INFLAMMATION

A reaction of the microcirculation characterized by movement of fluid and white blood cells from the blood into extravascular tissues. This is frequently an expression of the host's attempt to localize and eliminate metabolically altered cells, foreign particles, microorganisms or antigens.

Cardinal manifestations of Inflammation, i.e. **redness, heat, pain and diminished function** reflect increases vascular permeability, movement of fluid into extracellular space and effect of inflammatory mediators.

**Categories of Inflammation**- Classified by type of cells in tissue or exudate

**Acute (exudative)**
- Polymorphonuclear leukocytes
- Mast cells and eosinophils

**Chronic (proliferative)**
- Nongranulomatous
  - Lymphocytes and plasma cells
- Granulomatous
  - Epithelioid histiocytes, giant cells

**Inflammatory Cells**

**Polymorphonuclear leukocyte**
- Primary cell in **acute inflammation (polys = pus)**
- Multilobed nucleus, pink cytoplasm
- First line of cellular defense
- Phagocytizes bacteria and foreign material
- Digestive enzymes can destroy ocular tissues (e.g. retina)

**Abscess**: a focal collection of polys

**Suppurative inflammation**: numerous polys and tissue destruction (pus)

**Endophthalmitis: Definitions:**

**Endophthalmitis**: An inflammation of one or more ocular coats and adjacent cavities. Sclera not involved. Clinically, usually connotes vitreous involvement.

**Panophthalmitis**: Usually a suppurative endophthalmitis that spreads to involve the sclera and orbital tissues

**Exogenous**: Due to entrance of organisms from external environment, e.g., bacteria introduced by perforating corneal wound, foreign bodies.
- Common organisms: staph, strep, gram negative rods, fungi

**Endogenous:**
Organisms gain entrance by vascular channels or nerves
Common organisms
  Bacteria: (Meningococcus, Nocardia)
  Fungus: (Candida, Aspergillus)
  Protozoans: (Toxoplasmosis)
  Viruses: (CMV, herpes simplex, varicella zoster)

**Bacterial** endophthalmitis—large vitreous abscess; relatively acute onset
**Fungal** endophthalmitis—vitreous microabcesses; more indolent; not as “hot”

**Eosinophil**
- Bilobed nucleus, orange granular cytoplasm
- Allergic reactions
- Modulates mast cell-mediated reactions
- Phagocytizes antigen-antibody complexes
- Parasite-associated inflammatory reactions

*Many EOSINOPHILS = parasites or allergy*

**Eosinophilic Granuloma**
- Superior lateral orbit, bone destruction,
- Localized variant of Langerhans cell histiocytosis, histiocytes with nuclear folds,
- CD1a, Langerin (CD207), S-100 positive, clonal proliferation, EM shows Birbeck granules or racket bodies, role of chemotherapy controversial

**Lymphocyte**
- Round blue nucleus with scanty cytoplasm
- Key cell in humoral and cell-mediated immune responses
- Multiple subtypes:
  - B cells
  - Effector T cells (Delayed hypersensitivity, mixed lymphocyte reactivity)
  - Cytotoxic killer cells
  - Regulator T cells (Helper T cells, Suppressor T cells)
  - Cytotoxic Natural Killer (NK) cells
  - Null cells

**Plasma Cell**
- Eccentric "cartwheel" nucleus
- Basophilia of cytoplasm reflects RNA in RER
- Perinuclear "hof"- Golgi apparatus
- Activated "B" lymphocyte
- Antibody synthesis and secretion, antibody "factory"

**Plasmacytoid cell**
- Plasma cell with granular eosinophilic cytoplasm (or lymphocyte with plasma cell-like nucleus)

**Russell body**
- Round immunoglobulin crystal formed in "constipated" plasma cells

**Morula cell (of Mott)**
- Contains multiple grape-like Russell bodies

**Mast Cell**
- Called tissue basophil, but probably from other BM precursor
- Superficially resembles plasma cell, but stains + for MPS
Binds IgE to surface, contact with antigen causes degranulation and release of histamine and heparin
Cause of acute anaphylaxis, allergic conjunctivitis, etc.

**Chronic Nongranulomatous Inflammation:**
Inflammatory infiltrate composed of lymphocytes and plasma cells;
Usually denotes activation of immune system, e.g., "endogenous iridocyclitis"
(occasionally, lymphocytes and plasma cells may represent the acute response to certain viruses)

**Macrophage (histiocyte, monocyte)**
Large mononuclear cell with eccentric reniform nucleus
Second line of cellular defense
Body's primary phagocytic cell
Enormous phagocytic capacity with little tissue damage
Regulate lymphocytic responses
- Antigen presentation (process antigens, present to T helper cells in association with class II MHC molecules)
- Produce lymphokine IL-1, monokines
Transform into epithelioid cells, inflammatory giant cells
In eye, frequently contain phagocytized substances, e.g., lens material, melanin, lipid, blood breakdown products

**Epithelioid Histiocyte** (activated macrophage)
Activation caused by large quantities of relatively insoluble or indigestible antigen, or organisms that proliferate intracellularly
Abundant eosinophilic cytoplasm, large vesicular nucleus with nucleolus
Groups of cells superficially resemble epithelium, hence name.
**Necessary for diagnosis of granulomatous inflammation!!!**
Fuse to form inflammatory giant cells.

**Inflammatory giant cells**
**Langhan's giant cell**
Peripheral rim of nuclei, homogenous cytoplasm

**Foreign body giant cell**
Contains or surrounds foreign material, nuclei random
If foreign body is too large, body "walls it off" with "insulation" of foreign body giant cells (e.g., precipitates on IOL's)

**Touton giant cell**
Peripheral wreath of foamy lipid surrounds ring of nuclei
Characteristic finding in JXG, also seen in other lipid disorders such as necrobiotic xanthogranuloma, Erdheim-Chester disease, orbital xanthogranuloma with adult onset asthma (see appendix)

**Chronic Granulomatous Inflammation:**
Infiltrate contains **epithelioid cells and/or giant cells**. Generally a response to large quantities of insoluble antigen or organisms that grow intracellularly.
Eyes with granulomatous inflammation may harbor organisms (bacteria, fungi, acid fast bacteria) or foreign matter
May be a response to endogenous material acting as a "foreign body", e.g., lipid in chalazion, cholesterolosis; keratin in ruptured dermoid cyst.
Clinically, large, greasy "mutton fat" keratic precipitates denote granulomatous inflammation

**Work-up!! Clinical work-up, special stains (Gram, AFB, GMS, polarization etc.**
may reveal causative organisms, foreign bodies, specific diagnosis, etc.

Patterns of Granulomatous Inflammation

Diffuse:
Borders ill-defined, epithelioid cells and giant cells randomly distributed against background of lymphocytes and plasma cells. "Salt and pepper" pattern.
Examples: sympathetic uveitis, lepromatous leprosy

Discrete (sarcoidal):
Discrete nodule or aggregate of epithelioid cells surrounded by rim of lymphocytes.
Examples: sarcoidosis, miliary tuberculosis, tuberculoid leprosy.

Sarcoidosis
Discrete noncaseating granulomas
Retinal perivascular candle wax drippings (taches de bougie) = potential for CNS Involvement
Uveitis; granulomas; Busacca and Koepppe nodules

Zonal:
Palisade of granulomatous inflammation surrounds central antigenic nidus.
Concentric zones of lymphocytes and plasma cells surround first zone.
Examples: rheumatoid scleritis, pseudorheumatoid nodule

Phacoanaphylactic endophthalmitis (phacoantigenic uveitis)
Rare autoimmune inflammatory response to lens protein
An immune complex disease that develops when normal tolerance to lens protein is lost, not a cell-mediated rejection of "foreign tissue" (Contrary to prior teachings lens proteins are not totally sequestered or organ specific. They are normally found in aqueous and expressed in other extraocular tissues. Anti-lens antibodies are found in some normal individuals).
Zonal chronic granulomatous inflammation: polys infiltrate central lens material, then epithelioid histiocytes, nonspecific mononuclear cell infiltrate
Zonal pattern caused by antibody/antigen ratio in immune complexes
No penetrating wound or history of trauma in 20%
Concurrence with sympathetic ophthalmia (3-7%), unrelated immunologically

Granulation tissue
Seen in reparative phase of chronic inflammation.
Components: polys, lymphocytes, plasma cells, macrophages, proliferating capillaries, myofibroblasts.

Pyogenic Granuloma: an exuberant proliferation of granulation tissue
Typically follows surgery or trauma, drainage of chalazion
Note: granulation tissue usually is nongranulomatous.
Term derives from granular appearance of healing wounds noted in premicroscopic era. Smooth surface, radiating vessels

Specific ocular inflammatory diseases
Necrotizing Retinitides
Cytomegalovirus Retinitis
CMV is a Herpesvirus
Necrotizing retinitis with hemorrhage in immuno-incompetent patients. Frequent ocular manifestation of HIV/AIDS before HAART (28-45% of patients developed CMV retinitis) “Mustard and catsup fundus”, enlarged cells with "owl's eye" Cowdry type A intranuclear and intracytoplasmic inclusions.

**Toxoplasmosis**
Classically was congenital and acquired *in utero*; acquired cases more common than previously thought
Retinochoroiditis, primary retinal infection by crescentic tachyzoites with coagulative necrosis, secondary granulomatous choroiditis, vitritis
Intraretinal cysts (bradyzoites) cause recurrent disease

**ARN, BARN syndromes** (acute retinal necrosis syndrome)
Acute necrotizing viral retinitis in presumably healthy individuals
Herpesviruses H. simplex and varicella-zoster have been isolated

**PORN Syndrome** (progressive outer retinal necrosis) varicella-zoster

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**TRAUMA AND WOUND HEALING**

**Basic principles of ocular trauma**

**Destruction**

Prolapse, incarceration and loss of intraocular tissues
e.g., anterior uvea, lens, vitreous, retina

**Trauma opens up new surfaces and substrates for cellular proliferation-** *in vivo*
"tissue culture"
e.g., epithelial downgrowth (through wound or by implantation), fibrous ingrowth (along scaffold of incarcerated vitreous), preretinal gliosis (on ILM after PVD)

**Hemorrhage**-expulsive choroidal hemorrhage (not only surgical complication, common with trauma, infectious corneal perforation); vitreous hemorrhage, hemorrhagic retinal detachment

**Penetrating and perforating injuries**

**Penetration**: partial thickness wound *(into)*

**Perforation**: full thickness wound *(through)*
You must specify structure. A *perforating* wound of the cornea is a *penetrating* wound of the globe!!!

**Sympathetic uveitis (ophthalmia)**
Bilateral granulomatous uveitis (autoimmune disorder) after unilateral injury
Classically follows injury or surgery with uveal incarceration (? YAG cyclodestruction, association with Behçet Disease, proton beam irradiation for melanoma).
Time period for safe prophylactic enucleation 1-2 weeks

Classic histopathological features:

- **Diffuse granulomatous infiltrate thickens uveal tract**
- **Sparing of choriocapillaris, retina**
- **Dalen-Fuchs nodules** (not pathognomonic, also in sarcoidosis)
- **Pigment phagocytosis by epithelioid cells**
- Plasma cells uncommon

Cases have developed after evisceration (antigen in emissarial canals)
Association with phacoanaphylaxis (3-7%) – both diseases share traumatic etiology
Enucleation of inciting eye may decrease severity of inflammation in sympathizing eye, contrary to prior teachings
Uveal thickening more pronounced in blacks, eosinophilia
Sparing of choriocapillaris may reflect prompt enucleation

Contusion Injuries
Iridodialysis- thinnest part of iris avulsed from ciliary body
Cyclodialysis- disinsertion of ciliary body from scleral spur. Frequently associated with hyphema due to proximity of greater arterial circle of iris.

Angle Recession (post-contusion angle deformity)
During contusion, lens acts as "ball valve"
Tear into anterior face of ciliary body, or cyclodialysis, hyphema
Post-hyphema, 60% incidence of angle recession
Late glaucoma in small percentage of patients caused by scarring, endothelialization and Descemetization of trabecular meshwork
Secondary synechial closure can hide recession clinically
Fusiform configuration of ciliary muscle results from ischemic atrophy of its inner part
Drop line parallel to optic axis through scleral spur to evaluate angle

Chemical injuries
Acid burns: acid precipitates tissue proteins
Histology: superficial coagulative necrosis of conjunctival and corneal epithelium
Alkali burns: alkali denatures proteins and can penetrate deeply; fat saponified
Vascular endothelial cells and fibroblasts necessary for repair are killed
Ischemic “porcelain conjunctiva”. Histology: corneal and conjunctival necrosis; cataract; glaucoma; uveitis, late symblepharon, entropion

Intraocular foreign bodies
Vegetable matter: violent inflammatory response, often contaminated, fungus, etc.
Glass and plastic: usually inert (IOLs)
Iron: deposits in neuroepithelial structures; siderosis- cataract, heterochromia, glaucoma, retinal degeneration, ferrous (Fe+2) more toxic (“ferrous is furious”)
Copper: deposits in basement membranes (Descemet, lens capsule); Pure copper-purulent endophthalmitis; <85% copper-Chalcosis: Kayser-Fleischer ring, sunflower cataract, retinal degeneration

Hyphema- Corneal blood staining
Hemoglobin particles in corneal stroma, not rbc’s; keratocytes contain hemosiderin
Development depends on duration, IOP, health of endothelium
Healthy endothelium, high IOP, 48 hrs = blood staining
Organization of hyphema-fibrosis, anterior synechias
Vitreous hemorrhage
Complications include:
Cholesterolosis bulbi- blood breakdown major source of intraocular cholesterol crystals, "Synchisis scintillans"
Hemosiderosis (liberation of iron with toxic effects)
Iron deposits in neuroepithelial structures
Hemolytic glaucoma, ghost cell glaucoma
Tractional retinal detachment due to organization, vitreous bands

Atrophia bulbi
Atrophia bulbi with shrinkage (clinical "phthisis bulbi")
Rectus muscle traction on hypotonous globe causes "squared-off" appearance.
Lacks disorganization seen below

**Atrophia bulbi with shrinkage and disorganization**
(Pathological ptthsis bulbi)
Globe small (16-18mm), hypotonous, sclera thickened and folded
General disorganization of intraocular contents
Cyclitic membrane and total retinal detachment common
Numerous large drusen and osseous metaplasia of RPE

**Intraocular bone- osseous metaplasia of the RPE**- located on inner surface of Bruch’s membrane

**CONGENITAL ANOMALIES**

**Cryptophthalmos**
Intact layer of skin covers eye, poor eyelid development, partial or complete
Some have **Fraser Syndrome** (cryptophthalmos-syndactyly syndrome):
cryptophthalmos, renal agenesis, laryngeal stenosis, syndactyly, aural and genital anomalies

**Uveal Coloboma** - defect caused by faulty closure of embryonic fissure
May involve iris, ciliary body, choroid, optic nerve and retina
Located inferonasally, bilateral
Usually sporadic, may be inherited (usually autosomal dominant) with no associated systemic anomalies
Syndromes with Colobomas: CHARGE, Cat-Eye, Kabuki, Wolf-Hirschhorn (4p-)
Compatible with useful vision (absolute scotoma with choroidal coloboma)
Within the coloboma:
Adjacent uvea does not differentiate. It may undergo dysplasia or metaplasia with formation of cartilage, muscle or fat
Overlying retina may be absent or dysplastic
Microphthalmos with cyst (colobomatous cyst) – cyst lined by neuroectoderm

**Trisomy 21** (Syndrome of Langdon Down)-most common chromosomal syndrome
“Mongoloid appearance with up and outward slanting palpebral fissures; almond shaped eyes, epicanthal folds, refractive errors, cataract, strabismus, congenital ectropion, Brushfield spots, keratoconus with hydrops, increased number of vessels crossing disc rim

**Trisomy 13** (Patau syndrome)- formerly 13-15 or D trisomy
Chromosomal anomaly with most severe ocular involvement
Anophthalmos, synophthalmos, microphthalmos,
Coloboma with intraocular cartilage (usually in eyes <10mm)
PHPV/PFV, retinal dysplasia
Cleft lip and palate, holoprosencephaly, arrhinencephaly

**Cyclopia-Synophthalmia**
True cyclopia is rare, most cases are synophthalmia
Not fusion anomaly; rather, failure of bilateral differentiation
Single optic nerve, anterolateral structures most differentiated
Nasal proboscis above single midline orbit

**Holoprosencephaly** (brain not divided into two hemispheres)
Mutations in human sonic hedgehog gene (7q36), SIX3 sine oculo homeobox gene (2p21); association with 13 trisomy; toxic effect of veratum alkaloid cyclopamine in lambs

**Lowe Syndrome**
Oculocerebrorenal syndrome of Lowe
X-linked, aminoaciduria, renal rickets

**Congenital cataract and glaucoma**, lens increscences
Corneal keloids, lens changes in female carriers

**Aniridia** (iris hypoplasia)
Caused by mutations in PAX6 (homeobox) gene

**Categories**

**AN1- 85%**
Familial aniridia (most cases in this category)
Autosomal dominant with incomplete penetrance and expression
Isolated ocular defect, foveal hypoplasia, corneal “dystrophy”, glaucoma, etc.

**AN2- 13%** (**Miller Syndrome, WAGR**)
Sporadic nonfamilial aniridia and Wilms tumor
Deletion or mutation in short arm of chromosome 11 (11p-)
Associations include:
Wilms tumor of kidney (nephroblastoma), genitourinary abnormalities, mental retardation, craniofacial dysmorphism, hemihypertrophy
Incidence of aniridia in patients with Wilms tumor is 1/73 (1.4%)
Incidence of Wilms' tumor in sporadic aniridia is 34%

**AN3- 2%** (**Gillespie Syndrome**)
Autosomal recessive aniridia, Mental retardation, cerebellar ataxia
Structural defects in cerebellum and brain
Do not develop Wilms' tumor

**Congenital Rubella Embryopathy** (Gregg syndrome)
Congenital cataracts, deafness, cardiac defects (patent ductus)
Retention of lens nuclei in embryonic nucleus (not pathognomonic)
Virus remains viable in lens for several years
"Salt and pepper" retinopathy
May have congenital glaucoma, inflammation

**Phakomatoses (disseminated hereditary hamartomas; neurocutaneous hamartoses, Familial Tumor Syndromes (WHO))**

**Hamartoma**: a congenital tumor composed of tissues normally found in an area, e.g., choroidal hemangioma

**Choristoma**: a congenital tumor composed of tissues NOT normally found in an area, e.g., choroidal osteoma; phakomatous choristoma (Zimmerman tumor), eyelid odontogenic choristoma, conjunctival osseous choristoma

**Phakomatous choristoma (Zimmerman tumor)**
Lower nasal eyelid or anterior orbital tumor of infants, probably congenital
A choristoma of lenticular anlage composed of cells resembling lens epithelium surrounded by thick PAS + lens capsule-like basement membrane, cells express lens proteins

**Neurofibromatosis (NF-1, VRNF (von Recklinghausen neurofibromatosis))**
Autosomal dominant, 1/3-4000 live births; proliferation of Schwann cells
Plexiform neurofibromas of eyelid and orbit -"bag of worms", enlarged nerves, "S"-shaped lid fissure
Congenital glaucoma if upper lid involved
Skin lesions- fibroma molluscum, elephantiasis neuromatosa
Cafe-au-lait spots- (six or more >1.5 cm diameter in patients over age 5 yrs, five or more >0.5 cm diameter in patients less than age 5 yrs are diagnostic)
Hamartomatous thickening of uvea, ovoid bodies resemble tactile corpuscles
Lisch nodules- melanocytic hamartomas of iris (92% > age 5 yr., 100% > age 20
Sphenoid bone dysplasia- "Orphan Annie sign", pulsating exophthalmos
Orbital Schwannomas
Optic nerve gliomas [25% have NF (15-70%), other CNS tumors
Gene on chromosome 17 (17q11.2), 50% of cases are new mutations
NF gene product neurofibromin interacts with protein product of ras oncogene, dampens growth stimulatory signals.

Neurofibromatosis, Type II, NF-2 -
Merlin gene on chromosome 22 (22q12.2)
Bilateral acoustic neuromas (schwannomas), presenile PSC cataract, epiretinal membranes, combined hamartoma of RPE and retina (25%), optic nerve sheath meningiomas, oculomotor paresis (12%)

Sturge Weber Syndrome (encephalotrigeminal angiomatosis)
Nonhereditary, congenital (mosaicism for lethal gene??)
Nevus flammeus ("port wine mark"), facial venous angiomatosis
Glaucoma if upper lid involved
Diffuse choroidal hemangioma, "tomato catsup" fundus
Ipsilateral hemangioma of meninges and brain, seizures (80%); MR
"Train track" intracranial calcification

Klippel-Trénaunay-Weber Syndrome (port wine mark, hypertrophy of bones and soft tissues, local gigantism)

Phacomatosis pigmentovascularis: nevus flammeus and melanocytosis; MM risk

Tuberous Sclerosis Complex (TSC, Bourneville's Syndrome)
Autosomal dominant, variable penetrance, high rate of new mutations, TSC1 suppressor gene on chromosomes 9 (9q34 hamartin) and TSC2 on chromosome 16 (16p13 tuberin)
Hamartin and tuberin form complex- suppresses mTOR signaling
Seizures in 80-90%;
Facial adenoma sebaceum (angiofibromas, not sebaceous lesions)
Astrocytic hamartomas of retina ("mulberry nodules")- 50%- rarely progressive
  Rare progressive retinal tumors resemble giant cell astrocytomas of brain
Astrocytic hamartomas of optic disk (giant drusen of optic nerve)
Astrocytic hamartomas of brain (calcify forming "brain stones")
  Subependymal giant cell astrocytomas (SEGA)
Before calciospherites form, retinal lesions can resemble small retinoblastomas
"Ash leaf" skin lesions, shagreen patch, subungual fibromas
Visceral tumors: renal angiomyolipomas, cardiac rhabdomyomas (43%), subpleural cysts, spontaneous pneumothorax,

Von Hippel-Lindau (VHL, Angiomatosis Retinae)
Autosomal dominant with incomplete penetrance; VHL tumor suppressor gene on chromosome 3 - 3p26-p25); VHL protein targets hypoxia inducible factor 1a (HIF1a) for degredation. Genetic testing important

Retinal hemangioblastomas with large feeder vessels, in 50%, 50% bilateral
  Only 5% diagnosed before age 10; new lesions at 2 year intervals- monitor
Tumors may involve optic disk or nerve
  Hemangioblastoma with foamy lipid-laden stromal cells and capillary-caliber vessels. Stromal cells show loss of heterozygosity c/w true neoplastic component, Upregulation of VEGF stimulates capillary proliferation
  Coats’ disease-like exudative maculopathy common

Cerebellar Hemangioblastoma in 35-75% (Lindau was a neurologist)
  Most common cause of death, posterolateral in cerebellum, 80% cystic
**Pheochromocytoma** (<10%); polycythemia 10-25%
**Endolymphatic sac tumor** - deafness, vertigo, tinnitus – 11%
**Renal Cell Carcinoma** - 1/3 of patients; increasing incidence with age

**Wyburn-Mason Syndrome** - nonhereditary
- Retinal and systemic arteriovenous malformations (AVM’s); 86% supratentorial
- 23-30% % have associated midbrain vascular malformation

**Ataxia-Telangiectasia** (Louis-Bar)- autosomal recessive; ATM gene, 11q23
- Conjunctival telangiectases, oculomotor disturbances
- Hypoplastic thymus, deficient cell mediated immunity, deficient IgA, increased incidence of lymphoma. elevated alpha fetoprotein

**Multiple Endocrine Neoplasia Syndrome IIb** (RET proto-oncogene, 10q11.2) AD, 50% sporadic. Enlarged corneal nerves, typical faces, Marfanoid habitus, submucosal neuremas, dry eyes. Pheochromocytomas (45%), neuroendocrine medullary thyroid carcinoma (100%): c-cells, elevated calcitonin, early metastases

**Cavernous Hemangioma of the Retina**
- Light bulbs with fluid level, some patients have CNS and skin lesions
- KRIT1/CCM1 gene (7q21-q22)$^\beta$

**Iris pigment epithelial flocculi or cysts and aortic dissecting aneurysms** (ACTA2 gene encoding vascular smooth muscle actin 10q23.3)

FYI: *Phakomatosis is an outdated term and concept and term. Neither the AAO’s monograph on Inherited Diseases and the Eye (Traboulsi) nor the WHO’s text on CNS Tumors includes the term in the index. The WHO lists the disorders as familial cancer syndromes*

**Abusive Head Trauma (AHT, shaken baby syndrome)**
- Massive hemorrhagic retinopathy including hemorrhagic detachments of ILM (and schisis of ILM), paramacular retinal folds, optic nerve sheath hemorrhage, juxtapapillary intrascleral hemorrhage, hemorrhage within orbital fat

**EYELID**

**Anatomy-Histology**
- **Layers**
  - Skin (epidermis and dermis)
  - Subcutaneous tissue
  - Orbicularis muscle (elliptical sheet of concentrically arranged fibers)
  - Pretarsal plane (vessels and nerves)
  - Tarsal plate (flat semilunar plates of dense collagenous tissue- provide rigidity)
  - Palpebral conjunctiva

- **Upper versus lower lid**
  - Upper lid- longer, rectangular configuration, tarsus much longer, more meibomian glands
  - Lower lid- shorter, triangular configuration, fewer meibomian glands

- **The gray line** (anatomic landmark for lid surgery)
  - Between lash line and orifices of meibomian glands
  - Corresponds histologically to most superficial portion of the orbicularis muscle, (muscle of Riolan).

**Eyelid glands**
- Sebaceous (holocrine)
- Meibomian glands - tarsal plate
- Zeis glands (empty in to lash follicles)

Sweat glands
Eccrine sweat glands
Three segments: secretory portion, intradermal duct, intraepithelial duct (eccrine sweat pore)
Apocrine sweat gland (glands of Moll)- decapitation secretion, apical snouts, empty into lash follicles
Accessory lacrimal glands
Glands of Wolfring (Ciaccio)- superior margin of tarsal plate; 2-5 upper, 2 lower
Glands of Krause- conjunctival cul-de-sac, 42 glands in upper, 6-8 in lower
Glands of Popoff (caruncle)- give rise to oncocytomas

Skin Pathology Terminology

Acanthosis-thickening of squamous epithelium due to proliferation of "prickle cells"
Hyperkeratosis-excess production of surface keratin layer, epidermal granular layer present
Parakeratosis-retained parallel pyknotic nuclei in keratin layer. Epidermis lacks granular cell layer

A characteristically feature of...

Actinic Keratosis
Sun-exposed skin; fair-skinned, middle-aged individuals
Scaly, keratotic flat-topped lesions; early erythematous nodules
Epithelial dysplasia (partial-thickness replacement by atypical cells)
Parakeratosis with focal loss of granular cell layer, dyskeratosis
Irregular buds of atypical keratinocytes extend into papillary dermis
Openings of pilosebaceous units spared, underlying dermis shows elastotic degeneration (similar to that seen in pinguecula and pterygium)
Progression to squamous cell carcinoma uncertain- 12-13% incidence reported in past. Recent large series found much lower incidence (0.1%), spontaneous regression common.
Squamous cell carcinoma arising from actinic keratosis thought to have excellent prognosis compared to SCC de novo (incidence of metastasis only 0.5%)

Acantholysis-prickle cells separated by spaces. Results from rupture of intercellular bridges

A characteristically feature of...

*Inverted Follicular Keratosis - (IFK)
"Irritated seborrheic keratosis"
Acantholysis, squamous eddies, inflammation
Can recur rapidly if incompletely excised

Dyskeratosis-aberrant intraepithelial keratinization of single cells (e.g. HBID)
Dysplasia-disorderly cellular maturation. The normal maturational sequence of cells is disturbed. Partial thickness replacement of epithelium by atypical cells.
Mild dysplasia-less than 50% replacement
Severe dysplasia-more than 50% replacement
Note: the differentiation between severe dysplasia and carcinoma in situ is subjective and may not be clear cut

Carcinoma in situ-full thickness replacement of epithelium by malignant cells without invasion through basement membrane.
Invasive Squamous Cell Carcinoma-malignant cells have broken through epithelial basement membrane and have invaded dermis or substantia propria
Anaplasia—frank cytologic malignancy (pleomorphism, anisocytosis, abnormal nuclei and mitotic figures)

Congenital and Developmental Lesions
Cryptophthalmos, microblepharon, coloboma, ankyloblepharon, ankyloblepharon filamentum adnatum, blepharophimosis, epicanthus, euryblepharon, epiblepharon
Distichiasis—accessory row of lashes arises from meibomian glands
Ptosis

Aging changes
Dermatochalasis, senile entropion, senile ectropion

Inflammatory Lesions
*Hordeolum (stye)
Acute infection of lash follicle (external) or Meibomian gland (internal)
*Chalazion
Chronic lipogranulomatous inflammatory reaction to sebum in tissues. (endogenous "foreign body" reaction)
Epithelioid cells and giant cells surround empty lipid vacuoles (fat dissolved out by tissue solvents)
Submit recurrent chalazia to rule-out sebaceous carcinoma
Atypical chalazion-like lesions in some xanthogranulomatous disorders

Fungal Infections
Blastomycosis, Coccidioidomycosis, Cryptococcosis, Sporotrichosis

Parasitic Infestations
Phthiriasis palpebrarum
Pubic lice, often sexually transmitted, 30% of patients may have another sexually transmitted disease, lice droppings can cause follicular conjunctivitis.
Be sure to examine lashes!!!

Demodicosis - (Demodex folliculorum and brevis)
D. folliculorum mites live in hair follicle, feed secluded in follicle during day, prowl on skin surface at night. Extremely common, suspect in chronic blepharitis, pathogenic? - corneal manifestations have been reported
D. brevis are smaller, live within sebaceous glands

Myiasis—fly larvae, esp. Dermatobia hominis, intraocular involvement rare
Subcutaneous dirofilariasis—zoonose, D. tenuis (raccoon) in USA
Leishmaniasis—
Cysticercosis—larval form of t. Solium

Cysts
*Epidermal Inclusion Cysts (Follicular cyst, infundibular type)
Round or oval, single lumen (unilocular)
Lined by keratinized stratified squamous epithelium
Filled with foul-smelling, cheesy keratin debris
Epithelial lining of cyst may connect with epidermis via pore

*Dermoid Cyst (cystic dermoid—anterior orbit)
Lining epithelium has epidermal appendages, hair shafts mixed with keratin in lumen, sebaceous and sweat glands. Nasal dermoids may have conjunctival epithelial lining

*Sweat Ductal Cysts (sudoriferous cysts, hydrocystomas)
Multilocular, branching lumen appears empty or contains serous fluid. Lined by dual layer of epithelium resembling sweat duct.
Most are eccrine hydrocystomas
Apocrine hydrocytomas: lined by apocrine cells with eosinophilic cytoplasm and “apical snouts” of decapitation secretion. Fluid in lumen often pigmented, contains lipofuscin; may simulate melanocytic lesions.

Vascular lesions

*Capillary Hemangioma
"Strawberry" hemangioma- perinatal onset; express placental antigens
Grows rapidly, then involutes
Cosmetic blemish, danger of amblyopia
Nonencapsulated; early lesions composed of sheets of endothelial cells, mitoses may be numerous; later, capillary spaces appear as lesion loses cellularity
RX: observation, beta-blockers (propranolol), steroid injections in past, cryo, sclerosing solutions, interferon alfa 2a, surgery

In Dermatology literature, acquired lesions are called pyogenic granulomas

*Cavernous Hemangioma
Large blood-filled spaces lined with endothelium, fibrous septa

Lymphangiomia
Many present at birth, slowly progressive, do not involute,
Poorly circumscribed lesion, anastomosing lymphatics lined by single layer of endothelium, hemorrhage into lesion common-"chocolate cyst", D2-40 immuno stain stains lymphatic endothelium; part of spectrum of low flow vascular malformation that includes varices

Glomus tumor, cutaneous angiosarcoma, Kaposi sarcoma

Epidermal lesions: basics for histopathological evaluation

<table>
<thead>
<tr>
<th>Basal cell lesions are BLUE</th>
<th>Squamous cell lesions are PINK</th>
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<tbody>
<tr>
<td>Benign lesions rest anterior to plane of epidermis (benign-&quot;above&quot;)</td>
<td>Malignant lesions invade deep to the plane of the epidermis (malignant-&quot;below&quot;)</td>
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</tbody>
</table>

Benign Epithelial Tumors

*Squamous papilloma-keratinized epidermal fronds with fibrovascular cores. (note: papilloma is a growth pattern)

*Seborrheic keratosi-benign papillomatous proliferation of basal cells, ("blue-above") lesion of elderly, sits like a button on surface of skin, greasy keratin crust, may be pigmented, pseudo-horn cysts, hyperkeratosis, adenoid variant with interweaving bands of bland epithelial cells.

Umbilicated or Cup-shaped Lid Lesions

Keratoacanthoma (? benign)
Molluscum Contagiosum
Basal cell carcinoma

Keratoacanthoma (? benign)
Squamous lesion with central keratin-filled crater, elderly patients
Rapid onset (weeks), spontaneous involution, "pushing margins", overhanging buttress of normal skin at margin
Configuration on low magnification suggests diagnosis; It is Impossible to differentiate from squamous cell carcinoma in small biopsy.

Note: Classically thought to be a benign variant of pseudoepitheliomatous hyperplasia; However, many authorities now consider keratoacanthoma to be a variant of squamous cell carcinoma. Deeply invasive and metastatic lesions have been reported.
Recommended therapy for eyelid keratoacanthoma: **total excision** (preferably with frozen sections)

**Viral Lesions**

**Molluscum Contagiosum**
- Lobular acanthosis with large basophilic inclusions of pox virus (Henderson-Patterson corpuscles), dome or crater configuration, cause of follicular conjunctivitis, massive eyelid involvement in HIV/AIDS

**Verruca Vulgaris**
- Papilloma with spire-like fronds, apical parakeratosis, viral inclusions, coarse keratohyaline granules, HPV 2 (DNA papovavirus)

**Herpes simplex** *(vesicles, intranuclear inclusions, multinuclear giant cells)*

**Herpes zoster**

**Common Eyelid Malignancies**

**Basal Cell Carcinoma**
- Most common eyelid malignancy in Caucasians (18-39 times more common than squamous cell carcinoma)- rare in African Americans, rare in India
- Location: Lower lid> medial canthus > upper lid> outer canthus
  - "Blue" and "below"
  - Variants: nodular, nodulo-ulcerative, multicentric, cystic, diffuse (morpheaform), pigmented variant can be confused with melanoma
  - Histology: tongues and islands of basaloid cells connected to overlying dermis (If no connection, "adnexal carcinoma"), peripheral palisading, retraction artifact, stromal desmoplasia,
  - Malignant morpheaform variant- slender infiltrating tendrils of "Indian file" cells, margins indistinct
  - Metastases extremely rare, lethal tumors directly invade cranial cavity with secondary meningitis
  - "Rodent ulcers"-hideous, neglected cases
  - Dysregulated or aberrant Hedgehog (Hh) signaling has been implicated in the pathogenesis of BCC. Smoothened inhibitors such as vismodegib for advanced, unresectable or metastatic disease (drug very expensive)

**Nevoid basal cell carcinoma syndrome** *(Gorlin-Goltz Syndrome)*
- Mutations in patched1 gene (PTCH1) -q22.32, vismodegib therapy
- Found in 0.7% of patients with BCC, Autosomal dominant
- Multiple BCC in young patients (10-30), odontogenic jaw cysts, skeletal anomalies (bifid ribs), palmar and plantar pits, neurologic anomalies, endocrine disorders
- Skin lesions occur around puberty, tumor may contain osteoid or bone.
- Clinically may be confused with Brooke's tumor.

**Sebaceous Carcinoma** *(or Sebaceous Gland Carcinoma)*
- More common than ocular adnexal squamous cell carcinoma in Caucasians
- Most common eyelid malignancy in India
- Elderly (rare before 40), more common in females, Asians
- Predilection for eyelids, 2/3's arise from upper lid, extremely rare elsewhere in body (General pathologists often unfamiliar; may misdiagnose)
- Can arise from meibomian glands, Zeis glands (sebaceous glands of lash follicles), or sebaceous glands in caruncle
- Broad clinical spectrum - may mimic chalazion or chronic blepharoconjunctivitis (masquerade syndrome)- misdiagnosis common
- Histology-
Lobules of cells with foamy, lipid laden cytoplasm, (Oil red O fat stain can establish diagnosis in less differentiated cases- must be done on frozen sectioned tissue --*Save wet tissue if you suspect!!!*);

New Adipophilin Immuno stain works on routine paraffin sections

Islands of central necrosis (comedocarcinoma pattern)

Intraepithelial "Pagetoid" or “bowenoid” invasion and/or replacement of overlying epithelia – 47%

Mortality-15% in old AFIP series; better recently

Spreads by direct extension, node and distant metastases (lung, liver, brain, skull) possible

Factors associated with Poor Prognosis (Rao et al, AFIP)-

Upper lid origin, size>10mm, Meibomian gland origin, Sx > 6 mo., infiltrative growth pattern, poor sebaceous differentiation, pagetoid invasion, lymphatic, vascular and orbital invasion.

RX: early diagnosis, wide local excision with frozen section control of margins, radiation for palliation of advanced cases only!!!

Benign sebaceous lesions

Senile sebaceous gland hyperplasia- mature sebaceous lobules, central duct

Umbilicated lesions often misdiagnoses as basal cell carcinoma

Sebaceous adenoma

Muir Torre Syndrome- multiple sebaceous gland neoplasms and visceral cancer, esp. carcinoma of colon; germline mutations in MSH2, MSH6 & MLH1 DNA mismatch repair (MMR) genes (2p) cause microsatellite instability; Carriers are heterozygous, tumors lack nuclear staining; MMR defects rare in typical sebaceous carcinoma, suspect in adenomas and low-grade carcinomas

Squamous cell carcinoma

Elderly fair-skinned individual, lower lid margin most common

More common than basal cell in upper lid and outer canthus!!!

Only 5% of lid epithelial tumors (12-39 BCC / 1 SCC),

Potential for regional or distant metastasis

Early skin lesions rarely metastasize (especially if arise from actinic keratosis), wide local excision usually curative

Polygonal cells with pink eosinophilic cytoplasm, nuclear atypia, infiltrating cords into dermis, dyskeratotic cells, keratin pearls

Melanocytic tumors-

Arise from nevus cells, epidermal melanocytes, dermal melanocytes.

Neural crest origin, nevus cells arranged in nests, lack dendritic processes

Benign melanocytic tumors

*NEVI (nevocellular origin) 3 types

Junctional - flat, pigmented; nests of nevus cells at epidermal-dermal JUNCTION. Thought to have malignant potential

Compound-usually slightly elevated or papillomatous, pigmented. Nevoid nests at JUNCTION and in DERMIS, junctional component gives malignant potential

Intradermal (dermal) -most common type; papillomatous, dome-shaped or pedunculated, many slightly pigmented or amelanotic, hair shafts indicate intradermal variety, malignant change extremely rare. Amelanotic lesions frequently misdiagnosed clinically as papillomas

Nevoid nests separated from epidermis by collagenous GRENZ ZONE, may "infiltrate" orbicularis muscle.

Nevus Polarity-

Type A nevus cells in upper dermis larger;
Type B in mid-dermis smaller, lymphoid;
Type C in lower dermis fibroblastic, spindled nuclei, little or no melanin.

Other types of nevi
Blue nevi and cellular blue nevi (dermal melanocytes-spindled or dendritiform)
Nevus of Ota (oculodermal melanocytosis)
Balloon cell nevi
Spitz nevus (spindle or epithelioid cell nevus ("juvenile melanoma")
Congenital intradermal nevi (large (> 2cm) nevi are melanoma precursors 4-6%)

Benign pigmented lesion arising from dermal melanocytes
Blue nevi and cellular blue nevi
Nevus of Ota (oculodermal melanocytosis)

Benign pigmented lesions arising from epidermal melanocytes
Freckle (ephelis)-hyperpigmentation of basal cells, melanocytes not increased.
Lentigo simplex- evolving junctional nevus; increased number of basal melanocytes, elongated rete ridges
Lentigo senilis- 90% of elderly whites, evolves into adenoid seborrheic keratosis

Malignant Melanocytic Tumors
*Malignant melanoma- rare (1% of eyelid malignancies in U.S.)
Lentigo maligna (Hutchinson's malignant freckle)
Elderly, sun-exposed skin, flat pigmented macule with irregular borders
Diffuse hyperplasia of atypical pleomorphic melanocytes at basal cell layer,
involves pilosebaceous units. Malignant transformation in 25-30%
Lentigo maligna melanoma- (vertical growth phase) - fascicles of spindle-shaped cells. 10% metastasize. 5 year survival -90%

Superficial spreading melanoma (Pagetoid melanoma)
Patients younger, nonexposed skin (upper back, legs); spreading faintly palpable macule with irregular outlines, variable pigmentation. Pagetoid nests in all levels of epidermis, Invasive phase marked by papules and nodules, varicolored appearance, white areas of spontaneous regression, 5 year survival- 69%

Nodular melanoma
Age 40-50, 2 men/1 woman, always palpable, rapid growth 5 year survival-44%

Acral lentiginous melanoma- palms and soles, subungual regions
Skin melanomas and nevi
20% of nodular and 50% of superficial spreading arise from nevi
Clinical signs of malignant transformation:
Change in color (red, white and blue, sudden darkening)
Change in size
Crusting, bleeding, ulceration
Softening or friability
Pain, itching, or tenderness
Change in shape (e.g., rapid elevation of flat lesion)
Change in surrounding skin (e.g., redness, swelling, satellites)

Prognostic factors in dermal malignant melanoma

Clark classification

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL I</td>
<td>epidermis only, basement membrane intact</td>
<td>100% LMM</td>
</tr>
<tr>
<td>LEVEL II</td>
<td>early invasion of papillary dermis</td>
<td>100% LMM</td>
</tr>
<tr>
<td>LEVEL III</td>
<td>fills entire papillary dermis</td>
<td>80% SSM</td>
</tr>
<tr>
<td>LEVEL IV</td>
<td>reaches reticular dermis</td>
<td>65% NM</td>
</tr>
<tr>
<td>LEVEL V</td>
<td>-invades subcutaneous tissues</td>
<td>15% NM</td>
</tr>
</tbody>
</table>
**Tumor thickness (Breslow)**
- <0.76 MM: 100% five year survival
- >01.5 MM: <50% five year survival

**Histologic type** - LMM best, SSM intermediate, nodular worse

**Other factors** - associated with poor prognosis: male sex, lesions of trunk and mucous membranes, lymph node involvement, amelanotic lesions, mitotic index, absence of lymphocytic infiltrate at base of lesion.

**BRAF and C-KIT activating mutations** - therapeutic targets
- "vemurafenib" for V600E BRAF mutation.

**Familial atypical mole melanoma (FAM-M) syndrome (dysplastic nevus syndrome, B-K mole syndrome)**
- Autosomal dominant; multiple large atypical nevi in childhood,
- Patients at high risk for cutaneous melanoma, intraocular tumors reported

**Other eyelid lesions**

* **Xanthelasma**
  - Soft flat or slightly elevated yellowish plaques - inner canthi
  - May have normal lipids, half have lipid disorders
  - Aggregates of foamy, lipid-laden histiocytes around vessels in dermis.
  - (Note: atypical xanthelasma-like lesions may herald xanthogranulomatous disorders: Erdheim-Chester Disease, necrobiotic xanthogranuloma with paraproteinemia, orbital xanthogranuloma with adult-onset asthma

**Fibrous histiocytoma**

**Juvenile xanthogranuloma (JXG) macronodular type**

**Langerhans' histiocytosis**

**Lipoid proteinosis** (Urbach-Wiethe) 1q21 extracellular matrix protein gene 1
- Autosomal recessive, multiple waxy nodules along lid margins (moniliform blepharosis), hoarseness due to laryngeal involvement, intracranial calcification
- Deposits of hyaline material in dermis, submucosa

**Sweat Gland Tumors**

**Syringoma**
  - Multiple facial nodules, young women
  - Tadpole-shaped ductules with dual epithelial lining in desmoplastic stroma

**Eccrine acrospiroma (clear cell hidradenoma)**

**Syringocystadenoma papilliferum**

**Hidradenoma papilliferum**

**Pleomorphic adenoma (benign mixed tumor of skin)**

**Endocrine mucin-producing sweat gland carcinoma**

**Mucinous sweat gland adenocarcinoma (can metastasize)**

**Eccrine sweat gland adenocarcinoma (signet ring carcinoma)**

**Adenoma and apocrine adenocarcinoma of gland of Moll**

**Tumors of hair follicle origin**

**Pilomatrixoma** (pilomatricoma, calcifying epithelioma of Malherbe)
  - Reddish mass on upper lid or brow, basophilic hair matrix cells and necrotic shadow cells, calcification develops in necrotic areas of shadow cells, foreign body giant cells common

**Trichoepithelioma (Brooke tumor)**
  - Multiple tumors may be inherited as autosomal dominant; CYLD gene, 16q12.1)
  - Multiple horny cysts with fully keratinized center surrounded by islands of proliferating basaloid cells

**Trichofolliculoma**
  - Most differentiated pilar tumor, hamartoma
Slightly elevated umbilicated nodule, small white hairs in pore highly suggestive
Central dilated hair follicle filled with keratin surrounded by branching immature hair follicles

**Trichilemmoma**
- Benign, arises from glycogen-rich clear cells of outer hair sheath
- Solitary papules or nodules with irregular rough surface
- Lobular acanthosis of PAS+, diastase-sensitive clear cells
- Central hyalinization, usually several hair follicles
- Peripheral palisading, distinct basement membrane

**Cowden disease**: multiple hamartomas, especially facial trichilemmomas; marker for breast or thyroid cancer (AD, 10q23, PTEN tumor suppressor gene)

**Eyelid involvement in systemic disease**

**Sarcoidosis**
- Ocular involvement in 38%, skin involvement in 23%
- Slightly elevated and umbilicated papules, may be partially depigmented in blacks; noncaseating epithelioid tubercles

**Primary systemic amyloidosis**
- Multiple confluent yellowish or waxy papules, hemorrhage (purpura) spontaneously, or with minor trauma

**Leprosy**
- Ocular involvement most common in lepromatous leprosy
- Madarosis (loss of brows and lashes) starts laterally

**Mycosis fungoides**
- Cutaneous t-cell lymphoma, Lutzner cells, Pautrier abscesses

**Lymphomatoid papulosis**: CD30 positive, may resemble keratoacanthoma

**Miscellaneous Eyelid Lesions** - rare!!

**Merkel cell tumor** (cutaneous apudoma, trabecular carcinoma)
- Dermal neuroendocrine tumor with neurosecretory granules
- Painless violaceous or reddish-blue cutaneous nodule, carcinoid-like histology
- 20% fatal, wide local resection with frozen section control, focal CK20 staining
- Merkel cell polyoma virus

**Phakomatous choristoma (Zimmerman tumor)**

**Pseudorheumatoid nodule** (granuloma annulare)
- 1st decade, lateral canthus and lateral upper lid
- Zonal granuloma surrounding central necrobiotic collagen
- No associated systemic disease

**Nodular fasciitis**: benign reactive proliferation of myofibroblasts

**Juvenile fibromatosis** (also orbit, pediatric tumor, distinguish from fibrosarcoma)

**Granular cell tumor** (granular cell myoblastoma)
- Benign lid margin nodule composed of cells with abundant acidophilic granular cytoplasm, PAS + granules, basement membrane, s-100 +, ? Modified Schwann cells

**Eyelid metastases**
- Common primaries: breast, lung, cutaneous malignant melanoma, may mimic atypical chalazion clinically
- Breast metastases may have "histiocytoid" histology

**Erdheim-Chester disease**- xanthogranulomatous infiltrate, atypical xanthelasma

**Necrobiotic xanthogranuloma** – "atypical xanthelasma", necrosis, mult myeloma

**Carney complex** (autosomal dominant syndrome- PRKAR1A- 17q)
- Myxomas, spotty mucocutaneous pigmentation, and endocrine abnormalities
Myxomas- skin, breast, heart (cardiac myxomas: multiple, ventricular, early onset)
**Pigmented spots** on face, conjunctiva, *plica semilunaris*
Rare testicular tumors in males (large cell calcifying sertoli tumors), endocrine abnormalities
Eye findings can herald potentially fatal cardiac myxoma

**Intravascular papillary endothelial hyperplasia**
Most within distended vein, confusion with angiosarcoma, also orbit

**Silica granuloma of the eyelid**
Foreign body granuloma, may mimic sarcoidosis

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**CONJUNCTIVA**

**Histology**
Nonkeratinized squamous epithelium with goblet cells
Substantia propria: loose connective tissue stroma
Palpebral conjunctiva firmly adherent to tarsus
Substantia propria of bulbar conjunctiva is areolar, permits chemosis

**Pseudoglands of Henle**
Gland-like invaginations formed by proliferating tarsal conjunctival epithelium and goblet cells, lymphocytes and plasma cells in stroma

**Acute conjunctivitis**
Hyperemia, chemosis and exudation
- **Bacterial conjunctivitis**-
  Conjunctival smear: polys, bacteria
  Remember: *gonococcus will be blue on Giemsa stain*
- **Viral conjunctivitis**
  Conjunctival smear: lymphocytes

**Chronic conjunctivitis**

**Follicular conjunctivitis**

- **Follicles**: gray-white round to oval elevations, avascular center, vessels at periphery
  - Well-circumscribed focus of **lymphoid hypertrophy**: reactive hyperplasia of conjunctiva’s resident population of lymphocytes
  - Overlying epithelium usually thinned.

**Differential diagnosis of follicular conjunctivitis**

- **Infectious - acute**
  Adenoviruses- (Type 3-PCF [pharyngoconjunctival fever], Type 8-EKC);
  Herpes simplex virus; Newcastle virus (swimming pool conjunctivitis);
  Enterovirus 70 (acute hemorrhagic conjunctivitis); Inclusion conjunctivitis of adults (paratrachoma); Blood-borne (measles, German measles)
- **Infectious- chronic**
  Trachoma, Psittacosis, Moraxella, Infectious mononucleosis
- **Non-infectious**
  Pseudotrachoma, Topical medications (IDU, Eserine, Atropine), Cosmetics, Antigenic material (e.g. molluscum contagiosum, "crab" droppings, allergy (exogenous agents), physiological folliculosis of childhood

**Papillary hypertrophy** (conjunctival papillae)
Nonspecific change, tarsal conjunctiva, **central vascular tuft**, pale avascular valleys, epithelial proliferation, stromal hyperplasia. Deep infoldings of epithelium, rich vascular stroma with chronic inflammatory cells, granulation tissue
Vernal conjunctivitis
- Bilateral, recurrent, adolescents with atopic history
- Itching, worse in spring, thick ropy discharge with eosinophils (Maxwell-Lyon sign)
- Giant “cobblestone” papillae- upper tarsus, limbal papillae, Horner-Trantas dots
- Path- chronic papillary hypertrophy
- Epithelial hypertrophy, then atrophy
- Fibrovascular papillary core contains perivascular and diffuse infiltration of lymphocytes and plasma cells, numerous eosinophils
- Trantas dot: intra- and subepithelial collection of eosinophils, cellular debris
- Limbal vernal: more common in blacks

Giant papillary conjunctivitis
- Similar to vernal, soft and hard CL's, ocular prostheses
- Fewer eosinophils than vernal, basophils

Parinaud oculoglandular syndrome
- Granulomatous conjunctivitis with regional lymphadenopathy (preauricular node)
  - Differential diagnosis: Bacterial conjunctivitis, cat scratch fever (silver stain for bacteria- Bartonella henselae), Tularemia, Tuberculosis, Actinomycosis, Leptothrix, syphilis, Rickettsia, Chlamydia (Lymphogranuloma venerenum), Viruses (especially Ebstein-Barr [infectious mono]), Sarcoidosis

Chlamydial conjunctivitis
- **TRIC agent** (trachoma, inclusion, conjunctivitis) small obligate intracellular parasites sensitive to antibiotics, elementary body, initial body, inclusions

Trachoma
- One of the most significant causes of blindness in the world
- Spread by direct contact, secretions, insects, poor hygiene
- Bilateral keratoconjunctivitis, may be asymmetrical
- Initial epithelial infection followed by subepithelial inflammation with follicles in substantia propria

Conjunctival smear: polys and lymphocytes
- Epithelial cells contain initial bodies, basophilic intracytoplasmic inclusions of Halberstaedter and Prowaczek
- Immunohistochemical stains available

WHO Diagnostic Criteria (must have 2)
1. Lymph follicles on the upper tarsus
2. Conjunctival scarring (Arlt's line)
3. Vascular pannus (Inflammatory pannus destroys Bowman membrane)
4. Limbal follicles or remnants of limbal follicles in late stages (Herbert's pits)

MacCallan classification
- STAGE I: Initial conjunctival follicle formation, diffuse punctate keratitis, early pannus
- STAGE IIA: Florid follicular conjunctivitis with follicular necrosis
- STAGE IIB: Papillary conjunctivitis
- STAGE III: Cicatricial stage with secondary sequelae
- STAGE IV: Arrest of the disease

Inclusion conjunctivitis (paratrachoma)
- Inclusion blenorrhea in infants, major cause of acute purulent conjunctivitis in newborn
- Inclusion conjunctivitis in adults - venereal disease. Follicles in lower fornix

Conjunctival Membranes
**True membrane**
Inflammatory exudate **firmly adherent to epithelium, bleeding** occurs when peeled, e.g.-diphtheria, gonococcus, beta-hemolytic strep, Stevens-Johnson syndrome

**Pseudomembrane**
Less adherent, **peels without bleeding**. e.g., -viral (HSV, adenovirus 8 [EKC], adenovirus 3 [PCF]); bacterial (staph, pneumococcus, meningococcus, pseudomonas, coliforms); chemical burns, ocular pemphigoid, foreign body, ligneous conjunctivitis

**Ligneous conjunctivitis (AR mutations in plasminogen gene, 6q26)**
Bilateral, chronic pseudomembranous conjunctivitis, begins in childhood, may recur
Massive, woody accumulation of **fibrin** (not MPS), granulation tissue
An autosomal recessive systemic disease- similar lesions in vagina, other mucosae; obstructive hydrocurephalus has been reported

**Mycotic, parasitic conjunctivitis, etc.**

**Rhinosporidiosis**
Large round fungus causes infectious strawberry-like papilloma studded with white microabscesses, pathognomonic histology with sporanga, large round trophozoites, rare in USA, most cases in India

**Ophthalmia nodosa**
Caterpillar hairs (setae), may invade anterior chamber

**Synthetic fiber granuloma** (**“teddy bear granuloma”**)
Epibulbar foreign body granulomatous response to synthetic fabric "fuzz balls", can mimic ophthalmia nodosa, fabric fibers contain delustering agent,

**Allergic conjunctival granuloma** (**Ashton**)
Presumed parasitic granulomas; Splendore-Hoeppli phenomenon (eosinophilic deposits of antigen-antibody complexes)

**Filaria- Loa loa “eye worm”**

**Allergic conjunctivitis**

**Contact hypersensitivity** (acute allergic conjunctivitis)
Hay fever, animal dander, topical drugs
Chemosis, itching, dermatitis
Eosinophils in smear
Acute anaphylactic reaction due to mast cell degranulation
? cell-mediated hypersensitivity reaction

**Phlyctenular conjunctivitis**
Hypersensitivity to bacterial proteins
2-3 mm whitish inflammatory nodules on bulbar conjunctiva surrounded by zone of dilated vessels, epithelial ulceration

**Degenerations**

**Pinguecula**
Raised yellowish-white mound of degenerated subepithelial connective tissue near limbus in interpalpebral space (actinic elastosis)
Probably related to environmental exposure, light damage
Histology: solar elastosis, acellular homogeneous deposit, basophilia, thickened vermiform collagen fibers, late hyaline deposits. Elastotic material stains positively with Verhoeff-van Gieson elastic stain, but is not sensitive to elastase digestion.
Similar findings in some cases of pterygium
Material may stimulate granulomatous response in advanced cases (“actinic granuloma”)

**Amyloidosis**
- Yellow, avascular deposits, bulbar or palpebral conjunctiva
  - "Starch-like" acellular eosinophilic material, Congo Red, Crystal Violet, Thioflavin-T positive, apple-green birefringence, dichroism with polarization microscopy. Often light chain amyloid, but typically unassociated with systemic disease

**Conjunctival Cysts and Tumors**

**Congenital Cysts**
- Inclusion Cysts
  - Lined by conjunctival epithelium; lumen empty or filled with mucous; traumatic or surgical implantation

**Ductal Cyst**
- Analogue of sudoriferous cysts in skin, arise from accessory lacrimal glands
  - Dual layer of epithelium, clear lumen

**Solid Epibulbar Dermoid**
- Choristomatous mound of interweaving, coarsely-thickened collagen fibers covered by skin-like epithelium, often with epidermal appendages (hair, sebaceous and sweat glands).
  - An isolated finding, or in association with **Goldenhar syndrome**:
    - (epibulbar solid dermoids, preauricular appendages, aural fistulas)

**Complex Choristoma**: also contains cartilage, fat and/or lacrimal gland elements

**Dermolipoma (dermolipoma)**
- Choristoma of fat and connective tissue,
  - Can extend deep within orbit, avoid surgery or excise carefully!

**Epibulbar Osseous Choristoma** - mature bone, superotemporal quadrant

**Pyogenic Granuloma**
- Fleshy red mass of exuberant granulation tissue ("proud flesh")
  - Aberrant inflammatory repair response.
  - May form after surgery, e.g, chalazion I&D, strabismus, etc (see inflammation)

**Conjunctival Neoplasms** - 3 basic categories:

**Squamous** - proliferation of conjunctival squamous epithelium

**Lymphoid** - proliferation of normal resident population of lymphocytes

**Melanocytic**

**Squamous lesions (OSSN - Ocular Surface Squamous Neoplasia)**

**Squamous Papilloma**
- Benign proliferation of conjunctival epithelium as multiple fronds with central fibrovascular cores
  - Vascular "hair-pin" loops clinically
  - Bulbar or palpebral conjunctiva
  - Can be multiple and recurrent, especially in children
  - Many are viral lesions (HPV, human papilloma virus), DNA hybridization
  - NOTE: conjunctival dysplasia or squamous carcinoma can have papillomatous configuration.

**Inverted Papilloma**

**Hereditary Benign Intraepithelial Dyskeratosis**
- Inherited disorder of triracial "Haliwa-Saponi Indians" in North Carolina. 4q35
  - Nonmalignant leukoplakic squamous lesions of conjunctiva and other mucous membranes marked by dyskeratosis (single cell keratinization)

**Actinic keratosis**
Focal, leukoplakic; epidermoid cells, parakeratosis, actinic elastosis
Rarely recur

**Conjunctival Intraepithelial Neoplasia (CIN, OSSN: Ocular Surface Squamous Neoplasia, Dysplasia)**

A disease spectrum characterized by a replacement of the conjunctival epithelium by atypical squamous cells. Basal germinative layer involved first. Characteristically abrupt transition between normal and acanthotic dysplastic epithelium. Interpalpebral limbal location, keratinization (leukoplakia) clinical marker for squamous lesion, often diffuse, some lesions gelatinous, frequently recur

- Mild dysplasia: < 50% of epithelium replaced
- Severe dysplasia: >50% of epithelium replaced

Some cases are caused by viral infection with human papillomavirus (HPV)

In situ DNA hybridization has demonstrated HPV 16/18

**Carcinoma in situ:**

Total replacement of epithelium by frankly malignant cells.

Epithelial basement membrane is intact, no invasion into substantia propria

Spindle and epidermoid variants.

**Invasive squamous cell carcinoma:**

Malignant cells have broken through epithelial basement membrane invading substantia propria

Squamous cell carcinoma may have papillary growth pattern

Rarely can invade interior of globe, eyelid, orbit

More common in Middle East, Africa (association with HIV/AIDS in Africa)

Rarely metastasizes, excise locally

**Mucoepidermoid carcinoma**

Rare variant of squamous cell with mucin production

Behaves more aggressively with early invasion and recurrence

**Spindle Cell Carcinoma** (sarcomatoid squamous cell carcinoma) aggressive, poorly-differentiated variety of squamous cell carcinoma, may be cytokeratin (-)

**Lymphoid tumors** (See further discussion in orbit section)

Arise from conjunctiva's resident population of lymphocytes

“Salmon-patch” or fish-flesh appearance clinically

Reactive lymphoid hyperplasias, atypical lymphoid hyperplasia or malignant lymphomas. Most are stage IE well-differentiated lymphocytic lymphomas, i.e.,

**Extranodal Marginal Zone Lymphomas (EMZL)** - (WHO classification)

These also have been called MALT lymphomas (lymphomas of mucosa associated lymphoid tissue or MALTomas: CD20+, CD5-, CD10-, CD23-)

**Systemic malignant lymphoma rarely presents as a conjunctival lesion.**

Associated systemic disease in 20% (prior, concurrent or subsequent -Jakobiec)

31% in Shields clinical series; esp with forniceal or midepibulbar involvement

Follicular appearance suggests benign process clinically

Benign lesions have following histopathological features:

- Germinal centers (N.B. residual follicles may be present in EMZL)
- Abundant capillaries with plump endothelial cells
- Polymorphous infiltrate containing mixture of cells, i.e., mature lymphocytes, plasma cells, eosinophils.

?? Polyclonal infiltrate with immunohistochemical markers

(recent studies suggest this is not always the case!)

NB: Marker studies cannot be optimally performed on formalin-fixed tissue, fresh tissue gives best results and is mandatory for flow cytometric analysis.
Signs of malignancy: monomorphic infiltrate, cytologic atypia, monoclonality
Management: noninvasive systemic workup, low dose radiotherapy, ? rituximab
Questionable association of conjunctival MALT lymphoma with with *Helicobacter pylori* or *C. psitacci* infection is controversial; ? role of antibiotics

**Melanocytic tumors**

*Racial (constitutional) melanosis*

*Pigment in squamous cells* - no atypical melanocytic hyperplasia
Note: squamous tumors in darkly pigmented individuals may be pigmented due to secondary acquired melanosis – contain bland dendritic melanocytes

*Freckles (ephelis)*
Congenital, increased melanin in basal epithelium, normal number of melanocytes

*Nevi*
Nests of benign nevus cells along epithelial base (junctional activity) and/or substantia propria, may be amelanotic
A congenital lesion- typically enlarge or become more pigmented at puberty or during pregnancy, cosmesis often an indication for excision
3 variants:

*Junctional*: nevus cells confined to epithelial-subepithelial junction (anterior to the epithelial basement membrane)
Junctional nevi of the conjunctiva are extremely rare!!! (They are nearly impossible to distinguish from primary acquired melanosis in a small biopsy without an adequate clinical history...
The junctional component diminishes with age- A junctional nevus of the conjunctiva in an adult is PAM until proven otherwise!!!)

*Subepithelial*: nevoid nests confined to substantia propria

*Compound*: (Most conjunctival nevi are compound!!)
Nevus cells in both locations. **Cystic or solid epithelial rests** are very common in compound conjunctival nevi, They suggest a nevus clinically, but do not rule-out melanoma because malignant transformation of nevi is possible; size of cysts increases with age

*Blue nevi*- Slender pigmented spindle cells and dendritiform cells in substantia propria

*Cellular blue nevi*
Combined nevus- combination of nevocellular and blue nevus

*Nevus of Ota*
(Congenital Oculodermal Melanocytosis)
Slate gray pigmentation due to dendritiform nevus cells deep in substantia propria and episclera, associated blue nevus of periocular skin
Heterochromia iridum reflects diffuse nevus of uvea
Predisposition to uveal, orbital, & meningeal melanoma; not conjunctival MM

*Primary acquired melanosis* (PAM, Reese's Cancerous Melanosis. C-MIN)
Unilateral pigmentation in middle-aged or elderly whites
Insidious onset, waxes and wanes, malignant potential
32% incidence of progression to melanoma in older series (much too high!!). Shields’ recent series- 13% progression to melanoma – (PAM with severe atypia)
Extent in clock hours is another important prognostic factor

PAM **without atypia** - epithelial hyperpigmentation with or without melanocytic hyperplasia restricted to basilar region of epithelium without nuclear
hyperchromaticity or prominent nucleoli. Very low risk for conjunctival melanoma (0%- Shields)

**PAM with atypia: Atypical melanocytic hyperplasia or malignant melanoma in situ involving conjunctival epithelium**

*High risk for developing conjunctival melanoma!!!*

- 75% if PAM contains epithelioid cells
- 90% if intraepithelioid pagetoid spread is present
  
  (Only 20% if atypical melanocytes confined to basilar part of the epithelium)

Atypical cells confined to epithelium constitute radial growth phase

**Vertical growth phase** - invasive malignant melanoma

PAM can be amelanotic (primary acquired melanosis sine pigmento) and can occur in blacks (rare)

UV (Wood's light) may highlight subtle pigmentation

Management: Observe carefully with photographic documentation. Biopsy thickened areas (presumptive melanomas), excision, cryotherapy, ? mitomycin C

**Zimmerman Classification of PAM**

- Stage I-Benign Acquired Melanosis
  - A. with minimal melanocytic hyperplasia (increased melanin within epithelium)
  - B. with atypical melanocytic hyperplasia
    - 1. mild to moderately severe
    - 2. severe ("in situ" malignant melanoma)

- Stage II-Malignant Acquired Melanosis
  - A. with superficially invasive melanoma (tumor thickness < 1.5mm)
  - B. with more deeply invasive melanoma (tumor thickness > 1.5mm)

**Malignant melanoma of the conjunctiva**

Relatively rare: uveal/conjunctiva MM ratio 10/1 (AFIP)

26% mortality, unpredictable behavior

(Note: Callender classification is not applicable to conjunctival melanomas!! )

Can arise from:

- **Primary acquired melanosis (majority of cases)**
  - Preexisting nevus
  - De novo (nodular melanoma)

Primary acquired melanosis found in 75%, Nevi 25%

Conjunctival melanomas behave like skin melanomas, not uveal melanomas

Have BRAF mutations like skin melanomas (not found in uveal melanomas)

Lymphatic spread common (preauricular and intraparotid nodes)-poor prognosis.

Within lymph nodes melanoma cells gain access to blood vessels via anastomoses between lymphatics and blood vessels.

Sentinel node biopsy has its advocates

Factors associated with poor prognosis: extralimbal tumor location, nasal location, caruncular involvement, involvement of surgical margins, de novo melanoma without PAM, inadequate initial surgical management
Differential Diagnosis of Pigmented Epibulbar Lesions

<table>
<thead>
<tr>
<th>Congenital Melanosis</th>
<th>Acquired Melanosis</th>
<th>Nevus</th>
<th>Malignant Melanoma</th>
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<tr>
<td>Inflammation</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
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</tbody>
</table>

Other pigmented lesions of the conjunctiva

- **Argyrosis** (silver containing eye drops, Argyrol)
- **Senile scleral plaque (of Cogan) calcification**
- **Ochronosis** (alkaptonuria; homogentisic acid oxidase deficiency)
- **Drug deposits** (epinephrine; phenothiazine; tetracycline)
- **Cosmetics** (mascara, kohl)

**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 membrane absent, anterior third of stroma scarred and vascularized, Descemet membrane very thin.

**Solid epibulbar dermoids** and complex choristomas (see conjunctiva)
- **Goldenhar syndrome** (hemifacial microsoma with epibulbar dermoids)
- **Axenfeld/Rieger syndrome**
  - (dysembryogenesis of the angle, "mesodermal dysgenesis", angle cleavage syndromes) AD, several genes- (PITX3, PITX2, FOXC1, RIEG2)
  - A clinical spectrum that includes:
    - **Posterior embryotoxon of Axenfeld**
      - Prominent, anteriorly displaced Schwalbe’s ring
    - **Axenfeld Anomaly**
      - Posterior embryotoxon plus iris processes to ring
      - 50% have glaucoma
    - **Rieger Syndrome**
Axenfeld anomaly plus iris stromal defects such as hypoplasia, slit pupils, polymoria, pseudocoria; Skeletal and dental anomalies, umbilical hernia; Autosomal dominant, 50% have glaucoma

**Peters Anomaly**
- Bilateral central corneal opacities, iridocorneal and keratolenticular adhesions
  - Descemet and Bowman membrane absent centrally, anterior polar cataract
  - Mutations in PAX6, PITX2, CYP1B1 or FOXC1, fetal-alcohol syndrome, Accutane®

**Posterior Ulcer of von Hippel**
- Congenital corneal opacities
  - Resembles Peters but no lens involvement
  - Endothelium and Descemet membrane absent centrally

**Posterior Keratoconus**
- Posterior umbilication of central corneal stroma
  - Descemet 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, stromal loss, ulceration

**Fungal**
- Fungal hyphae permeate stroma, often located deep - may be missed in superficial scraping, readily perforate Descemet membrane & invade anterior chamber
  - In USA, 80% caused by Aspergillus, Candida, or Fusarium

**Mycobacterial**
- *M. tuberculosis*, atypical mycobacterial infections, leprosy

**Descemetocele**: herniation of Descemet membrane through floor of deep corneal ulcer

**Infectious Pseudocrystalline keratopathy**
- Large interlamellar bacterial colonies with vaguely crystalline configuration
  - Adjoining stroma relatively non-inflammed
  - 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 membrane (suggestive of Herpes but also seen in other entities

**Deep keratitis with ulceration** (metaherpetic keratitis)
Stromal thinning, perforation, Descemetocoele

**Granulomatous reaction to Descemet membrane**
(classically associated with chronic herpetic keratitis, but not pathognomonic)

**Parasitic keratitis- Onchocerca volvulus** (onchocerciasis)
"River blindness"- major cause of blindness worldwide
Vector (black similian 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 bathing in hot tubs while wearing lenses
PK may be necessary, patients typically have severe pain (? neurotropism)
Annular infiltrate (ring ulcer) - a late finding
Amoebic cysts, trophozoites, moderate necrosis in stroma, loss of epithelium and keratocytes. Cysts are readily seen in routine H&E stains; previously touted Calcofluor white fluorescent stain no longer available in many areas

**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 membrane lost; deep vessels (posterior 1/3 of stroma);
  thickening of Descemet membrane, occasionally massive with formation of hyalinized bridges and strands
  Tuberculosis, leprosy, Cogan Syndrome (non-luetic IK with deafness)
  Protozoal (see above), onchocerciasis (see above), systemic disease
  (sarcoidosis, Hodgkin disease, mycosis fungoides), foreign bodies (insect hairs [ophthalmia nodosa]), plant material, drugs (systemic gold, arsenic),
  trachoma (see conjunctiva)

**Inflammatory pannus**
Peripheral ingrowth of fibrovascular membrane beneath epithelium

**Bowman membrane is destroyed** (classically seen in Trachoma)

**Degenerative pannus**
Common finding in chronically edematous corneas

**Bowman membrane intact**
Fibrous tissue interposed between base of epithelium and Bowman membrane

**Peripheral ulcerations**
Marginal ulcers
Staphylococcal toxins

Collagen vascular diseases: Lupus, periarteritis nodosa, Wegener granulomatosis, rheumatoid arthritis

Ring ulcers

Moore 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 ulcer
Bilateral, slowly progressive, males
Trough-like stromal thinning begins superiorly
Epithelium intact, Bowman and superficial stroma lost
Vascularization, occasional lymphocytes and plasma cells

Corneal degenerations

*Pterygium (pter: "wing" - lesion resembles insect wing)
Interpalpebral fissure, most common nasally
Caused by environmental factors: light, dust, wind?? limbal stem cell loss??
Resembles conjunctiva histologically, but invades cornea
Increased stromal vessels, often has elastotic degeneration of collagen
Bowman membrane lost; overlying epithelial dysplasia possible

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

*Chronic actinic keratopathy (elastotic degeneration)
(Many synonyms: climatic droplet keratopathy, spheroidal degeneration, Labrador keratopathy, Bietti 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 light
Yellow olive oil-droplet appearance clinically
May coexist with calcific band keratopathy

Salzmann’s Nodular Degeneration
Whitish focal mounds of subepithelial hyaline connective tissue; Bowman 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 underdeveloped regions frequently follows measles keratitis

Keratoconjunctivitis sicca
Deficient tear or mucous production
Corneal drying, SPK, filamentary keratitis (detached strands of epithelium and mucous)

**Sjögren 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. Increased infant mortality. Malnourished children in underdeveloped countries, alcoholics in USA

**Bitot 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, inferior half of cornea, iron-calcium protein complex

**Secondary amyloidosis**

**Keratoconus**
- Bilateral, onset around puberty, heredity questionable
  - Association with: Down syndrome, atopic dermatitis, Ehlers-Danlos, Marfan syndrome, Leber congenital amaurosis, floppy mitral valve syndrome, hard contacts, floppy eyelid syndrome, eye rubbing
  - Central stromal ectasia, abnormal consistency of cornea, wiggly dehiscences in Bowman membrane, DM thin, endothelium often healthy
  - Munson sign, Vogt striae, stromal folds, Rizutti sign
  - Ruptures in Descemet lead to acute hydrops (especially in Down syndrome)

**Fleischer ring surrounds cone (iron in epithelium)**
- Cause uncertain,? abnormality in extracellular matrix?, ? defect in tissue metalloproteinase inhibitors?
- DALK – pneumatic artifact in stroma from air injection

**Pellucid degeneration**
- Resembles keratoconus histopathologically, hydrops possible

**CORNEAL RINGS**

<table>
<thead>
<tr>
<th>Corneal iron lines - ferritin particles within epithelium</th>
</tr>
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<tbody>
<tr>
<td><strong>Fleischer</strong> ring: keratoconus, surrounds base of cone</td>
</tr>
<tr>
<td><strong>Hudson-Stähli</strong>: horizontal, line of lid closure, physiological aging</td>
</tr>
<tr>
<td><strong>Stocker</strong>: advancing head of pterygium</td>
</tr>
<tr>
<td><strong>Ferry</strong> line: in front of filtering bleb (Ferry = filter)</td>
</tr>
</tbody>
</table>

**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 hepatolenticular degeneration)
- Copper in Descemet 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)

*NOTE:* Granular, lattice, Avellino and Reis-Bückler dystrophies have been shown to be associated with different mutations of the **TGFBI gene (formerly BIGH3)** on the long arm of chromosome 5. The corneal epithelium is rich in TGFBI protein (also called **keratoepithelin**). 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 dystrophy** is caused by mutations in corneal epithelium-specific keratins K3 and K1

The 2015 Revision of the IC3D Classification of Corneal Dystrophies now classifies corneal dystrophies as 1. epithelial and sub-epithelial dystrophies, 2. epithelial-stromal dystrophies caused by mutations in TGFBI, 3. stromal dystrophies, and 4. endothelial dystrophies. Category 2 includes the five corneal dystrophies caused by mutations in the TGFBI gene including Reis-Bücklers and Thiel-Behnke dystrophies that previously were classified as Bowman layer dystrophies. The classification also placed dystrophies into evidence-based categories.

**Modified Classification of Corneal Dystrophies (Revised IC3D Classification- 2015)**

**Epithelial and sub-epithelial dystrophies,**

**Meesman Corneal dystrophy** (Stocker-Holt)
- 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)

**Epithelial Basement Membrane Dystrophy** (Map, dot and fingerprint dystrophy, Cogan microcystic dystrophy)
A clinical spectrum that results from poor epithelial adhesion to its basement membrane

**Most cases are not inherited, not considered a dystrophy**
(rare autosomal dominant cases have been reported)
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 within disorderly epithelium
- **Fingerprint**: parallel relucent lines of basement membrane separating tongues of reduplicated epithelium
- **Map (geographic)**: subepithelial connective tissue resembling degenerative pannus

**Lisch Epithelial Corneal Dystrophy** (band-shaped and whorled microcystic dystrophy)
Foci of epithelial cells contain intracytoplasmic vacuoles- Xp22.3

**Gelatinous droplike corneal dystrophy** (Familial Subepithelial Amyloidosis)
Massive subepithelial amyloid deposits, recurs rapidly after PK
Caused by mutations in **TACSTD2** gene (1p32.1),
Amyloid contains lactoferrin, but lactoferrin gene normal, many cases in Japan

**Epithelial-stromal dystrophies caused by mutations in TGFBI**

**Reis-Bückler Corneal Dystrophy**
Autosomal dominant, begins in first decade with recurrent erosions
Subepithelial scarring, ring-shaped opacities
A superficial variant of granular dystrophy, may be confused with lattice dyst.
Irregular "saw-toothed" epithelium, subepithelial connective tissue, destruction of Bowman layer. Laminated pannus contains intensely eosinophilic crystalloids that stain like material in granular dystrophy (red with Masson trichrome)
TGFBI mutation- mutant kerato-epithelin, 5Q31.1

**Thiel-Behnke Corneal dystrophy**
Very similar to Reis-Bückler clinically and pathologically, but storage material is composed by "curly filaments" shown by TEM; TGFBI mutation (also 10q24).1 Cases of Thiel-Behnke were reported as Reis-Bückler's in American literature

**Lattice Corneal Dystrophy, type I (LCDI, Biber-Haab-Dimmer, Bückler Type III)**

**Localized corneal amyloidosis** (Klintworth),
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
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, 5q31.1
(Other variants: III, IIIA, I/III, IV)
Note: Meretoja syndrome or familial amyloidosis, Finnish type, previously was called Lattice Corneal Dystrophy, Type II
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 lax itchy skin, typical mask-like "hound dog" facies with protruding lips, pendulous ears, systemic amyloid deposits
Amyloid deposits composed of mutant gelsolin, an enzyme involved in actin metabolism. GSN gene 9q34

Granular Corneal Dystrophy, Type 1 (GCD1, Groenow Type I, Bückler 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, 5q31.1

Granular Corneal Dystrophy, type 2 (GCD2, formerly Avellino Dystrophy)
Combines features of granular and lattice type I, TGFBI mutation

Polymorphic Amyloid Dystrophy (Klintworth) - Lattice variant, "ice chips" TGFBI

Representative TGFBI Mutations in TGFBI Corneal Dystrophies

<table>
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<tr>
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<td>Granular type I</td>
<td>Arg555Trp</td>
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<td>Reis-Bückler</td>
<td>Arg555Gln</td>
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<tr>
<td>Lattice type IIIA</td>
<td>Pro501Thr</td>
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</table>

Stromal Dystrophies
Macular Corneal 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 (+)
Schnyder Corneal Dystrophy (SCD, formerly Schnyder central stromal crystalline dystrophy (SCD)
Autosomal dominant, UBIAD1 gene, (1p34.1-p36).
Needle shaped polychromatic cholesterol crystals in anterior stroma, prominent bilateral arcus; **No longer called crystalline** because only 50% have crystals!!
Diffuse stromal clouding in some may necessitate PK (age 40-50)
? association with systemic lipid disorder in some cases (xanthelasma, elevated serum lipids)

**Fleck Corneal Dystrophy (François-Neetens Fleck Dystrophy dystrophie mouchetée)**
- Vision normal, flecks in stroma found incidentally
- Autosomal dominant, occasionally unilateral, PIP5K gene (2q35).
- Swollen keratocytes contain GAGs, lipid

**Others**
- Congenital Stromal Corneal Dystrophy- Decorin gene
- Posterior Amorphous Corneal Dystrophy
- Central Cloudy Dystrophy of Francois
- Pre-Descemet corneal dystrophy

Note: Corneal Stromal Dystrophies Classically included; Granular, Lattice and Macular Dystrophies, Granular and Lattice are caused by mutation in the TGFBI gene and are included in that category.

**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)

**Endothelial dystrophies**

**Fuchs Endothelial Corneal Dystrophy** (FECD, cornea guttata)
- Primary endothelial dystrophy (Adult onset); 5% over age 40 in the USA
- Anvil-shaped guttate excrescences of abnormal basement membrane material secreted on Descemet 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), endothelial cells often contain iris pigment epithelial melanin
- Complex inherited disorder, FH often negative, many genes, rare COL8A2 mutations

**Congenital Hereditary Endothelial Dystrophy (CHED)**
- Two types: rare autosomal dominant, more common recessive- **SLC4A11 gene**
  - Thickened edematous stroma, massively thickened Descemet, atrophic or nonfunctioning endothelium

**Posterior Polymorphous Corneal Dystrophy** (Schlichting)
- Irregular blebs or vacuoles at level of Descemet 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; several genes implicated(? TCF8 )
- **Endothelial cells have epithelial characteristics**: (multilayered, tonofilaments, multiple microvilli, surface keratin differentiation)

**X-linked endothelial Corneal Dystrophy**

**Iridocorneal Endothelial (ICE) Syndrome-** (unilateral, not a dystrophy)
Corneal Involvement in Systemic Diseases
Systemic mucopolysaccharidoses
Severe, early opacification in MPS-IH (Hurler), I-S (Scheie), VI (Maroteaux-Lamy) – corneal disease in Hurler’s not ameliorated by bone marrow transplant
Mucolipidoses
Fabry disease (alpha galactosidase deficiency)
Cornea verticillata in 90% of affected males
Wilson disease: Kayser-Fleischer ring, Copper in Descemet membrane
Ochronosis (alkaptonuria): brown granules in sclera, peripheral Bowman
Refsum 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 crystalline dystrophy
Cholesterol (Schnyder’ crystalline dystrophy)
Plant sap injury (Dieffenbachia)
Clofazimine (antibiotic for leprosy, reversible if treatment stopped)
Enlarged Corneal Nerves
MEN Type IIb (ganglioneuromas?) – medullary thyroid CA, elevated calcitonin
Hereditary Ichthyosis
Hansen Disease (leprosy)
Keratoconus
Refsum 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 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, Tb, 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 Sclerosis
Usually unilateral limitation of motility, proptosis, retrobulbar pain, field loss, retinal detachment, uveal effusion, disk edema, optic neuritis, may mimic uveal tumor

Histology: Nodular Sclerosis
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) Sclerosis
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 lenticonus: bilateral, males, X-linked Alport's syndrome of hereditary hemorrhagic nephritis, deafness, abnormal type 4 collagen (rare association with posterior polymorphous dystrophy)
Posterior lenticonus: 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 associated 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 pearly nuclear cataract, retained nuclei in embryonic nucleus
Lowe syndrome: discoid lens, capsular increscences
Down 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 in plaque 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)**

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 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)

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 may occur in sclerotic 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%; possible association with rubella infection

**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, Weil-Marchesani), or by mutations that affect fibrillin structure secondarily (homocystinuria, sulfite oxidase deficiency).**

**Marfan 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, steel puddlers), also an aging change; no association with glaucoma

Pseudoexfoliation of lens capsule (Exfoliation Syndrome, PXE)
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 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
LOXL-1 gene (Lysyl oxidase-like 1), 15q24.1

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 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. (EM: spirally birefringent concentrically multilaminated "rice grains")
Wilson Disease (Hepatolenticular degeneration)
- Sunflower cataract, Kayser-Fleischer ring
- Deposition of copper in lens capsule, Descemet membrane
Similar findings occur in chalcosis; Copper deposition also has been reported in primary biliary cirrhosis, familial cholestatic cirrhosis, monoclonal gammopathies associated with multiple myeloma and pulmonary carcinoma.

Diabetes mellitus

Galactosemia

Fabry disease
- X-linked deficiency of alpha-galactosidase A; Xq22.1
- 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 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 (common in abusive head trauma) punctate Gunn's dots may be visible on inner surface
  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 endothelial cell 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)
Lipidized histiocytes in the subretinal space or outer retina may also appear as hard exudates.

Circinate retinopathy
Ring of hard exudate surrounding focus of leakage

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, HIV/AIDS
Confined to territory of radial peripapillary capillaries

Angioid streaks
Breaks in calcified Bruch’s membrane
Pseudoxanthoma elasticum (peau d’orange fundus)- major association
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 all 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)

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. There are NO ganglion cells in foveola

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 simultaneous 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
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
Chemotherapeutic agents

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 Maculopathy (Age-related macular degeneration, senile macular degeneration, SMD, ARMD)
Major public health problem, leading cause of irreversible blindness in people over age 50 in developed world
More common in blue-eyed patients, rare in blacks: suggest pathogenic role of chronic light exposure
Chronic inflammation may play a role in pathogenesis. Inflammatory mediators and complement components found in drusen and damaged RPE cells. Strongly associated with a common variant of complement factor H (CFH) gene- 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 and involution of choriocapillaris; AREDS

"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
   Focal deposits of extracellular debris located between the basal lamina of the retinal pigment epithelium and the inner collagenous layer of Bruch’s membrane.

Complex composition, confusing classification schemes
   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)

Soft Drusen- found only in macula, amorphous membranous debris
   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

**Vascular Endothelial Growth Factor and VEGF inhibitors, OCT**

**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, peripapillary atrophy, peripheral punched-out spots
Focal chronic choroiditis, organisms rarely found

**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 – CME after cataract surgery
In past very high incidence with iris supported IOL's
Secondary finding over choroidal tumors, especially hemangioma
Occurs with peripheral uveitis, peripheral tumors
OCT and anti-VEGF therapy (Lucentis, Avastin), intravitreal Kenalog®
Initial intracellular edema within Mueller cells? (Fine, Brucker)

**SD-OCT (spectral domain optical coherence tomography)**
Powerful technology to assess retinal disease; CME, SRF
Retinal layers on OCT do not correlate exactly with histopathology
4 outer lines: XLM, ellipsoid of inner segments; cone OS/contact cylinder region; RPE

**Ophthalmic lasers (argon, krypton, dye, 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
**Non-syndromic RP is caused by more than 3000 mutations in 57 different genes.** Examples: RHO, PDE6A, PDE6B, CNGA1, SAG, RPE65, RLBP1, ABCA4, RGR, RDS, ROM1, PROM1, NRL, CRX, RP1, RP2, RPGR, CRB1, and TULP1.4
Some encode proteins involved in rod phototransduction cascade:
- Rhodopsin (RHO)
  - 15-20% 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
  - arrestin guanylate cyclase activating protein
- 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- 13% of cases, 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"
   Macromelanosomes (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)- 18 variants recognized–
   CEP290- most common gene – 20% of cases
   RPE65 gene – taget of gene therapy in humans and Briard dogs
   Sector retinitis pigmentosa
   Usher 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** (in periphery)
   Stellate maculopathy does not stain with fluorescein: OCT all layers
   ? abnormal vitreous-like material in retina (Brownstein)

**Macular dystrophies** (hereditary, bilateral)
   **Fundus flavimaculatus** (Stargardt disease) 1p21-p13
   Once thought to be a 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 derivative A2-E in outer segments that poison RPE's phagolysosomal system, leading to accumulation of lipofuscin in RPE, with resultant “terminal constipation” of RPE cells.
   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 disease (Vitelliform macular dystrophy)**
Dominant, bestrophin gene (BEST1) on chromosome 11q (11q13)
Some cases of adult vitelliform 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 deletion 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- mutations in arrestin or rhodopsin kinase; some patients may develop late retinal degeneration

**Gyrate atrophy** (autosomal recessive ornithine-delta-aminotransferase deficiency)

**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.

CHM gene which encodes for Rab escort protein-1 (REP1),

**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**

**Syndromic RP:** Bardet-Biedl, Senior Loken, Bassen-Kornzweig, Bietti corneoretinal crystalline dystrophy, cystinosis, neuronal ceroid lipofuscinosis, Refsum disease, autosomal dominant cerebellar ataxia type II, Joubert syndrome, Hallervorden Spatz, etc.

**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**

Many cotton wool spots are a marker for retinal ischemia

Intraretinal Microvascular Abnormalities (IRMA)

**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
Diabetic iridopathy

Iris neovascularization (NVI, 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  
**Vitreous**  
**Chronic retinal detachment**  
- Funnel or morning glory configuration, photoreceptor degeneration, gliosis, macrocystic degeneration; may have secondary pigmentary retinopathy  
- Proliferative vitreoretinopathy,  

**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 disease, Scintillatio nivea)
- 2% incidence, unilateral (80%), increases with age
- Generally does not interfere with vision
- **Spherules of calcium hydroxyapatite** attached to vitreous framework (Not calcium soap as previously stated)
- 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, crystals sink to bottom of globe

**Primary Amyloidosis Of The Vitreous**
- Vitreous involvement in Familial Amyloidotic Polyneuropathies (FAP's); 18q12.1
- 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, important cause of treatment failure, 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 cases have large B cell lymphocytic lymphoma
- 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 Disease**—rarely mimics primary CNS lymphoma with bilateral vitritis, dementia, Cells PAS (+), contain causative bacteria *Tropheryma whipplei*
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

Intraocular Tumors

Uveal Malignant Melanoma
- Most common primary intraocular tumor in white adults

Risk Factors
- Race
  - Uveal malignant melanoma is predominantly a tumor of blue-eyed Europeans (2/3’s of cases occur in patients of European descent who comprise 13% of world’s population - Retinoblastoma is most common primary malignant IOT
  - Incidence in U.S. whites is 8.5 times greater that blacks
  - Incidence in USA is 21 times greater than in Taiwan (6 vs. 0.28/million)
  - Tumors in blacks are larger, more pigmented, more necrotic and have same survival as tumors in whites.

- Age
  - Incidence increases with age, median age at diagnosis - 53 (AFIP), 59 (COMS)
  - Larger tumors, poorer survival with increasing age:

<table>
<thead>
<tr>
<th>Size</th>
<th>Median age</th>
<th>10 year survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>small [&lt;10 mm]</td>
<td>53 yr.</td>
<td>80%</td>
</tr>
<tr>
<td>medium [10-15 mm]</td>
<td>56 yr.</td>
<td>60%</td>
</tr>
<tr>
<td>large [ &gt;15 mm]</td>
<td>61 yr.</td>
<td>35%</td>
</tr>
<tr>
<td>with metastases</td>
<td>65 yr.</td>
<td>----</td>
</tr>
</tbody>
</table>
* Survival after enucleation [Non tumor deaths excluded]

- Male = female in COMS study

Predisposing Lesions
- Genetic mutations
- GNAQ/GNA11
  - GNAQ mutations present in 50% of uveal melanomas
  - Also found in Nevus of Ota, blue nevis, ocular melanocytosis
  - An early or initiating event - present at all stages of malignant progression
  - G-protein-coupled receptor (RAF/MEK/ERK pathway)
- BAP1 - (very important prognostic marker)
  - 84% incidence of inactivating mutations in in class II uveal melanomas
  - Association with monosomy 3
loss of chromosome 3 appears to uncover recessive mutations in chromosome 3

Congenital ocular or oculodermal melanocytosis [Nevus of Ota]
1/400 lifetime risk of MM in Caucasians
Uveal nevi- estimated rate of malignant transformation- 1/9000 (Singh)
Neurofibromatosis
Dysplastic nevus syndrome (familial atypical mole melanoma syndrome)
Ultraviolet light- more common in blue eyes, inferior iris
Chemical carcinogens?? Pregnancy

**BDUMP Syndrome**- (Bilateral diffuse uveal melanocytic proliferation associated with systemic malignancy).
Remote effect of disseminated malignancy
Bilateral diffuse thickening of uvea with pigmented nodules. "giraffe skin" fundus
Melanomas may arise from generalized low-grade spindle cell proliferation

**Clinical Presentation of Uveal Melanoma**
Incidental finding on routine examination

*Visual Loss*
- Retinal Detachment [solid and/or serous, rarely hemorrhagic], foveal overhang, CME (peripheral tumors), cataract formation [CB tumors], vitreous hemorrhage [rare, usually requires retinal perforation]
- Extrascleral extension [anterior or orbital mass with proptosis]
- Glaucoma
- Iris heterochromia
- Inflammatory signs mimicking endophthalmitis or orbital cellulitis- necrotic tumors
Unsuspected tumor diagnosed in pathology lab in blind painful eye

**Gross Pathology**

**Choroidal Tumors**- most common location
Pathologic classification by size: (LTD- largest tumor diameter)

**Small**- LTD ≤ 10 mm- most are discoid tumors confined to choroid
**Medium**- LTD 11- 15 mm
- Most break through Bruch’s membrane and grow in subretinal space
- Typical mushroom or collar button configuration (63%)
- Dilated vessels in head of mushroom caused by cinch-like effect of Bruch’s membrane on waist of tumor.

**Large**- LTD > 15 mm
- Tumor invades and destroys ocular tissues, may fill globe
- Extrascleral extension more common
- May be diffuse infiltrating type
  - Uncommon, grows laterally with little choroidal thickening
  - Extrascleral extension more common

**Ciliary body melanomas**
- Less common than choroidal tumors – poorer prognosis
- Diagnostic delay- may be asymptomatic, no RD
- Tend to have a more spherical shape
- Can invade anterior chamber anterior ("tip of the iceberg")
- Diffuse type of malignant melanoma may cause ring configuration around circumference of angle and ciliary body. Prone to anterior extrascleral extension
- Can cause cataract; sentinel vessels, CME
Cytology and Histopathology

Callender Classification [modified by McLean et al, 1978]

Association between mortality and cytology or cell type of melanoma

**Spindle cells**
- Bipolar cells with spindle-shaped cytoplasm- arranged in parallel fascicles
- Grow as syncytium- cellular margins indistinct by LM

**Spindle A** - slender cigar-shaped nucleus with finely dispersed chromatin and indistinct nucleolus. Nuclei often have chromatin stripe or streak caused by fold in nuclear membrane (most benign)

**Spindle B** - plumper, oval nucleus with coarser chromatin and a more prominent nucleolus

**Intermediate cells** - nuclear characteristics intermediate between spindle B and epithelioid

**Epithelioid melanoma cells** - most malignant
- Polyhedral cells with abundant glassy cytoplasm
- Large and pleomorphic, bizarre giant cells occasionally seen
- Poorly cohesive with distinct cytoplasmic borders
- Large round to oval nucleus with peripheral margination of coarse chromatin (chromatin clumped along interior of nuclear membrane)
- Prominent eosinophilic or purple nucleolus

"Epithelioid cells look back at you!"

**Four subcategories of tumors based on cytology cellular constituents**

**Spindle cell nevus** - composed entirely of benign spindle A cells

**Spindle cell melanoma**
- Composed of malignant spindle A, spindle A and B or Spindle B cells
- A. 72% 15 year-survival

**Mixed cell melanoma** - very common
- Mixture of spindle and epithelioid cells –
- 86% of medium and large posterior tumors in COMS study

**Epithelioid cell melanoma** - rare, poorest prognosis
- Composed predominantly of epithelioid cells

**Other pathologic features**
- RPE and outer retinal degeneration at tumor apex
- Retinal invasion common, retinal perforation rare; epiretinal seeding
- Most cases have secondary exudative retinal detachment
- 13% incidence of extrascleral extension (tumors extend extraocularly along scleral emissarial canals, vortex veins)
- Optic nerve invasion rare (usually in cases with diffuse growth pattern)

**Orange pigment** - macrophages laden with lipofuscin; indicates actively growing lesion, but is not pathognomonic for melanoma

**Prognostic Features**

**Clinical Risk Factors (AJCC)**
- **Size**
- **Ciliary body involvement**
- **Extraocular extension**
Histopathologic Risk Factors

Cell type (modified Callender classification)

Patients with spindle cells tumors have better prognosis than patients whose tumors contain epithelioid cells (survival of 4728 patients at AFIP):

<table>
<thead>
<tr>
<th>Cell type</th>
<th>5-yr-survival</th>
<th>10-yr-survival</th>
<th>15-yr-survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spindle cell nevus</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Spindle melanoma</td>
<td>90%</td>
<td>79%</td>
<td>72%</td>
</tr>
<tr>
<td>Mixed cell, Epithelioid cell, and Necrotic</td>
<td>58%</td>
<td>44%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Tumor size - as important as cell type
1. Tumors can be difficult to accurately measure
2. **Largest tumor diameter (LTD) is best prognostic indicator:**

<table>
<thead>
<tr>
<th>Size</th>
<th>Dimensions</th>
<th>5-yr-survival</th>
<th>10-yr-survival</th>
<th>15-yr-survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>&lt; 11 mm</td>
<td>86%</td>
<td>76%</td>
<td>70%</td>
</tr>
<tr>
<td>Medium</td>
<td>11-15 mm</td>
<td>66%</td>
<td>51%</td>
<td>43%</td>
</tr>
<tr>
<td>Large</td>
<td>&gt; 15 mm</td>
<td>56%</td>
<td>41%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Cell type and tumor size are most important factors that can be assessed histopathologically

Other Prognostic Factors Assessable During Routine Pathologic Exam

- Extraocular extension
- Mitotic activity- more mitoses- worse prognosis
- Lymphocytic infiltration- associated with worse prognosis
- Vascular mimicry patterns (formerly called extracellular matrix patterns (EMP) or vascular loops and networks (Folberg)
- Necrosis- more necrotic tumors have worse prognosis- may present with inflammatory signs such as orbital cellulitis
- Pigmentation- not very important- more pigmented tumor- worse prognosis
- Melanophagic infiltration- poorer prognosis

Prognostic Factors Assessed By Special Testing

- Chromosomal Abnormalities – monosomy 3, trisomy 8q
  - Monosomy 3- 50% die within 3 years
- Gene expression Profile (Harbour)
  - Proprietary commercial test- expensive
  - Class IA melanomas - low-grade, do not metastasize.
  - Class IB melanomas – New category- late metastasis
  - Class 2 melanomas - high risk for early metastases, primitive neural/ectodermal stem cell-like phenotype, contain epithelioid cells, vacular mimicry patterns
- **BAP1 gene inactivation- strongly associated with metastasis**
  - Size and variability in nucleolar size (ISDNA, MTLN)- research techniques
  - Loss of HLA-1 expression- Better Survival
Hypothesis: NK-cell mediated surveillance in blood during hematogenous metastasis

Metastasis (At least 30% die from metastatic disease)
Hematogenous spread-
Uveal melanoma has a predilection for hepatic metastasis
Liver mets in more than 90% of cases, detected first in 80%
More than 50% of patients with metastatic uveal melanoma are dead within 1 year.
Currently, no good therapy for metastatic uveal melanoma
Late metastases occur in some patients.

Diagnosis
Indirect Ophthalmoscopy
Observation for growth
Ultrasonography- acoustically hollow, low internal reflectivity, choroidal excavation
IVFA (No pattern pathognomonic for MM)
FNAB- limited application, reserve for tumors in which diagnostic uncertainty persists after routine tests (e.g. woman with history of breast cancer who has solitary choroidal mass that could be amelanotic melanoma)
P32 test- not specific for melanoma, largely abandoned, indications rare

Therapy
Observation for growth ? (some large nevi indistinguishable from melanomas by all clinical criteria except growth) Enucleation is not a medical emergency!

Enucleation- still treatment of choice for large tumors
Zimmerman’s hypothesis- “Enucleation may disseminate tumor cells and increase tumor deaths” (NOT TRUE)

Radiation:
Plaques (plaque brachytherapy) radiation source (Iodine125 in USA)
placed on sclera over tumor for calculated period of time, now outpatient
Charged particle beams (Proton beam, Helium Ion)
Mortality post-plaque similar to enucleation (COMS)

TTT (transpupillary thermotherapy – form of laser therapy- thin tumors
Plaque plus hyperthermia (experimental)
Photoocoagulation- only effective for very small tumors.
Cryotherapy
Local resection- iridectomy, iridocyclectomy, partial lamellar sclerouvectomy

Collaborative Ocular Melanoma Study (COMS- prospective NEI study)
Very small tumors- observation
Small to medium sized tumors
Randomized to I125 plaque versus enucleation
Survival after enucleation and plaque are similar, confirming prior nonprospective data
Large tumors- randomized enucleation versus enucleation versus preop EBRT
Preop EBRT does not improve survival

The Futility of Local Therapy?
It is thought that most uveal melanomas already have metastasized (clinically inapparent micrometastases) when the patient presents to the ophthalmologist. Local treatment has no effect on survival. Metastatic melanoma responds poorly to therapy. It is hoped that early chemo might improve survival if high-risk patients could be identified (FNAB for gene expression classes, monosomy 3 studies, immuno markers)

Metastatic melanoma - current therapy is largely ineffective; poor survival
Iris melanoma
Iris affected least often - inferior iris most common location
Best prognosis - 4% overall mortality (actually may be higher)
Visible to patient, small size at detection
Most pigmented tumors of the iris are benign nevi - only 6.5% grow when observed for 5 years.
Treat by local resection [iridectomy or iridocyclectomy if CB extension present]
Reserve enucleation for tumors with epithelioid cells or intractable glaucoma
Diffuse iris melanomas that cause heterochromia and secondary glaucoma
usually (89%) contain epithelioid cells

Differential Diagnosis of Posterior Uveal Melanoma)

Nevus
- Malignant transformation rare - photos and observe
- Suspicious nevi: larger, overlying drusen, even serous detachment

Melanocytoma (magnocellular nevus)
- Maximally pigmented magnocellular nevus; more common in blacks
- Classically an optic nerve tumor, but can occur anywhere in uvea
- Can enlarge, but malignant transformation extremely rare
- Bleached sections required to disclose bland cellular details during diagnosis

Choroidal hemangioma
- Benign cavernous hemangioma; thin walled vessels, scant stroma
- Sporadic tumors: localized, orange mass
- Sturge-Weber: diffuse tumors - “tomato catsup” fundus
- Cystoid retinal edema, exudative retinal detachment
- Distinguish with IVFA, US;
- Treatment with PDT or radiation to preserve eye

Uveal metastases – 50% breast, 20% lung
Most common intraocular malignancy (autopsy series - many cases not seen clinically)
- Often multiple, amelanotic nummular lesions, posterior pole (greatest blood flow)
- One third of patients have no history of cancer/some primaries remain occult
- Women-breast carcinoma, prior history of mastectomy (50% of mets are breast)
- Men-occult lung primary (20% of mets are lung)
- Treatment - irradiate to conserve vision
- Role of FNAB (Fine Needle Aspiration Biopsy) - confirm diagnosis when standard tests are equivocal, e.g. met vs amelanotic mm in woman

Congenital Hypertrophy of the RPE (Halo nevus)
- Flat black circular or oval lesion with depigmented lacunae, surrounding halo
- RPE cells hypertrophic with macromelanosomes
- Localized scotoma
- POFL’s (pigmented ocular fundus lesions) in Gardner's syndrome (Familial adenomatous polyposis with extracolonic manifestations and colon carcinoma) are bilateral, multiple and do not resemble solitary sporadic CHRPE or typical bear tracks.
- CHRPE occasionally enlarge, rarely evolve into solid tumors

Congenital grouped pigmentation of the RPE (Bear tracks)
- A variant of RPE hypertrophy - cells contain more melanin, larger granules.
**Tumors of the Retinal Pigment Epithelium**
- Reactive proliferation of RPE is very common
- True RPE neoplasms are extremely rare
- Benign adenomas and cytologically malignant adenocarcinomas
- Bands of tumor cells on septa; very atypical cells, low proliferative index
- Cells often coexpress cytokeratin (CK7) and Melan A
- Malignant RPE tumors locally infiltrate, but do not metastasize
- Some are deeply pigmented, abrupt margins, retinal invasion, exudation

**Combined Hamartoma of the RPE and Retina**

**Tumors of the Ciliary Epithelium**
- Very rare (except Fuchs or coronal adenoma)
- Adenomas and adenocarcinomas, from pigmented or nonpigmented epithelium
- Arise from epithelium on inner surface of ciliary body, not from stroma
- Bands of tumor cells on septa; pools of MPS

**Leiomyoma**
- Most cases found in young woman
- Amelanotic tumors usually located in supraciliary space, may show increased transillumination
- Mesectodermal type resembles neural tumor by LM but shows smooth muscle differentiation immunohistochemistry (smooth muscle actin+) or TEM

**Peripheral Nerve Sheath Tumors** - rare (choroidal Schwannoma)
- **Retinal vasoproliferative tumor** - probably reactive proliferation of glial cells, vessels, primary and secondary types

**Choroidal Osteoma** (osseous choristoma)
- Young women (67%), may be bilateral (20%)
- Yellow-orange, scalloped margins, can decalcify and involute, CNV
- Plaque of bone in choroid, w/u with CT, US
- Bone within choroidal stroma, not its surface like osseous metaplasia of RPE

**Other Lesions That Can Simulate Posterior Uveal Melanoma**

**Hemorrhagic Vascular Lesions**
- Age related macular degeneration (disciform degeneration)
- Age-related extramacular degeneration (peripheral disciform degeneration)
- Hemorrhagic detachment of the RPE or retina

**Inflammatory Lesions**
- **Posterior scleritis** (nodular)
  - More common in women, inflammatory signs, cloudy subretinal fluid
  - Same color as surrounding fundus, concentric choroidal folds
  - Ultrasound: retrobulbar edema, thickened sclera and choroid, high internal reflectivity
- **Chorioretinal granuloma** (sarcoidosis, tuberculosis, syphilis, etc.)

**Cystic Lesions**
- Degenerative retinoschisis
- Iridociliary cysts

**Choroidal detachment**

**Uveal Effusion Syndrome**

**Rhegmatogenous retinal detachment**

**Others**
- Vitreous hemorrhage
- Subluxed lens
- Compression of globe from external mass
Most common intraocular tumor in children (1/15-20,000 births)
World-wide: most common primary intraocular tumor
Decreasing incidence with age. Majority diagnosed by age 4.
Observed in premature babies and rarely in adults.
No sex preference, 33% bilaterality.

Clinical Presentations

**Leukocoria** (white pupil) the "amaurotic cat's eye reflex"  
90% of patients with retinoblastoma in North America and Europe present with leukocoria.
Other common causes of leukocoria include toxocariasis, persistent hyperplastic primary vitreous (PHPV), and Coats disease.

**Strabismus**- present in 35%
Children with strabismus should have fundus exam to rule-out a small foveal retinoblastoma or other foveal pathology
Fixed dilated pupil, hyphema, NVG and heterochromia iridis (rare)

**Pseudoinflammatory presentation**

**Pseudohypopyon** (tumor seeds in AC, endophytic or diffuse infiltrative tumors)

**Aseptic orbital cellulitis** due to extensive necrosis of tumor and intraocular structures in eyes with severe glaucoma.
Orbital tumor due to massive extrascleral extension (third world)
Congenital retinoblastoma (very rare!!!)

Clinical Work-up

EUA, Computed tomographic scanning, magnetic resonance imaging, ultrasound, and fluorescein angiography may provide useful clinical information. Avoid needle biopsy

Gross Pathology

White, encephaloid appearance with calcific flecks (mini- "brain tumor")

**Growth Patterns**

**Endophytic** growth pattern: arises from inner retina, seeds vitreous, may mimic inflammation

**Exophytic** growth pattern: arises from outer retinal layers, causes solid retinal detachment; retinal vessels course over mass

Most tumors have **mixed** growth pattern

**Diffuse infiltrative**: least common (1.4%), no obvious mass, diffuse growth within retina; late presentation (mean age 6 years) with pseudoinflammatory signs- pseudohypopyon – always unilateral

Histopathology

**Poorly differentiated neuroblastic cells with basophilic nuclei, scant cytoplasm; apoptotic cells, many mitoses**
Tumor arises from and destroys retina
Blue, pink and purple areas under low magnification
BLUE- viable tumor cells with basophilic nuclei and scanty cytoplasm.
Viable cells form 90-110µ cuffs around vessels giving rise to lobular pattern
PINK- eosinophilic zones of tumor necrosis  
(tumor has striking tendency to outgrow blood supply)
PURPLE- foci of dystrophic calcification within necrosis
DNA deposition - basophilic DNA released by tumor necrosis preferentially deposits around vessels, lens capsule, in trabecular meshwork, ILM

Iris neovascularization, often with PAS, found in 50%

Tumor seeds - form when viable tumor cells are shed into vitreous or subretinal fluid. Outermost cells are viable; innermost cells are necrotic.

Characteristic Signs of Differentiation

Flexner-Wintersteiner Rosettes
- Early photoreceptor differentiation
  - Central lumen corresponds to subretinal space, filled with hyaluronidase-resistant acid mucopolysaccharide similar to inter-photoreceptor matrix material
  - Cellular apices joined by XLM-like zonulae adherentes
  - Cilia (9+0) project into lumen
- (Despite what the Academy manual says F-W rosettes are not pathognomonic for RB, they are also found in medulloepithelioma, pineal tumors!)
- Numerous rosettes are found in tumors from very young children.
- Retinoblastomas in older children are usually poorly differentiated.

Homer Wright Rosettes (after James Homer Wright)
- Neuroblastic differentiation
  - No true lumen, tangle of neural filaments fills central space
  - Often observed in neuroblastoma, medulloblastoma, less frequently in retinoblastoma (mnemonic: Homer Simpson likes jelly donuts - no hole)

Fleurettes
- Advanced photoreceptor differentiation
  - Small bouquet-like aggregate of benign-appearing tumor cells
  - Cells are aligned along segment of "XLM"
  - "Flowers" comprising bouquet are bulbous, eosinophilic inner segments
  - Photoreceptor outer segment disks occasionally are found (by EM)
  - Found in area of tumor that appears less cellular, more eosinophilic
- Cells show low nuclear-cytoplasmic ratio, low mitotic activity, absent necrosis, greater resistance to radiation

Retinoma, retinocytoma
- Benign variant of retinoblastoma with prominent areas of photoreceptor differentiation (fleurettes); some consider precursor of retinoblastoma
- Bland nuclei, eosinophilic fibrillar cytoplasm, calcification within viable tumor
- Resistant to radiation (like most benign tumors)
- Previously thought clinically to be spontaneously-regressed retinoblastomas
- Fish flesh appearance with cottage cheese calcification, surrounding annulus of atrophic RPE
- Both copies of Rb1 gene are abnormal in retinoma/retinocytoma; additional mutations necessary for progression to retinoblastoma
- May be a precursor to retinoblastoma

Complete Spontaneous Necrosis (regression)
- True spontaneous regression
- Associated with severe inflammation and phthisis bulbi, (?) secondary to NVG
- Typical foci of calcification persist in fibrous matrix

Biological behavior and spread:
- Most retinoblastomas exhibit relentless progression. If left untreated, the tumor fills the eye and completely destroys the internal architecture of the globe. Regardless of the pattern of growth, there is a striking tendency to invade the optic disc and optic nerve. The tumor may spread along the nerve to the chiasm and the contralateral
optic nerve or may spread through the pia to the subarachnoid space with seeding along the neuraxis.

**Metastasis/Extension:**
1. Direct Infiltration - along optic nerve to brain - into orbit - into cranium through foramina or bone
2. Dispersion of tumor cells through subarachnoid space to brain and spinal cord
3. Hematogenous dissemination to **lungs, bones, and brain.** Unlike uveal melanoma this is an uncommon event unless there is extraocular extension.
4. Lymphatic spread after invasion of the conjunctiva. There may be massive pre-auricular and cervical lymphadenopathy.
5. **Metastases typically occur within 2 years of treatment.**
6. Recurrence is due to retained tumor cells in orbit or beyond the point of optic nerve transection

**Prognostic features:**

**Optic nerve invasion-**
- Retinoblastoma tends to invade optic nerve (unlike melanoma)

**Survival correlates with depth of invasion:**
- No invasion-8%, prelaminar 15%, retrolaminar 44%, line of resection 64%
  - (Retrolaminar invasion usually indication for adjuvant chemotherapy)
- Tumor can directly extend to brain, gain access to CSF

**Choroidal invasion** (role controversial) massive choroidal invasion- defined as greater than 3mm, full thickness

**Orbital invasion** (AFIP- more important than choroidal invasion)
- Iris, anterior chamber and trabecular meshwork invasion- magnitude of effect unclear
- Absence of rosettes, fleurettes
- Lymphadenopathy with anterior perforation, conjunctival invasion
- ? Diffuse growth pattern (delay in diagnosis)
- Pseudoinflammatory presentation (delay in diagnosis)

Prospective Study sponsored by Children’s Oncology Group (ARET0332) currently investigating chemotherapy in patients with high risk histologic features

**High Risk Histopathologic Features that are Indications for Adjuvant Chemo:**
- Retrolaminar optic nerve invasion,
- Massive uveal invasion (massive >3mm)
- any degree of concurrent optic nerve and uveal invasion

**Risk factors associated with mortality**

<table>
<thead>
<tr>
<th>Invasion of ocular coats</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroid</td>
<td>1.8</td>
</tr>
<tr>
<td>Sclera</td>
<td>3.9</td>
</tr>
<tr>
<td>Orbit</td>
<td>21.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invasion of optic nerve</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected</td>
<td>3.8</td>
</tr>
<tr>
<td>Unresected</td>
<td>8.7</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>2.9</td>
</tr>
<tr>
<td>Incorrect diagnosis</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Treatment (See Oncology Notes – in evolution):**
Small lesions are treated with chemotherapy, TTT, Radioactive plaques, photocoagulation, cryotherapy, (recent trend to avoid EBRT to prevent secondary tumors)

Large tumors - usually enucleated when unilateral
if bilateral, more severely involved eye is often enucleated with vision sparing therapy applied to the less involved eye.

Chemotherapy (Chemoreduction) now used as initial management of many cases with bilateral tumors, or after enucleation if high-risk histopathologic features present

Intraarterial chemotherapy- delivers chemo directly to eye via ophthalmic artery;
use increasing; currently available in a few centers;
Ischemic atrophy of outer retina and choroid can occur; theoretical risk for metastases

Intravitreal Chemotherapy- appears to be effective for vitreous seeds;

Advanced tumors - Radiotherapy, chemotherapy, and orbital exenteration may be employed

Genetic variants of Retinoblastoma

<table>
<thead>
<tr>
<th>VARIANTS</th>
<th>Frequency</th>
<th>Avg Age</th>
<th>Bilateral*</th>
<th>Transmission?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic (somatic mutation)</td>
<td>64%</td>
<td>24 mos.</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Sporadic (germinal mutation)</td>
<td>21%</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Familial*</td>
<td>5-10%</td>
<td>12 mos.</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Chromosome deletion (13Q-)</td>
<td>&lt;5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*Approximately 70% have bilateral tumors, can have multifocal tumors, secondary tumors)

The Retinoblastoma Gene: The Paradigmatic Recessive Oncogene
Located on long arm of chromosome 13 (13 Q 1-4 band)
RB gene sequence contains 180,388 base pairs
The RB gene protein product (928 amino acids) is found in the nucleus
RB protein involved in control of the cell cycle (necessary for terminal differentiation)
During G1 resting phase RB protein forms complex with E2F transcription factor
Phosphorylation of RB protein causes separation from E2F.
Uncomplexed E2F activates a variety of other genes necessary for DNA synthesis.
Absence of RB protein causes continual cell division and lack of terminal differentiation (i.e. cancer).
Tumor virus proteins (adenovirus E1A and SV40 large T) cause tumors by binding to and inactivating RB protein.
Familial cases appear to be autosomal dominant (50% of offspring inherit)
The retinoblastoma (RB) gene actually is recessive at the molecular level;
Normal individuals have two functional copies of the RB gene (RB, RB)
Familial cases are heterozygous for retinoblastoma gene (RB, rb)
Tumors develops when both normal genes in a single retinal cell are lost or inactivated. (rb, rb)
Familial cases and sporadic germinal cases are genotypically heterozygous for the Rb gene (RB, rb). (Sporadic germinal cases are new familial cases.)
The genotype of a heterozygous carrier of retinoblastoma includes one functional and one inactivated gene. A single functional gene prevents malignant transformation. The spontaneous mutation rate of RB gene is $<10^{-7}$ or greater.
Development of each retina requires $10^{8}$ cellular divisions. Therefore, strictly by
chance, at least one cell in both retinas of a genotypically heterozygous individual will lose both normal suppressor genes permitting malignant transformation. Tumors in cases of familial retinoblastoma are frequently (2/3's) bilaterally and can be multifocal. Bilateral involvement indicates that the patient is a carrier of familial retinoblastoma. Unfortunately, the opposite is not true. One-third of familial cases have unilateral tumors.

Sporadic somatic retinoblastomas result from the sequential inactivation of both genes in a single retinal cell in a patient whose genotype is normal (RB,RB). Sporadic somatic tumors are unilateral because the probability of this occurrence in more than one retinal cell is exceedingly small. Most retinoblastomas are sporadic somatic.

Autosomal dominant inheritance in familial cases is mimicked by the inheritance of heterozygosity with subsequent gene inactivation:

<table>
<thead>
<tr>
<th>carrier</th>
<th>normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB rb</td>
<td>X</td>
</tr>
<tr>
<td>RBRB = 50% RB rb + 50% RB RB</td>
<td></td>
</tr>
</tbody>
</table>

Chromosomal deletion (13Q-) retinoblastomas resemble familial cases. In this variant the gene deletion is karyotypically obvious. Patients with 13Q- syndrome have other systemic abnormalities including mental retardation, imperforate anus, genital malformations and facial anomalies including low-set ears, a broad nasal bridge, and a thin upper lip

Rb1+/+ Retinoblastoma
No mutations in Rb1 gene; tumor caused by amplification of NMYC gene. Early onset, aggressive, poorly differentiated, large nuclei with nucleoli, no FW rosettes, No tumor risk for fellow eye or siblings

Additional facts:
* Familial cases develop earlier (12 months) because only one gene has to be inactivated (ony 1 "hit" necessary –Knudson’s 2 hit hypothesis)
* Sporadic somatic cases develop later because two genes have to be inactivated (2 "hits" required)
* Retinoblastoma is a disease of early childhood (average age 18 mo.) because gene inactivation usually occurs during cellular division. Most cellular division in retina ceases before birth.
* If a patient has bilateral retinoblastoma, you must assume that the disease can be transmitted to his offspring. (bilateral =hereditary)
  (Unfortunately, the opposite is not true! Due to incomplete penetrance of gene, 1/3 of hereditary cases have unilateral tumors. 10-15% of unilateral sporadic tumors are heritable germinal mutations).

ASSOCIATED MALIGNANCIES:
Patients who are carriers of familial retinoblastoma are predisposed to develop other malignant tumors. Second Tumors are most common cause of death in Rb patients in the USA
Survivor of bilateral retinoblastoma has a 20-50% chance of developing a second tumor within 20 years. (AFIP series - 26% within 30 years)
These non-ocular tumors include osteogenic sarcoma (most common), chondrosarcoma, other soft tissue sarcomas, carcinomas of the upper respiratory passages, malignant melanomas, and carcinomas of the skin.
The majority of second tumors are **post-irradiation**, occurring within the field of irradiation (reason for trend away from EBRT.

Osteosarcoma of the lower extremities is the most common tumor outside of radiation therapy fields. Patients have a 500X increased incidence of osteogenic sarcoma of the femur.

**Trilateral Retinoblastoma**: ectopic retinoblastoma of the pineal gland or parasellar region. Occurs in bilateral or familial retinoblastoma. Fleurettes and Flexner-Wintersteiner rosettes may be observed in the intracranial tumor. decreased incidence after chemoreduction

The retinoblastomas gene has also been implicated in other systemic malignancies including breast and lung cancer

Some oncoviruses (SV40, HPV. adenovirus) are thought to produce cancer by making proteins that complexes and inactivates the suppressor protein product of the RB gene.

**Genetic counseling: risk that subsequent child will have retinoblastoma:**

**Unilateral retinoblastoma**
- Affected parent with no affected children- 3%
- Normal parents, one affected child 3%
- One affected parent, one affected child 30%

**Bilateral retinoblastoma**
- One affected parent, no affected child 40%
- Normal parents, one affected child 10%
- One affected parent, one affected child 50%

---

**The Differential Diagnosis of Retinoblastoma**

<table>
<thead>
<tr>
<th>Three most common simulating lesions: toxocariasis, PHPV and Coats’ disease</th>
</tr>
</thead>
</table>

**Ocular Toxocariasis** *(Nematode Endophthalmitis)*
- Ocular manifestation of visceral larva migrans- *Toxocara canis*
- Unilateral, end of first decade, exposure to puppies
- Diffuse nematode endophthalmitis, vitreous abscess with retinal fold, subfoveal granuloma
- Larval fragment in eosinophilic abscess- serial sections usually necessary
- Negative ELISA for Toxocara antigen excludes

**PHPV / PFV** *(Persistent Hyperplastic Primary Vitreous or Persistent Fetal Vacuclature)*

- **Congenital** *(present at birth), unilateral*
- Eye usually **microphthalmic** at birth
- Retrolental fibrovascular plaque, patent hyaloid vessel
- **Inwardly-drawn ciliary processes**
- Iris shunt vessels, other persistent fetal vessels
- Lens may contain fat or even bone
- Alternate term - **PFV: persistent fetal vasculature** *(Goldberg)*
- Untreated eyes often develop secondary closed angle glaucoma

**Coats disease**
- Exudative retinal detachment caused by congenital retinal vascular abnormalities
- Unilateral, usually towards end of first decade, 2/3’s in boys, macular lipid
- Leaky retinal telangiectases, mililiary aneurysms, adjacent capillary nonperfusion
- Massive retinal thickening by hard exudates
Subretinal fluid rich in protein and lipid (foamy histiocytes, cholesterol clefts)
Bilateral Coats-like picture in **facioscapularhumeral muscular dystrophy**

**Retinopathy of Prematurity** (retrolental fibroplasia)
Premature infants, supplemental oxygen therapy
Vitreoretinal neovascularization at posterior margin of peripheral nonperfused retina
Tractional retinal detachment- masses of detached retina can mimic retinoblastoma
Often bilateral and not present at birth (shared features with retinoblastoma)
Usually affects temporal retina, foveal dragging

**Embryonal Medulloepithelioma** (second most common primary pediatric IOT)
Symptomatic - age 4, diagnosed age 5, rare cases in adults
Arises from embryonic medullary epithelium, most ciliary body tumors, rare ON tumors
Cords and sheets of polarized neuroepithelial cells, pools of hyaluronic acid
**Teratoid tumors** (38%) contain heteroplastic elements: cartilage, muscle, brain
2/3’s are malignant- contain undifferentiated retinoblastoma-like areas, sarcomatous stroma, rosettes, show invasive behavior
Fatalities after extrascleral extension, recur after local resection
Rare Association with **pleuropulomonary blastoma** – DICER1 germline mutations 14q31

**Astrocytic Hamartomas and Astrocytomas**
Tuberous sclerosis or NF- early lesions may be confused with retinoblastomas
Most patients with TSC have nonprogressive astrocytic hamartomas
Rare retinal giant cell astrocytomas- may grow

**Norrie Disease**
X-linked recessive
Bilateral masses of malformed detached retina (pseudogliomas)
Deafness, mental retardation
Norrin gene mutations in x-linked exudative vitreoretinopathy, predispose to severe ROP

**Incontinentia pigmenti** (Bloch Sulzburger)
X-linked dominant (lethal in males)
Peripheral vitreoretinal neovascular nonperfusion (congenital nonperfusion), RD
Post-natal vesiculo-bullous skin lesions rich in eosinophils, secondary marbleized pattern of skin pigmentation. Other CNS, dental and ocular anomalies
**NEMO/IKK gamma** gene on Xq28- activates eosinophil chemokine eotaxin

**Retinal dysplasia**
Most cases trisomy 13, rare isolated cases in normal patients
Dysplastic rosettes are larger, contain multiple retinal layer

Other...
**Retinal Astrocytomas** (Giant Drusen of ON, Tuberous Sclerosis)
Colobomas
Myelinated nerve fibers (papilla leporina)
Congenital cataract
Retinal detachment, vitreous hemorrhage, trauma
### The Differential Diagnosis of Retinoblastoma and Simulating Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoblastoma</td>
<td>X</td>
<td>X</td>
<td>Mean 18 mo</td>
<td>Calcification on imaging; pseudoinflammatory presentations</td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>X</td>
<td>-</td>
<td>6-11 yrs</td>
<td>Contact with puppies; eosinophilic abscess, serial sections to disclose worm fragment, negative ELISA excludes</td>
</tr>
<tr>
<td>PHPV / PFV</td>
<td>X</td>
<td>-</td>
<td>Present at birth</td>
<td>Microphthalmic eye with retrolental fibrovascular plaque, inwardly-drawn ciliary processes, iris shunts and other persistent fetal vessels</td>
</tr>
<tr>
<td>Coats Disease</td>
<td>X</td>
<td>Rare</td>
<td>18 mo to 18 yrs, peak end of 1st decade</td>
<td>2/3’s male, abnormal leaky retinal vessels (Leber’s miliary aneurysms), bullous RD with lipid-rich subretinal fluid, massive exudation; bilateral cases my have fascioscapulohumeral muscular dystrophy</td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td>-</td>
<td>X</td>
<td>In early infancy, but not congenital</td>
<td>Premature infants, supplemental oxygen therapy</td>
</tr>
<tr>
<td>Incontinentia pigmenti (Bloch-Sulzberger)</td>
<td>-</td>
<td>X</td>
<td>Infancy</td>
<td>Perinatal bullous eruption with eosinophilia, whorled skin pigmentation develops, nonperfusion of periphery, X-linked dominant – lethal in males, NEMO gene, eotaxin</td>
</tr>
<tr>
<td>Norrie Disease</td>
<td>-</td>
<td>X</td>
<td>Congenital</td>
<td>Males, x-linked recessive, bilateral pseudogliomas caused by detachment of dysplastic retina, deafess, mental retardation, Norrin gene (plays role in other disorders)</td>
</tr>
<tr>
<td>Medulloepithelioma</td>
<td>X</td>
<td>-</td>
<td>4 years (rare – adults)</td>
<td>“diktyoma”, benign and malignant, teratoid and nontertoid, teratoid tumors contain cartilage, muscle brain</td>
</tr>
<tr>
<td>Retinal Dysplasia</td>
<td>X</td>
<td>-</td>
<td>Congenital</td>
<td>Microphthalmia, most have trisomy 13</td>
</tr>
<tr>
<td>Astrocytic Hamartoma of TSC</td>
<td>X</td>
<td>-</td>
<td>Early infancy</td>
<td>Tuberous sclerosis complex, family history, seizure disorder, retinal lesion easily confused with early RB Rare progressive giant cell astrocytomas</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td>Colobomas, congenital cataract, myelinated nerve fibers, retinal detachment, vitreous hemorrhage, trauma, endogenous endophthalmitis</td>
</tr>
</tbody>
</table>
ORBITAL DISEASE

Most orbital diseases cause ocular proptosis or exophthalmos
Direction of proptosis suggests location of lesion

Lymphoid Tumors and Orbital Inflammation

Orbital inflammatory disease and "pseudotumors' are more common than true neoplasms

Thyroid ophthalmopathy (Graves' disease, Graves' orbitopathy)

- Most common cause of unilateral or bilateral exophthalmos
- Proptosis due to enlargement of extraocular muscles, edema of orbital tissue
- An immunological disease that affects both the EOM's and the thyroid
- Orbitopathy can occur with high, normal or low thyroid function
- Pathogenesis remains unclear- ? T-lymphocyte imbalance; B cells may produce anti-muscle antibodies; orbital fibroblasts may play important role as target cells
- Enlarged muscles show foci of chronic nongranulomatous infiltration, secondary fibrosis.
- Inflammation spares tendon, orbital fat (in contrast to pseudotumor)
- Mast cells do not secrete excess MPS

Idiopathic orbital inflammation (idiopathic orbital pseudotumor)

- Explosive onset, pain, muscle paresis, visual loss, proptosis
- Can be acute, subacute or chronic, unilateral or bilateral; chronic cases rock-hard, can mimic carcinoma
- Inflammatory signs, inflammation sharply delimited by orbital septum at rim;
  - "Pink" polymorphous lymphoid infiltrate, lymphocytes, plasma cells, eosinophils, follicles, extensive fibrosis in sclerosing pseudotumor
- Heavy infiltration of orbital fat, involves muscle tendon; late fibrosis
- Following factors differentiate from lymphoid tumors:
  - Pink, not blue, hypocellular lesion with fibrosis, inflammatory signs
  - Exquisitely sensitive to corticosteroids

Variants (by structures involved)

- Myositis-diplopia and pain on movement, involves tendon (unlike Grave's), Dacryoadenitis, Periscleritis, Perineuritis, Trochleitis

Pathology: light polymorphic infiltrate, fibrosis, late orbital cirrhosis, perivascular lymphocytic cuffing (diapedesis, not vasculitis), concentric fibrous lamellae surround vessels, orbital fat involved, can have granulomas, eosinophils, germinal centers

A diagnosis of exclusion!! r/o specific inflammatory diseases

Note: Some physicians (e.g. radiotherapists) persist in applying the term orbital inflammatory pseudotumor to reactive or atypical lymphoid hyperplasias of the orbit. Ophthalmic pathologic convention includes such lesions in the spectrum of orbital lymphoid tumors. The term idiopathic orbital inflammation or pseudotumor should be reserved for the lesion described below whose characteristic clinical and pathological findings usually serve to differentiate it from lymphoid neoplasms.

Tolosa Hunt Syndrome (painful external ophthalmoplegia)

IgG4-Related Disease- some cases of sclerosing pseudotumor; may have systemic sclerosing conditions; diagnostic criteria and importance not entirely clear. Follicular lymphoid hyperplasia, storiform fibrosis, obliterator fibrosis, >100 eos/HPE in lacrimal gland

Other orbital inflammations and infections
Sarcoidosis (dacryoadenitis, S-sign)
**Orbital cellulitis:** infection usually invades from sinus

**Sub-periosteal abscess**

**Mucormycosis** (phycomycosis, zygomycosis)
- Large nonseptate hyphae with right angle branching - visible on H&E, vascular invasion with thrombosis and necrosis, acute and chronic granulomatous inflammation; fungus invades from sinuses, eschar a late sign
- Acidotic patients (e.g. poorly controlled diabetics), deferoxamine therapy in renal dialysis patients;

**Aspergillosis:** resembles mucormycosis, but in healthy patients

**Allergic Fungal Sinusitis**- fungus grows in “allergic mucous”, tissue not invaded

**Vasculitides**

**Granulomatosis with polyangitis** (Wegener granulomatosis or ANCA-associated granulomatous vasculitis)
- Necrotizing vasculitis of upper respiratory tract, lungs, and kidneys (necrotizing glomerulonephritis), cavities in lower lobes of lungs
- Limited form - no renal involvement, c-ANCA helpful diagnostic test but may not be positive in early cases. 28.5% have ophthalmic manifestations: proptosis (40%), scleritis (25%), peripheral corneal ulceration. May present with eye findings
  - **Path:** granulomatous vasculitis with fibrinoid necrosis, stellate interstitial necrosis, Langhan’s giant cells – orbit may lack classic histopathology

**Polyarteritis Nodosa**
- **Men 4:1, age 20-40,** infarcts skin, CNS
- Angiocentric inflammation with polys and lymphocytes
- Immune complex disease, nongranulomatous

**Orbital thrombophlebitis**

**Idiopathic midline destructive disease (NK cell lymphoma)**

**Angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma)**

**Kimura’s disease** (Asian males, eosinophilia, elevated IgE)- differs from above

**Lymphoid Tumors**

A histologic spectrum that includes polyclonal reactive lymphoid hyperplasias, cytologically indeterminate atypical lymphoid hyperplasias, and malignant lymphomas composed of cytologically atypical cells.

**Clinical Characteristics**
- **Average age 60** (later than other primary orbital tumors)
- Rare in childhood- **rule out leukemia!** (myeloid sarcoma)
- Insidious onset of painless, well-tolerated proptosis or conjunctival "salmon patch"; No inflammatory signs
- 90% of orbital lesions involve **superior orbit** behind septum, > 40% arise in lacrimal gland, affect palpebral lobe (epithelial tumors involve orbital lobe)
- CT Scan: Putty-like soft tissue molded by tissue planes, infiltrate may have straight-line angulations; diffuse "pregnant" pancake-like enlargement of lacrimal gland molds to globe, projects anterior to orbital septum.
- Bone destruction rare, except in rare cases of multiple myeloma
- EOM cases usually involve one muscle, **No** fibrosis, motility OK
- Gross pathology: soft friable tissue lacks connective tissue stroma
- Salmon color due to fine capillarity within lesion
Two thirds of ocular adnexal lymphoid tumors are monoclonal B cell malignant Non-Hodgkin’s lymphomas. Most of these are low-grade. Many are MALT lymphomas 50-60% (*extranodal marginal zone lymphomas of mucosa associated lymphoid tissue*)

**Reactive Follicular Lymphoid Hyperplasias**
Polymorphic infiltrate with lymphocytes, plasma cells, eosinophils
Germinal centers with immunoblasts, tingible-body macrophages, polarity, mitoses confined to germinal center, BCL-2 negative
T-cell rich (≥ 60% T-cells, mainly T-helper; resembles systemic circulation) B cells polyclonal

**Atypical Lymphoid Hyperplasias**
(Cytologically indeterminate, borderline or "gray zone" lesions)
Monomorphic lesion with scant or no follicles, composed of well-differentiated lymphocytes.
Immunohistochemistry discloses that 70% of atypical lymphoid hyperplasia are monoclonal, i.e., they actually are low grade lymphocytic lymphomas (see below)

**Malignant Lymphoma** (monomorphic infiltrate)

Most ocular lymphomas are diffuse (16% follicular).
Essentially, all orbital lymphomas are monoclonal B cell tumors (typically composed of more than 60% CD20+ B lymphocytes).
Monoclonal B cells express only 1 type of light chain (kappa or lambda)
Lymphomas are best classified by **Flow Cytometry**

**Flow cytometry** requires adequate quantity of fresh, unfixed tissue
Limited Immunophenotypic analysis can also be performed on paraffin embedded tissue, but stains for light chains (clonality) usually don’t work

**Gene rearrangement studies** – questionable efficacy in the conjunctiva

The majority of ocular adnexal lymphomas are low-grade small lymphocytic lymphomas. 50-80% are classified as extranodal marginal zone lymphomas (EMZL) of mucosa-associated lymphoid tissue (MALT lymphomas, MALTomas)

Flow cytometry and immuno markers are used to distinguish other types of lymphoma in **WHO classification**, e.g. follicular lymphoma, mantle zone lymphomas, CLL, diffuse large B cell lymphoma.

**Immunohistochemical staining of common adnexal lymphomas**

<table>
<thead>
<tr>
<th>Class of lymphoma</th>
<th>Lymphoma cells express</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALT (EMZL)</td>
<td>CD20+, CD5−, CD10−, CD23-</td>
</tr>
<tr>
<td>FOLLICULAR</td>
<td>CD20+, CD5−, CD10+, CD23+, bcl-2+</td>
</tr>
<tr>
<td>MANTLE ZONE</td>
<td>CD20+, CD5+, CD10−, CD23−, Cyclin D-1+ (bcl-1)</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>CD20+, CD5+, CD10−, CD23+</td>
</tr>
<tr>
<td>Diffuse Large B cell</td>
<td>CD20+, CD5+/−, CD10+/−</td>
</tr>
</tbody>
</table>

**CLL/SLL** Small lymphocytic lymphoma- tissue deposits of CLL

**MALT**- small lymphocytes, monocytoid lymphocytes, lymphoepithelial lesions, residual follicles- often contain plasma cells, indolent course, GI cases associated with **H pylori** infection; may be cured by antibiotics in gut, possibly conjunctiva
Follicular Lymphoma- 3 grades, higher grades contain more centroblasts, malignant follicles have ill-defined mantle zone, lack polarization and tingible body macrophages (CD20+, CD10+, follicles bcl-2 +)

Mantle Cell Lymphoma – small to medium lymphocytes with irregular nuclei, elderly men, widely disseminated at presentation; poor prognosis (CD20+, CD5+, bcl-1 +)

Systemic Involvement* in Ocular lymphoid Tumors
*Prior, concurrent or subsequent (Knowles, Jakobiec, et al, Human Pathol 21: 595, 1990)

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctiva</td>
<td>20%</td>
</tr>
<tr>
<td>Orbit</td>
<td>35%</td>
</tr>
<tr>
<td>Eyelid</td>
<td>67%</td>
</tr>
<tr>
<td>All sites</td>
<td>33%</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>38%</td>
</tr>
<tr>
<td>Polyclonal ocular lesion*</td>
<td>29%</td>
</tr>
<tr>
<td>Monoclonal ocular lesion</td>
<td>33%</td>
</tr>
</tbody>
</table>

Approximately one-third of patients with ocular lymphoid tumors have a history or, have, or will develop extraocular lymphoma!!!

The site of involvement and the cytologic type of lymphoma do correlate somewhat with systemic disease:

- Patients who have conjunctival lesions are less likely to have extraocular lymphoma.
- Patients with eyelid lesions (involving skin surface anterior to orbital septum) are more likely to have extraocular lymphoma.
- Patients with low-grade ocular lymphomas are less likely to have extraocular lymphoma.
- Patients with higher grades of ocular lymphoma are more likely to have extraocular lymphoma.

Most important prognostic factor - the extent of the disease at the time of initial presentation disclosed by a thorough clinical staging. The vast majority of patients presenting with a clinical stage 1E ocular adnexal lymphoid proliferation, regardless of histopathology or immunophenotypic analysis have a benign indolent clinical course" (Knowles et al, Coupland et al)

All patients with an ocular adnexal lymphoid tumor need a thorough systemic evaluation by a hematologist/oncologist.

This should include: a bone marrow biopsy and CT body scans, PE, CXR, CBC with differential, flow cytometric analysis with monoclonal antibodies, Coombs, serum protein electrophoresis

Long term follow-up with examinations every 6 months

Therapy

- Stage IE, No systemic involvement- RADIOTHERAPY with eye shielding
  - Low grade lesions- 1500-2000 rads
  - High grade lesion- 2000-3000 rads
- Extraocular (systemic) lymphoma present- CHEMOTHERAPY or immunotherapy
Supplement with adjunctive ocular radiotherapy if ocular regression subtotal

Other Lymphoid Tumors

Plasma cell tumors- myeloma, bone destruction
Lymphoplasmacytoid tumors- Waldenstrom's macroglobulinema, Dutcher bodies
Post-transplantation lymphoproliferative disorder (EBV, immunosuppression)
Hodgkin's disease
Burkitt's lymphoma (EBV infection)
Mycosis fungoides: T-cell cutaneous lymphoma, convoluted cerebriform nuclei, Pautrier abscesses

Reactive Lymphoid Hyperplasia of the Uvea- probably MALT lymphoma
Multifocal choroiditis-like picture, biopsy epibulbar component

Myeloid or Granulocytic Sarcoma (leukemic infiltrate. "chloroma")
Suspect in children with “lymphoma”
Confirm granulocytic differentiation with immuno or Leder esterase stains
May present when peripheral blood normal
A major cause of bilateral proptosis in children

ORBITAL TUMORS

A different spectrum of orbital tumors occurs in children and adults

<table>
<thead>
<tr>
<th>Category</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Dermoid cyst, teratoma</td>
<td>Cavernous hemangioma</td>
</tr>
<tr>
<td>Vascular</td>
<td>Capillary hemangioma</td>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td></td>
<td>Lymphangioma</td>
<td></td>
</tr>
<tr>
<td>Neural</td>
<td>Plexiform neurofibroma</td>
<td>Schwannoma</td>
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<tr>
<td></td>
<td>Optic Nerve Glioma</td>
<td>Optic nerve meningioma</td>
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<tr>
<td>Mesenchymal</td>
<td>Rhabdomyosarcoma</td>
<td>Fibrous histiocytoma</td>
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<tr>
<td>Hematopoietic</td>
<td>Granulocytic sarcoma</td>
<td>Lymphomas</td>
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<tr>
<td></td>
<td>Histiocytoses</td>
<td></td>
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<tr>
<td>Metastatic</td>
<td>Neuroblastoma, Ewing's</td>
<td>Carcinomas (lung, breast)</td>
</tr>
<tr>
<td></td>
<td>Sarcoma, Wilms' Tumor</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Epithelial tumors of lacrimal gland</td>
<td></td>
</tr>
</tbody>
</table>

Well-circumscribed orbital tumors

Cavernous Hemangioma
Schwannoma
Hemangiopericytoma
Fibrous Histiocytoma / Solitary Fibrous Tumor
Epithelial Tumors of the Lacrimal Gland
Primary orbital melanoma

Vascular Tumors

Cavernous Hemangioma
Most common adult vascular tumor, middle aged females
Well tolerated, low grade proptosis, normal vision and motility
Discrete, round, encapsulated lesion; stagnant circulation - little opacification with CT contrast
Histology: large cavernous blood-filled, endothelial-lined spaces, fibrous interstitium with smooth muscle

**Hemangiopericytoma**
Well-circumscribed, lights-up with contrast, "stag-horn" vessels, metastatic potential; many hemangiopericytomas are solitary fibrous tumors; the latter often have “hemangiopericytomaous vascular pattern”

**Lymphangioma** (spectrum includes orbital varix, AVM’s) – see below

- **Orbital Varix**
- **Arteriovenous Malformations**
- **Venous Angiomas**
- **Glomus Tumor, glomangioma**
- **Vascular Leiomyoma**
- **Klippel-Trenaunay-Weber Syndrome**
- **Blue Rubber Bleb Nevus Syndrome**
- **Intravascular Papillary Endothelial Hyperplasia**
- **Angiosarcoma (Malignant Hemangioendothelioma)**
- **Kaposi's Sarcoma** – homosexual men, HHV8

**Mesenchymal Tumors**

**Fibrous Histiocytoma** (fibroxanthoma)
In the past, said to be most common mesenchymal tumor of adults, mean age 43 (4-85) – Many cases would be classified as solitary fibrous tumor (SFT) today
Orbit is site of predilection, superior (43%), nasal
Fibroblasts and histiocytes, storiform pattern
Benign, malignant and locally aggressive variants, excise totally!!

**Solitary fibrous tumor (SFT)** – pattern-less pattern, fibrous bands between cells, many cases have hemangiomatous vascular pattern. **Imuno:** STAT6+, CD34+, CD99", bcl-2+ (many cases diagnosed as hemangiopericytoma or fibrous histiocytoma in past)

**Fibroblastic Tumors**

- **Nodular Fasciitis**
- **Fibroma**
- **Juvenile Fibromatosis or myofibromatosis**
- **Fibrosarcoma (rare)**
- **Myxoma**

**Tumors Of Adipose Tissue**
Orbital fat inert - least likely to spawn tumors
**Herniation Of Orbital Fat**- Some cases have features seen in pleomorphic lipoma (froict cells and lock hem nuclei) - not a sign of malignancy

**Tumors of Smooth Muscle**- very rare, most post radiation
- **Leiomyoma, Leiomyosarcoma**

**Fibro-osseous And Cartilaginous Tumors**
Most arise from bones of orbit and sinuses
- **Ivory Osteoma**- most common, dense, mature bone
- **Fibrous Osteoma**
- **Fibrous Dysplasia**
  Trabeculae of woven bone without osteoblasts in fibrous stroma-
- **Juvenile Ossifying Fibroma (psammomatoid)**
Osteosarcoma - sinus origin, with or without prior radiotherapy
Cartilaginous Tumors – very rare
Chondroma
Mesenchymal Chondrosarcoma

Neural tumors
Schwannoma (neurilemmoma)
Round, encapsulated, associated with peripheral nerve, may be painful
Antoni A: cellular area with palisading spindle cell nuclei, Verocay bodies
Antoni B: loose myxomatous area
Plexiform neurofibroma (NF 1)
Diffuse neurofibroma (NF 1)
Isolated neurofibroma (no NF by definition)

Lacrimal Gland Tumors
10-15% of orbital lesions biopsied (relatively rare tumors)
(In routine non-referral clinical practice, inflammatory and lymphoid lesions of the lacrimal gland are 5 times more common than epithelial tumors)
Limited spectrum of epithelial tumors: no Warthin's tumors, mucocoeidermoid carcinoma rare, oncocyotomas and acinic cell tumors very rare
LG is a minor salivary gland: greater incidence of malignancies than parotid
**Important factors in clinical evaluation** (Jakobiec)
- Duration and types of symptoms:
  - Short duration (<6mo-1yr): inflammation, lymphoid or malignant epithelial malignancies
  - Pain: inflammation or epithelial malignancy
  - Presence or absence of bony destruction on x-ray
  - Bone changes and short duration: epithelial malignancy
- Overall configuration of soft tissue lesion on axial and coronal CT
  - **Rounded or globular- epithelial tumor**
    - Long duration, well-tolerated - BMT
    - Short duration, significant symptoms: malignant tumor
  - **Diffuse molded enlargement of lacrimal gland: lymphoid or inflammatory**
  - Involvement of palpebral lobe: lymphoid or inflammatory (most epithelial tumors arise from deep orbital lobe, do not project beyond orbital rim)

"50-50" **RULE** (not true in clinical practice: most inflammatory or lymphoid!!)
- 50% of lacrimal gland lesions are **inflammatory**
- 50% are **epithelial**
- 50% of the epithelial tumors are **benign** (BMT)
- 50% are **malignant**
- **Adenoid Cystic Carcinoma**
- **Malignant Mixed Tumor, rare types of adenocarcinoma**

Epithelial Tumors of the Lacrimal Gland
Benign Mixed Tumor (Pleomorphic Adenoma)-50%
- Usually arise from deep orbital lobe, rarely palpebral, accessory, skin
- Painless, slowly progressive mass, well-tolerated Proptosis-"down and in"
- 60% in men, age 7-77 (mean age 39)
- Tumor cells contain specific gene fusions involving PLAG1 and HMGA2 oncogenes; confirm diagnosis with immunostain for PLAG1.
CT: rounded or ovoid lesion, lacrimal fossa accentuated, regular well-corticated pressure indentation
Gross: encapsulated with "bosselations" (actually a pseudocapsule)
Cut surface may show mucinous and myxomatous areas
Histology:

- **Mixture of epithelial and mesenchymal elements**
- **Epithelial ductules** composed of double layer of cells:
  - Inner cuboidal to columnar epithelium, outer flattened or spindled "myoepithelial" cells
  - Stromal cells derived from outer layer, undergo metaplasia (myxoid tissue, cartilage, rarely bone and fat), tyrosine crystals
- TEM studies show origin from lacrimal gland duct cells (small secretory granules), outer cells not myoepithelial, actually basal germinal cells,

**Management: complete excision within capsule** (Lateral orbitotomy)

- Do not biopsy suspected BMT!!! 1/3 will recur
- Recurrences can invade orbital soft tissue, bone, brain
- Widely separated non-encapsulated "tumorlets"
- Malignant degeneration possible

**Adenoid Cystic Carcinoma**
Second most common epithelial tumor of lacrimal gland (25-30%)

- **Highly malignant**, short duration of SX (6mo-1 year), dismal prognosis
- 58% in women, average age at presentation 40 years, can occur in children
- Pain, numbness, ptosis, motility problems due to **perineural invasion**
- CT: globular, rounded but with more serrated, irregular border. May have medial or posterior orbital extension
- Destructive or sclerotic **bone changes** in 80%
- Infiltrative malignancy, dissection may be difficult
- Tumor invades nerves and bone early

**Histology-five patterns**

- **Cribriform** ("Swiss cheese")
  - Not true ductules, hence "adenoid"
- **Basaloid** (solid)
- **Sclerosing**
- **Comedocarcinoma** (lobules with central necrosis)
- **Tubular** (true duct formation)
- **Cylindromatous pattern**: tumor nests surrounded by thick basement membrane

- Immuno stain for MYB specific, but not present in all cases

**Prognosis: overall 10 year survival 20%**
- Basaloid component- 21% 5 yr. survival, 3 year median
- No basaloid component- 71% 5 yr. survival, 8 year median
- Death from perineural invasion through superior orbital fissure into middle cranial fossa, late (5-10 years) pulmonary metastases

**Management (Controversial)**
If Dx is suspected on clinical grounds, biopsy through lid; wait for permanent section diagnosis (not frozen sections); then exenteration, en bloc resection of tumor and contiguous bone, or radical orbitectomy including roof and lateral orbital wall.

- ? improved survival with neoadjuvant cytoreductive intraarterial chemotherapy followed by exenteration and intravenous chemotherapy (Tse)

**Malignant Mixed Tumor- 13% (4-24%)**

73 Eagle- Pathology Review Outline
Malignant transformation of BMT, patients older than BMT
  Adenoid cystic in BMT age 43 (67% women)
  Adenocarcinoma in BMT age 52 (72% men)
  Multiple recurrences of BMT age 64
With multiple recurrences of BMT, 10% malignant in 20 years, 20% in 30yrs
Histology: clone of poorly-differentiated adenocarcinoma in most cases
  squamous, acinar or sebaceous differentiation,
Prognosis: death within 3 years of malignant degeneration, lymphatic spread via
  lacrimal gland lymphatics, lung metastases
Management: radical surgery with parotid and cervical lymph node dissection if
  no mets; if mets, debulk and localized radiotherapy
Mucoepidermoid Carcinoma
  Rare, better prognosis than other epithelial malignancies
  Exenteration, or wide local excision
  "Paving stone" squamous elements and mucous-producing goblet cells.
Adenocarcinoma de novo
  Poorly differentiated, older men (mean age 56)
  Management, prognosis similar to MMT
Rarer types of lacrimal gland carcinoma
  Acinic cell carcinoma, primary ductal adenocarcinoma, basal cell
  adenocarcinoma, lymphoepithelial carcinoma, epithelial-myoepithelial carcinoma,
  cystadenocarcinoma

Orbital Tumors In Children
Dermoid Cyst- (Cystic Dermoid) epidermal inclusion cyst with epidermal
  appendages associated with lining epithelium; result from entrapment of skin with its
  epidermal appendages in bony sutures within developing skull
  Lesions in nasal orbit may have conjunctival epithelial differentiation
Congenital Orbital Teratoma
Vascular Tumors
  Capillary Hemangioma
    CT: poorly circumscribed, infiltrating, without capsule, placental antigens
    Lymphangioma- recent controversy about terminology- Presence of lymphatic
      endothelium confirmed by D2-40 immuno stain
      Vascular channels larger and more variable than those in cavernous
      hemangioma, contain lymphoid foci, may enlarge suddenly- lymphoid
      hyperplasia secondary to URI; intraläsional hemorrhage- chocolate cyst
      formation; propranolol – first line of therapy
Rhabdomyosarcoma
  Average age 7 years, boys more common
  Fulminant and rapidly developing proptosis
  Superior orbit most commonly involved
  Rapid growth may mimic inflammatory disease
  CT: deceptively well circumscribed, contrast enhances
  60% erode lamina papyracea, may arise in sinus and invade orbit
  Gross: flesh to yellow-colored, hemorrhage rare
Histology: not encapsulated, often infiltrates, occasional "pushing margins"
  Variants:
    Embryonal: most common, fascicles of tumor cells, loose myxomatous
      stroma, little collagen, spindle cells, strap cells, cells with eosinophilic
      cytoplasm (rhabdomyoblasts), cross-striations uncommon (<60%)
Botryoid: Submucosal (conj) presentation of embryonal rhabdomyosarcoma
Nicholson's cambium layer-denser beneath epithelium

Alveolar: second most common, inferior orbit, related to EOM
Cells enclosed by alveolar-like connective tissue trabeculae. Cells large, polygonal with abundant eosinophilic cytoplasm. Translocations t (92:13) and t (1:13); FKHR gene at 13q14 is site of translocation.
Tumors with the PAX3-FKHR translocation have a poorer prognosis.

Differentiated (pleomorphic)-rarest in orbit, older patients
Striated muscle differentiation obvious, cross-striations, strap cells with abundant eosinophilic cytoplasm, spider cells, glycogen; arises within preformed striated muscle

Most are embryonal, arise from pluripotential mesenchyme, not muscle
Confirm diagnosis with immunohistochemistry (myogenin, MyoD, muscle specific actin, desmin- transcription factors myogenic and MyoD are more accurate.)
electron microscopy: thick 150 Å myosin filaments, sarcomeric units with Z bands, glycogen, basement membrane; admixture of fibrocytoid cells
If no evidence of striated muscle differentiation: embryonal sarcoma

Management: expedient biopsy to confirm diagnosis, radiotherapy (5-6000cGy) combined with two-drug chemotherapy using dactinomycin and vincristine (IRS III regimen 32). Exenteration rarely needed

Prognosis: 80% survival with radio- and chemotherapy, poorer with sinus involvement

Eosinophilic Granuloma (superior lateral orbit, bone destruction, localized form of Langerhan cell histiocytosis, CD-1a, Langerin (CD207), S-100 positive, Birbeck granules or racket bodies)

Granulocytic Sarcoma (chloroma, myeloid sarcoma)
Leukemic Infiltrate, orbital infiltration may antedate peripheral leukemia and bone marrow involvement
Confirm with immunohistochemical stains (e.g. MPO, stem cell markers CD34, CD117; older Leder esterase stain for granulocytic differentiation

Orbital "lymphoma" in a child is a leukemic infiltrate until proven otherwise!!

Burkitt's Lymphoma: Poorly differentiated B cell lymphoma, "starry sky", EBV

Sinus Histiocytosis With Massive Lymphadenopathy (Rosai-Dorfman)
Large S-100 positive histiocytes phagocytize lymphocytes (emperipolesis)

Metastases

Neuroblastoma
Late stages in children with known tumor, Periocular hemorrhages-"raccoon eyes"

Ewing's Sarcoma
Highly malignant (95% fatal) bone marrow tumor; related to PNET; CD99 +

Secondary Orbital Tumors

Metastases
Breast carcinoma- “Indian file” pattern, signet ring cells; sclerosing type may produce enophthalmos, many are lobular carcinomas

Direct infiltration from contiguous structures:
Eyelid tumors (basal cell, sebaceous gland carcinoma, squamous cell, melanoma)
Conjunctival tumors (mucoepidermoid and squamous cell carcinoma, malignant melanoma)
Intraocular tumors (uveal melanoma, retinoblastoma)
Carcinomas arising in paranasal sinuses
**Mucocele**—cystic invasion of ciliated respiratory epithelium in patients with paranasal sinus disease
**Intracranial Meningioma**

**Optic Nerve**

**Optic Nerve Tumors**

**Optic Nerve Glioma (Juvenile Pilocytic Astrocytoma)**
Most between age 2-6, 90% before age 20, slight female predominance.
Association with neurofibromatosis 10-50% (frequency may be underestimated because cafe au lait spots develop after therapy)
Unilateral visual loss and axial proptosis, disk pallor (with or without papilledema), strabismus, optic canal enlargement, afferent pupillary defect
Fusiform swelling of nerve; tumor confined by intact dura, no invasion of orbital tissues, kinking or buckling of ON on CT
Proliferation of benign, spindle-shaped pilocytic astrocytes
**Rosenthal fibers**—eosinophilic clumps of filaments (crystalline, ubiquitin)
In neurofibromatosis-tumor often invades pia and proliferates subdurally in subarachnoid space (central ON remnant on CT)
Mucinous degeneration can cause sudden increase in proptosis
RX: controversial: follow typical lesions, surgery or irradiation if threat of chiasmal involvement

**Malignant Optic Nerve Gliomas In Adults**
Most cases rapidly fatal

**Optic Nerve Meningioma**
Benign tumor arises from meningotheelial cells of arachnoid of ON meninges
Severe visual loss, minimal proptosis, optociliary shunts, often optic atrophy
(Note: optociliary shunts actually are retinal-choroidal venous collaterals!!)
**Primary**—arise from optic nerve meninges
**Secondary**—invades from orbit
**Ectopic**—from ectopic rests of meningotheelial cells
Tumor begins in meninges, may break through dura and invade orbital tissues
CT: diffuse swelling of ON with enlargement at orbital apex
May have calcification (psammoma bodies)
Meningothelial or transitional: paving stone clusters and whorls of cells, Intranuclear vacuoles of herniated cytoplasm, **psammoma bodies**
Optic nerve meningiomas may behave more aggressively in children

**Melanocytoma**
**Medulloepithelioma**
**Hemangioblastomas (von Hippel)**
**Combined Hamartoma of Retina and RPE**

**Optic Nerve Aplasia**
**Optic Nerve Hypoplasia**
**Optic Nerve Pit**
Usually unilateral, temporal disk margin
Probably related to anomalies in fetal fissure closure
Localized serous detachments and retinoschisis involving macula
Origin of fluid uncertain (No leakage on IVFA): vitreous probably source
Optic Nerve Coloboma
Incomplete closure of fetal fissure
Localized to disk or part of more widespread coloboma
Sporadic or autosomal dominant
2/3’s bilateral

Microphthalmos With Cyst
Large cystic coloboma inferior to optic nerve
May produce superior displacement and proptosis of small globe

Morning Glory Disc Anomaly (MGDA)
Severe visual loss, funnel-shaped optic nerve with central connective tissue,
surrounding elevated annulus of disturbed chorioretinal pigment, vessels emerge
from disk edge – association with carotid stenosis, moyamoya disease in 50%

Colobomas With Choristomatous Malformation
Heterotopic fat, smooth muscle may be present. Usually found in congenitally
blind eye

Optic Disk Edema (Papilledema)
ASSOCIATIONS: systemic hypertension, increased intracranial pressure,
decreased intraocular pressure, increased intraocular pressure, increased
intraorbital pressure, hypercapnia

Swelling results from blockage of axoplasmic flow at lamina cribrosa
Lamina cribrosa distorted by pressure gradient between intraocular and
intracranial pressure. (Usually displaced anteriorly except in acute glaucoma)

Histopathology:
Nerve head swollen, narrowing of physiological cup
Lateral displacement of peripapillary retina, photoreceptors
Buckling (folds) of outer retina (Paton's folds)
Shallow peripapillary serous exudate
Late: gliosis, optic atrophy, cytoid bodies

Optic Disk Drusen
Not related to giant optic disk drusen or drusen of Bruch's membrane
Sporadic or familial, occurs in retinitis pigmentosa (0.3-2%)
Histology: anterior to lamina cribrosa within scleral ring, many nasal
Calcified, concentrically laminated globular aggregates
Pathogenesis: blockage of axoplasmic flow in eyes with narrow scleral canal?
Calcified mitochondria in prelaminar corpora amylacea may serve as nidus for
further calcification (Tso)

Giant Drusen Of Optic Disk
Epipapillary astrocytic hamartoma with calcospherites (Tuberous Sclerosis)

Optic Neuritis
Ophthalmoscopic Classification
Retrobulbar Neuritis
Papillitis
Neuroretinitis
Topographic Classification
Perineuritis
Periaxial Neuritis
Axial Neuritis
Transverse Neuritis
Pathogenetic Classification
Secondary to intraocular inflammation
Secondary to orbital disease
Secondary to osseous and/or sinus disease
Secondary to intracranial disease
Secondary to vascular disease
Metastatic infections
Systemic demyelinating diseases
Nutritional and/or toxic
Hereditary

**Leber's hereditary optic atrophy (LHON)**
transmitted by mitochondrial DNA; NADH subunit 4 mutations; ND4
G11778A “Wallace mutation” is most common- poor prognosis for visual recovery, T14484C best prognosis

**Optic Atrophy**
Gross: shrinkage of parenchyma, redundant dura, widened subarachnoid space
Microscopic: Loss of axons and myelin sheaths, increase in glial cells (astrocytes), thickening of pial septa, widening and deepening of physiological cup.
Primary (descending): lesion in orbit or CNS
Secondary (ascending): primary lesion in retina or disk

**Schnabel's Cavernous Optic Atrophy**
Follows acute rise in IOP? Not all cases have glaucoma
Retrolaminar cavernous spaces contain hyaluronic acid (? from vitreous)
No gliosis or histiocytic reaction

**Pseudo-Schnabel's- silicone oil**; may migrate to CNS

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**GLAUCOMA**

**Definition 1. (Quigley):** An optic neuropathy associated with a characteristic excavation of the optic disc and a progressive loss of visual field sensitivity

**Definition 2. (Yanoff):** A syndrome characterized by an elevation of intraocular pressure of sufficient degree or chronicity to produce tissue damage. Visual loss results from death of retinal ganglion cells and their axons.

Glaucoma kills retinal ganglion cells and ganglion cells axons that compose the optic nerve

**Mechanisms Of Axonal Death**

**Vascular Theory**

**Mechanical Theory**
Blockage of axoplasmic flow due to compression of axons in posteriorly-bowed lamina cribrosa. Laminar pore size correlates with clinical field defects (Quigley)-superior and inferior pores are more delicate, and hence, deformable
? Lack of neurotrophic factors causes apoptosis of ganglion cells

**Intraocular Pressure:** balance between production and outflow of aqueous.
Most glaucomas secondary to aqueous outflow obstruction

**Outflow Pathways**

**Primary: Trabecular Meshwork**

**Secondary:** posterior uveoscleral via vortex veins, ? iris vessels

**Basic Angle Anatomy**
To find scleral spur in sections, follow longitudinal ciliary muscle to its insertion.
Trabecular meshwork and Schlemm’s canal are nestled in anterior crotch of scleral spur

**Developmental Glaucoma**

**Primary Congenital Glaucoma**
Most cases recessive, bilateral, males, 40% at birth, 86% first year
Rule of 2/3’s: 2/3’s male, 2/3’s affected by age 1 yr., 2/3’s autosomal recessive-mutations in cytochrome P4501B1 gene (CYP1B1) on chromosome 2 (2p22-p21)
Theories: Barkan’s Membrane, absence of Schlemm’s canal,
*Fetal* angle configuration:
- Anterior insertion of iris root and ciliary processes
- Ciliary muscle fibers continuous with trabecular beams
- Mesenchymal tissue in angle

**Buphthalmos (“ox eye”)**
- Corneal and anterior segment enlargement, limbal ectasia
- Haab's striae (Descemet ruptures) circumferential or horizontal
  (oblique in forceps injuries)

** Syndromes with Congenital Glaucoma**
- Axenfeld/Rieger syndrome (50% have glaucoma)
- Lowe's syndrome- congenital cataract and glaucoma
- Aniridia
- Sturge-Weber (if nevus flammeus involves upper lid, mechanisms:
dysembyrogenesis, NVI, elevation of episcleral venous pressure
Neurofibromatosis (if plexiform neurofibroma involves upper lid)
  Several mechanisms, may have "distinctive gonioscopic findings" due to
  hamartomatous infiltration of angle

**Primary Open Angle Glaucoma (POAG, COAG)**
Most common type, angle open gonioscopically, insidious elevation of IOP,
Hereditry important, poorly understood, linked to 14 genes, myocilin (MYOC)
Theories:
- Deposition of material in juxtacanalicular CT. e.g. Rohen's tendon and tendon
  sheath material, Mutant GLC1a gene product (myocilin), GAG's
- Loss of trabecular endothelial cells leads to fusion of trabecular beams,
decreased porosity, obliteration of trabecular cul de sacs abutting
  juxtacanalicular connective tissue (Alvarado)
- Abnormalities of giant vacuoles in Schlemm's canal endothelium
- Sclerosis in scleral spur blocking posterior uveoscleral outflow
- Decreased CD44H and hyaluronan in JCT

**Primary Closed Angle Glaucoma**
Anatomic predisposition- small hyperopic eyes with crowded anterior segment
Rare before age 40
- Shallow anterior chamber with narrow angle
- Acute attacks: injection, pain, steamy cornea, fixed dilated pupil, GI sx, N&V
  Most patients have asymptomatic course and do not suffer acute attacks.
  Functional pupillary block or plateau iris mechanisms
  Diminished loss of iris volume during papillary dilatation; expansion of choroidal
  volume (Quigley)
  Peripheral anterior synechia formation
  Papilledema (acute blockage of axoplasmic flow due to laminar distortion)
**Clinical stigmata of prior acute attack:**
- *Segmental iris atrophy* (focal ischemic iris necrosis)
- *Dilated, irregular pupil* (spincter and dilator necrosis)
Glaukomflecken (focal anterior lens epithelial necrosis)

Secondary Closed Angle Glaucoma

Angle closed by permanent peripheral anterior synechias

Causes Of Secondary Angle Closure Glaucoma:

Chronic Primary Angle Closure

Persistent Flat Chamber- wound leak, post-filtering surgery
Inflammation- (posterior synechias, iris bombe’)
  - Seclusion of pupil- 360° posterior synechias
  - Occlusion of pupil- pupillary membrane

Other Causes Of Pupillary Block:

  - Phacomorphic (lens enlargement in elderly)
  - Absent or nonpatent iridotomy or iridectomy, iridovitreal synechias,
  - Dislocated lens, microspherophakia, anterior displacement of lens-iris
  - diaphragm posterior tumors, exudative RD, post-PRP
  - Cysts (anterior chamber or iris)

Malignant Glaucoma (ciliolenticular or ciliovitreal block)

Secondary Proliferative Glaucomas

Neovascular Glaucoma (NVI, rubeosis Iridis)

  - Angiogenic factor produced by ischemic retina, tumors, inflammation,
  - Abnormal vessels on normally avascular anterior surface of iris lack thick
    collagen coat of normal iris vessels
  - Clinically transparent fibrovascular membrane flattens anterior iris surface
  - Myofibroblasts provide motive force for angle closure, ectropion iridis

Many Causes of NVG:

  - Anterior Uveitis
  - Primary And Secondary Closed Angle Glaucoma
  - Post-Operative Anterior Segment Ischemia Or Necrosis
    (after retinal or strabismus surgery)
  - Associated With Proliferative Retinopathy
    Proliferative Diabetic Retinopathy
    Ischemic Central Retinal Vein Occlusion- "90 day glaucoma"
    Ischemic Oculopathy (Carotid Occlusion, Pulseless Disease)
  - Chronic Retinal Detachment, i.e., Coats' Disease
  - Ciliary Artery Occlusion With Retinal Infarct
  - Intraocular Inflammation
  - Various Pseudogliomas (Norrie's, ROP, late Coats' Disease)
  - Sickle Hemoglobinopathy
  - Post-traumatic Vitreous Hemorrhage
  - Retinoblastoma (50% Of Cases)

Epithelial Downgrowth

  - Contact inhibition by healthy endothelium may inhibit epithelium

Iridocorneal Endothelial (ICE) Syndrome (Proliferative Endotheliopathy
  with Iris Abnormalities)

  - Unilateral glaucoma in young to middle-aged women; synechias develop
    in open angle

Endothelial proliferation and secondary iris abnormalities

  - Cogan-Reese (Iris Nevus) Syndrome
    Flattening and effacement of iris stroma, pigmented iris nodules

  - Chandler's Syndrome
    Corneal edema at low IOP

80 Eagle- Pathology Review Outline
Essential Iris Atrophy
- Proliferating endothelium produces synechias in open angle;
- tractional iris holes, endothelial dystrophy

Fibrous Ingrowth (Stromal Overgrowth)

Secondary Open Angle Glaucoma (angle open gonioscopically)
- Cellular proliferation before angle closure
- Occlusion of open angle by cells, material or debris
  - Hyphema (blood, ghost cells, sickle cells)

  The "-lytic" Glaucomas: classically caused by macrophages laden with:
  - Denatured lens material (phacolytic glaucoma),
    - Milky anterior chamber, crystals
  - Free high molecular weight lens protein alone? (Epstein)
  - Blood break-down products (hemolytic glaucoma)
    - Classically hemosiderin-laden macrophages, also ghost cells
  - Melanin from necrotic tumors (melanomalytic glaucoma)
    - Also caused by necrotic melanocytomas (melanocytomalytic glaucoma)

Glaucomatocyclitic Crisis (Posner-Schlossman)
- Unilateral, age 20-50, inflammatory signs minimal,
- Episodic, associated with POAG, ?trabeculitis

Pigmentary Glaucoma (pigment dispersion syndrome)
- Young myopic males, iridodonesis, inverse pupillary block
- Krukenburg spindle (melanin phagocytized by endothelium)
- Iris transillumination: radial spokes correspond to zonular bundles
- Heavy trabecular pigmentation; TM blocked by melanin
  - Campbell's Theory: zonular abrasion of pigment from posterior iris pigment epithelium; similar mechanism 2O PC IOL'S

Pseudoxefoliation of the Lens Capsule (Exfoliation Syndrome, glaucoma capsulare)
- EM evidence for synthesis of PXE within trabecular meshwork

Alpha-Chymotrypsin Induced Ocular Hypertension
- Zonular fragments after ICCE with enzymatic zonulysis

Corticosteroid Glaucoma

Schwartz-Matsuo Syndrome
- Open angle glaucoma in eye with chronic rhegmatogenous RD
- TM blocked by photoreceptor outer segments

Tumor Cells
- Anterior tumors: seeding or direct infiltration ("ring" melanomas)
- Note: posterior tumors usually produce closed angle glaucoma due to forward displacement of lens-iris diaphragm or iris neovascularization

Damaged Outflow Pathways

Post-Contusion Angle Deformity

Trabecular Scarring in Uveitis, Siderosis

Corneoscleral and Extraocular Disease
- Elevated episcleral venous pressure (carotid cavernous fistula, cavernous sinus thrombosis, mediastinal syndromes), pressure on globe (tumors, thyroid, retinal surgery)

Tissue Changes Secondary To Elevated Intraocular Pressure

  Retina: Glaucomatous Retinal Atrophy
    - Atrophy of nerve fiber and ganglion cell layer, gliosis
Inner retinal atrophy secondary to ischemia (e.g., CRAO) also involves inner part of inner nuclear layer, hyalinized appearance

**Optic Nerve: Glaucomatous Optic Atrophy**
Cupping, posterior bowing of lamina cribrosa, loss of nerve tissue anterior to lamina, widened subarachnoid space, widened pial septa

**Sclera:** staphylomas (ectasias lined by uveal tissue) staph & uva = grape

**Cornea:** epithelial edema, bullous keratopathy, band keratopathy, degenerative pannus, secondary ABM changes
Appendices

Other inflammatory diseases

Necrobiotic xanthogranuloma,
Touton giant cells, necrosis, association with myeloma

Erdheim-Chester disease
Bilateral, bone changes, retroperitoneal fibrosis

Orbital xanthogranuloma with adult onset asthma

Subacute sclerosing panencephalitis (SSPE, Dawson's encephalitis)
Fatal measles (paramyxovirus) slow virus infection of CNS
May present with macular retinitis
Eosinophilic nuclear inclusions in neuronal and glial cells

Behçet's disease
Pathological hallmark is vasculitis
Chronic nongranulomatous uveitis, hypopyon, aphthous ulcers
Perivasculitis and vasculitis leading to hemorrhagic retinal infarction, retinal detachment.

Herpes zoster
Perineuritis and perivasculitis affecting posterior ciliary arteries and nerves
Patchy necrosis and post-necrotic atrophy of anterior segment
Retinal perivasculitis, non-specific choroiditis, scleritis, keratitis

INFLAMMATORY SEQUELAE

Cornea
Scarring
Calcific band keratopathy: basophilic granules in Bowman membrane

Inflammatory pannus: subepithelial fibrovascular and inflammatory ingrowth with destruction of Bowman membrane (trachoma)

Degenerative pannus: fibrous tissue interposed between base of epithelium and intact Bowman membrane (seen in chronic corneal edema)

Anterior chamber
Organization of hypopyon or proteinaceous exudates
Retrocorneal fibrous membranes
Peripheral anterior synechias (PAS)
Posterior synechias- seclusio pupillae (360° posterior synechias)

Occlusio pupillae- pupillary membrane

Iris:
PAS, posterior synechias, pupillary membranes, atrophy, neovascularization,

Lens
Anterior subcapsular cataract
Posterior subcapsular cataract

Ciliary body
Cyclitic membrane-retrolental collagenous membrane extending from ciliary body to ciliary body. Often results from organization and scarring of vitreous. Contraction leads to detachment of pars plana. Ciliary muscle remains adherent to scleral spur attachment. Ciliary body pivots on attachment.

Vitreous
Organization of inflammatory debris may lead to cyclitic membrane, fibrous vitreous bands. Trational retinal detachment, posterior vitreous detachment.

**Retina**

**Cystoid macular edema (CME)**
- Retinal vascular leakage vs. Mueller cell edema caused by inflammatory mediators
- High incidence in iris-supported IOL’s suggests production of prostaglandins, etc. by iris.
- Reactive gliosis, may be massive
- Intraretinal pigment migration (pseudoRP)
- Chorioretinal scarring
- Hypertrophy and hyperplasia of RPE
- Drusen formation (abnormal basement membrane material)
- Papillary proliferation of RPE follows loss of contact inhibition after retinal detachment

**Fibrous and Osseous Metaplasia of the RPE**
- Large quantities of collagen and basement membrane material deposited on surface of Bruch’s membrane.
- Contains lacunae of RPE cells (pseudoadenomatous proliferation)
- Bone results from dystrophic calcification, very common in “end stage” blind painful eyes.
- Common sites: peripapillary or at ora (Ringschwiele)

**Optic nerve**
- Papillitis
- Papilledema

**Entire globe**

**Wound healing**

**Skin wounds**
- Migration of epithelium beneath necrotic tissue and blood clot
- Fibronectin binds epithelium to underlying dermis
- Inflammatory cells and connective tissue proliferation in dermis
- Superficial scab lost with maturation of epithelium

**Central corneal wounds (full thickness)**
- Avascular tissue, absence of granulation tissue
- Stromal lips swell, wound gapes anteriorly and posteriorly
- Descemet membrane retracts and curves inwardly, fibrin plug
- Anterior surface re-epithelialized, epithelial plug fills anterior wound gape
- Fibroblasts enter, elaborate collagen
- Endothelial migration and regeneration of Descemet membrane
- Active phase of wound healing: 4-5 weeks, not totally complete at 6 months

**Limbal wound (cataract incision)**
- Involves granulation tissue derived from episclera and conjunctival substantia propria
- Superficial part of well-apposed wound sealed by epithelial migration, fibrin clot, and granulation tissue proliferation within superficial substantia propria within 24 hours
- Posterior wound gapes, Descemet membrane curves inwardly
- Granulation tissue enters external stromal wound at 8-10 days
At 2 weeks granulation tissue extends full length of wound, endothelial migration covers posterior aspect
Collagen production, maturation, reorientation

**Iris**
No healing of unsutured wounds, iridectomies remain patent unless closed by pigment epithelial migration

**Lens**
Small rents in capsule may be repaired by fibrous metaplasia of lens epithelium and capsular reformation.
Posterior synechias may close defect
Most lens wounds lead to cataract formation

**Sclera**
Sclera itself does not participate in healing of defects
Full-thickness wounds healed by ingrowth of granulation tissue from both episclera and superficial choroid

**Surgical Complications**
"Surgical confusion"- misdiagnosis, faulty technique

**General Complications**
Cataract surgery
Expulsive hemorrhage
Vitreous loss, vitreous incarceration, vitreous wick
Detachment of Descemet membrane
Endothelial decompensation- aphakic and pseudophakic bullous keratopathy
Flat chamber, wound leak
Choroidal detachment
Iris incarceration
Filtering bleb
Secondary glaucoma
Retained lens material
Capsular opacification
Dislocation of capsular bag (pseudoexfoliation)
Epithelial ingrowth, implantation cysts
Fibrous ingrowth (stroma overgrowth)
"Sputtering hyphema"-vascularization of posterior wound lip
Soemmerring ring cataract
Elschnig pearls, capsular fibrosis (after ECCE)
Cystoid macular edema (CME)
Uveitis
Endophthalmitis
Localized endophthalmitis "in the bag" (P. acnes, C. parapsilosis)
Retinal detachment
State of aphakia predisposes to RD post ICCE
Small horseshoe breaks at posterior vitreous base after ICCE, much lower incidence of RD after ECCE

**Nonsurgical trauma**
**Corneal abrasion**
Healing by sliding of wing cells, reconstitution of normal epithelial thickness by basal cell proliferation
**Corneal facette** – concave defect in Bowman, anterior stroma filled with epithelium
Corneal edema

- Breaks in Descemet membrane (e.g. forceps injury)

Lens

- **Subluxation**- partial disruption of zonules, lens remains in posterior chamber, but not in normal position
- **Dislocation**- (luxation)- complete zonular disruption, lens in vitreous or anterior chamber
- **Vossius ring** (imprint of iris pigment epithelium on anterior lens)
- **Contusion rosette** (petalliform cataract, clinical marker for contusion)

Iris

- **Sphincter tear**

Retina

- **Dialysis**: Disinsertion of neurosensory retina from ora serrata due to sudden traction at vitreous base
- **Retinitis sclopetaria** – distant effect of missile
- **Post-traumatic pigmented retinopathy (pseudo-RP)**
- **Commotio retinae** (Berlin's "edema"- actually reflects photoreceptor damage; may lead to macular cyst or lamellar hole

Hemorrhages

- Choroidal rupture
- Avulsion of optic nerve

Rupture of the globe

- Occurs most commonly at:
  - Limbus, opposite side
  - Beneath insertions of recti (sclera thinner)
  - Equator
  - Around optic nerve

Organization of blood and inflammatory debris

- Cellular proliferation leading to formation of cyclitic membranes, preretinal membranes, transvitreal membranes.
- Membranes may form on pre-existing scaffolds (e.g. vitreous to wound)
- Contraction of membranes leads to secondary changes:
  - Contraction of cyclitic membranes: ciliary body detachment and hypotony
  - Vitreal membranes: tractional retinal detachment
  - Pre- and retro-retinal membranes- fixed folds,
  - PVR-contraction of membranes due to myofibroblasts

Radiation

Premalignant Eyelid lesions

- **Actinic Keratosis (Premalignant Lesion)**
- **Bowen’s disease**
  - Sharply demarcated red scaly plaques, fair complexion, avg. age 55
  - Intradermal squamous cell carcinoma with bizarre multinucleated cells (squamous cell carcinoma in situ)
  - Association with primary internal cancer has been questioned recently. Some cases are caused by arsenic exposure

Radiation dermatosis

- Effect depends on total dose. Lid changes include loss of lashes, acute and chronic dermatitis with pigmented changes, atrophy, telangiectases, involution of meibomian glands, post irradiation tumors

Xeroderma pigmentosa
Autosomal recessive defect in DNA repair (UV light specific endonuclease)  
Freckles and scaling in early stage, develop variety of malignant tumors: BCC, SCC, MM, sarcomas-3% incidence of skin malignant melanoma

* **Pseudoepitheliomatous hyperplasia**  
  Tumor-like proliferation of epithelium in response to inflammatory stimulus; acanthosis, inflammatory cells within epithelium

**Conjunctiva**

**Congenital lesions**  
Cryptophthalmos, epitarus, congenital ectropion, congenital lymphedema, hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber)

**Immunological disorders with conjunctival findings**  
Ataxia telangiectasia (Louis-Bar)  
Hereditary angioneurotic edema (C1 esterase inhibitor deficiency, autosomal dominant)  
Toxic epidermal necrosis (Lyell's syndrome)  
Wiskott-Aldrich syndrome

**Vascular abnormalities**

**Hyperemia**  
Primary- Response to inflammation  
Secondary- Passive (vascular congestion due to venous obstruction)  
e.g.: space occupying orbital lesions, increased viscosity  
Active- Increased filling of arterial system, e.g.: arterialization in carotid-cavernous fistula; external carotid  
shunting in internal carotid occlusion.  
Paroxysmal- associated with simultaneous lacrimation, rhinorrhea  
Charlin’s syndrome (migranous nasociliary neuritis)  
Horton’s cephalgia, Sluder's syndrome ( neuralgia of the sphenopalatine ganglion)

Vascular sludging  
Increased blood viscosity or decreased circulatory velocity

**Chemosis**  
Edema due to increased permeability of conjunctival vessels

**Subconjunctival hemorrhage**  
Differential diagnosis:  
  Idiopathic (spontaneous without sequelae),inflammation, including febrile illness, SBE, hypertension and arteriosclerosis, trauma, orbital stasis, vitamin C deficiency (scurvy), menstruation, trichinosis, hemorrhagic diathesis  
  Kaposi’s sarcoma (AIDS) can mimic subconjunctival hemorrhage

**Telangiectasia**  
Rendu-Osler-Weber, Louis-Bar, Fabry's disease, Sturge-Weber

**Microaneurysms**  
Diabetes, hypertension, arteriosclerosis, carotid occlusion  
Sickle hemoglobinopathy (Paton's sign), in Hb SS disease, comma-shaped

**Conjunctival inflammation**

**Common indications for penetrating keratoplasty (or DSEK)**  
**Endothelial Decompensation (PK or DSEK)**  
  * **Fuchs dystrophy**  
    Descemet thickened with guttate excrescences
Aphakic bullous keratopathy (ABK)
Descemet membrane thin without guttae, marked endothelial atrophy

Pseudophakic bullous keratopathy (PBK)
Descemet membrane thin without guttae, marked endothelial atrophy

Keratoconus
Old herpetic keratitis
Acute keratitis
Old interstitial keratitis
Corneal dystrophies other than Fuchs - extremely rare!!

Lamellar Corneal Surgery Specimens
DSEK specimens (Descemet stripping endothelial keratectomy)
Embed and section or flat preps- sheets of Descemet membrane
Fuchs- irregular in caliber, guttae, variable endothelial atrophy, pigment in endothelium
PBK- No guttae, more severe endothelial loss
Failed DSEK – thin lamella of posterior stroma, Descemet membrane, endothelial atrophy
PK post DSEK- endothelial graft usually firmly adherent

DALK (Deep anterior lamellar keratopathy)
For keratoconus or anterior pathology
Thick lamella of anterior stroma; posterior stromal tissue; air bubbles in stroma ("pneumatic artifact")
Presence of Descemet membrane on posterior lamella indicates conversion of DALK to PK