

Introduction to Ophthalmic Pathology

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April 2011

APPROVED

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Objectives

- To be familiar with the pathological features of the most common blinding diseases in the U.S.A.

- » Cataracts
- » Glaucoma
- » Diabetes mellitus
- » Age-related macular degeneration

Take a moment to memorize these common causes of blindness.

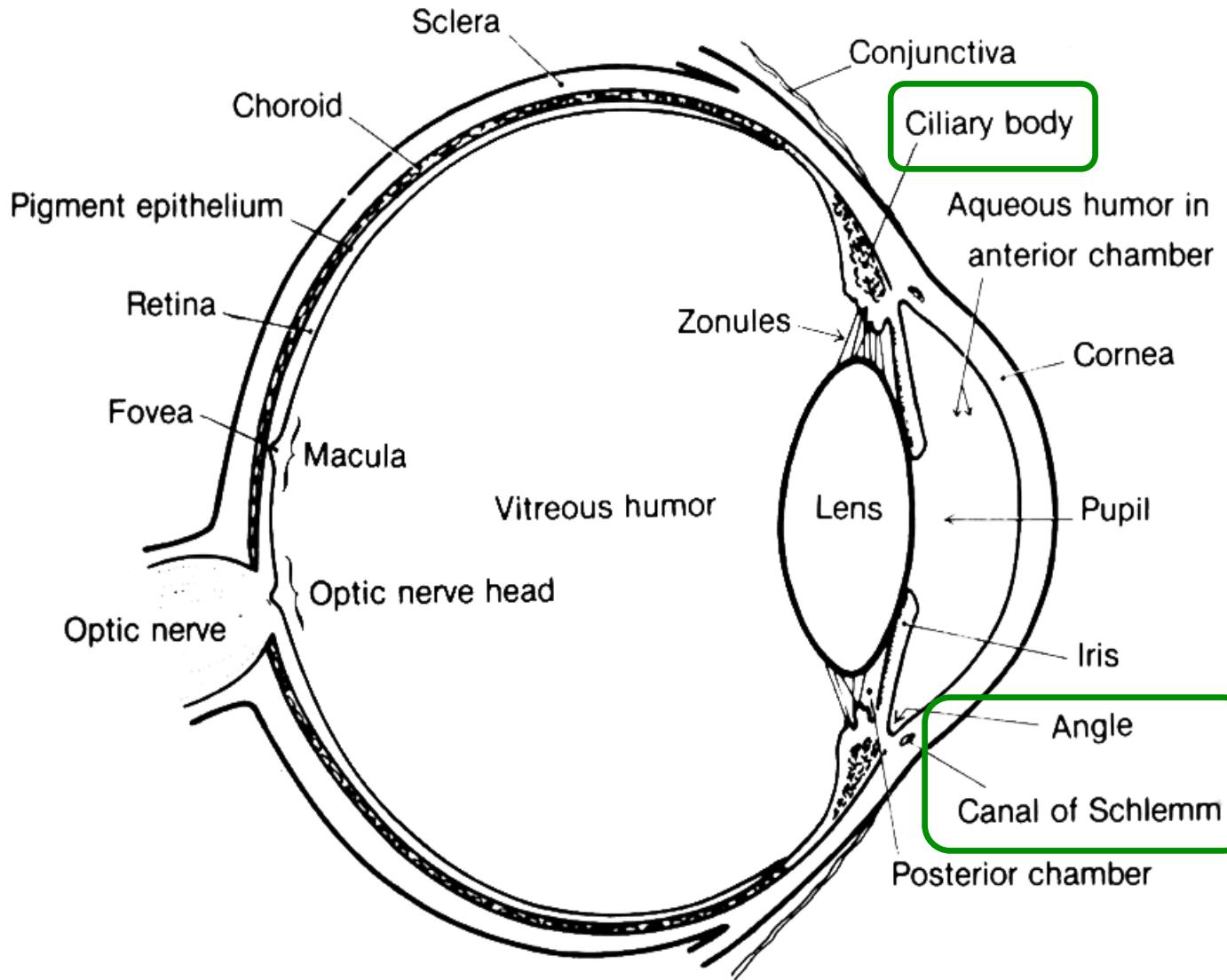
- To be aware of the most common primary intraocular malignant tumors of adults and children

- » Uveal melanoma
- » Retinoblastoma

Adults typically

Children typically

Anatomy of the Eye



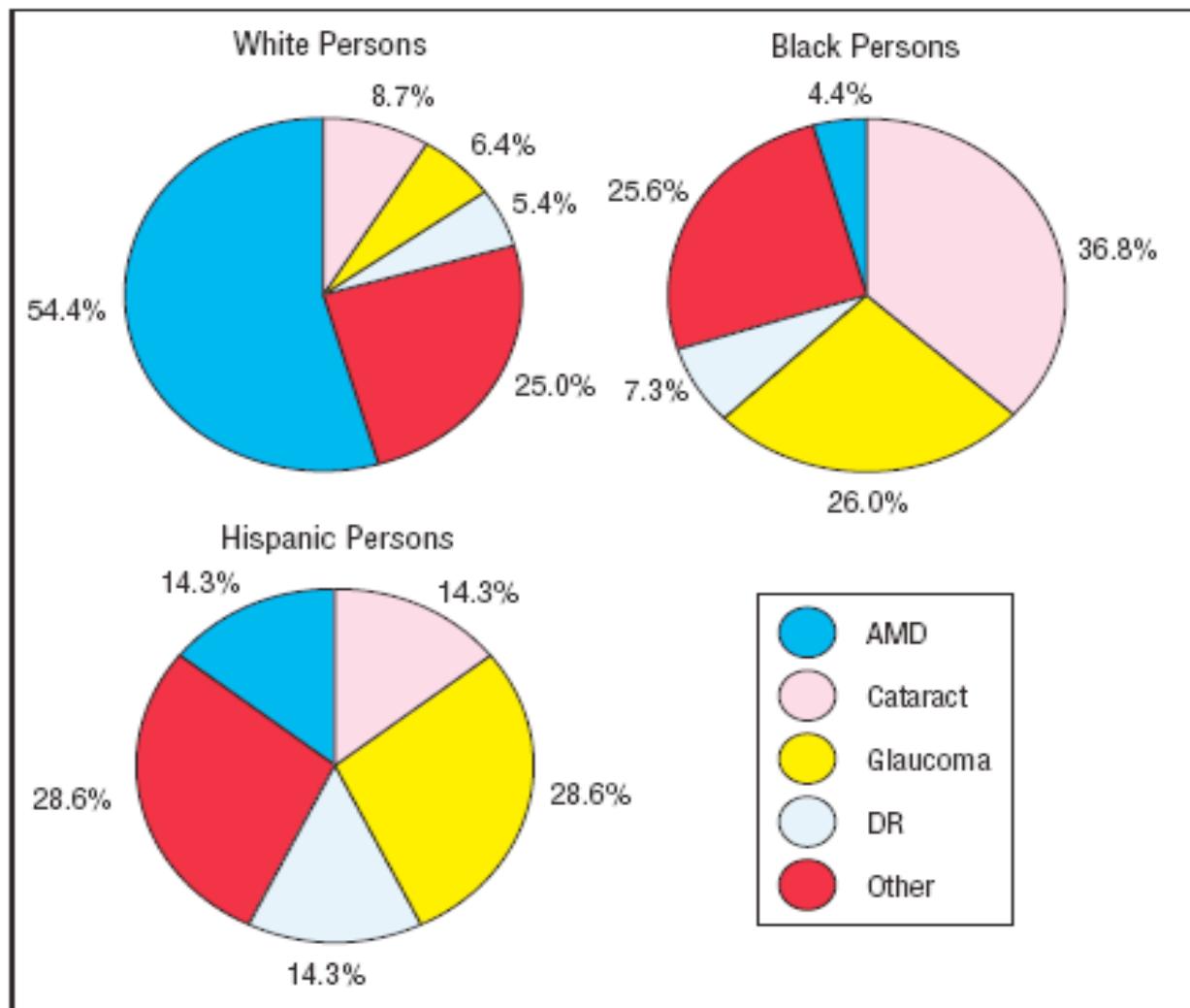
CATARACTS

are extremely common and many people have cataract surgery by the time they are ~70.

Crystalline Lens

- Provides refraction, in addition to that from the cornea
- Lens capsule (basement membrane) encloses the epithelium and lens fibers
- Cataract: lenticular opacity
 - » Many histological forms depending on location of cataractous change within the lens
 - » A major cause of blindness

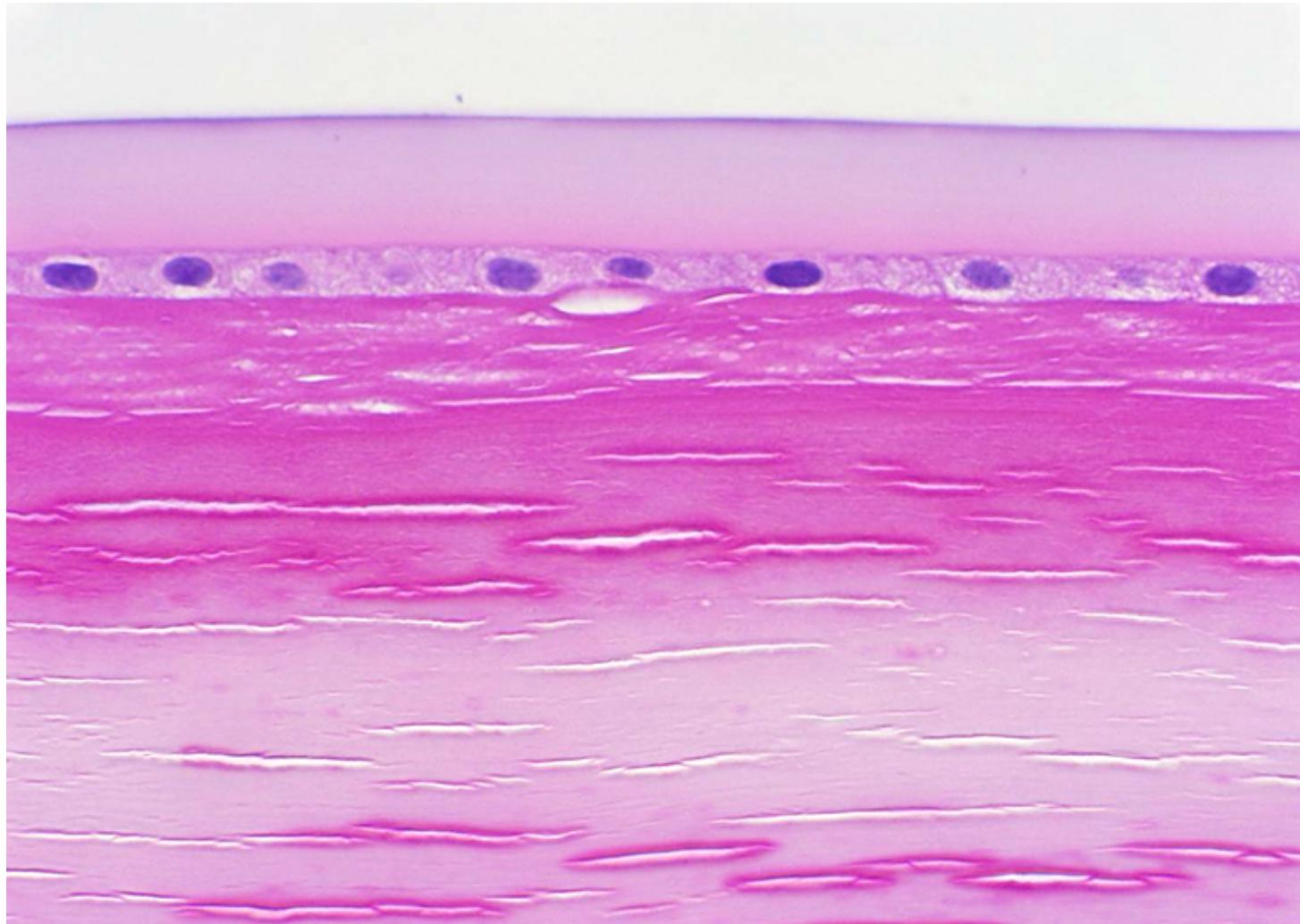
There are many ways to get opacity in the lens. The variants are described next.



**Definition of blindness is:
vision worse than
20/200 in the best
eye with
corrections.**

Figure 2. Causes of blindness (best-corrected visual acuity <6/60 [$<20/200$] in the better-seeing eye) by race/ethnicity. AMD indicates age-related macular degeneration; DR, diabetic retinopathy.

Crystalline Lens - Anterior

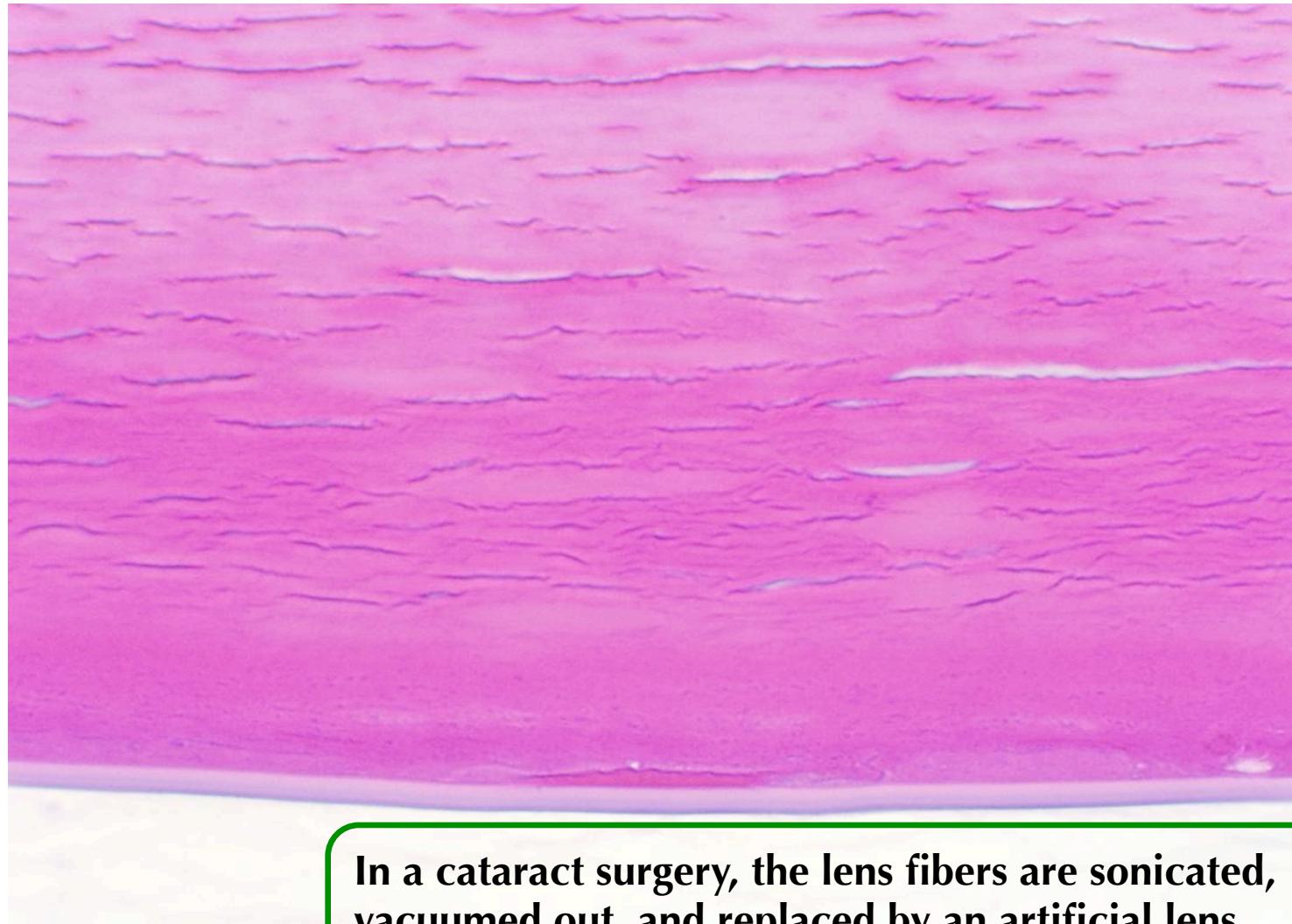


← Capsule
← Epithelium

← Lens Fibers

The lens capsule is thicker anteriorly than posteriorly. Also, there are no epithelial cells in healthy lenses posteriorly.

Crystalline Lens - Posterior



← Lens Fibers

← Capsule

In a cataract surgery, the lens fibers are sonicated, vacuumed out, and replaced by an artificial lens. Sometimes the thin posterior capsule ruptures.

Brunescence (Brown) Cataract

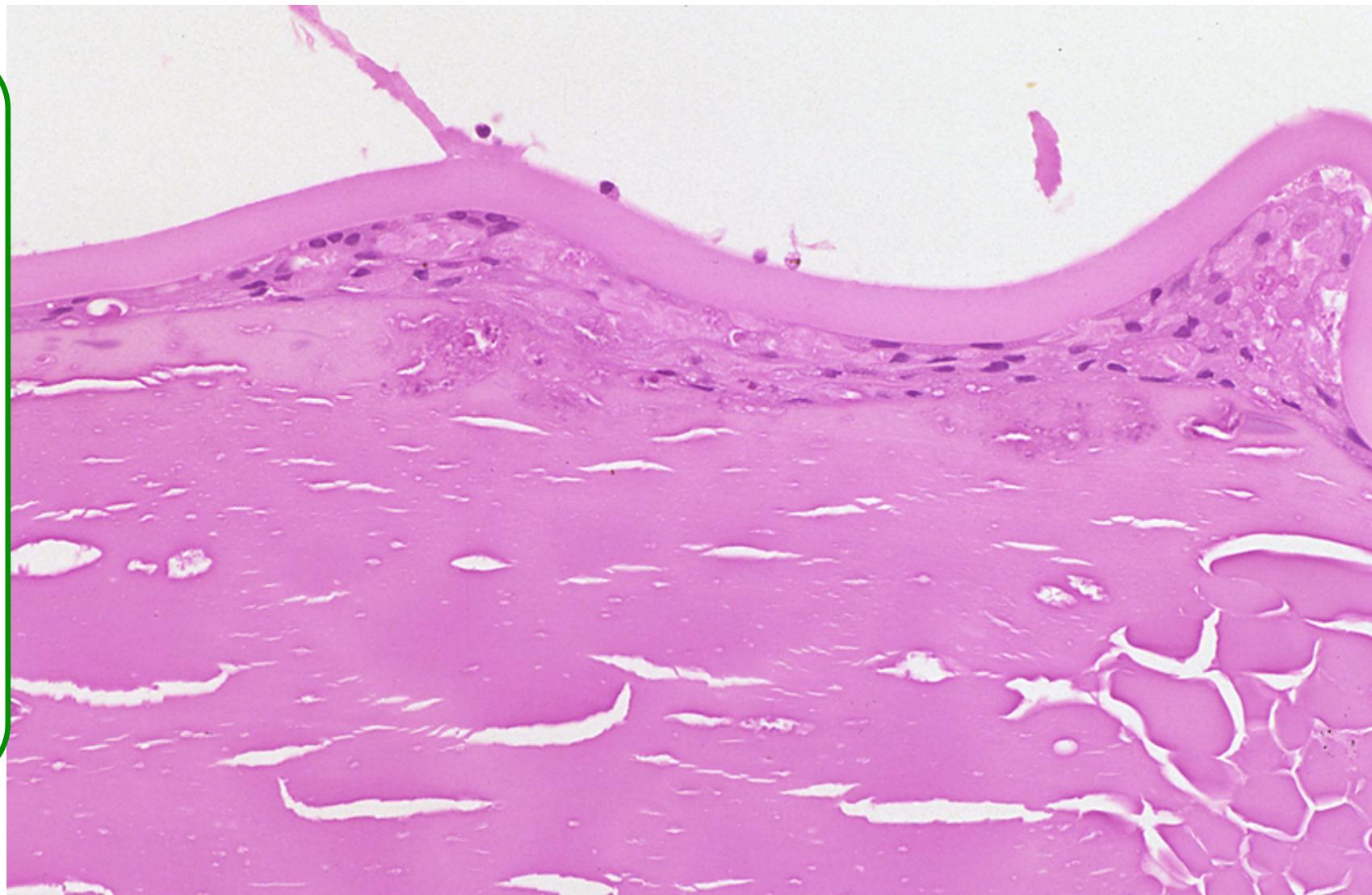


This
discoloration
will cause
changes in color
vision.

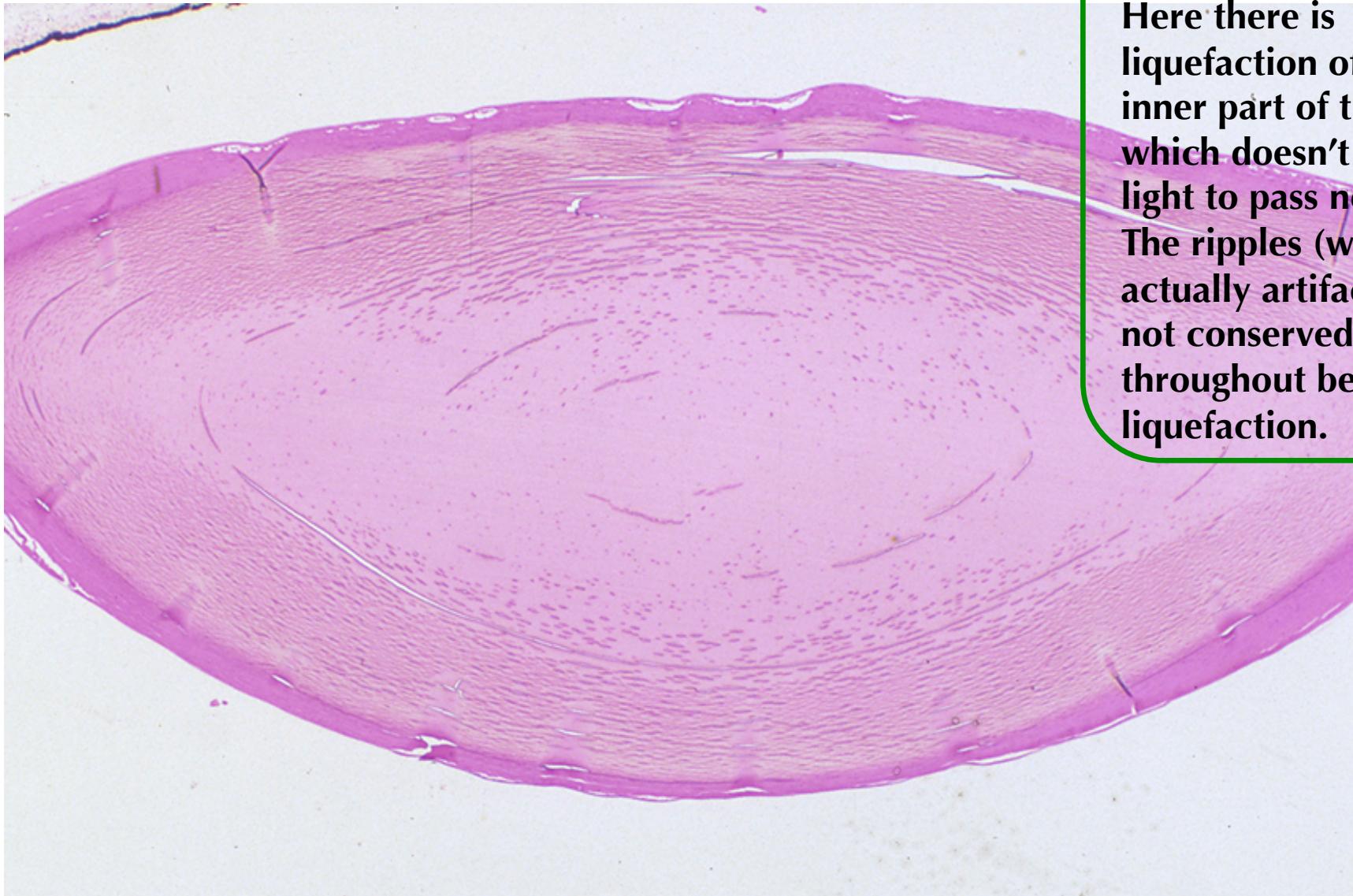
Anterior Subcapsular Cataract

Ant. Subcap.
Cataract

Note the
proliferation in
the epithelial
cell layer
beneath the
capsule, which
does not allow
light to pass
normally.

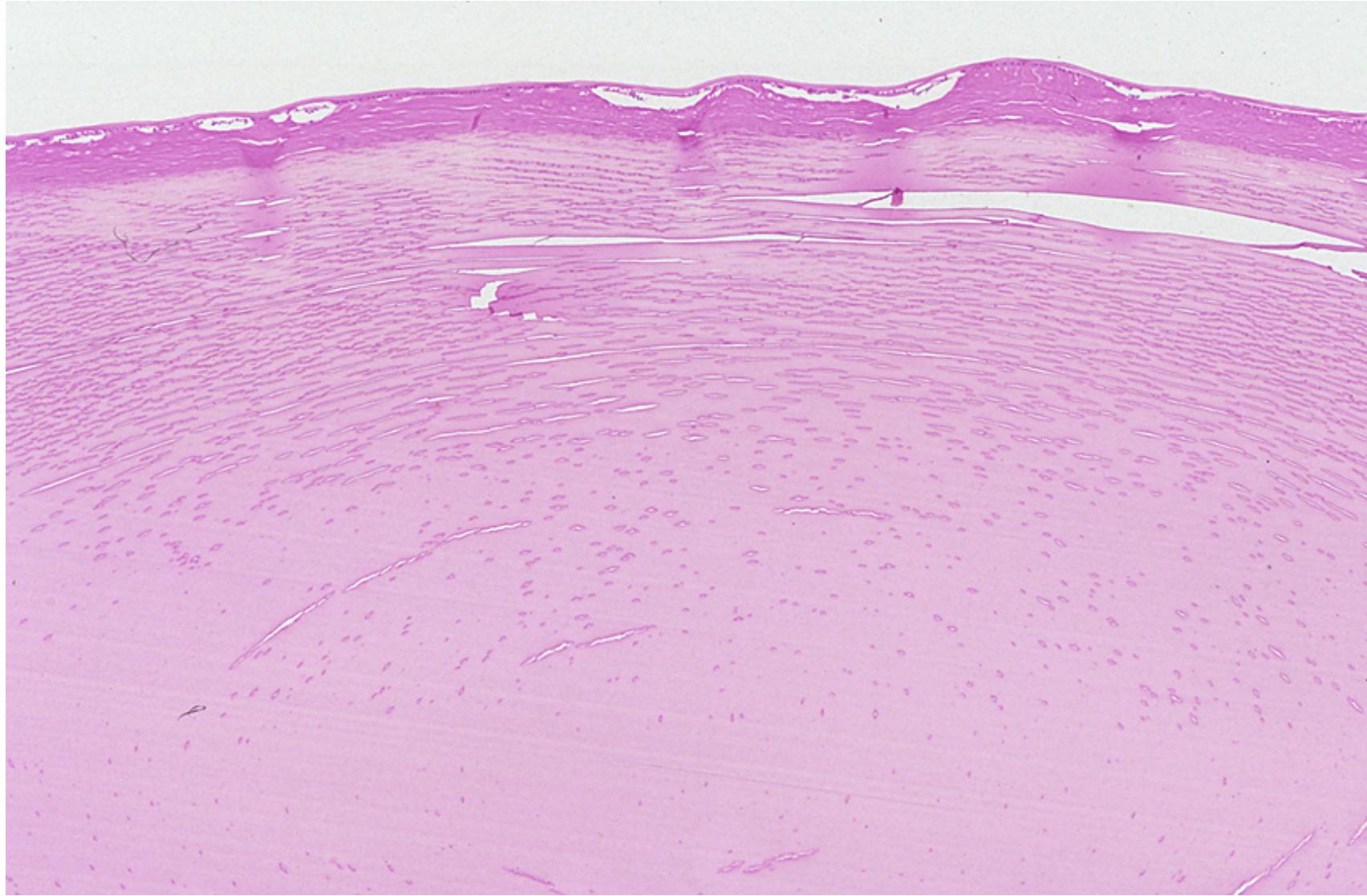


Nuclear Cataract

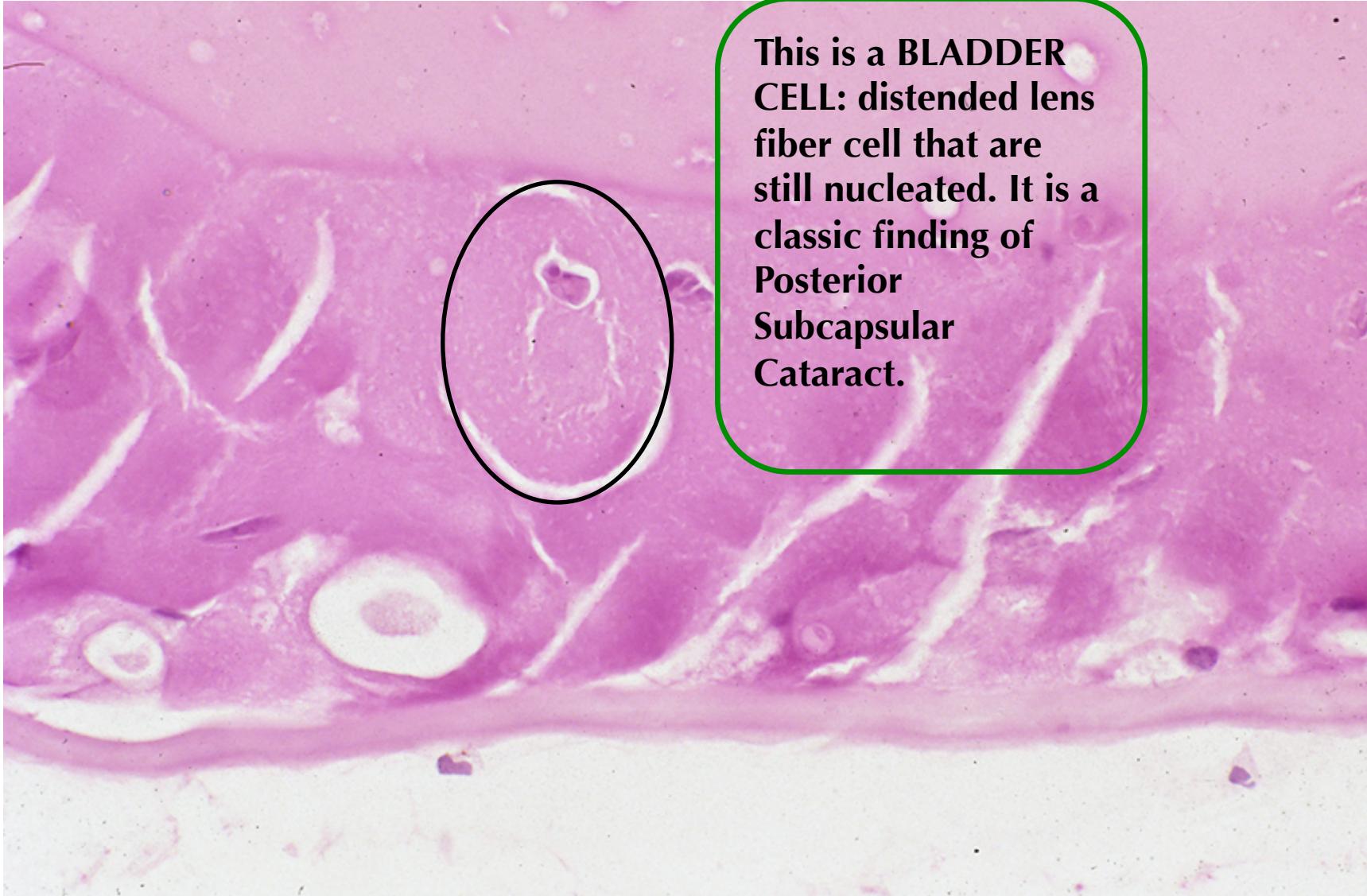


Nuclear Cataract:
Here there is liquefaction of the inner part of the lens, which doesn't allow light to pass normally. The ripples (which are actually artifacts) are not conserved throughout because of liquefaction.

Nuclear Cataract



Posterior Subcapsular Cataract



This is a BLADDER CELL: distended lens fiber cell that are still nucleated. It is a classic finding of Posterior Subcapsular Cataract.

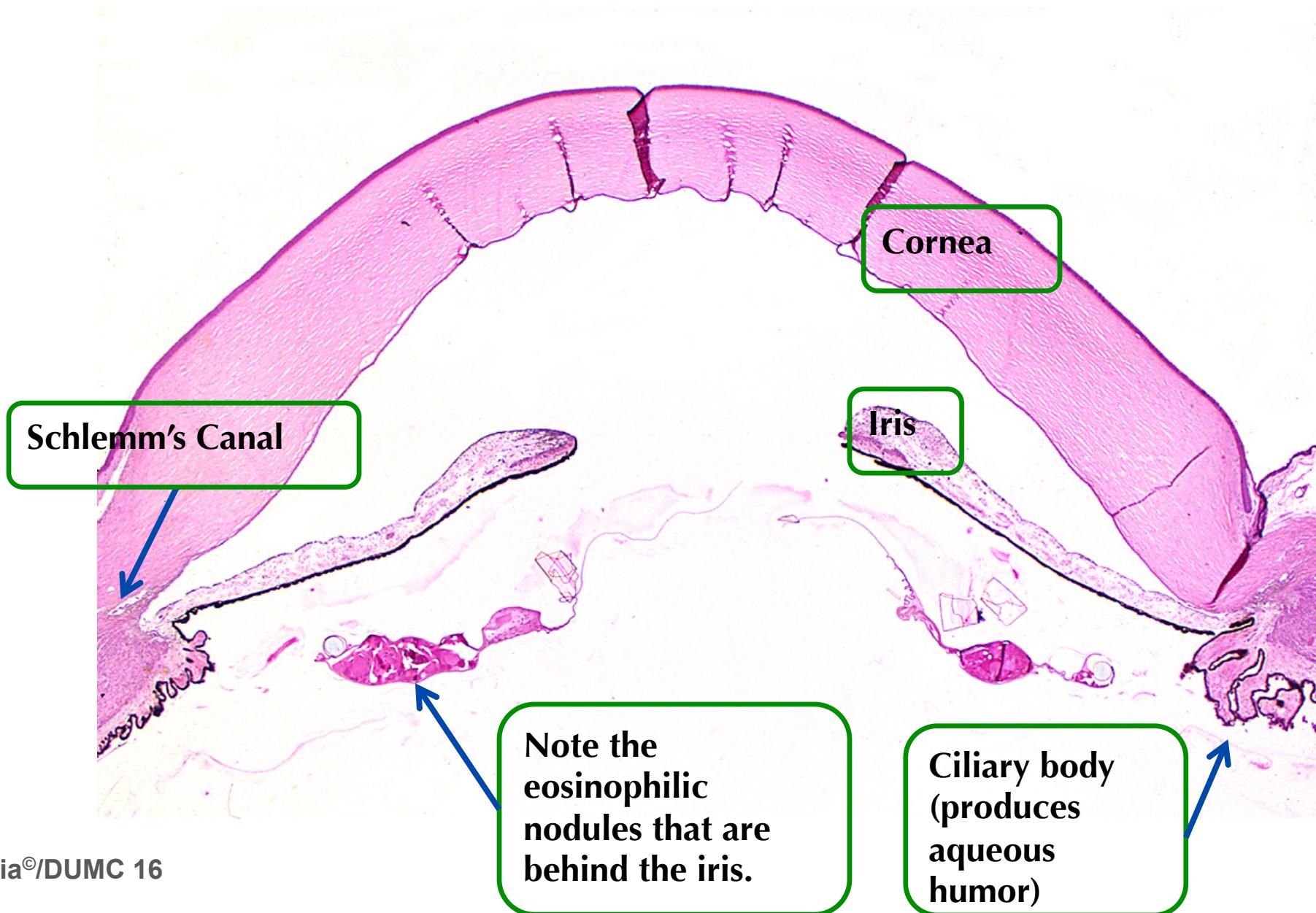
Bladder cells

Soemmerring Ring Cataract

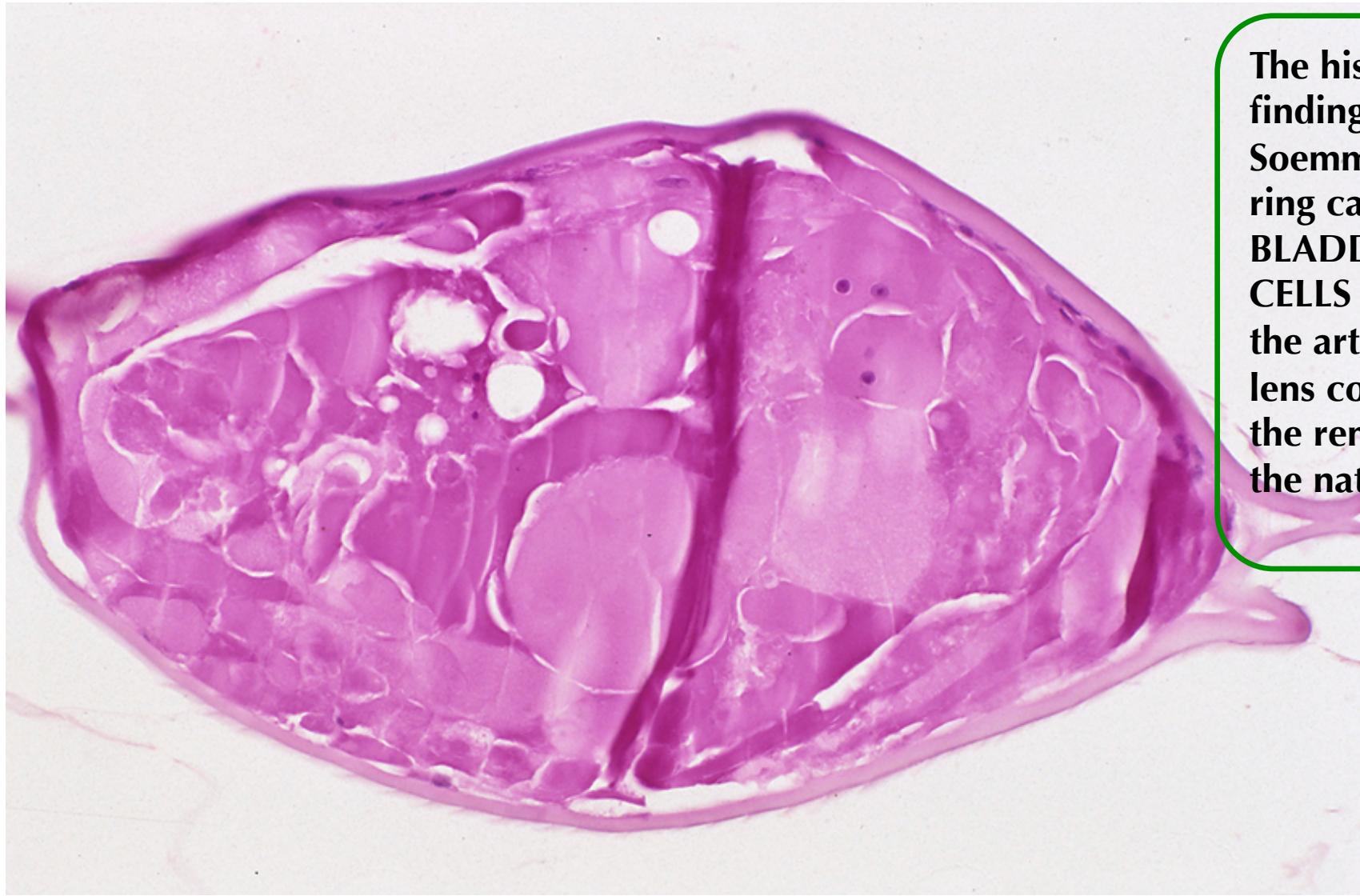


Soemmerring Ring Cataract is a **BENIGN** side effect of cataract surgery. There is proliferation of lens epithelial cells at the lens margins that do **NOT** obstruct vision because it is behind the iris.

Soemmerring Ring Cataract



Soemmerring Ring Cataract



The histological finding in Soemmerring ring cataracts is **BLADDER CELLS** where the artificial lens contacts the remnants of the natural lens.

GLAUCOMA

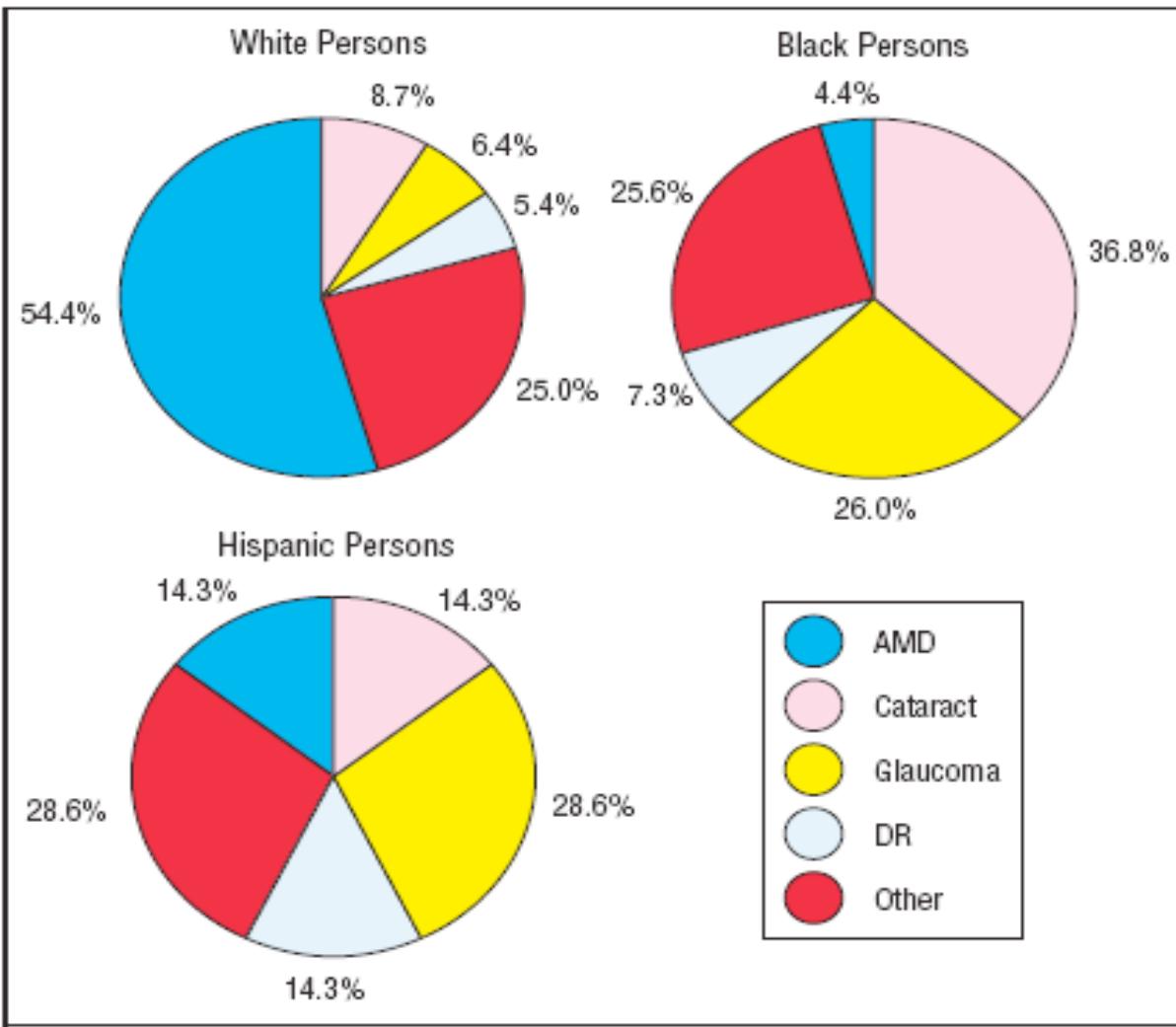


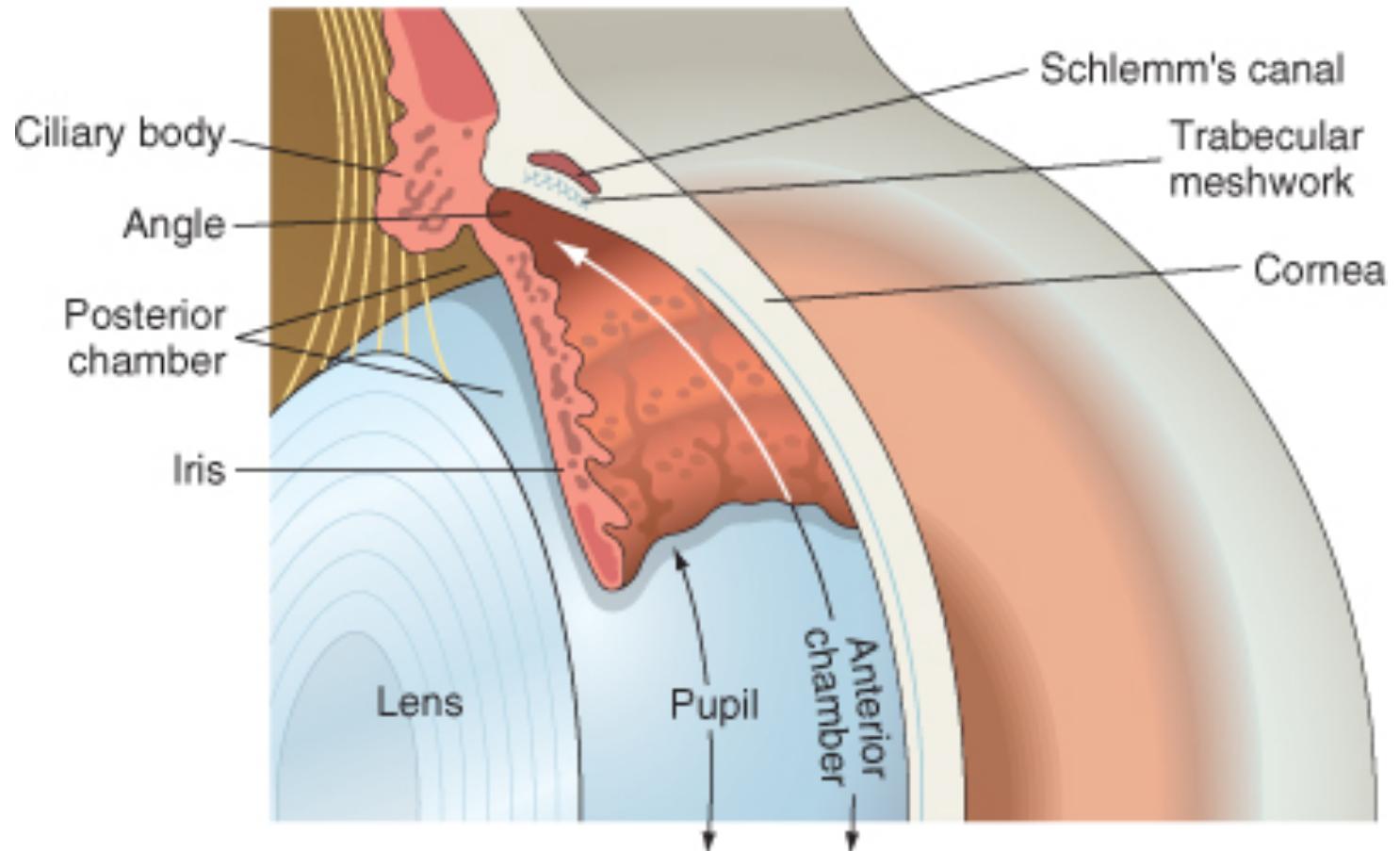
Figure 2. Causes of blindness (best-corrected visual acuity <6/60 [$<20/200$] in the better-seeing eye) by race/ethnicity. AMD indicates age-related macular degeneration; DR, diabetic retinopathy.

Glaucoma is a more common cause of blindness in blacks and Hispanics. This is unrelated to the higher rates of diabetes because most glaucoma is “open-angle” not diabetes-related “angle-closure glaucoma.” There is more about this distinction in Tuesday’s lecture.

Anterior Segment Anatomy

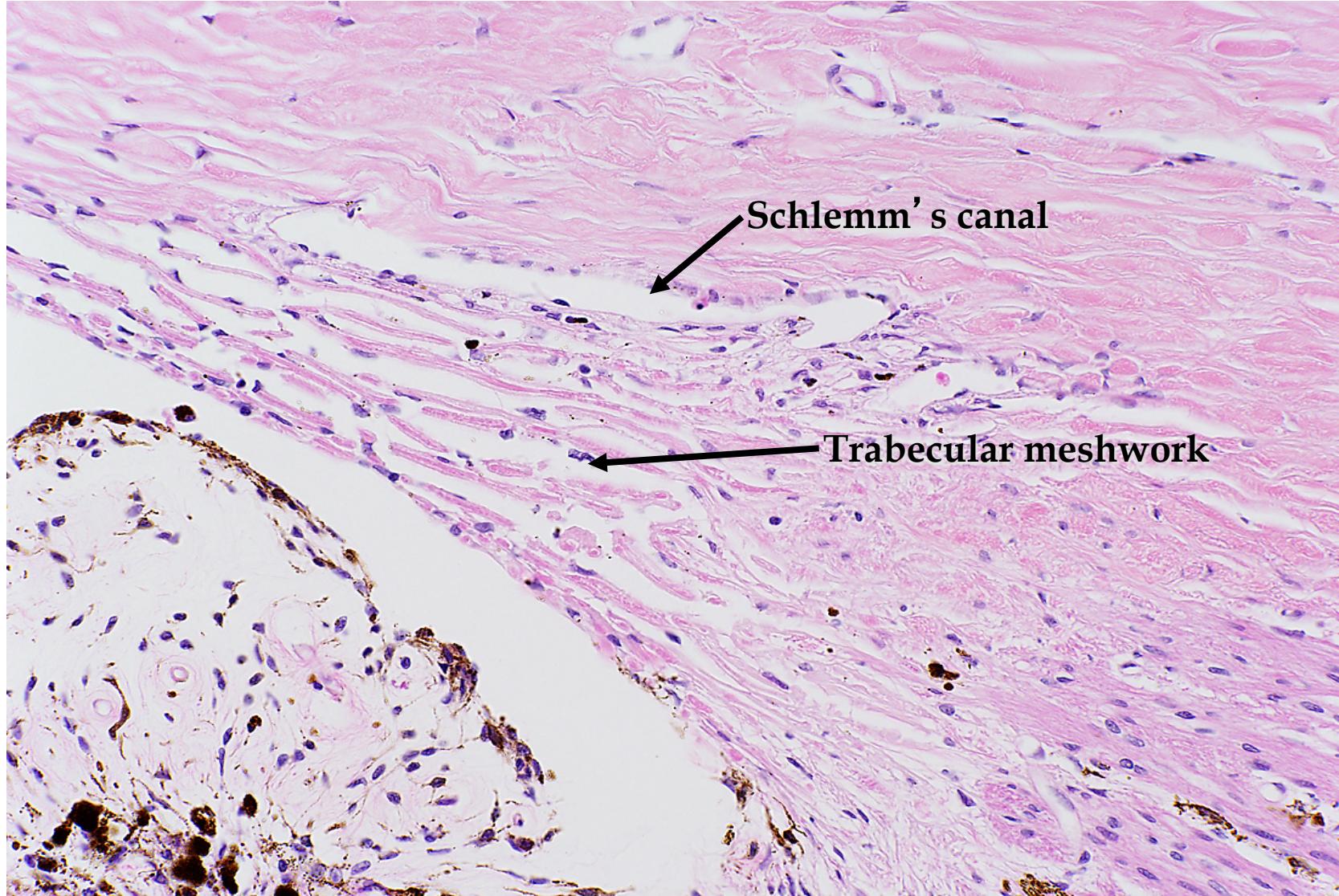
Aqueous humor is produced in the ciliary body, flows out the pupil, is strained in the trabecular meshwork, enters Schlemm's canal, and finally is resorbed into a venous plexus surrounding the canal.

ANTERIOR AND POSTERIOR CHAMBERS



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Anterior Chamber Angle



Retina

The damage of increased intra-ocular pressure (aka glaucoma) manifests in the retina, not the anterior structures of the eye.

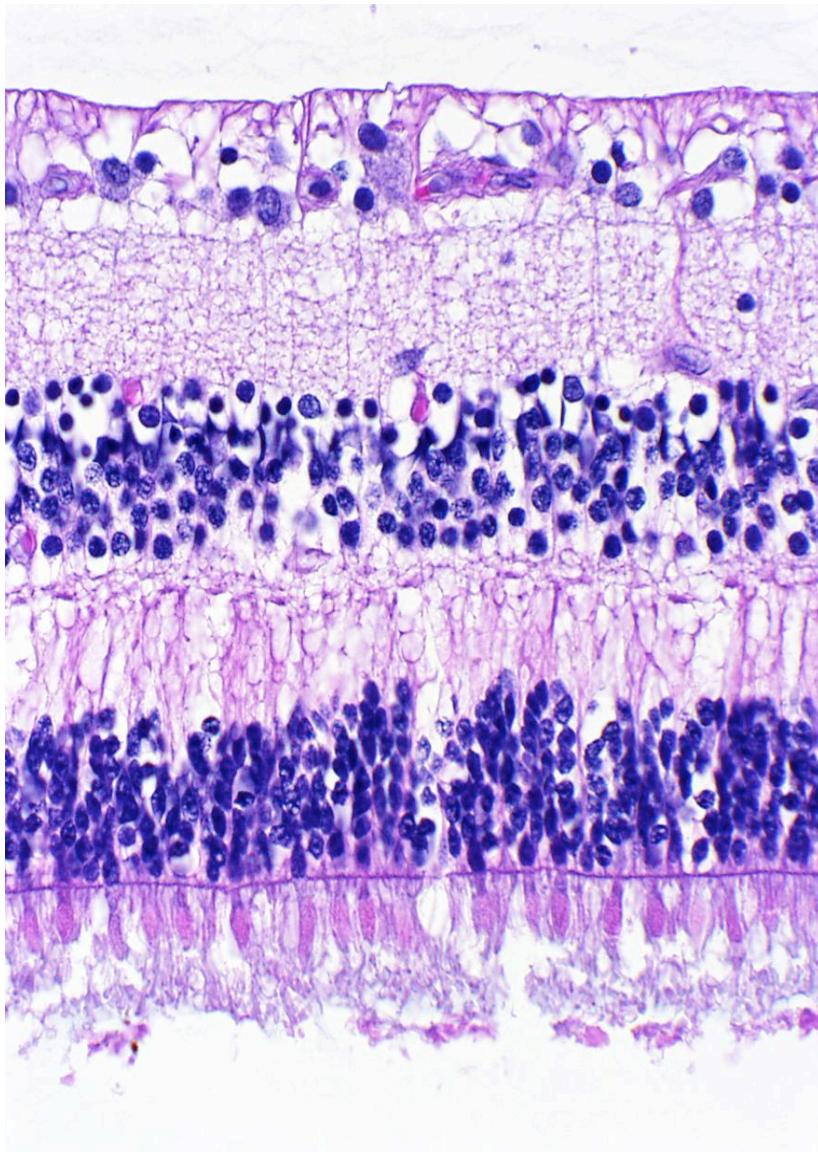
● Neurosensory retina

- » Converts light into electrical impulses for transmittal to brain
- » Rods: “black and white” picture
- » Cones: “color” picture

● Retinal pigment epithelium

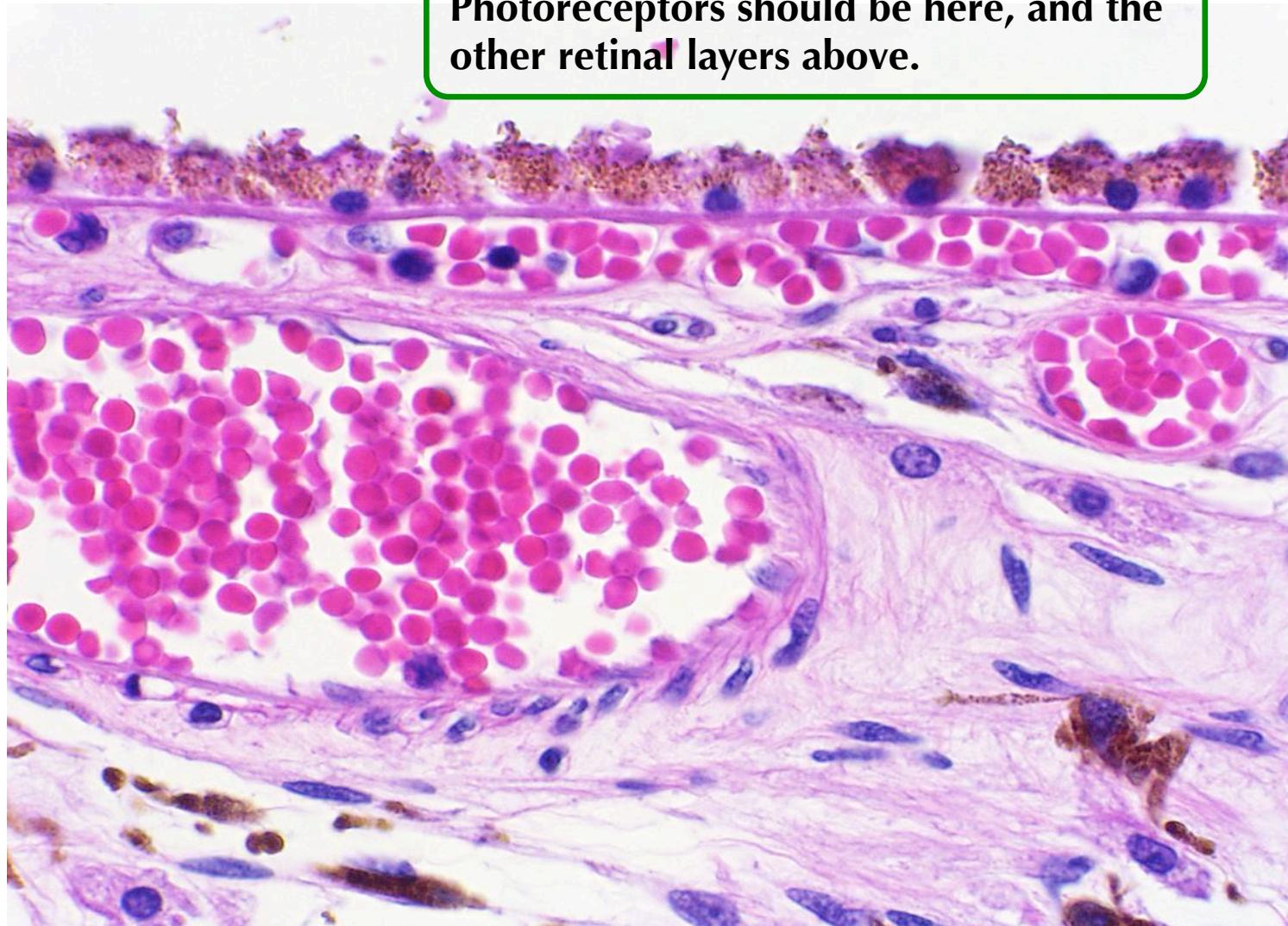
- » Absorbs light passing through retina (prevents reflection)
- » Phagocytosis and degradation of shed photoreceptor discs
- » Part of blood-retinal barrier

Neurosensory Retina



- Inner limiting membrane
- Nerve fiber layer
- Ganglion cell layer
- Inner plexiform layer
- Inner nuclear layer
- Outer plexiform layer
- Outer nuclear layer
- External limiting membrane
- Outer segments of photoreceptors (rods and cones)

Retinal Pigment Epithelium & Choroid



Photoreceptors should be here, and the other retinal layers above.

RPE
Bruch's membrane
Choriocapillaris

The choriocapillaris is a rich capillary network essential for supplying the RPE and outer retina.

Glaucomatous Damage

Causes of glaucoma.

- +/- changes in anterior chamber angle
 - » Primary open-angle glaucoma most common
 - » Secondary open-angle glaucoma
 - Particles in trabecular meshwork)
 - » Angle-closure glaucoma
 - Many causes

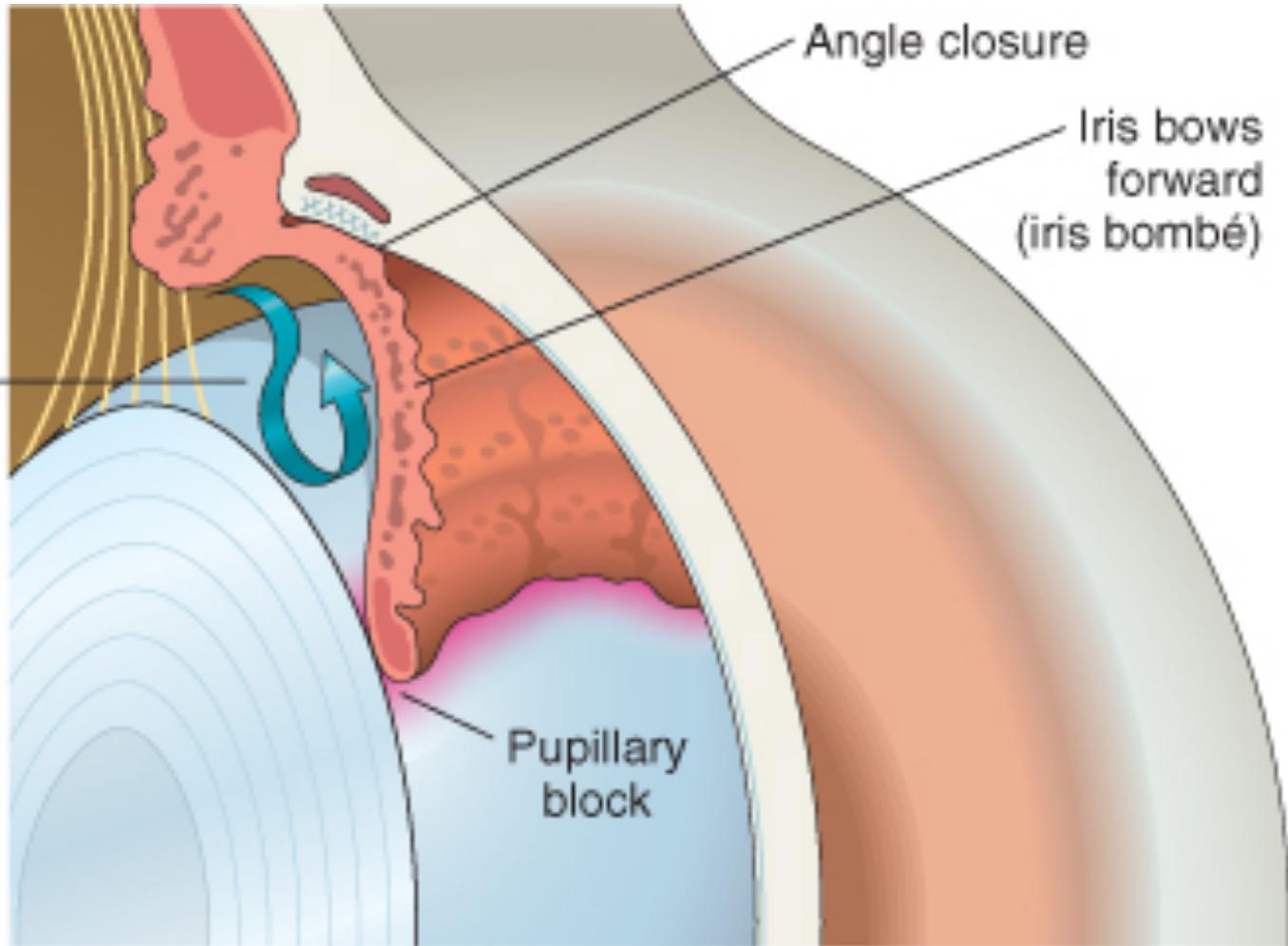
Effects of glaucoma on retina.

- Atrophy of the retinal ganglion cell layer
- Atrophy of the optic nerve
- Blindness

Angle Closure

Glaucoma: One type of glaucoma – more on how this happens in lecture
04.12.1

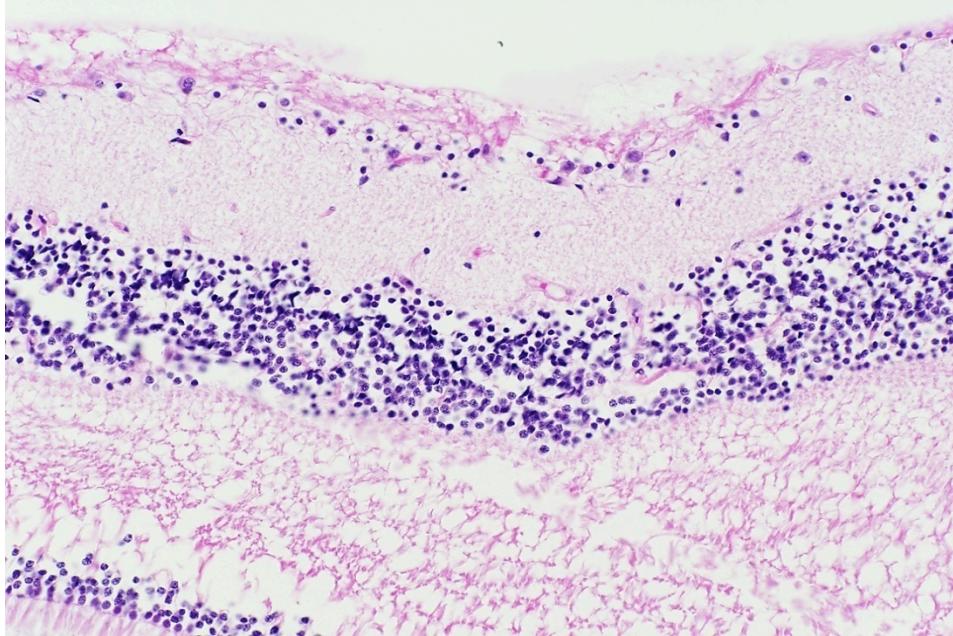
Obstructed flow leads to increased posterior chamber pressure



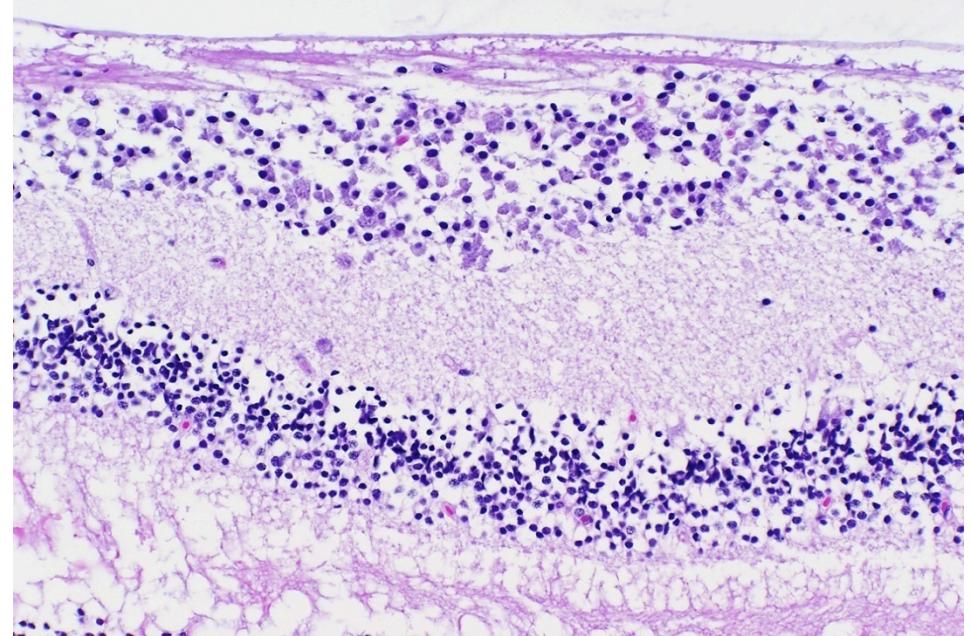
PRIMARY ANGLE CLOSURE GLAUCOMA

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Glaucomatous Retinal Damage



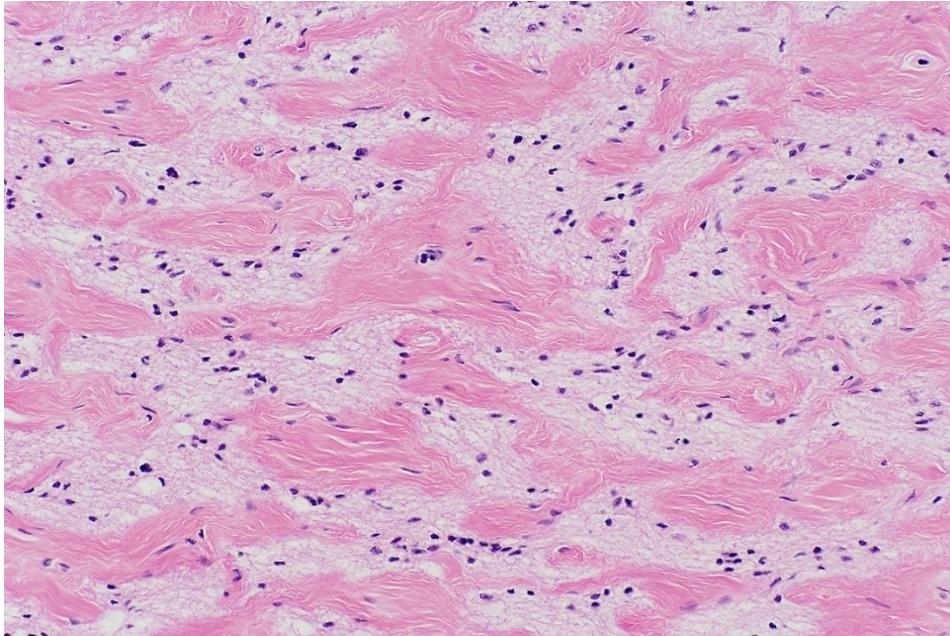
Macula with severe loss of ganglion cells



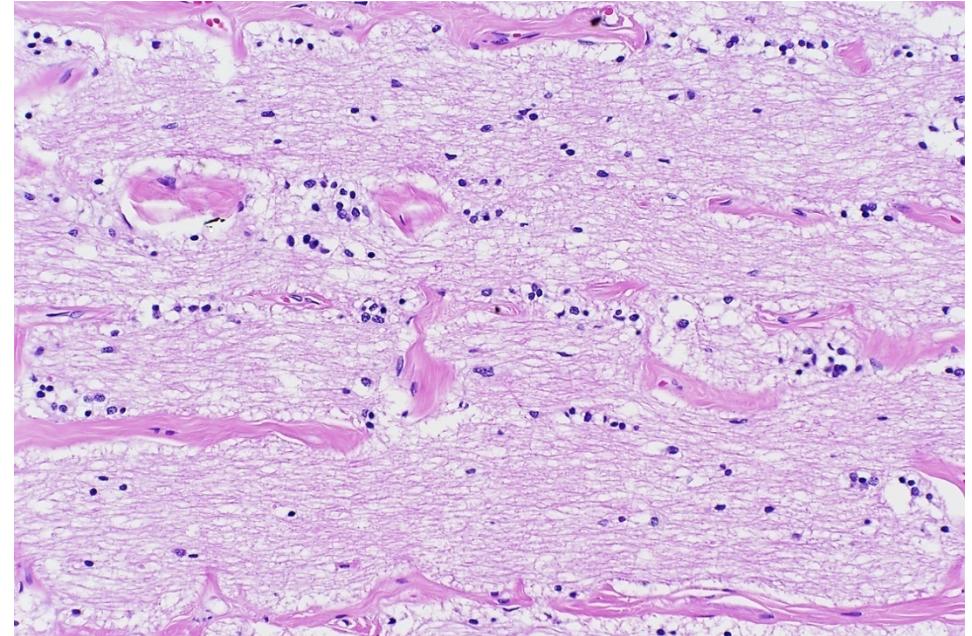
Macula with no loss of ganglion cells

Note the loss of ganglion cells in inner layer. The loss of these cells leads to blindness and optic nerve atrophy.

Glaucomatous Optic Nerve Damage



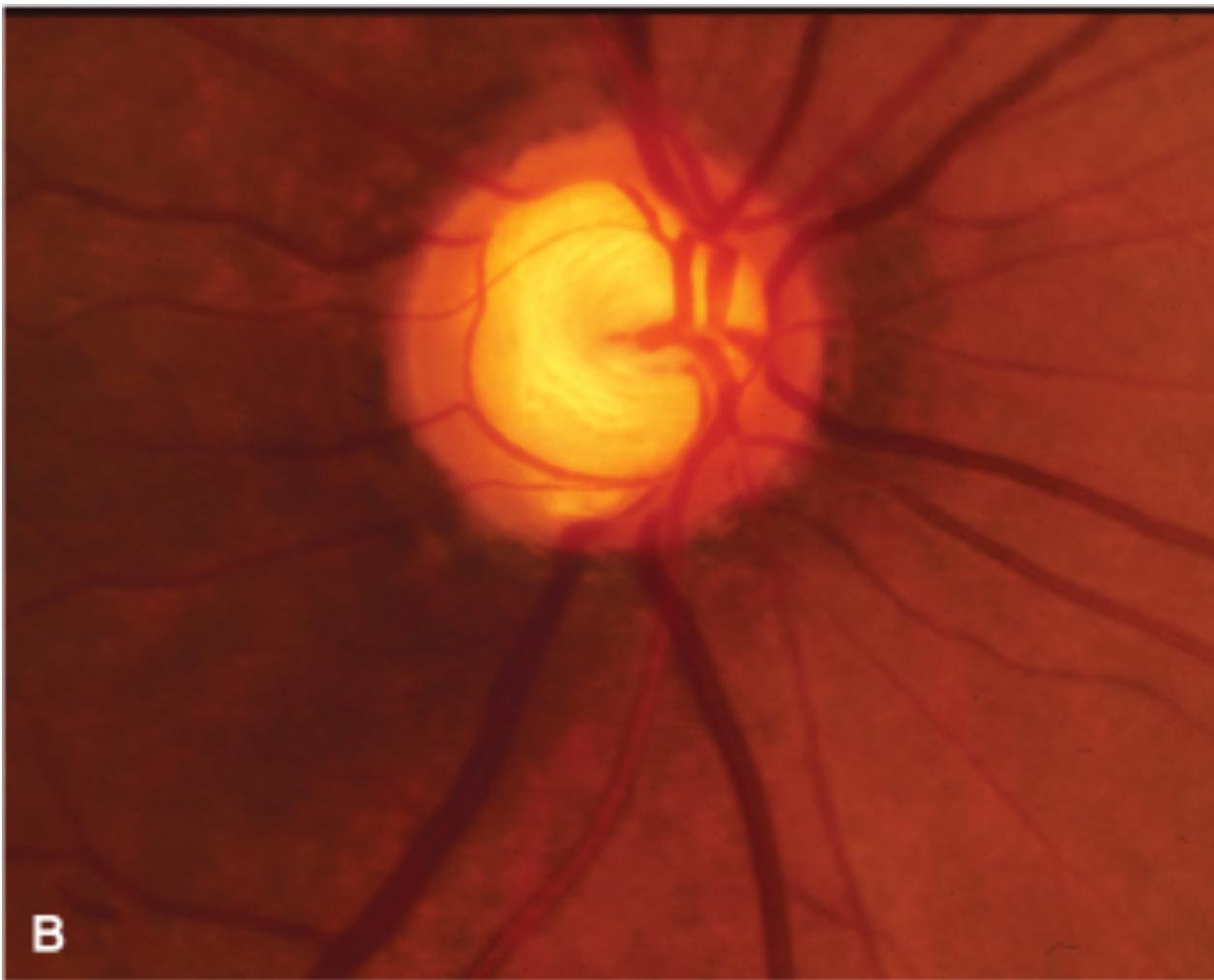
Optic nerve with moderate atrophy



Optic nerve with no atrophy

Without normal signaling from ganglion cells, the optic nerve axons degenerates and undergoes fibrosis progressively with glaucoma.

Glaucomatous Optic Nerve Cupping



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The optic nerve begins to look like a “rabbit burrow” due to atrophy. It also becomes whiter as it undergoes fibrosis and loses vascularization.

DIABETES MELLITUS

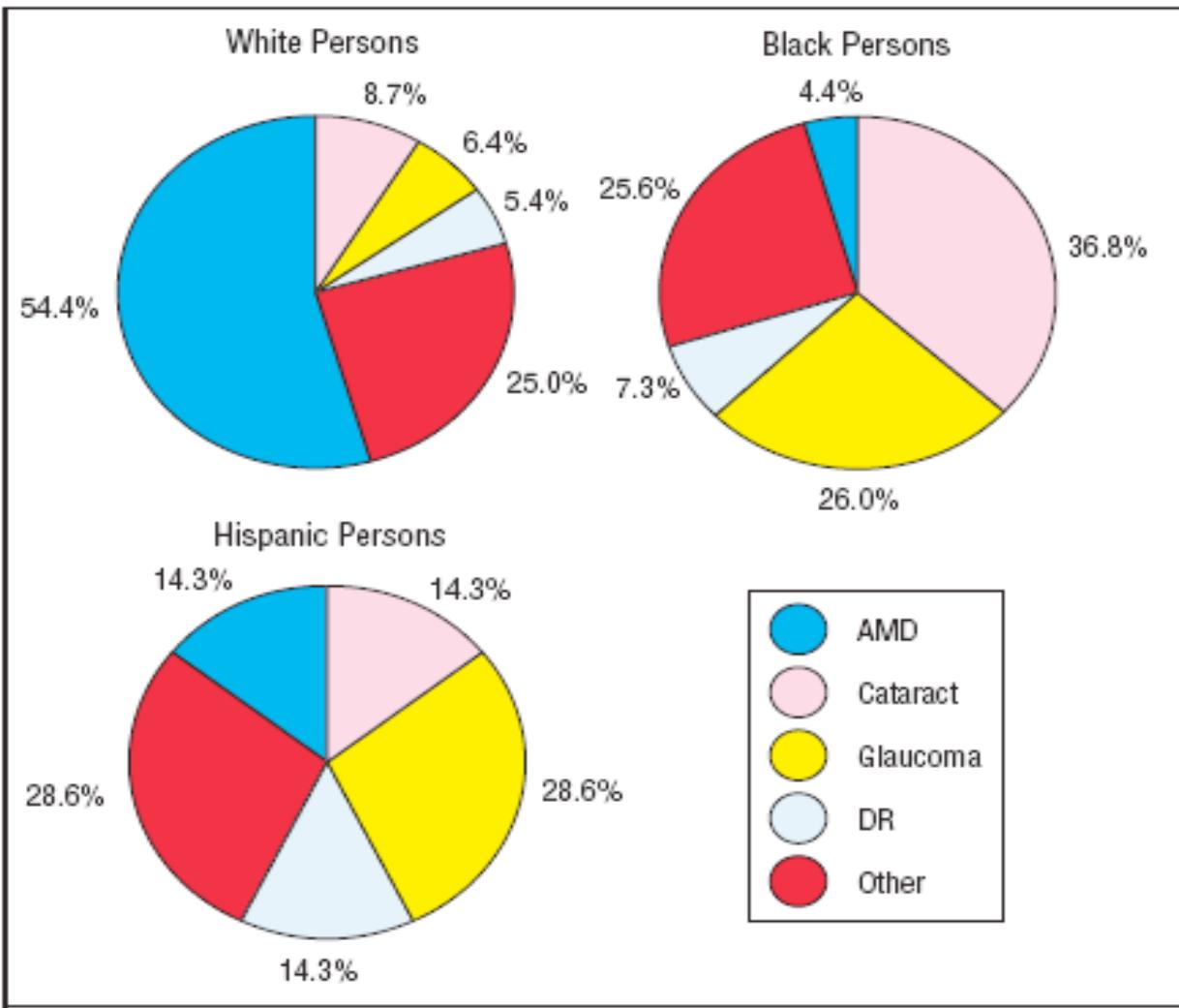


Figure 2. Causes of blindness (best-corrected visual acuity <6/60 [$<20/200$] in the better-seeing eye) by race/ethnicity. AMD indicates age-related macular degeneration; DR, diabetic retinopathy.

Diabetic Retinopathy

- Frequency after 3-4 years of diabetes:

- » Insulin-dependent: 19%
- » Non-insulin-dependent: 24%

- Frequency after 20 years of diabetes

- » Insulin-dependent: “nearly all” (50% proliferative)
- » Non-insulin-dependent: About 60% (10% proliferative)

- Fourth or fifth most common cause of blindness in U.S.A. depending on race/ethnicity

There are two types:

1. Background
2. Proliferative

Diabetic retinopathy is one of the reasons why tight control of blood glucose is so important.

Diabetic nephropathy and peripheral neuropathy are two other major sequelae with diabetes.

Diabetic Retinopathy

Diabetic retinopathy's underlying pathology is blood vessel changes with the following properties, possibly due to pericyte death.

● **Background (preproliferative) diabetic retinopathy**

- » Thickened basement membrane of retinal blood vessels
- » Decreased pericytes
- » Microaneurysms

Physical findings by fundoscopic exam.

- » Macular edema
- » Hemorrhages
- » Cotton wool spots (nerve fiber layer microinfarcts)
- » Intraretinal angiogenesis (intraretinal microangiopathy)

Diabetic Retinopathy

- **Proliferative diabetic retinopathy**

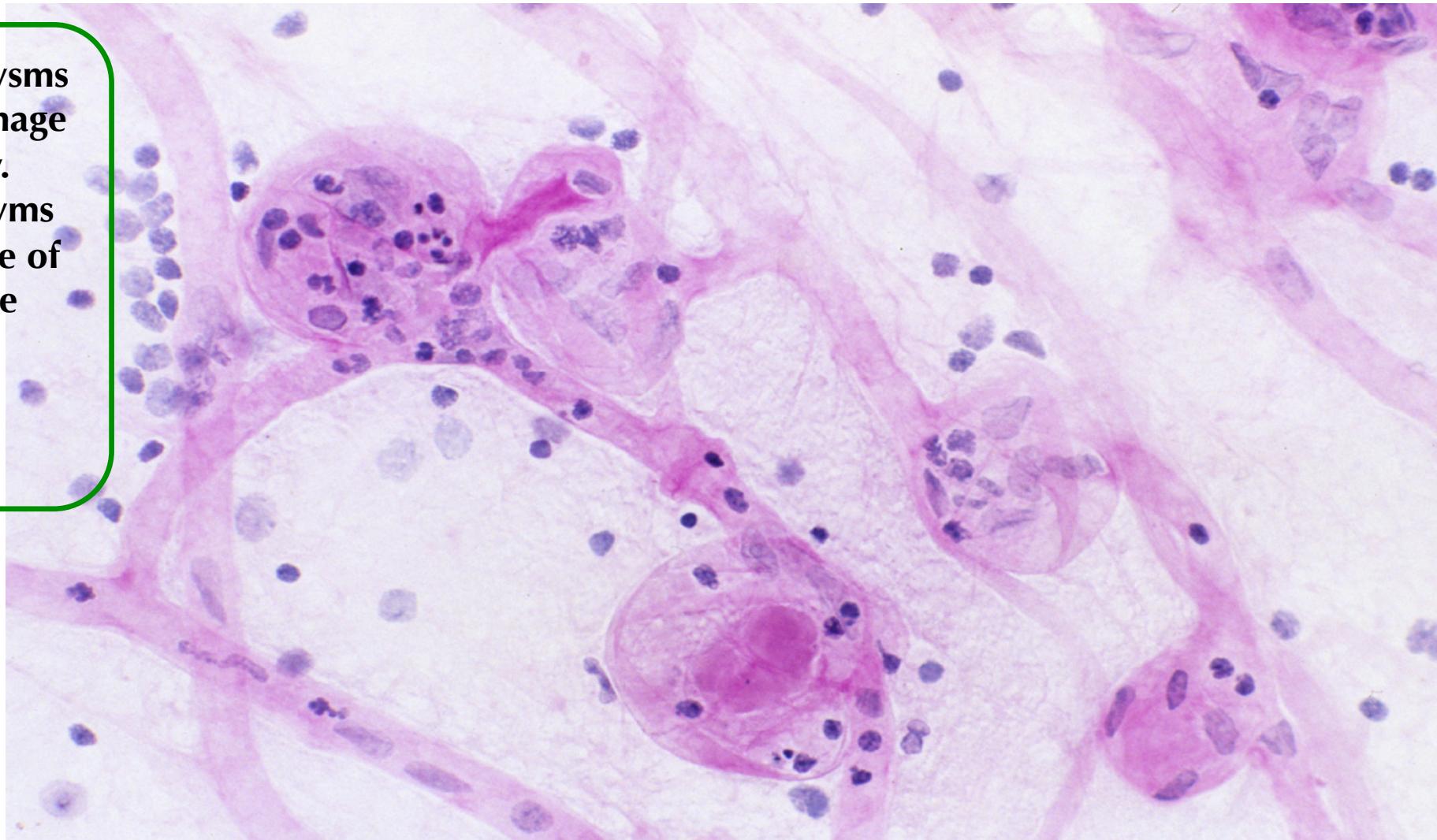
- » New vessels on either surface of optic disc or retina

- Vessels must penetrate internal limiting membrane
- Complications
 - Traction retinal detachment
 - Hemorrhage
 - Iris neovascularization

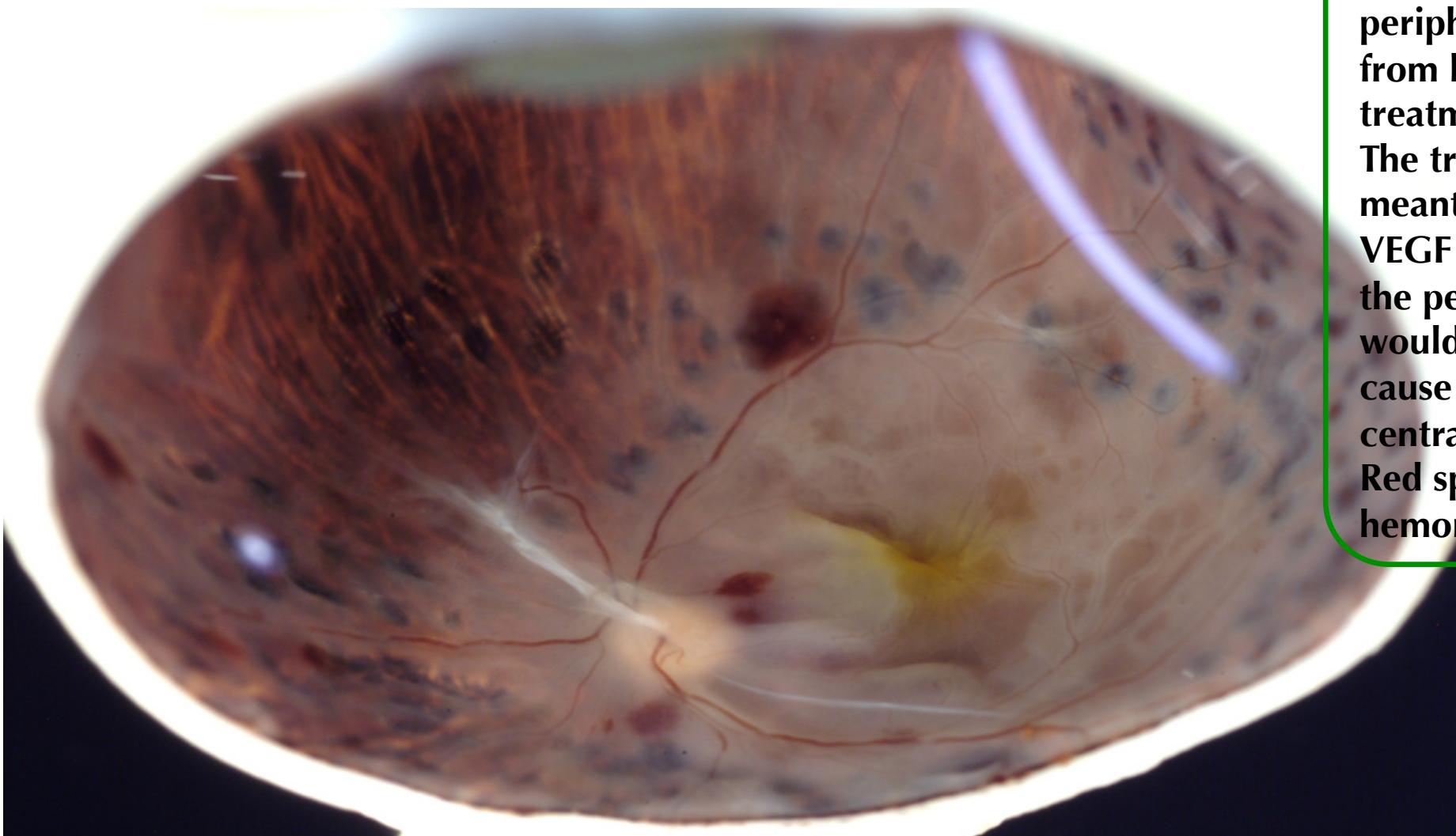
Neovascularization occurs because of ischemia, which is problematic because of retinal detachment, hemorrhage, light obstruction.

Diabetic Microaneurysms

Microaneurysms will hemorrhage and be leaky. Microaneurysms arise because of poor pericyte health.

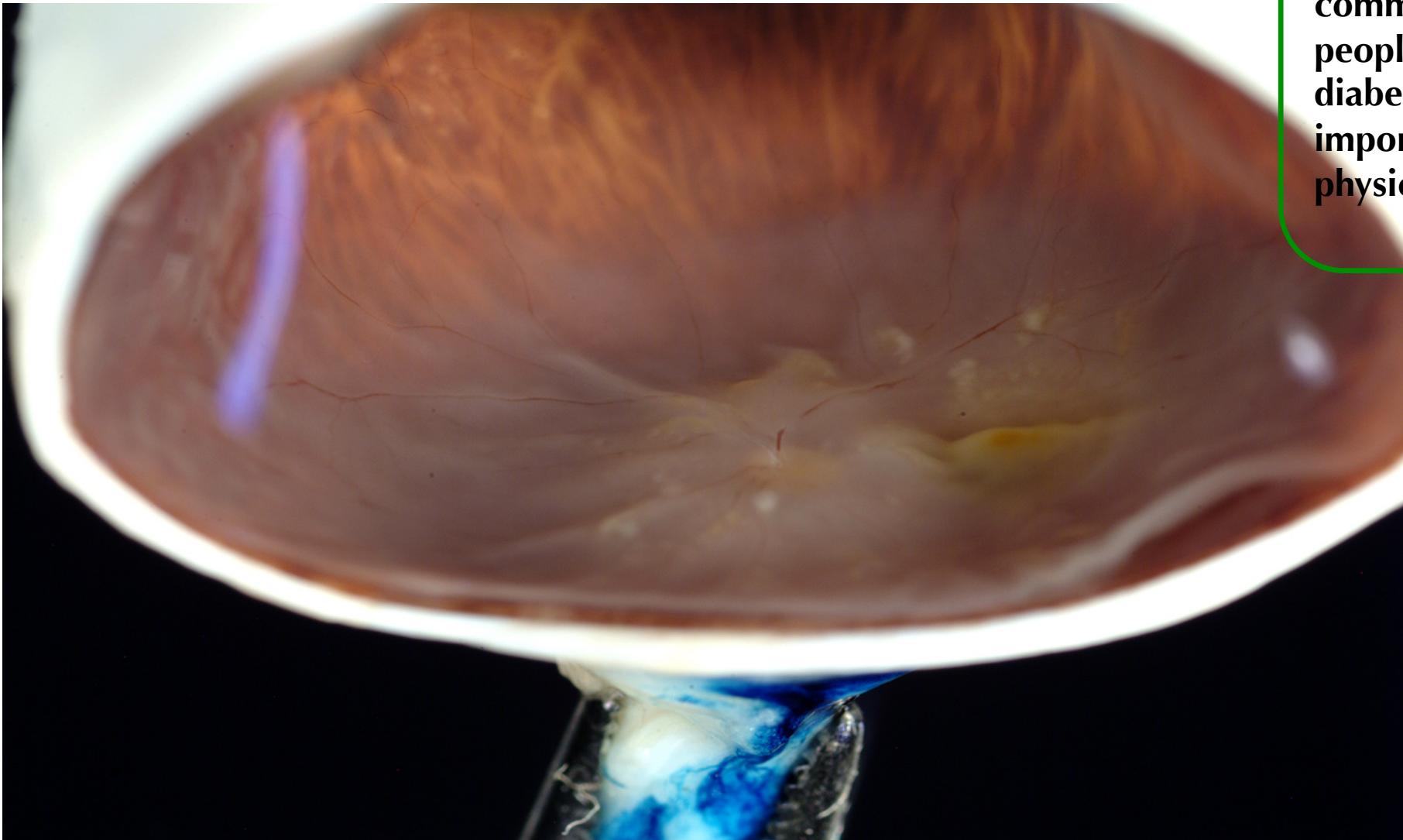


Diabetic Retinal Hemorrhages



Black spots peripherally are from laser burn treatment. The treatment is meant to reduce VEGF release from the periphery that would otherwise cause angiogenesis centrally. Red spots are hemorrhages.

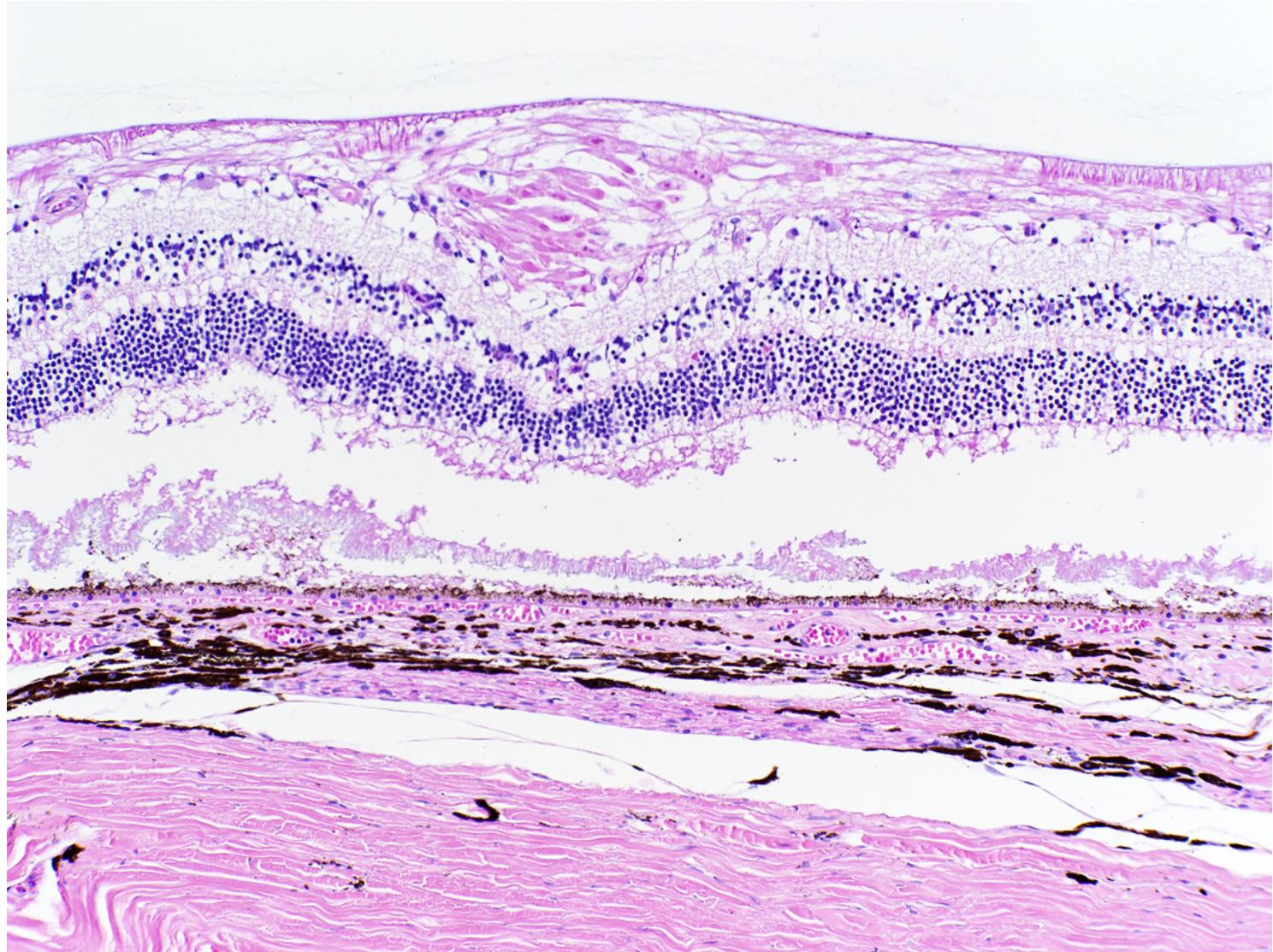
Cotton Wool Spots



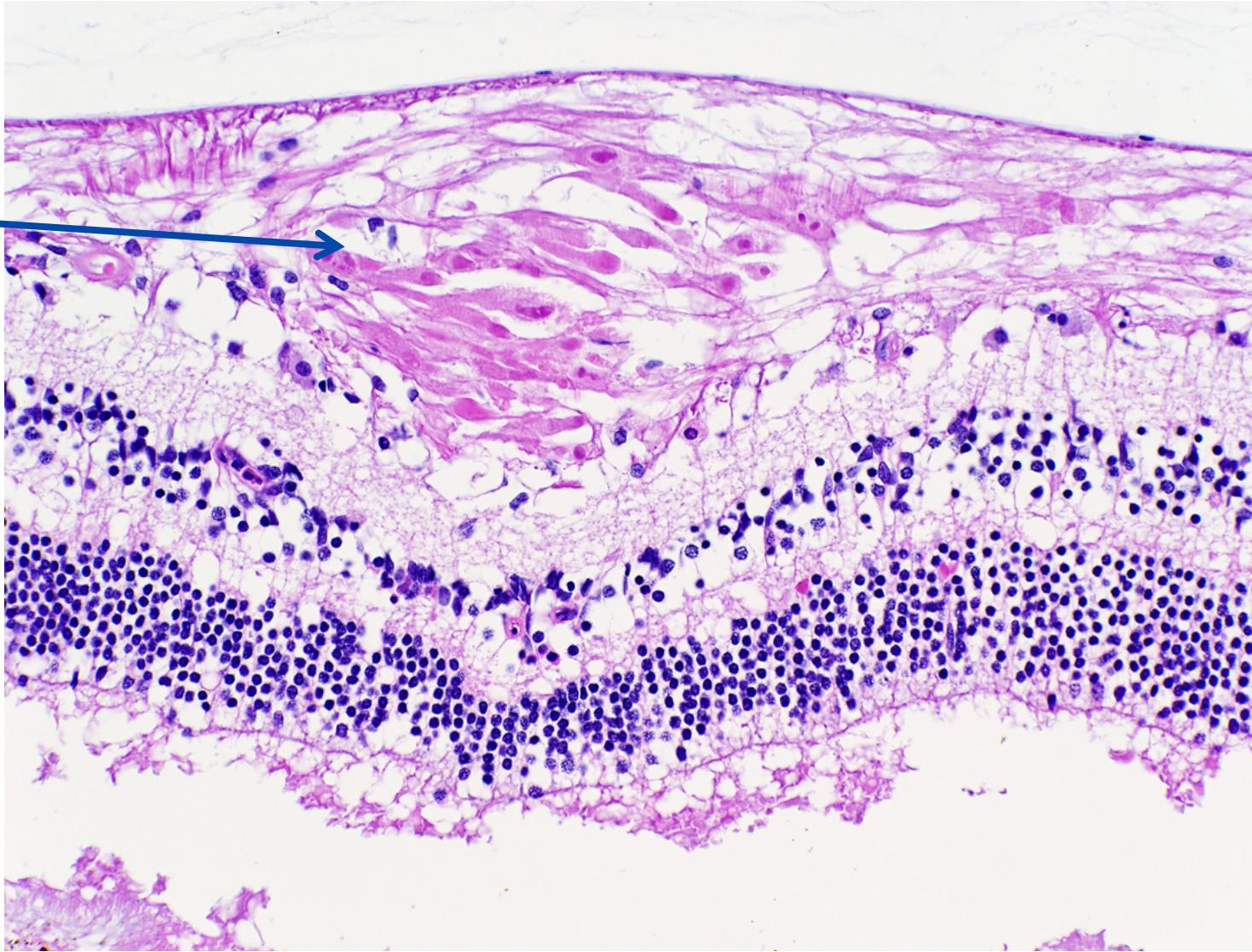
Cotton wool appears on surface of retina, commonly in people with diabetes. This is an important physical finding.

Cotton Wool Spot

A pathology resident gets this slide from autopsy. He asks you what you notice. Well... what do you notice?

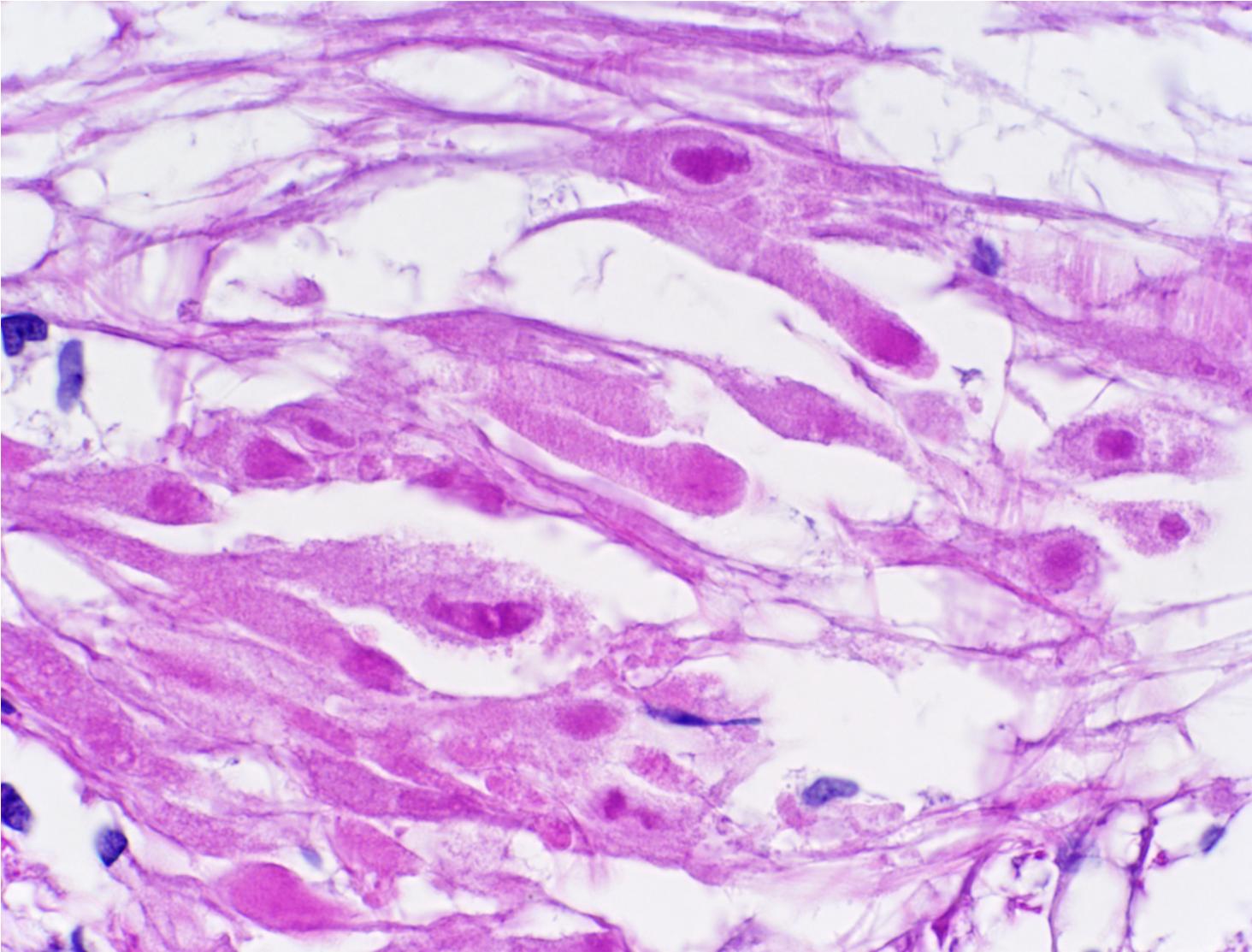


Cotton Wool Spot



You notice swelling of axons due to ischemia. This is clearly diabetic retinopathy.

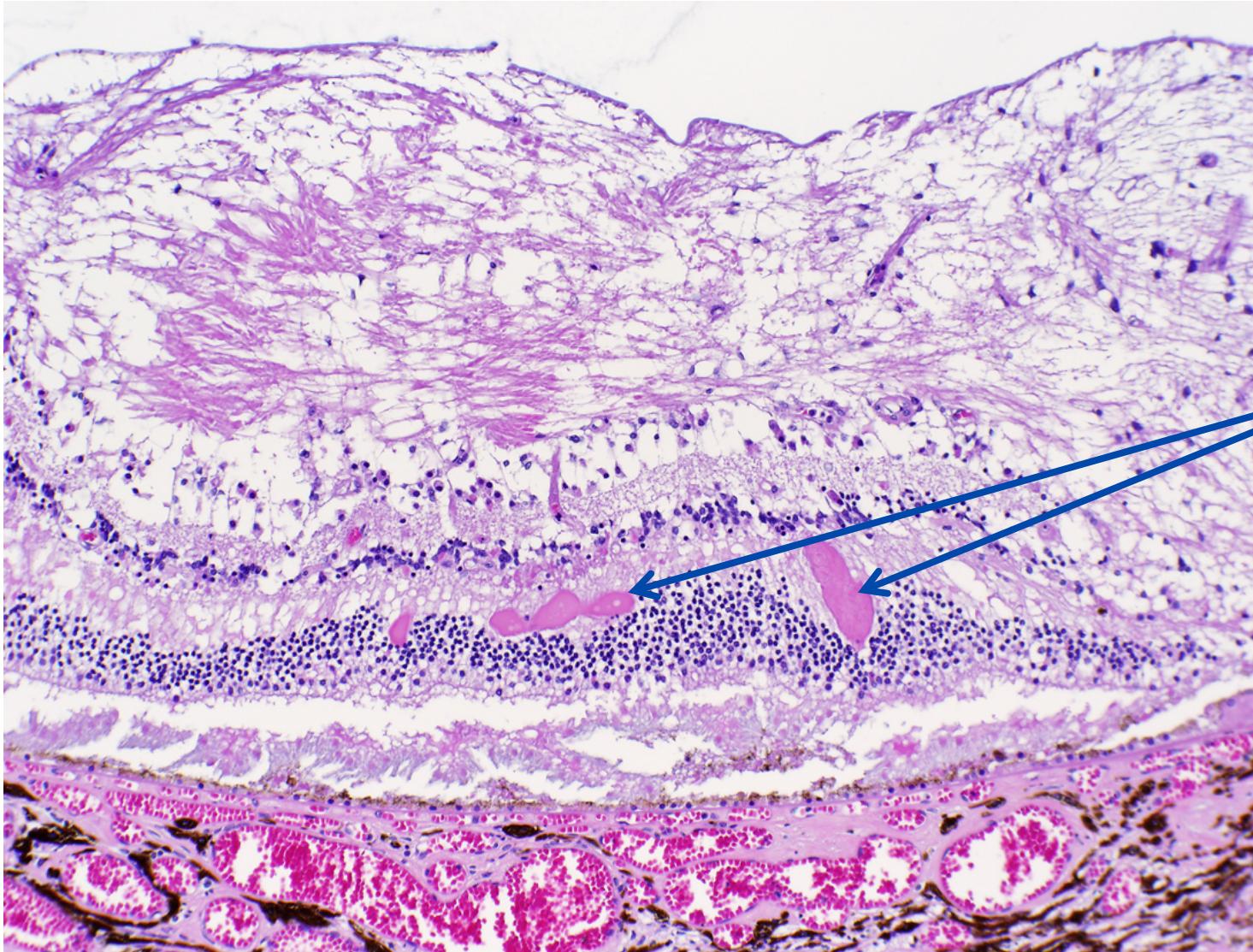
Cotton Wool Spot



He then asks:

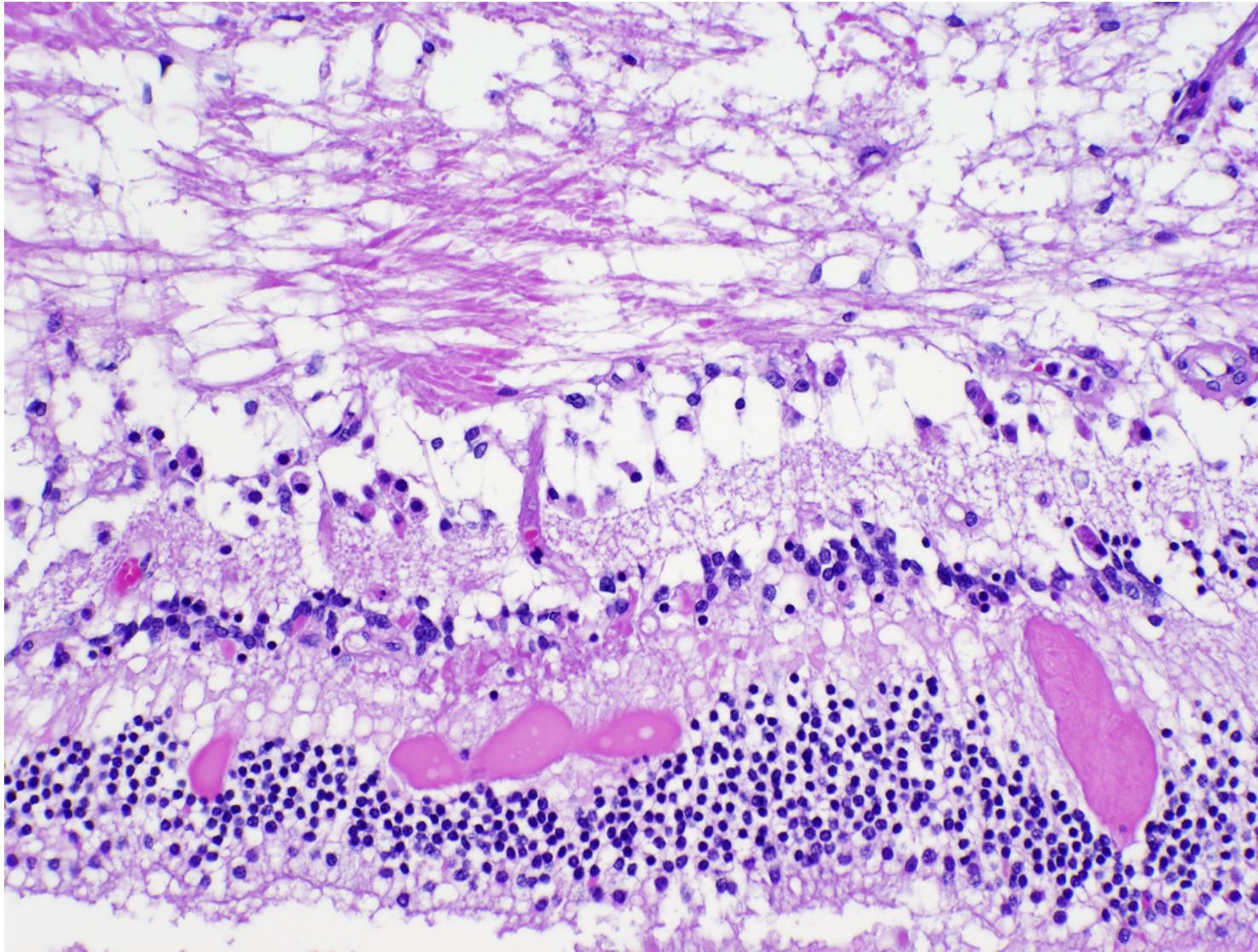
What is another classic finding associated with cotton wool spots other than axonal swelling?

Fluid Leakage (Exudate)

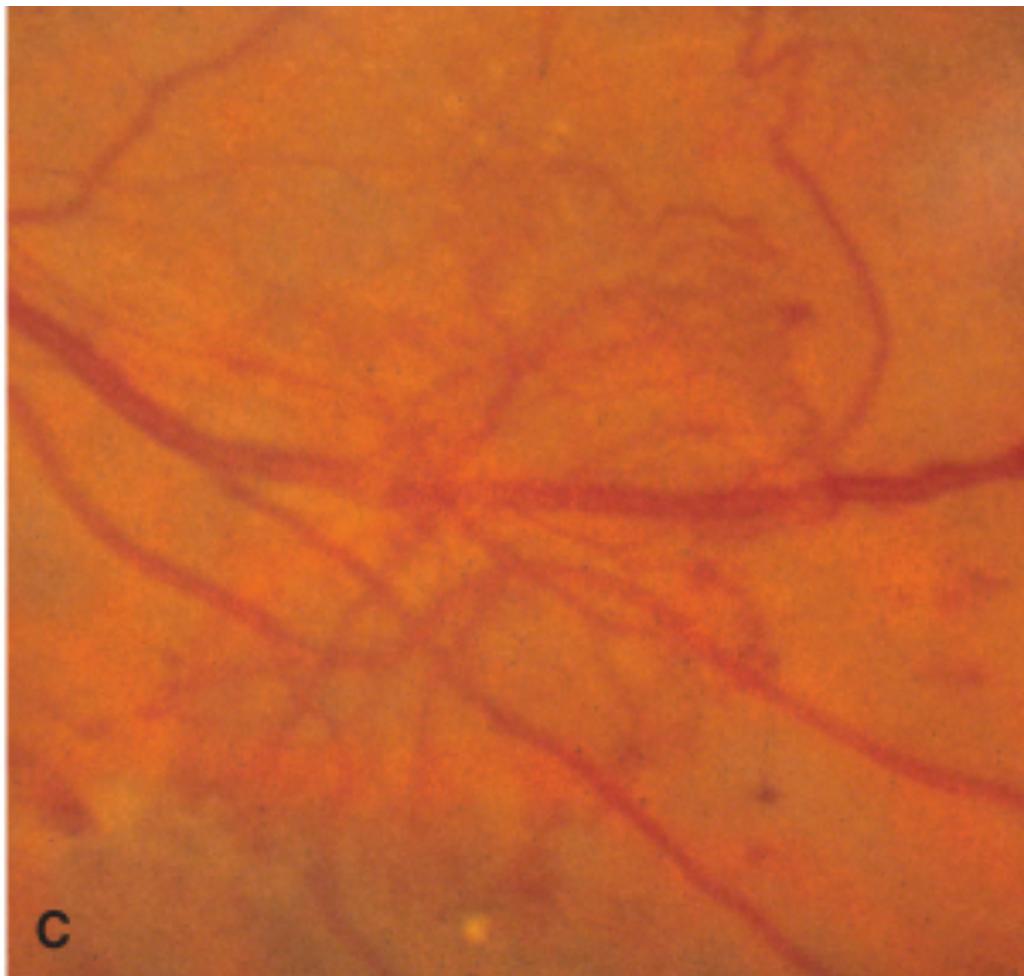


You reply:
Exudate is also common in cotton wool spots. There is a lot of fluid filled space here. This interferes with vision obvi.

Fluid Leakage (Exudate)



Proliferative Diabetic Retinopathy

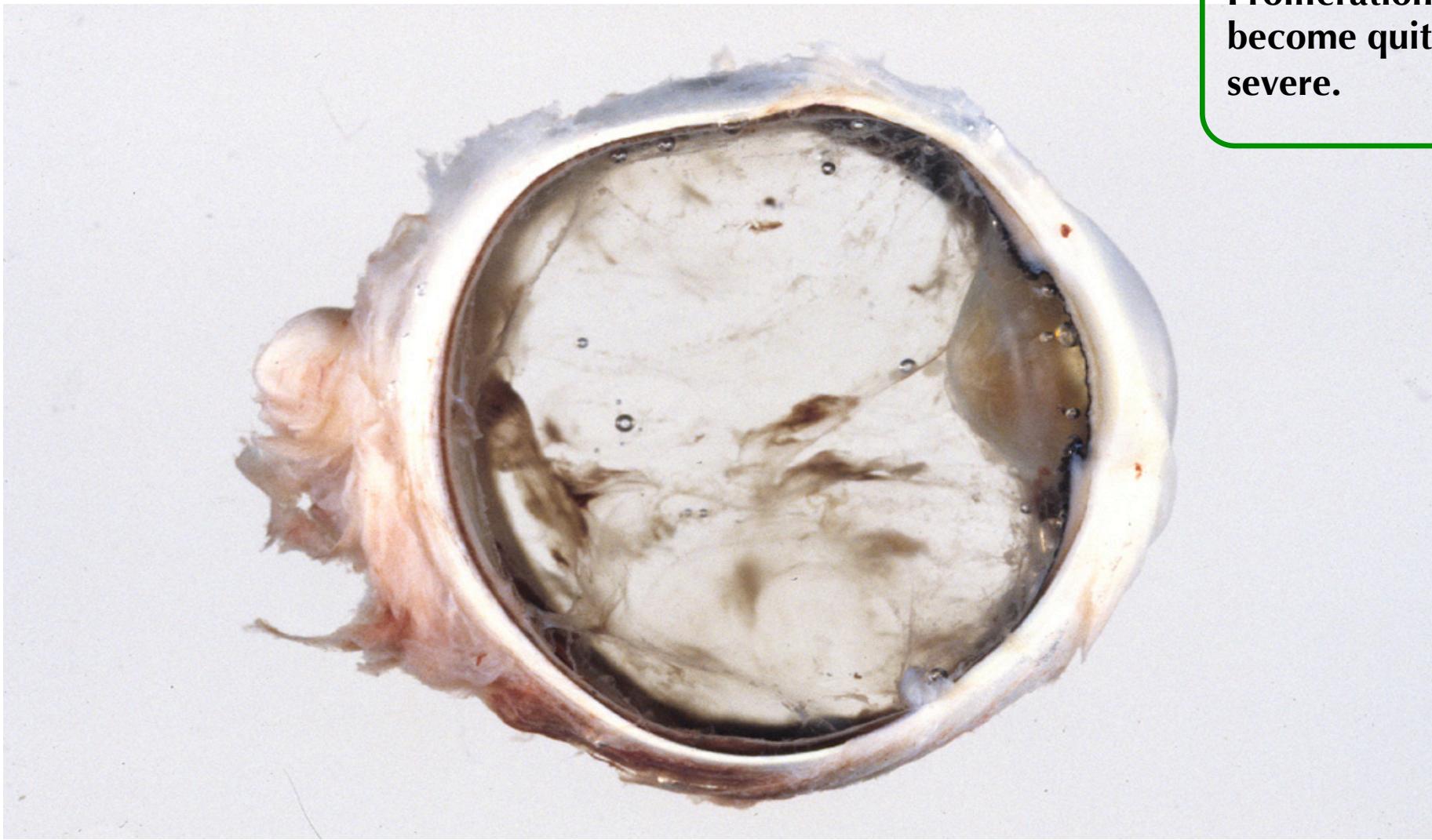


Vessels will proliferate in proliferative diabetic retinopathy.

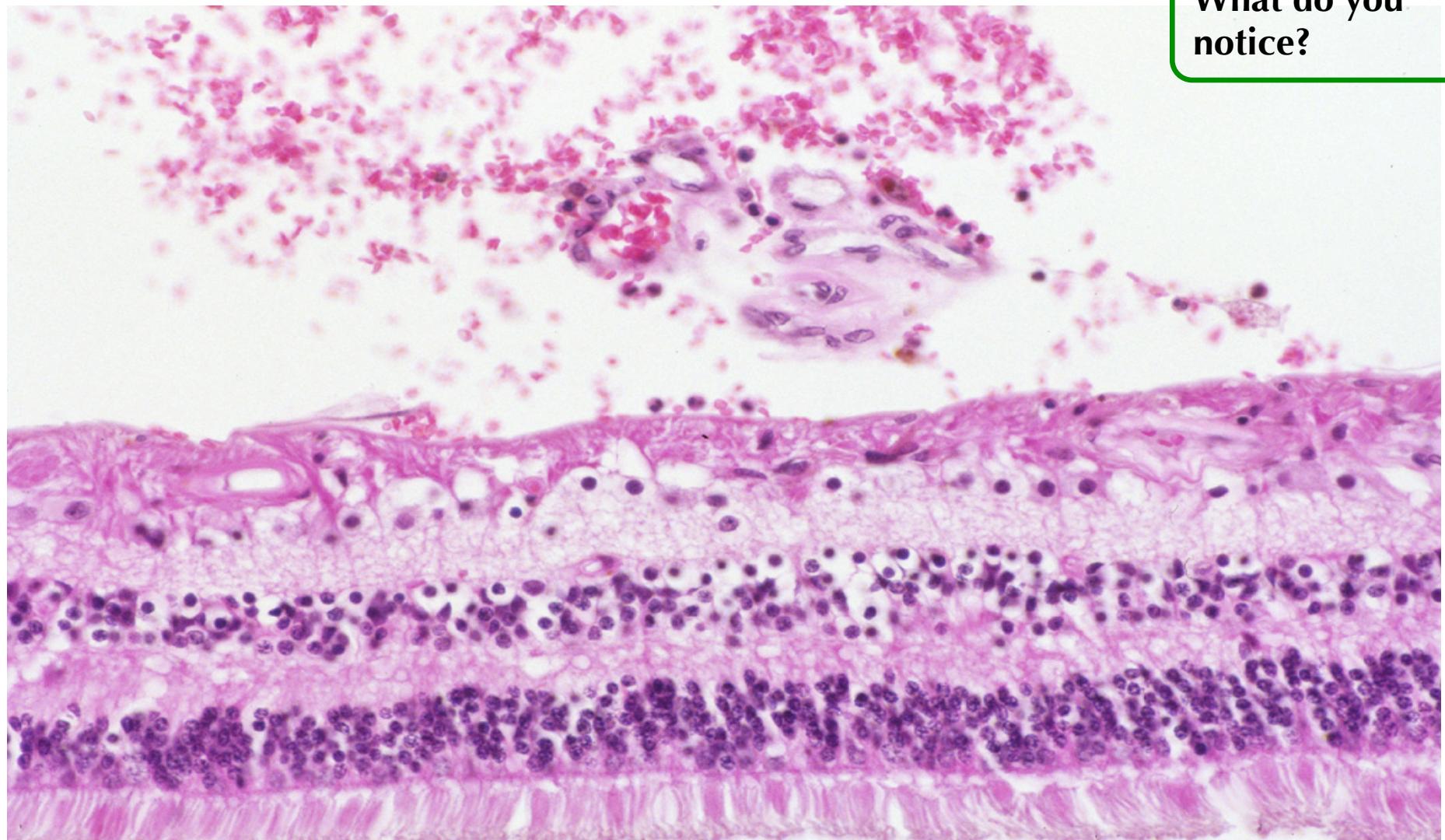
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Proliferative Diabetic Retinopathy

Proliferation can become quite severe.



Proliferative Diabetic Retinopathy



What do you notice?

On the previous slide you should have noticed the cluster of hemorrhagic vessels on the surface of the retina.

AGE-RELATED MACULAR DEGENERATION

Half of blind white persons are blind because of AMD.

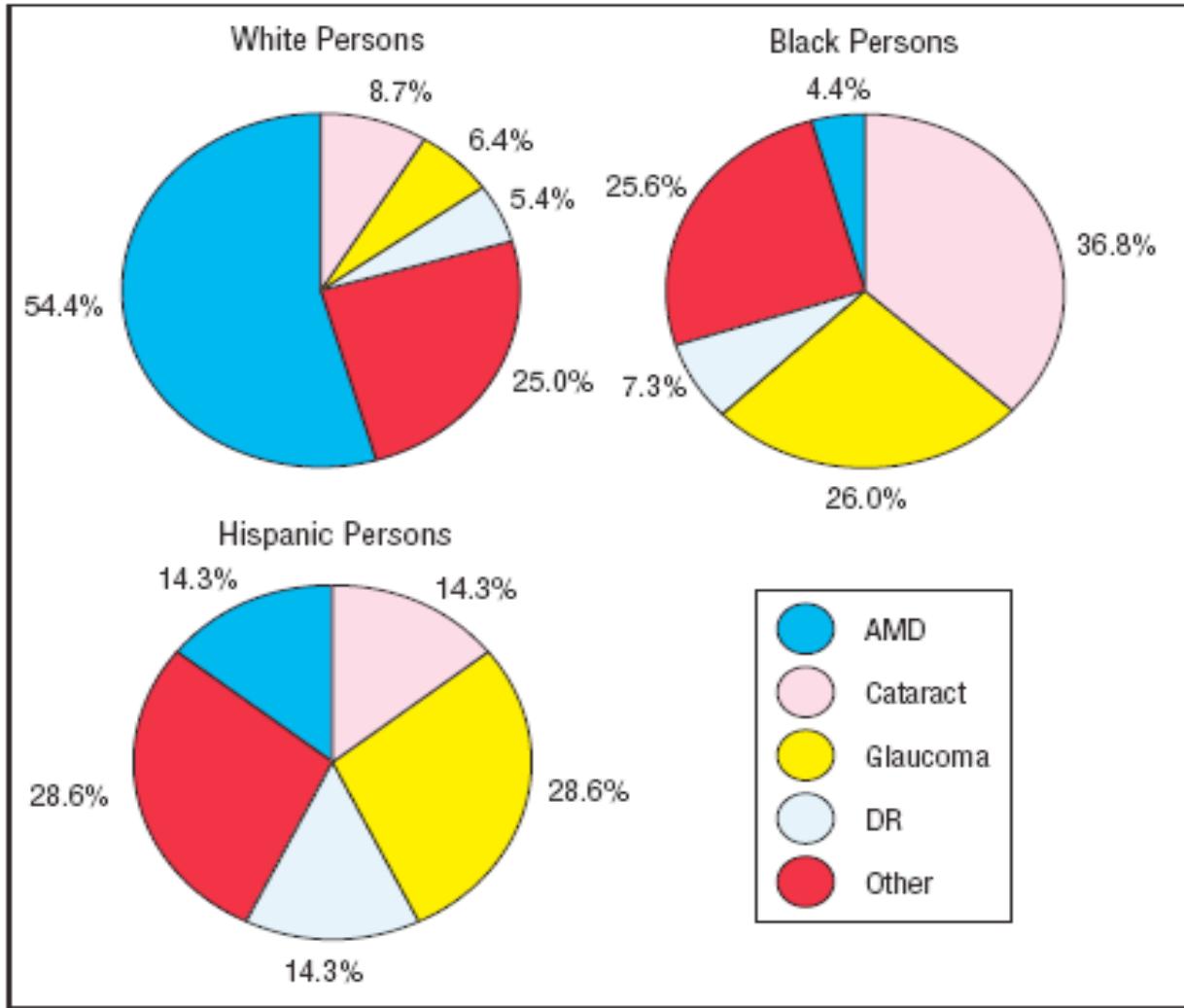


Figure 2. Causes of blindness (best-corrected visual acuity <6/60 [$<20/200$] in the better-seeing eye) by race/ethnicity. AMD indicates age-related macular degeneration; DR, diabetic retinopathy.

Age-related Macular Degeneration

- Prevalence estimated to be approximately 1.5-1.9% in developed countries, with a dramatic increase with advancing age
- Estimated that more than 15% of white women older than 80 years of age have neovascular AMD and/or geographic atrophy

Age-related Macular Degeneration

- Risk factors: Older age, female sex, white race, cigarette smoking, consumption of angiotensin-converting enzyme inhibitors
- Genetic factors: Complement factor H variants
 - » Complement factor H in circulation and on surface of cells inhibits the activation of C3 to C3a and C3b and inactivates C3b
 - » Ameliorates inflammation secondary to activation of the complement cascade

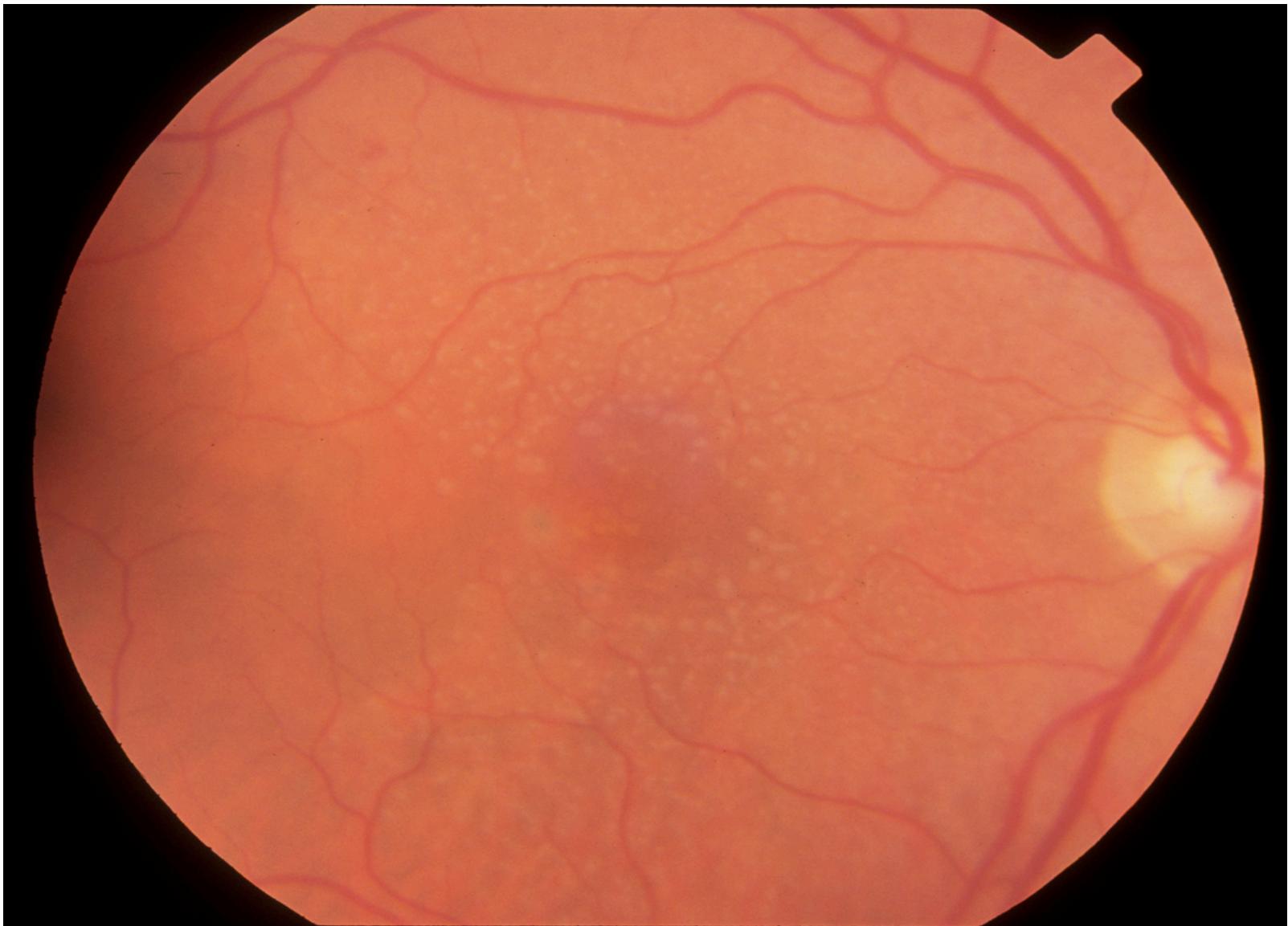
Genetics not important. Age, sex, smoking and ACEi use are important risk factors.

Age-related Macular Degeneration

- Complement factor H variants

- » Drusen are a manifestation of a chronic inflammatory stimulus
- » I have not observed any increased numbers of inflammatory cells in the choroid of eyes with AMD versus age-matched controls without AMD (unpublished observation)
- » If AMD is truly a chronic inflammatory state, then it is chemically and not cellularly mediated

Genetics not important.

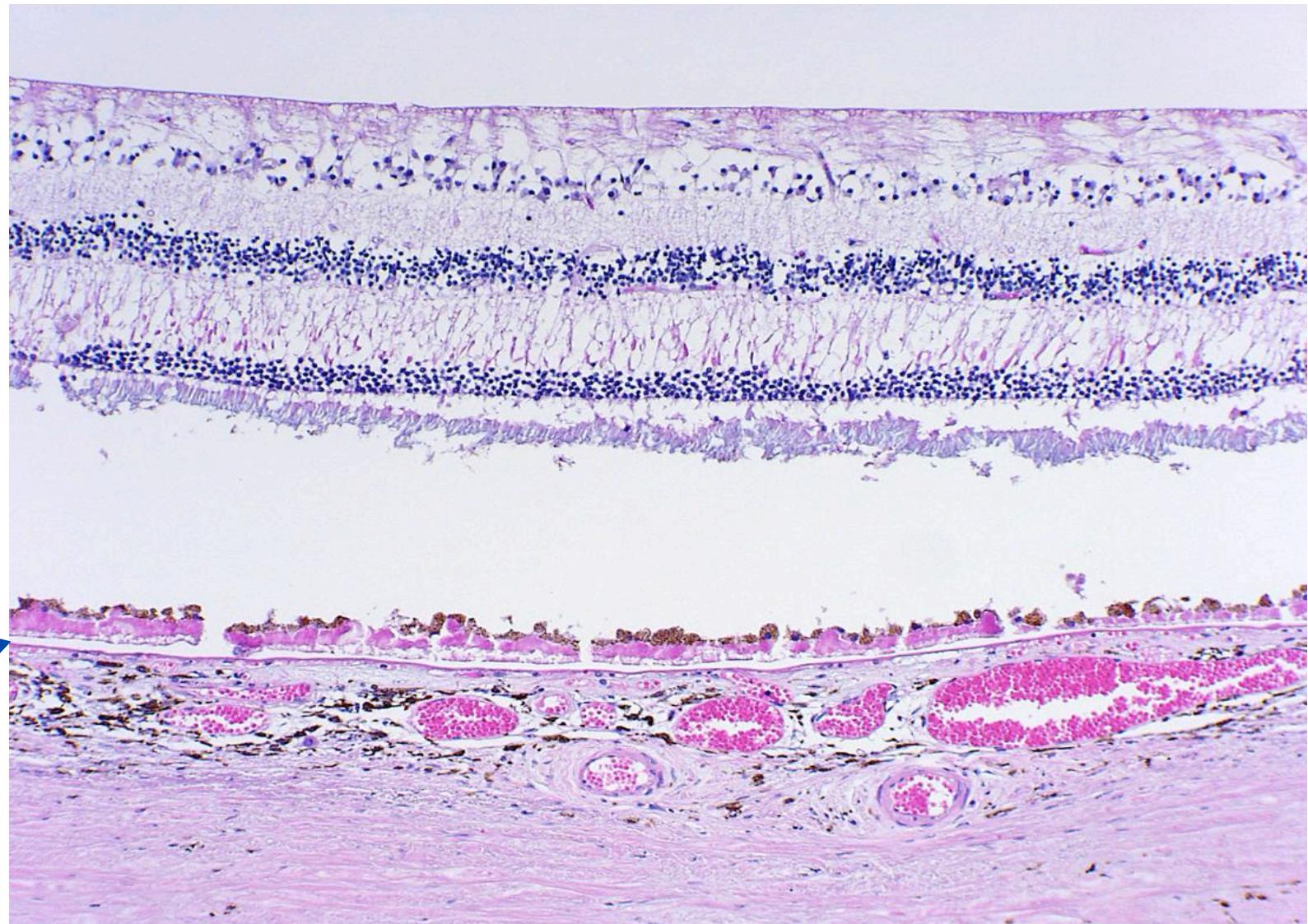


What do you
see?

On the previous slide you should have seen small white spots (called drusen) in the macula.

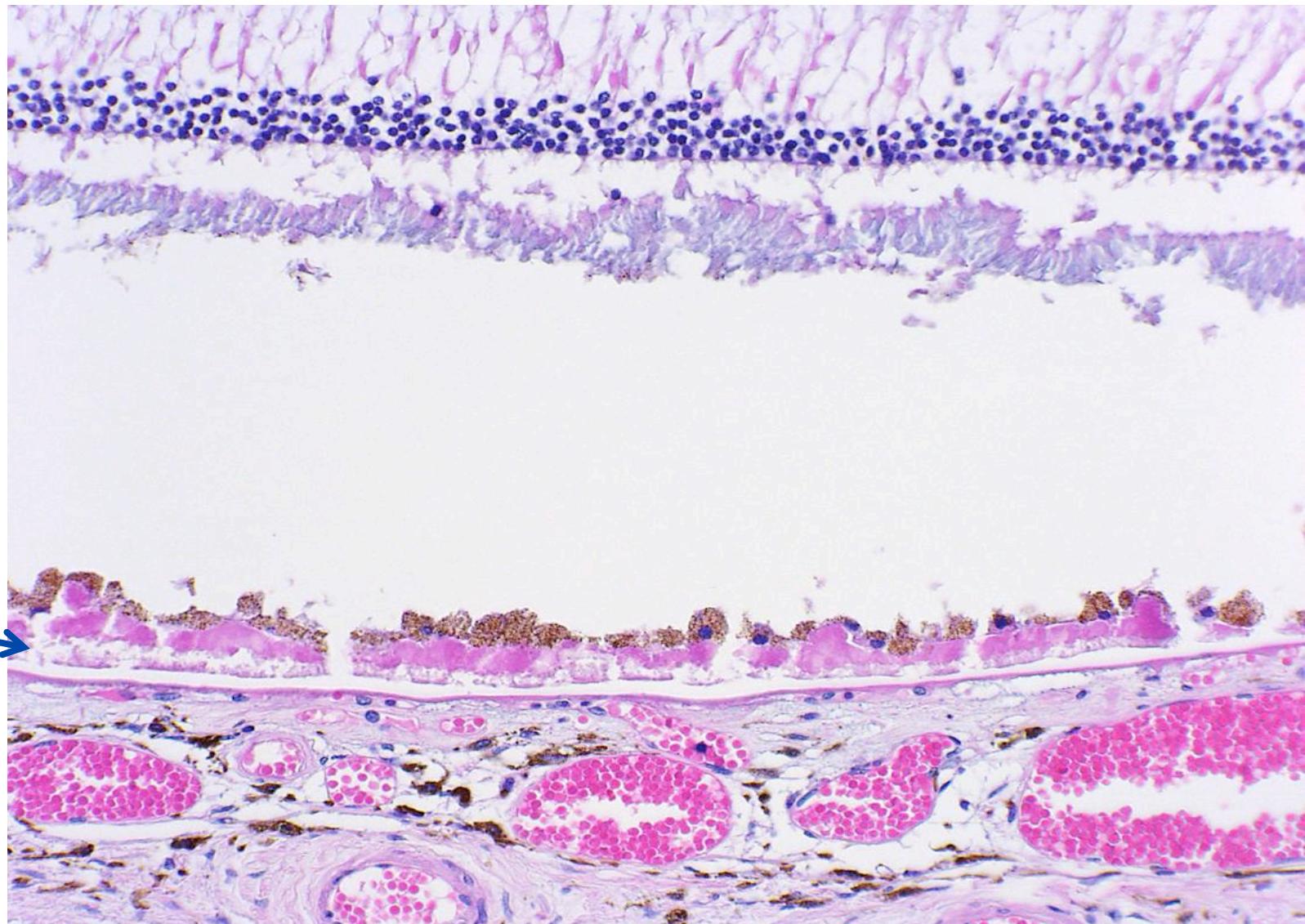
In dry AMD, there is buildup of material between RPE and Bruch's membrane

Atrophic (“dry”) AMD



Atrophic (“dry”) AMD

Material builds up
causes
photoreceptor
dysfunction.



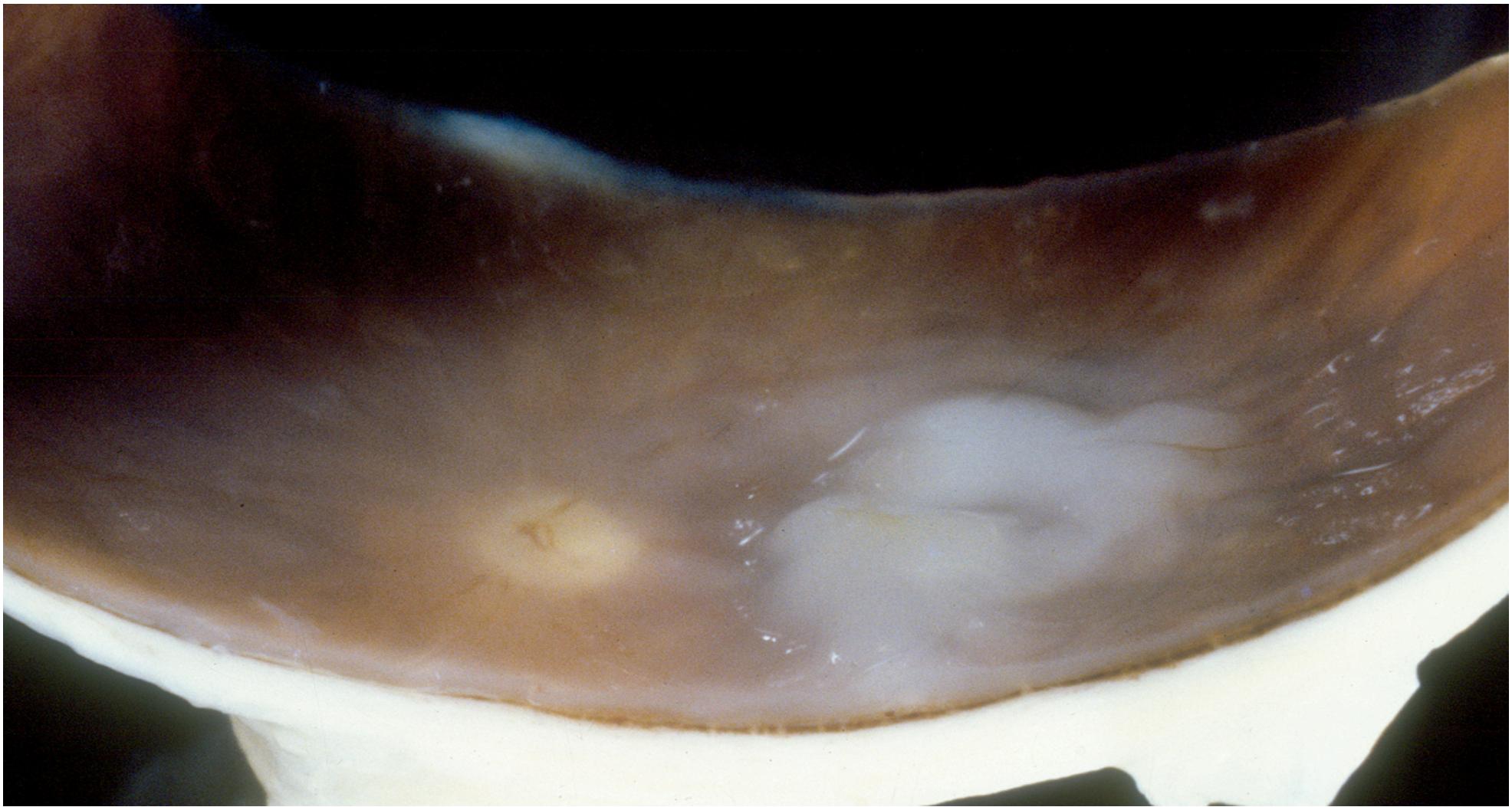
Exudative (“wet”) AMD



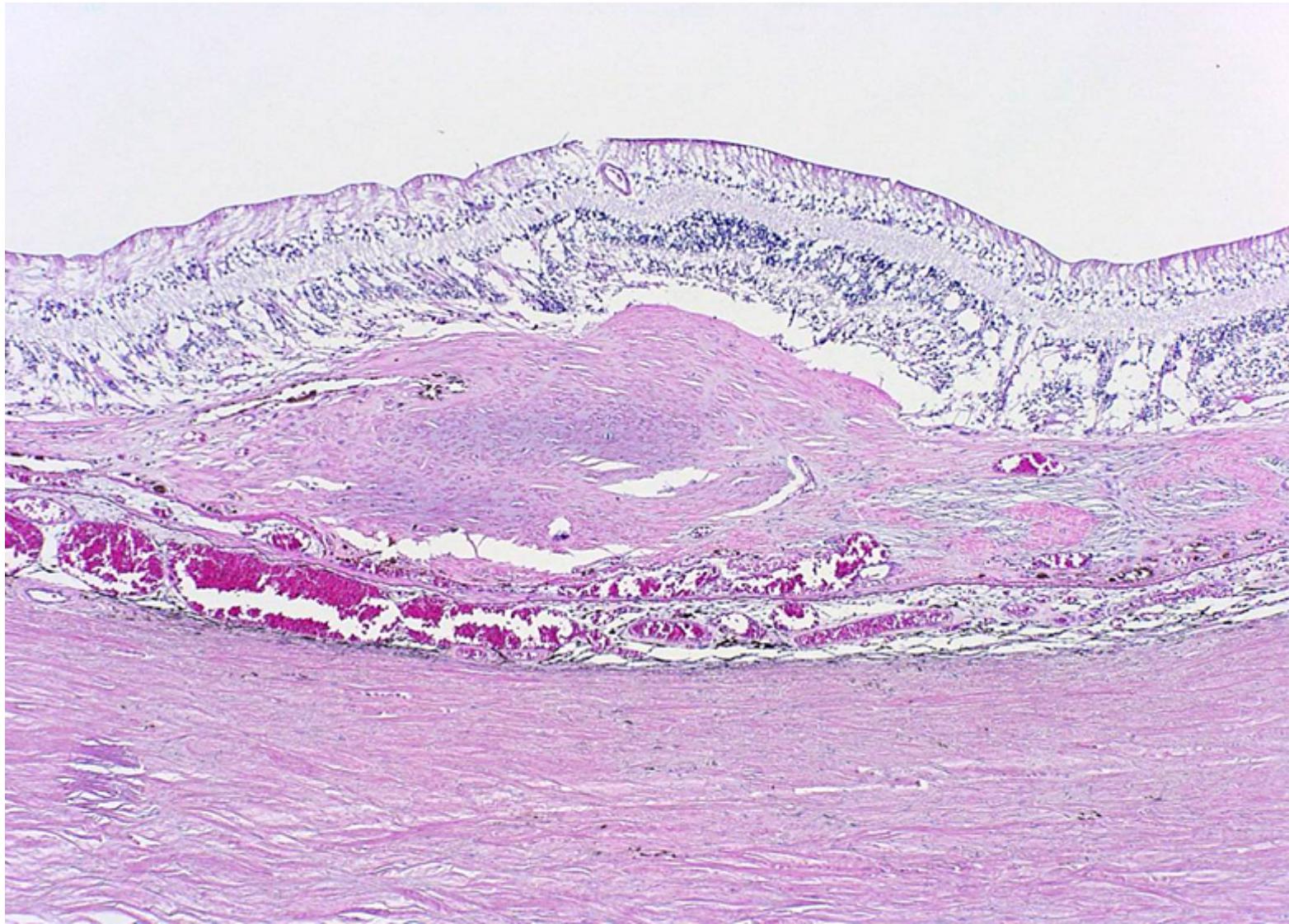
Note the color change. This is hemorrhage in the macula due to wet AMD.

Exudative (“wet”) AMD

Large fibrous
proliferation in
macula.



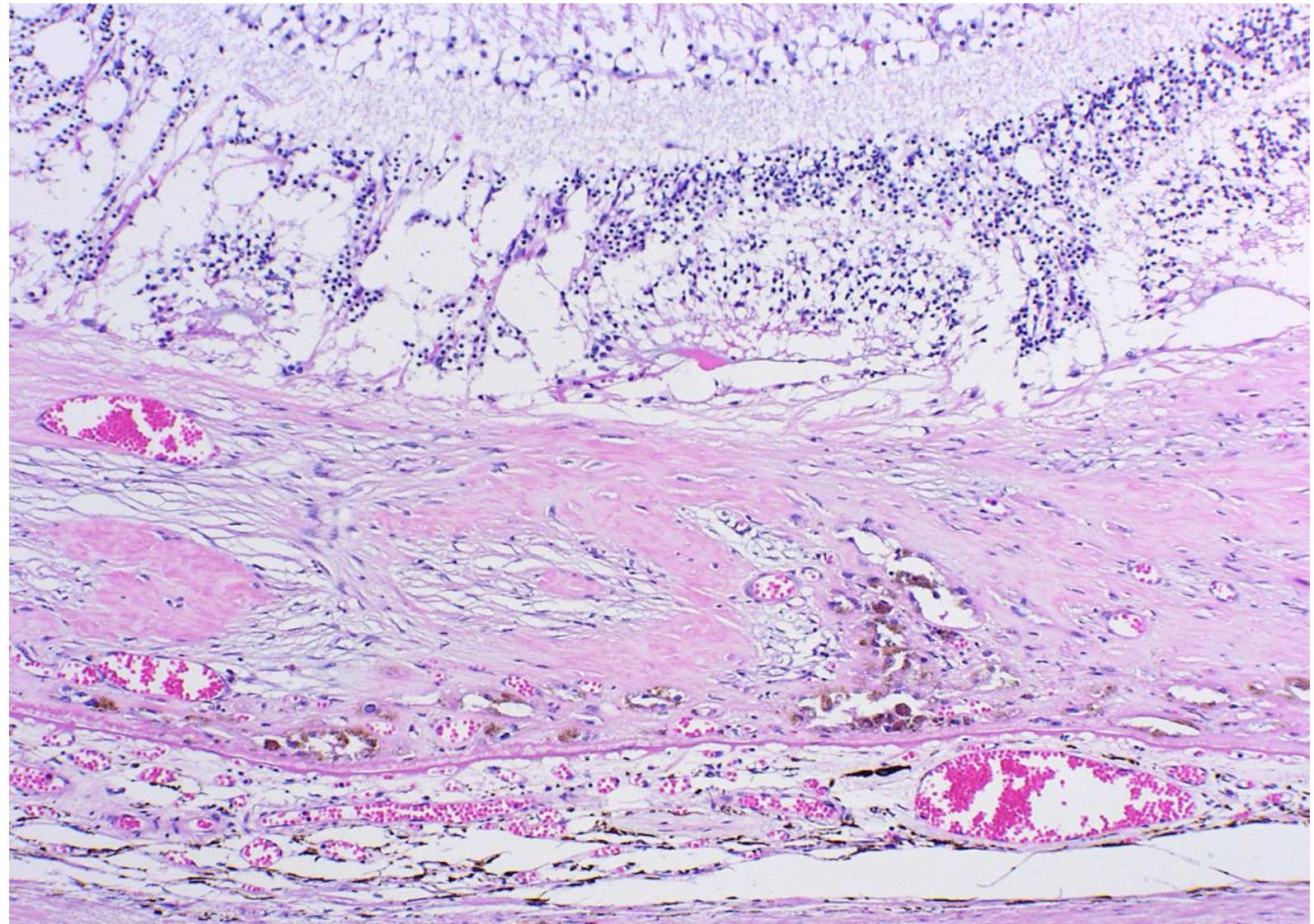
Exudative (“wet”) AMD



What do you notice?

Exudative (“wet”) AMD

Note the scar tissue located on the retina side of Bruch's membrane and the blood vessel proliferation.



PRIMARY INTRAOCULAR MALIGNANT TUMORS

Intraocular tumors are quite rare. There are two main types:

1. uveal melanoma
2. retinoblastoma.

Uvea

● Iris

- » Regulates amount of light passing through lens
 - Sphincter muscle around pupillary margin
 - Dilator muscle in peripheral iris

● Ciliary body

- » Adjusts shape of lens to focus light
- » Produces aqueous humor to nourish cornea and regulate intraocular pressure

● Choroid

- » Provides nutrients and oxygen to outer retina
- » Melanin reduces glare within the eye

What is the Uvea?
The cell layer between the sclera and retina. It includes the iris, ciliary body, and choroid (and RPE).

Uveal Melanoma

● Melanoma

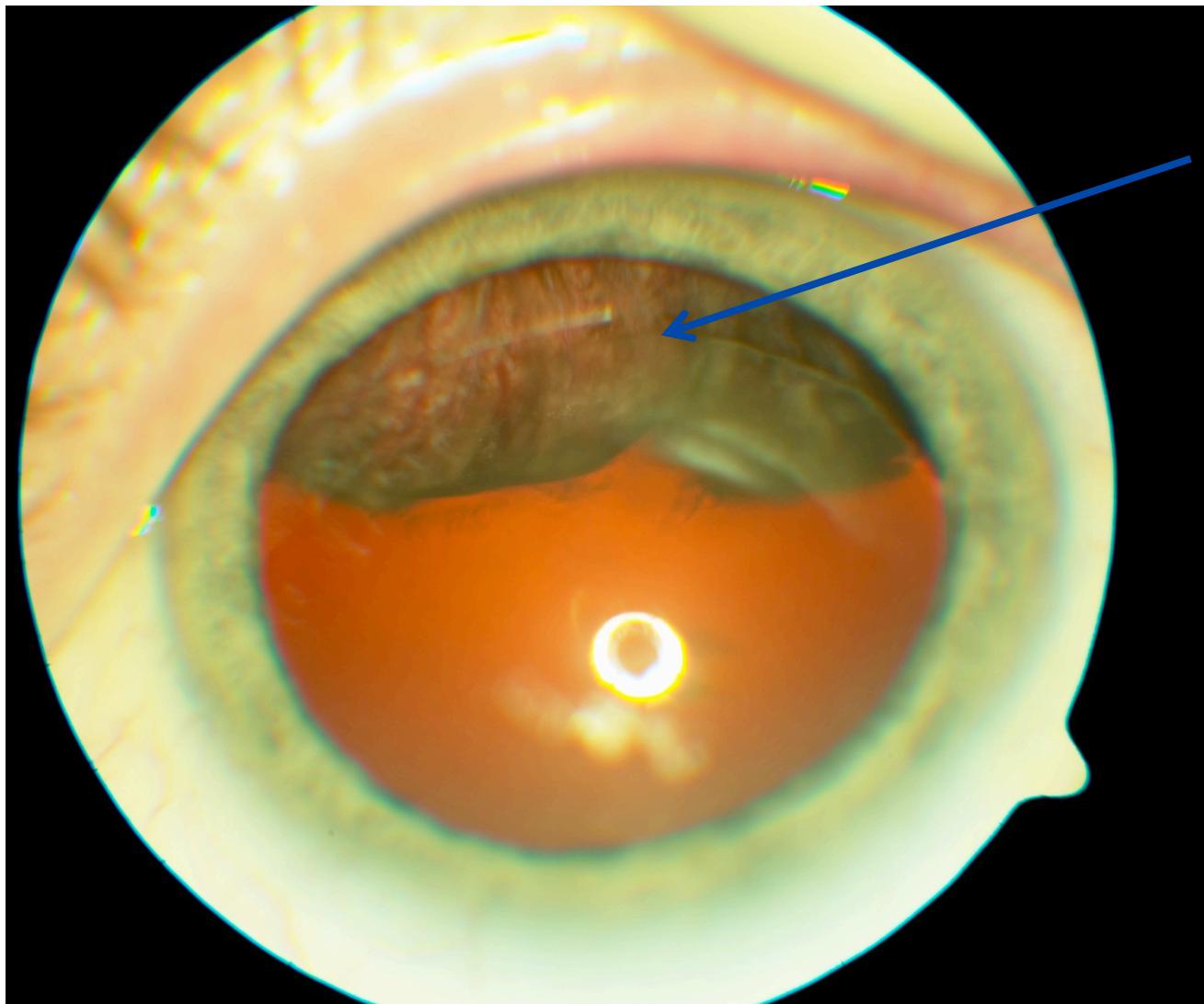
- » Uncommon Rare!
- » Incidence increases with age (>20 per million per year by age 70)
- » Choroid > ciliary body > iris
- » Major prognostic factors: location (iris tumors more indolent), tumor size, tumor cell morphology
- » Hematogenous metastasis (liver usually first)
- » May metastasize many years after treatment

Choroidal Melanoma



Note the hyperpigmented, dome-shaped mass on fundus.

Ciliary Body-Choroidal Melanoma

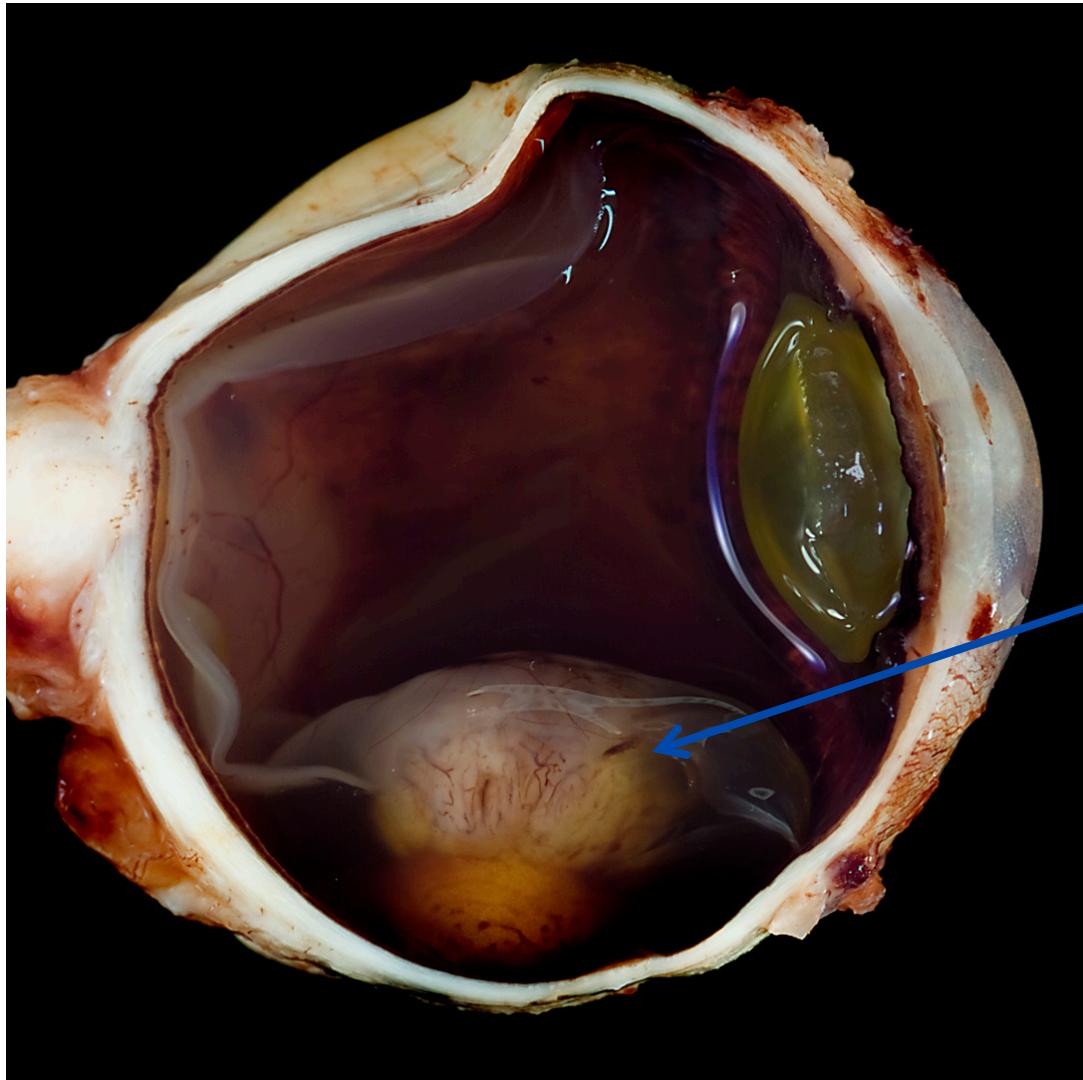


This is a dilated pupil with a uveal melanoma of the ciliary body.

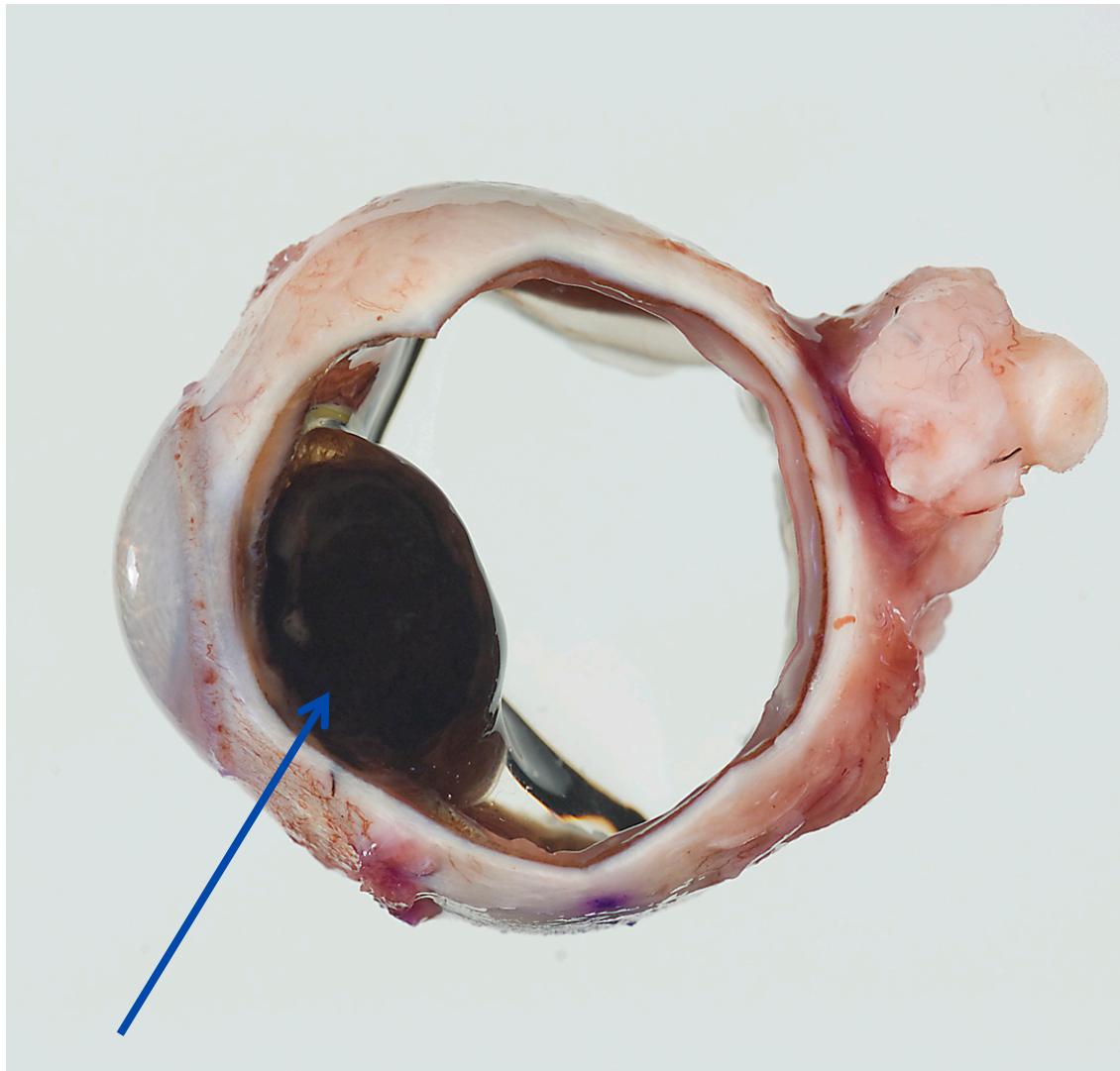
Uveal Melanoma – Extraocular Extension



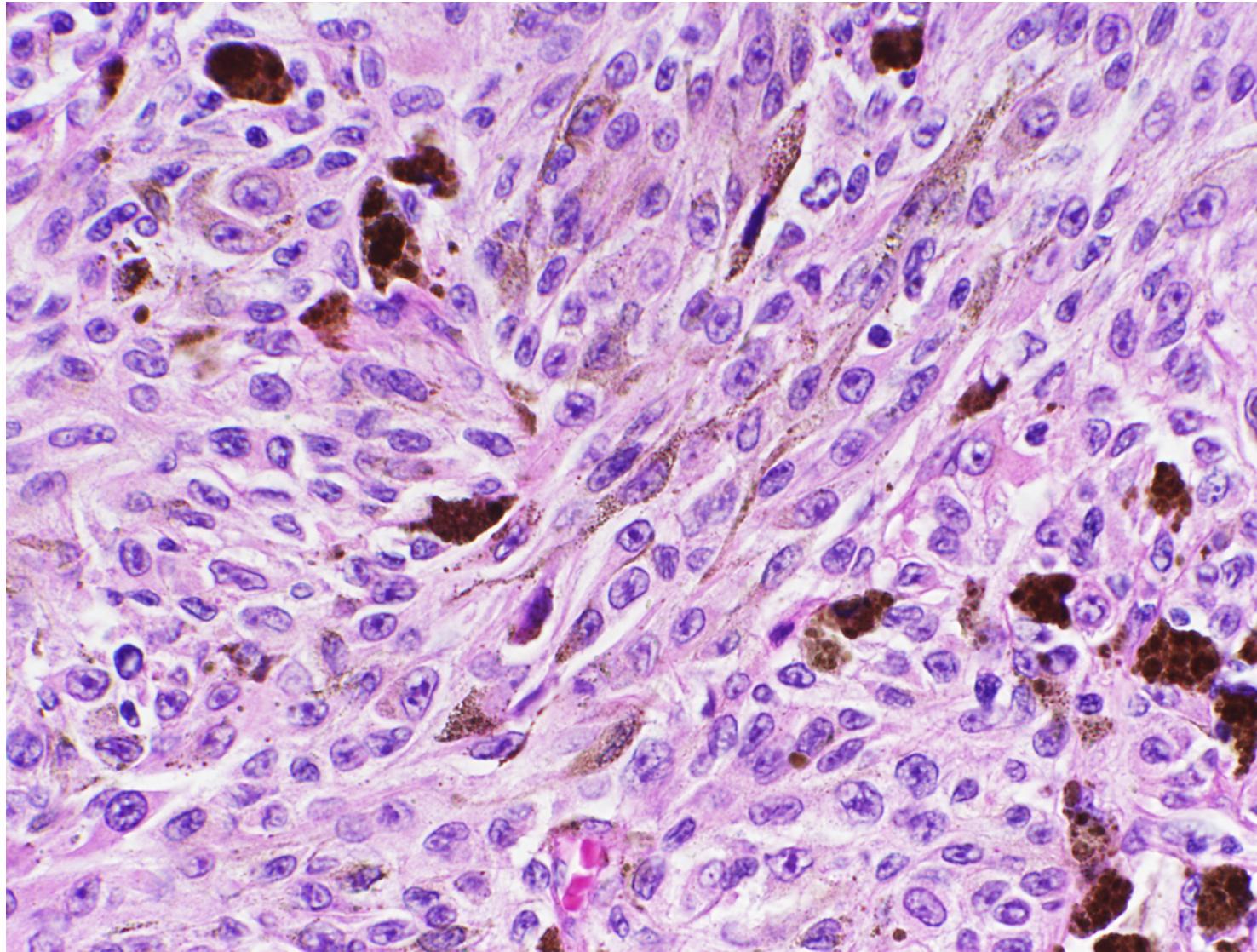
Choroidal Melanoma



Ciliary Body Melanoma



Choroidal Melanoma

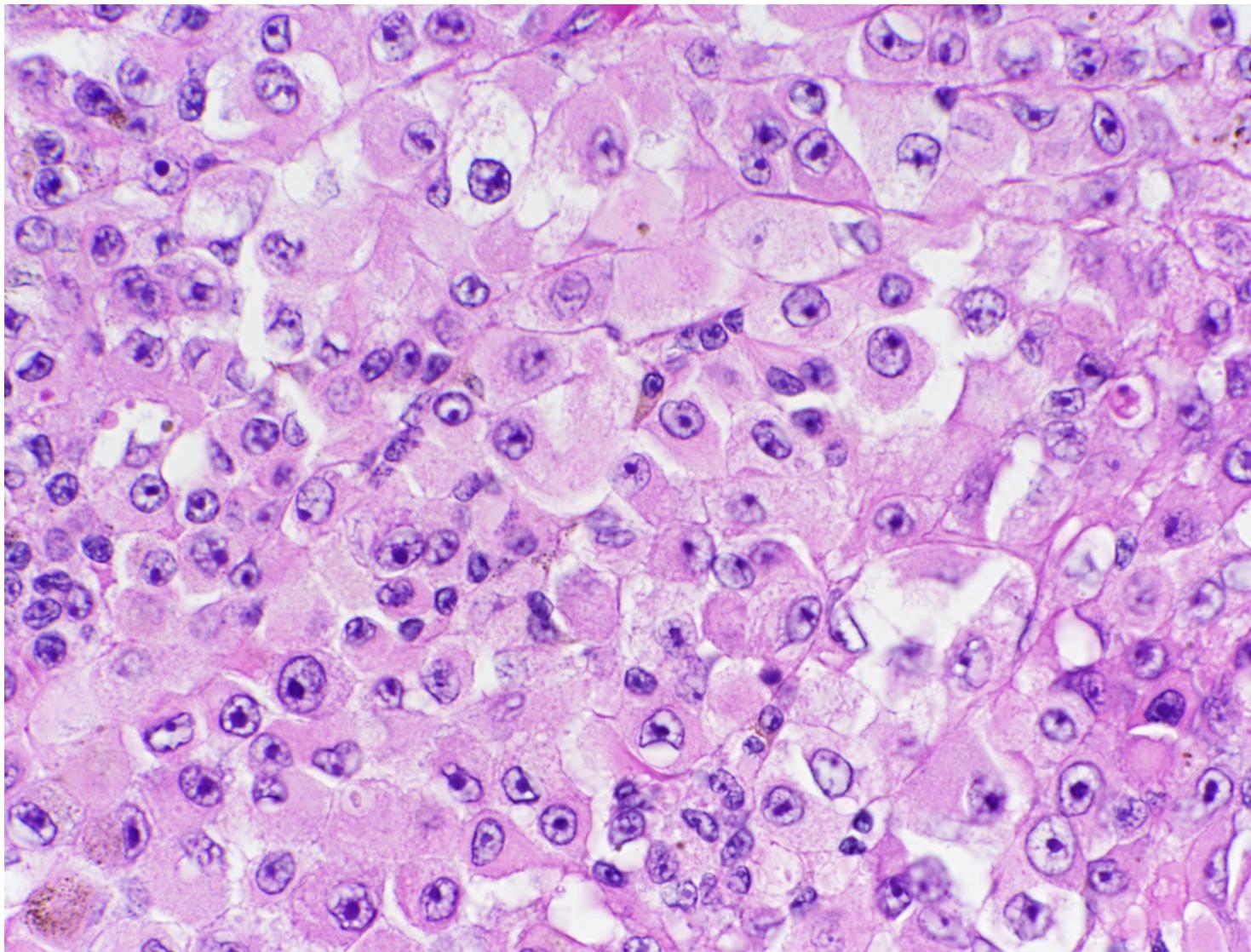


Spindle tumor cells

Most uveal melanoma is a mixture of spindle and epithelioid tumor cells.

Spindle tumor cells:
Oblong cells,
small nucleoli;
lots of melanin

Choroidal Melanoma



Epithelioid tumor cells

Epithelioid tumor cells:
Larger nucleoli,
epithelioid shape cells.
Carries a worse prognosis.

Retinoblastoma

- Most common primary intraocular malignancy of children
- By far the most common retinal neoplasm
- Cell of origin is neuronal
- ≈40% of cases in children with germ-line mutation of one *RB* allele
 - » First tumor suppressor gene discovered
 - » May be bilateral
 - » “Trilateral” retinoblastoma: tumors in both eyes along with a pinealoblastoma

Retinoblastoma

- Pathology of hereditary and sporadic types of retinoblastoma is the same
- Tumor cells may be undifferentiated
 - » Small, round cells with hyperchromatic nuclei
- Well-differentiated tumors have photoreceptor differentiation
 - » Flexner-Wintersteiner rosettes ←
 - » Fleurettes (rare in my experience) ←

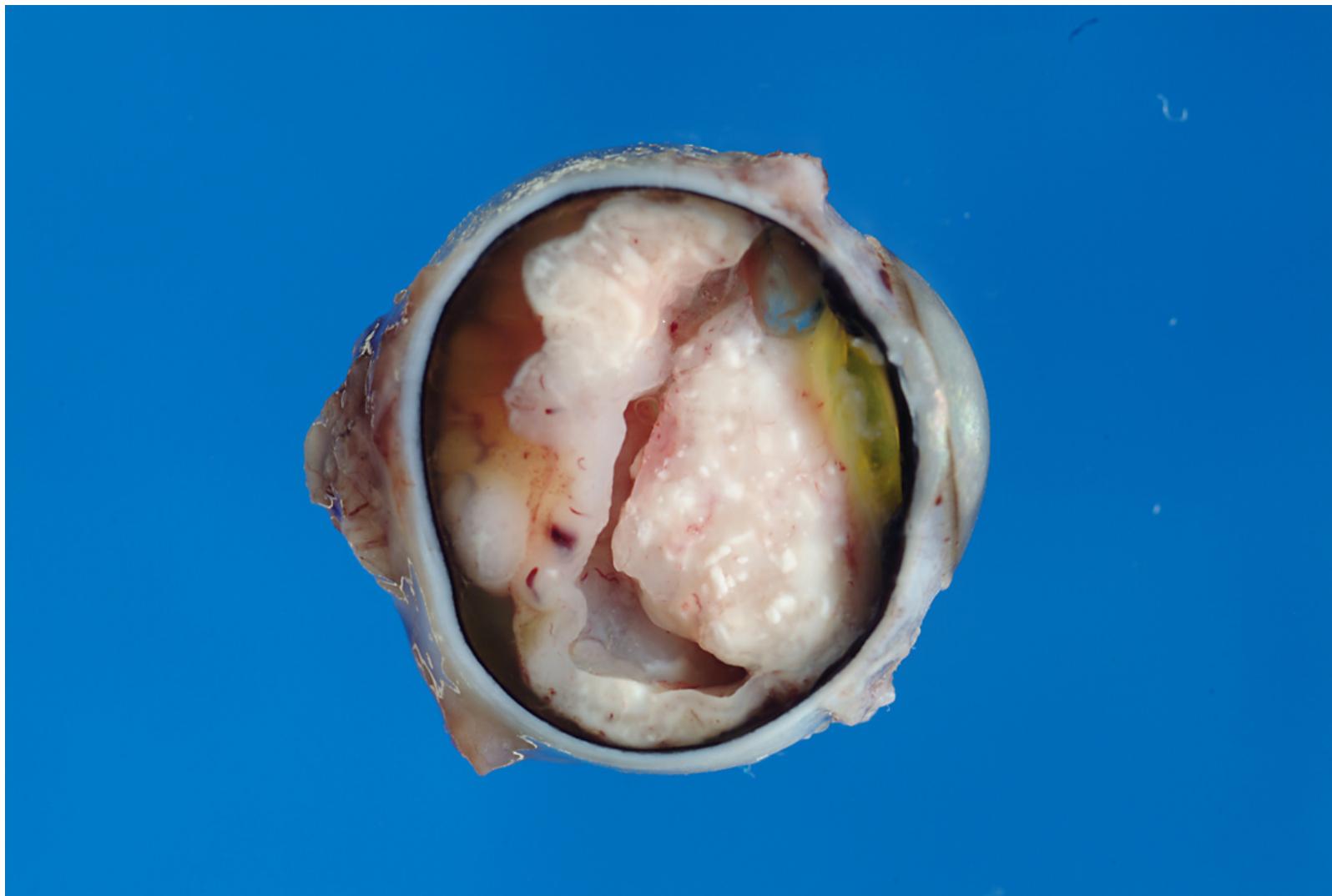
These do not affect prognosis, but it gives pathologists something to do.

Retinoblastoma

● Prognostic factors

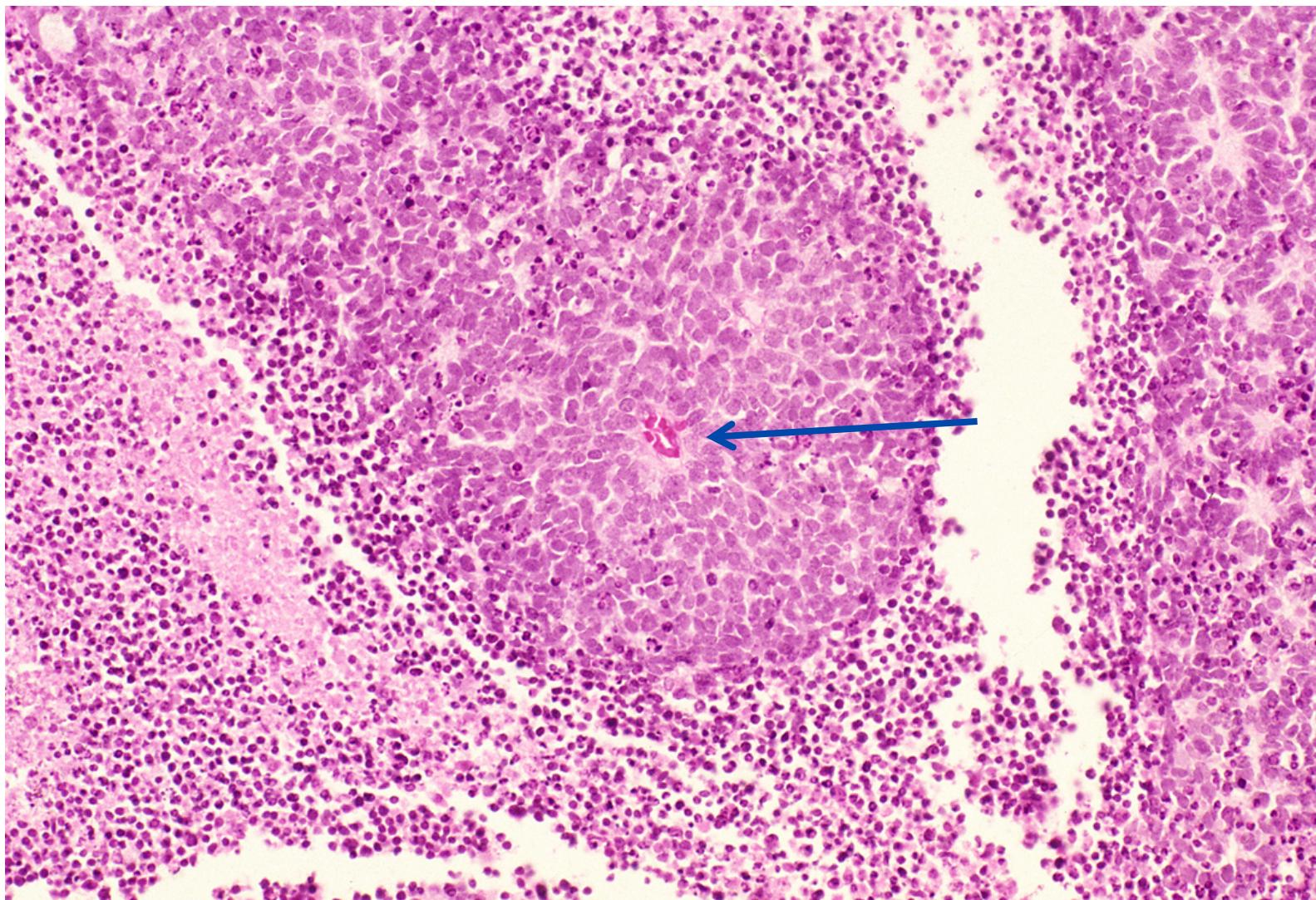
- » Adversely affected by:**
 - Extraocular extension**
 - Invasion along the optic nerve**
 - Possibly by choroidal invasion**
- » Not affected by degree of tumor differentiation**

Retinoblastoma



Typical Rb:
multi-lobular,
very large at
presentation
with calcified,
white specks.

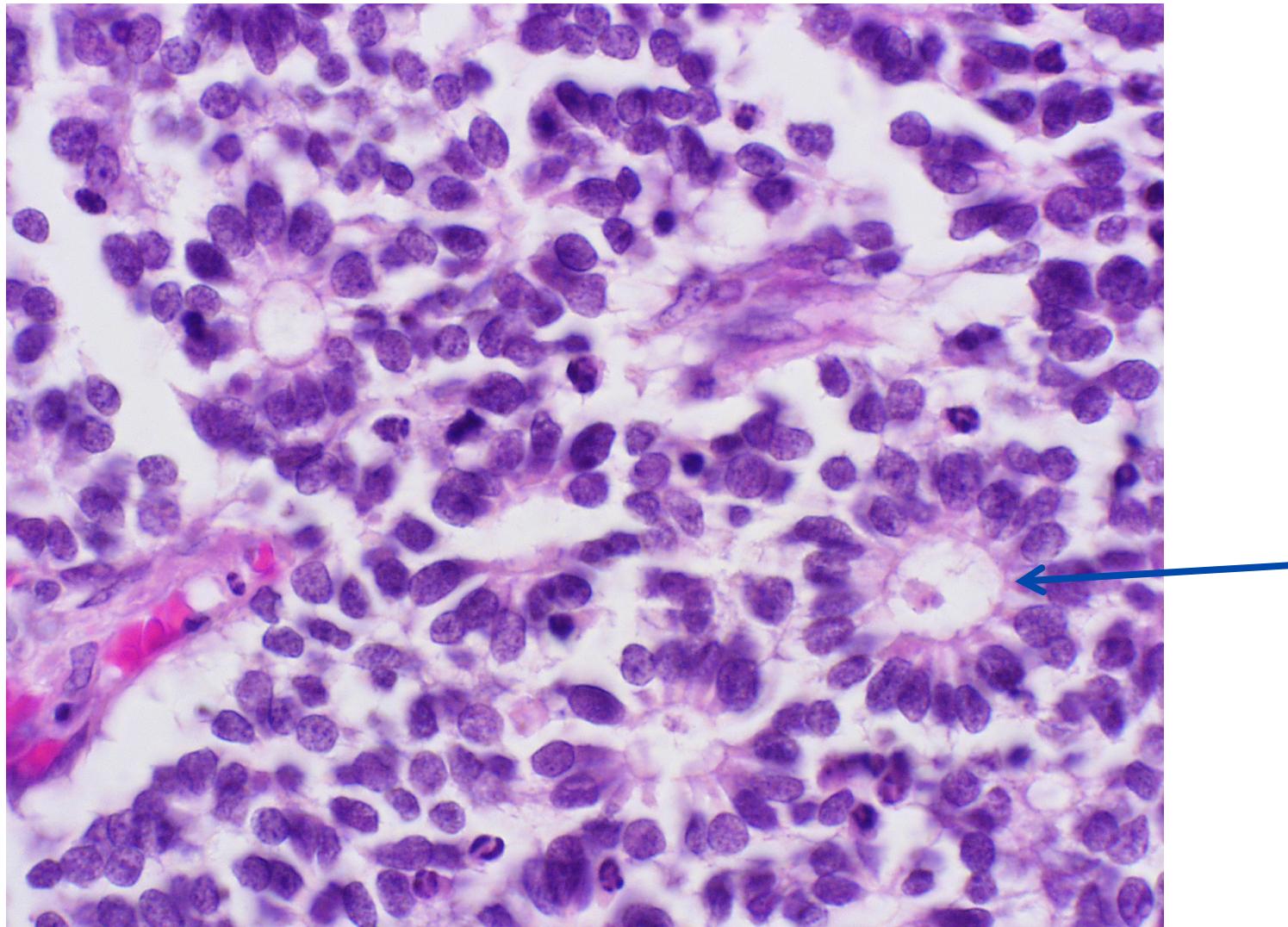
Retinoblastoma



Tumor necrosis

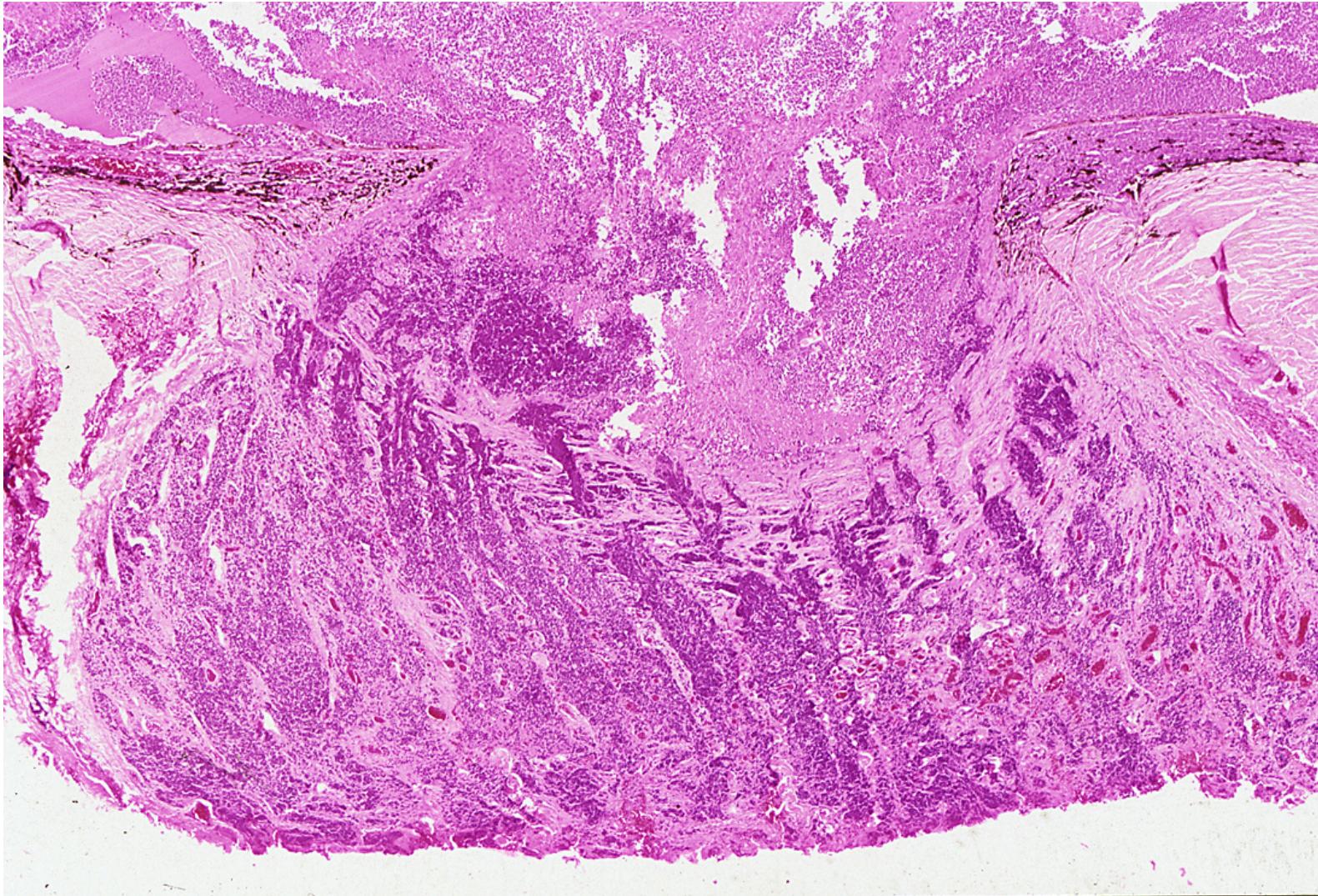
Necrosis is very prevalent in Rb.
Note the survival of cancer cells around artery.

Retinoblastoma



Flexner-Wintersteiner rosettes

Retinoblastoma



How far back does the tumor go into the optic nerve? This informs prognosis.

Optic Nerve Invasion by Tumor

Write down the answers to these questions. Answers to follow.

- 1. A patient presents with blindness. What is on the differential?**
- 2. What is the role of the RPE?**
- 3. A patient presents with cotton wool spots. What is the likely diagnosis?**
- 4. What canal drains aqueous humor?**
- 5. A patient presents with a pale and invaginated optic disc. What is the diagnosis?**

Image Challenge

Just for fun – not tested.

Q: What is the diagnosis?

1. Anterior uveitis
2. Carotid cavernous sinus fistula
3. Graves' disease
4. Orbital lymphoma
5. Scleral rupture



Image Challenge

Q: What is the diagnosis?

Answer:

2. Carotid cavernous sinus fistula

Just for fun – not tested.

The patient had inferior chemosis and conjunctival injection. Contrast-enhanced computed tomography of the orbit showed a dilated left superior ophthalmic vein, and angiography confirmed the presence of a carotid cavernous sinus fistula. The patient had complete resolution following embolization of the fistula.

Read More: *N Engl J Med* 2011;364:e15



Answers to mini quiz

- 1. Cataracts, AMD, glaucoma, diabetic retinopathy**
- 2. Prevent light reflection, recycle spent photoreceptor discs, blood-retina barrier**
- 3. Diabetic retinopathy**
- 4. Schlemm's**
- 5. Glaucoma**