

## Ocular Pathology Review

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### 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; relative acute onset  
**Fungal** endophthalmitis- **vitreous microabscesses**; 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  
EOSIINOPHILS = parasites or allergy

### **Eosinophilic Granuloma**

superior lateral orbit, bone destruction,  
localized variant of Langerhan's histiocytosis,  
Histiocytes - S-100 positive, EM shows Birbeck granules or racket bodies

### **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 (tissue basophil)**

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)

Monokine production

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 (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 (tache de bougie) ?= CNS

Involvement

Uveitis; granulomas; Busacca and Koeppe nodules

### **Zonal:**

Palisade of granulomatous inflammation surrounds central antigenic nidus.

Concentric zones of lymphocytes and plasma cells surround first.

Examples: rheumatoid scleritis

### **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.

## **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 HARRT (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**

Most cases are congenital and are acquired in utero

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 ?healthy individuals

Herpesviruses H. simplex and varicella-zoster have been isolated

## 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)

### 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).

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 disease 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

### 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

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

**Iron:** deposits in neuroepithelial structures; **siderosis-** cataract, heterochromia, glaucoma, retinal degeneration, **ferrous (Fe+2) more toxic**

**Copper:** deposits in basement membranes (Descemet's, 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:**

**Cholesterosis bulbi-** blood breakdown major source of intraocular cholesterol crystals, "Synchysis scintillans"

**Hemosiderosis** (liberation of iron with toxic effects)

**Iron deposits in epithelial structures**

**Hemolytic glaucoma, ghost cell glaucoma**

Tractional retinal detachment due to organization, vitreous bands

### **Atrophic 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 phthisis 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**

## **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

### **Coloboma**

**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

No associated systemic anomalies

Compatible with useful vision (absolute scotoma with choroidal coloboma)

Within the coloboma:

Adjacent uvea (mesodermal origin) does not differentiate. It may undergo dysplasia or metaplasia with formation of cartilage, muscle or fat

Overlying retina may be absent or dysplastic

Colobomatous cyst (microphthalmos with cyst)

**Trisomy 13** (Patau's 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, 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 hedge hog gene; association with 13 trisomy

**Lowe's Syndrome**

Oculocerebrorenal syndrome of Lowe

X-linked, aminoaciduria, renal rickets

**Congenital cataract and glaucoma**, lens increscences

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's 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's Syndrome)

Autosomal recessive aniridia, Mental retardation, cerebellar ataxia

Structural defects in cerebellum and brain

Do not develop Wilms' tumor

**Congenital Rubella Embryopathy** (Gregg's 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)**

**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's tumor)

**Phakomatous choristoma (Zimmerman's 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, expresses lens proteins

**Neurofibromatosis (NF-1, VRNF (von Recklinghausen's neurofibromatosis))**

Autosomal dominant, 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- (>6.>1.5 cm 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, normal NF gene product interacts with protein product of **ras** oncogene and dampens growth stimulatory signals.

**Neurofibromatosis, Type II, NF-2**

Gene on chromosome 22, bilateral acoustic neuromas  
Presenile PSC cataract, epiretinal membranes, combined hamartoma of RPE and retina, optic nerve sheath meningiomas

**Sturge Weber Syndrome (Encephalotrigeminal angiomatosis)**

Nonhereditary (congenital (mosaicism for lethal gene??)  
Nevus flammeus ("port wine stain"), facial cavernous angioma  
Glaucoma if upper lid involved  
Diffuse choroidal hemangioma, "tomato catsup" fundus  
Ipsilateral hemangioma of meninges and brain,  
"Train track" intracranial calcification

**Tuberous Sclerosis Complex (Bourneville's Syndrome)**

Autosomal dominant, variable penetrance, TSC suppressor genes on chromosomes 9 and 16 (9q34 and 16p13)  
Seizures in 80-90%  
Facial adenoma sebaceum (angiofibromas, not sebaceous lesions)  
Astrocytic hamartomas of retina ("mulberry nodules")- 50%- rarely progressive  
Retinal tumors may 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  
Before calcospherites form, retinal lesions can resemble small retinoblastomas  
"Ash leaf" skin lesions, shagreen patch, subungual fibromas  
Visceral tumors: renal angiomyolipomas, cardiac rhabdomyomas, subpleural cysts

**Von Hippel-Lindau (Angiomatosis Retinae)**

Autosomal dominant with incomplete penetrance (tumor suppressor gene on chromosome 3)  
**Retinal angioma** (hemangioblastoma) with large feeder vessels, 50% bilateral  
Tumors may involve optic disk or nerve  
Capillary hemangioma with foamy lipid-laden stromal cells. Stromal cells show loss of heterozygosity c/w true neoplastic component, produce VEGF

- Coats' disease-like exudative maculopathy common
- Cerebellar Hemangioblastoma** in 20% (Lindau was a neurologist)
- Most common cause of death, posterolateral in cerebellum, 80% cystic
- Pheochromocytoma** (3-10%)
- Renal Cell Carcinoma**- very high incidence (5th decade)
- Wyburn-Mason Syndrome** - nonhereditary
  - Retinal arteriovenous malformation
  - 23-30% % have associated midbrain vascular malformation
- Ataxia-Telangiectasia** (Louis-Bar)- autosomal recessive
  - Conjunctival telangiectases, oculomotor disturbances
  - Hypoplastic thymus, deficient cell mediated immunity, deficient IgA, increased incidence of lymphoma. elevated alpha fetoprotein
- Multiple Endocrine Neoplasia Syndrome IIB**
  - Pheochromocytomas, medullary thyroid carcinoma, enlarged corneal nerves, typical facies, Marfanoid habitus, mucosal neuromas, dry eyes

## 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

#### 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 swear 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)

### 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 (IFK-inverted follicular keratosis)

**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  
filiforme 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**

**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)

Mites live in hair follicle, feed secluded in follicle during day, prowl on skin surface at night. Extremely common, suspect in chronic blepharitis, pathogenic?

**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  
Pore may connect lumen with skin surface

**\*Dermoid Cyst** (cystic dermoid- anterior orbit)

Lining epithelium has **epidermal appendages**, hair shafts, 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 hydrocystomas**: lined by apocrine cells with eosinophilic cytoplasm and **decapitation secretion**. **Fluid often pigmented**, may simulate melanocytic lesion.

**Vascular lesions**

**\*Capillary Hemangioma**

"Strawberry" hemangioma- perinatal onset  
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: intralesional steroids, cryo, sclerosing solutions  
In Dermatology literature, acquired lesions are called pyogenic granuloma

**\*Cavernous Hemangioma**

Large blood-filled spaces lined with endothelium, fibrous septa

**Lymphangioma**

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"

**Glomus tumor, cutaneous angiosarcoma, Kaposi's sarcoma**

**Epidermal lesions: basics for histopathological evaluation**

**Basal cell lesions are BLUE, Squamous cell lesions are PINK**

Benign lesions rest anterior to plane of epidermis (**benign-"above"**)

Malignant lesions invade deep to the plane of the epidermis (**malignant-"below"**)

**Benign Epithelial Tumors**

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

\***Seborrheic keratosis**-benign papillomatous proliferation of basal cells, ("blue-above") lesion of elderly, sits like a button on skin, greasy keratin crust, may be pigmented, pseudo-horn cysts, hyperkeratosis, adenoid variant

### **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", buttress of normal skin

Configuration on low magnification suggests diagnosis; Impossible to differentiate from squamous cell carcinoma in small biopsy.

Note: Classically thought to be a benign variant of pseudoepitheliomatous hyperplasia; However, some 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 pox viral inclusions (Henderson-Patterson corpuscles), dome or crater configuration, cause of follicular conjunctivitis, massive eyelid involvement in AIDS

#### **Verruca Vulgaris**

Papilloma with spire-like fronds, apical parakeratosis, viral inclusions, coarse keratohyaline granules, HPV 2

#### **Herpes simplex**

#### **Herpes zoster**

### **Common Eyelid Malignancies**

#### **\*\*Basal Cell Carcinoma**

Most common eyelid malignancy (18-39 times more common than squamous cell carcinoma),

Location: Lower lid > medial canthus > upper lid > outer canthus

#### **"Blue" and "below"**

3 types grossly: nodular, 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, stromal desmoplasia, retraction artifact**

#### **desmoplasia, retraction artifact**

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

#### **Nevoid basal cell carcinoma syndrome (Gorlin-Goltz Syndrome)**

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**

More common than squamous cell carcinoma  
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)**  
Histology-  
Lobules of cells with foamy, lipid laden cytoplasm, (fat stains on frozen sections can establish diagnosis in less differentiated cases--**Save wet tissue if you suspect!!!!**)  
Islands of central necrosis (comedocarcinoma pattern)  
**"Pagetoid" invasion and/or replacement of overlying epithelia**  
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

### **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-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**

Balloon cell nevi

Spitz nevus (spindle or epithelioid cell nevus ("juvenile melanoma"))

Congenital intradermal nevi (large (> 2cm) nevi are melanoma precursors 4-6%)

Blue nevi and cellular blue nevi (dermal melanocytes)

Nevus of Ota (oculodermal melanocytosis)

#### **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**-resembles junctional nevus clinically; increased number of basal melanocytes, elongated rete ridges (progresses into adenoid seborrheic keratosis)

**Lentigo senilis**-90% of elderly whites,

#### **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

<b>Clark classification</b>	<b>5 year survival</b>
LEVEL I - epidermis only, basement membrane intact	100% LMM
LEVEL II - early invasion of papillary dermis	100% LMM
LEVEL III - fills entire papillary dermis	80% SSM
LEVEL IV - reaches reticular dermis	65% NM
LEVEL V -invades subcutaneous tissues	15% NM

**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.

**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
- 2/3's have normal lipids, also seen in hyperlipidemia syndromes
- Aggregates of foamy, lipid-laden histiocytes around vessels in dermis.

**Fibrous histiocyoma**

**Juvenile xanthogranuloma (JXG)** macronodular type

**Langerhans' cell histiocytosis**

**Lipoid proteinosis** (Urbach-Wiethe)

- Autosomal recessive, multiple waxy nodules along lid margins, mucous membrane
- Deposits of hyaline material in dermis

**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)**

**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** (calcifying epithelioma of Malherbe)

- Reddish mass of upper lid or brow, basophilic cells and shadow cells,
- calcification in necrotic areas of shadow cells, inflammatory giant cells

**Trichoepithelioma** (Brooke's tumor)

- Multiple tumors may be inherited as autosomal dominant
- 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's disease:** multiple facial trichilemmomas; marker for breast or thyroid cancer

#### **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

#### **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

##### **Phakomatous choristoma (Zimmerman's 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**

##### **Necrobiotic xanthogranuloma**

##### **Carney's complex (autosomal dominant syndrome)**

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

## CONJUNCTIVA

### Histology

Nonkeratinized stratified columnar 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

Giant 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, prostheses

Fewer eosinophils than vernal, basophils

### **Parinaud's 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 venereum), 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's 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 blenorrhoea 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**

Bilateral, chronic pseudomembranous, begins in childhood, recurrent

Massive, woody accumulation of **fibrin** (not MPS), granulation tissue

Systemic disease- similar lesions in vagina, other mucosae

**\*\*Caused by heritable mutations in plasminogen**

## **Mycotic, parasitic conjunctivitis, etc.**

### **Rhinosporidiosis**

Large round fungus causes infectious strawberry-like papilloma studded with white microabscesses, pathognomonic histology, rare in USA, common in India

### **Ophthalmia nodosa**

Caterpillar hairs (setae), may invade anterior chamber

### **Synthetic fiber granuloma**

Epibulbar foreign body granuloma in response to synthetic fabric "fuzz balls", can mimic ophthalmia nodosa, delustering agent

### **Allergic conjunctival granuloma (Ashton)**

Presumed parasitic granulomas; Splendore-Hoeppli phenomenon (eosinophilic deposits of antigen-antibody complexes)

### **Filaria**

## **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

Probably related to environmental exposure, light damage

Histology: solar elastosis, acellular homogeneous deposit, basophilia, thickened vermiform collagen fibers. Elastotic material stains positively with Verhoeff-van Gieson elastic stain, but is not sensitive to elastase digestion.

Similar findings in pterygium

### **Amyloidosis**

Yellow, avascular deposits, bulbar or palpebral conj.

"Starch-like" acellular eosinophilic material, Congo Red, Crystal Violet, Thioflavin-T positive,

Apple-green birefringence, dichroism with polarization microscopy.

## **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 Dermoid**

Choristomatous mound of interweaving, coarsely-thickened collagen fibers covered by skin-like epithelium; contains epidermal appendages (hair, sebaceous and sweat glands).

Isolated finding, or in association with **Goldenhar's syndrome:**

(epibulbar solid dermoids, preauricular appendages, aural fistulas)

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

**Dermolipoma** (dermolipoma)

Choristoma of fat and connective tissue,  
Can extend deep within orbit, avoid surgery or excise carefully!

**\*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.

**Hereditary Benign Intraepithelial Dyskeratosis-**

Inherited disorder of triracial "Haliwa-Saponi Indians" in North Carolina.  
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, conjunctival 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, 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

Can invade interior of globe, eyelid, orbit

More common in Africa, Middle East

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-** aggressive, poorly-differentiated variety of squamous cell carcinoma.

**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 Many are stage IE well-differentiated lymphocytic lymphomas, i.e.,

**Extranodular Marginal Zone Lymphomas (MZL)** - (REAL classification)

These also have been called **MALT lymphomas** (lymphomas of mucosa associated lymphoid tissue.

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

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

Follicular appearance suggests benign process clinically

Benign lesions have following histopathological features:

Germinal centers (N.B. follicles may be present in MZL)

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

**Melanocytic tumors**

**Racial melanosis**

Note: squamous tumors in blacks may be pigmented due to secondary acquired melanosis

**Freckles (ephelis)**

Congenital, increased melanin in basal epithelium, normal number of melanocytes

**\*Nevi**

Nests of benign nevus cells along epithelial base and/or substantia propria, may be amelanotic

Congenital lesion- typically enlarge or become more pigmented at puberty or during pregnancy , cosmesis usually 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...

**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 nevus clinically but do not rule-out melanoma because malignant transformation of nevi possible

Blue and 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)**

Unilateral pigmentation in middle-aged or elderly whites

Insidious onset, waxes and wanes, malignant potential

Overall, approximately 20% develop malignant melanoma

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

**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's 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/conj MM ratio 10/1 (AFIP)

26% mortality, unpredictable behavior

Can arise from:

**Primary acquired melanosis (majority of cases)**

Preexisting nevus

De novo (nodular melanoma)

Primary acquired melanosis found in 75%, Nevi 25%

Behave like skin melanomas (Callender classification is not applicable to conjunctival 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.

## Differential Diagnosis of Pigmented Epibulbar Lesions

	<b>Congenital Melanosis</b>	<b>Acquired Melanosis</b>	<b>Nevus</b>	<b>Malignant Melanoma</b>
<b>Location</b>	episcleral subepithelial	intraepithelial	intraepithelial	intraepithelial subepithelial
<b>Course</b>	stationary progressive	waxes and wanes		stationary
<b>Special Features</b>	heterochromia iris		pseudocysts	
<b>Pigmentation</b>	slate gray	variable	variable	variable
<b>Inflammation</b>	(-)	(+)	(+)	(++)

### Other pigmented lesions of the conjunctiva

**Argyrosis**

**Senile scleral plaque (of Cogan)**

**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's absent, anterior third of stroma

Scarred and vascularized, Descemet's membrane very thin.

**Solid epibulbar dermoids** and complex choristomas (see conjunctiva)

**Goldenhar's syndrome**

**Axenfeld/Rieger syndrome**

(dysembryogenesis of the angle, "mesodermal dysgenesis" angle cleavage syndromes)

A **clinical spectrum** that includes:

**Posterior embryotoxon of Axenfeld**

Prominent, anteriorly displaced Schwalbe's ring

**Axenfeld's Anomaly**

Posterior embryotoxon plus iris processes to ring

50% have glaucoma

**Rieger's Syndrome**

Axenfeld's anomaly plus iris stromal defects such as hypoplasia, slit pupils, polycoria, pseudocoria;

Skeletal and dental anomalies, umbilical hernia;

Autosomal dominant, 50% have glaucoma

**Peters' Anomaly**

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

**Posterior Ulcer of von Hippel**

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

**Posterior Keratoconus**

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

**Congenital Corneal Staphyloma**

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

**Inflammatory Conditions**

**Acute keratitis and corneal ulcerations**

**Bacterial**

Polys collect between lamellae, basophilic necrosis, loss of stroma

**Fungal**

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

**Mycobacterial**

M. tuberculosis, atypical mycobacterial infections, leprosy

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

**Infectious Pseudocrystalline keratopathy**

Large interlamellar bacterial colonies with vaguely crystalline configuration Stromal relatively noninflamed

Avirulent strains of Streptococci sequestered by glycocalyx

Typically occurs in corneal grafts on chronic steroid therapy

**Viral Keratitis**

**Chronic keratitis**

Lymphocytes, plasma cells, vascularization

**Herpes simplex disciform keratitis**

**\*Herpes Simplex Keratitis**

Most common infectious keratitis leading to visual loss in USA and Europe;

HSV type I; frequent recurrence due to latent virus in Gasserian ganglion

Dendritic keratitis

Primary epithelial infection, Cowdry type A intranuclear inclusion bodies, cultures positive in 75%

**Geographic epithelial keratitis**

**Disciform keratitis** (deep stromal keratitis without ulceration)

Cultures negative, but TEM has shown virus in stroma

May be primarily an immune reaction to persistent viral antigen rather than infection (recent controversy)

Scarring, lymphocytes and plasma cells

Granulomatous reaction to Descemet's membrane (suggestive of Herpes but also seen in other entities)

**Deep keratitis with ulceration** (metaherpetic keratitis)

Stromal thinning, perforation, Descemetocele

**Granulomatous reaction to Descemet's membrane**

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

**Parasitic keratitis- Onchocerca volvulus** (onchocerciasis)

"River blindness"-major cause of blindness worldwide

Vector (black simulian fly) breeds in swift-running mountain streams

Adult worms breed in dermal nodules releasing microfilaria

Secondary closed angle glaucoma due to keratitis; chorioretinal degeneration

**Protozoal keratitis-**

**\*Acanthamoeba keratitis** (*A. castellani*, polyphaga)

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

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

Annular infiltrate (ring ulcer) a late finding

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

**Chronic keratitis**

Lymphocytes, plasma cells, vascularization

**Interstitial (stromal) keratitis**

**Herpes simplex disciform keratitis (see above)**

**Luetic (syphilis)- Old luetic IK**

In patients with congenital syphilis; first or second decade;

Rarely seen in acquired syphilis, unilateral, sectoral.

Acute "salmon patch", severe photophobia, edema, lymphocytic infiltrate

Late findings: faint nebulous corneal opacity, deep ghost vessels

Bowman's membrane lost; deep vessels (posterior 1/3 of stroma);

thickening of Descemet's membrane, occasionally massive with formation of hyalinized bridges and strands

Tuberculosis, leprosy, Cogan's syndrome (non-luetic IK with deafness),

protozoal (see above), onchocerciasis (see above), systemic disease

(sarcoidosis, Hodgkin's disease, mycosis fungoides), foreign bodies [insect

hairs (ophthalmia nodosa, plant material), drugs (systemic gold, arsenic

(allergic reaction), trachoma (see conjunctiva)

**Inflammatory pannus**

Peripheral ingrowth of fibrovascular membrane beneath epithelium.

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

**Degenerative pannus**

Common finding in chronically edematous corneas

**Bowman's membrane intact**

Fibrous tissue interposed between base of epithelium and Bowman's membrane

**Peripheral ulcerations**

**Marginal ulcers**

Staphylococcal toxins

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

**Ring ulcers**

**Mooren's ulcer**

In USA, unilateral disease of elderly

In Africa, severe bilateral disease in young

Central overhanging margin of ulcer

Immune disorder?, ischemic necrosis? limbal collagenase? assoc with Hepatitis C

**Terrien's ulcer**

Bilateral, slowly progressive, males

Trough-like stromal thinning begins superiorly

Epithelium intact, Bowman's and superficial stroma lost  
Vascularization, occasional lymphocytes and plasma cells

### **Corneal degenerations**

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

Interpalpebral fissure, most common nasally  
Resembles pinguecula histologically but invades cornea  
Caused by environmental factors: light, dust, wind?? limbal stem cell loss??  
Senile elastosis of collagen, hyalinization, basophilia  
Bowman's membrane lost; overlying epithelial dysplasia possible

#### **\*Calcific band keratopathy**

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

#### **\*Chronic actinic keratopathy** (elastotic degeneration)

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

#### **Salzmann's Nodular Degeneration**

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

#### **Lipid keratopathy**

Secondary deposition in heavily vascularized stroma

#### **Corneal keloid**

Massive scarring and thickening of stroma; epidermalization common

#### **Corneal staphyloma**

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

#### **Keratoconjunctivitis sicca**

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

#### **Sjögren's syndrome** (triad)

##### **Keratoconjunctivitis sicca, xerostomia, rheumatoid arthritis**

Lacrimal gland infiltrated with lymphocytes with persistent myoepithelial islands (lymphoepithelial lesion of Godwin); lymphoma develops in 10%

#### **Xerophthalmia** (avitaminosis A)

Corneal epithelial keratinization, epidermalization; night blindness, keratomalacia and perforation. Malnourished children in underdeveloped countries, alcoholics in USA

#### **Bitot's spot**

#### **Exposure keratopathy**

#### **Dellen (Fuchs)**

Focal stromal thinning central to elevated limbal lesion, surface ulceration.

#### **Neurotrophic keratopathy** (neuroparalytic keratopathy)

#### **White limbal girdle of Vogt**

**White ring of Coats:** ring opacity at level of Bowman's, inferior half of cornea, iron-calcium protein complex

**Secondary amyloidosis**

**Keratoconus**

Bilateral, onset around puberty, heredity questionable

Association with: Down's syndrome, atopic dermatitis, Ehlers-Danlos, Marfan's syndrome, Leber's congenital amaurosis, floppy mitral valve syndrome, hard contacts, eye rubbing

Central stromal ectasia, Munson's sign, Vogt's striae stromal folds, **dehiscences in Bowman's membrane**

Ruptures in Descemet's lead to **acute hydrops** (especially in Down's syndrome)

**Fleischer ring surrounds cone (Iron in epithelium)**

Cause uncertain, ? abnormality in extracellular matrix? ? defect in tissue metalloproteinase inhibitors?

**Pellucid degeneration**

Resembles keratoconus histopathologically, hydrops possible

**CORNEAL RINGS**

**Fleischer Ring**

**Corneal iron lines-ferritin particles within epithelium**

Hudson-Stähli: horizontal, line of lid closure, physiological aging

Fleischer ring: keratoconus, surrounds base of cone

Stocker: advancing head of pterygium

Ferry line: in front of filtering bleb (Ferry = filter)

**Arcus Senilis**

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

**Arcus Juvenilis**

Arcus at an early age (< age 40 in males may be significant for ASCVD)

May occur in Type II and III hyperlipoproteinemia

Corneal lipid deposition also occurs in hypolipidemia syndromes :LCAT deficiency, fish eye disease, Tangier disease

**Kayser-Fleischer Ring** (Wilson's Hepatolenticular degeneration)

Copper in Descemet's membrane (corneal copper also in chalcosis, rare cases of myeloma or lung tumors that make copper transport proteins)

## Corneal dystrophies

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

**Dystrophy: Modern concepts**

Inherited genetic disorder (defective enzyme or structural protein)

Not evident at birth (becomes clinically evident later)

Pathology localized to an ocular tissue (systemic effects absent or inapparent)

*Specific genetic defects recently have been elucidated in several dystrophies:*

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

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

### Representative TGFBI Mutations in Corneal Dystrophies

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

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

**Meesman's dystrophy**

Autosomal dominant, early onset, recurrent erosions, good vision

Myriad small punctate intraepithelial vacuoles, may pool fluorescein at corneal surface. Abnormal epithelial cells contain cytoskeletal "**peculiar substance**"

Thickened epithelial basement membrane. Increased epithelial fragility caused by:

**heritable defect in corneal epithelial specific cytokeratins K3 and K12**

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

A clinical spectrum that results from poor epithelial adhesion to its basement membrane

Autosomal dominant, healthy middle-aged women

(Identical histopathological changes found in 56% of eyes with chronic bullous keratopathy, recurrent erosions)

Pathogenesis: poor epithelial adhesion or bulla formation permits epithelial reduplication and/or folding with excess sub- or intraepithelial production of basement membrane material and collagen. Normal epithelial maturation modified by anatomical constraints

Clinical subtypes (often coexist)

**Microcystic:** white putty-like contents reflect degenerated epithelial cells trapped in disorderly epithelium

**Fingerprint:** parallel lucent lines of basement membrane separating tongues of reduplicated epithelium

**Map** (geographic): subepithelial connective tissue resembling degenerative pannus

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

### **Dystrophies of Bowman's Membrane**

#### **Reis-Bückler's dystrophy**

Autosomal dominant, begins in first decade with recurrent erosions  
Subepithelial scarring, ring-shaped opacities  
May be confused with lattice dystrophy, superficial variant of granular dystrophy  
Irregular "saw-toothed" epithelium, subepithelial connective tissue, destruction of Bowman's layer. Laminated pannus contains intensely eosinophilic crystalloids that stain like material in granular dystrophy (red with Masson trichrome)  
βig-H3 mutation- mutant kerato-epithelin

#### **Thiel- Behnke Honeycomb dystrophy**

Very similar to Reis-Bückler's clinically and pathologically, but storage material is composed by "curly filaments" shown by TEM; TGFBI mutation  
Cases called Reis-Bückler's in American literature actually are Thiel-Behnke

#### **Primary gelatinous droplike dystrophy** (Familial Subepithelial Amyloidosis)

Many cases in Japan  
Amyloid contains lactoferrin, but caused by mutations in M1S1 gene, not gene for lactoferrin

### **Stromal Dystrophies**

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

Autosomal dominant, most benign clinically, visual loss late  
Bilateral, central superficial ring or crumb-like opacities

**Hyaline** "rock-candy" stromal deposits stain intensely **red with Masson**

**Trichrome** (acid fuchsinophilia) , more eosinophilic than normal stroma, PAS (-), MPS (-), Luxol fast blue (+++), less birefringent than normal stromal lamellae.

TEM: electron-dense granules with periodicity

Can recur in graft, material may be produced by epithelium

**TGFBI gene mutation**- mutant TGFBI protein forms granules

#### **Lattice Dystrophy, type I** (Biber-Haab-Dimmer, Bückler's Type III)

**Localized corneal amyloidosis** (Klintworth), ? AA amyloid (never confirmed)

Autosomal Dominant, bilateral, onset first decade

PK usually necessary in 4th or 5th decade

Delicate branching relucet lines in stroma (Not degenerating corneal nerves)

Recurrent erosions; superficial scarring can mimic Reis-Bückler's

Intrastromal and subepithelial deposits of **amyloid**

Amyloid stains **Congo red**, crystal violet, thioflavin T Positive

**Apple green birefringence** and **dichroism** with polarization microscopy

Material also PAS (+), argyrophilic (Wilder's reticulum)

Can recur in graft

**TGFBI gene mutation** - mutant protein forms amyloid

#### **Avellino Corneal Dystrophy**

Combines features of granular and lattice type I, TGFBI mutation

#### **Lattice Dystrophy, Type II (Meretoja syndrome)**

Lattice dystrophy in patients with autosomal dominant systemic amyloidosis.

Midperipheral deposits, less visual loss. (actually may represent amyloid degeneration of corneal nerves)

Cranial nerve palsies, dry itchy skin, typical mask-like "hound dog" facies with protruding lips

Amyloid deposits composed of mutant **gelsolin**, an enzyme involved in actin metabolism.

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

**Macular Dystrophy-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 (+)**

**Mnemonics** for three classic stromal dystrophies:

Mickey Mouse Goes Home to L.A.

Marilyn Monroe Got Hers in L.A.

(Macular, Mucopolysaccharide; Granular, Hyaline; Lattice, Amyloid)

**Schnyder's central stromal crystalline dystrophy**

Autosomal dominant

Needle shaped polychromatic **cholesterol** crystals in anterior stroma, prominent bilateral arcus

Diffuse stromal clouding in some may necessitate PK (age 40-50)

? association with systemic lipid disorder in some cases ( xanthelasma, elevated serum lipids)

**François-Neetan's Fleck Dystrophy (dystrophie mouchetée)**

Vision normal, flecks in stroma found incidentally

Autosomal dominant, occasionally unilateral

Swollen keratocytes contain MPS, lipid

**Congenital Hereditary Stromal Dystrophy**

Autosomal dominant, bilateral corneal clouding

Stationary, normal epithelium, normal corneal thickness

Collagen fibers half normal diameter (15nm)

**Pre-Descemet's Dystrophy**

Cornea farinata: age related degenerative change

Other entities (see Spencer, Vol 1, p336)

**Deep Filiform Dystrophy**

Enlarged keratocytes contain fat and phospholipid inclusions

Resembles cornea farinata, may be same entity

**Endothelial dystrophies**

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

Primary endothelial dystrophy (Adult onset)

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

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

**Congenital Hereditary Endothelial Dystrophy (CHED)**

Two types: rare autosomal dominant, more common recessive  
Thickened edematous stroma, massively thickened Descemet's, atrophic or nonfunctioning endothelium

#### **Posterior Polymorphous Dystrophy** of Schlichting

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

Most autosomal dominant, some recessive

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

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

### **Corneal Involvement in Systemic Diseases**

#### **Systemic mucopolysaccharidoses**

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

#### **Mucopolidoses**

#### **Fabry's disease** (alpha galactosidase deficiency)

Cornea verticillata in 90% of affected males

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

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

#### **LCAT deficiency, fish eye disease, Tangier disease**

#### **Gout**

#### **Cystinosis**

#### **Multiple myeloma, protein dyscrasias**

### **Corneal crystals**

Cystinosis, tyrosinemia,

Immunoglobulin (multiple myeloma)

Uric acid (gout)

Bietti's crystalline dystrophy

Cholesterol (Schnyder's crystalline dystrophy)

Plant sap injury (Dieffenbachia)

Clofazimine (antibiotic for leprosy, reversible if treatment stopped)

### **Enlarged Corneal Nerves**

MEN Type IIb (ganglioneuromas?)

Hereditary Ichthyosis

Hanson's Disease (leprosy)

keratoconus

Refsums 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

Scleral icterus

Congenital ectasias and staphylomas

Ochronosis (alkaptonuria)- homogentisic acid oxidase deficiency, autosomal recessive, 70% have worm-shaped pigment deposits anterior to rectus muscles  
**Cogan's senile scleral plaque:** deposition of calcium salts (calcium phosphate) anterior to rectus tendon insertions, gray translucent appearance clinically.  
Episcleral osseous choristoma-upper temporal quadrant

## **Inflammation**

### **Simple episcleritis**

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

### **Nodular episcleritis**

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

### **Primary scleritis**

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

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

**Infectious scleritis-** gram negative bacteria (*Pseudomonas*), fungi

### **Anterior scleritis**

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

### **Posterior Scleritis**

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

### **Histology: Nodular Scleritis**

Zonal necrotizing granuloma surrounding sequestrum of scleral collagen, fibrinoid necrosis, chronic inflammation, fusiform thickening, immune complex deposition with complement activation. When collagen has been destroyed, inflammation and swelling recede, uvea herniates into defect

### **Histology: Diffuse (Brawny) Scleritis**

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

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

**Presence of microabscesses and necrosis suggests infectious scleritis**

## **LENS**

### **Congenital Anomalies**

Posterior umbilication-fixation artifact in young eyes  
Lenticonus  
Capsular thinning or defects allows cortex to bulge

**Anterior:** bilateral, males, Alport's syndrome of hereditary hemorrhagic nephritis, deafness, abnormal type 4 collagen (relationship to posterior polymorphous?)

**Posterior:** unilateral, sporadic

Lens coloboma

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

Congenital cataract

Many hereditary, autosomal dominant

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

Anterior pyramidal cataract (congenital anterior subcapsular cataract)

Posterior variants result from abnormal hyaloid resorption

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

Lowe's syndrome: discoid lens, capsular increscences

Down's syndrome

## **Cataract**

**Opacification or optical dysfunction of crystalline lens**

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

**4 basic types of cataract recognized histopathologically**

*(Lens has limited vocabulary of histopathologic expression)*

**Anterior subcapsular cataract**

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

Cells surrounded by basement membrane capsules

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

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

**Posterior subcapsular cataract**

**Posterior migration of lens epithelium** (normal termination at lens equator);

**bladder or Wedl cell** formation (eosinophilic globular cells that have nuclei!!)

Clinically interferes with near vision early, causes glare symptoms

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

**Cortical Degeneration**

Lens fibers fragment, ooze degenerated protein, liquefaction

Vacuoles, water clefts, total liquefaction (Morgagnian cataract)

**Morgagnian globules** (round, eosinophilic, NO NUCLEI!!!)

Liquefied cortex exerts osmotic effect (intumescent cataract)

Lens substance can leak through intact capsule

Loss of substance leads to shrunken hypermature cataract with prune-like

wrinkled capsule; can incite bland macrophagic response, **phacolytic glaucoma**

Cholesterol crystals (Christmas tree cataract)

**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 artifactual clefts

Urochrome photo-oxidation pigment: blue-yellow color defects

Lenticular myopia due to increased index of refraction

Cataracta brunescens, cataracta nigra

Calcium oxalate crystals in nucleus

**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)

### Complicated cataracts

#### **Fuchs' heterochromic cyclitis**

Low grade asymptomatic uveitis, no rx required; fine stellate or filiform kp's  
Involved eye lighter in 90%; iris darker in inverse or paradoxical heterochromia due to severe stromal atrophy  
Patients tolerate cataract surgery well  
Fine vessels in angle without synechia formation, filiform hyphema; secondary open angle glaucoma in 10-50%

#### **Chronic uveitis**

Sarcoidosis, juvenile rheumatoid arthritis (RF seronegative ANA+, pauciarticular)  
Retinitis pigmentosa (posterior subcapsular)

Tumors- ciliary body tumors compress lens, cause posterior migration of lens cells

**Glaukomflecken**- focal areas of lens epithelial necrosis with associated cortical damage post acute attack, ? toxins in stagnant aqueous

### Aldose reductase and osmotic cataracts (Sugar Cataracts)

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

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

**Galactokinase deficiency**: rare cause of presenile cataract in adults

### Ectopia lentis (spontaneous dislocation of the lens)

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

#### **Marfan's syndrome** (arachnodactyly)

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**  
Zonules deficient in cysteine, reduced sulfhydryl cross-linking weakens fibrillin  
Blonde, marfanoid habitus, increased urinary excretion of homocystine (detect with **sodium nitroprusside test**,  
Lens dislocates **down** and in, or into anterior chamber (90%)  
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** (brachydactyly)- autosomal recessive or dominant  
Dominant form linked to fibrillin-1 gene

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

#### **Tertiary syphilis**

#### **Trauma**

### **Lens Capsular Abnormalities**

#### **True Exfoliation** of lens capsule (capsular delamination)

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

#### **Pseudoexfoliation of lens capsule** (Exfoliation Syndrome)

Abnormal extracellular matrix material (of complex composition); produced by lens epithelial cells, extruded through lens capsule

Found on anterior lens capsule, posterior iris, ciliary body, zonules, vitreous face.

On lens: central disk, clear interval, peripheral zone

Flakes at pupillary margin suggest diagnosis in undilated patient

Associated with **secondary open angle glaucoma** (glaucoma capsulare) 50%

Abnormal iris- pigment epithelial "sawtoothing", poor dilation

Pigment dispersion-Sampaolesi's line

Ocular manifestation of **systemic elastosis** (also found in conj, skin, lung, liver)

Immunoreactive with zonular elastic microfibrillar proteins

Abnormal zonules- high incidence of **IOL and capsular dislocation**

≈

### **Traumatic Cataract**

Perforating injuries, ruptured lens

**Vossius ring**: iris pigment on lens capsule

**Contusion cataract** (petalliform cataract or contusion rosette)

Sign of old contusion injury, look for angle recession

**Soemmerring's ring cataract**: donut of residual equatorial cortex

**Siderosis lentis**: iron deposited in epithelium

**Chalcosis lentis**: copper deposited in basement membrane

**Mercurialentis**- mercury deposition in lens capsule (occupational)

#### **Electrical cataract**

#### **Argon laser cataract**

Blue light absorbed by yellow sclerotic nucleus; avoid with krypton red

#### **Phacoanaphylactic endophthalmitis (phacoantigenic uveitis)**

#### **Localized endophthalmitis (*Propionibacterium acnes*, *Candida parapsilosis*),**

Large bacterial (or fungal) colonies grow within capsular bag post ECCE, white plaques, delayed chronic granulomatous response

### **Toxic cataracts**

Corticosteroids: posterior subcapsular, dose uncertain

Occurs in approximately 1/3 (12-60%) with chronic daily dose of 10mg

Incidence 20% if patient receives >15mg prednisolone for 2-8 years-

Anticholinesterases: anterior subcapsular vacuoles (84%)

Naphthalene, DNP, triparanol, mercury, phenothiazine

### **Cataract Associated with Systemic Diseases**

**Myotonic Dystrophy**- chromosome 19, unstable CTG trinucleotide repeat accumulates.

Myotonia, testicular atrophy, frontal baldness, cataract, Presenile cataract with polychromatic anterior and posterior subcapsular cortical crystals. (spirally birefringent concentrically multilaminated "rice grains")

**Wilson's Disease** (Hepatolenticular degeneration)

Sunflower cataract, Kayser-Fleischer ring

Deposition of copper in lens capsule, Descemet's membrane

Similar findings occur in chalcosis; Copper deposition also has been reported in multiple myeloma, lung carcinoma

**Diabetes mellitus**

**Galactosemia**

**Fabry's disease**

X-linked deficiency of alpha-galactosidase A

Sphingolipidosis, storage of ceramide trihexoside

Cornea verticillata (Fleischer-Gruber) 90% of affected males

Posterior spoke-like opacities

**Hereditary hyperferritinemia**-crystals of L-ferritin

### **Cataract Associated With Skin Diseases**

Atopic dermatitis (Andogsky's Syndrome),

Ectodermal dysplasias (Rothmund, Werner)

Acrodermatitis enteropathica

## **Retina**

### **A peripheral colony of brain cells**

#### **Anatomy:**

3 neuron system, 10 layers

#### **Retinal hemorrhages**

**Flame** or splinter (superficial retinal hemorrhages)

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

**Blot and dot**

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

**Scaphoid** or boat-shaped (two types)

1. **Sub-ILM**: hemorrhagic detachment of internal limiting membrane

2. **Sub-hyaloid**: blood between ILM and posterior hyaloid

True subhyaloid hemorrhages do occur in patients with proliferative diabetic retinopathy

**Sub-RPE** hemorrhages

**Dark**-colored, can be confused with choroidal melanoma

**Roth spot**

White centered hemorrhage, central abscess in SBE,

Also leukemic cells, central nidus of fibrin

#### **Blood retinal barrier - analogous to blood-brain barrier**

**Inner**- retinal capillary tight junctions

**Outer**- RPE tight junctions (fenestrated choriocapillaries leak)

#### **Retinal exudates**

**Hard, yellow waxy exudates**

**Pools of eosinophilic lipoproteinaceous material in outer plexiform layer**: "watershed zone" between retinal and choroidal circulations.

Fluid derived from leaky retinal capillaries, competent capillaries absorb water, leaving protein and lipid behind  
May be phagocytized by macrophages (Gitter cells)

**Circinate retinopathy**

Ring of hard exudate surrounding leaking focus

**Macular star**

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

**Cotton wool spots** (soft exudates)

**Microinfarctions of nerve fiber layer** due to occlusion of precapillary arteriole  
**Blockage of axoplasmic flow** in nerve fiber axons traversing ischemic focus produces **Cytoid bodies** or end bulbs of Cajal: swollen axons with eosinophilic nucleoid composed of dammed organelles.

**Clinical marker for retinal ischemia**, e.g. preproliferative diabetic retinopathy  
Isolated finding in collagen vascular disease, AIDS  
Confined to territory of radial peripapillary capillaries

**Angioid streaks**

**Breaks in calcified Bruch's membrane**

Pseudoxanthoma elasticum (Peau d'orange fundus)  
Paget's disease of bone  
Sickle cell (Hb SS)

Subretinal neovascularization and disciform degeneration a complication

**Central retinal artery occlusion**

**Ischemic infarction** of retina

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

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

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

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

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

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

**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 choroidal infarction

Severe visual loss, A wave of ERG absent

**Retinal Venous Occlusions**

### **85% branch, 70% superotemporal**

Associations: AS, hypertension, DM, >age 50, male,

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 arteriolar sclerosis**

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, Seegrists 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**- (bull's-eye maculopathy)

Dose related, primary effect on RPE?, drug stored in melanin granules

**Thioridazine** (Mellaril) -high doses

**Methoxyflurane** (anesthetic)

Crystalline retinopathy, oxalate crystals

**Chloramphenicol** (chronic use in cystic fibrosis)

Atrophy of maculopapillary bundle, cecocentral scotomas

**Quinine**

**Tamoxifen**: nonsteroidal antiestrogen- breast cancer therapy, flecklike retinopathy

**Nicotinic acid** (Gass)- atypical nonleaking CME

**Canthaxanthine** (crystalline retinopathy)- tanning agent

Others...

## THE MACULA,

### Definitions:

**Macula:** macula lutea-"yellow spot", nonspecific clinical term.

Darker on IVFA: xanthophyll, more lipofuscin and melanin in taller rpe cells

**Fovea:** "pit"- depression in retina, 1 DD in size

**Foveola:** Floor of pit, greatest retinal thinning, avascular; anatomy: only photoreceptors, outer nuclear layer, some Henle fibers,

### Age Related Macular Degeneration (Senile macular degeneration, SMD, ARMD)

More common in blue-eyed patients, rare in blacks: suggest pathogenic role of chronic light exposure

#### "DRY" ARMD

RPE degeneration, pigment clumping, areolar loss of RPE with concomitant degeneration of outer retina; ? Role of light damage, ARMD and drusen less common in blacks;

#### "WET" ARMD:

Choroidal neovascular membranes (CNV), exudation, focal serous detachment of retina, hemorrhagic RPE detachment, organization of hemorrhage, subretinal scar formation (disciform degeneration)

RPE cells contribute to collagen production in vascularized scar

**A CLINICAL SPECTRUM:** "wet" and "dry" variants can be found in same patient

### Aging Changes in Bruch's Membrane:

Thickening, pas positivity, focal calcification, drusen

**Drusen-** a clinical marker for "sick" RPE

**Deposits of extracellular matrix material** on inner surface of Bruch's membrane.

Probably made by "sick" or stressed RPE cells

#### **Hard drusen** (cuticular)

Globular excrescences of densely hyaline PAS (+) material

Association with dry or atrophic ARMD has been questioned (Green)

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

**Basal laminar deposit** (very important variant of diffuse soft drusen)

#### **May be quite extensive, but not evident clinically**

Thick diffuse layer of abnormal 1000 Å banded basement membrane material ("curly collagen") located between plasma membrane and basement membrane of RPE.

Composition: laminin, type IV collagen, heparin sulfate proteoglycans

Appears as pink granular band between Bruch's membrane and RPE.

Very common pathologic finding in ARMD (84% "wet", 53% "dry", 19% control - Grossniklaus)

Predisposes to RPE detachment and tears, SRNVM, disciform degeneration

May interfere with biochemical modulation of choriocapillaries by RPE, barrier to diffusion, bind or sequester angiogenesis factors, displaces RPE from blood supply

#### **Basal Linear Deposit -**

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

#### **Subretinal Neovascular Membrane** (CNV, choroidal neovascular membranes)

New vessels derived from choroid, extend through breaks in Bruch's membrane

Vessels leak, bleed with resultant hemorrhagic RPE and/or retinal detachment.

Disciform scar caused by organization of hemorrhage by granulation tissue and collagenous connective tissue (disciform degeneration).

Propensity for foveal and parafoveal region

Excised membranes very difficult to orient histopathologically

**Hemorrhagic Detachment of the RPE**-can mimic choroidal melanoma

**Diseases with SRNVM, disciform scar formation**

ARMD

Focal choroiditis ( e.g , presumed ocular histoplasmosis syndrome)

Angioid streaks

Myopic degeneration

Choroidal rupture

Central serous (rare)

Dominant drusen

Choroidal tumors

Juvenile disciform degeneration

### **Ocular Histoplasmosis Syndrome (POHS)**

Triad:

Disciform degeneration of macula, focal chronic choroiditis, organisms rarely found

Peripapillary atrophy, peripheral punched-out spots

### **Macular Holes (Idiopathic)**

Shrinkage of prefoveal cortical vitreous exerts lateral traction on retina causing localized foveal detachment, then hole. (fibrocellular membranes rarely found)

Better VA after surgery reflects smaller size of sealed hole and resorption of SRF.

#### **Classification of macular holes (Gass)**

Stage I- foveal detachment (impending hole or macular cyst) - about 50% progress

Stage II- early hole formation

Stage III- full thickness hole with vitreofoveal detachment

Stage IV- full-thickness hole with posterior vitreous detachment

### **Cystoid Macular Edema (CME)**

Multiple cystoid spaces in macula with petalloid appearance on IVFA

Irvine-Gass Syndrome - post cataract surgery

Very high incidence with iris supported IOL's

Secondary finding over choroidal tumors, especially hemangioma

Occurs with peripheral uveitis, peripheral tumors

OCT and intravitreal kenalog

### **Ophthalmic lasers**

**Argon, krypton, diode:** thermal coagulation. (Light absorbed by pigment, converted to heat)

Blue argon wavelengths absorbed by yellow macular pigment, damage retina

Green argon wavelengths absorbed by blood, melanin

Red krypton wavelengths absorbed by melanin, not by blood or luteal pigment

**YAG:** short pulse mode does not rely on thermal coagulation; optical breakdown "explosion" physically disrupts tissues

**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, total blindness

Attenuation of retinal vessels, waxy pallor of optic disc, bone spicule pigmentation in peripheral fundus

Posterior subcapsular cataract, macular edema, optic disk drusen

### **Genetics**

Sporadic 39%, dominant 20%, recessive 37%, sex-linked 4%,  
Consanguinity 30-40%  
Severity: Autosomal dominant < autosomal recessive < X-linked  
**More than 25 genes cause RP** (genes located on chromosomes 1, 3, 4, 5, 6, 7,  
8, 11, 14, 15, 16, 17, 19, and X (most identified by linkage studies)

**8 specific RP genes have been identified**

4 encode protein involved in rod phototransduction cascade:

Rhodopsin

20-25% of patients with dominant RP- most single AA substitutions  
(missense mutations), most common His-23-Pro

a and b subunits of rod c-GMP-phosphodiesterase

a subunit of c-GMP-gated cation channel

4 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 VIIa, RPGR

**Histopathology**

Primary photoreceptor degeneration- atrophy involves outer retina

Loss of photoreceptors, ONL

Bone spicule pigmentation caused by intraretinal RPE migration

TEM: intraretinal formation of new perivascular "Bruch's membrane"

Macromelanosome (PR atrophy may allow RPE to invade retina)

RPE usually fairly well preserved

**Variants of Retinitis Pigmentosa**

Sector retinitis pigmentosa

Usher's Syndrome (association of RP and hearing loss- 3 types)

Retinitis pigmentosa with Coats'-like response

Leber's congenital amaurosis

Retinitis punctata albescens

**X-linked Juvenile Retinoschisis**

**Split in nerve fiber layer**

Stellate maculopathy does not fill with fluorescein

? abnormal vitreous-like material in retina (Brownstein)

**Macular dystrophies** (hereditary, bilateral)

**Fundus flavimaculatus** (Stargardt's disease)

Once thought to be primary RPE disease, but causative **ABCR gene** is expressed  
only in photoreceptor outer segments. Defect in abcr transport protein leads to  
accumulation of toxic vitamin A derivatives in outer segments that poison RPE's  
phagolysosomal system.

Autosomal recessive, onset in teens

Yellow pisciform flecks in RPE, atrophic macular degeneration

RPE PAS+, cells contain massive amounts of abnormal lipofuscin

Posterior RPE cells massively enlarged

**"Dark" choroid** on IVFA, vermilion fundus due to **RPE lipofuscin**

Fundus flavimaculatus without macular lesion lacks abnormal pigment

**Best's disease (Vitelliform macular dystrophy)-**

Dominant, unidentified gene on chromosome 11, abnormal EOG

Similar disease caused by defects in peripherin/RDS gene

Egg yolk lesion "scrambles" with age, Abnormal EOG

RPE disease with increased amounts of abnormal lipofuscin

### **Kearns-Sayre Syndrome**

Progressive external ophthalmoplegia, heart block, atypical pigmentary retinopathy  
"Salt and pepper" retinopathy, no bone spicules, ? primary RPE disease, involves posterior fundus, defect in **mitochondrial DNA**

Other mitochondrial cytopathies (MERRF, MELAS) occasionally affect retina

### **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.

### **Oguchi Disease**

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

### **Gyrate atrophy**

**Hyperornithinemia**, ornithine aminotransferase deficiency

Ornithine may act as an RPE toxin

### **Choroideremia**

X-linked degeneration of RPE, choroid and photoreceptors (primary site unknown)

Asymptomatic female carriers have patchy pigmentation and RPE and choroidal degeneration.

Rab geranylgeranyl transferase deficiency

### **Mucopolysaccharidoses**

Inherited deficiencies of catabolic lysosomal exoenzymes.

Fibrillogranular and multimembranous inclusions.

Outer retinal atrophy due to RPE degeneration; marked in Sanfilippo (MPS III); mimics primary retinitis pigmentosa

### **Sphingolipidoses**

## **Diabetes mellitus**

### **Diabetic retinopathy**

#### **Microangiopathy**

**Loss of capillary pericytes** (Normal endo/pericyte = 1/1)

Role of sorbitol in pericyte loss

Thickening of capillary basement membranes

Capillary nonperfusion (capillaries are totally avascular)

Neovascularization of disk and retina

Angiogenic factor (**VEGF**- vascular endothelial growth factor) produced by ischemic retina

#### **Microaneurysms**

Seen in diabetes and other retinal diseases with ischemia

DM: mainly posterior pole, CRVO: throughout retina, others: periphery

50-100 $\mu$ , most not ophthalmoscopically visible (One sees associated hemorrhage)

Increased number of endothelial cells (proliferation versus migration)

Wall initially thin and leaky, thickens, PAS (+), eventual occlusion

#### **Background retinopathy**

Hemorrhages, hard exudates, retinal edema

#### **Preproliferative retinopathy**

Cotton wool spots a marker for retinal ischemia

#### **Proliferative retinopathy**

Neovascularization of disk, retina, iris; angiogenic factor (VEGF)

New vessels proliferate on scaffold of partially detached vitreous  
Progressive vitreous detachment rips vessels causing subhyaloid and vitreous hemorrhage  
Scarring and organization of hemorrhage produces vitreoretinal

Traction, tractional retinal detachment

#### **Diabetic iridopathy**

Iris neovascularization (Rubeosis iridis):

Higher incidence post-lensectomy

Lens acts as barrier to anterior diffusion of angiogenic factor

**Diabetic lacy vacuolization** of iris pigment epithelium

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

#### **Basement membrane thickening**

Retinal capillaries

Nonpigmented ciliary epithelium (can be diagnostic)

Corneal epithelial basement membrane (epithelium can desquamate as sheet)

#### **Diabetic cataract**

Role of aldose reductase, sorbitol

**Albinism** (many types, tyrosine negative and positive)

**Foveal hypoplasia** (? Related to pigment lack, not metabolic defect; occurs in different varieties), 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 continuous with typical cystoid

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 contain myeloma protein; opacified by fixation (white)

**Retinal detachment**

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

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

**True retinal detachment**

Photoreceptor degeneration, eosinophilic proteinaceous fluid in subretinal space,

RPE budding or papillary proliferation with chronicity

**Artificial 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**

Tumors (most melanomas, hemangiomas, metastases)

Uveal effusion, Harada's, toxemia of pregnancy, oxygen toxicity

**Tractional retinal detachment**

Proliferative diabetic retinopathy

**Chronic retinal detachment**

Photoreceptor degeneration, gliosis, macrocystic degeneration

Proliferative vitreoretinopathy, funnel or morning glory configuration

## Vitreous

**Posterior vitreous detachment**

63% incidence in 8th decade, rare before age 55

7.5% have associated vitreous hemorrhage, 15% have retinal breaks

Flashes, floaters, "ring of Vogt" (peripapillary condensation)

Important role in retinal detachment

### **Vitreous opacities**

Hyaloid remnants (muscae volitantes-"flying flies")

#### **Vitreous hemorrhage**

Blood breakdown products in chronic hemorrhages ("**ochre membrane**")

**ghost cells**, hemoglobin globules, hemosiderin-laden macrophages: Hemolytic, ghost cell glaucoma

Complications: organization leading to tractional RD, hemosiderosis (repeated hemorrhage)

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

#### **Asteroid hyalosis** (Benson's disease, Scintillatio nivea)

Classically: globules of **calcium soap** (recently shown to be **calcium hydroxyapatite**) attached to vitreous framework

Unilateral; generally does not interfere with vision

Gray spheres with Maltese cross birefringence on polarization

#### **Synchysis Scintillans** (Cholesterolosis bulbi)

Rare, bilateral, blind eyes, young patients

**Cholesterol** crystals derived from old hemorrhage

Not fixed to vitreous framework, sinks to bottom of globe

#### **Primary Amyloidosis Of The Vitreous**

Vitreous involvement in Familial Amyloidotic Polyneuropathies (FAP's)

Amyloid comprised of mutant transthyretin (prealbumin)

Several missense (AA substitutions) mutations identified (many patients have Met 30 variant)

Often presents in elderly patients with no family history

Associations include cardiac disease, amyloid neuropathy, carpal tunnel syndrome

Amyloid probably enters via retinal vessels

### **Intravitreal Tumor Cells**

#### **Retinoblastoma**

Vitreous seeding common in advanced cases, poor prognostic sign

#### **Primary Lymphoma of CNS and Retina (NHL-CNS)**

("ocular reticulum cell sarcoma")

Bilateral vitritis, CNS lymphoma, dementia

Poor prognosis (mean survival 22 months)

Most are large cell lymphocytic lymphomas

Reticulum cell sarcoma is incorrect, outdated term

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 also can involve vitreous secondarily; Uveal involvement typical in such cases

**Whipple's Disease**- rarely mimics primary CNS lymphoma with bilateral vitritis, dementia, Cells PAS (+), contain bacteria *Tropheryma whippelii*

**Metastatic Skin melanoma**- predilection for retinal and vitreous metastasis

### **Vitreous Membranes (proliferative vitreoretinopathy, PVR)**

**RPE, glial cells, myofibroblasts**

Vitreous detachment allows cells to proliferate on inner and outer surface of retina, along scaffold of detached vitreous  
 Membranes cause fixed folds, inoperable RD  
 Proliferation on posterior face of detached vitreous responsible for funnel shape of chronic RD  
 Anterior variant of PVR- organization of vitreous on pars plana inaccessible to vitrectomy; anterior loop retinal detachment, posterior traction on iris

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

## 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  
 Incidence in U.S. whites is 8.5 times greater than 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:

Size	Median age	10 year survival*
small [<10 mm]	53 yr.	80%
medium [10-15 mm]	56 yr.	60%
large [ >15 mm]	61 yr.	35%
with metastases	65 yr.	----

\* Survival after enucleation [ Non tumor deaths excluded]

Male = female in COMS study

### **Predisposing Lesions**

Congenital ocular or oculodermal melanocytosis [**Nevus of Ota**]  
Uveal nevi- estimated rate of malignant transformation- 1/10,000- 15,000/ year  
Neurofibromatosis  
Dysplastic nevus syndrome (BK mole 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**

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 with retinal perforation ]  
Extrascleral Extension [ anterior or orbit 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  
Diagnostic delay- 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 diffuse growth pattern)

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

**Prognostic Features**

**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):

Cell type	5-yr-survival	10-yr-survival	15-yr-survival
Spindle cell nevus	100%	100%	100%
Spindle melanoma	90%	79%	72%
Mixed cell, Epithelioid cell, and Necrotic	58%	44%	37%

**Tumor size-** as important as cell type

1. Tumors can be difficult to accurately measure

2. **Largest tumor diameter (LTD) is best prognostic indicator:**

Size	Dimensions	5-yr-survival	10-yr-survival	15-yr-survival
Small	< 11 mm	86%	76%	70%
Medium	11-15 mm	66%	51%	43%
Large	> 15 mm	56%	41%	35%

### Cell type and size are most important factors

#### Other prognostic factors

**Mitotic activity**- more mitoses- worse prognosis

**Extraocular extension**

**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

**Anterior location** (ciliary body tumors worse than choroidal in some series)

**Size and variability in nucleolar size** (ISDNA, MTLN)- research techniques

**"Vascular" patterns**-(Folberg) Vascular loops and networks,

**Lymphocytic infiltration**- associated with worse prognosis

#### 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.

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)

P<sup>32</sup> 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 larger tumors

**Zimmerman's hypothesis**- Enucleation may disseminate tumor cells and increase tumor deaths ( Has never been proven or disproved) Immunological factors are probably also involved.

#### Radiation:

**Plaques** (brachyradiotherapy) radiation source placed on sclera over tumor for calculated period of time

**Charged particle beams (Proton beam, Helium Ion)**

Mortality similar to enucleation in nonrandomized studies

**Plaque plus hyperthermia (experimental)**

**Photocoagulation**- only effective for very small tumors.

**Cryotherapy**

**Local resection**- iridectomy, iridocyclectomy, partial lamellar sclerouvectomy

**TTT (transpupillary thermotherapy)**

**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

### **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- observe for growth  
Treat by local resection [iridectomy or iridocyclectomy if CB extension present]  
Reserve enucleation for tumors with epithelioid cells or intractable glaucoma  
Iris melanomas that contain epithelioid cells are more likely to cause secondary glaucoma and heterochromia  
Diffuse iris melanoma spreads through iris stroma without causing a mass

### **Differential Diagnosis of Posterior Uveal Melanoma)**

#### **Nevus**

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

#### **Melanocytoma**

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 cellular details during diagnosis

#### **Choroidal hemangioma**

Benign cavernous hemangioma  
Sporadic tumors localized, orange mass  
Sturge-Weber- diffuse tumors-"tomato catsup" fundus  
Cystoid retinal edema, exudative retinal detachment  
Distinguish with IVFA, US; Some cases treated with radiation to preserve eye

#### **Uveal metastases**

**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)

#### **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  
CHRPE-like 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 extremely rare  
Benign adenomas and cytologically malignant adenocarcinomas  
Malignant RPE tumors locally infiltrate, but do not metastasize  
Some are deeply pigmented, abrupt margins

**Combined Hamartoma of the RPE and Retina**

**Tumors of the Ciliary Epithelium**

Very rare (except Fuchs' adenoma)  
Adenomas and adenocarcinomas, from pigmented or nonpigmented epithelium  
Arise from epithelium on inner surface of ciliary body, not from stroma

**Leiomyoma**

Most cases found in young woman  
Amelanotic tumors usually located in supraciliary space, transmits light  
Mesectodermal type resembles neural tumor by LM but shows smooth muscle differentiation by EM and immunohistochemistry

**Peripheral Nerve Sheath Tumors- rare**

**Retinal vasoproliferative tumor-** reactive proliferation of glial cells, vessels, pseudoadenomatous proliferation of RPE

**Choroidal Osteoma** (Osseous choristoma)

Young women, often bilateral with scalloped margins  
Plaque of bone in choroid, W/U with CT, US  
Unlike osseous metaplasia of RPE bone within, not on choroid

**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, Tbc, 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**

## RETINOBLASTOMA

Most common intraocular tumor in children (1/15-20,000 births)  
Among nonwhites, 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 tumors)

**Orbital cellulitis**-like picture 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

### Histopathology

**Poorly differentiated 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%

**Spheroidal aggregates** - 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)

#### **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)

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

#### **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 preauricular 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

Tumor can directly extend to brain, gain access to CSF

Retrolaminar invasion usually indication for adjuvant chemotherapy

**Choroidal invasion** (role controversial)

**Orbital invasion** (AFIP- more important than choroidal invasion)

Absence of rosettes, fleurettes

Lymphadenopathy with anterior perforation, conjunctival invasion

? Diffuse growth pattern (delay in diagnosis)

Pseudoinflammatory presentation (delay in diagnosis)

**Risk factors associated with mortality** Odds Ratio

Invasion of ocular coats	
Choroid	1.8
Sclera	3.9
Orbit	21.6
Invasion of optic nerve	
Resected	3.8
Unresected	8.7
Bilaterality	2.9
Incorrect diagnosis	2.5

**Treatment:**

**Small lesions** are treated with radiotherapy, radioactive applications, photocoagulation, diathermy, cryotherapy

**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.

Chemoreduction used in initial management of some cases.

**Advanced tumor** - Radiotherapy, chemotherapy, and orbital exenteration may be employed

**Genetic variants of Retinoblastoma**

VARIANTS	Frequency	Avg Age	Bilateral *	?Transmission?
Sporadic (somatic mutation)	64%	3 mos.	NO	NO
Sporadic (germinal mutation)	21%		YES	YES
Familial*	5-10%	12 mos.	YES	YES
Chromosome deletion (13Q-)	<5%			

(\*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.

"OLD" GENETICS":

Familial cases are **autosomal dominant** (50% of offspring inherit)

"NEW" GENETICS:

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 develop 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  $<10^{-7}$  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.**

**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.

In familial cases autosomal dominant inheritance is mimicked by the inheritance of heterozygosity with subsequent gene inactivation:

**carrier      normal**

**RB rb X RBRB = 50% RB rb + 50% RB RB**

**Additional facts:**

\*Familial cases develop earlier (12 months) because only one gene has to be inactivated (1 "hit"-Knudson)

\*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.**

A 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.

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 in the pineal gland or parasellar region. Occurs bilateral or familial retinoblastoma. Fleurettes and Flexner-Wintersteiner rosettes may be observed in the intracranial tumor

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, on 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**

Three most common simulating lesions: **toxocariasis, PHPV and Coats' disease**

#### **Ocular Toxocariasis** (Nematode Endophthalmitis)

Ocular manifestation of visceral larva migrans- *Toxocara canis*

Unilateral, end of first decade

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 Vaculature*)

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
- Leaky retinal telangiectases, miliary aneurysms, adjacent capillary nonperfusion
- Massive retinal thickening by hard exudates
- Subretinal fluid rich in protein and lipid (foamy histiocytes, cholesterol clefts)
- 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
- Medulloepithelioma** (second most common primary pediatric IOT)
  - Symptomatic - age 4, diagnosed age 5
  - Arise 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
- Astrocytomas**
  - Tuberous sclerosis or NF- large tumors may be confused with retinoblastomas
  - Most patients with TSC have nonprogressive astrocytic hamartomas
  - Rare 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 bad 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 marbled pattern of skin pigmentation. Other systemic and ocular anomalies
- Retinal dysplasia**
  - Most cases trisomy 13, rare isolated cases in normal patients
  - Dysplastic rosettes are larger, contain multiple retinal layers

**Differential Diagnosis of Leukocoria**  
Retinoblastoma and Simulating Lesions (Pseudogliomas)

<b>Lesion</b>	<b>Unilateral</b>	<b>Bilateral</b>	<b>Age</b>	<b>Comments</b>
<b>Retinoblastoma</b>	X	YES	18 mo.	Calcium on ultrasound, CT
<b>Toxocariasis</b>	X	----	6-11 yr.	contact with puppies Negative ELISA excludes
<b>PHPV</b>	X	----	<b>At birth</b>	Eye typically microphthalmic with inward-drawn ciliary processes, iris shunt vessels
<b>Coats' Disease</b>	X	RARE	18 mo-18 yr. (end 1st decade)	2/3's male, ST quadrant, leaky telangiectatic vessels exudative RD with lipid, massive exudation
<b>ROP</b>		X	In infancy, but not congenital	Prematurity, Oxygen RX
<b>Retinal Dysplasia</b>		X	Congenital	Microphthalmia, most 13 trisomy
<b>Incontinentia Pigmenti</b> vascular		X	INFANCY	Bullous skin eruptions, Skin pigmentation. Retinal  abnormalities, Dental and CNS abnormalities; X-linked dominant (lethal in males) 2 0 retinal detachment
<b>Norrie's Disease</b>		X	Congenital	Males, X-linked recessive, Deafness, mental retardation Norrin (gene product)
<b>Medulloepithelioma</b>	X	--	4 yrs	"Diktyoma", benign and malignant; teratoid and nonteratoid. Teratoid tumors contain cartilage, muscle, brain, most ciliary body

**Other...**

Retinal Astrocytomas (Giant Drusen of ON, Tuberous Sclerosis)  
Colobomas  
Myelinated nerve fibers  
Congenital cataract  
Retinal detachment, vitreous hemorrhage, trauma,

**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  
enlarged muscles show foci of chronic nongranulomatous infiltration, secondary fibrosis.

Inflammation spares tendon, orbital fat.

Mast cells do not secrete excess MPS

**Idiopathic orbital inflammation (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)

**Other orbital inflammations and infections**

**Sarcoidosis (dacryoadenitis, S-sign)**

**Orbital cellulitis:** usually invades from sinus

**Mucormycosis** (phycomycosis, zygomycosis)

Large nonseptate hyphae visible on H&E, vascular invasion with thrombosis and necrosis, acute and chronic granulomatous inflammation

Acidotic patients ( e.g, poorly controlled diabetics), fungus invades from sinuses.

deferroxamine therapy in renal dialysis patients; eschar a late sign

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

**Allergic Fungal Sinusitis-** fungus grows in "allergic mucous", does not invade

**Vasculitides**

**Wegener's Granulomatosis**

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

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

**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**

**Angiolymphoid hyperplasia with eosinophilia**

**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 leukemic infiltrate (granulocytic 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 lymphomas. Most of these are low-grade lymphomas. The remainder are polyclonal lymphoid hyperplasias**

**Reactive Follicular Lymphoid Hyperplasias**

Polymorphic infiltrate with lymphocytes, plasma cells, eosinophils

Germinal centers with immunoblasts, tingible-body macrophages, mitoses confined to germinal center

T-cell rich ( $\geq 60\%$  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)

**More than half of ocular adnexal lymphomas are low grade small lymphocytic lymphomas. 78% are low-grade small or intermediate lymphocytic lymphomas. Many are *extranodular marginal zone lymphomas* (EMZL)- these also are called *MALT lymphomas*.**

**Most ocular lymphomas are diffuse ( 16% follicular).**

**Histologic classification of 69 ocular adnexal lymphomas (Knowles and Jakobiec)**

Small lymphocytic	31	45%
Small lymphocytic, plasmacytoid	8	11.6%
Intermediate lymphocytic	15	21.7%
Small cleaved	8	11.6%
Mixed small and large cell	2	2.9%
Large cell	5	7.2%
<b>Total higher grades</b>	<b>15</b>	<b>21.7%</b>
<b>Total small or intermediate</b>	<b>54</b>	<b>78.3%</b>

Essentially all orbital lymphomas are **monoclonal B cell tumors** composed of more than 60% B lymphocytes.

Monoclonal B cells express only 1 type of light chain (kappa or lambda)

Immunophenotypic (lymphocyte typing ) studies are best performed on fresh, unfixed tissue. **Flow cytometry must be performed on fresh tissue.**

### **Systemic Involvement\* in Ocular Lymphoid Tumors**

\*Prior, concurrent or subsequent (Knowles, Jakobiec, et al, Human Pathol 21: 595, 1990)

Conjunctiva	20%
Orbit	35%
Eyelid	67%
All sites	33%
Bilateral lesions	38%
Polyclonal ocular lesion*	29%
Monoclonal ocular lesion	33%

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

According to Knowles, Jakobiec et al "classifying ocular lymphoid lesions as benign or malignant histopathologically, and as monoclonal or polyclonal immunophenotypically is not useful in predicting eventual outcome including the occurrence of extraocular lymphoma."

In their series 29% of patients with polyclonal ocular lymphoid proliferations had a prior history of lymphoma, were found to have concurrent extraocular lymphoma when evaluated systemically, or subsequently developed systemic lymphoma.

The site of involvement and the cytologic type of lymphoma do correlate somewhat with systemic disease, i.e.....

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 small or intermediate lymphocytic ocular lymphomas are less likely to have extraocular lymphoma.

Patients with higher grades of ocular lymphoma are more likely to have extraocular lymphoma.

"The single most important prognostic factor in patients presenting with an ocular lymphoid infiltrate is the extent of the disease discovered after a thorough clinical staging at the time of initial presentation. 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)

**N.B.-Some of the preceding has not been confirmed by subsequent studies.**

**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, SPEP)

The workup should be repeated q 6 months x 5 years.

**Therapy**

**No systemic involvement- RADIOTHERAPY with eye shielding**

Low grade lesions- 1500-2000 rads

high grade lesion- 2000-3000 rads

**Extraocular (systemic ) lymphoma present- CHEMOTHERAPY**

Supplement with adjunctive ocular radiotherapy if ocular regression subtotal

References

Knowles DM, Jakobiec FA, McNally L et al: Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa ( Orbit, conjunctiva and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987, Human Pathology 21: 959-973, 1990.

Medeiros LJ, Harris NL: Lymphoid infiltrates of the orbit and conjunctiva: A morphologic and immunophenotypic study of 99 cases. Am J Surg Pathol 13: 459, 1989.

**Other Lymphoid Tumors**

**Plasma cell tumors-** myeloma, bone destruction

Lymphoplasmacytoid tumors- Waldenstrom's macroglobulinemia, Dutcher bodies

Hodgkin's disease

Burkitt's lymphoma

Mycosis fungoides: T-cell cutaneous lymphoma, convoluted cerebriform nuclei,

Pautrier abscesses

**Reactive Lymphoid Hyperplasia of the Uvea- probably MALT lymphoma**

**Myeloid or Granulocytic Sarcoma** (leukemic infiltrate. "chloroma")

Suspect in children, R/O with Leder esterase stain

May present when peripheral blood normal

Major cause of bilateral proptosis in children

**ORBITAL TUMORS**

**A different spectrum of orbital tumors occurs in children and adults**

Category	Children	Adults
<b>congenital</b>	Dermoid cyst, teratoma	
<b>vascular</b>	Capillary hemangioma Lymphangioma	Cavernous hemangioma Hemangiopericytoma

<b>neural</b>	Plexiform neurofibroma Optic Nerve Glioma	Schwannoma Optic nerve meningioma
<b>mesenchymal</b>	Rhabdomyosarcoma	Fibrous histiocytoma
<b>hematopoietic</b>	Granulocytic sarcoma Histiocytoses	Lymphomas
<b>metastatic</b>	Neuroblastoma, Ewing's Sarcoma, Wilms' Tumor	Carcinomas (lung, breast)
<b>other</b>		Epithelial tumors of lacrimal gland

### Well-circumscribed orbital tumors

Cavernous Hemangioma  
Hemangiopericytoma  
Schwannoma  
Fibrous Histiocytoma  
Solitary Fibrous Tumor  
Epithelial Tumors of the  
Lacrimal Gland

### 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

#### Orbital Varix

#### Arteriovenous Malformations

#### Venous Angiomas

#### Glomus Tumor

#### Vascular Leiomyoma

#### Klippel-Trenaunay-Weber Syndrome

#### Blue Rubber Bleb Nevus Syndrome

#### Intravascular Papillary Endothelial Hyperplasia

#### Angiosarcoma (Malignant Hemangioendothelioma)

#### Kaposi's Sarcoma

### Mesenchymal Tumors

#### Fibrous Histiocytoma (fibroxanthoma)

Most common mesenchymal tumor of adults, mean age 43 (4-85)  
Orbit is site of predilection, superior (43%), nasal  
Fibroblasts and histiocytes, storiform pattern

Benign, malignant and locally aggressive variants, **excise totally!!**

**Solitary fibrous tumor** - pattern-less pattern, CD34+ (similar to fibrous  
histiocytoma in many respects)

#### Fibroblastic Tumors

#### Nodular Fasciitis

#### Fibroma

#### Juvenile Fibromatosis

## **Fibrosarcoma**

### **Myxoma**

#### **Tumors Of Adipose Tissue**

Orbital fat inert-least likely to spawn tumors

**Herniation Of Orbital Fat**-Some cases may be pleomorphic lipomas with floret cells- controversial topic

**Atypical lipoma** and **liposarcoma**- rare!!

#### **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**-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 (rare lesions)

(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 tumor, mucoepidermoid carcinoma rare, oncocytomas and acinic cell tumors very rare

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, 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)

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

**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 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.

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

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

**Adenocarcinoma de novo**

Poorly differentiated, older men (mean age 56)

Management, prognosis similar to MMT

**Mucoepidermoid Carcinoma**

Rare, better prognosis than other epithelial malignancies

Exenteration, or wide local excision

"Paving stone" squamous elements and mucous-producing goblet cells.

**Orbital Tumors In Children**

**Dermoid Cyst-(Cystic Dermoid)** epidermal inclusion cyst with epidermal appendages associated with lining epithelium; nasal lesions may have conjunctival epithelial differentiation

**Congenital Orbital Teratoma**

**Vascular Tumors**

**Capillary Hemangioma**

CT: poorly circumscribed, infiltrating, without capsule

**Lymphangioma-** recent controversy about terminology- presence of lymphatic endothelium recently confirmed.

Vascular channels larger and more variable than those in cavernous hemangioma, contain lymphoid foci, may enlarge suddenly- lymphoid hyperplasia secondary to URI; intralesional hemorrhage- chocolate cyst formation

**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 connective tissue trabeculae. Cells large, polygonal with abundant eosinophilic cytoplasm. Translocations t (92:13) and t (1:13)

**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 embryonal**, arise from pluripotential mesenchyme, not muscle

Confirm diagnosis with immunohistochemistry (muscle specific actin, desmin)

TEM: 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, Langerhan's histiocytosis, 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

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"

**Sinus Histiocytosis With Massive Lymphadenopathy**

**Metastases**

**Neuroblastoma**

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

**Ewing's Sarcoma**

Highly malignant (95% fatal) bone marrow tumor

## Secondary Orbital Tumors

**Metastases**

**Breast carcinoma- "Indian file" pattern, signet ring cells;** sclerosing type may produce enophthalmos

**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 ( $\alpha$  B 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 meningotheial 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 meningotheial 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)

Meningotheial 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

**Astrocytic Hamartoma**

**Melanocytoma**

**Medulloepithelioma**

**Angiomas (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 involving macula

Origin of fluid uncertain ( No leakage on IVFA): CSF versus vitreous origin

### **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 Syndrome**

Severe visual loss, funnel-shaped optic nerve with central connective tissue, surrounding elevated annulus of disturbed chorioretinal pigment, vessels emerge from disk edge

### **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 differential between intraocular and intracranial pressures. (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, cytooid bodies

### **Optic Disk Drusen**

Not related to giant disk drusen or drusen of Bruch's membrane

Sporadic or familial, seen 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**

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 optic atrophy- transmitted by mitochondrial DNA)**

### **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

Retrolaminar cavernous spaces contain hyaluronic acid (? from vitreous)

No gliosis or histiocytic reaction

**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 constituting 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. Lamellar 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

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**

Corneal and anterior segment enlargement, limbal ectasia

Haab's striae (Descemet's 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: dysembryogenesis, 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,

Heredity important, poorly understood

#### **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  
Injection, pain, steamy cornea, fixed dilated pupil, GI sx, N&V  
Functional pupillary block or plateau iris mechanisms  
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** (sphincter 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')

o

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, iridovitreous 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 (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

**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

**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 2 PC IOL'S

**Pseudoexfoliation 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 zonolysis

**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, Erdheim-Chester disease

#### **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's membrane

**Inflammatory pannus**- subepithelial fibrovascular and inflammatory ingrowth with **destruction of Bowman's membrane** (trachoma)

**Degenerative pannus**: fibrous tissue interposed between base of epithelium and intact Bowman's 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. Tractional 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's 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's 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's 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**

### **General Complications**

"Surgical confusion"- misdiagnosis, faulty technique

Cataract surgery

Expulsive hemorrhage

Vitreous loss, vitreous incarceration, vitreous wick

Detachment of Descemet's 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 edema**

Breaks in Descemet's 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**

#### **Post-traumatic pigmentary retinopathy (pseudo-RP)**

**Comotio 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, retroretinal 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
- Vitreous membranes: tractional retinal detachment
- Pre- and retro-retinal membranes- fixed folds,
- PVR-contraction of membranes due to myofibroblasts

### **Radiation**

#### **Cavernous Hemangioma of the Retina**

Light bulbs with fluid level, some patients have CNS and skin lesions.

### **Premalignant Eyelid lesions**

#### **\*Actinic Keratosis (Premalignant Lesion)**

#### **Bowen's disease**

Sharply demarcated red scaly plaques, fair complexion, avg. age 55  
Intra-dermal 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 pigmentary 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, epiptarsus, 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**

#### **\*Endothelial Decompensation**

##### **Aphakic bullous keratopathy (ABK)**

Descemet's membrane thin without guttae, marked endothelial atrophy

##### **Pseudophakic bullous keratopathy (PBK)**

Descemet's membrane thin without guttae, marked endothelial atrophy

##### **Fuchs' dystrophy**

Descemet's thickened with guttate excrescences

#### **Keratoconus**

Old herpetic keratitis

Acute keratitis

Old interstitial keratitis

Corneal dystrophies other than Fuchs -extremely rare!!