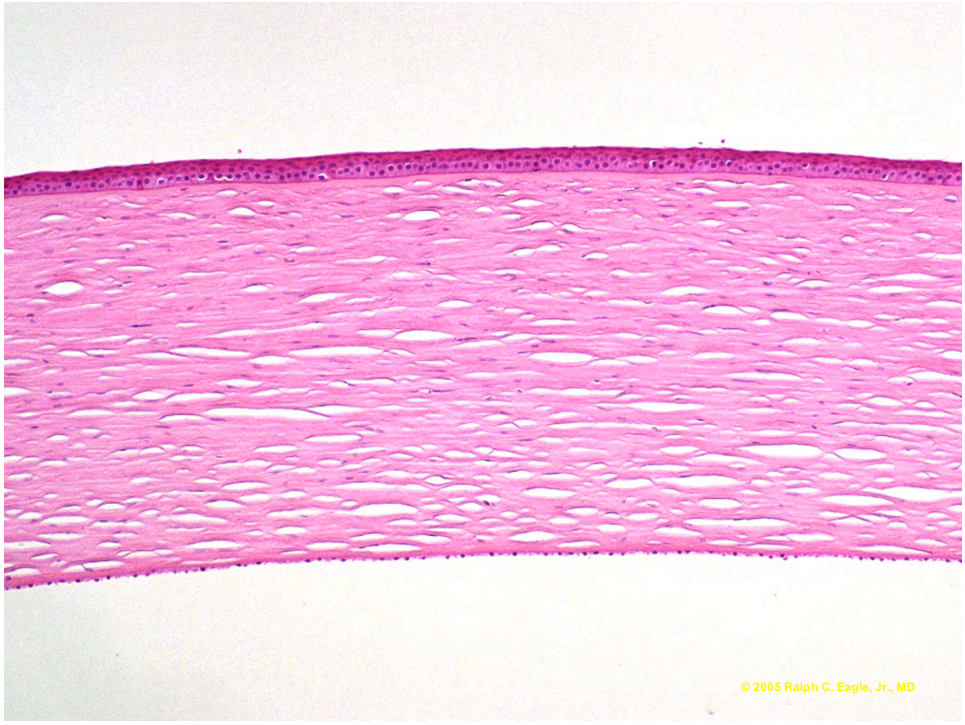
Illustrated Eye Pathology Outline
Part 3

CORNEA



Congenital Lesions

Microcornea <11mm

Megalocornea >13mm

X-linked inheritance, deep anterior chamber, no dm ruptures

Cornea Plana

Bilateral, familial (autosomal dominant or recessive)

Corneal flattening with peripheral opacification

Sclerocornea

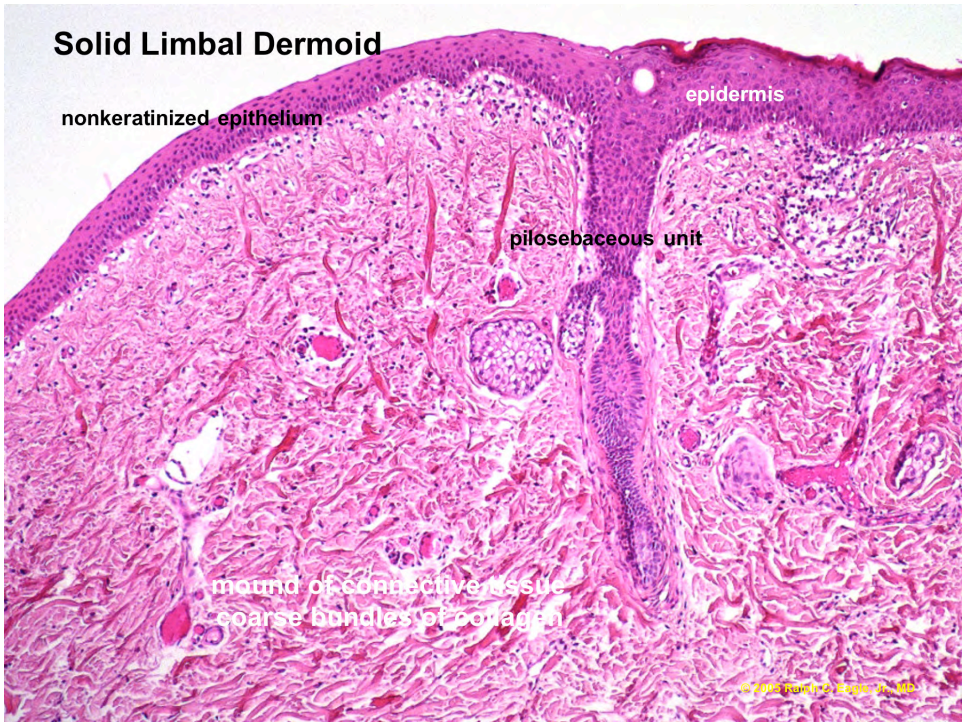
Cornea diffusely scarred and vascularized resembling sclera

No hereditary pattern

Epithelium thickened, Bowman's absent, anterior third of stroma

Scarred and vascularized, Descemet's membrane very thin.

Solid epibulbar dermoids and complex choristomas (see conjunctiva)



Goldenhar's syndrome (hemifacial microsomia with epibulbar dermoids)
Axenfeld/Rieger syndrome
(dysembryogenesis of the angle, "mesodermal dysgenesis", angle cleavage syndromes) AD, several genes- (PITX3, PITX2, FOXC1)
A **clinical spectrum** that includes:

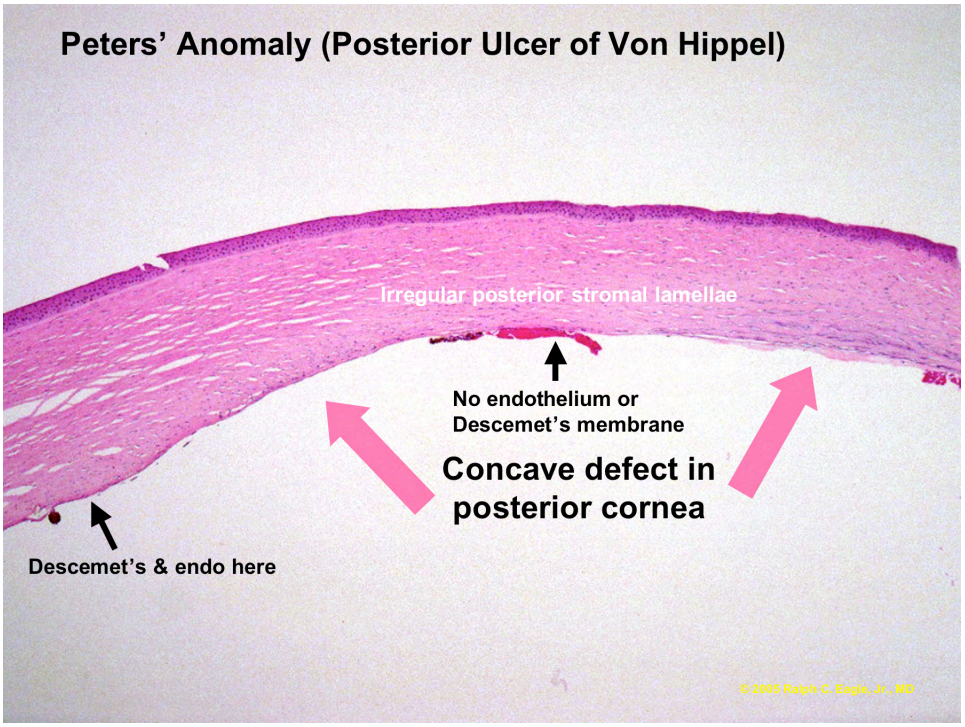
Posterior embryotoxon of Axenfeld
Prominent, anteriorly displaced Schwalbe's ring

Axenfeld's Anomaly
Posterior embryotoxon plus iris processes to ring
50% have glaucoma

Rieger's Syndrome
Axenfeld's anomaly plus iris stromal defects such as hypoplasia, slit pupils, polycoria, pseudocoria;
Skeletal and dental anomalies, umbilical hernia;
Autosomal dominant, 50% have glaucoma

Peters' Anomaly

Bilateral central corneal opacities, iridocorneal and keratolenticular adhesions
Descemet's and Bowman's membrane absent centrally, anterior polar cataract
PAX 6 mutations, can occur with fetal-alcohol syndrome, Accutane®



Posterior Ulcer of von Hippel

Congenital corneal opacities
Resembles Peters' but no lens involvement
Endothelium and Descemet's membrane absent centrally

Posterior Keratoconus

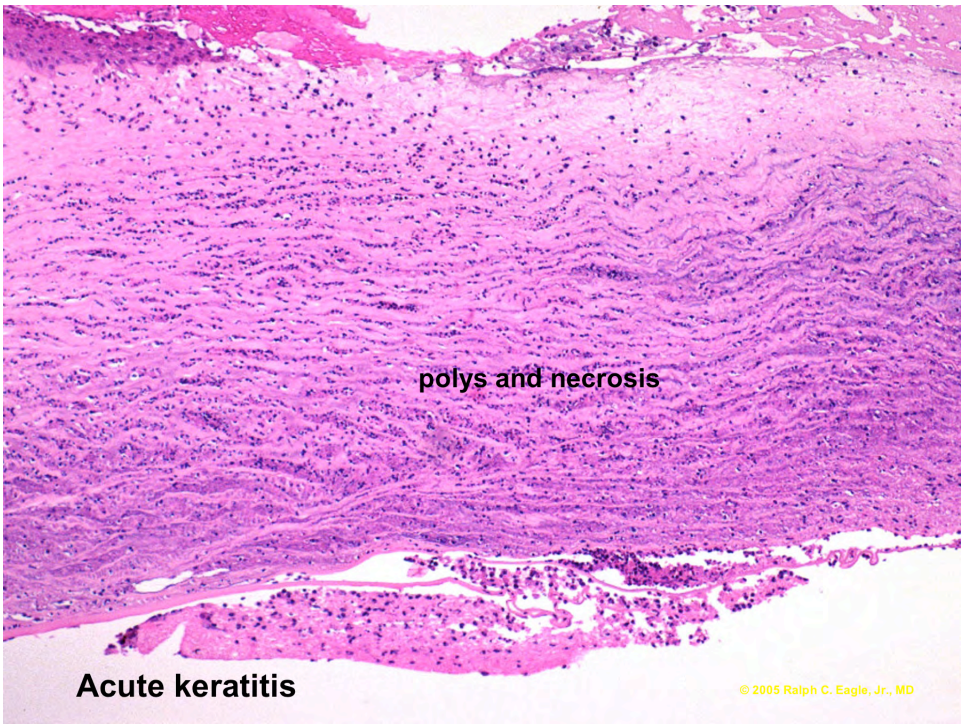
Posterior umbilication of central corneal stroma
Descemet's membrane present, but thin

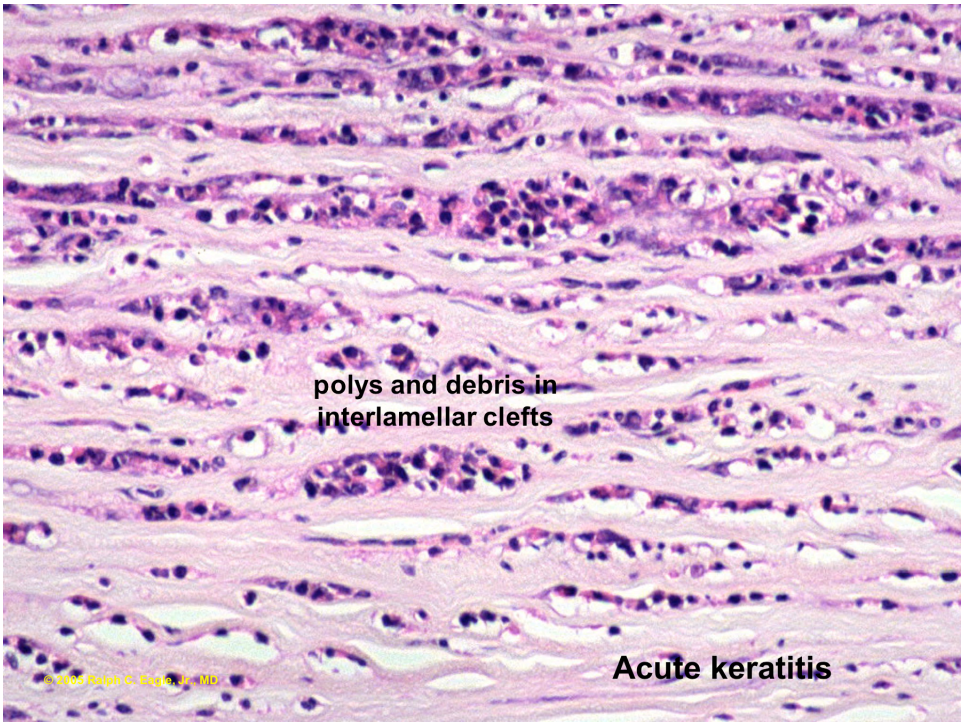
Congenital Corneal Staphyloma

Markedly atrophic iris adheres to back of markedly thickened, scarred, and vascularized cornea

Inflammatory Conditions
Acute keratitis and corneal ulcerations
Bacterial

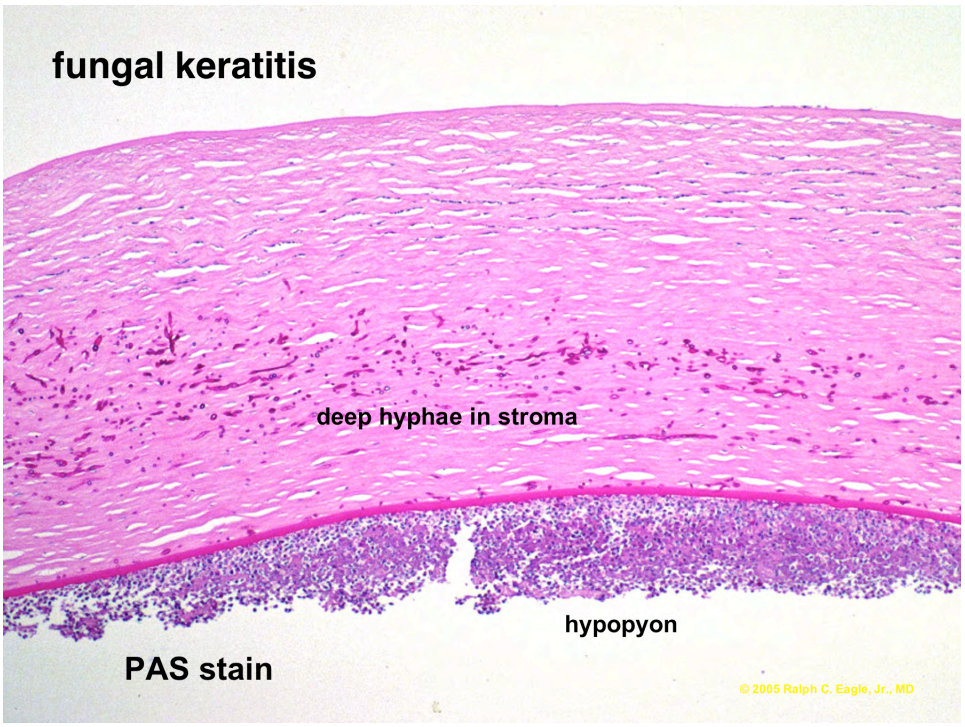
Polys collect between lamellae, basophilic necrosis, loss of stroma

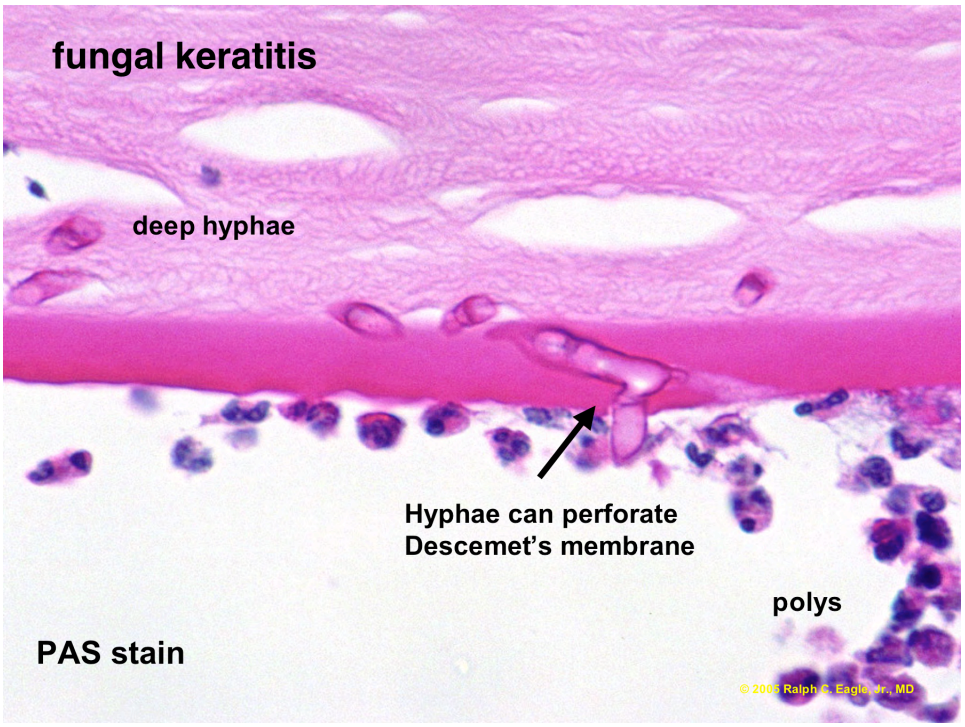


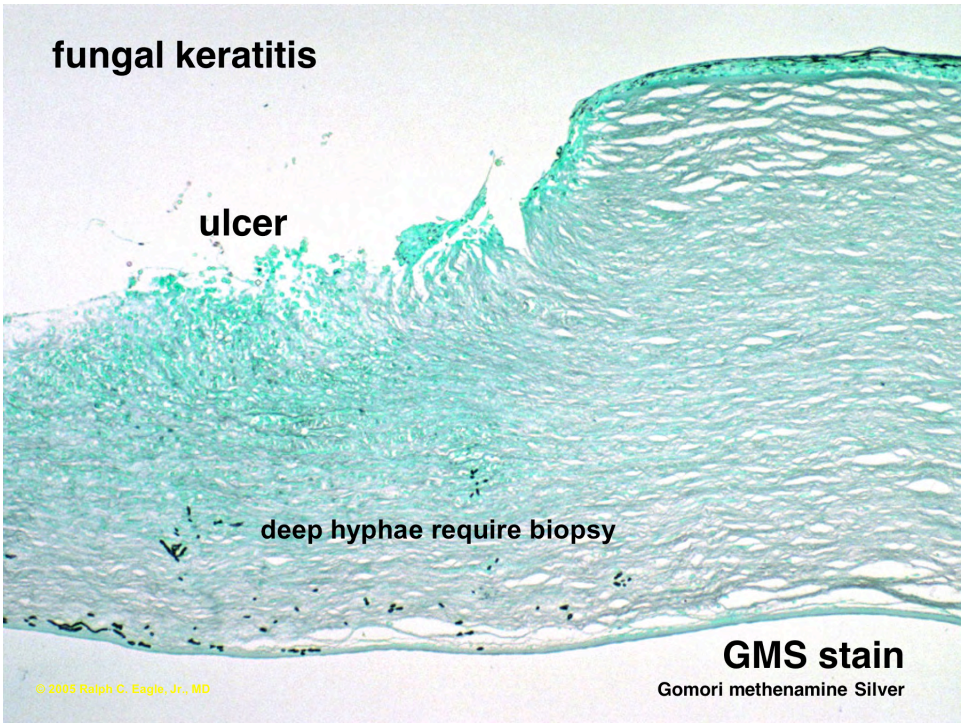


Fungal

Fungal hyphae permeate stroma, often located deep- may be missed in superficial scraping, can invade anterior chamber

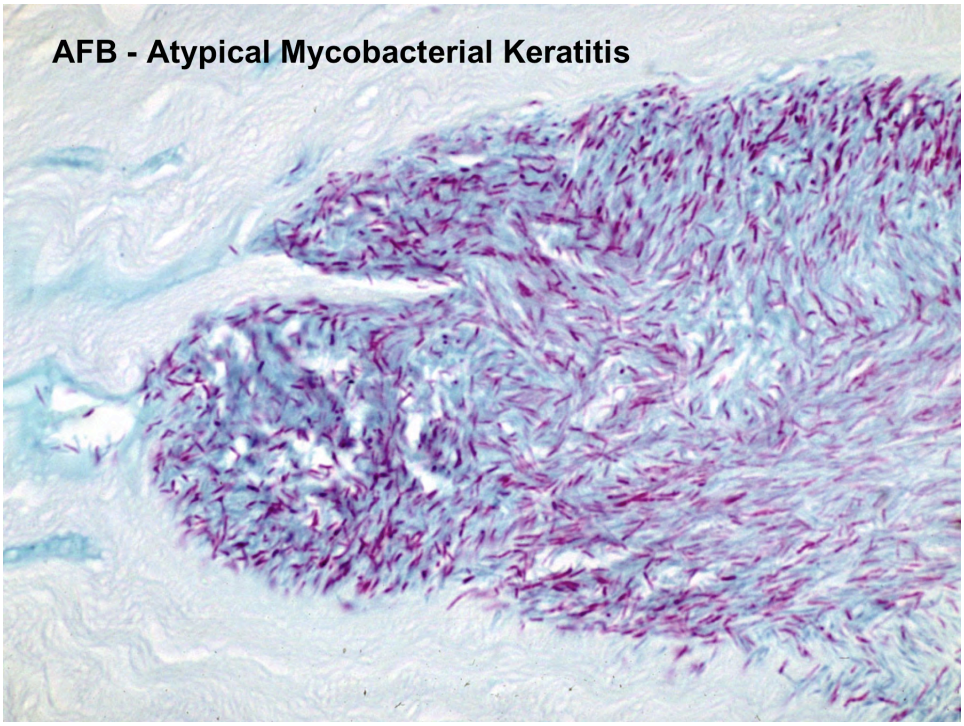




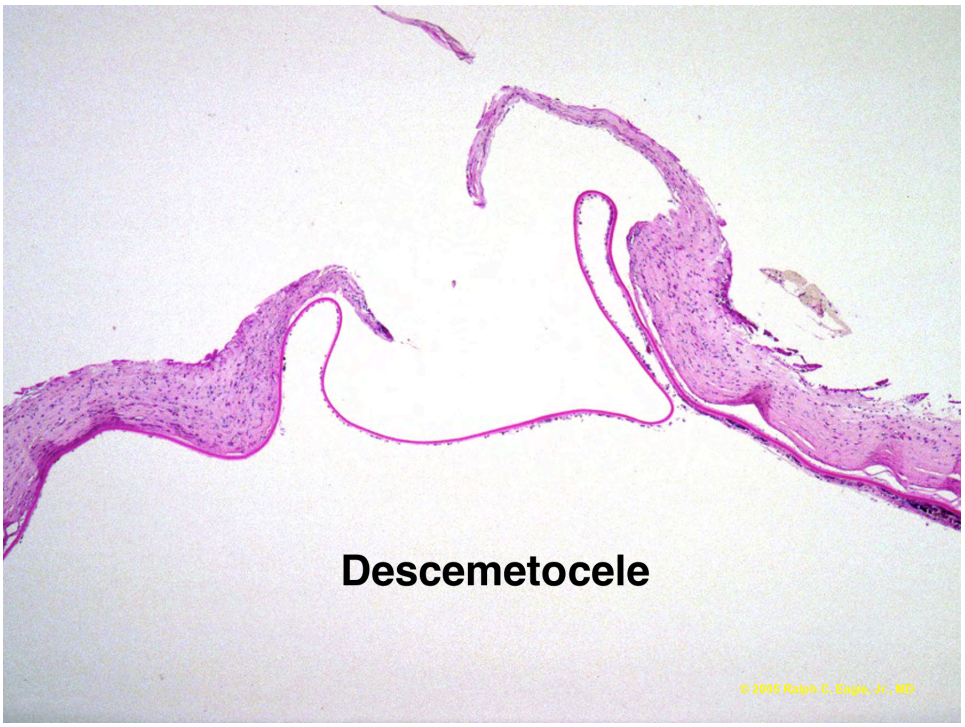


Mycobacterial

M. tuberculosis, atypical mycobacterial infections, leprosy

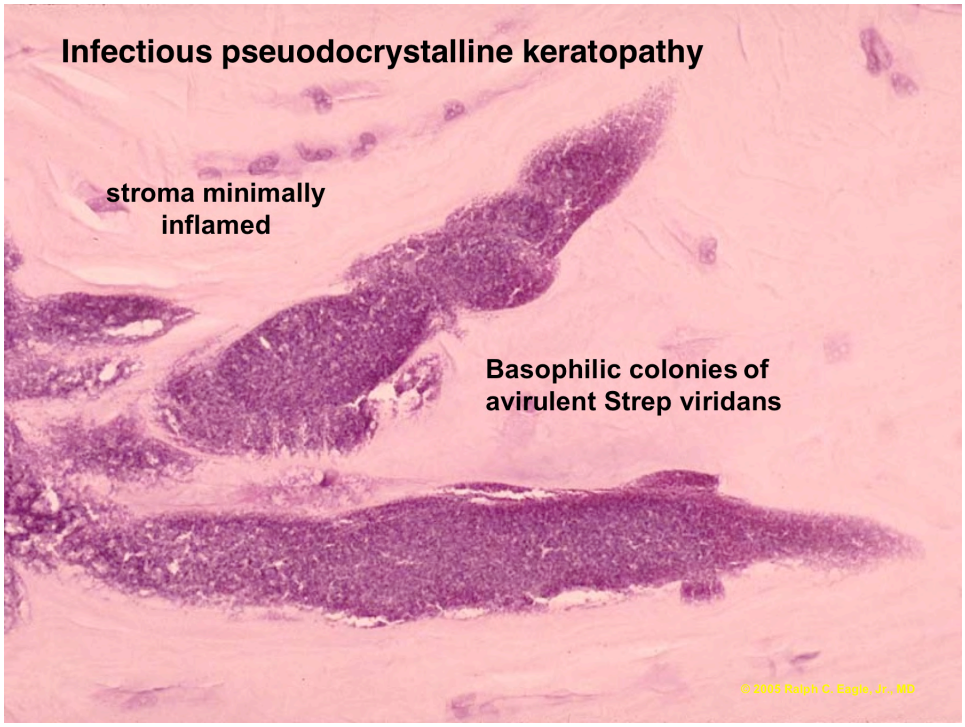


Descemetocele: herniation of Descemet's membrane through floor of corneal ulcer



Infectious Pseudocrystalline keratopathy

Large interlamellar bacterial colonies with vaguely crystalline configuration
Stromal relatively noninflammed
Avirulent strains of Streptococci sequestered by glycocalyx
Typically occurs in corneal grafts on chronic steroid therapy



Viral Keratitis
Chronic keratitis

Lymphocytes, plasma cells, vascularization

Herpes simplex disciform keratitis

***Herpes Simplex Keratitis**

Most common infectious keratitis leading to visual loss in USA and Europe; HSV type I; frequent recurrence due to latent virus in Gasserian ganglion
Dendritic keratitis
Primary epithelial infection, Cowdry type A intranuclear inclusion bodies, cultures positive in 75%

Geographic epithelial keratitis

Disciform keratitis (deep stromal keratitis without ulceration)

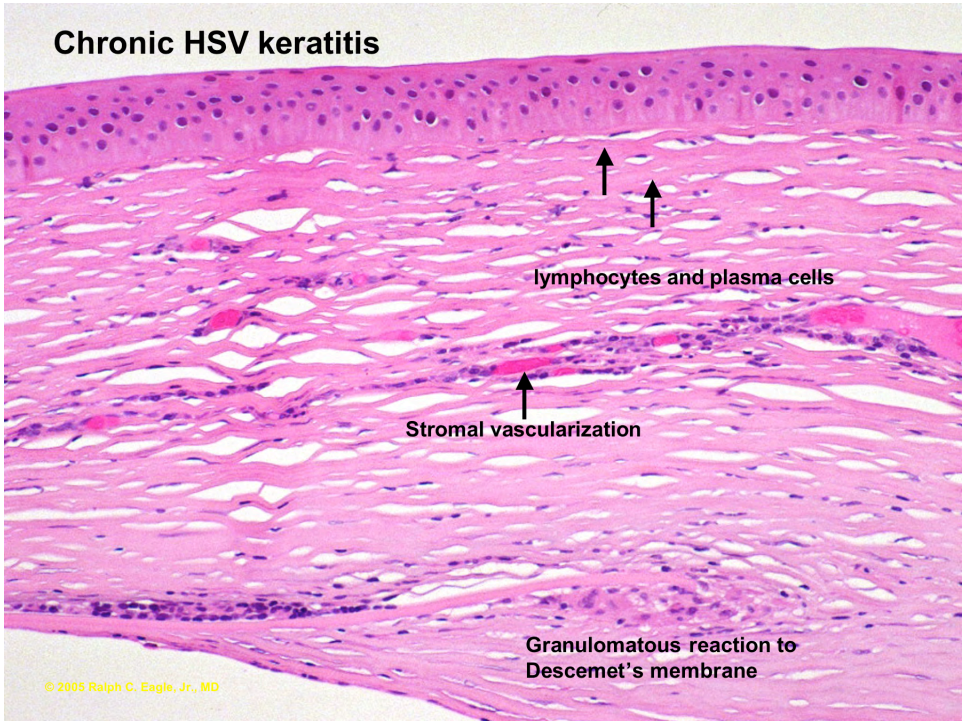
Cultures negative, but TEM has shown virus in stroma
May be primarily an immune reaction to persistent viral antigen rather than infection (recent controversy)
Scarring, lymphocytes and plasma cells
Granulomatous reaction to Descemet's membrane (suggestive of Herpes but also seen in other entities

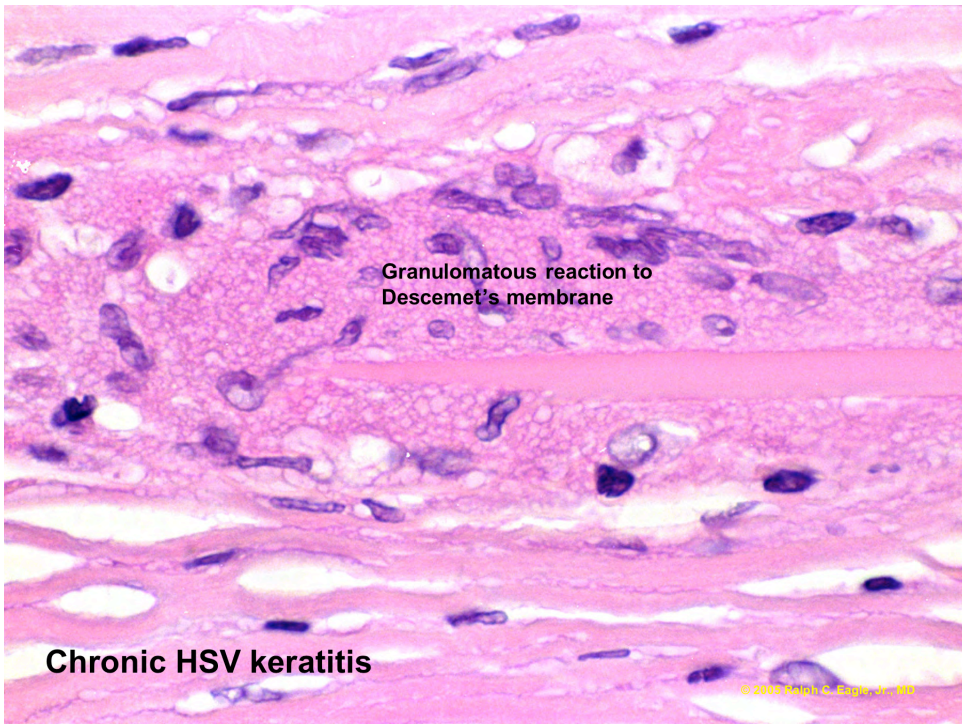
Deep keratitis with ulceration (metaherpetic keratitis)

Stromal thinning, perforation, Descemetocele

Granulomatous reaction to Descemet's membrane

(classically associated with chronic herpetic keratitis, but not pathognomonic)





Parasitic keratitis- **Onchocerca volvulus** (onchocerciasis)
"River blindness"-major cause of blindness worldwide
Vector (black simulian fly) breeds in swift-running mountain streams
Adult worms breed in dermal nodules releasing microfilaria
Secondary closed angle glaucoma due to keratitis; chorioretinal degeneration

Protozoal keratitis-

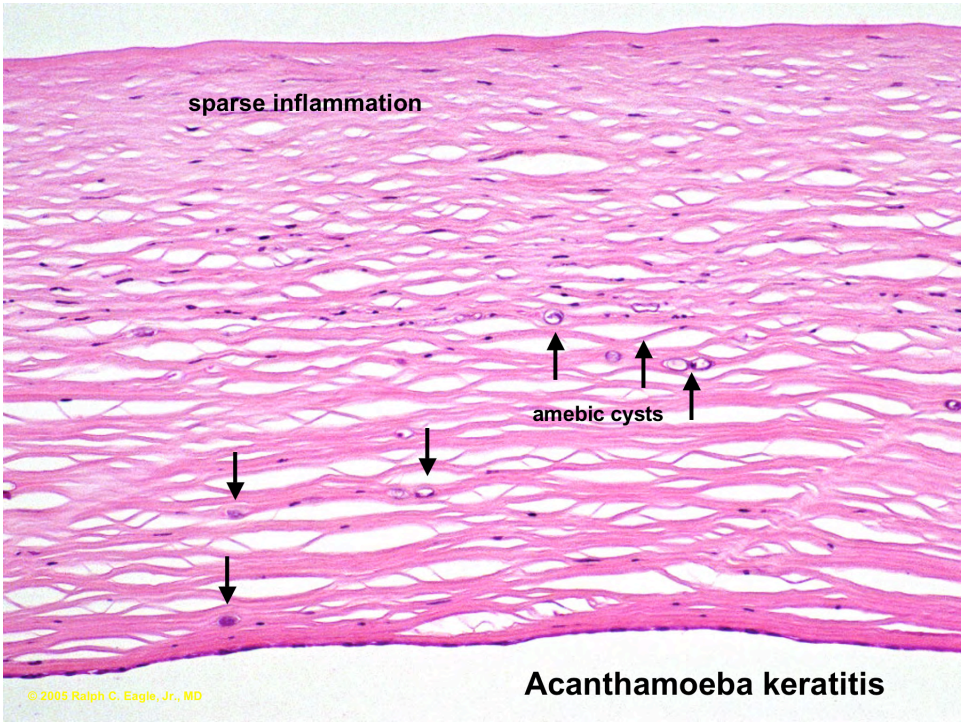
*__Acanthamoeba keratitis__ (A. castellani, polyphaga)

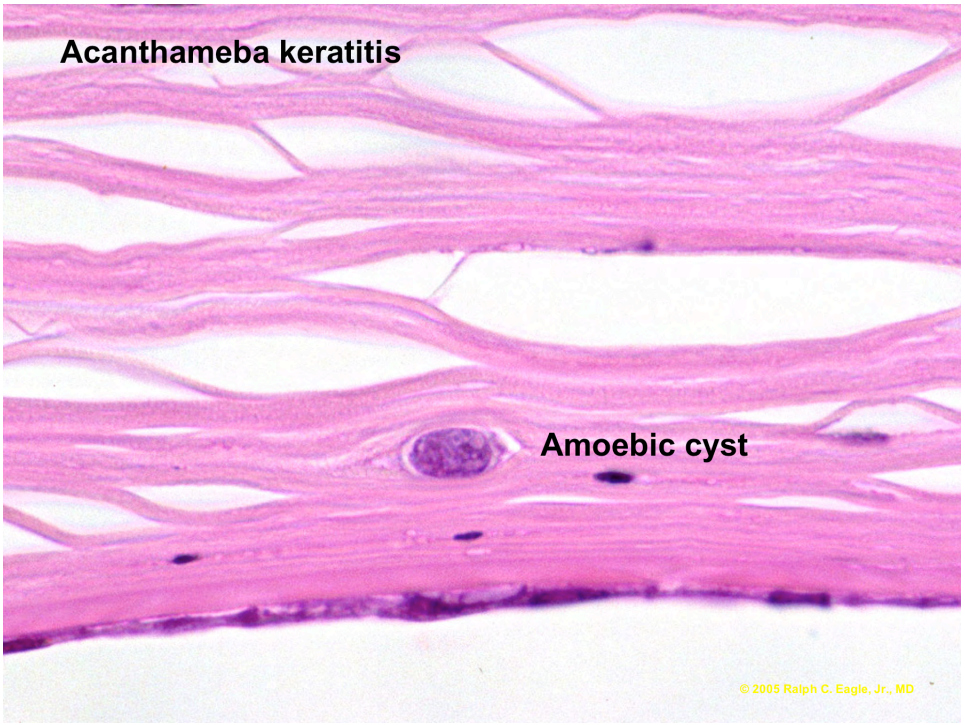
Soft contact wearers, contaminated solutions, homemade saline, swimming or hot tubs while wearing lenses

PK often necessary, patients have severe pain (?neurotropism)

Annular infiltrate (ring ulcer) a late finding

Amoebic cysts, trophozoites, moderate necrosis in stroma, loss of epithelium and keratocytes. Calcofluor white fluorescent dye aids rapid diagnosis





Chronic keratitis

Lymphocytes, plasma cells, vascularization

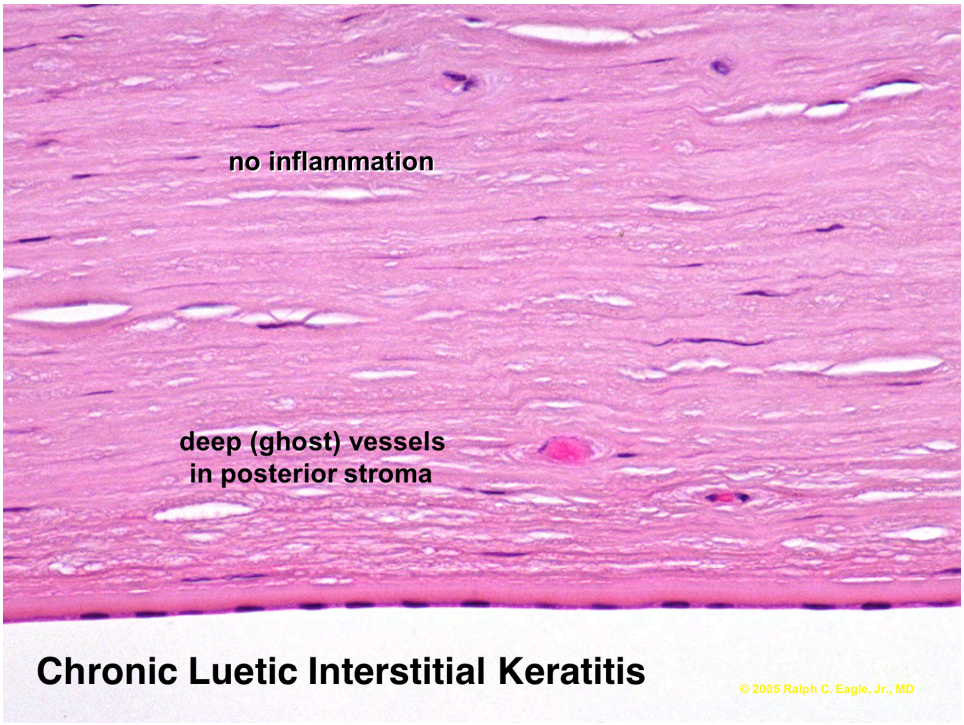
Interstitial (stromal) keratitis

Herpes simplex disciform keratitis (see above)

Luetic (syphilis)- Old luetic IK

In patients with congenital syphilis; first or second decade;
Rarely seen in acquired syphilis, unilateral, sectoral.
Acute "salmon patch", severe photophobia, edema, lymphocytic infiltrate
Late findings: faint nebulous corneal opacity, deep ghost vessels
Bowman's membrane lost; deep vessels (posterior 1/3 of stroma);
thickening of Descemet's membrane, occasionally massive with formation of hyalinized bridges and strands

Tuberculosis, leprosy, Cogan's syndrome (non-luetic IK with deafness)
Protozoal (see above), onchocerciasis (see above), systemic disease (sarcoidosis, Hodgkin's disease, mycosis fungoides), foreign bodies (insect hairs [ophthalmia nodosa]), plant material, drugs (systemic gold, arsenic), trachoma (see conjunctiva)


no inflammation
deep (ghost) vessels
in posterior stroma
Chronic Luetic Interstitial Keratitis
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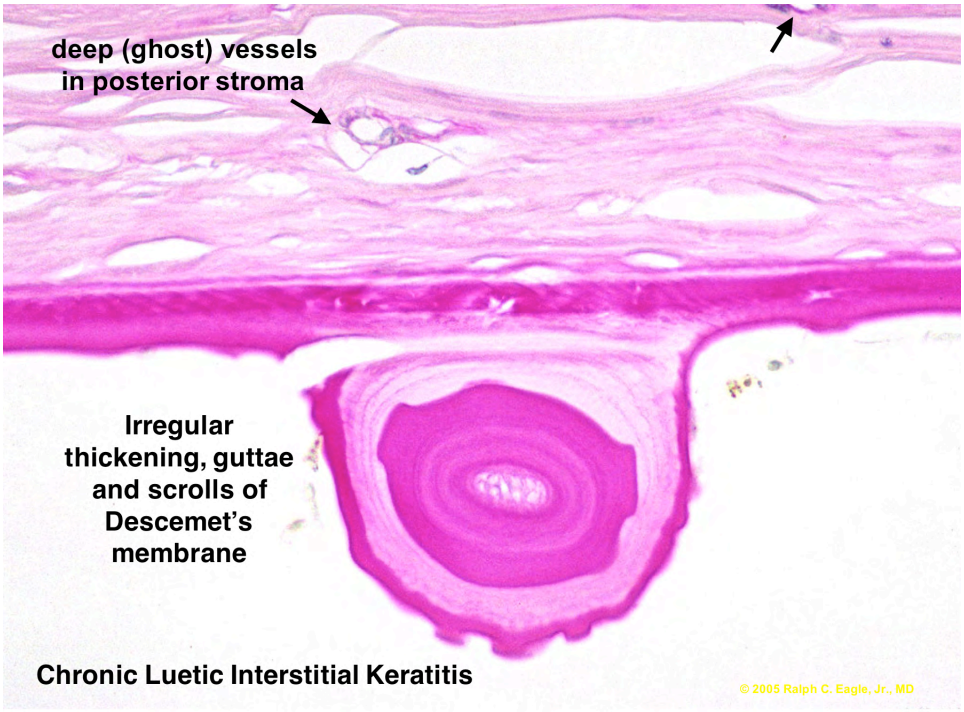
deep (ghost) vessels
in posterior stroma
Irregular
thickening, guttae
and scrolls of
Descemet's
membrane
Chronic Luetic Interstitial Keratitis
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Inflammatory pannus
Peripheral ingrowth of fibrovascular membrane beneath epithelium
Bowman's membrane is destroyed (classically seen in Trachoma)
Degenerative pannus
Common finding in chronically edematous corneas
Bowman's membrane intact
Fibrous tissue interposed between base of epithelium and Bowman's membrane

Peripheral ulcerations
Marginal ulcers
Staphylococcal toxins
Collagen vascular diseases: Lupus, periarteritis nodosa, Wegener's granulomatosis, rheumatoid arthritis

Ring ulcers
Mooren's ulcer
In USA, unilateral disease of elderly
In Africa, severe bilateral disease in young
Central overhanging margin of ulcer
Immune disorder? ischemic necrosis? limbal collagenase? assoc with Hepatitis C
Terrien's ulcer
Bilateral, slowly progressive, males
Trough-like stromal thinning begins superiorly
Epithelium intact, Bowman's and superficial stroma lost
Vascularization, occasional lymphocytes and plasma cells

Corneal degenerations

***Pterygium** (pter: "wing"-lesion resembles insect wing)

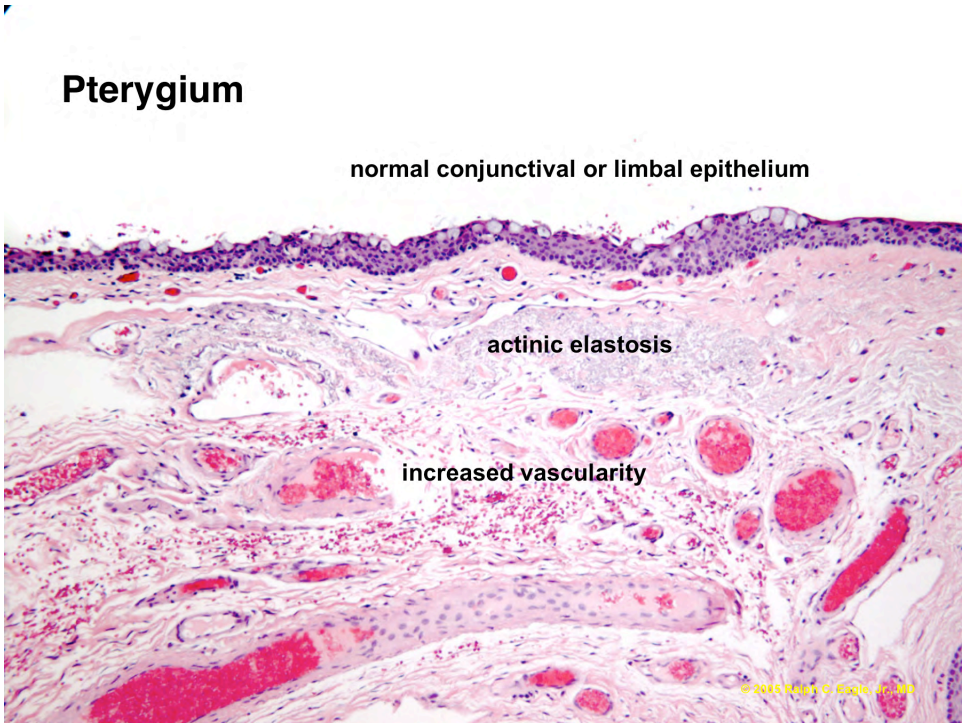
Interpalpebral fissure, most common nasally

Resembles pinguecula histologically but invades cornea

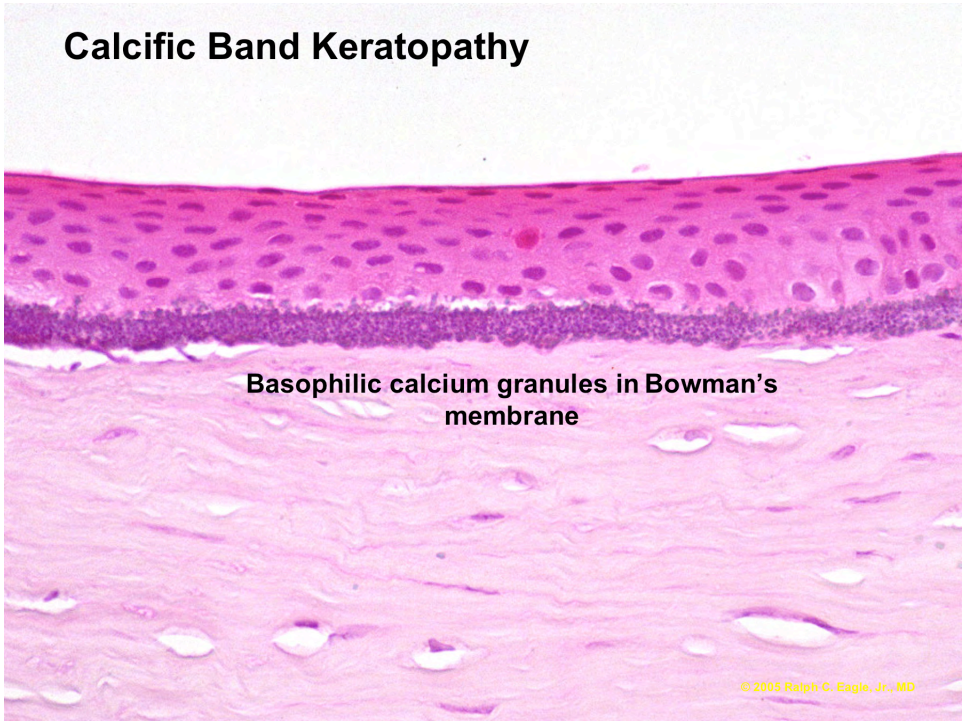
Caused by environmental factors: light, dust, wind?? limbal stem cell loss??

Senile elastosis of collagen, hyalinization, basophilia

Bowman's membrane lost; overlying epithelial dysplasia possible



***Calcific band keratopathy**
Interpalpebral cornea, begins at limbus, clear zone, holes
Calcification of Bowman's and anterior stroma secondary to ocular inflammation (Still's disease, sarcoidosis), or systemic disease (hypercalcemia, vitamin D intoxication, Fanconi's syndrome, gout, myotonic dystrophy, hypophosphatemia, "milk-alkali" syndrome, silicon oil, chronic RD)
Basophilic granules in Bowman's membrane



*__Chronic actinic keratopathy__ (elastotic degeneration)
(many synonyms: spheroidal degeneration, Labrador keratopathy, Bietti's hyaline degeneration, etc.)
Common etiologic factor is **light damage**
Round, droplike deposits of amorphous, hyaline mildly basophilic material, stains + with Verhoeff-van Gieson elastic stain, autofluorescent to UV
Yellow oil-droplet appearance clinically
May coexist with calcific band keratopathy

Salzmann's Nodular Degeneration
Whitish focal mounds of subepithelial hyaline connective tissue; Bowman's membrane destroyed (massive focal degenerative pannus, ?cause)

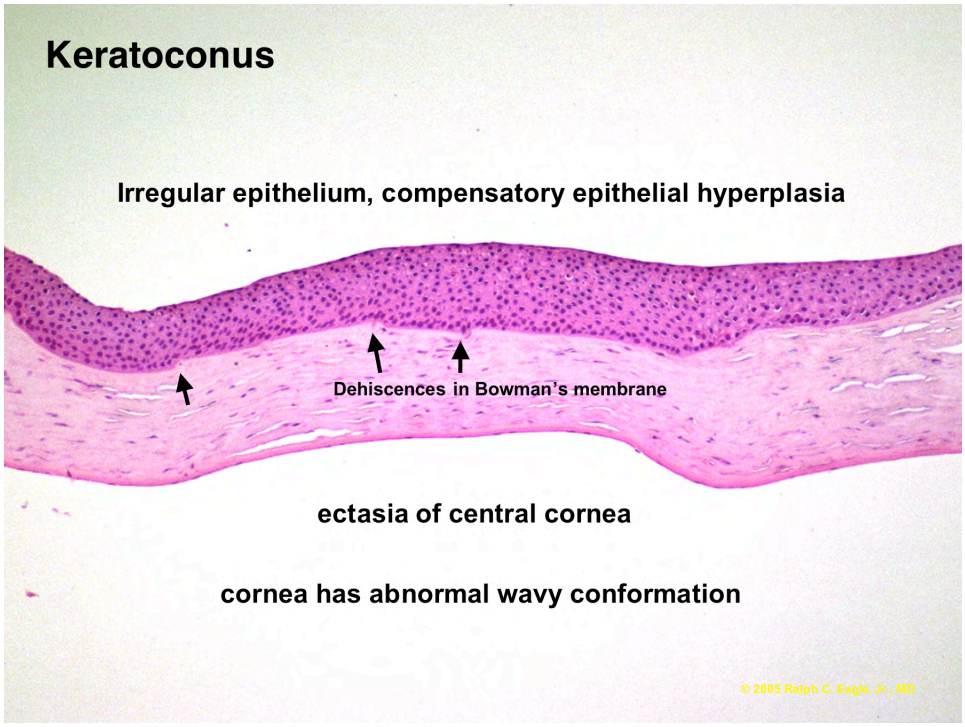
Lipid keratopathy
Secondary deposition in heavily vascularized stroma

Corneal keloid
Massive scarring and thickening of stroma; epidermalization common

Corneal staphyloma
Atrophic iris adheres to posterior surface of massively thickened cornea
In Third World frequently follows **measles keratitis**

Keratoconjunctivitis sicca
Deficient tear or mucous production
Corneal drying, SPK, filamentary keratitis (detached strands of epithelium and mucous)
Sjøgren's syndrome (triad)
Keratoconjunctivitis sicca, xerostomia, rheumatoid arthritis
Lacrimal gland infiltrated with lymphocytes with persistent myoepithelial islands (lymphoepithelial lesion of Godwin); lymphoma develops in 10%
Xerophthalmia (avitaminosis A)
Corneal epithelial keratinization, epidermalization; night blindness, keratomalacia and perforation. Malnourished children in underdeveloped countries, alcoholics in USA
Bitot's spot
Exposure keratopathy
Dellen (Fuchs)
Focal stromal thinning central to elevated limbal lesion, surface ulceration.
Neurotrophic keratopathy (neuroparalytic keratopathy)
White limbal girdle of Vogt
White ring of Coats: ring opacity at level of Bowman's, inferior half of cornea, iron-calcium protein complex
Secondary amyloidosis

Keratoconus
Bilateral, onset around puberty, heredity questionable
Association with: Down's syndrome, atopic dermatitis, Ehlers-Danlos, Marfan's syndrome, Leber's congenital amaurosis, floppy mitral valve syndrome, hard contacts, eye rubbing, floppy eyelid synddrome
Central stromal ectasia, **dehiscences in Bowman's membrane** Munson’s sign, Vogt’s striae, Rizutti’s sign, stromal folds,
Ruptures in Descemet's lead to **acute hydrops** (especially in Down's syndrome)
Fleischer ring surrounds cone (Iron in epithelium)
Cause uncertain, ? abnormality in extracellular matrix? ? defect in tissue metalloproteinase inhibitors?


Keratoconus
Irregular epithelium, compensatory epithelial hyperplasia
Dehiscences in Bowman's membrane
ectasia of central cornea
cornea has abnormal wavy conformation
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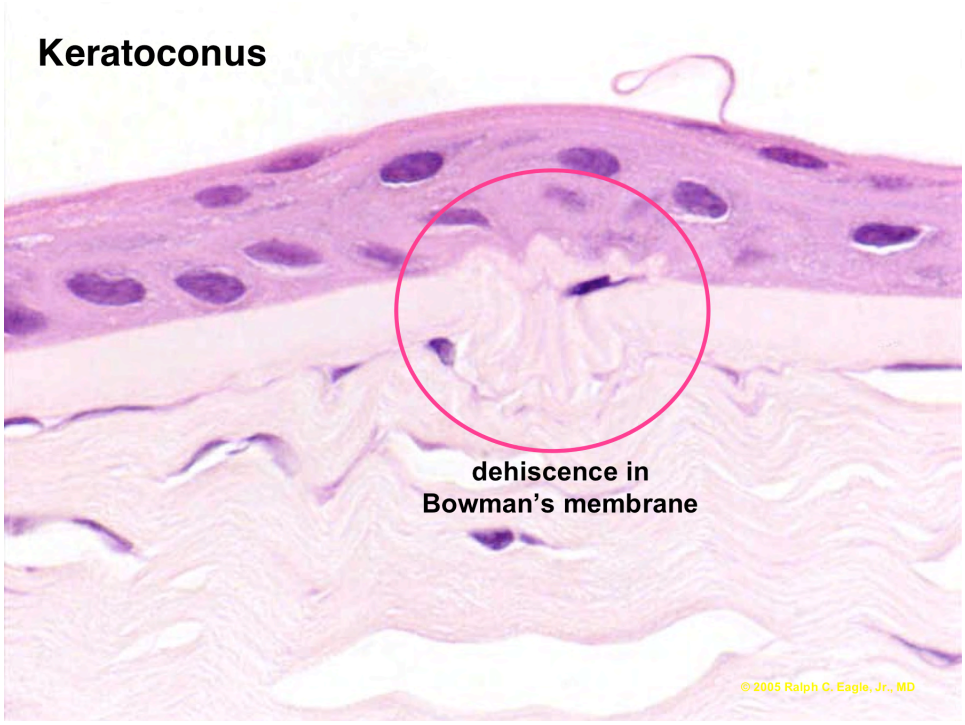
Keratoconus
dehiscence in
Bowman's membrane
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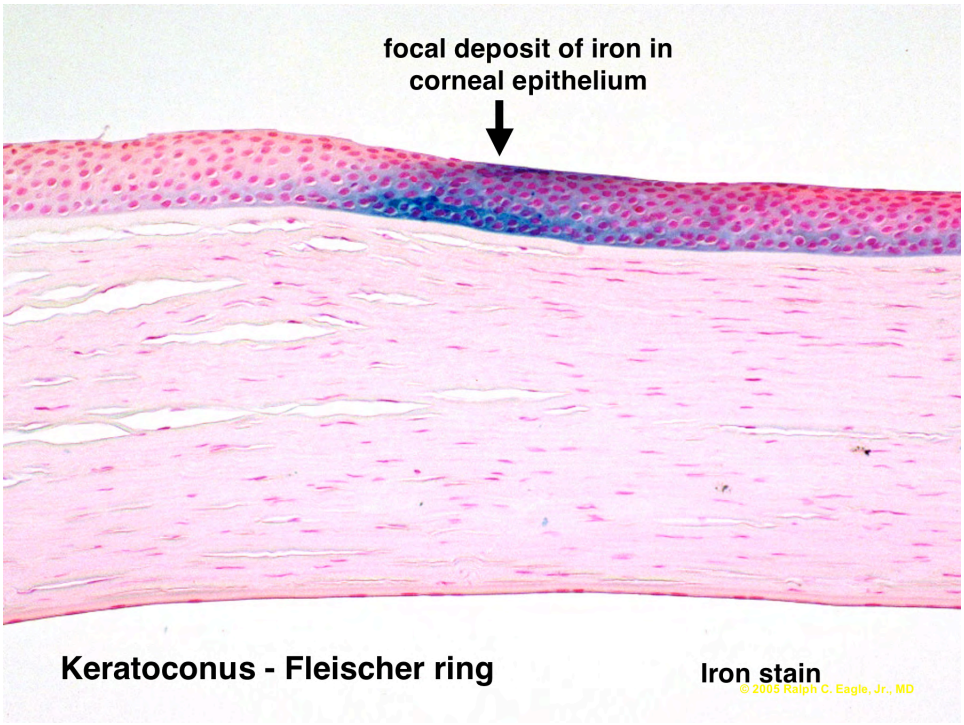


Pellucid degeneration
Resembles keratoconus histopathologically, hydrops possible

CORNEAL RINGS
Fleischer Ring

Corneal iron lines-ferritin particles within epithelium
Hudson-Stähli: horizontal, line of lid closure, physiological aging
Fleischer ring: keratoconus, surrounds base of cone
Stocker: advancing head of pterygium
Ferry line: in front of filtering bleb (Ferry = filter)

Arcus Senilis
Deposition of lipid in stroma, similar clinically inapparent deposit in sclera

Arcus Juvenilis
Arcus at an early age (< age 40 in males may be significant for ASCVD)
May occur in Type II and III hyperlipoproteinemia
Corneal lipid deposition also occurs in hypolipidemia syndromes :LCAT deficiency, fish eye disease, Tangier disease

Kayser-Fleischer Ring (Wilson's Hepatolenticular degeneration)
Copper in Descemet's membrane (corneal copper also in chalcosis, rare cases of myeloma or lung tumors that make copper transport proteins)

Corneal dystrophies

Definition: **In classic Ophthalmic usage, dystrophy usually denotes an inherited, relatively symmetric bilateral disease unassociated with vascularization or inflammation in its early stages. Commonly applied to hereditary diseases of the cornea and macula.**

Dystrophy: Modern concepts

Inherited genetic disorder (defective enzyme or structural protein)
Not evident at birth (becomes clinically evident later)
Pathology localized to an ocular tissue (systemic effects absent or inapparent)
Specific genetic defects recently have been elucidated in several dystrophies:

***NOTE:** Granular, lattice, Avellino and Reis-Bückler's dystrophies have been shown to be associated with different mutations of the **TGFBI (BIGH3)** on the long arm of chromosome 5. The corneal epithelium is rich in **TGFBI** protein. (also called **kerato-epithelin)** Different patterns of aggregation or precipitation of the mutant forms of **TGFBI** protein presumably are responsible for the various clinical manifestations of the several dystrophies. (see table of mutations below)

Meesman's dystrophy is caused by mutations in corneal epithelium-specific keratins K3 and K12.

Representative TGFBI Mutations in Corneal Dystrophies

Corneal Dystrophy	Mutation
Lattice type I	Arg124Cys
Avellino	Arg124His
Granular	Arg555Trp
Reis-Bückler's	Arg555Gln
Lattice type IIIA	Pro501Thr

Anterior Dystrophies (Epithelial, Subepithelial and Bowman's Membrane)

Meesman's dystrophy

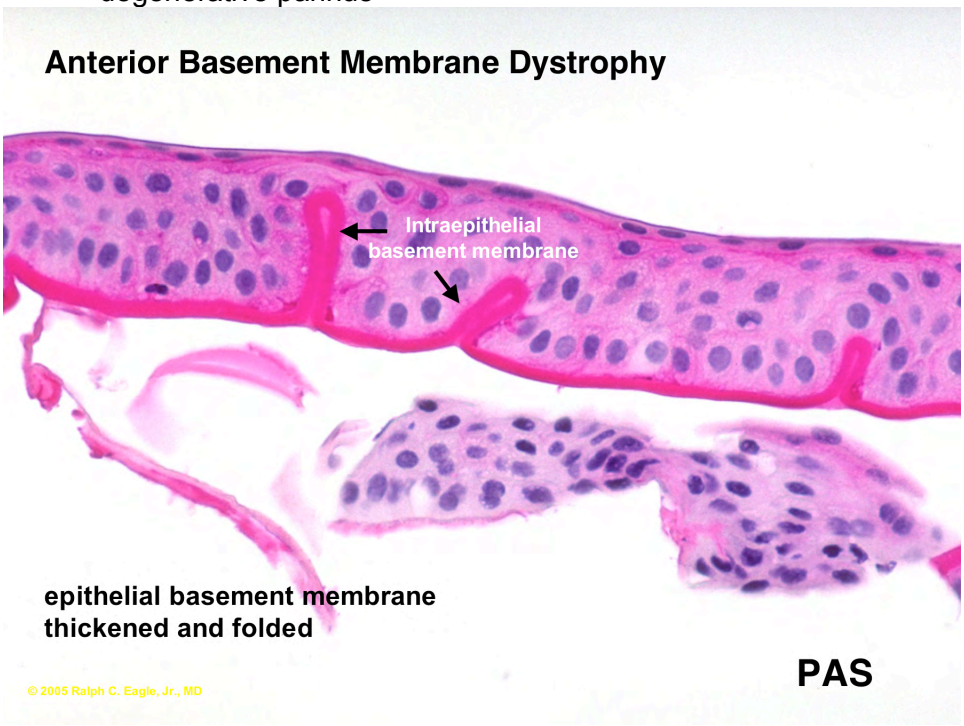
Autosomal dominant, early onset, recurrent erosions, good vision
Myriad small punctate intraepithelial vacuoles, may pool fluorescein at corneal surface. Abnormal epithelial cells contain cytoskeletal "**peculiar substance**"
Thickened epithelial basement membrane. Increased epithelial fragility caused by mutations in corneal epithelial specific cytokeratins K3 and K12 (12q12-q13)

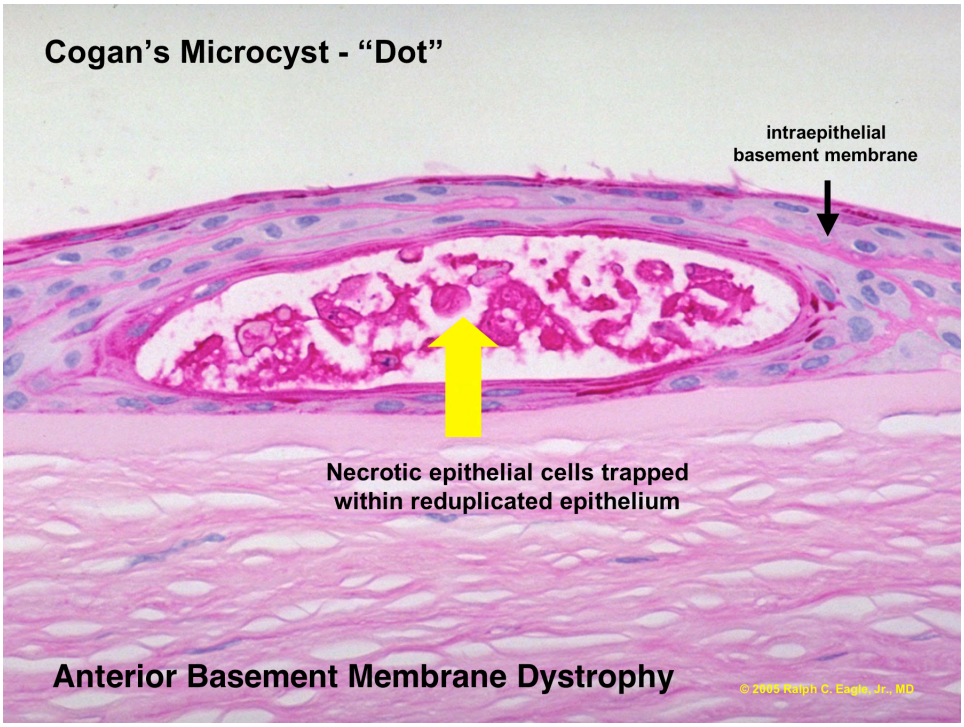
Map, dot and fingerprint dystrophy (Anterior basement membrane dystrophy, Cogan's microcystic dystrophy)

A clinical spectrum that results from poor epithelial adhesion to its basement membrane
Autosomal dominant, healthy middle-aged women
(Identical histopathological changes found in 56% of eyes with chronic bullous keratopathy, recurrent erosions)
Pathogenesis: poor epithelial adhesion or bulla formation permits epithelial reduplication and/or folding with excess sub- or intraepithelial production of basement membrane material and collagen. Normal epithelial maturation modified by anatomical constraints

Clinical subtypes (often coexist)

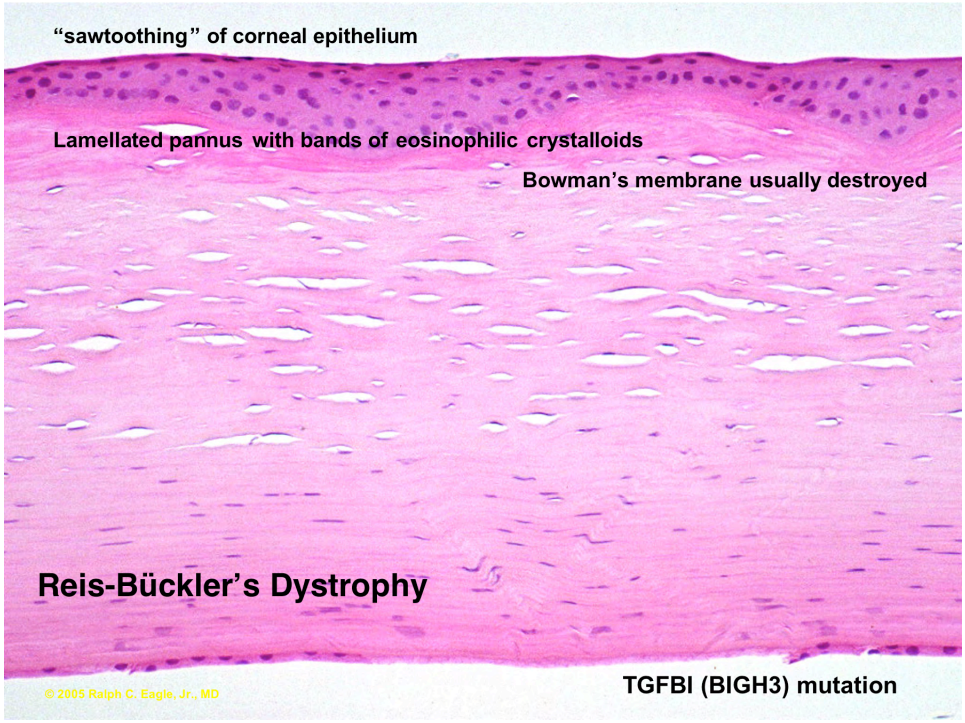
Microcystic: white putty-like contents reflect degenerated epithelial cells trapped in disorderly epithelium
Fingerprint: parallel relucent lines of basement membrane separating tongues of reduplicated epithelium
Map (geographic): subepithelial connective tissue resembling degenerative pannus





Lisch Dystrophy (band-shaped and whorled microcystic dystrophy)
Foci of epithelial cells contain intracytoplasmic vacuoles- X chromosome

Dystrophies of Bowman's Membrane
Reis-Bückler's dystrophy (CDB1)
Autosomal dominant, begins in first decade with recurrent erosions
Subepithelial scarring, ring-shaped opacities
May be confused with lattice dystrophy, superficial variant of granular dystrophy
Irregular "saw-toothed" epithelium, subepithelial connective tissue, destruction of Bowman's layer. Laminated pannus contains intensely eosinophilic crystalloids that stain like material in granular dystrophy (red with Masson trichrome)
TGFBI mutation- mutant kerato-epithelin

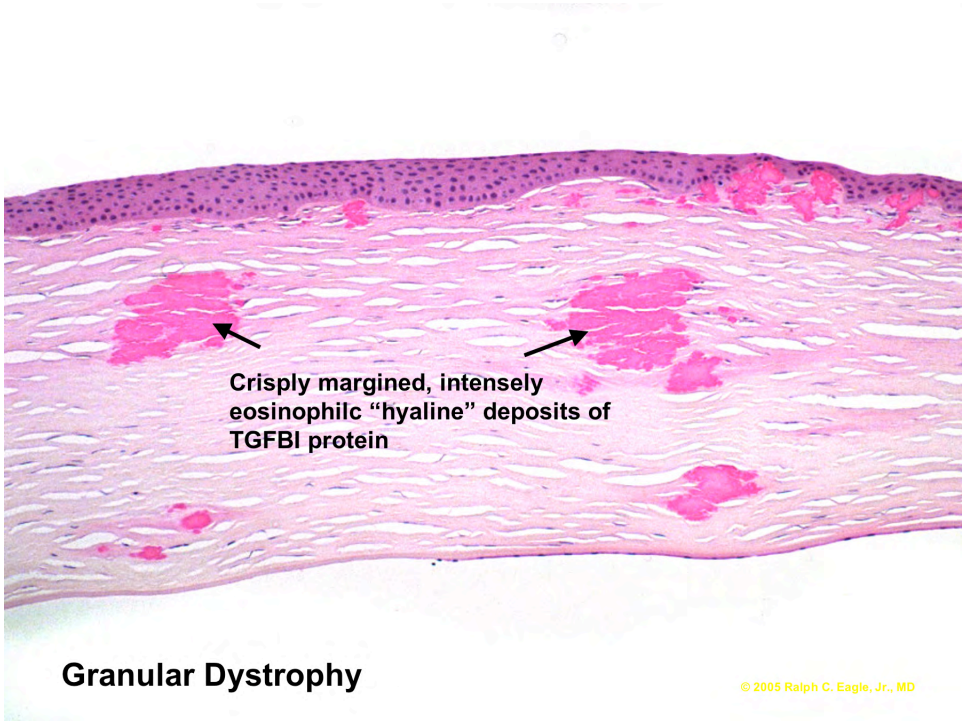


Thiel- Behnke Honeycomb dystrophy (CDB2)
Very similar to Reis-Bückler's clinically and pathologically, but storage material is composed by "curly filaments" shown by TEM; TGFBI mutation
Cases called Reis-Bückler's in American literature actually are Thiel-Behnke
Primary gelatinous droplike dystrophy (Familial Subepithelial Amyloidosis)
Many cases in Japan
Amyloid contains lactoferrin, but caused by mutations in M1S1 gene, not gene for lactoferrin

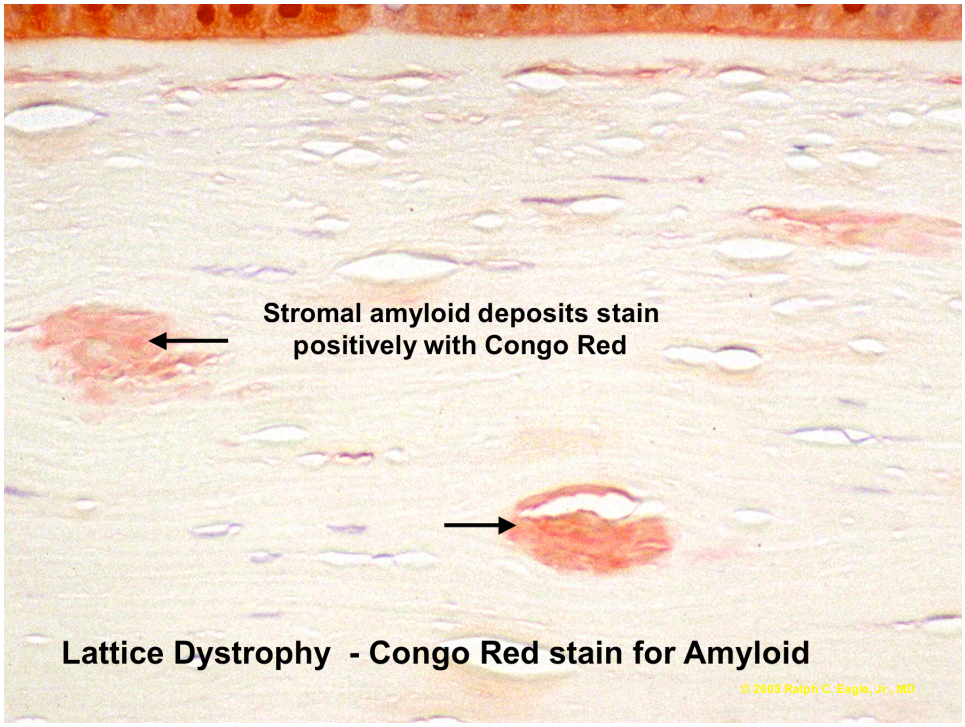
Stromal Dystrophies

Granular Dystrophy (Groenow Type I, Bückler's Type I)

Autosomal dominant, most benign clinically, visual loss late
Bilateral, central superficial ring or crumb-like opacities
Hyaline "rock-candy" stromal deposits stain intensely **red with Masson Trichrome** (acid fuchsinophilia) , more eosinophilic than normal stroma, PAS (-), MPS (-), Luxol fast blue (+++), less birefringent than normal stromal lamellae.
TEM: electron-dense granules with periodicity
Can recur in graft, material may be produced by epithelium
TGFBI gene mutation- mutant TGFBI protein forms granules



Lattice Dystrophy, type I (Biber-Haab-Dimmer, Bückler's Type III)
- **Localized corneal amyloidosis** (Klintworth), ? AA amyloid (never confirmed)
- Autosomal Dominant, bilateral, onset first decade
- PK usually necessary in 4th or 5th decade
- Delicate branching relucent lines in stroma (Not degenerating corneal nerves)
- Recurrent erosions; superficial scarring can mimic Reis-Bückler's
- Intrastromal and subepithelial deposits of **amyloid**
- Amyloid stains **Congo red**, crystal violet, thioflavin T Positive
- **Apple green birefringence** and **dichroism** with polarization microscopy
- Material also PAS (+), argyrophilic (Wilder's reticulum)
- Can recur in graft
- **TGFBI gene mutation** - mutant protein forms amyloid


Stromal amyloid deposits stain positively with Congo Red
Lattice Dystrophy - Congo Red stain for Amyloid
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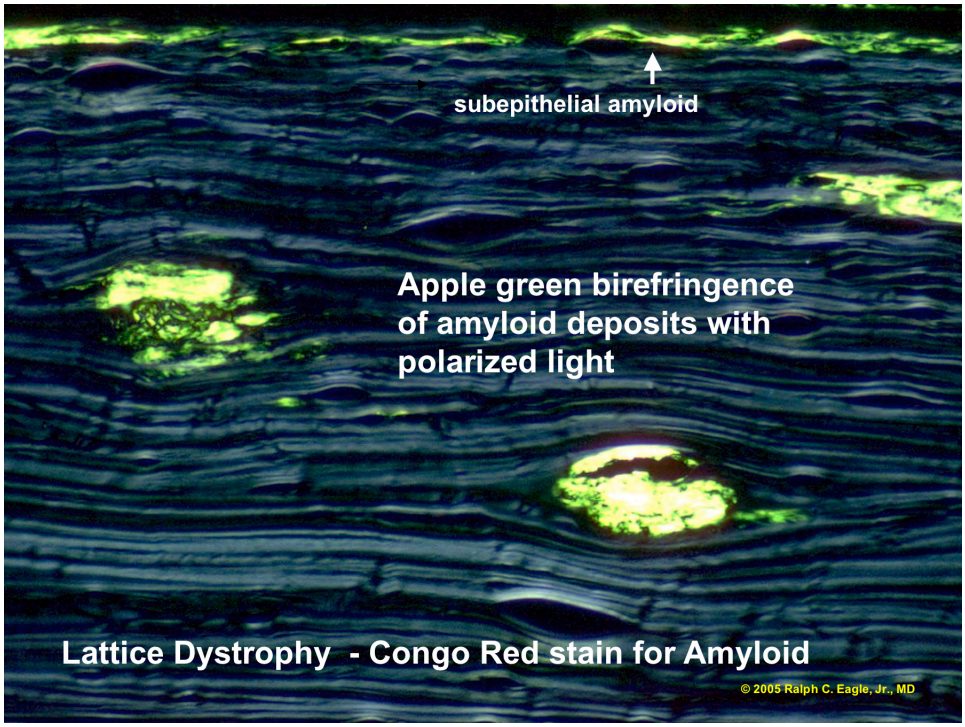
subepithelial amyloid
Apple green birefringence of amyloid deposits with polarized light
Lattice Dystrophy - Congo Red stain for Amyloid
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Avellino Corneal Dystrophy

Combines features of granular and lattice type I, TGFBI mutation

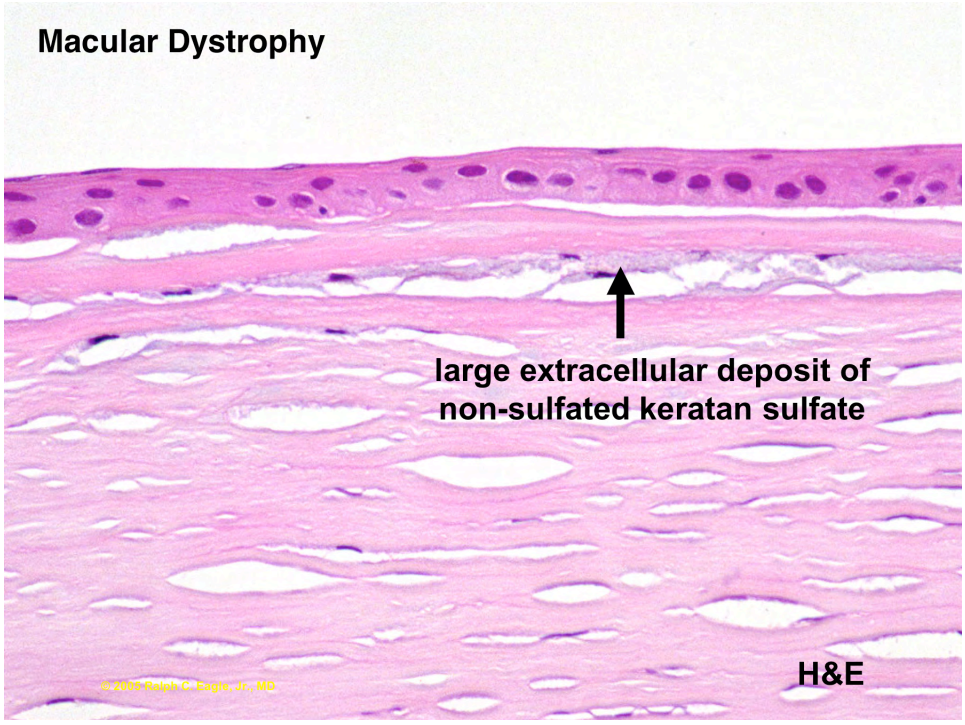
Lattice Dystrophy, Type II (Meretoja syndrome)

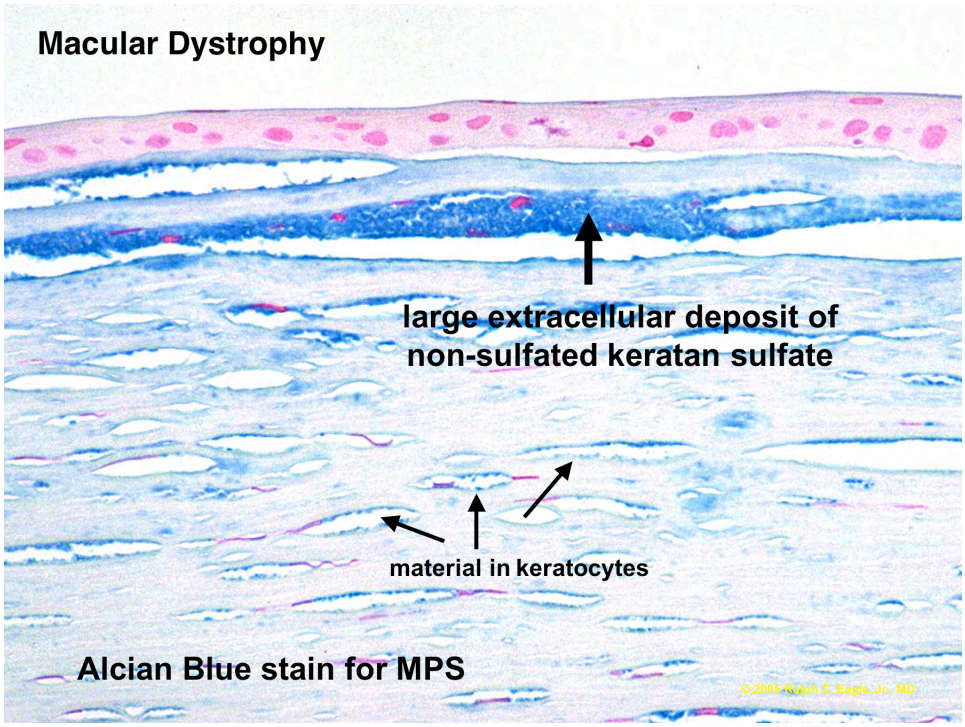
Lattice dystrophy in patients with autosomal dominant systemic amyloidosis.
Midperipheral deposits, less visual loss. (actually may represent amyloid degeneration of corneal nerves)
Cranial nerve palsies, dry itchy skin, typical mask-like "hound dog" facies with protruding lips
Amyloid deposits composed of mutant **gelsolin,** an enzyme involved in actin metabolism.

Polymorphic Amyloid Dystrophy (Klintworth)-Lattice variant; TGFBI mutation

Macular Dystrophy (16q22 CHST6 sulfotransferase gene)

Localized corneal mucopolysaccharidosis:
Autosomal Recessive!!, Most severe, visually disabling
Superficial opacities with indistinct borders begin axially.
Diffuse stromal haze between opacities, may need PK in third decade
The corneal manifestation of an otherwise benign systemic disorder
Heterogenous- Type I patients lack circulating keratan sulfate in serum, cartilage
Defective sulfonation of keratan sulfate molecules (proposed Type I enzyme defect)
Insoluble non-sulfated keratan "sulfate" accumulates in keratocytes, endothelium, and between stromal lamellae; abnormal stromal hydration
Unlike systemic mucopolysaccharidoses the **corneal stroma is not thickened.**
Colloidal iron stain or Alcian blue stain for MPS (+)




Macular Dystrophy
large extracellular deposit of
non-sulfated keratan sulfate
material in keratocytes
Alcian Blue stain for MPS
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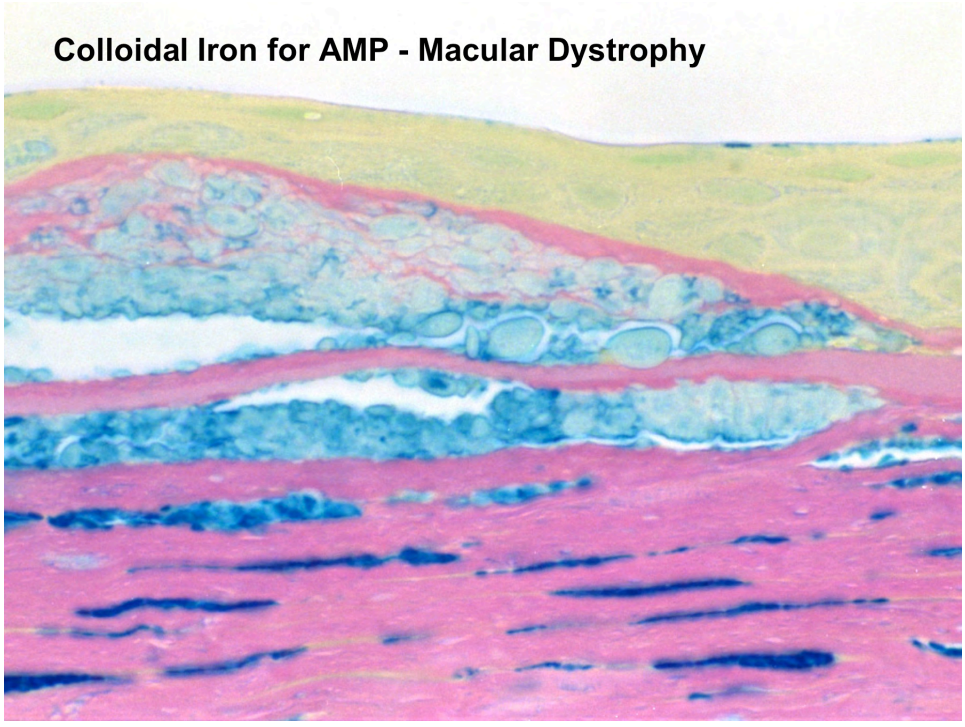
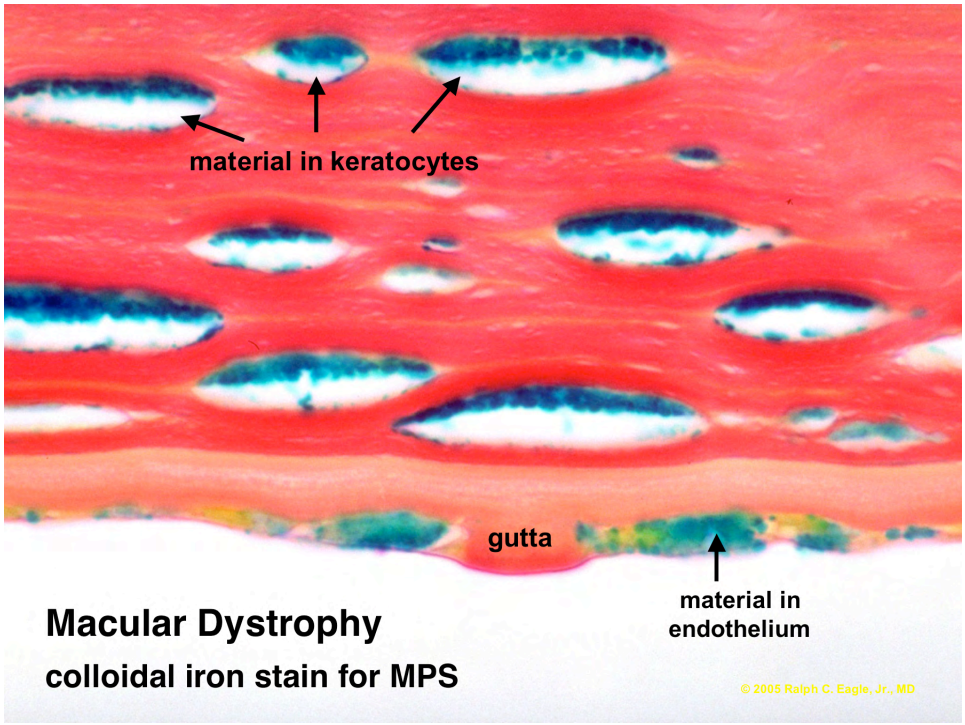

Colloidal Iron for AMP - Macular Dystrophy



Mnemonics for three classic stromal dystrophies:
Mickey Mouse Goes Home to L.A.
Marilyn Monroe Got Hers in L.A.
(Macular, Mucopolysaccharide; Granular, Hyaline; Lattice, Amyloid)

Schnyder's central stromal crystalline dystrophy
Autosomal dominant
Needle shaped polychromatic **cholesterol** crystals in anterior stroma, prominent bilateral arcus
Diffuse stromal clouding in some may necessitate PK (age 40-50)
? association with systemic lipid disorder in some cases (xanthelasma, elevated serum lipids)

François-Neetan's Fleck Dystrophy (dystrophie mouchetée)
Vision normal, flecks in stroma found incidentally
Autosomal dominant, occasionally unilateral
Swollen keratocytes contain MPS, lipid

Congenital Hereditary Stromal Dystrophy
Autosomal dominant, bilateral corneal clouding
Stationary, normal epithelium, normal corneal thickness
Collagen fibers half normal diameter (15nm)

Pre-Descemet's Dystrophy
Cornea farinata: age related degenerative change
Other entities (see Spencer, Vol 1, p336)

Deep Filiform Dystrophy
Enlarged keratocytes contain fat and phospholipid inclusions
Resembles cornea farinata, may be same entity

Congenital Stromal Dystrophy – Decorin Gene

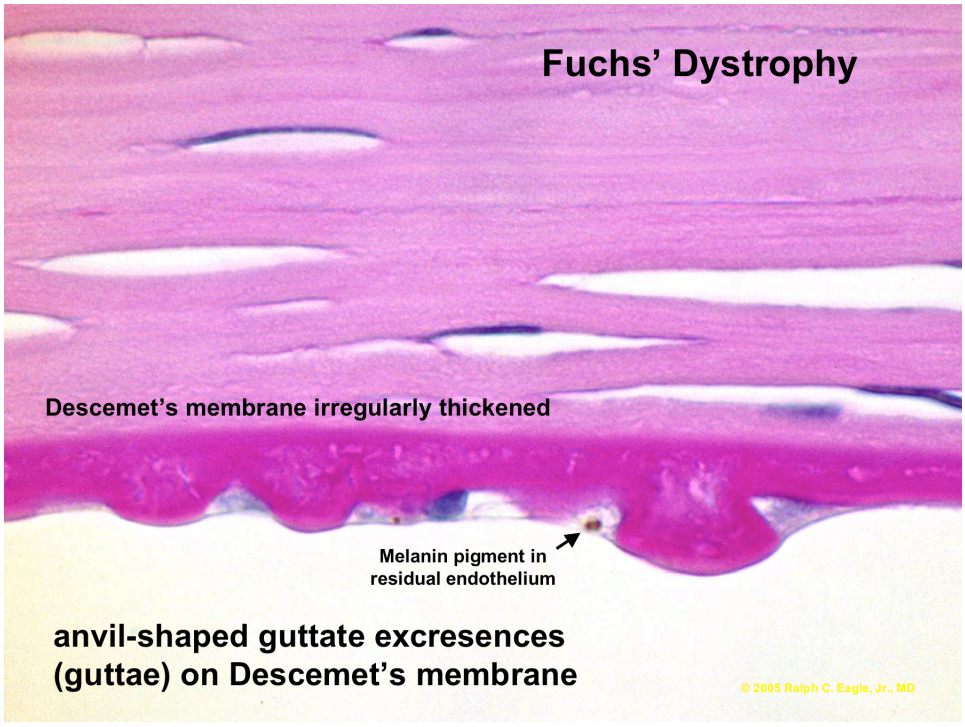
Endothelial dystrophies

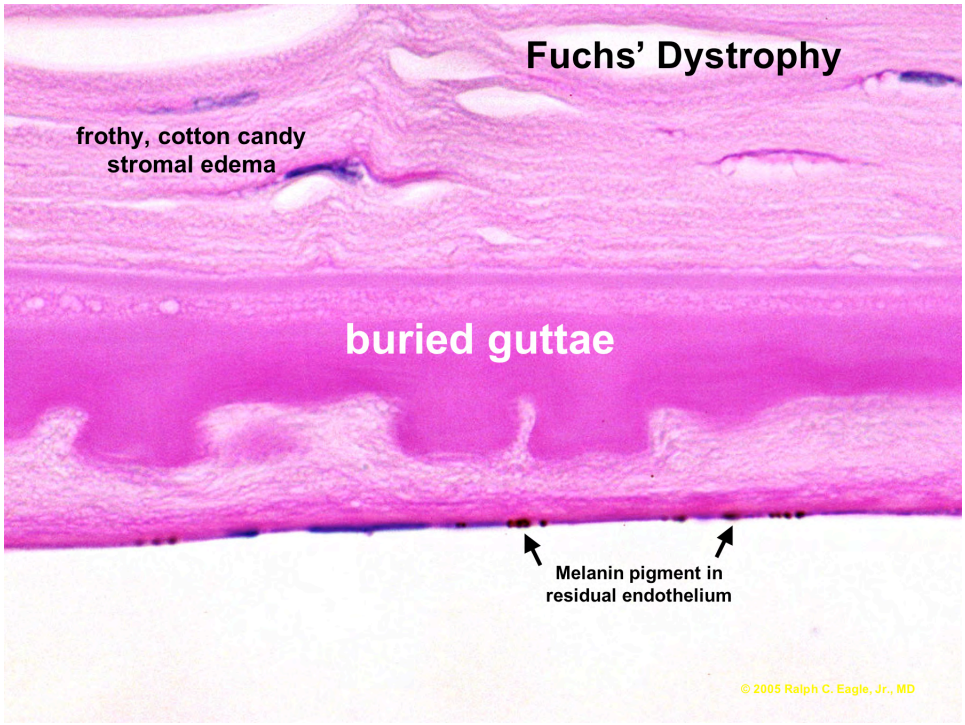
***Fuchs' Combined Dystrophy** (cornea guttata)

Primary endothelial dystrophy (Adult onset)

Anvil-shaped guttate excrescences of abnormal basement membrane material secreted on Descemet's membrane; DM thickened, often multilaminar, guttae may be "buried" by retrocorneal membrane; pigment phagocytized by endothelium.

Secondary stromal edema, bullous keratopathy (Fuchs described epithelial changes)





Congenital Hereditary Endothelial Dystrophy (CHED)

Two types: rare autosomal dominant, more common recessive

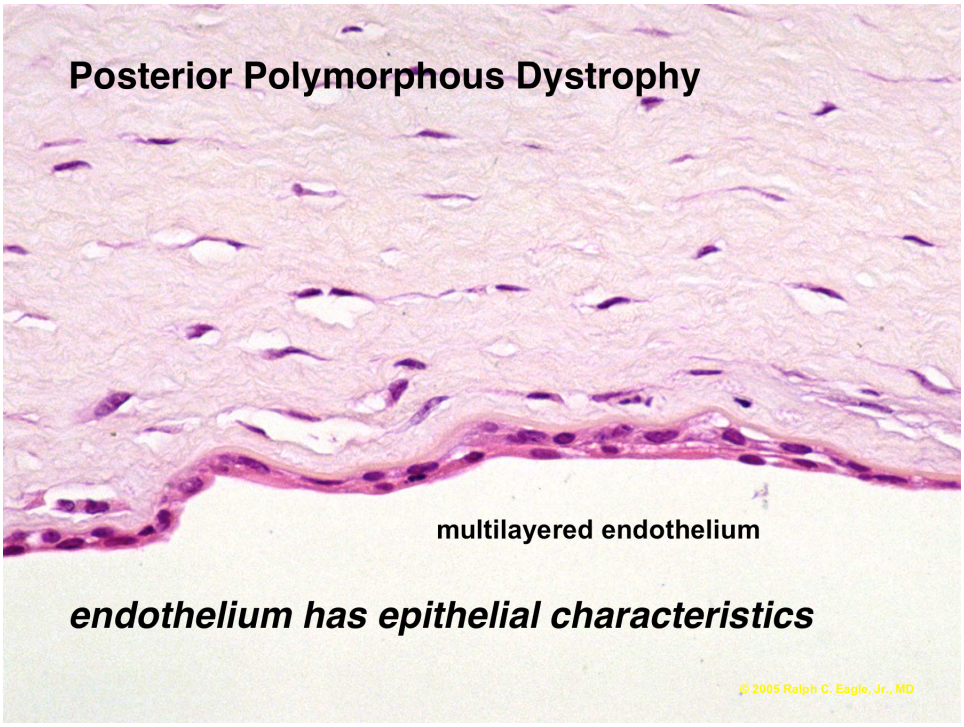
Thickened edematous stroma, massively thickened Descemet's, atrophic or nonfunctioning endothelium

Posterior Polymorphous Dystrophy of Schlichting *(COL8A2 gene, 20q11)*

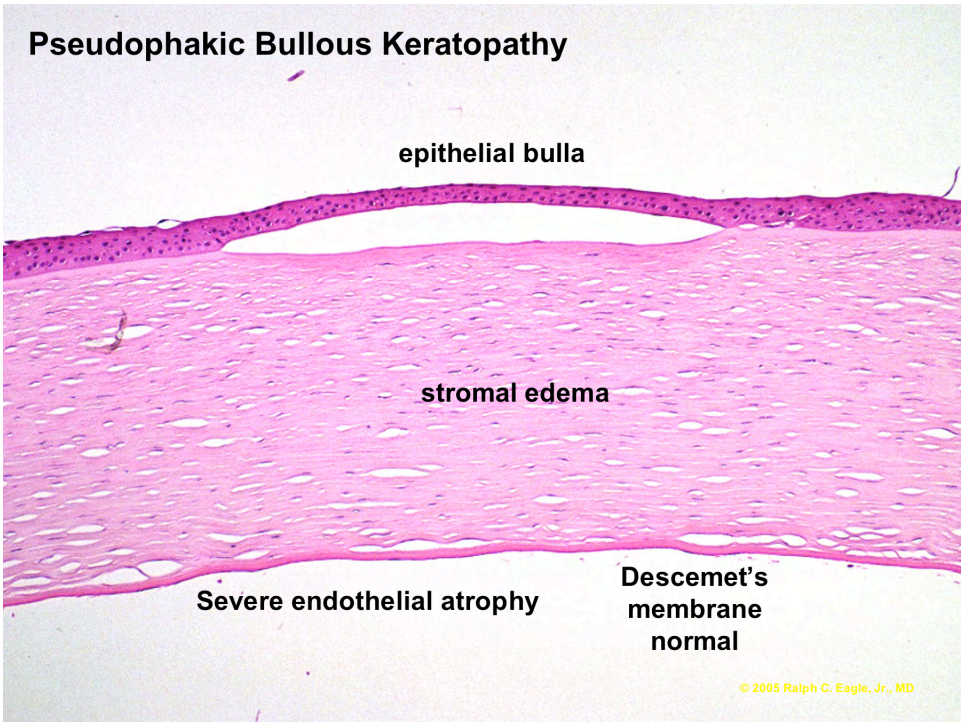
Irregular blebs or vacuoles at level of Descemet's membrane surrounded by gray opacification. Heterogenous disease spectrum also includes congenital corneal opacification, gutters or troughs, changes resembling ICE syndrome or Axenfeld-Rieger syndrome

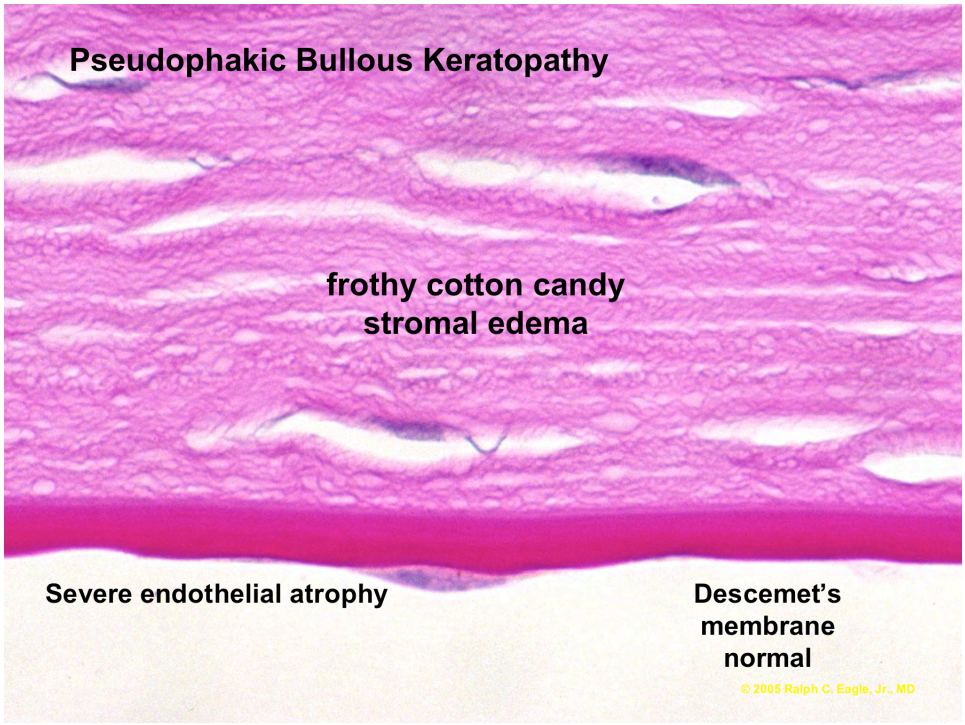
Most autosomal dominant, some recessive

Endothelial cells have epithelial characteristics: (multilayered, tonofilaments, multiple microvilli, surface keratin differentiation)



Iridocorneal Endothelial (ICE) Syndrome- (not a dystrophy)




Pseudophakic Bullous Keratopathy
frothy cotton candy
stromal edema
Severe endothelial atrophy
Descemet's
membrane
normal
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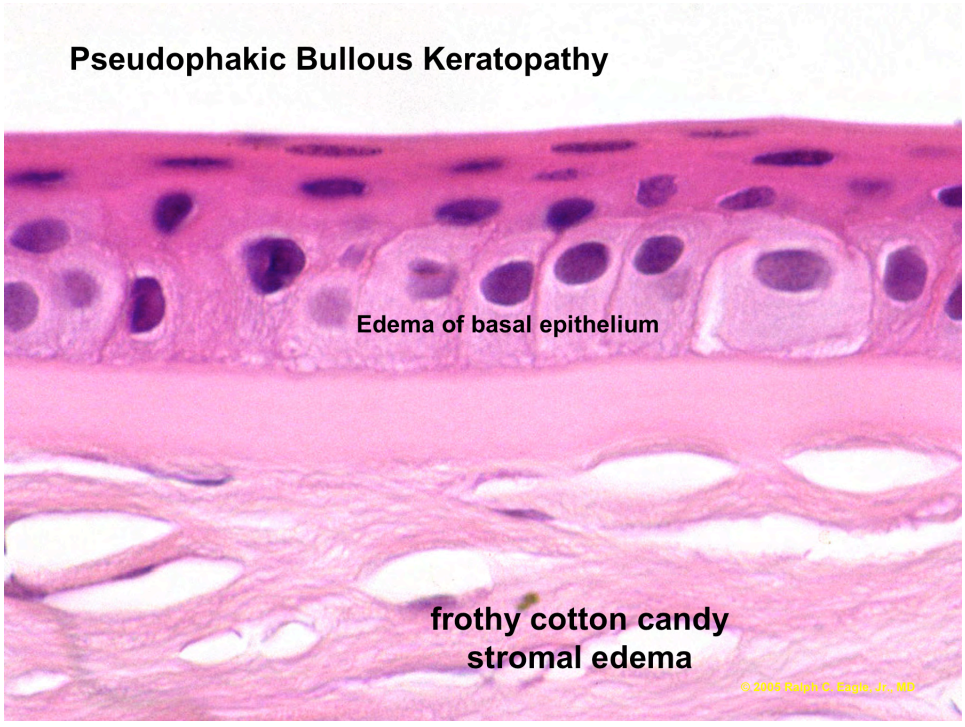
Pseudophakic Bullous Keratopathy
Edema of basal epithelium
frothy cotton candy
stromal edema
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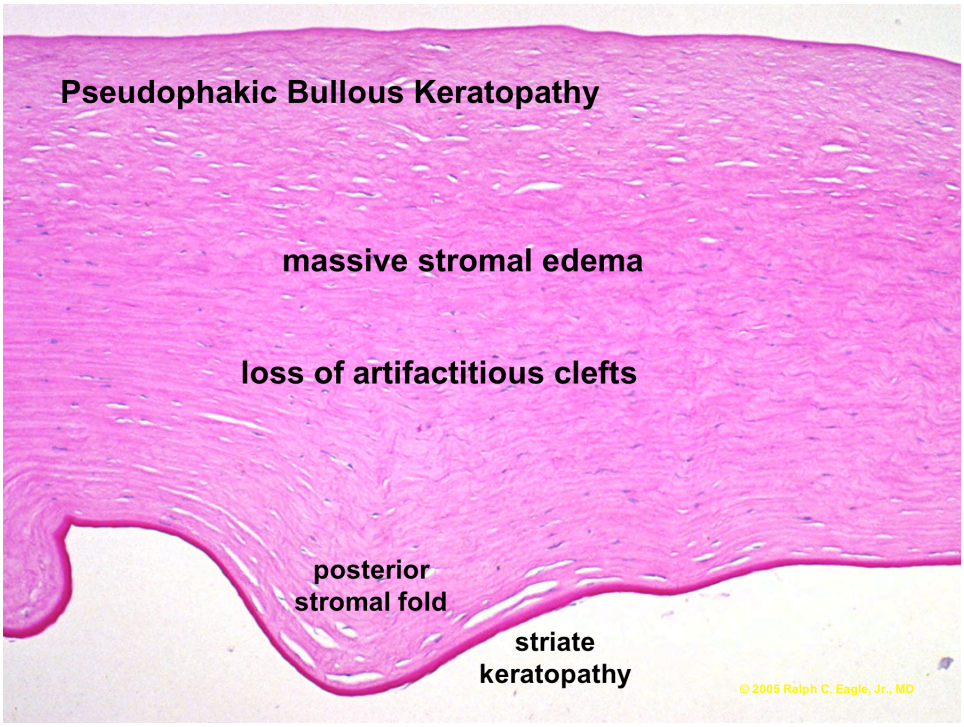


Corneal Involvement in Systemic Diseases

Systemic mucopolysaccharidoses
Severe, early opacification in MPS-IH (Hurler), I-S (Scheie), VI (Maroteaux-Lamy)

Mucolipidoses

Fabry's disease (alpha galactosidase deficiency)
Cornea verticillata in 90% of affected males

Wilson's disease: Kayser-Fleischer ring, Cu in Descemet's membrane

Ochronosis (alkaptonuria): brown granules in sclera, peripheral Bowman's

Refsum's disease

LCAT deficiency, fish eye disease, Tangier disease

Gout

Cystinosis

Multiple myeloma, protein dyscrasias

Corneal crystals

Cystinosis, tyrosinemia,
Immunoglobulin (multiple myeloma)
Uric acid (gout)
Bietti's crystalline dystrophy
Cholesterol (Schnyder's crystalline dystrophy)
Plant sap injury (Dieffenbachia)
Clofazimine (antibiotic for leprosy, reversible if treatment stopped)

Enlarged Corneal Nerves

MEN Type IIb (ganglioneuromas?)
Hereditary Icthyosis
Hanson's Disease (leprosy)
keratoconus

Refsum's Disease
Fuchs corneal dystrophy
Primary amyloidosis
failed PKP
congenital glaucoma
acanthamoeba keratitis
neurofibromatosis type I

Sclera

Blue sclera- osteogenesis imperfecta tarda, autosomal dominant; sclera thin, type I collagen fibers are immature, 50% reduced diameter
Congenital ectasias and staphylomas
Scleral icterus
Ochronosis (alkaptonuria)- homogentisic acid oxidase deficiency, autosomal recessive, 70% have worm-shaped pigment deposits anterior to rectus muscles
Cogan's senile scleral plaque: deposition of calcium salts (calcium phosphate) anterior to rectus tendon insertions, gray translucent appearance clinically.
Episcleral osseous choristoma - upper temporal quadrant

Inflammation

Simple episcleritis
- Spontaneous, recurrent; average age in 50's; sexes equal
- Pain, injection; may last several weeks despite steroids
- Histology: nongranulomatous, vascular dilation, perivascular lymphocytic infiltration

Nodular episcleritis
- Pathology similar to rheumatoid scleritis, but limited to episclera
- Palisade of epithelioid cells bordering central fibrinoid necrosis

Primary scleritis
- More severe than episcleritis, visual loss possible
- More prevalent in women, later onset, >50
- 10-33% have co-existing **rheumatoid arthritis**; rheumatoid arthritis patients who have scleritis have poorer prognosis.
- Systemic manifestations (cardiac, pulmonary, etc) may prove fatal:
- Scleromalacia perforans: 21% 8-year-mortality

Other connective tissue diseases associated with scleritis: Wegener's granulomatosis, SLE, polyarteritis nodosa, relapsing polychondritis, IBD, (also gout, ochronosis)

Infectious scleritis- Gram negative bacteria (Pseudomonas), fungi, Tbc, lues

Anterior scleritis
- Symptoms: Redness, photophobia, severe pain, 50% bilateral
- Conjunctival and episcleral injection may mask scleral inflammation
- Scleral perforation with uveal prolapse (scleromalacia perforans) uncommon (15-20%)

Posterior Scleritis
- Usually unilateral limitation of motility, proptosis, retrobulbar pain, field loss, retinal detachment, uveal effusion, disk edema, optic neuritis, may mimic uveal tumor

Histology: Nodular Scleritis
- Zonal necrotizing granuloma surrounding sequestrum of scleral collagen, fibrinoid necrosis, chronic inflammation, fusiform thickening, immune complex

deposition with complement activation. When collagen has been destroyed, inflammation and swelling recede, uvea herniates into defect

Histology: Diffuse (Brawny) Scleritis

Sclera markedly thickened by diffuse involvement of large areas of scleral collagen by granulomatous inflammation

N.B.: Zonal pattern of chronic granulomatous inflammation surrounding a central nidus of necrotic sclera = systemic disease, e.g. rheumatoid arthritis, etc.

Presence of microabscesses and necrosis suggests infectious scleritis

LENS

Congenital Anomalies

Posterior umbilication - fixation artifact in young eyes

Lenticonus

Capsular thinning or defects allows cortex to bulge

Anterior: bilateral, males, Alport's syndrome of hereditary hemorrhagic nephritis, deafness, abnormal type 4 collagen (posterior polymorphous dystrophy- rare)

Posterior: unilateral, sporadic

Lens coloboma

Secondary to absence of zonules in ciliary body coloboma; rarely due to ciliary body tumor (e.g., embryonal medulloepithelioma)

Congenital cataract: *rule of thirds*

1/3 hereditary, 1/3 idiopathic 1/3 assoc with systemic disease

Zonular cataract: zone of opacified fibers, e.g. Neonatal tetany

Anterior pyramidal cataract (congenital anterior subcapsular cataract)

Posterior variants result from abnormal hyaloid resorption

Rubella cataract: dense nuclear cataract, retained nuclei in embryonic nucleus

Lowe's syndrome: discoid lens, capsular increscences

Down's syndrome

Cataract

Opacification or optical dysfunction of crystalline lens

"End-stage" or final common pathway of lens pathology - many causes

4 basic types of cataract recognized histopathologically

(Lens has limited vocabulary of histopathologic expression)

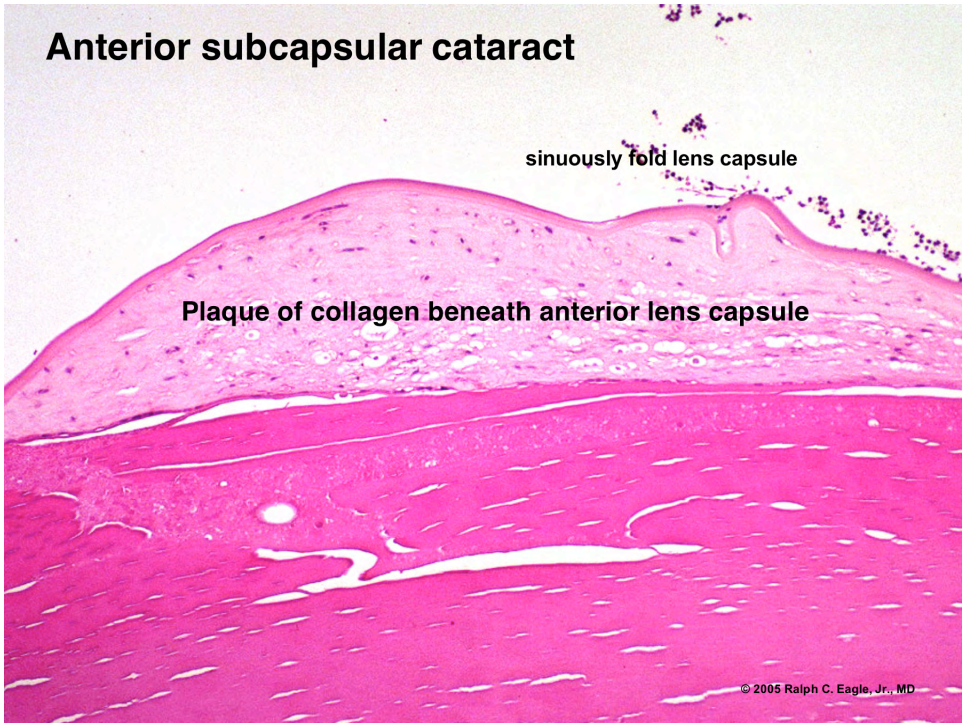
Anterior subcapsular cataract

Fibrous plaque beneath folded anterior capsule secreted by irritated metaplastic anterior epithelial cells

Cells surrounded by basement membrane capsules

Rare clinically, common in eye pathology lab; often hidden clinically by posterior synechias and pupillary membranes

*****Similar mechanism of epithelial proliferation and fibrosis operative in posterior capsular opacification and wrinkling (capsular fibrosis)***


Anterior subcapsular cataract
sinuously fold lens capsule
Plaque of collagen beneath anterior lens capsule
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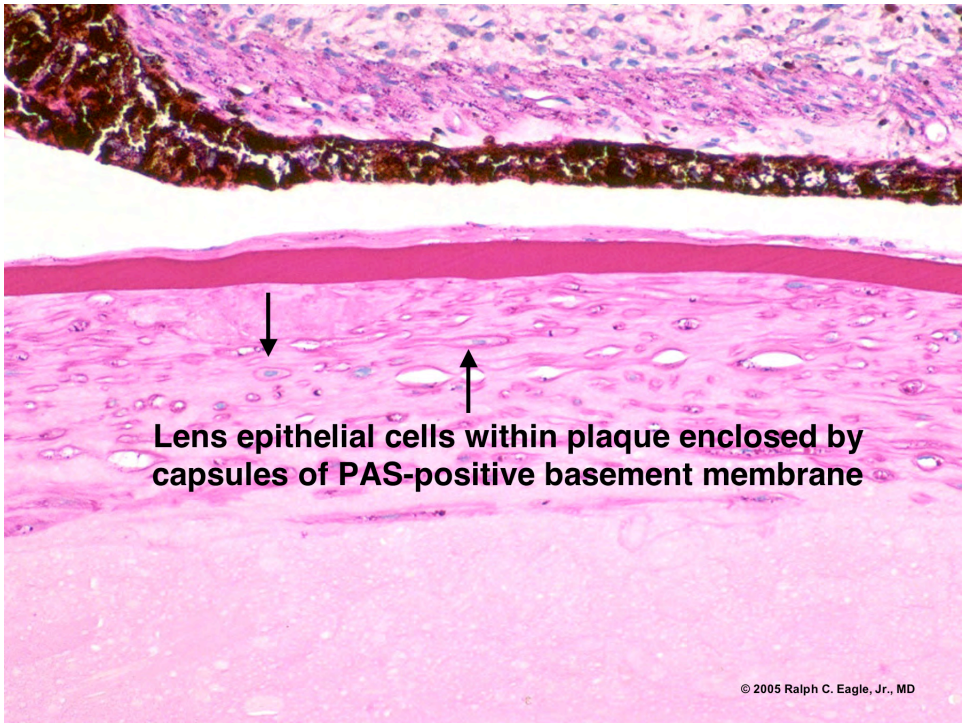
Lens epithelial cells within plaque enclosed by capsules of PAS-positive basement membrane
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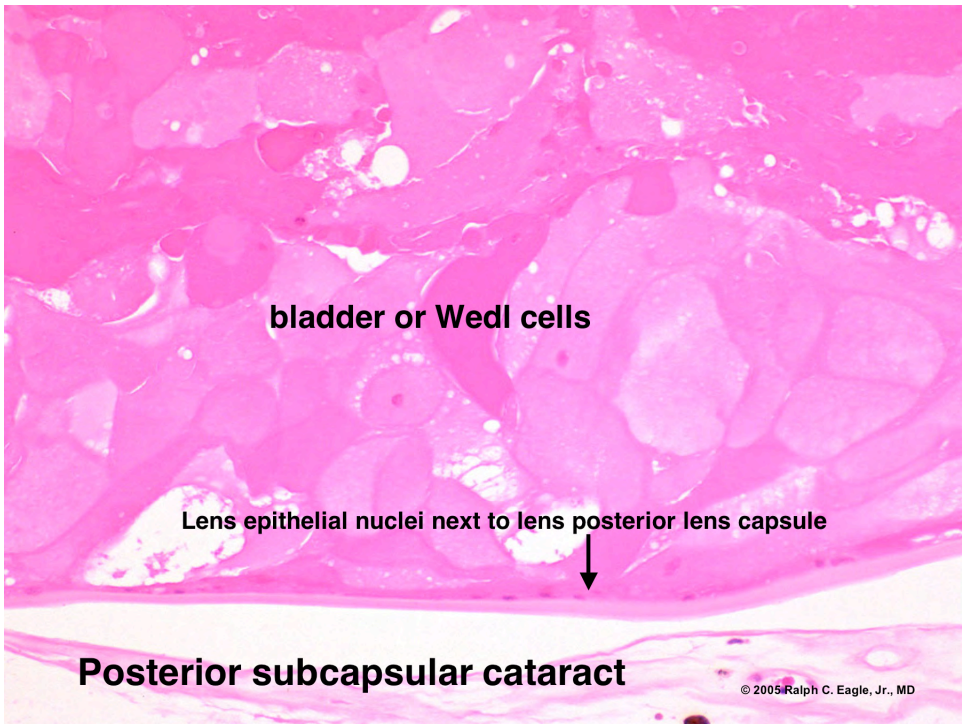
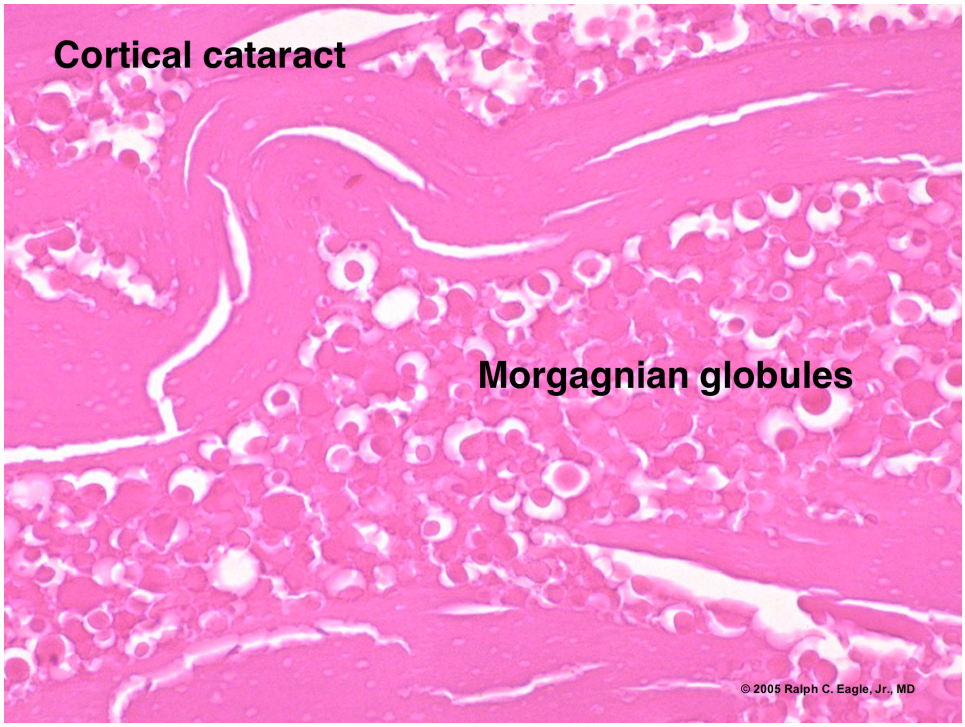
Posterior subcapsular cataract
Posterior migration of lens epithelium (normal termination at lens equator); **bladder or Wedl cell** formation (eosinophilic globular cells that have nuclei!!)
Clinically interferes with near vision early, causes glare symptoms



Elschnig's pearls- Wedl cells formed by **proliferation of residual lens epithelial cells post-ECCE**

Cortical Degeneration
Lens fibers fragment, ooze degenerated protein, liquefaction
Vacuoles, water clefts, total liquefaction (Morgagnian cataract)
Morgagnian globules (round, eosinophilic, NO NUCLEI!!!)
Liquefied cortex exerts osmotic effect (intumescent cataract)
Lens substance can leak through intact capsule
Loss of substance leads to shrunken hypermature cataract with prune-like wrinkled capsule; can incite bland macrophagic response, **phacolytic glaucoma**
Cholesterol crystals (Christmas tree cataract)


Cortical cataract
Morgagnian globules
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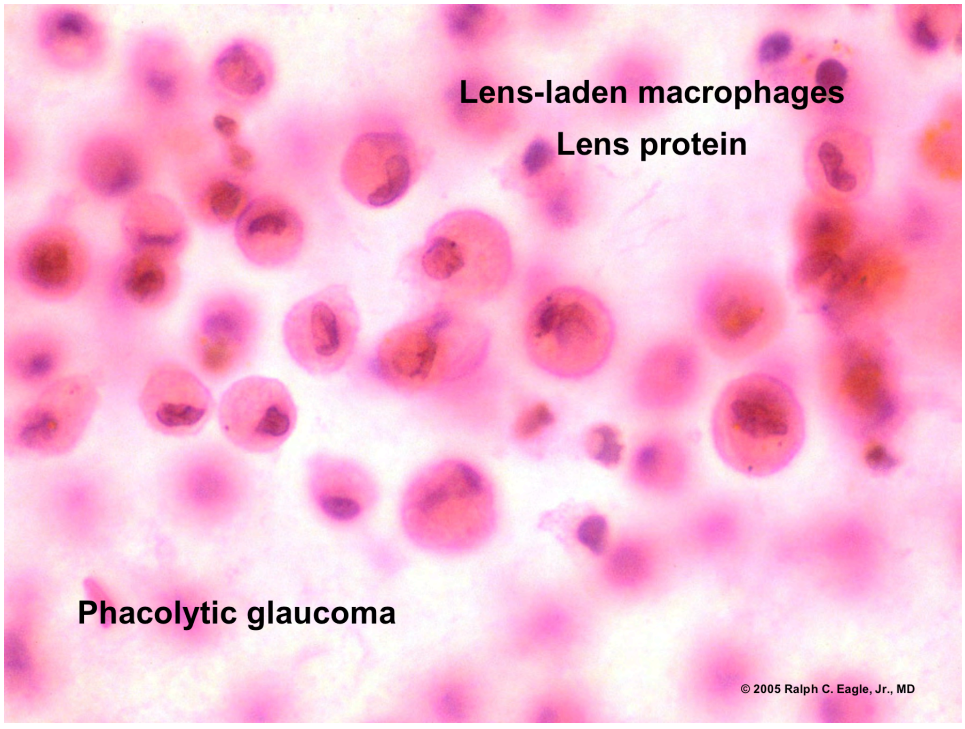
Lens-laden macrophages
Lens protein
Phacolytic glaucoma
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Nuclear Sclerosis
Inevitable in growth and development of lens
Old, inwardly sequestered lens fibers degenerate (analogous to desquamating keratin in skin)
Increased eosinophilia, loss of artifactitious clefts
Urochrome photo-oxidation pigment: blue-yellow color defects
Lenticular myopia due to increased index of refraction
Cataracta brunescens, cataracta nigra
Calcium oxalate crystals in nucleus

Complicated cataracts
Fuchs' heterochromic cyclitis
Low grade asymptomatic uveitis, no rx required; fine stellate or filiform kp's
Involved eye lighter in 90%; iris darker in inverse or paradoxical heterochromia due to severe stromal atrophy
Patients tolerate cataract surgery well
Fine vessels in angle without synechia formation, filiform hyphema; secondary open angle glaucoma in 10-50%
Chronic uveitis
Sarcoidosis, juvenile rheumatoid arthritis (RF seronegative ANA+, pauciarticular)
Retinitis pigmentosa (posterior subcapsular)
Tumors- ciliary body tumors compress lens, cause posterior migration of lens cells
Glaukomflecken- focal areas of lens epithelial necrosis with associated cortical damage post acute attack, ? toxins in stagnant aqueous

Aldose reductase and **osmotic cataracts (Sugar Cataracts)**
Diabetes mellitus: normal glycolytic pathway overwhelmed by elevated glucose level. Insoluble sugar alcohol **sorbitol** is synthesized by alternate aldose reductase pathway. Osmotic cataract formation. (Causes diabetic retinal microangiopathy too!)

Galactosemia: recessive hereditary defect in galactose 1-P uridyl transferase; mental retardation, oil droplet cataract; sugar alcohol dulcitol or galactitol formed by similar mechanism; dietary therapy

Galactokinase deficiency: rare cause of presenile cataract in adults

Ectopia lentis (spontaneous dislocation of the lens)

Lens dislocation in connective tissue disorders is caused by heritable mutations in elastic microfibrillar protein fibrillin (Marfan's, Weil-Marchesani), or by mutations that affect fibrillin structure secondarily (homocystinuria, sulfite oxidase deficiency).

Marfan's syndrome (arachnodactyly) 15q21, fibrillin 1 gene

Lens dislocates **up** and out (80%)

Tall stature, spidery digits, cardiac disease, dissecting aneurysm

Autosomal dominant defect in elastic microfibrillar glycoprotein **fibrillin-1,** major constituent of zonules (and framework for elastic tissue deposition)

Severe axial myopia, retinal detachment

Homocystinuria

Autosomal recessive, **cystathionine beta-synthase deficiency** (21q21.3)

Zonules deficient in cysteine, reduced sulfhydryl cross-linking weakens fibrillin

Blonde, marfanoid habitus, increased urinary excretion of homocystine (diagnose with serum homocystine levels)

Zonules absent; lens dislocates **down** and in, or into anterior chamber

PAS (+) layer of abnormal zonules on ciliary body; peripheral RPE degeneration

Platelet abnormality, hypercoagulability, tendency to **thromboembolic complications, especially** under general anesthesia, 75% die by age 30, MR

Weill-Marchesani Syndrome (bradydactyly)- autosomal recessive or dominant

Dominant form linked to fibrillin-1 gene; recessive 19p13

Short stature and digits, hearing defects, inflexible joints

Microspherophakia, secondary pupillary block glaucoma worsened by miotics

Lens dislocates axially

Other ocular anomalies: high lenticular myopia (15-20 D), cataract, microcornea

Dominant Spherophakia, McGavic Type

Sulfite oxidase deficiency-autosomal recessive

Infants with seizures, mental retardation, Lens dislocation in 50%

Most have molybdenum cofactor deficiency

Hyperlysinemia?- association with ectopic lentis has been doubted

Ehlers-Danlos Syndrome - only a single reported case

Anterior megaloglobus, ectopia lentis et pupillae, aniridia, buphthalmos

Trauma Tertiary syphilis

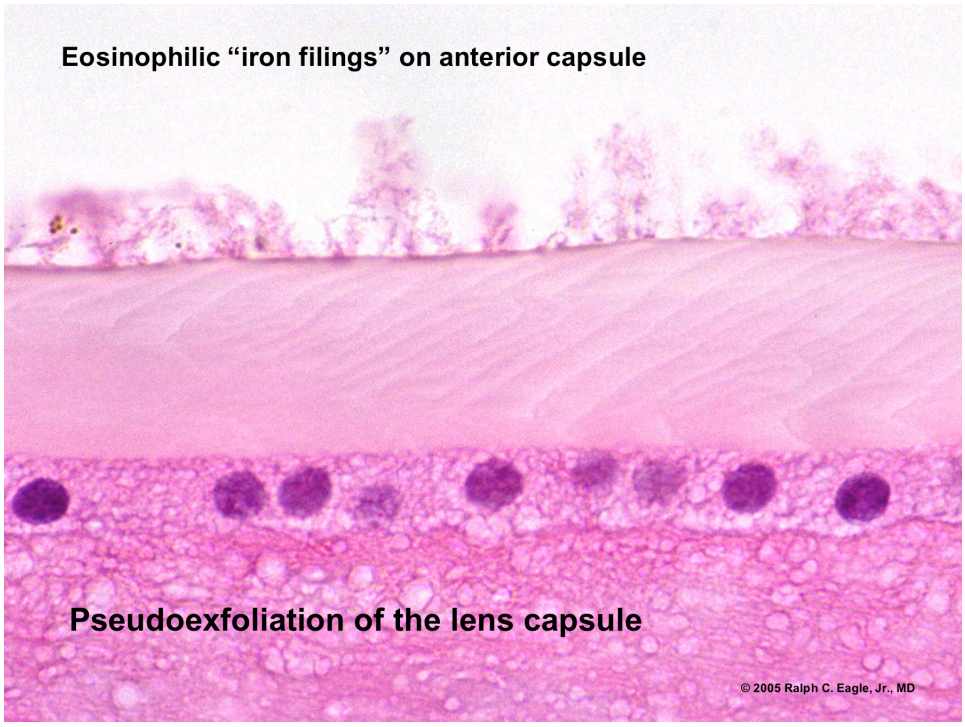
Lens Capsular Abnormalities

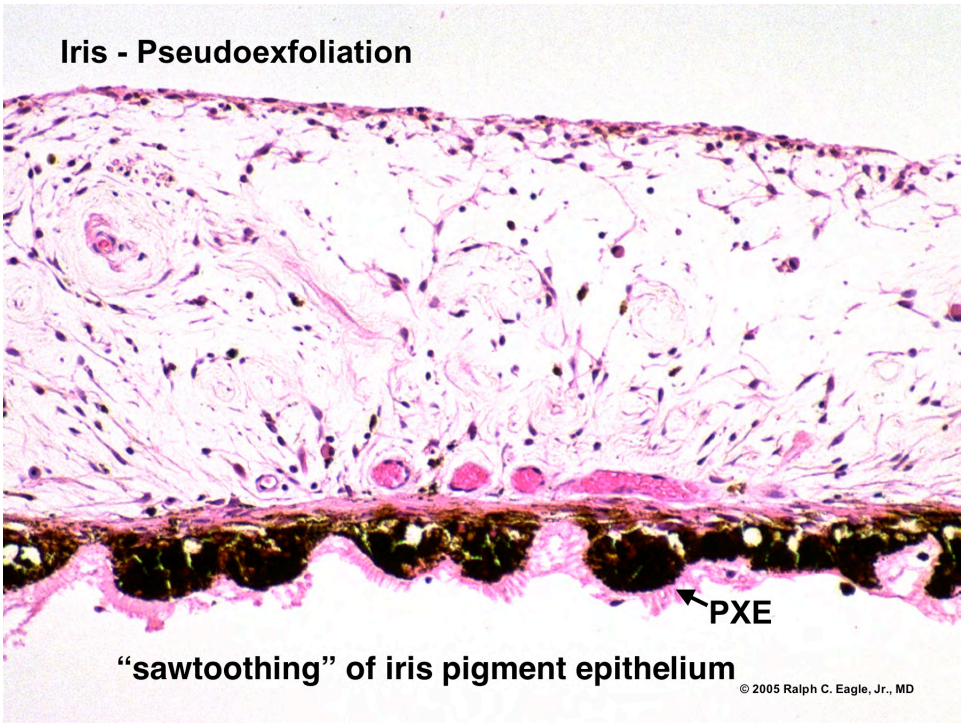
True Exfoliation of lens capsule (capsular delamination)

Split in capsule forms scrolls clinically, classically secondary to occupational exposure to infrared radiation (glass blowers), also an aging change; no association with glaucoma

Pseudoexfoliation of lens capsule (Exfoliation Syndrome)

Abnormal extracellular matrix material (of complex composition); produced by lens epithelial cells, extruded through lens capsule
Found on anterior lens capsule, posterior iris, ciliary body, zonules, vitreous face.
On lens: central disk, clear interval, peripheral zone
Flakes at pupillary margin suggest diagnosis in undilated patient
Associated with **secondary open angle glaucoma** (glaucoma capsulare) 50%
Abnormal iris- pigment epithelial "sawtoothing", poor dilation
Pigment dispersion-Sampaolesi's line
Ocular manifestation of **systemic elastosis** (also found in conj, skin, lung, liver)
Immunoreactive with zonular elastic microfibrillar proteins
Abnormal zonules- high incidence of **IOL and capsular dislocation**





Traumatic Cataract

Perforating injuries, ruptured lens
Vossius ring: iris pigment on lens capsule
Contusion cataract (petalliform cataract or contusion rosette)
Sign of old contusion injury, look for angle recession
Soemmerring's ring cataract: donut of residual equatorial cortex
Siderosis lentis: iron deposited in epithelium
Chalcosis lentis: copper deposited in basement membrane
Mercurialentis- mercury deposition in lens capsule (occupational)
Electrical cataract
Argon laser cataract
Blue light absorbed by yellow sclerotic nucleus; avoid with krypton red
Phacoanaphylactic endophthalmitis (phacoantigenic uveitis)
Localized endophthalmitis (*Propionibacterium acnes, Candida parapsilosis),*
Large bacterial (or fungal) colonies grow within capsular bag post ECCE, white plaques, delayed chronic granulomatous response

Toxic cataracts

Corticosteroids: posterior subcapsular, dose uncertain
Occurs in approximately 1/3 (12-60%) with chronic daily dose of 10mg
Incidence 20% if patient receives >15mg prednisolone for 2-8 years-
Anticholinesterases: anterior subcapsular vacuoles (84%)
Naphthalene, DNP, triparanol, mercury, phenothiazine

Cataract Associated with Systemic Diseases

Myotonic Dystrophy- chromosome 19, accumulation of CTG trinucleotide repeats
Myotonia, testicular atrophy, frontal baldness, cataract,
Presenile cataract with polychromatic anterior and posterior subcapsular cortical crystals. (spirally birefringent concentrically multilaminated "rice grains")

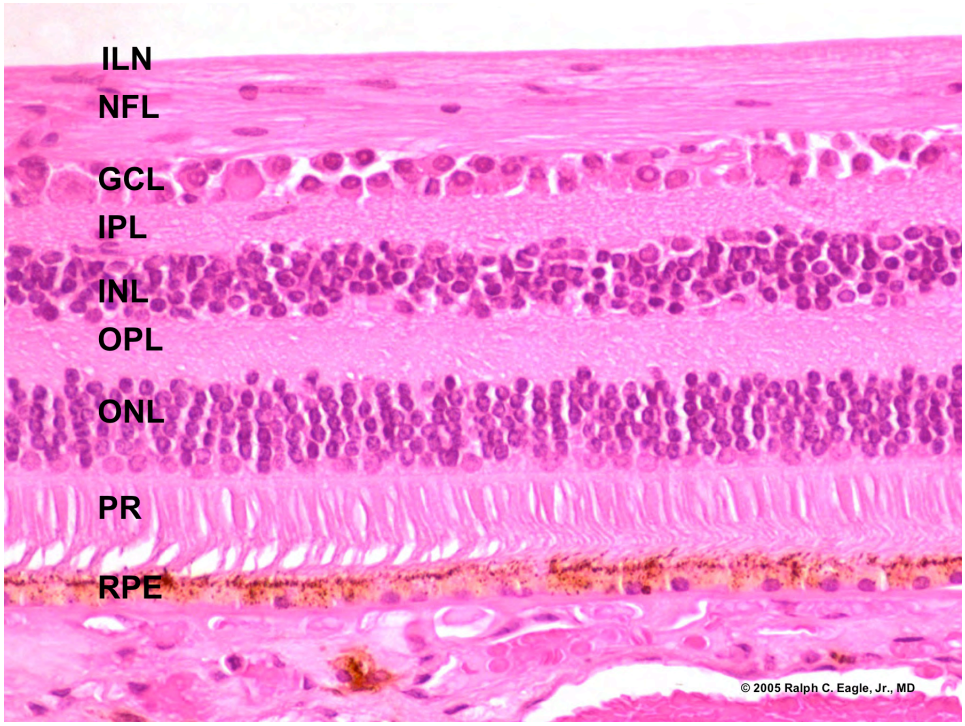
Wilson's Disease (Hepatolenticular degeneration)
Sunflower cataract, Kayser-Fleischer ring
Deposition of copper in lens capsule, Descemet's membrane
Similar findings occur in chalcosis; Copper deposition also has been reported in multiple myeloma, lung carcinoma
Diabetes mellitus
Galactosemia
Fabry's disease
X-linked deficiency of alpha-galactosidase A
Sphingolipidosis, storage of ceramide trihexoside
Cornea verticillata (Fleischer-Gruber) 90% of affected males
Posterior spoke-like opacities
Hereditary hyperferritinemia-crystals of L-ferritin

Cataract Associated With Skin Diseases
Atopic dermatitis (Andogsky's Syndrome),
Ectodermal dysplasias (Rothmund, Werner)
Acrodermatitis enteropathica

Retina

A peripheral colony of brain cells
Anatomy:

3 neuron system,10 layers



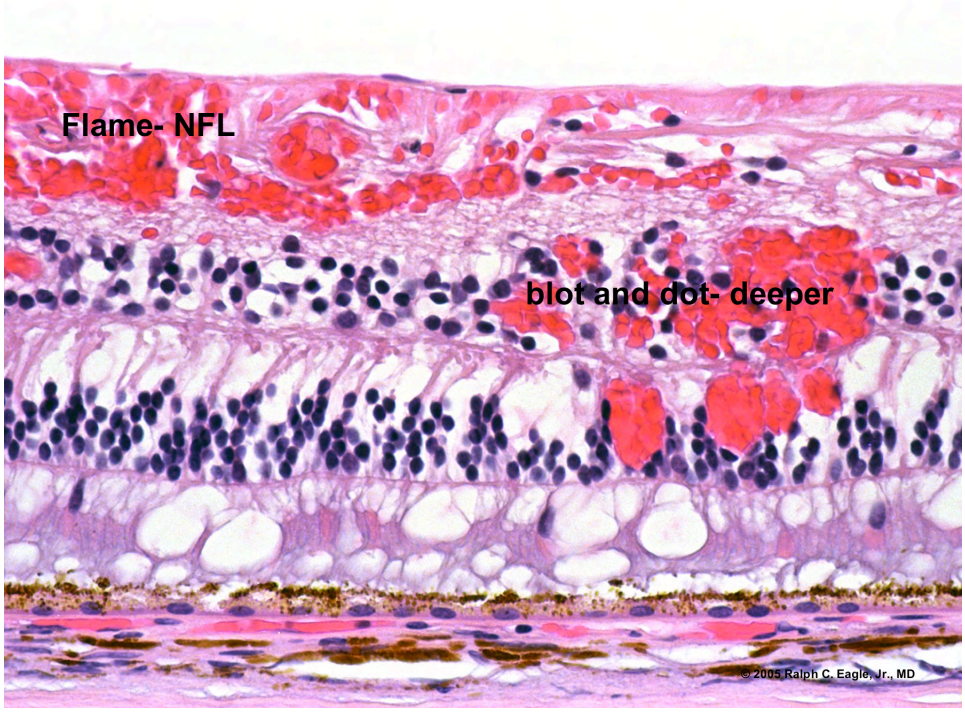
Retinal hemorrhages

Flame or splinter (superficial retinal hemorrhages)

Blood tracks along axons of **nerve fiber layer**

Blot and dot

Deep retinal layers, blood "corralled" by axons oriented perpendicular to Bruch's membrane



Scaphoid or boat-shaped (two types)

1. **Sub-ILM**: hemorrhagic detachment of internal limiting membrane
2. **Sub-hyaloid:** blood between ILM and posterior hyaloid

True subhyaloid hemorrhages do occur in patients with proliferative diabetic retinopathy

Sub-RPE hemorrhages

Dark-colored, can be confused with choroidal melanoma

Roth spot

White centered hemorrhage, central abscess in SBE,
Also leukemic cells, central nidus of fibrin

Blood retinal barrier – analogous to blood-brain barrier

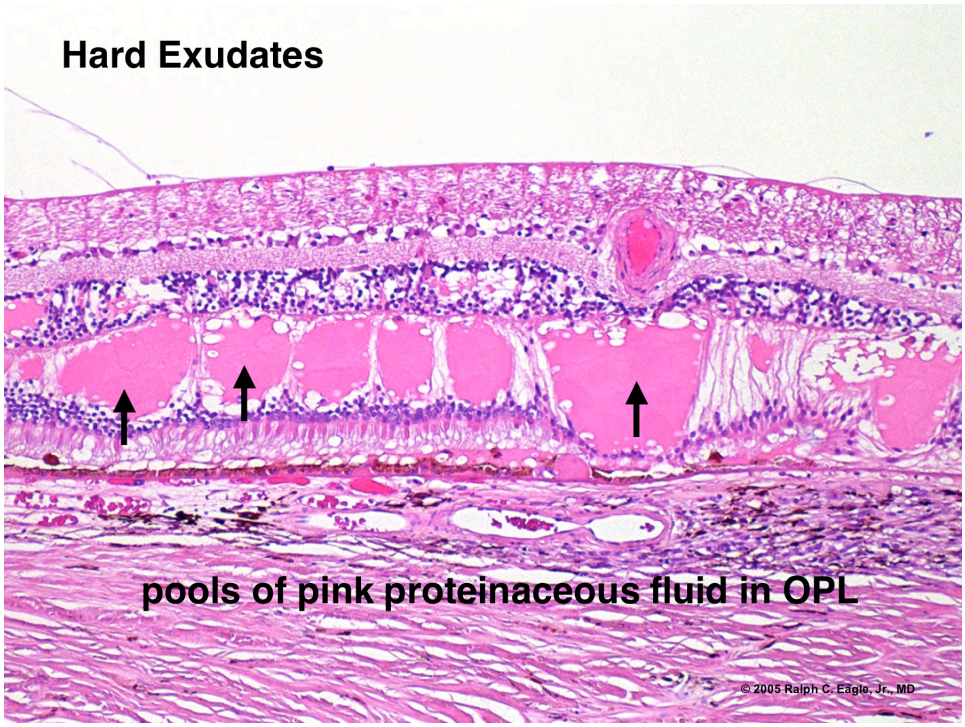
Inner- retinal capillary tight junctions

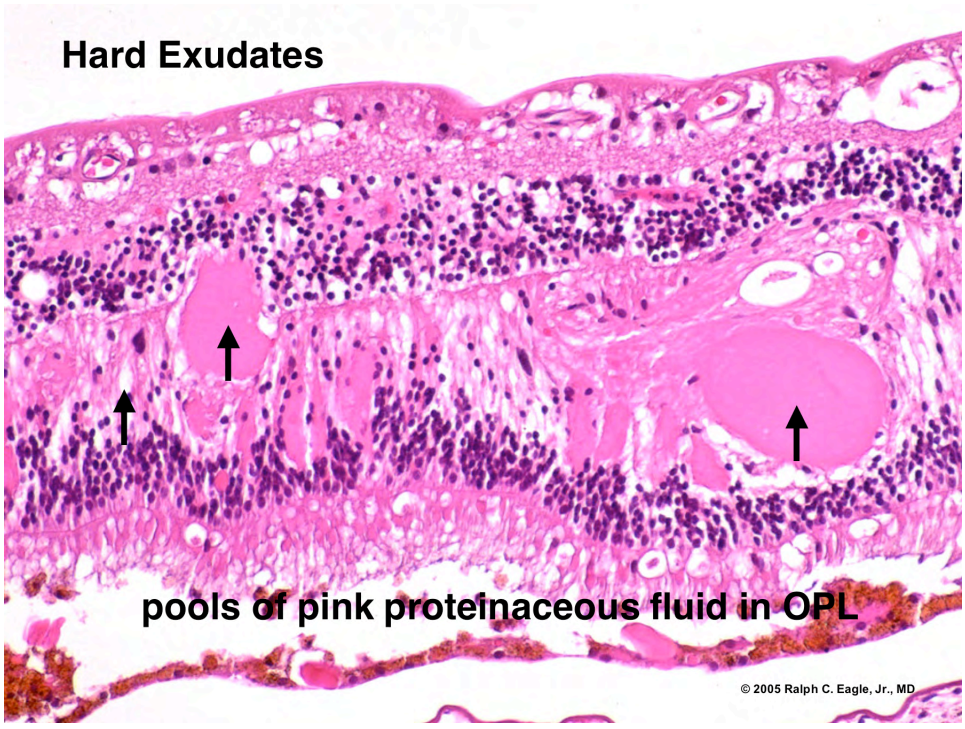
Outer- RPE tight junctions (fenestrated choriocapillaries leak)

Retinal exudates

Hard, yellow waxy exudates

Pools of eosinophilic lipoproteinaceous material in outer plexiform layer:
"watershed zone" between retinal and choroidal circulations.
Fluid derived from leaky retinal capillaries, competent capillaries absorb water, leaving protein and lipid behind
May be phagocytized by macrophages (Gitter cells)



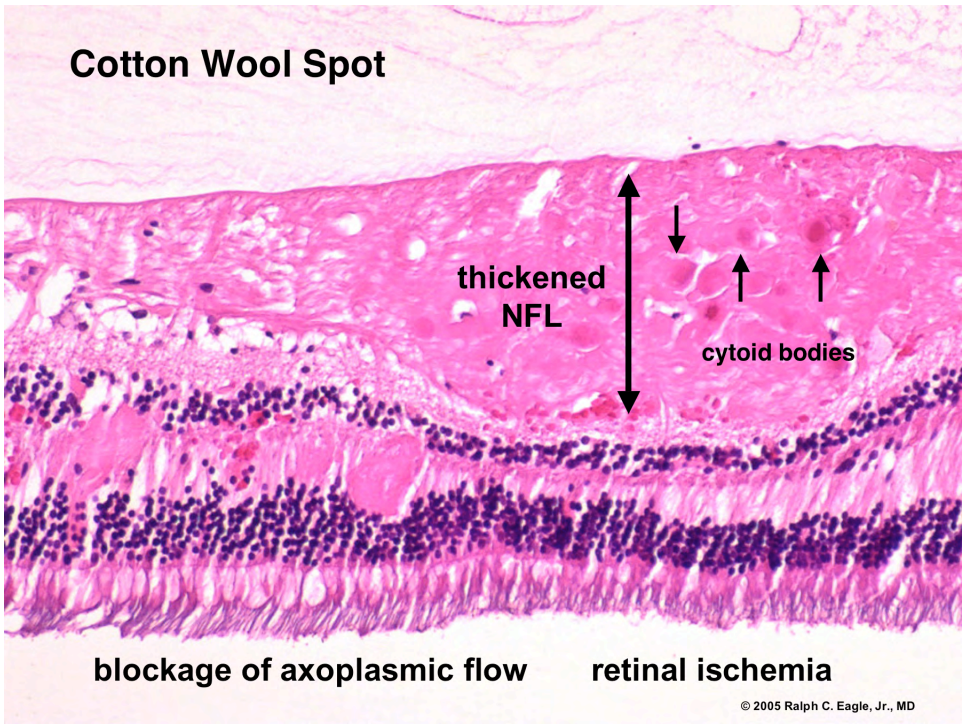


Circinate retinopathy
Ring of hard exudate surrounding leaking focus

Macular star
Stellate pattern of perifoveal hard exudates reflects **radial** orientation of **Henle fibers**

Cotton wool spots (soft exudates)

Microinfarctions of nerve fiber layer due to occlusion of precapillary arteriole
Blockage of axoplasmic flow in nerve fiber axons traversing ischemic focus produces **Cytoid bodies** or end bulbs of Cajal: swollen axons with eosinophilic nucleoid composed of dammed organelles.
Clinical marker for retinal ischemia, e.g. preproliferative diabetic retinopathy
Isolated finding in collagen vascular disease, AIDS
Confined to territory of radial peripapillary capillaries



Angioid streaks

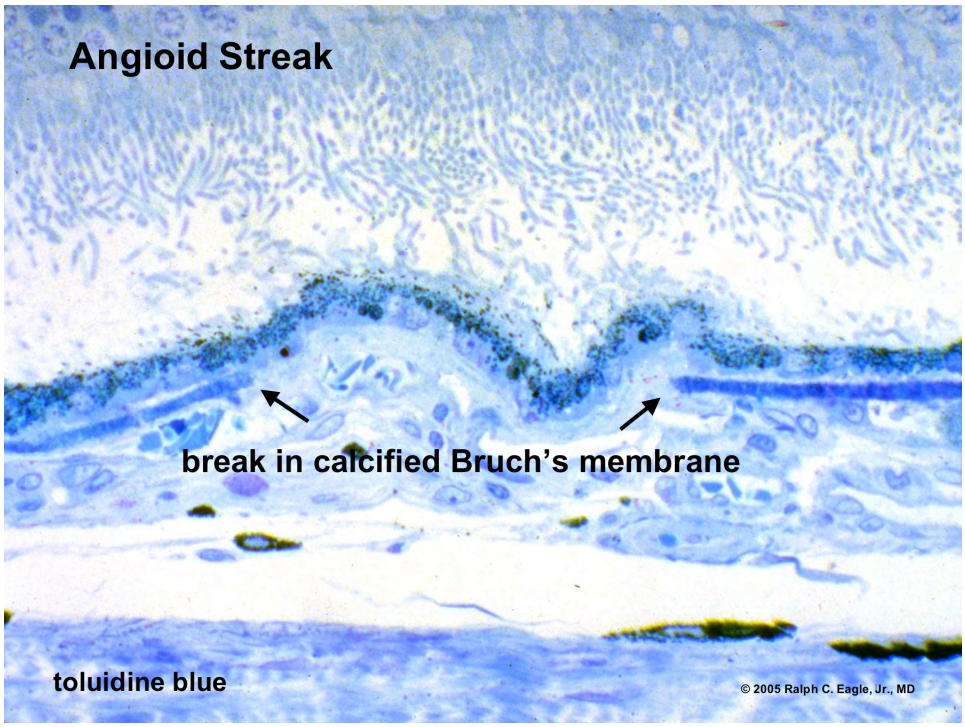
Breaks in calcified Bruch's membrane

Pseudoxanthoma elasticum (Peau d'orange fundus)

Paget's disease of bone, sickle cell (Hb SS)

Idiopathic, Ehlers-Danlos - ??

Subretinal neovascularization and disciform degeneration a complication



Central retinal artery occlusion

Ischemic infarction of retina

Clinical findings: sudden visual loss, milky-white loss of retinal transparency (regains in several days), slight retinal thickening

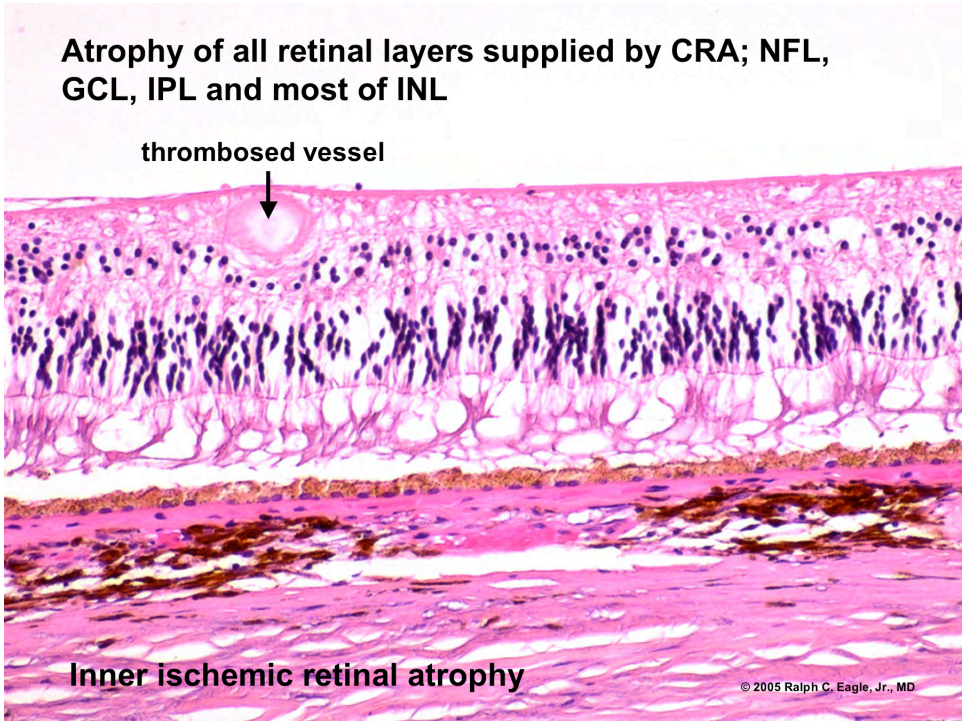
Early stages: coagulative necrosis, pyknosis, edema of inner retinal layers

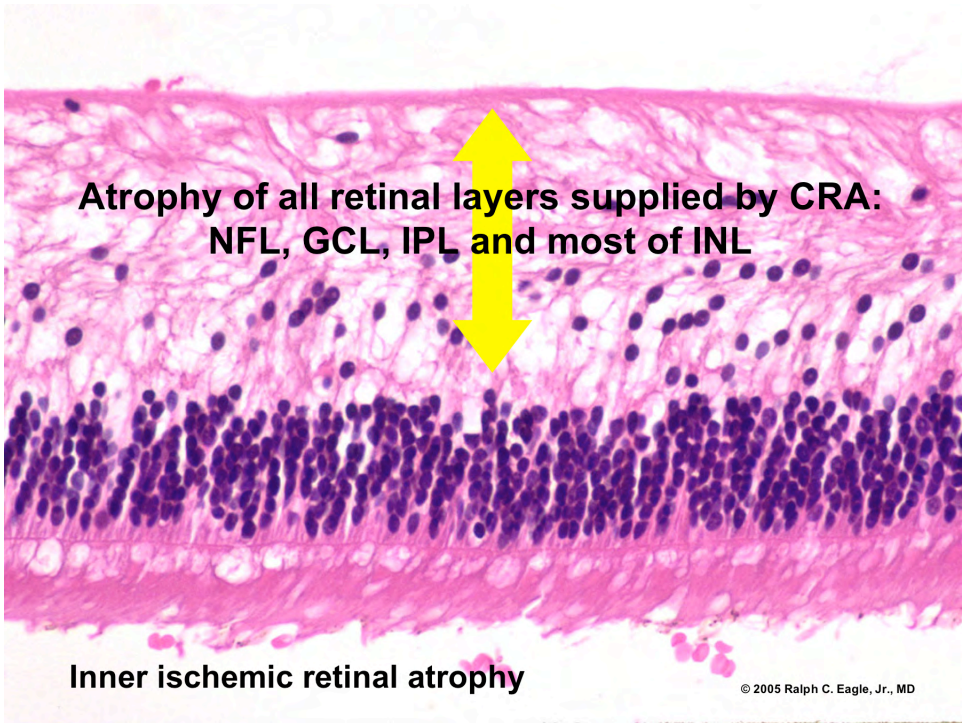
Macular **Cherry red spot** :"window" of thin, transparent foveolar retina surrounded by opacified infarcted tissue

Late stages: **"Inner ischemic retinal atrophy"** (atrophy of layers supplied by central retinal artery)

In contrast to glaucomatous atrophy, also **involves inner nuclear layer**

Inner layers have hyalinized appearance, gliosis absent (glial cells killed)




Atrophy of all retinal layers supplied by CRA:
NFL, GCL, IPL and most of INL
Inner ischemic retinal atrophy
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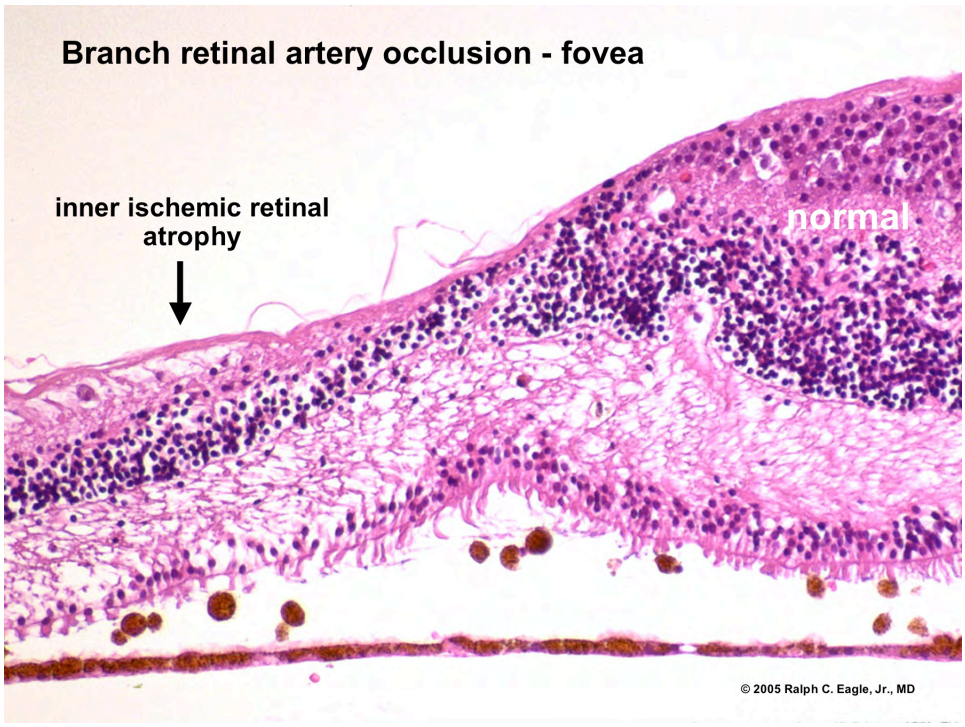
Branch retinal artery occlusion - fovea
inner ischemic retinal atrophy
normal
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Causes of CRAO:

*Atherosclerosis of CRA at or posterior to lamina cribrosa
(Atherosclerosis does not involve retinal arterioles)
*Emboli:
cholesterol (73%) or platelet fibrin (15%) from carotid plaques
calcific (11%) from heart
tumor (atrial myxomas in young patients)
*Vasculitis , e.g., **giant cell arteritis**, collagen vascular disease
Stat sed rate in elderly with CRAO!!

Cherry red spot in sphingolipidoses (e.g. **Tay-Sachs Disease**) results from storage of GM2 ganglioside in retinal ganglion cells. <u>There are NO ganglion cells in foveola</u>

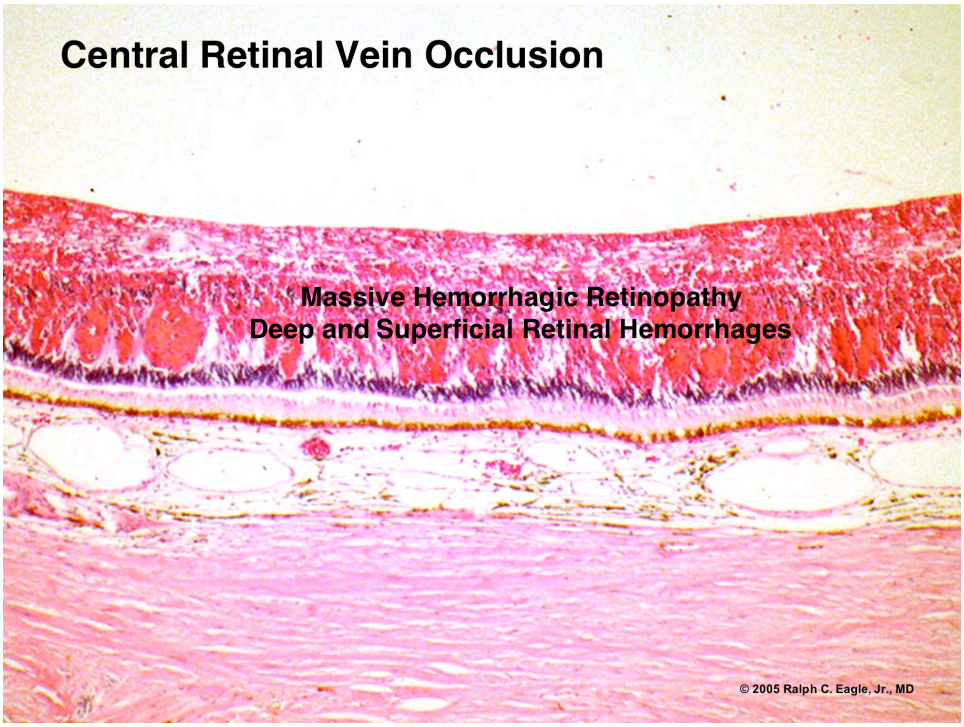
Tay-Sachs Disease- GM2 Gangliosidosis type I
TEM: multimembranous inclusions ("Zebra bodies")
Cherry red spot also seen in Sandhoff's, Niemann Pick, others..

Ophthalmic Artery Occlusion

Resembles CRAO, but no cherry red spot due to choroidal infarction
Severe visual loss, A wave of ERG absent

Retinal Venous Occlusions

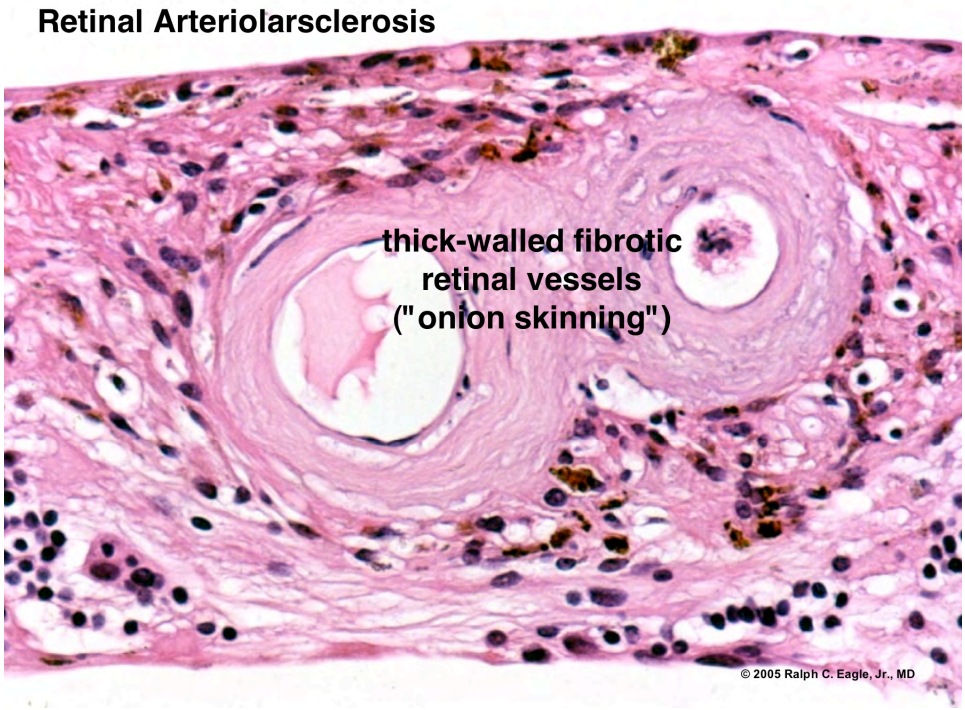
85% branch, 70% superotemporal
Associations: AS, hypertension, DM, >age 50, male, high body mass index (>20)
Local causes: glaucoma, papilledema, subdural, large optic disk drusen
Most related to arterial disease
Sclerotic artery compresses vein within common adventitial sheath; turbulence, endothelial damage, thrombosis of CRV within lamina
Hemorrhagic infarction of the retina
Early stages:
Edema, numerous deep and superficial hemorrhages, full-thickness and preretinal hemorrhages, hemorrhagic detachment, focal necrosis, cotton wool exudates, CME, shallow RD, disk edema
Late stages:
Disruption of retinal architecture, marked gliosis, hemosiderosis, hemosiderin-laden macrophages, thick walled vessels, neovascularization
CRV: recanalization, endothelial proliferation, phlebitis



Neovascular glaucoma ("90 Day glaucoma")-20% incidence in ischemic occlusions, NVD and NVE much less common
Ischemic CRVO occlusion characterized by: severe visual loss, cotton wool spots, capillary nonperfusion

Retinal arteriolarsclerosis

Chronic hypertension induces fibrosis in arteriolar wall
Healthy vessel walls transparent, only blood column in vessel seen
Widening of vascular light reflex, copper and silver wiring results from gradual obscuration of blood column by increasing fibrosis in wall.
AV crossing defects ("nicking") result from thickened arteriole hiding underlying venule



Hypertensive Retinopathy

Severe hypertension produces marked vasospasm, then muscular and endothelial necrosis and vascular incompetence and/or occlusion.
Edema, hard and soft exudates, exudative retinal detachment
Fibrinoid necrosis of vessels, optic disk edema
Choroidal vascular involvement: Elschnig's spots, Seegrist streaks

Retinal Arteriolar Macroaneurysms

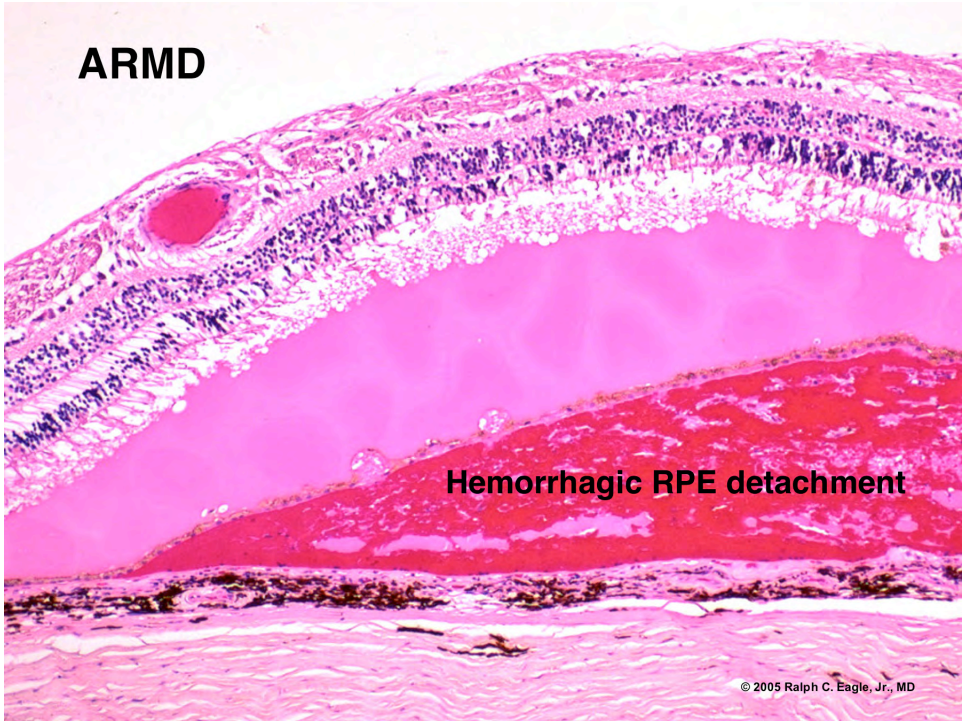
Arterioles posterior to equator, elderly patients with vascular disease: BP, ASCVD, 75% female. 67% hypertension
Edema, exudation, hemorrhage, (subretinal "H" can mimic MM)
Histology: greatly distended retinal arteriole, surrounding fibroglial proliferation, dilated capillaries, hemosiderin, exudates, hemorrhages.

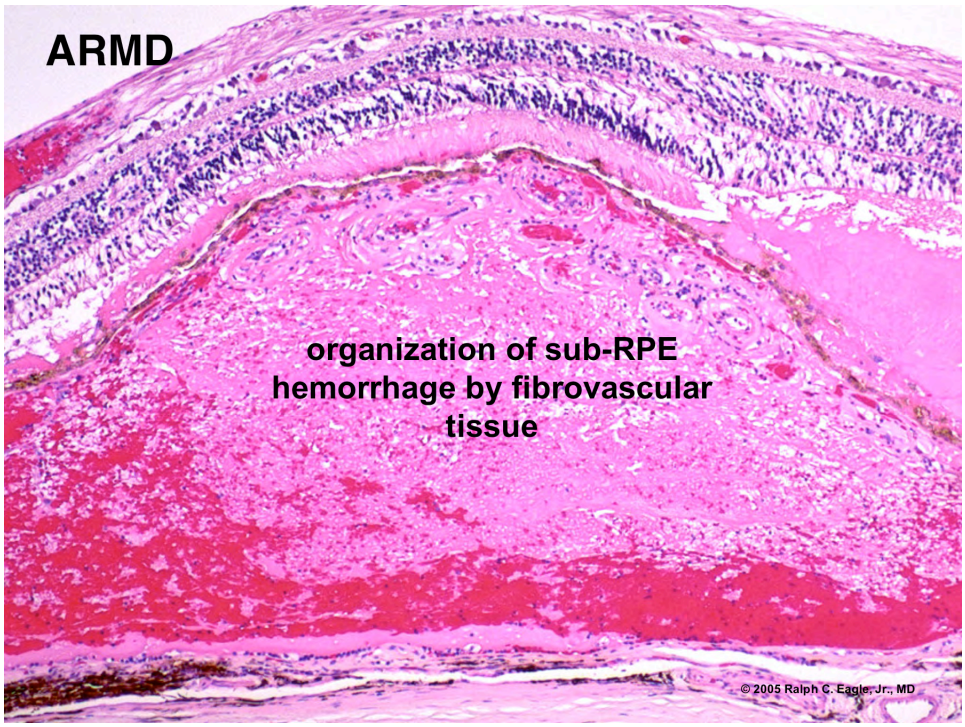
Toxic Maculopathies and Retinopathies

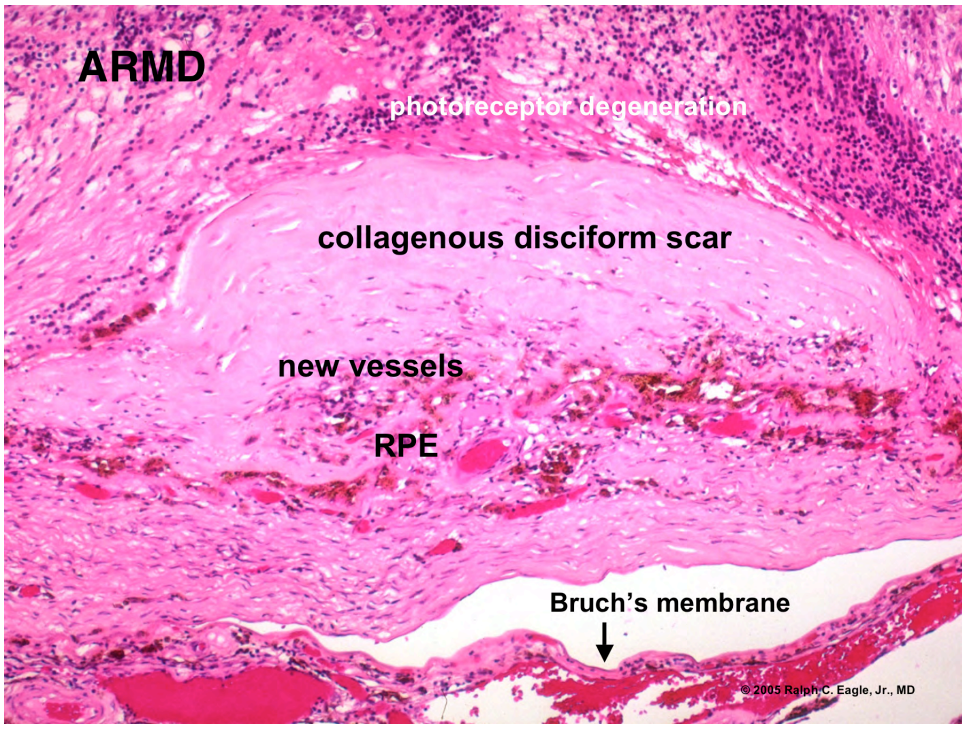
Gentamicin - inadvertent intraocular injection causes retinal infarction
Chloroquine, hydroxychloroquine (plaquenil)- (bull's-eye maculopathy)
Dose related, primary effect on RPE? - drug stored in melanin granules
Thioridazine (Mellaril) -high doses
Methoxyflurane (anesthetic)
Crystalline retinopathy, oxalate crystals
Chloramphenicol (chronic use in cystic fibrosis)
Atrophy of maculopapillary bundle, cecocentral scotomas

Quinine
Tamoxifen: nonsteroidal antiestrogen- breast cancer therapy, flecklike retinopathy
Nicotinic acid (Gass)- atypical nonleaking CME
Canthaxanthine (crystalline retinopathy)- tanning agent
Others...

THE MACULA,
Definitions:
Macula: macula lutea-"yellow spot", nonspecific clinical term.
Darker on IVFA: xanthophyll, more lipofuscin and melanin in taller RPE cells
Fovea: "pit"- depression in retina, 1 DD in size
Foveola: Floor of pit, greatest retinal thinning, avascular; anatomy: only photoreceptors, outer nuclear layer, some Henle fibers,
Age Related Macular Degeneration (Senile macular degeneration, SMD, ARMD)
More common in blue-eyed patients, rare in blacks: suggest pathogenic role of chronic light exposure
Strongly associated with a common variant in gene for complement factor H (CFH)- Tyr402His polymorphism 5-7x increased risk of AMD in homozygotes
"DRY" ARMD
RPE degeneration, pigment clumping, areolar loss of RPE with concomitant degeneration of outer retina; ? Role of light damage, ARMD and drusen less common in blacks;
"WET"ARMD:
Choroidal neovascular membranes (CNV), exudation, focal serous detachment of retina, hemorrhagic RPE detachment, organization of hemorrhage, subretinal scar formation (disciform degeneration)
RPE cells contribute to collagen production in vascularized scar
A CLINICAL SPECTRUM: "wet" and "dry" variants can be found in same patient







Aging Changes in Bruch's Membrane:

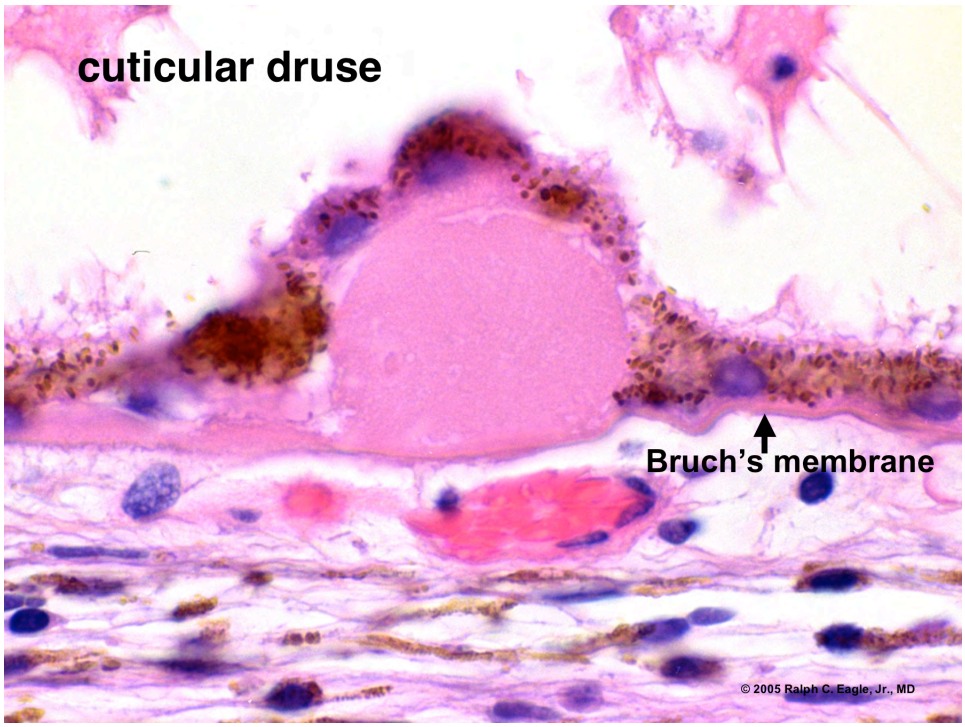
Thickening, PAS positivity, focal calcification, drusen

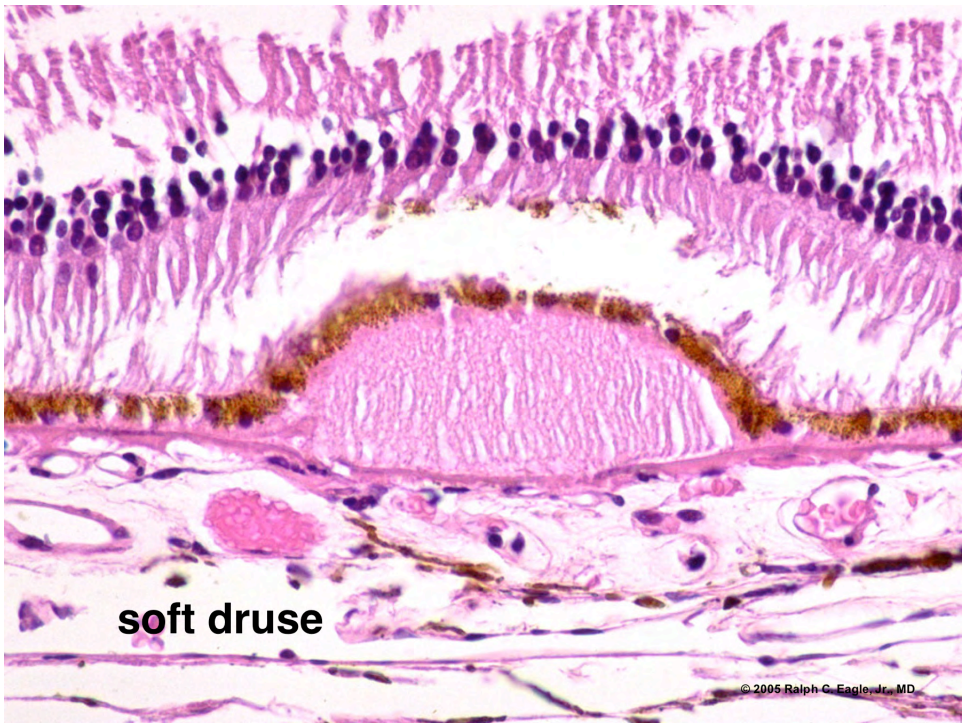
Drusen- a clinical marker for "sick" RPE

Deposits of extracellular matrix material on inner surface of Bruch's membrane. Probably made by "sick" or stressed RPE cells

Hard drusen (cuticular)

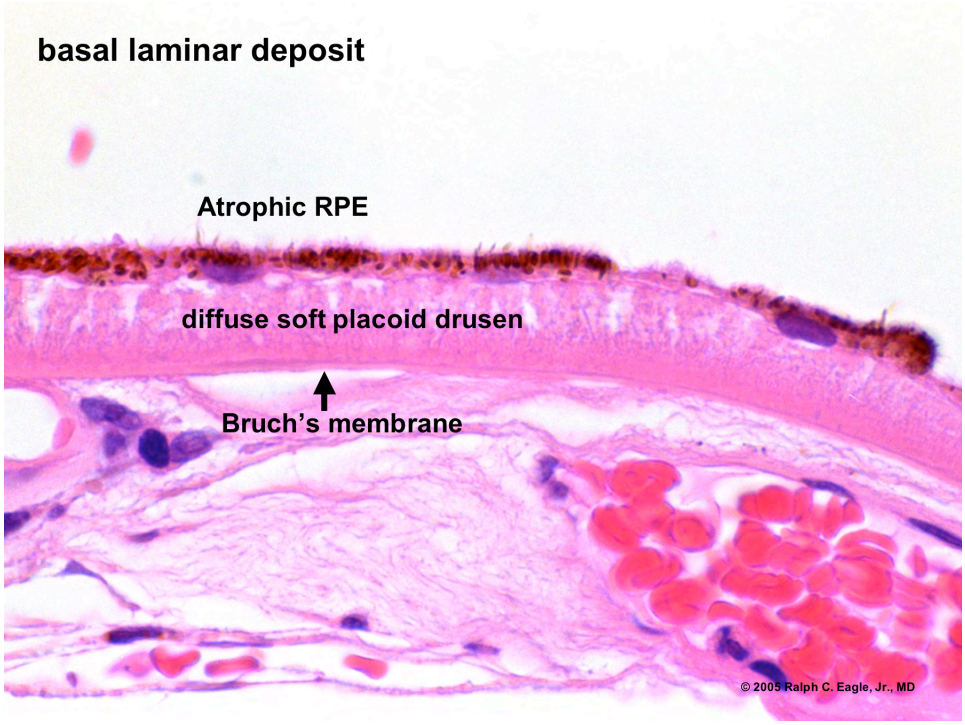
Globular excrescences of densely hyaline PAS (+) material
Association with dry or atrophic ARMD has been questioned (Green)

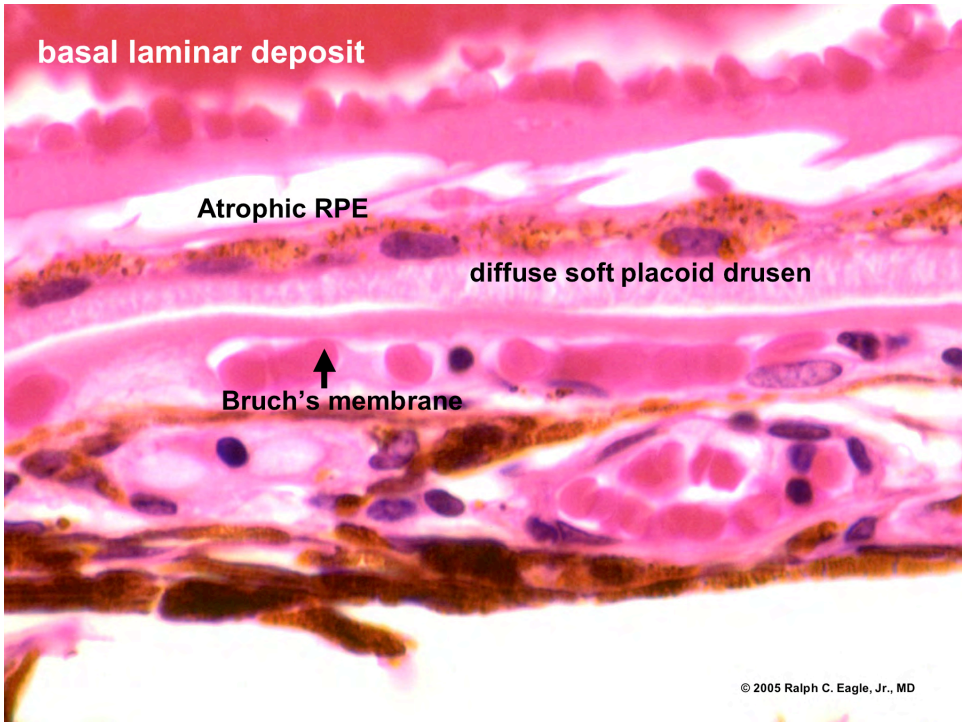




Diffuse drusen- very strong association with exudative ARMD (esp. basal laminar deposit)

Basal laminar deposit (very important variant of diffuse soft drusen)
May be quite extensive, but not evident clinically
Thick diffuse layer of abnormal 1000 Å banded basement membrane material ("curly collagen") located between plasma membrane and basement membrane of RPE.





Composition: laminin, type IV collagen, heparin sulfate proteoglycans
Appears as pink granular band between Bruch's membrane and RPE.
Very common pathologic finding in ARMD (84% "wet", 53% "dry", 19% control - Grossniklaus)
Predisposes to RPE detachment and tears, SRNVM, disciform degeneration
May interfere with biochemical modulation of choriocapillaries by RPE, barrier to diffusion, bind or sequester angiogenesis factors, displaces RPE from blood supply

Basal Linear Deposit
Second type of diffuse soft drusen composed of a layer of multivesicular phospholipid material localized within Bruch's membrane external to RPE basement membrane. It is impossible to distinguish from basal laminar deposit without electron microscopy

Subretinal Neovascular Membrane (CNV, choroidal neovascular membrane)
New vessels derived from choroid, extend through breaks in Bruch's membrane
Vessels leak, bleed with resultant hemorrhagic RPE and/or retinal detachment
Disciform scar caused by organization of hemorrhage by granulation tissue and collagenous connective tissue (disciform degeneration)
Propensity for foveal and parafoveal region
Excised membranes very difficult to orient histopathologically

Hemorrhagic Detachment of the RPE-can mimic choroidal melanoma

Diseases with SRNVM, disciform scar formation
ARMD
Focal choroiditis (e.g , presumed ocular histoplasmosis syndrome)
Angioid streaks
Myopic degeneration
Choroidal rupture
Central serous (rare)
Dominant drusen
Choroidal tumors
Juvenile disciform degeneration

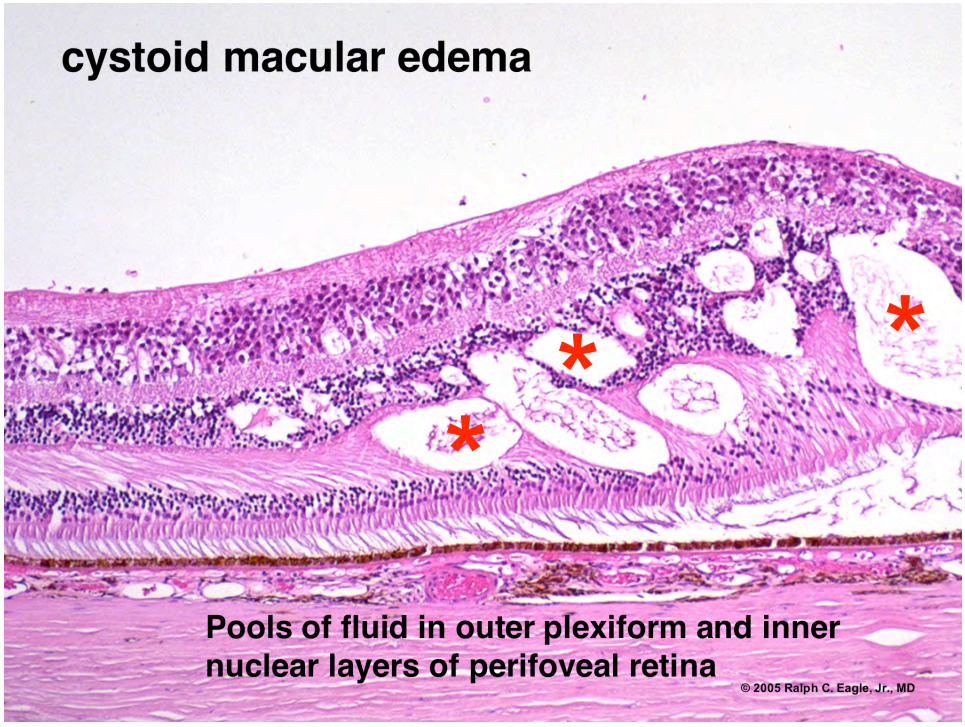
Ocular Histoplasmosis Syndrome (POHS)
Triad:
Disciform degeneration of macula, focal chronic choroiditis, organisms rarely found
Peripapillary atrophy, peripheral punched-out spots

Macular Holes (Idiopathic)
Shrinkage of prefoveal cortical vitreous exerts lateral traction on retina causing localized foveal detachment, then hole (fibrocellular membranes rarely found)
Better VA after surgery reflects smaller size of sealed hole and resorption of SRF

Classification of macular holes (Gass)
Stage I- foveal detachment (impending hole or macular cyst) – about 50% progress
Stage II- early hole formation
Stage III- full thickness hole with vitreofoveal detachment
Stage IV- full-thickness hole with posterior vitreous detachment

Cystoid Macular Edema (CME)

Multiple cystoid spaces in macula with petalloid appearance on IVFA
Irvine-Gass Syndrome – post cataract surgery
Very high incidence with iris supported IOL's
Secondary finding over choroidal tumors, especially hemangioma
Occurs with peripheral uveitis, peripheral tumors
OCT and intravitreal kenalog, anti-VEGF therapy (avastin)
Initial intracellular edema within Mueller cells (Fine, Brucker)



Ophthalmic lasers

Argon, krypton, diode: thermal coagulation.(Light absorbed by pigment, converted to heat)
Blue argon wavelengths absorbed by yellow macular pigment, damage retina
Green argon wavelengths absorbed by blood, melanin
Red krypton wavelengths absorbed by melanin, not by blood or luteal pigment
YAG: short pulse mode does not rely on thermal coagulation; optical breakdown "explosion" physically disrupts tissues
TTT (transpupillary thermotherapy), diode laser, large spot size, slow delivery, thermal effect
Excimer- molecular disruption

Retinitis pigmentosa (primary pigmentary retinopathy)

An extremely large heterogeneous group of diseases sharing:
Progressive photoreceptor degeneration typically leading to blindness by middle age
Rods affected more severely than cones in early disease
Night blindness and peripheral field loss, tunnel vision, blindness
Attenuation of retinal vessels, waxy pallor of optic disc, bone spicule pigmentation in peripheral fundus

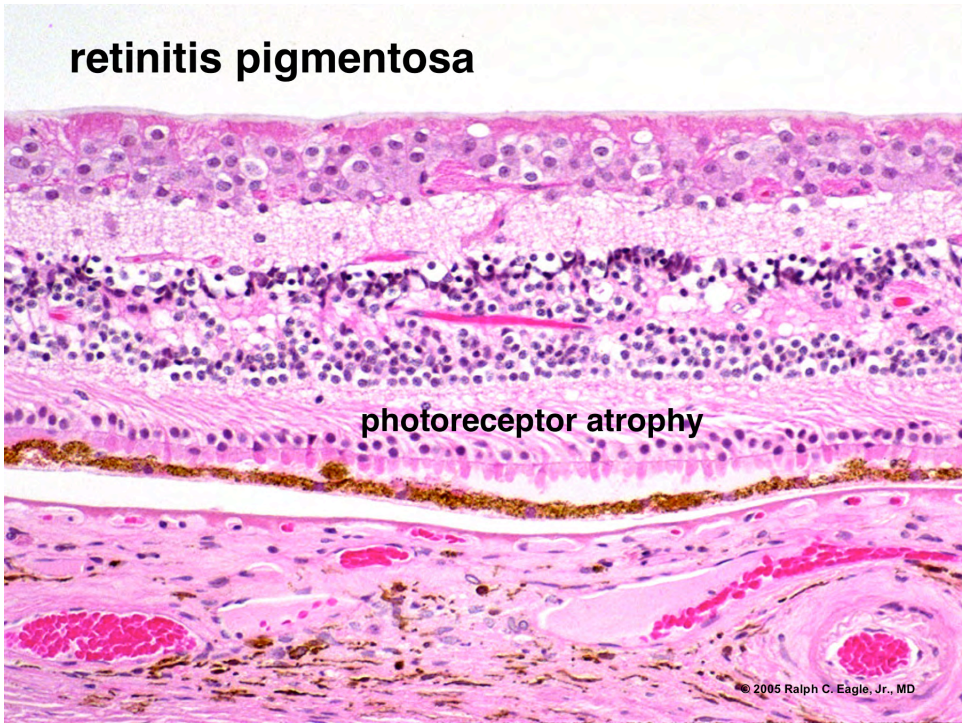
Posterior subcapsular cataract, macular edema, optic disk drusen

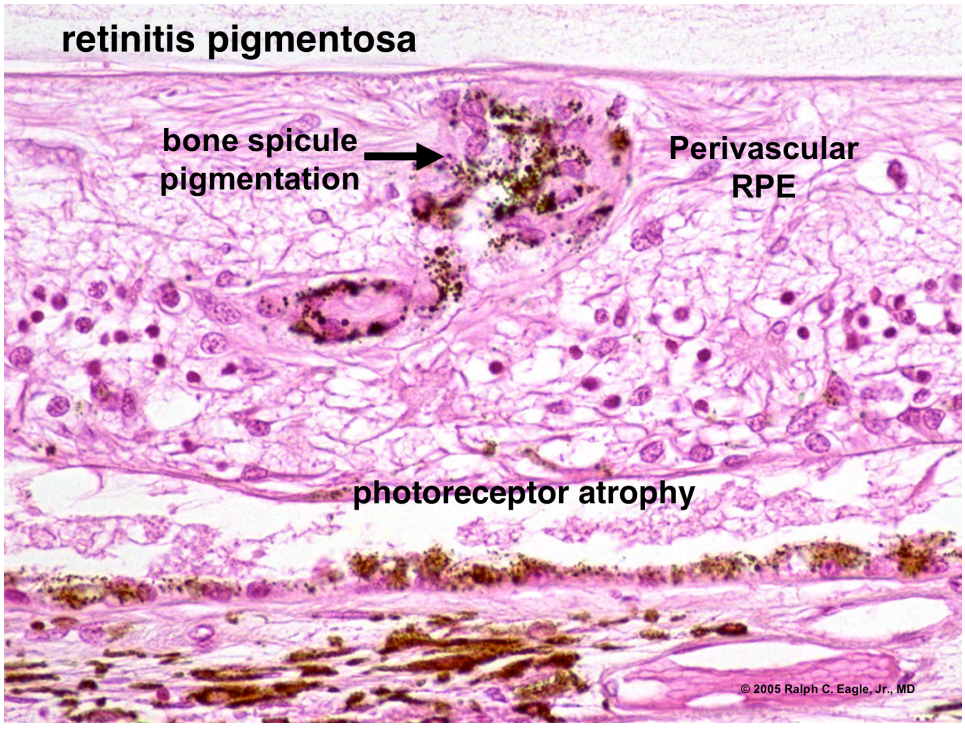
Genetics

Sporadic 39%, dominant 20%, recessive 37%, sex-linked 4%,
Consanguinity 30-40%
Severity: Autosomal dominant< autosomal recessive < X-linked
More than 150 genes cause RP and related disorders (genes located on chromosomes 1, 3, 4, 5, 6, 7, 8, 11, 14, 15, 16, 17, 19, and X (most identified by linkage studies)
19 RP genes are known (in 2000) RHO, PDE6A, PDE6B, CNGA1, SAG, RPE65, RLBP1, ABCA4, RGR, RDS, ROM1, PROML1, NRL, CRX, RP1, RP2, RPGR, CRB1, and TULP1.4
Some encode proteins involved in rod phototransduction cascade:
Rhodopsin (RHO)
20-25% of patients with dominant RP- most single AA substitutions (missence mutations), most common His-23-Pro
subunits of rod c-GMP-phosphodiesterase
subunit of c-GMP-gated cation channel
Others encode for proteins of unknown function
Peripherin/RDS
(Mutations also found in occasional patients with macular dystrophies such as Best's Vitelliform or Butterfly dystrophy)
(Null mutation cause photoreceptor degeneration in **RDS** mice)
ROM 1, Myosin 7A, RPGR, NRL

Histopathology

Primary photoreceptor degeneration- atrophy involves outer retina
Loss of photoreceptors, ONL
Bone spicule pigmentation caused by intraretinal RPE migration
TEM: intraretinal formation of new perivascular "Bruch's membrane"
Macromelanosome (PR atrophy may allows RPE to invade retina)
RPE usually fairly well preserved



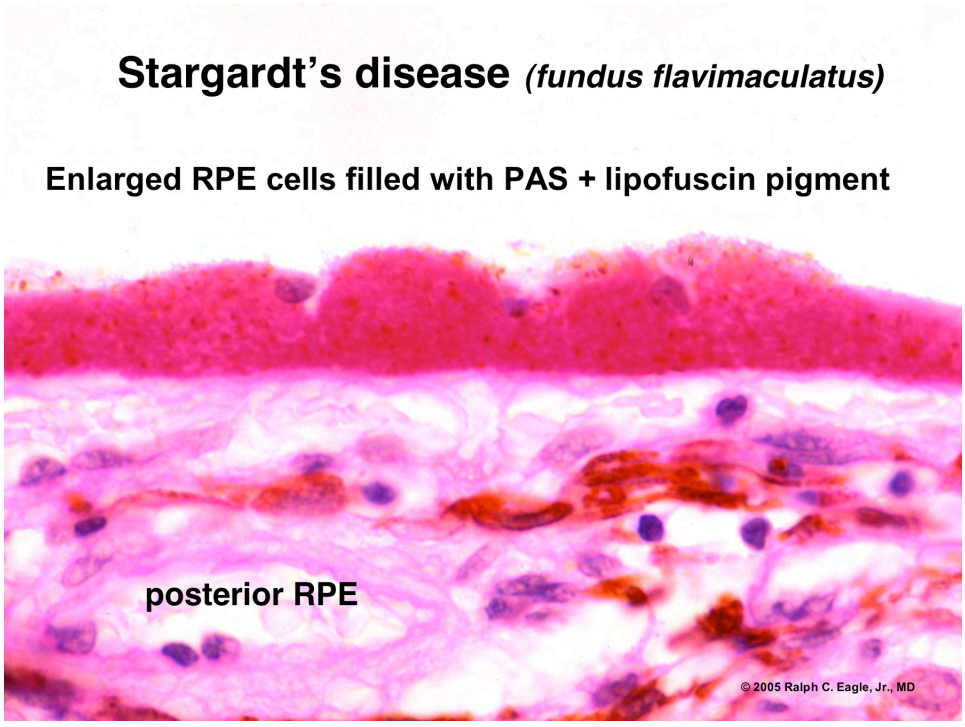


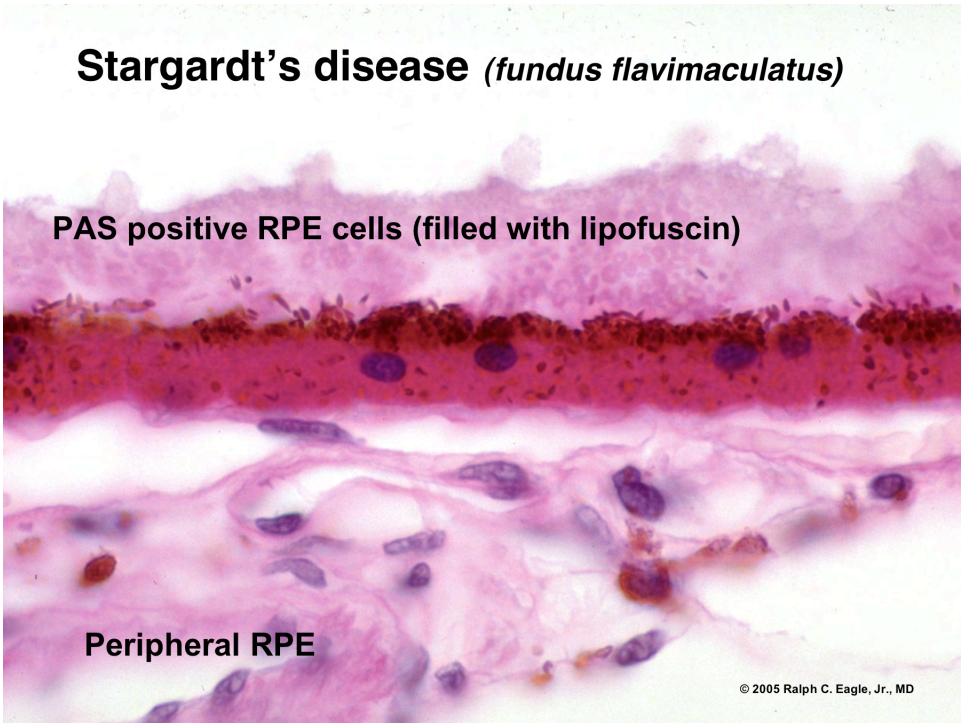
Variants of Retinitis Pigmentosa

Leber Congenital Amaurosis (congenital blindness of early onset RP)- 8 genes identified – Briard dogs with RPE65 gene canine model cured by gene therapy
Sector retinitis pigmentosa
Usher's Syndrome (association of RP and hearing loss- 3 types)
Retinitis pigmentosa with Coats'-like response

Retinitis punctata albescens

X-linked Juvenile Retinoschisis (Xp22.2) retinoschisin
Split in nerve fiber layer
Stellate maculopathy does not fill with fluorescein
? abnormal vitreous-like material in retina (Brownstein)
Macular dystrophies (hereditary, bilateral)
Fundus flavimaculatus (Stargardt's disease) 1p21-p13
Once thought to be primary RPE disease, but causative **ABCA4 gene** is expressed only in photoreceptor outer segments. Defect in abcr transport protein leads to accumulation of toxic vitamin A derivatives in outer segments that poison RPE's phagolysosomal system.
Autosomal recessive, onset in teens
Yellow pisciform flecks in RPE, atrophic macular degeneration
RPE PAS+, cells contain massive amounts of abnormal lipofuscin
Posterior RPE cells massively enlarged
"Dark" choroid on IVFA, vermilion fundus due to **RPE lipofuscin**
Fundus flavimaculatus without macular lesion lacks abnormal pigment





Best's disease (Vitelliform macular dystrophy)- gene
Dominant, **VMD2** gene on 11q13, bestrophin abnormal EOG
Similar disease caused by defects in peripherin/RDS gene
Egg yolk lesion "scrambles" with age, Abnormal EOG
RPE disease with increased amounts of abnormal lipofuscin

Sorsby Macular Degeneration
Dominant presenile macular degeneration; similar to ARMD clinically
Massive deposit of BLD-like material beneath RPE
Defect in gene (chromosome 22) encoding TIMP 3 (Tissue inhibitor of metalloproteinase 3)
Theory- mutant TIMP3 could inhibit MP that normally catabolize Bruch's membrane too well.

Kearns-Sayre Syndrome
Progressive external ophthalmoplegia, heart block, atypical pigmentary retinopathy; large deletions in **mitochondrial DNA**
"Salt and pepper" retinopathy, no bone spicules, involves posterior fundus,
Other mitochondrial cytopathies (MERRF, MELAS) occasionally affect retina

Oguchi Disease
Form of stationary night blindness- golden fundus reflex - Mizuo-Nakamura phenomenon- defects in arrestin or rhodopsin kinase; some patients may develop late retinal degeneration

Gyrate atrophy
Hyperornithinemia, ornithine aminotransferase deficiency
Ornithine may act as an RPE toxin

Choroideremia
X-linked degeneration of RPE, choroid and photoreceptors (primary site unknown)
Asymptomatic female carriers have patchy pigmentation and RPE and choroidal degeneration.
Rab geranylgeranyl transferase deficiency

Mucopolysaccharidoses

Inherited deficiencies of catabolic lysosomal exoenzymes.
Fibrillogranular and multimembranous inclusions.
Outer retinal atrophy due to RPE degeneration; marked in Sanfilippo (MPS III); mimics primary retinitis pigmentosa

Sphingolipidoses

Diabetes mellitus

Diabetic retinopathy

Microangiopathy

Loss of capillary pericytes (Normal endo/pericyte = 1/1)
Role of sorbitol in pericyte loss
Thickening of capillary basement membranes
Capillary nonperfusion (capillaries are totally avascular)
Angiogenic factor (**VEGF-** vascular endothelial growth factor) produced by ischemic retina
Neovascularization of disk and retina

Microaneurysms

Seen in diabetes and other retinal diseases with ischemia
DM: mainly posterior pole, CRVO: throughout retina, others: periphery
50-100µ, most not ophthalmoscopically visible (One sees associated hemorrhage)
Increased number of endothelial cells (proliferation versus migration)
Wall initially thin and leaky, thickens, PAS (+), eventual occlusion

Background retinopathy

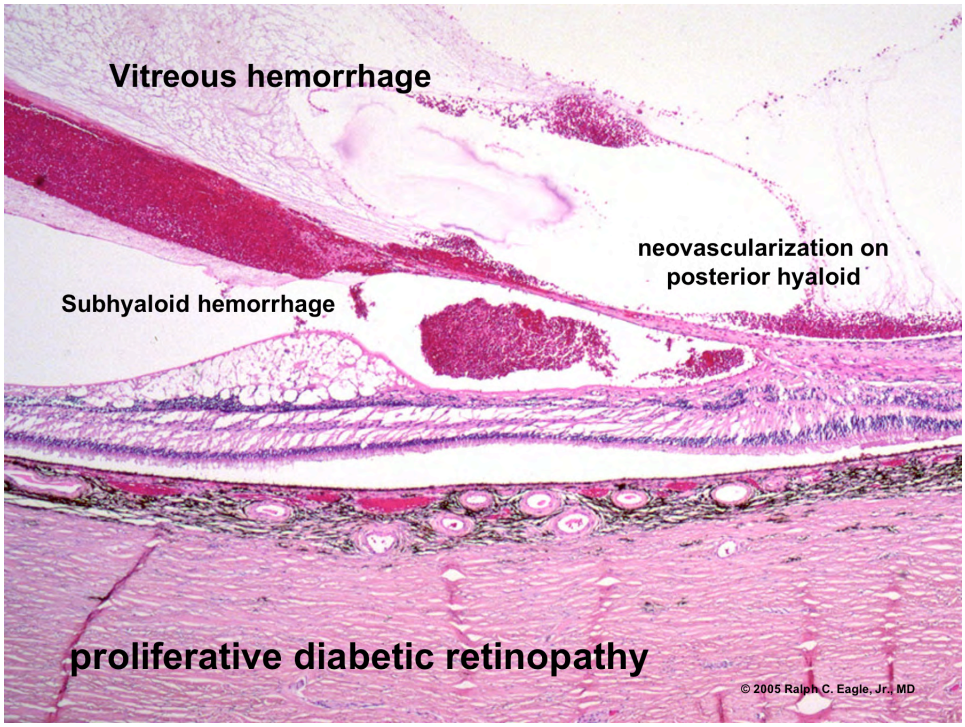
Hemorrhages, hard exudates, retinal edema

Preproliferative retinopathy

Cotton wool spots a marker for retinal ischemia

Proliferative retinopathy

Neovascularization of disk, retina, iris; angiogenic factor (VEGF)
New vessels proliferate on scaffold of partially detached vitreous
Progressive vitreous detachment rips vessels causing subhyaloid and vitreous hemorrhage
Scarring and organization of hemorrhage produces vitreoretinal
Traction, tractional retinal detachment


Vitreous hemorrhage
neovascularization on
posterior hyaloid
Subhyaloid hemorrhage
proliferative diabetic retinopathy
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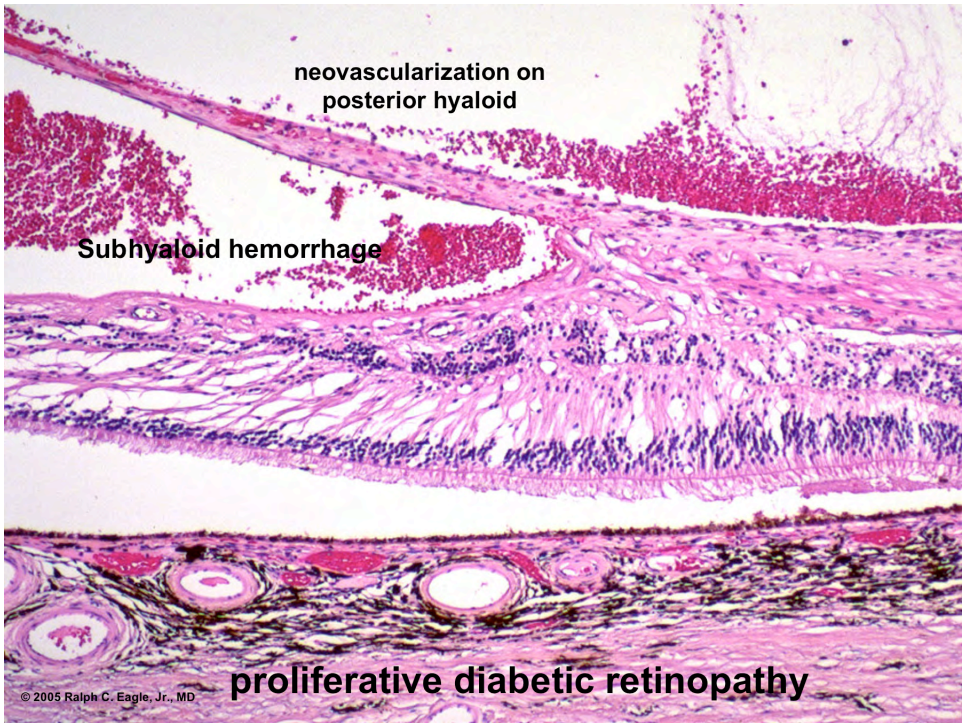
neovascularization on
posterior hyaloid
Subhyaloid hemorrhage
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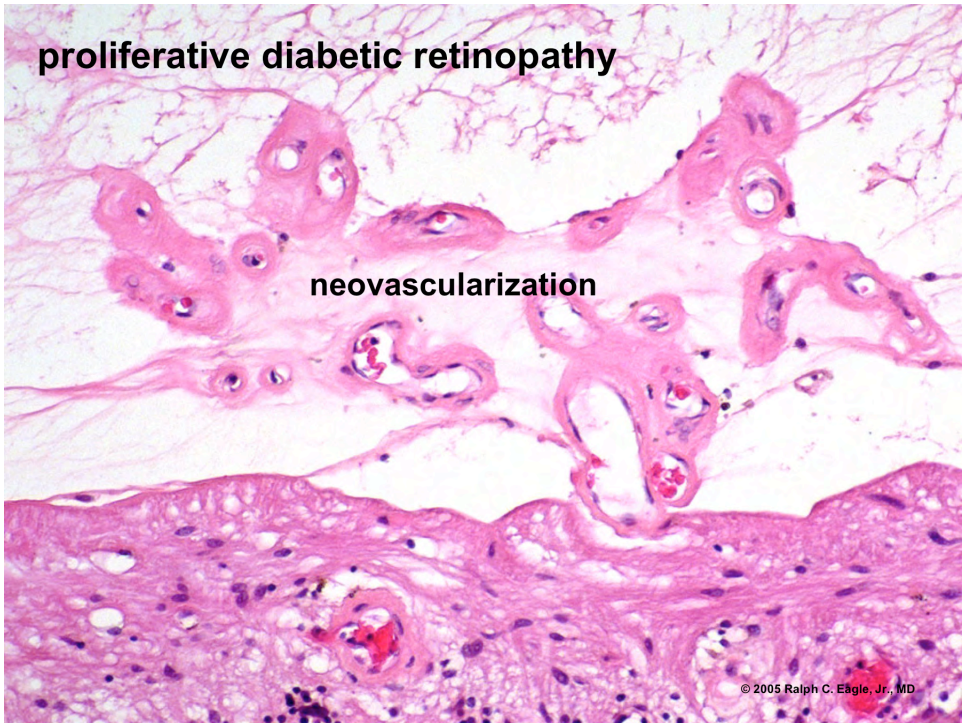
proliferative diabetic retinopathy


proliferative diabetic retinopathy
neovascularization
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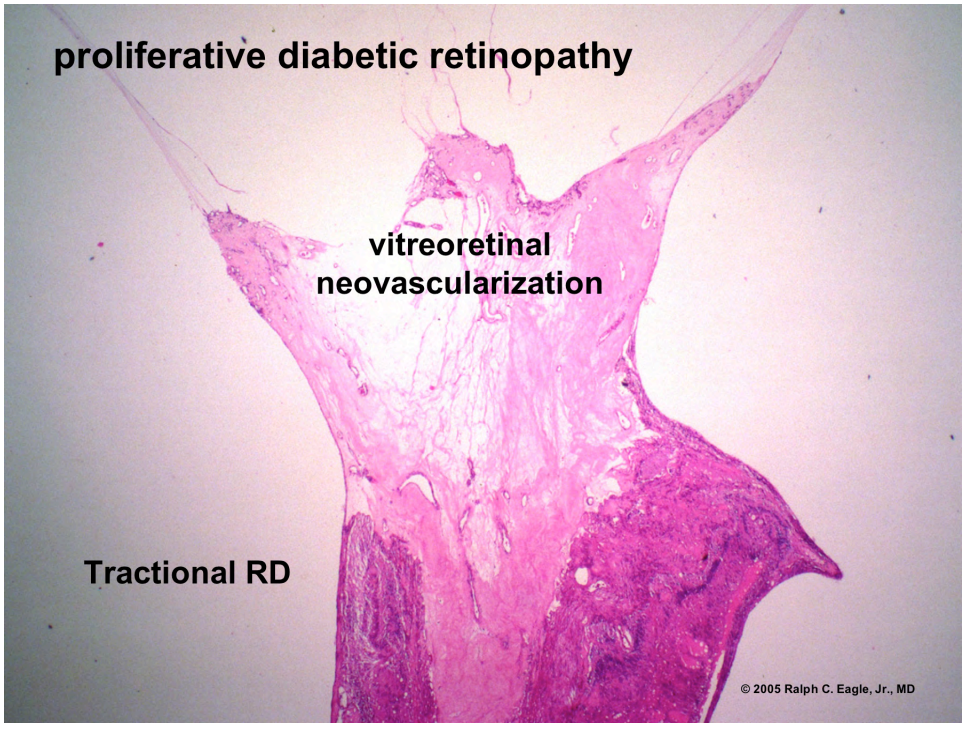
proliferative diabetic retinopathy
vitreoretinal
neovascularization
Tractional RD
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Diabetic iridopathy

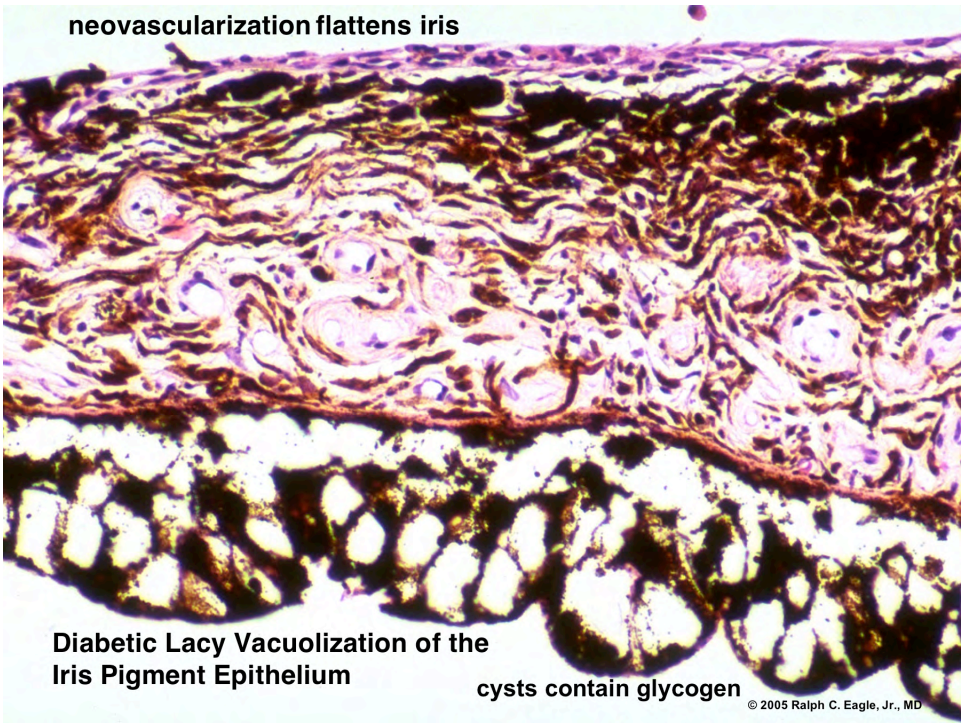
Iris neovascularization (Rubeosis iridis):

Higher incidence post-lensectomy

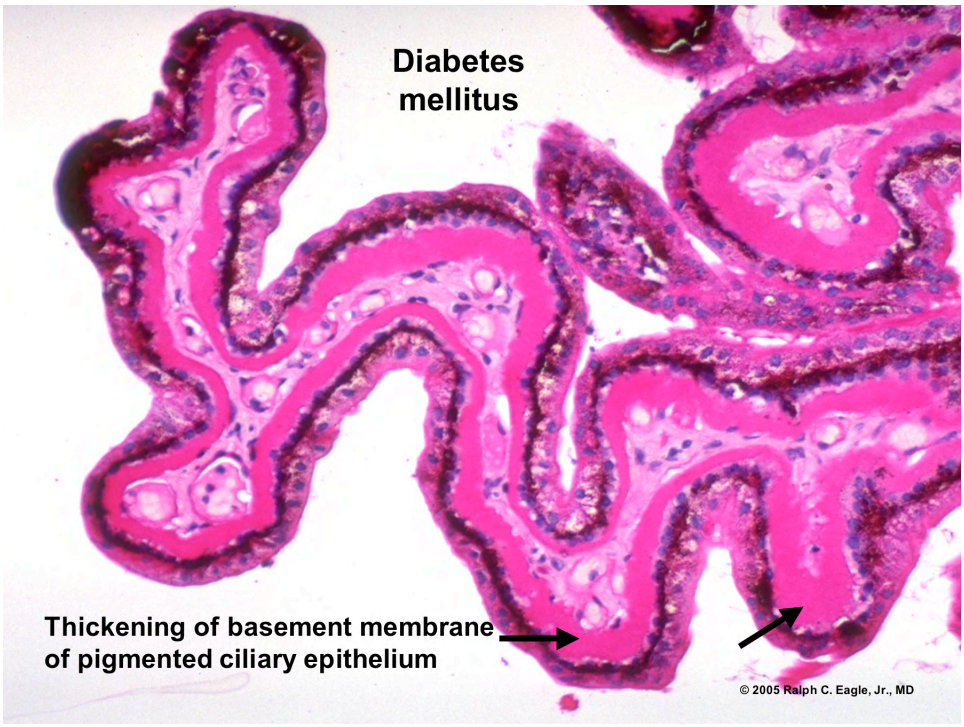
Lens acts as barrier to anterior diffusion of angiogenic factor

Diabetic lacy vacuolization of iris pigment epithelium

Glycogen-filled cysts in IPE, contents PAS (+) , diastase-sensitive



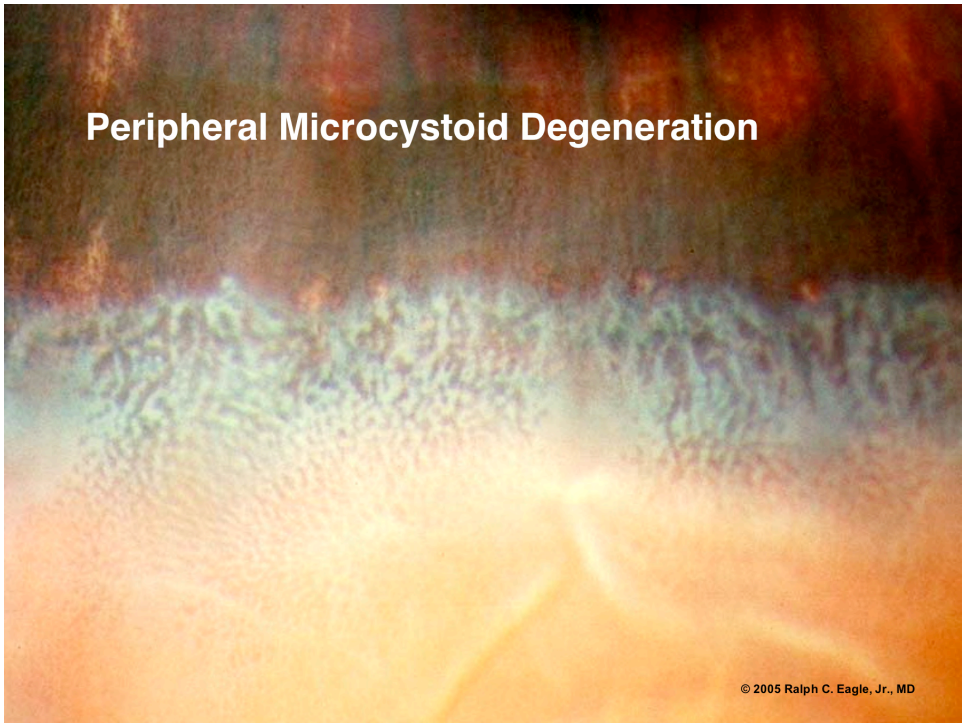
Basement membrane thickening
Retinal capillaries
Nonpigmented ciliary epithelium (can be diagnostic)
Corneal epithelial basement membrane (epithelium can desquamate as sheet)

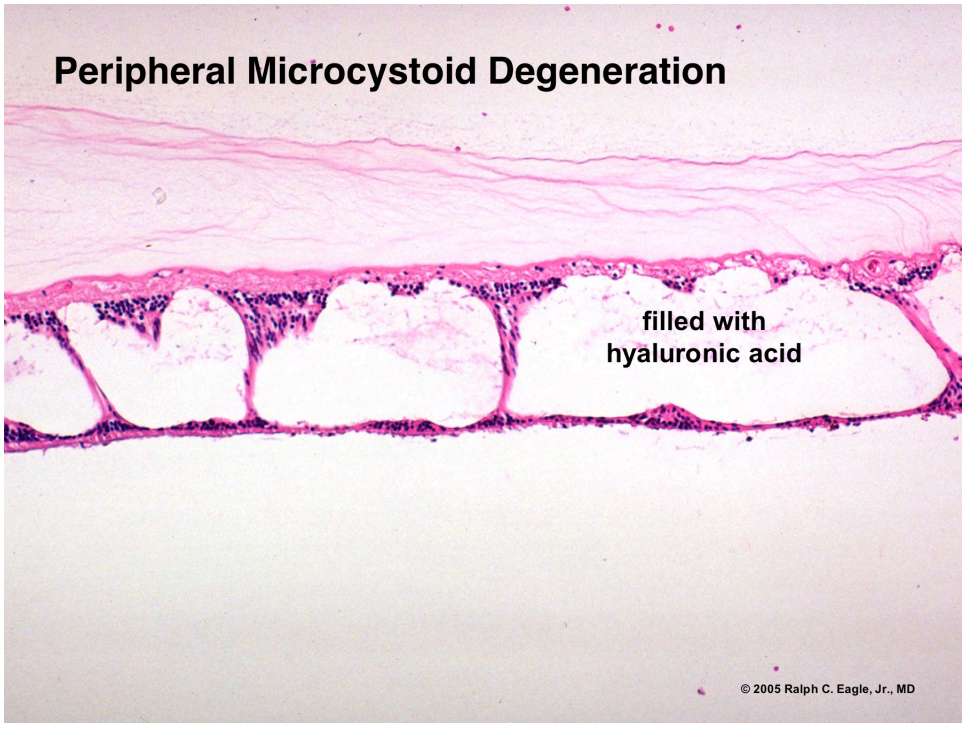


Diabetic cataract
Role of aldose reductase, sorbitol
Albinism (oculocutaneous and ocular albinism)
Foveal hypoplasia- occurs in varieties caused by different genes), iris transillumination
X-linked ocular albinism: macromelanosomes in RPE, skin

Sickle Cell Retinopathy
Proliferative retinopathy **most severe** in **Hb SC** disease
Blockage of retinal vessels by sickled cells leads to nonperfusion of temporal peripheral retina, peripheral shunts
Neovascular fronds (**sea fans**) develop at junction between perfused posterior and nonperfused peripheral retina
Late stages: hemorrhage, secondary retinal detachment
Black sunburst sign: chorioretinal scar with RPE proliferation secondary to old hemorrhage

Peripheral Retinal Degenerations
Peripheral microcystoid degeneration (typical)
Very common, found in all adults > 20 years
Blessig-Iwanoff cysts in outer plexiform layer
Filled with hyaluronidase-sensitive acid mucopolysaccharide
Coalescence of cysts leads to typical degenerative retinoschisis





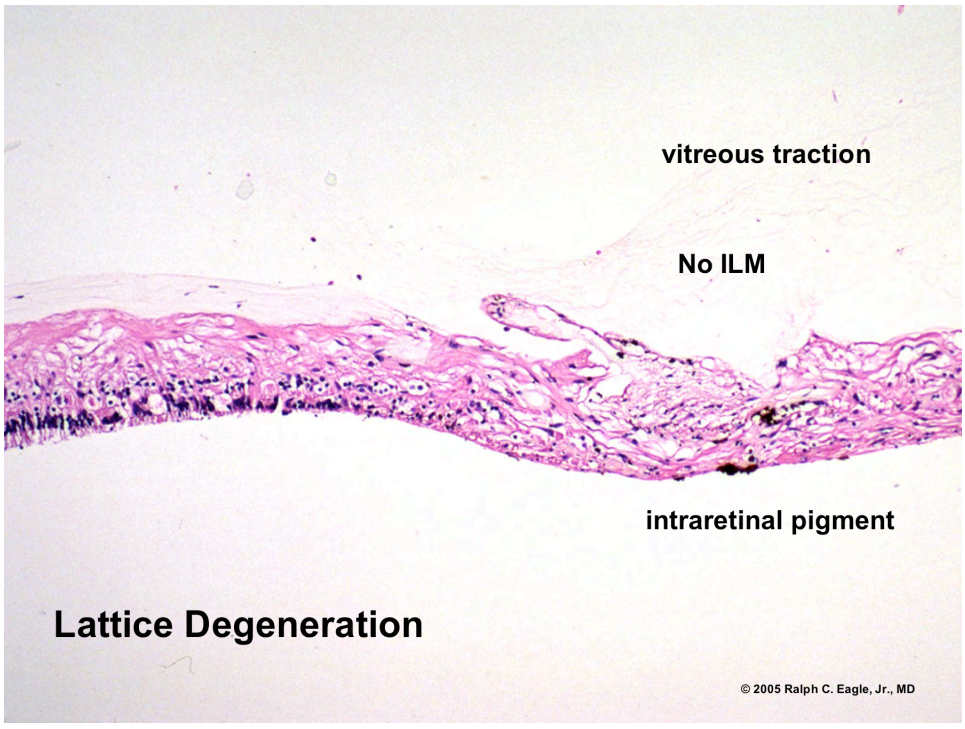
Reticular cystoid degeneration

18% of adults, bilateral in 41%
Posterior to, and contiguous with typical microcystoid
Finely stippled, inferior temporal quadrant
Cysts in nerve fiber layer
Can lead to reticular degenerative retinoschisis

Typical degenerative retinoschisis
1% of adults, inferotemporal retina
Split in outer plexiform layer, large holes in outer layer
Vessels in inner layer; irregular outer layer has beaten-metal appearance, turns white on scleral depression

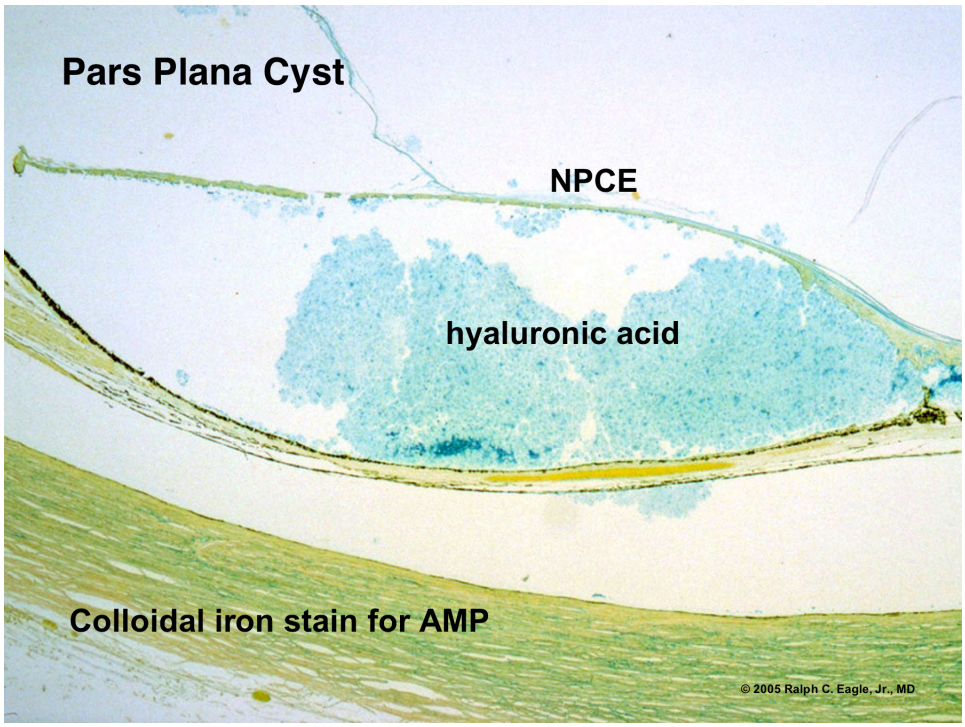
Peripheral Chorioretinal Degeneration
(Paving stone or Cobblestone degeneration, CRA)
Incidence 27% over age 20
Probably caused by choroidal vascular insufficiency
Pattern of outer ischemic atrophy: loss of choriocapillaris, RPE, outer retina
Chorioretinal scar: outer retina fused to bare Bruch's membrane

Lattice Degeneration (vitreoretinal degenerative process)
6-11% of population
Sharply demarcated, circumferentially-oriented areas of retinal thinning, anterior to equator, vertical meridians
Secondary RPE proliferation, Only 12% of lesions have white lines
Histology:
Discontinuity in ILM
Retinal thinning with loss of inner layers
Overlying pocket of liquefied vitreous
Vitreous condensation and gliosis at margins of pocket
Sclerosis of major vessels in lesion, capillary occlusion
RPE hypertrophy, hyperplasia and migration
Lattice predisposes to retinal breaks (firm adherence of vitreous to margin of lesions)
Posterior margin breaks, lattice in operculum (30%)



Pars Plana Cysts

Split between pigmented and nonpigmented layers of ciliary epithelium
Aging – cysts contain hyaluronic acid
Multiple myeloma- cysts filled with myeloma proteins are white after fixation



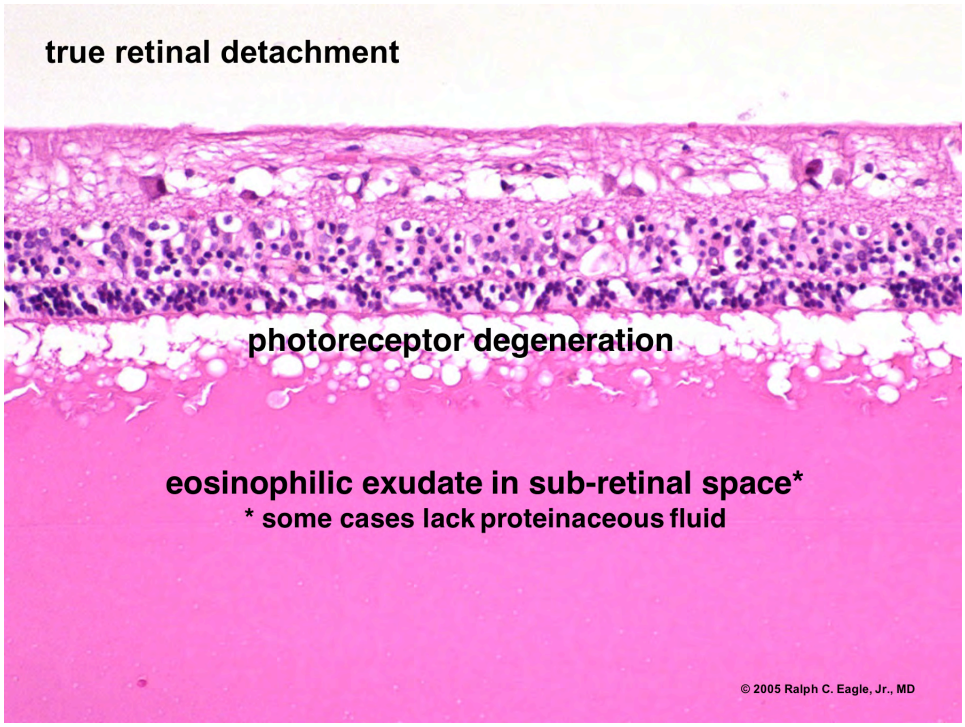
Retinal detachment

Fluid collects in potential space between inner and outer layer of optic cup; retinal separation a better term.

Artifactitious versus real RD in tissue sections (Almost all unopened eyes fixed by immersion in formaldehyde have an artifactitious retinal detachment.)

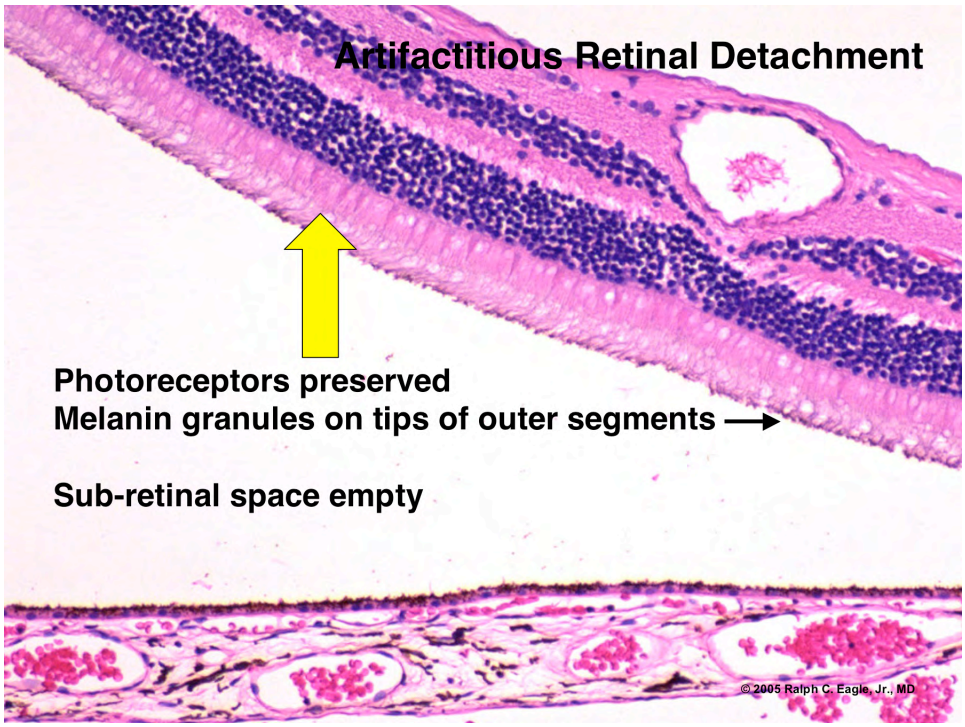
True retinal detachment

Photoreceptor degeneration, eosinophilic proteinaceous fluid in subretinal space, RPE budding or papillary proliferation with chronicity



Artifactitious retinal detachment:

No fluid in subretinal space, photoreceptors healthy, RPE granules adhere to outer segments

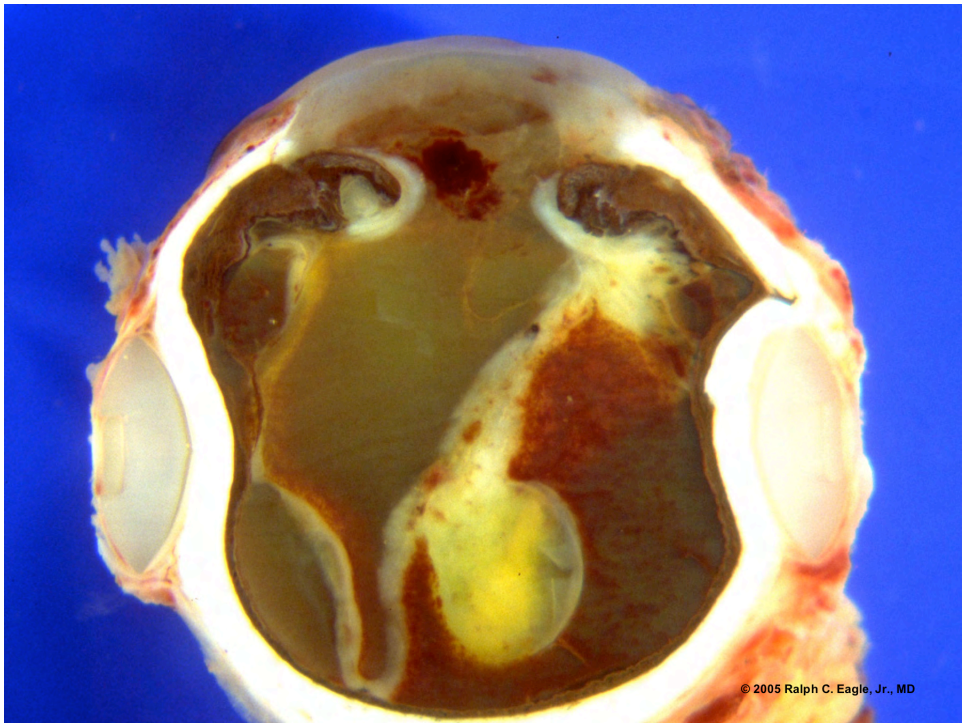


Rhegmatogenous retinal detachment
Secondary to **retinal holes and breaks**
Most holes due to vitreous traction in eyes with posterior vitreous detachment, vitreous degeneration, lattice degeneration
Horseshoe tears- “the horse always walks toward the optic disk”
Incidence of retinal holes: 4.8-10% (path), 5.8-13.7% (clinical)
Important prognostic criteria: **Symptoms**, subclinical detach, aphakia

Exudative retinal detachment (serous)
Tumors (most melanomas, hemangiomas, metastases)
Uveal effusion, Harada's, toxemia of pregnancy, oxygen toxicity

Tractional retinal detachment
Proliferative diabetic retinopathy

Chronic retinal detachment
Funnel or morning glory configuration, photoreceptor degeneration, gliosis, macrocystic degeneration; may have secondary pigmentary retinopathy
Proliferative vitreoretinopathy,



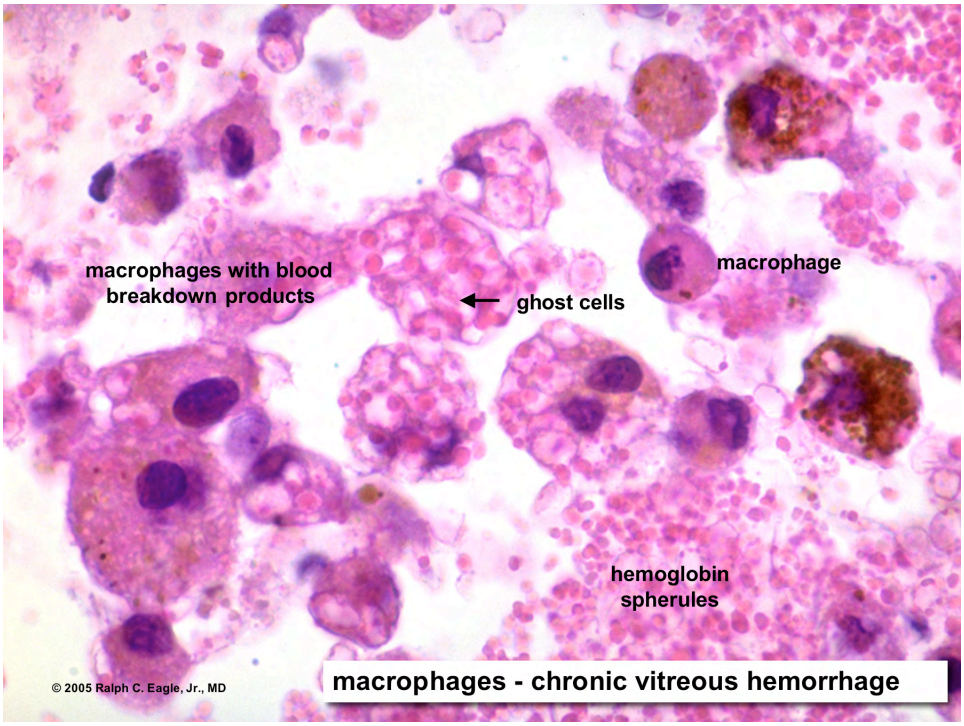
Vitreous

Posterior vitreous detachment
63% incidence in 8th decade, rare before age 55
7.5% have associated vitreous hemorrhage, 15% have retinal breaks
Flashes, floaters, Weiss ring (peripapillary condensation)
Important role in retinal detachment

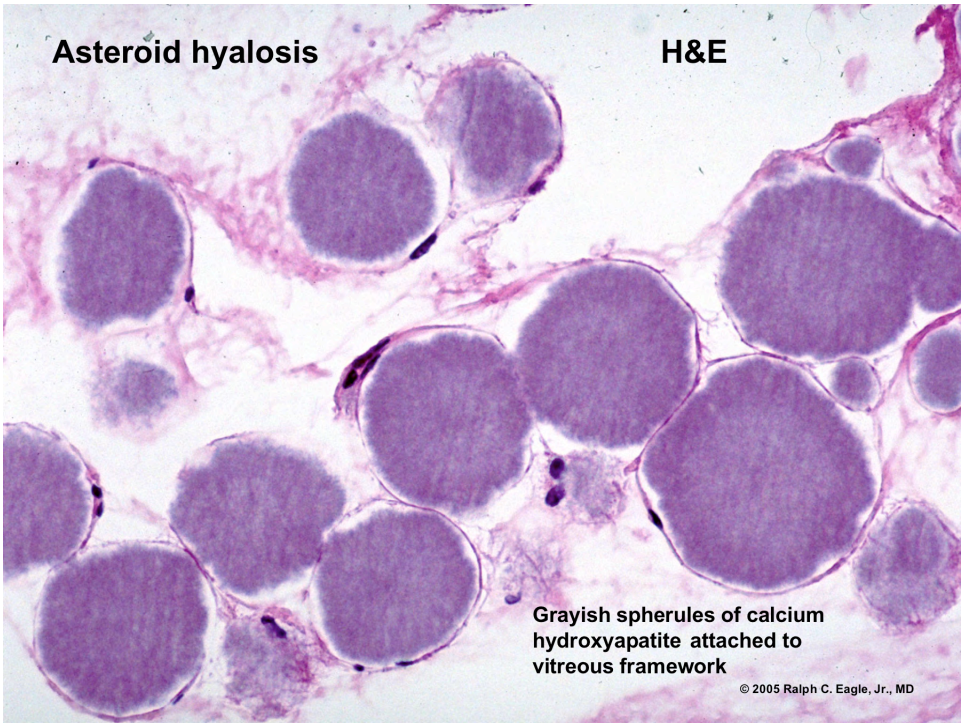
Vitreous opacities
Hyaloid remnants (muscae volitantes, or mouches volantes-"flying flies")

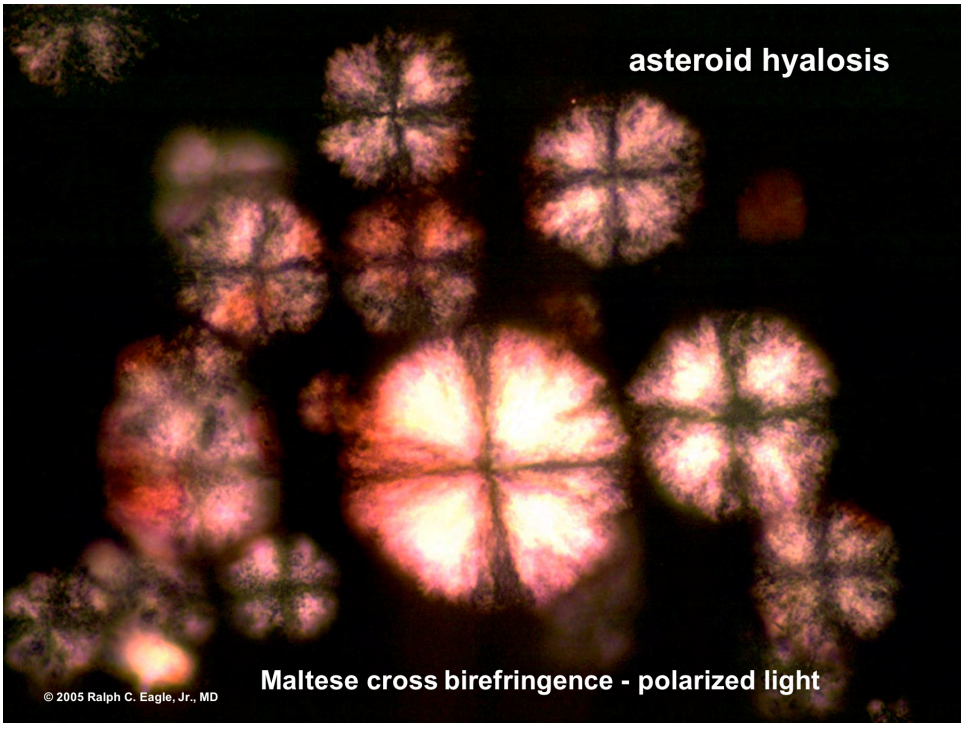
Vitreous hemorrhage
Blood breakdown products in chronic hemorrhages ("**ochre membrane**")
erythrocyte ghost cells, hemoglobin spherules, hemosiderin-laden macrophages: Hemolytic, ghost cell glaucoma,
Complications: organization leading to tractional RD, hemosiderosis (repeated hemorrhage)

Causes: trauma, retinal tears, PVD, diabetic retinopathy, sickle cell, Eales', disciform degeneration of the macula, tumors, Terson's syndrome (subarachnoid hemorrhage)



Asteroid hyalosis (Benson's disease, Scintillatio nivea)
2% incidence, unilateral (80%), increases with age
Generally does not interfere with vision
Spherules of calcium hydroxyapatite attached to vitreous framework (Classicallly: called **calcium soap** – not true!!
Gray spheres with Maltese cross birefringence on polarization

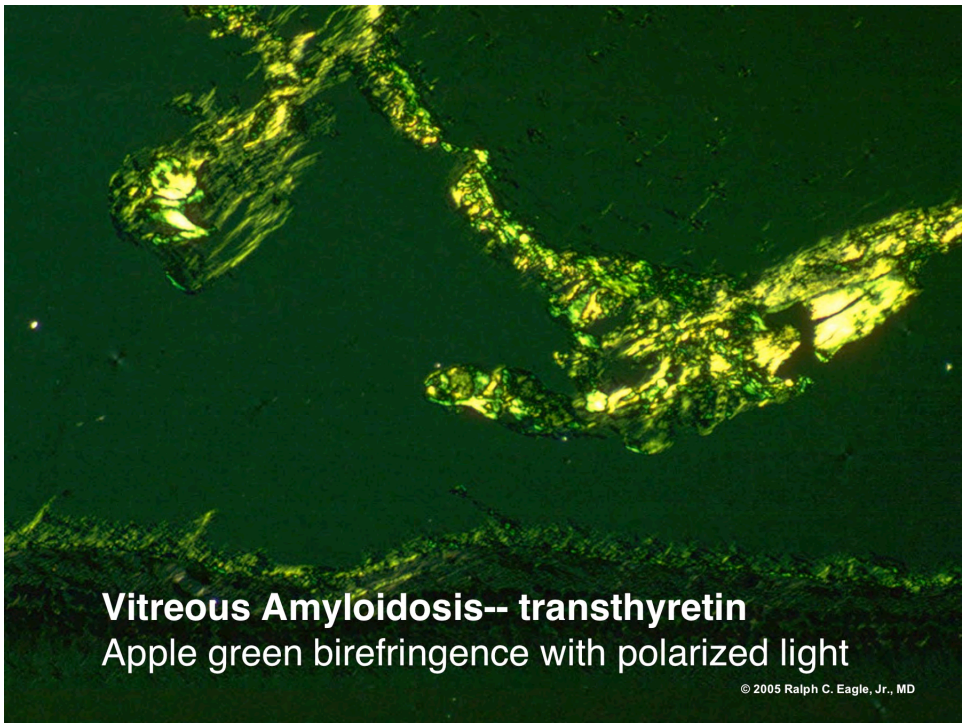




Synchisis Scintillans (Cholesterolosis bulbi)
Rare, bilateral, blind eyes, young patients
Cholesterol crystals derived from old hemorrhage
Not fixed to vitreous framework, sinks to bottom of globe

Primary Amyloidosis Of The Vitreous

Vitreous involvement in Familial Amyloidotic Polyneuropathies (FAP's)
Amyloid comprised of mutant transport protein **transthyretin** (prealbumin)
Several missence (AA substitutions) mutations (e.g. common Met 30 variant
Often presents in elderly patients with no family history
Associations include cardiac disease, amyloid neuropathy, carpal tunnel syndrome
Amyloid probably enters via retinal vessels



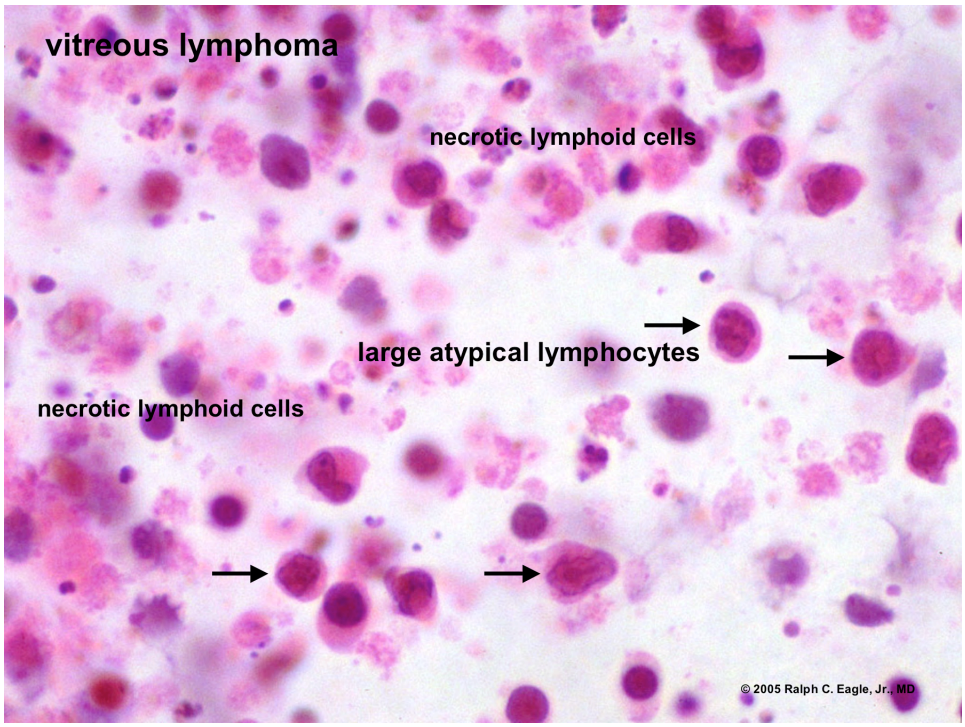
Intravitreal Tumor Cells

Retinoblastoma

Vitreous seeding common in advanced cases, poor prognostic sign

Primary Lymphoma of CNS and Retina (NHL-CNS)

("ocular reticulum cell sarcoma"- old, incorrect, outdated term)
Bilateral vitritis, CNS lymphoma, dementia
Poor prognosis (mean survival 22 months)
Most are large B cell lymphocytic lymphomas
Primary CNS lymphoma spares uvea, but sub-RPE deposits are common
No systemic involvement outside CNS
Diagnostic vitrectomy reveals:
Atypical lymphocytes with prominent nucleoli, mitoses, abundant cellular necrosis
NOTE: Systemic lymphomas can involve vitreous secondarily in rare cases, but; uveal infiltration is more typical in such cases



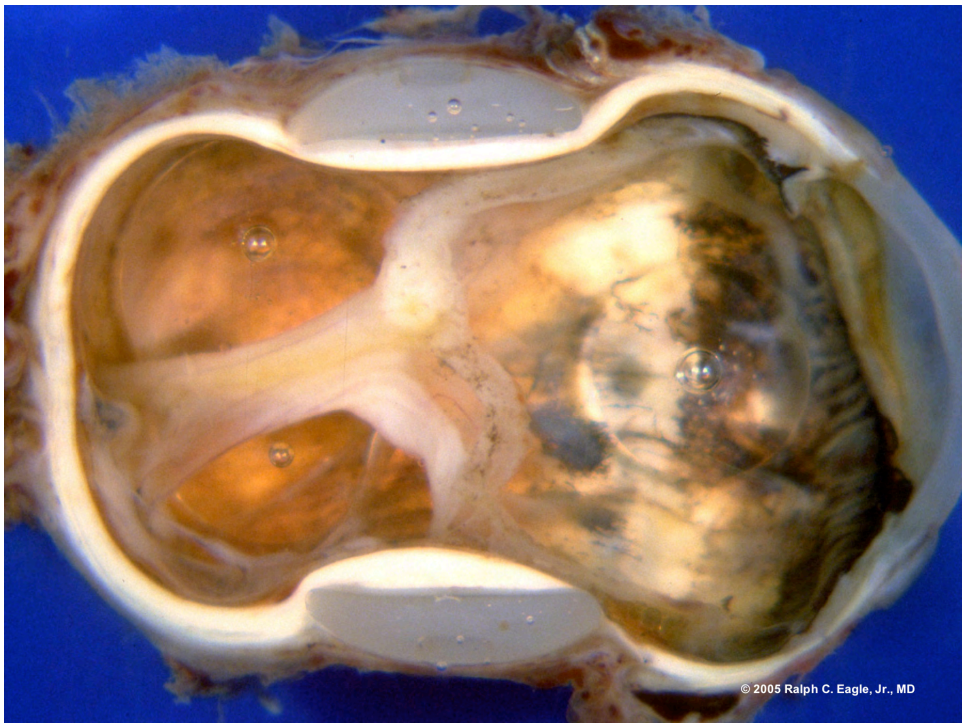
Whipple's Disease- rarely mimics primary CNS lymphoma with bilateral vitritis, dementia, Cells PAS (+), contain bacteria*Tropheryma whippelii*
Metastatic Skin melanoma- predilection for retinal and vitreous metastasis

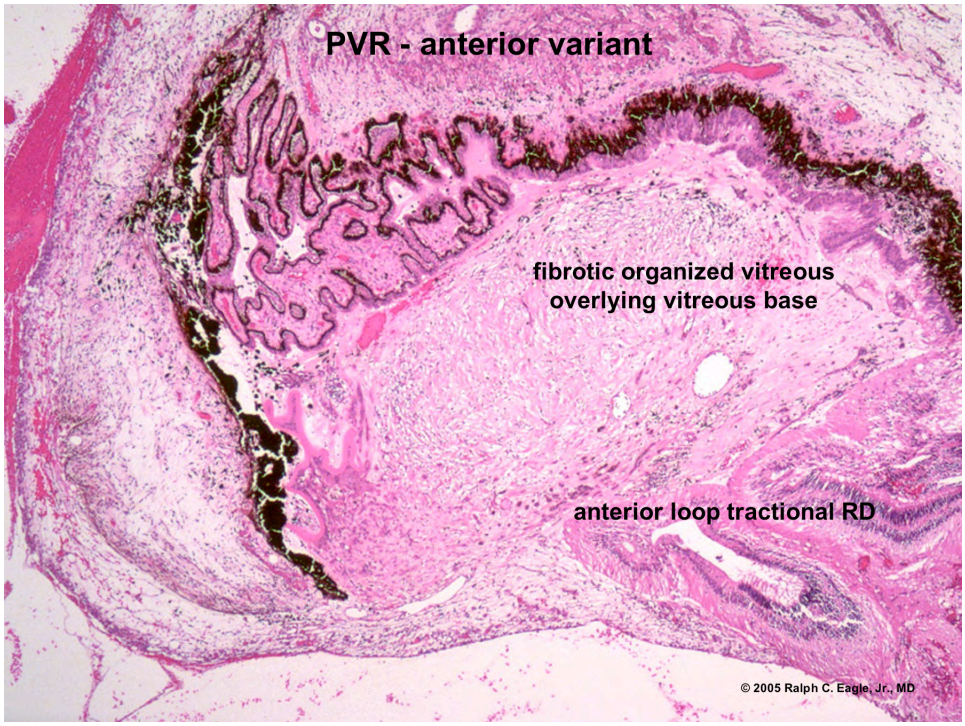
Vitreous Membranes (proliferative vitreoretinopathy, PVR)

RPE, glial cells, myofibroblasts

Vitreous detachment allows cells to proliferate on inner and outer surface of retina, along scaffold of detached vitreous
Membranes cause fixed folds, inoperable RD
Proliferation on posterior face of detached vitreous responsible for funnel shape of chronic RD

Anterior variant of PVR- organization of vitreous on pars plana inaccessible to vitrectomy; anterior loop retinal detachment, posterior traction on iris





Surface Wrinkling Retinopathy (Cellophane retinopathy)
Epiretinal glial proliferation; contraction of membrane folds ILM