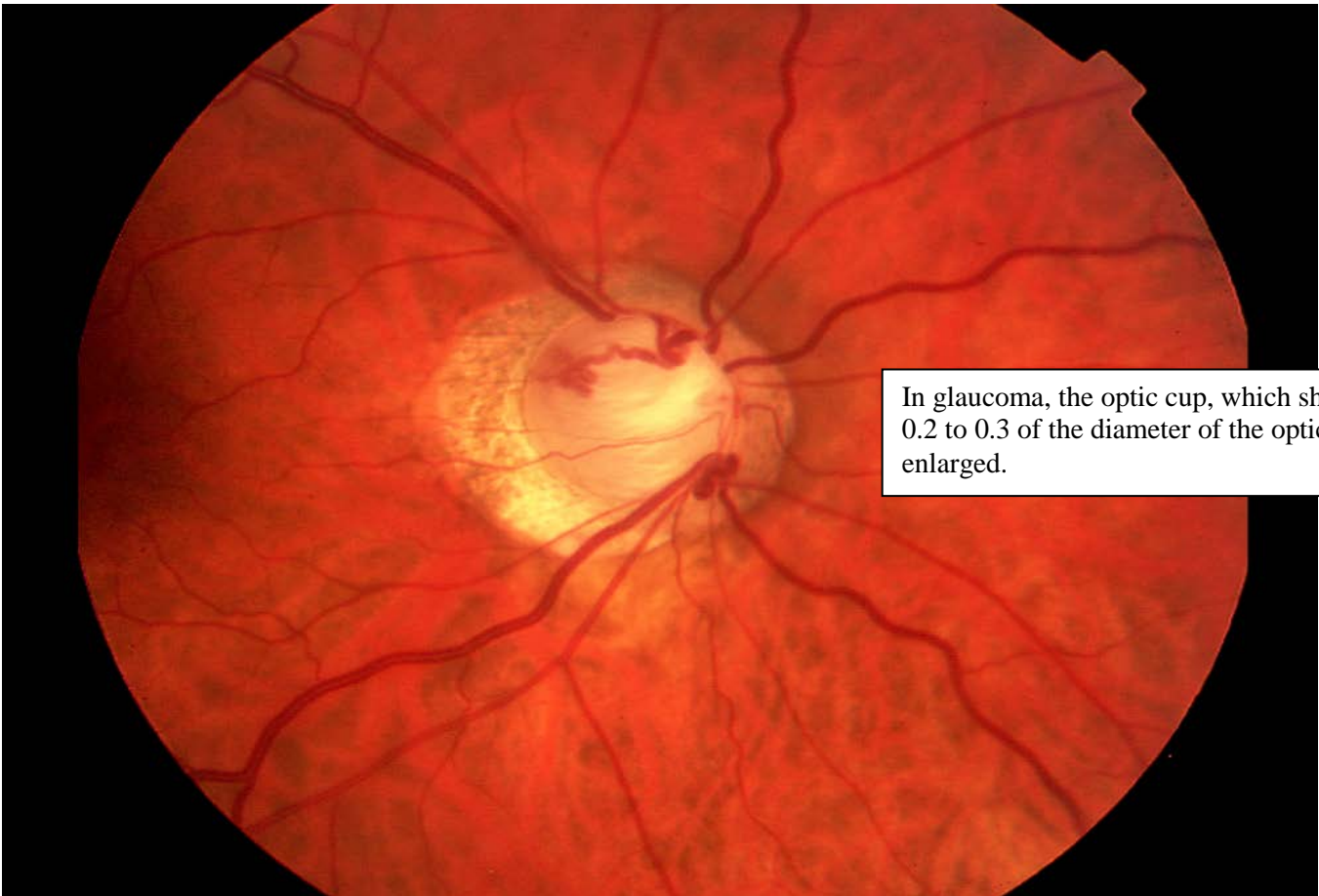
A. Chronic open-angle glaucoma is the most common form. It is treated by antihypertensive drops, laser treatment, or surgery to decrease the intraocular pressure.

B. Narrow-angle glaucoma is due to partial blockage of the flow in the anterior chamber, with narrowing of the anterior chamber angle. It is treated by drops or by laser peripheral iridectomy to restore flow.



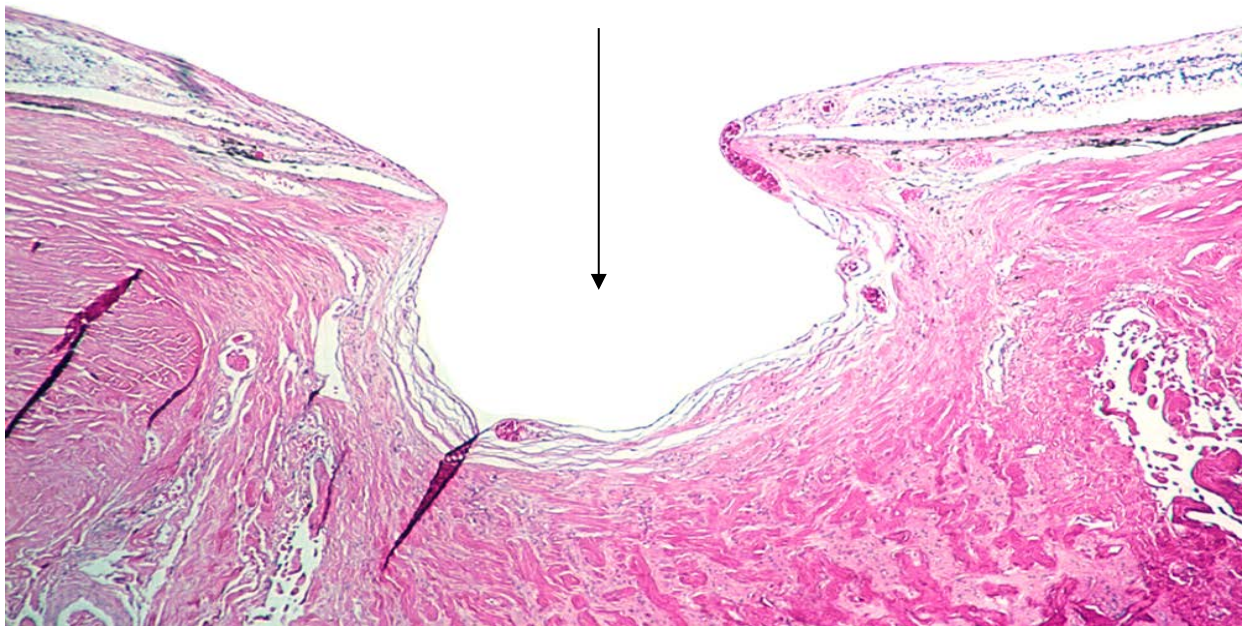
Narrow-angle glaucoma, with partial fusion of the iris to the cornea (arrow), blocking flow to the trabecular meshwork.





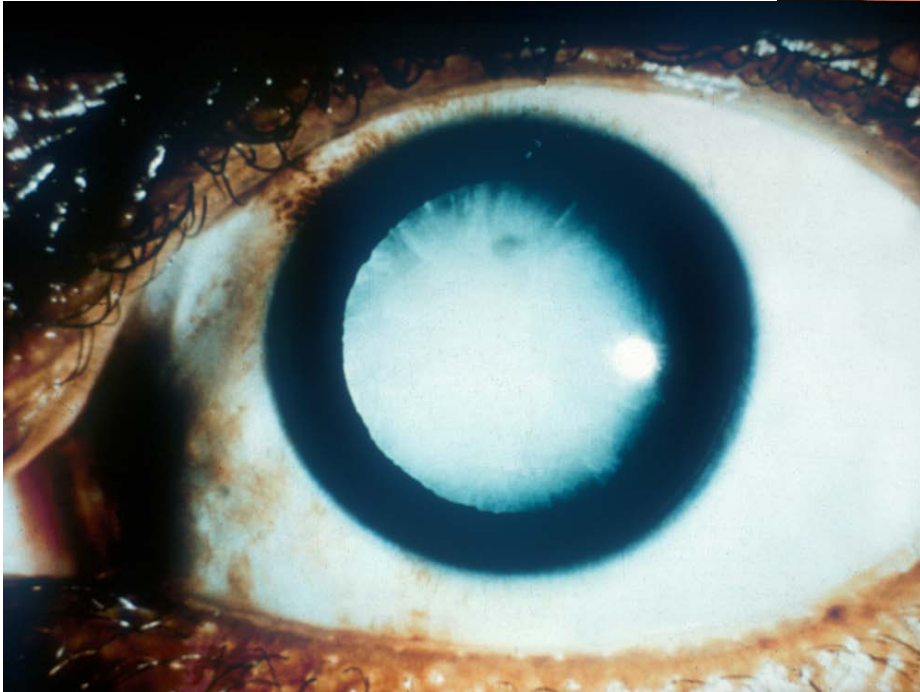
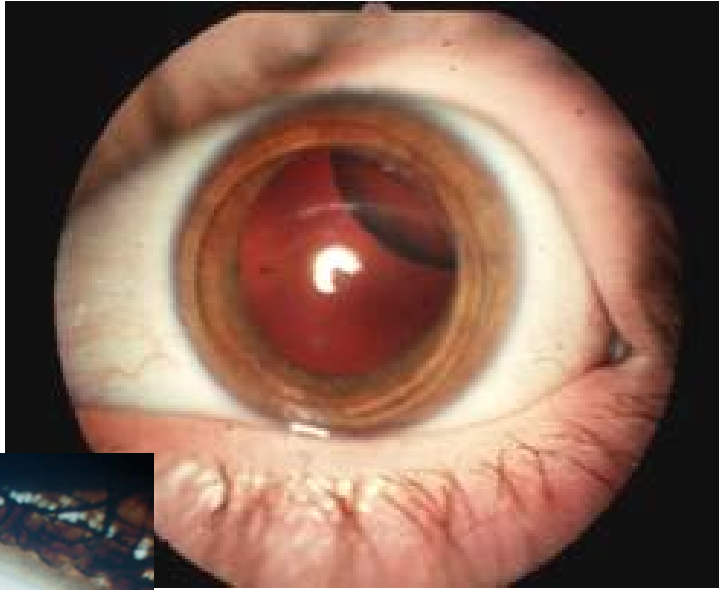
In glaucoma, the optic cup, which should be 0.2 to 0.3 of the diameter of the optic disk, is enlarged.

To right, is severe glaucoma, with an enormous, excavated optic cup (arrow).



#### IV. LENS

A. **Dislocations** – lens dislocation can happen in Marfan's syndrome (caused by a fibrillin gene mutation). These patients are very tall, and can have other problems such as aortic dissection. The dislocation is usually superior and temporal (see right). In homocystinuria patients, the lens dislocation is usually inferior and nasal.

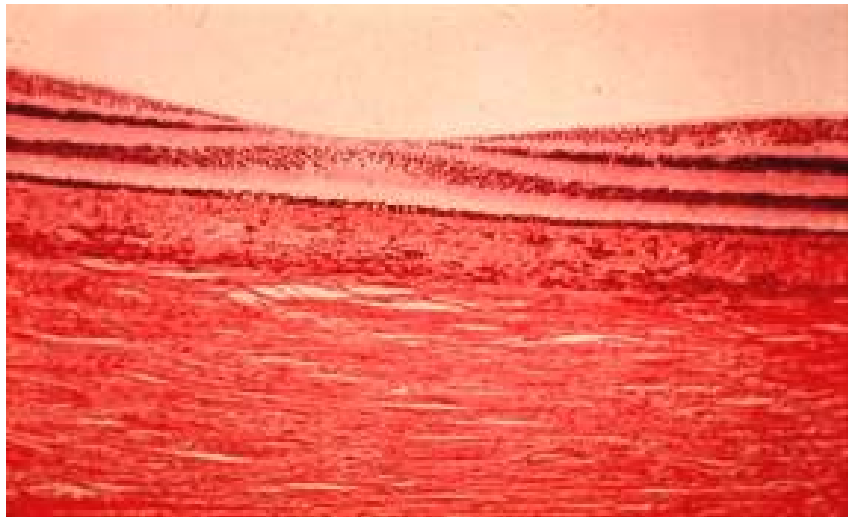
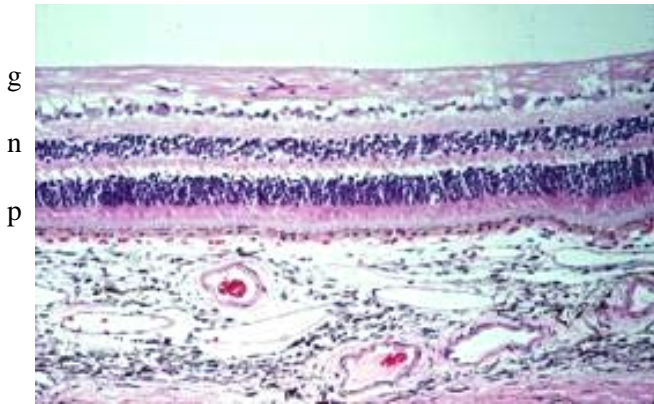


B. **Cataracts** – opacification of the lens. Relatively common in the elderly, especially with diabetes and UV-exposure. The cortical cells become rarefied, then liquify, with fragmentation of the lens fibers. There is a progressive increase in insoluble proteins in the nucleus of the lens, with hardening and often brown discoloration. To the left is the pale clinical appearance of a cataract. Below is an extracted lens with a nuclear cataract with a dark brown discoloration.





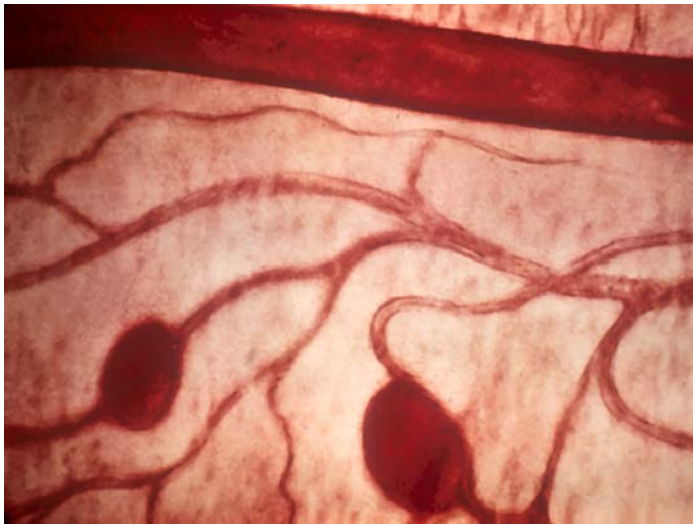
**VII. RETINA** – note, to right, the retina with the optic disk at far right. The retinal artery and vein come through the optic nerve, to the optic disk to supply retinal blood flow. The dark fovea is near the center. The fovea is the area of central vision. It has the best resolution and color vision (many cones are present). Below left is a retinal section, showing a ganglion cell layer near the top (g), two layers of neuronal nuclei (n), and pigmentary epithelium (p) underneath. Below right is the fovea. It is thin because the inner layers are displaced to the sides.



← Background diabetic retinopathy, with various kinds of hemorrhages (dark red) and exudates (pale yellow).

## VASCULAR DISEASES OF THE RETINA

1. **Diabetes mellitus** frequently causes retinal vascular disease, and is the most common cause of blindness from age 25 to 70. There are two kinds of diabetic retinopathy, background retinopathy, and the more serious proliferative retinopathy. In background retinopathy, one sees capillary microaneurysms, dot and blot and flame-shaped hemorrhages, hard exudates, and cotton-wool spots (soft exudates).



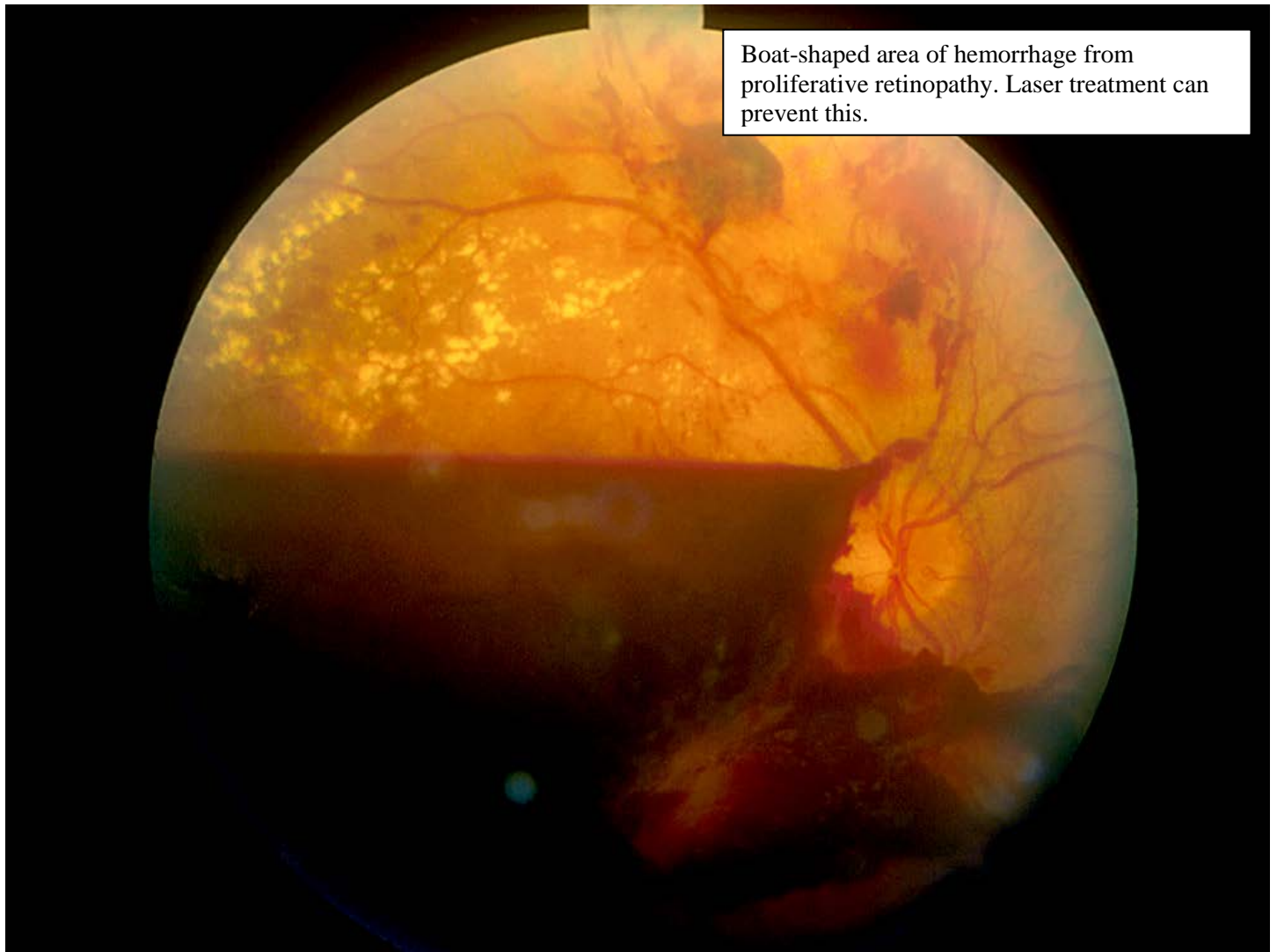
Diabetic capillary  
microaneurysms

In diabetic proliferative retinopathy, there is neovascularization (formation of small new vessels), hemorrhage, and fibrosis. This is the main cause of blindness in diabetics.



Neovascularization – small new  
vessels near the optic disk – in  
proliferative diabetic retinopathy.





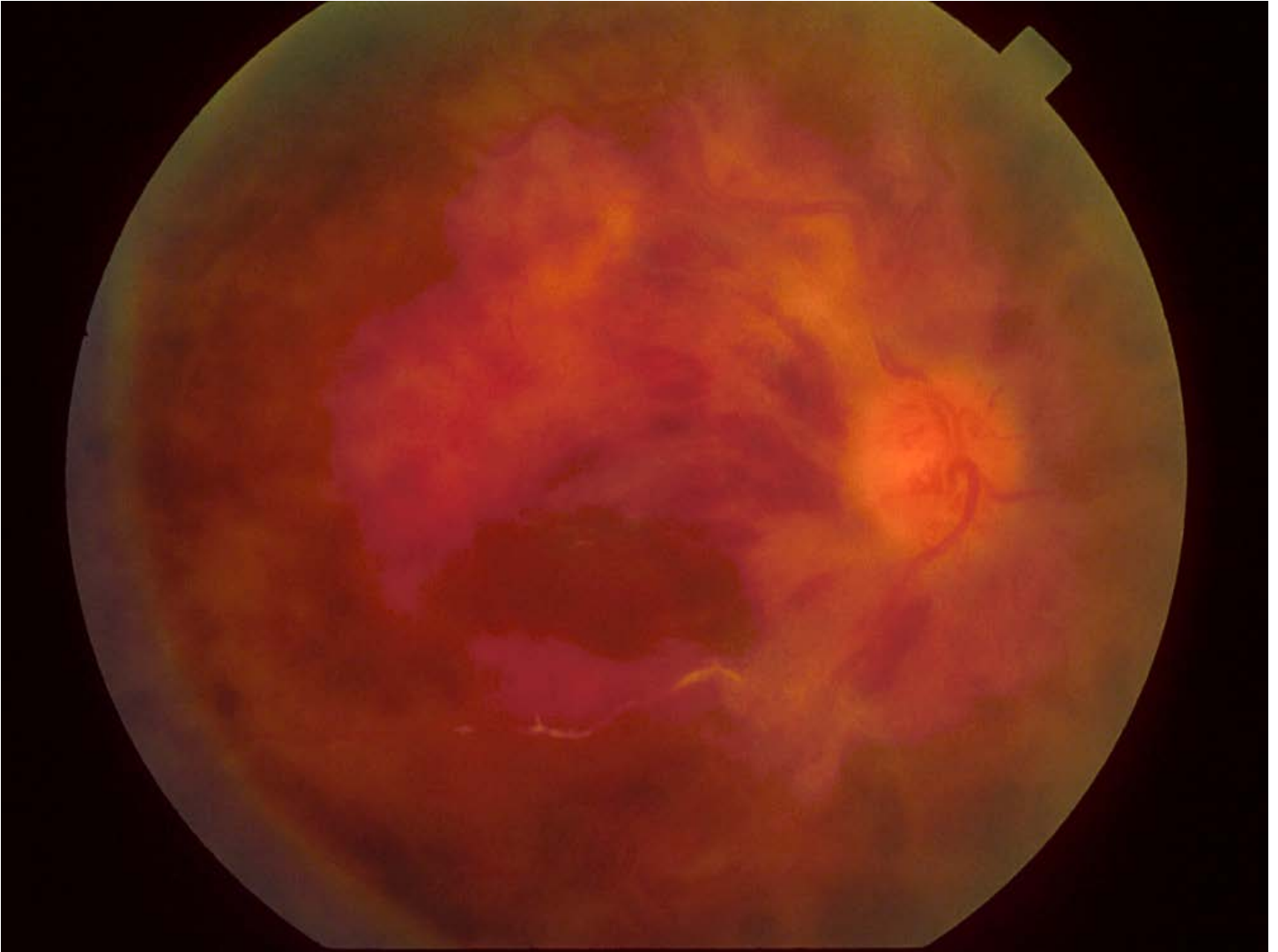
Boat-shaped area of hemorrhage from proliferative retinopathy. Laser treatment can prevent this.

2. **Hypertensive retinopathy** – many of the changes are similar to those of background diabetic retinopathy, including cotton-wool spots and hemorrhages. In addition, the retinal arterioles appear narrowed. With severe hypertension, papilledema can occur (see below).

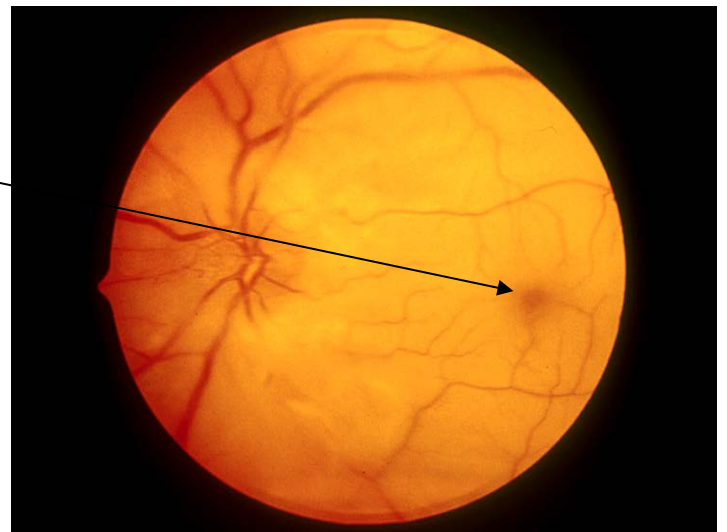


Hypertensive retinopathy, with cotton-wool spots (the small pale spots) and flame hemorrhages (red elongated spots).

3. **Central retinal vein occlusion** – causes engorgement of the eye with blood (below). Tortuous veins, hemorrhages, retinal edema and, if severe, retinal infarcts can occur.



4. **Central retinal artery occlusion** – causes blindness with a pale, necrotic retina. There is the appearance of a “cherry-red spot” at the fovea since the pale, necrotic retina is thinner there (arrow to right).



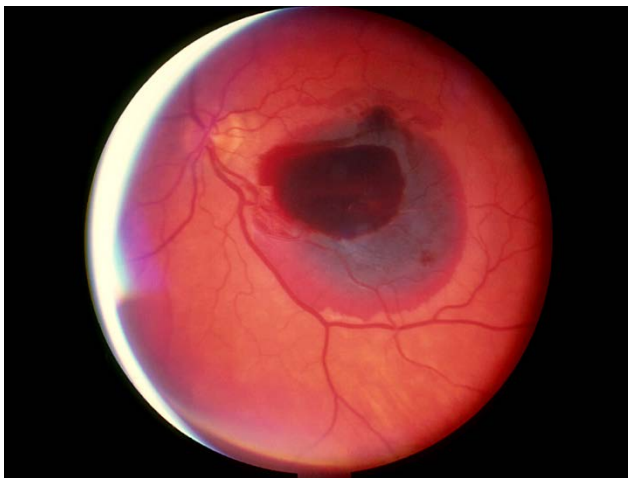


5. **Age-related macular degeneration** – is the most common cause of blindness in the elderly (and the most common cause of blindness overall). The common (90% of cases) atrophic or dry-type of macular degeneration is characterized by yellow deposits called drusen under the retina, then atrophy of the retinal pigment epithelium particularly at the macula. The less common “wet” form of macular degeneration has subretinal neovascularization and can have hemorrhages.

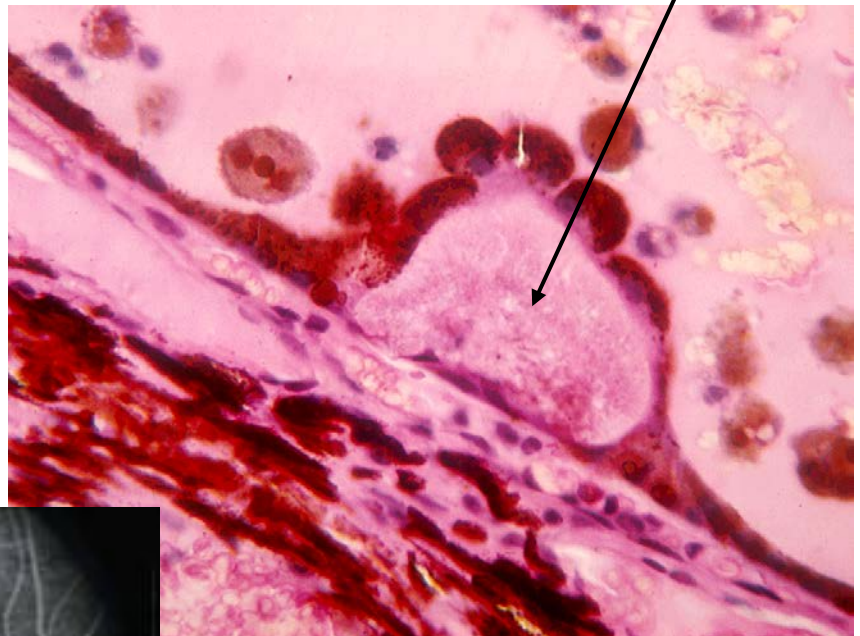


Pale yellow drusen surround the macula in this eye with dry-type macular degeneration.

A drusen (arrow) in dry macular degeneration.



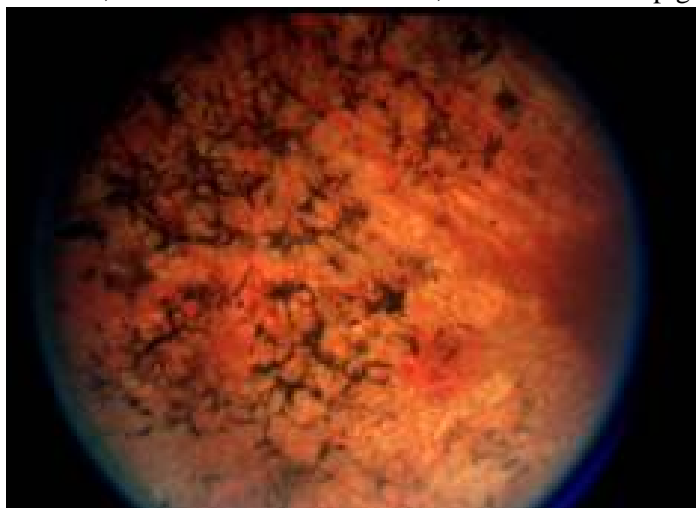
Area of retinal hemorrhage in wet macular degeneration.



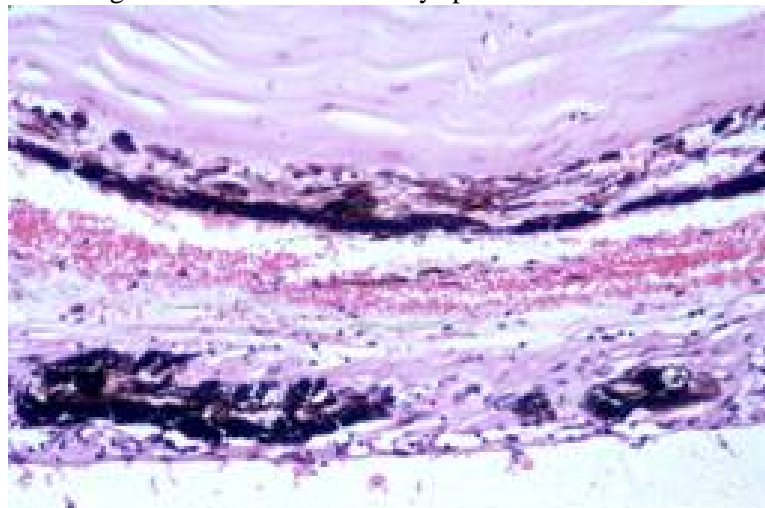
Fluorescein angiogram in wet macular degeneration, showing areas of increased fluorescence in the macula.



**D. Retinitis pigmentosa** – a progressive, inherited degenerative disease of the retina. There is “waxy pallor” of the optic disk, retinal arteriole attenuation, and black retinal pigment changes that are likened to bony spicules.



Abnormal retinal pigment in retinitis pigmentosa



Retinitis pigmentosa, showing pallor and “bony spicule” pigmentation of the retina.

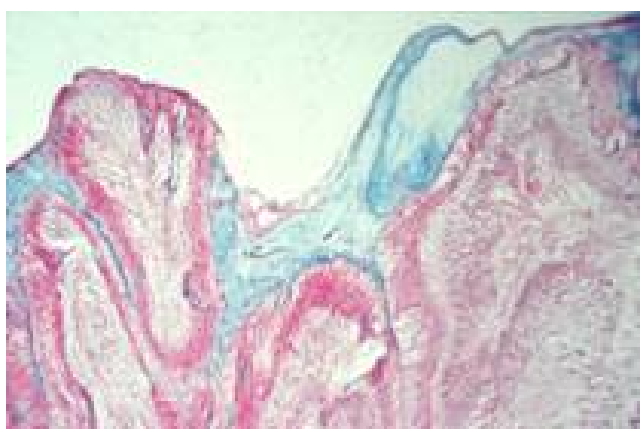
**E. Retinal detachment** - There are several reasons for a retina to detach: a tear or hole in the retina (rhegmatogenous retinal detachment, most common), high myopia, or fluid forming under the retina (exudative retinal detachment). Detachments can be treated by laser treatment or surgery. A complication of detachment called proliferative vitreoretinopathy, with scarring and glial cell proliferation, can cause failure of the repair.



Eye with complete retinal detachment (except at optic nerve).



Horseshoe-shaped tear in retina (at upper right), causing rhegmatogenous detachment.



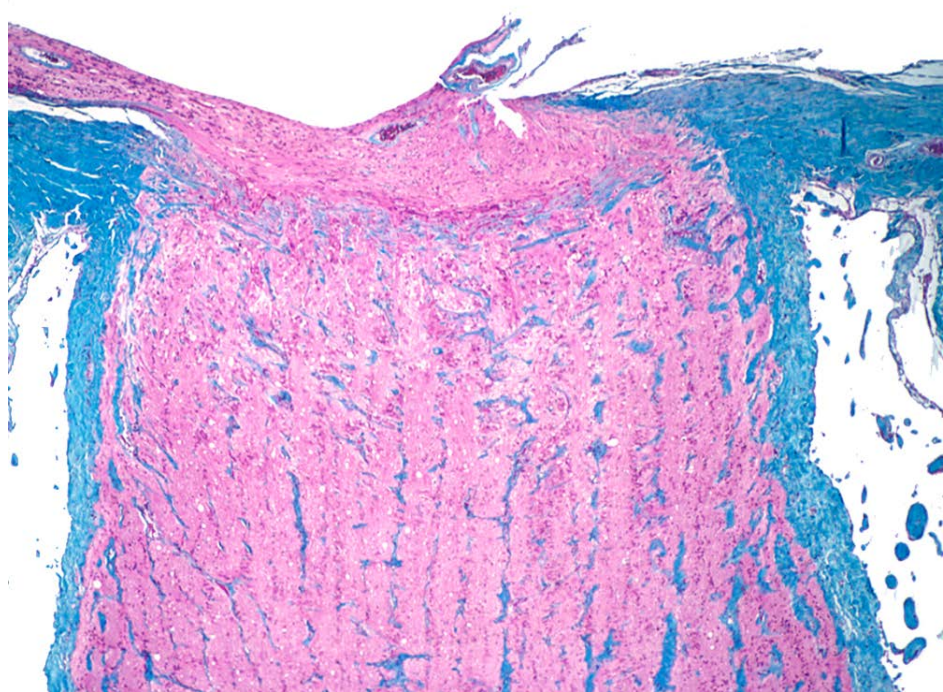
To left is a recurrent retinal detachment with proliferative vitreoretinopathy.



## VIII. OPTIC NERVE

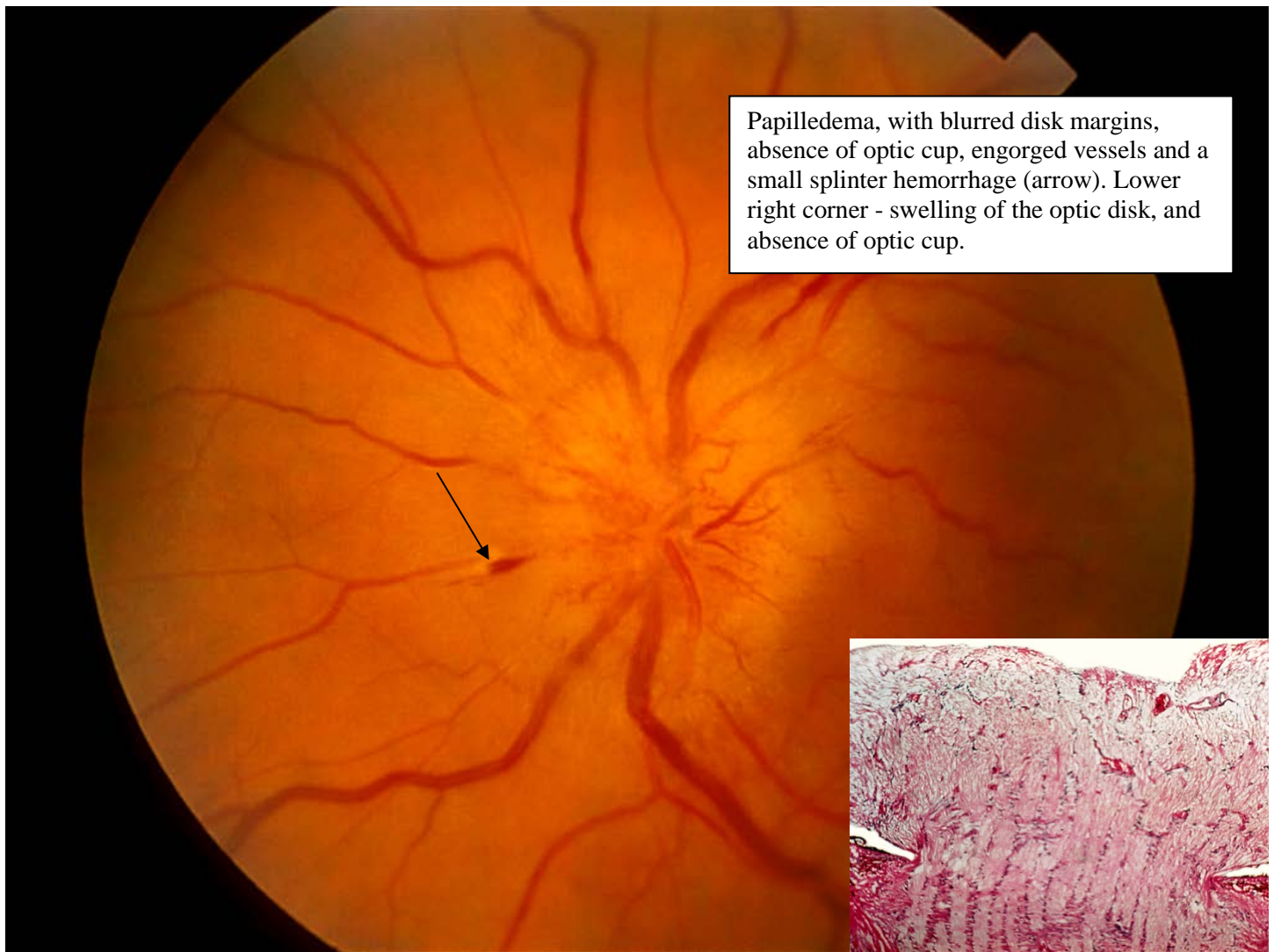


A normal optic nerve has a small pale central cup, about 0.2 of the diameter of the optic disc.

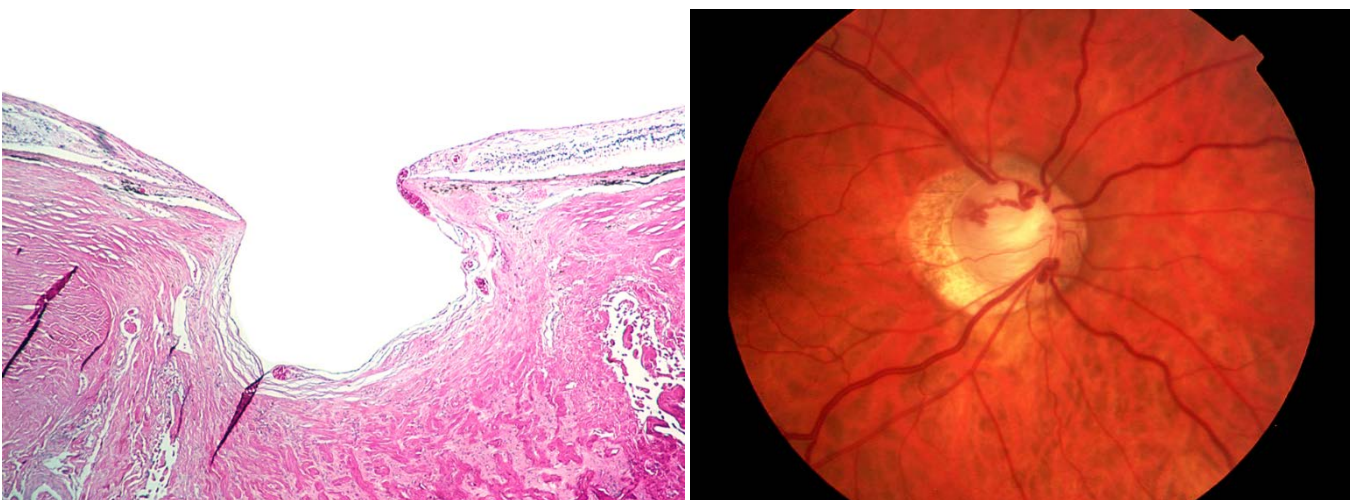


The optic nerve is part of the central nervous system. It has abundant myelinated axons. The nerve is surrounded by a fibrous sheath (blue).

**Papilledema** – increased intracranial pressure causes the head of the optic nerve to swell and protrude into the eye. The disk margins become blurred, and the vessels are engorged and can bleed. This finding must elicit a search for the cause of the increased intracranial pressure – it could be a tumor.

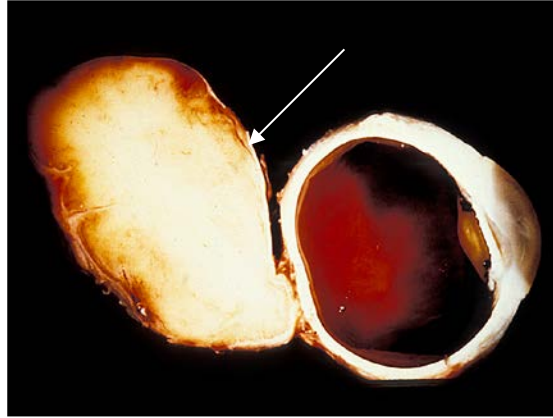


**Glaucomatous optic atrophy** – as discussed above, increased intraocular pressure causes damage at the optic disk, with enlargement of the optic cup (see below).

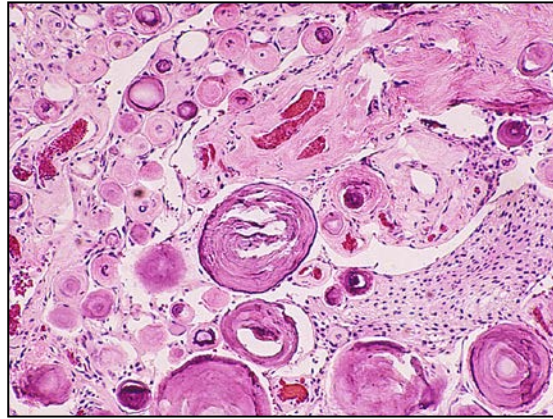




**OPTIC NERVE TUMORS** – In children, the most common optic nerve tumor is an **optic nerve glioma**, this is a kind of juvenile pilocytic astrocytoma (a very low-grade astrocytoma seen mainly in children). In scans, one sees fusiform swelling of the nerve. In older adults, the most common optic nerve tumor is a **meningioma**, a benign tumor of meningotheelial cells.



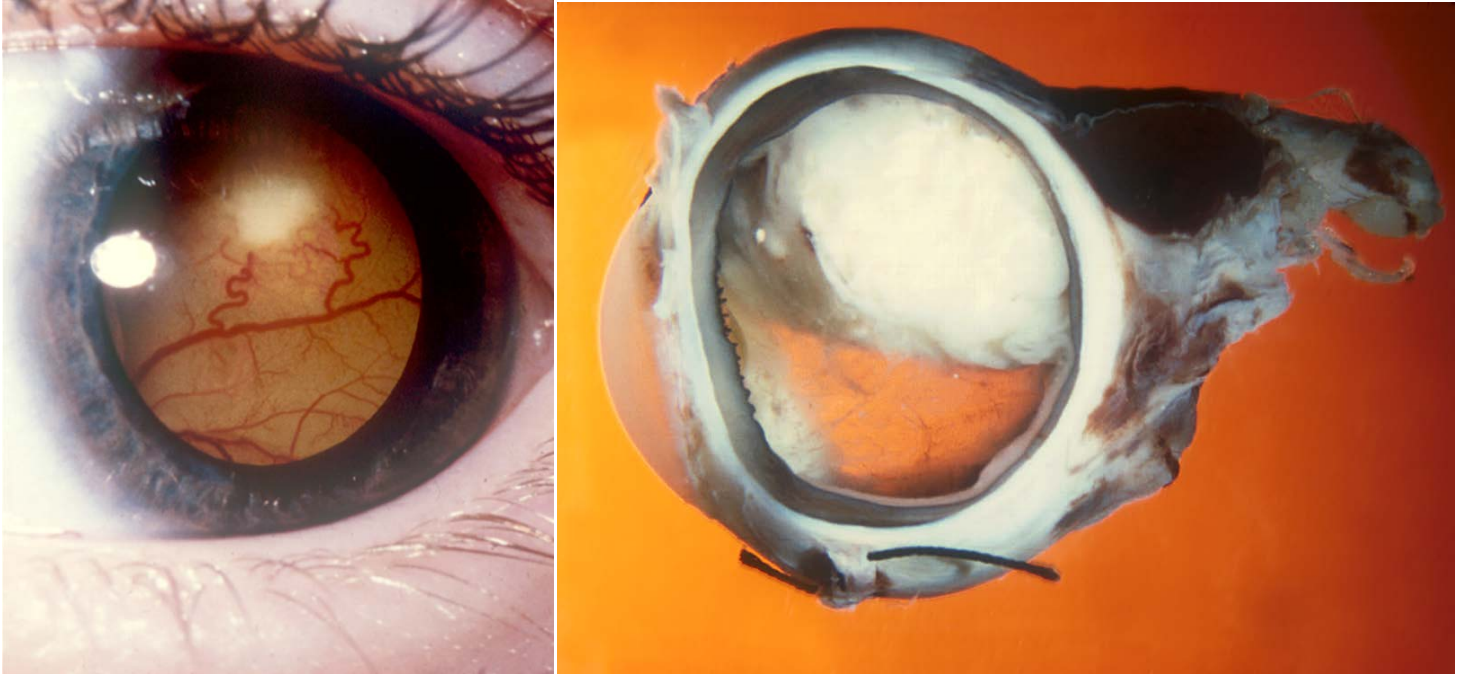
Optic nerve glioma, with fusiform swelling of the optic nerve, in a scan (above left) and gross specimen (above right).



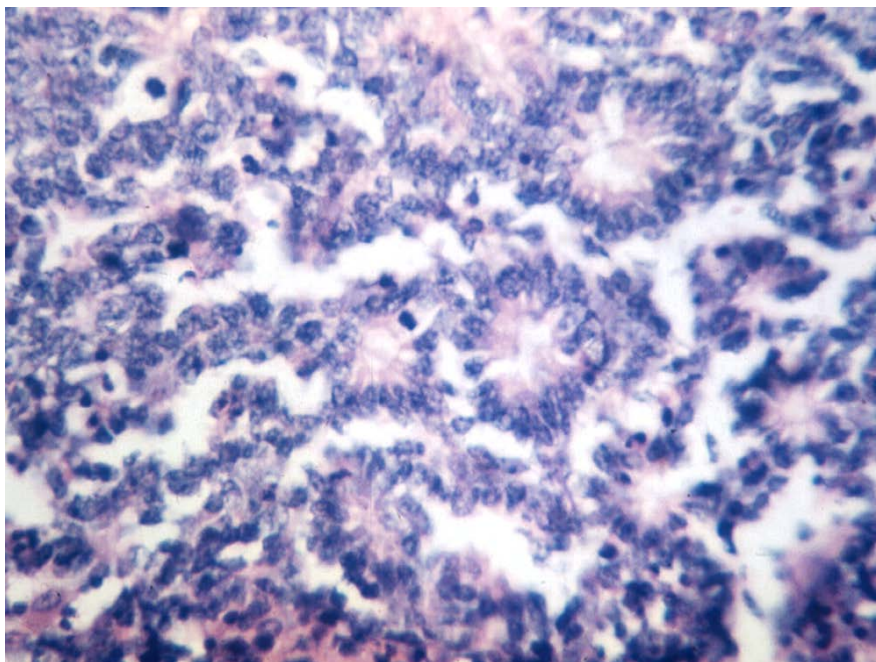
Meningioma with encasement of the optic nerve by tumor (above left, arrow). Above right is a section of a meningioma, which contains abundant round, laminated calcified bodies called psammoma bodies.

**INTRAOCULAR TUMORS** – In children, the most common intraocular tumor is a retinoblastoma, a small blue cell tumor differentiating like primitive retinal neurons. In older adults, the most common intraocular tumor is a malignant melanoma of the uvea.

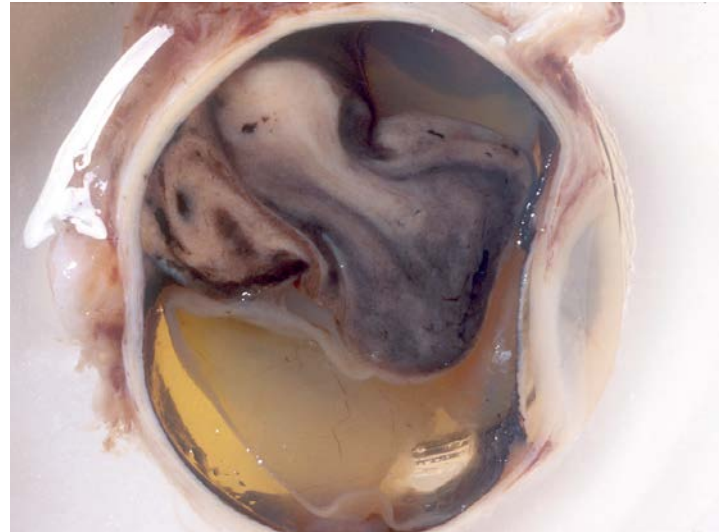
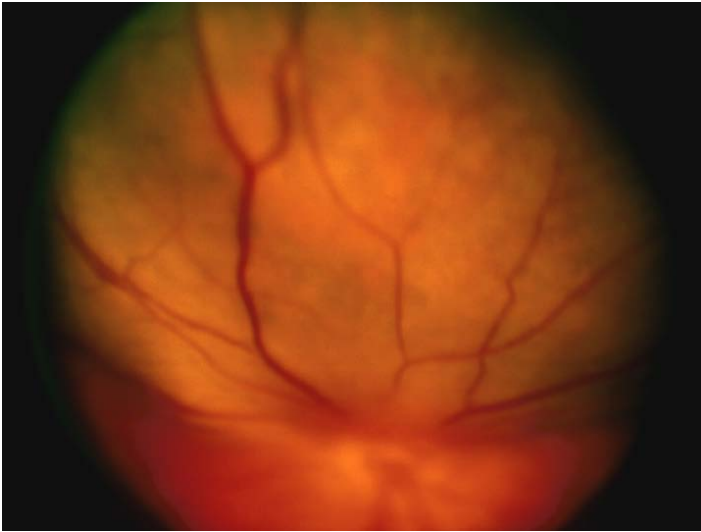
**Retinoblastomas** present with a pale retina where the tumor is, a finding called leukocoria or white pupil. Many are sporadic, but a few are due to mutations in the Rb gene. Hereditary cases are often bilateral. With modern treatment, most retinoblastomas are now curable.



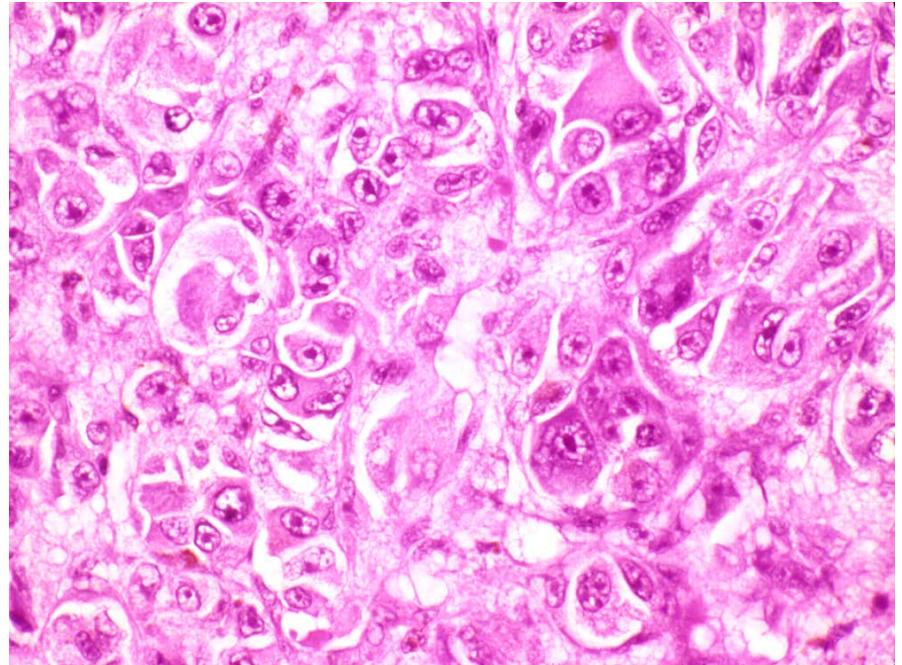
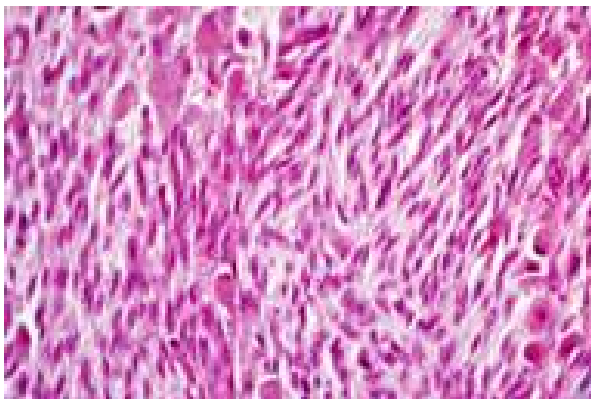
Above left, a child's eye with leukocoria due to a retinoblastoma. Above right, the resected eye showing a retinoblastoma, a white retinal tumor. Below, a section of a retinoblastoma, showing poorly differentiated primitive neurons forming the tumor. There are many rosettes – tumor cells forming around a small pale area. Areas of calcification (not shown) are common and can sometimes be seen in imaging studies. Tumor spread is via the optic nerve.







**Malignant melanomas** – most common intraocular tumor in adults. They often present as a dark or black mass, but some are amelanotic (contain no pigment) and are pale. Most arise in the uvea (which consists of the pigmented areas – the iris, ciliary body, and choroid). The tumor cells can be spindle, epithelioid (rounded), or a mixture of both. The tumors with epithelioid cells are more likely to metastasize. Above left, there is a melanoma in the out of focus area at the bottom of the field. Above right, the brown-black tumor replaces much of the eye.



Above left is a spindle cell melanoma. Right is an epithelioid melanoma, which has rounded, epithelioid cells and prominent nucleoli. Spindle cell melanomas are less likely to metastasize. Ocular melanomas spread via scleral vascular channels (below). Metastases are most common in the liver.

