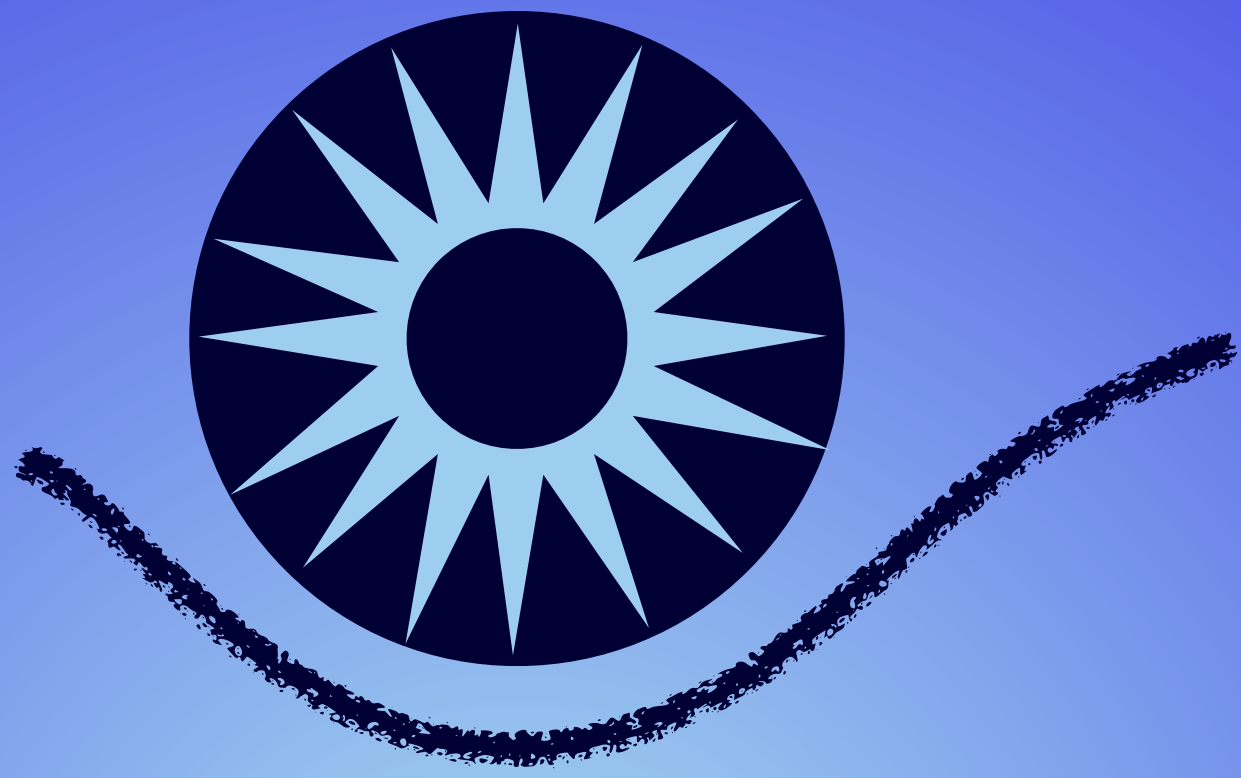
Ophthalmology PG Exam Notes



NOTES

2020

Retina

Dhaval Patel MD

I notes 2020

(Ophthalmology PG Exam Notes)

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This is a compilation effort from my Post-graduation preparation notes and multiple other sources. Whole of the Manual is now revised from advices received from students from all over the world. Any contributions or comments are welcomed in the effort to improve this Manual.
This manual is made to serve the Exam purpose and as a Handy Reference tool only.

If you are reading this, just drop a comment or critic at:
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Dedication

To The **GOD**, the Almighty, for Giving me Imagination & Curiosity which keeps me always learning, for Giving me fine skills from which I can do my best for patients…

To My Grand-Mother; **Tejaben Patel**, for Training my childhood in such a disciplined way which has helped me to become what I am today…

To My Parents; **Bharat & Sudha Patel** and My Parents-In-Law; **Anil & Neela Patel**, for Trusting me, Motivating me and Helping me in my difficult times…

To My Wife; **Dr Dhara Patel**, for Believing in my strengths, Always supporting me in my all ventures, Bearing with me when I don't give her enough time while I am busy in my all ongoing projects and many more innumerable things which I always forget as usual…

To My Brother; **Dr Keyur Patel**, for helping me getting all the knowledge regarding Medical Science in the other continent…

To My Brother-In-Law; **Raj Patel**, for Bringing out Computer Science Kid within me and Teaching me in-numerous tips and tricks while dealing with computers…

To My Many **Friends and Relatives**; naming them all is not possible but they have helped me to Refine my life in one or the other way…

To All the **Ophthalmologists;** for pouring their knowledge and skills in this field which has now become one of the finest speciality in Medical field…

To **Patients;** for creating a demand which keeps all the ophthalmologists motivated to keep inventing and innovating methods, models and devices for their benefits…

I NOTES 2020

Ophthalmology PG Exam Notes

Retina

If I have seen further than others,
It is by standing upon the shoulders of giants.
-Isaac Newton

Thank you GOD !

When I compiled first edition of this **iNotes** Manual in 2014, It was simple collection of few notes (*very much incomplete!*) which I prepared for my Post-graduate Ophthalmology Exams at AIIMS, New Delhi. Since then I am regularly receiving emails and messages regarding usefulness of these notes as a study material for Post-graduate students all across the world.

For last few years, I am getting emails asking that if I am going to bring any updated version of my **iNotes** as ophthalmology has advanced a lot in last 10 years. Hence from last one year I have started reading newer edition of books, recent question papers, gathered notes and presenting to you as completely new version as **iNotes 2020**.

In this edition of iNotes, I have tried to include clinical, practical and surgical tips which is going to be used in your future practice also so that this manual can be a handy book for you as a future reference too.

Also Remember, this is a "**Manual**" and not a "Complete Book", and Just like most of others, it is also far from Complete. One of the best way to utilise this for your exam preparation is to use this as a reference and make your personal manual by adding your own notes and topics asked in your university.

My Best wishes and Good luck to you All !!

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10-10–2020

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Anatomy and Physiology

RPE

- Highly specialized neuroectodermally derived pigmented cells
- **3.5 × 10^6** RPE cells – cuboidal monolayer
- The apical microvilli of the RPE cells interdigitate with the OS of the photoreceptors, while the RPE basal side is attached firmly to the underlying Bruch's membrane
- Brown color of the RPE is imparted by its melanin granules
- **Highest concentration of pigment is found in the peripheral retina**, the lowest in the macular
- **Specialized functions of the RPE**
  - ***Absorption of light:*** RPE cells possess the enzymatic mechanism to convert vitamin A to 11-*cis*-RAL as well as the mechanism to deliver it to the photoreceptors
  - ***Phagocytosis of rod outer segments:*** continuously shed OS → Binding of the rod OS is followed by invagination of the plasma membrane around the OS fragment, leading to its ingestion into a phagosome.
  - ***Role in visual cycle:*** reaction of photons with light-sensitive pigments
  - ***Role in maintaining avascular outer retina***: antiangiogenic activity of PEDF
  - ***Immune privilege:*** tight junctions between RPE; lack of lymphatic drainage from subretinal space; low levels of major histocompatibility antigen expression
  - ***Transport of nutrients, ions, and water:***
  - ***Secretion of cytokines and growth factors***

Muller Cell

- Retina contains two types of macroglial cell: astrocytes and Müller cells
- Astrocytes: crucial role in retinal vascularization; the localization of these cells in the mature retina is restricted to the nerve fiber and ganglion cell layers
- Heinrich Müller (1820–1864)
- Radial glial cells which span the entire thickness of the neural retina, from the subretinal space to the vitreal surface
  - Outer stem process: surround the photoreceptor inner segments
  - Inner stem process: funnel-shaped endfoot and forms ILM
  - Lateral processes: sheaths around the neuronal synapses
- 8–10 million regularly arranged Müller cells
- ***Functional retinal columns:*** Each Müller cell constitutes the core surrounded by one cone per Müller cell and up to 10 rods, as well as 6/4 inner nuclear layer neurons, and 2.5/0.3 ganglion cell layer neurons
- **Functions of Muller Cell**

- Light guidance
- Recycling of cone photopigments
- Regulation of the synaptic activity by neurotransmitter uptake
- Production of neurotransmitter precursors
- Trophic support of photoreceptors and neurons
- Antioxidative support of photoreceptors and neurons
- Removal of carbon dioxide
- Regulation of the extracellular pH
- Spatial potassium buffering
- Water clearance
- Contribution to edema development and resolution
- Regulation of the blood–retinal barrier
- Mediation of neurovascular coupling
- Regulation of the extracellular space volume
- Responses to mechanical stress
- Regulation of neuronal activity by release of gliotransmitters

Mechanisms of Normal Retinal Adhesion

- No anatomic junctions bridge the mammalian subretinal space
- Mixture of anatomic, physical, and metabolic factors
- ***Adhesive force:*** 100–180 dyn/cm in rabbit
- ***Temperature:*** adhesiveness drops rapidly postmortem at 37 °C, but remains near control levels for hours at 4 °C
- ***Ionic environment:*** calcium appears to be a necessary element for the maintenance of normal adhesiveness in the living eye
- ***Mechanical forces outside the subretinal space:*** fluid and vitreous pressure
  - ***Fluid pressure:***
    - Fluid is driven passively from vitreous to choroid by both intraocular pressure and the osmotic pressure of the extracellular fluid in the choroid.
    - ***Hydrostatic:*** RPE can pump fluid from the subretinal space to choroid at a very high rate (about 0.3 μL/h/mm^2 of RPE) comparable with that of aqueous secretion.
    - Resorption of detachments showed a rate of 0.11 μL/h/mm^2 of RPE = 3.5 mL of fluid per day which explains why a rhegmatogenous detachment can settle within 24 hours
    - ***Osmotic:*** intravenous injection of mannitol will increase retinal adhesiveness by roughly 50% within 1–2 hours of injection

- ***Vitreous support***
  - status of the gel → retinal hole in a young eye is blocked by gel pressure and can seal uneventfully; a hole in an old eye is more likely to allow fluid to enter the subretinal space and cause detachment
- ***Weight of Retina***

Mechanical forces inside the subretinal space

- ***Mechanical interdigitation***
  - RPE microvilli wrap closely around the tips of the outer segments, and this connection is strong enough to allow for daily phagocytosis of outer-segment fragments as the photoreceptors renew their disc material
  - Interdigitation begins to develop within 3 days of reattachment, but retinal adhesiveness does not return to normal until 5–6 weeks after reapposition
- ***Interphotoreceptor matrix properties***
  - Composed largely of proteins, glycoproteins, and proteoglycans
  - Berman
  - Cones: matrix stained by peanut agglutinin (**PNA**)
  - Rods: matrix stained by wheatgerm agglutinin (**WGA**)
  - Cone or rod matrix sheaths to serve as a structural bond between retina and RPE
- ***Metabolic factors***
  - Just 1 minute of ocular ischemia in living rabbits weakens adhesion dramatically
  - Metabolic inhibitors: cyanide, dinitrophenol → decreases adhesion
  - Transport inhibitors: ouabain, **Acetazolamide** → enhances adhesion

Pharmacologic modification of adhesion

- Mannitol: 50% increase in retinal adhesiveness
  - 2-3 hours
  - Fluid movement “pulling” the retina against the RPE
  - Dehydration of the IPM, which strengthens bonding characteristics
- Acetazolamide: 30–45% increase in retinal adhesiveness
  - 3-4 hours
  - Only occur when the RPE is basically healthy and receptive to metabolic stimulation
  - Not useful in: RD, CSR, DME, CME
  - Useful in: intraretinal cysts, retinitis pigmentosa, X-linked juvenile retinoschisis, enhanced S-cone syndrome and sometimes macular epiretinal membrane formation
- Cold temperature and ouabain: increase retinal adhesiveness

- Ionic changes: removal of local calcium and magnesium ions, or lowering the pH, causes a dramatic fall in retinal adhesive force

- ***Recovery of adhesiveness without retinopexy***
  - Restoration of normal adhesive strength requires 4–6 weeks
- ***Effects of retinopexy***
  - Laser photocoagulation produces a bond that approaches normal adhesive strength within 24 hours, possibly from local effects such as fibrin formation → reaches levels roughly twice normal by 2–3 weeks
  - Cryotherapy, however, weakens adhesion for the first week, after which the adhesive force rises
- **Pathophysiology of serous detachment**
  - A defect in the RPE barrier that allows access to the subretinal space
  - A source of fluid pressure, to move fluid in
  - An impairment of outward fluid transport (or a broad area of leakage), so fluid spreads and persists in the subretinal space

Bruch's Membrane

- Thin (2–4 μm), acellular, five-layered extracellular matrix located between the retina and choroid
- Anteriorly to the ora serrata, interrupted only by the optic nerve
- 1844, **Carl Ludwig Wilhelm Bruch**: lamina vitrea
- 6–7 weeks → inner layer is composed of ectodermal tissue and its outer layer is composed of mesodermal
- **Hogan**'s five-layer nomenclature for Bruch's membrane
  - RPE basal lamina (RPE-BL)
  - Inner collagenous layer (ICL)
  - Elastic layer (EL)
  - Outer collagenous layer
  - Choriocapillaris basal lamina (ChC-BL)
- **Gass** proposed a three-layer system (no basal laminas)
- **Changes with Ageing**
  - Profound accumulation of lipids
  - **Bird and Marshall's hypothesis**: lipophilic barrier in Bruch's blocked a normal, outwardly directed fluid efflux from the RPE (as opposed to leakage from CNV).
  - Fluorescent marker, **filipin**, which binds the 3β-hydroxy group of sterols to reveal unesterified (free) cholesterol (UC) or EC depending on tissue pretreatment
  - Bruch's membrane lipoproteins are found to be EC-enriched

- Bruch's membrane thickens throughout adulthood (20–100 years) two to threefold under the macula

Function of Bruch's membrane

Structural role

- Contributes to load bearing → withstands IOP and returns to its original shape when IOP decreases.
- Stretches to accommodate changes in choroidal blood volume
- Spring that pulls the lens during accommodation
- Elasticity in Bruch's membrane choroid preparations to be **7–19 MPa**
- Modulus of elasticity of human Bruch's membrane–choroid complex increases ($P < 0.001$) at a rate of ~1% per year

Transport role

- Hydraulic conductivity: (Lp)
  - RPE pumping rates: 11 μL/h/cm^2
  - ICL is responsible for most of the flow resistance in Bruch's membrane
  - L_p decreased significantly with age.
  - L_p of macular Bruch's membrane dropped more rapidly with age than did that of the periphery, consistent with an accelerated process occurring in the macula. (due to lipid deposition in AMD)
  - Decreased L_p and increased resistivity of Bruch's membrane with aging are closely related to the age-related accumulation of lipids, primarily EC
- Permeability to solute transport:
  - **Peclet number**: relative magnitude of convection of a species due to bulk flow to that of diffusion

Pathology

- ***AMD lesions***
  - Extracellular accumulation in tissue compartments anterior to the ICL → drusen and basal deposits
- Drusen
  - Donders and Wedl → "colloid bodies" (*Colloidkugeln*) or "hyaline deposits
  - Müller in 1856→ Drusen
  - Yellow-white deposits 30–300 μm
  - More numerous in peripheral retina than in macula
  - Theories for druse formation
    - Transformation of the overlying RPE and
    - ***Deposition of materials on to Bruch's membrane***.
  - Constituents: lipids → EC and UC, in Addition to phosphatidylcholine, other phospholipids, and ceramides

- Basal linear deposit BlinD
  - Thin (0.4–2 μm) layer located in the same sub-RPE
  - Rich in solid lipoprotein particles and lipid pools
  - BlinD and Druesen are alternate forms (layer and lump) of the same entity
- Basal laminar deposit BlamD
  - Small pockets between the RPE and the RPE-BL in many older normal eyes or a continuous layer as thick as 15 μm in AMD eyes
  - Containing laminin, fibronectin, type IV and type VI collagen
- Subretinal drusenoid debris SDD
  - Enriched in UC, apoE, vitronectin, and complement factor H
  - Called reticular drusen in a fundus view
- ***Neovascular AMD***
  - Angiogenesis along vertical and horizontal vectors: vertically across Bruch's membrane, and laterally external to the RPE (CNV1), subretinal space (CNV 2), or into the retina (CNV 3)
  - VEGF stimulation of choriocapillaris endothelium, compromise to Bruch's membrane, and participation of macrophages
- ***Angioid streaks***
  - Ruptures in Bruch's membrane by excess calcification of the elastic layer
  - PXE → mutations of a hepatically expressed lipid transporter ABCC6
  - abetalipoproteinemia gene (MTP) deficiency
- ***Thick basal laminar deposits***
  - AD: Sorsby fundus dystrophy, late-onset retinal degeneration (LORD) and malattia leventinese-Doyne honeycomb retinal dystrophy (ML-DH)

Vitreous

- 98% water and 2% structural proteins, extracellular matrix components, and miscellaneous compounds.
- ***Collagen***
  - Type **II** collagen comprises 75%
  - Type **Investigations** collagen accounts for up to 15% → linked with chondroitin sulfate glycosaminoglycan
  - Minor collagens of vitreous is type **XVIII**, progenitor of **endostatin**, a potent inhibitor of angiogenesis
  - Following vitrectomy, a type II procollagen is secreted. **(does not form gel)**
- ***Hyaluronan***
  - Synthesized by hyalocytes, the ciliary body, and/or Müller cells
  - Large polyanion

- ***Chondroitin sulfate***
  - Versican Wagner syndrome
- ***Noncollagenous structural proteins***
  - Fibrillins
  - Opticin: formerly **vitrican,** binds heparan and chondroitin sulfates

- ***Vitreoretinal interface***
  - **Posterior vitreous cortex**
    - 100–110 μm thick
    - **Vogt's or Weiss's ring:** when peripapillary tissue is torn away during PVD and remains attached around the prepapillary hole
    - **Hyalocytes** are mononuclear cells embedded in the posterior vitreous cortex 20–50 μm from the ILL posteriorly
    - **highest density**: vitreous base > posterior pole > equator
  - **The ILL of the retina**
    - type IV collagen, type VI collagen, which may contribute to vitreoretinal adhesion, and type XVIII, which binds **opticin**. Opticin binds to heparan sulfate, contributing to vitreoretinal adhesion
      - lamina rara externa
      - lamina densa
  - **Intervening extracellular matrix**
- ***Retinal sheen dystrophy:*** This ILL dystrophy has cystic spaces under the ILL and in the inner nuclear layer, and numerous areas of separation of the ILL from the retina with filamentous material
- **Variations at Vitreous Base**
  - Ora bays
  - Meridional folds
  - Meridional complexes
  - Peripheral retinal excavations
  - Retinal tufts: Noncystic retinal tufts, Cystic retinal tufts, Zonular traction tufts
  - Spiculate and nodular pigment epithelial hyperplasia
  - Retinal lattice “degeneration”
  - White-with-pressure, white-without-pressure
  - Verruca

Age-Related Vitreous Degeneration

- ***Liquefaction (synchysis)***

- After age 40: decrease in the gel volume and a concurrent increase in the liquid volume of vitreous
- Lacunae: pockets of liquid vitreous
- Single, large pocket forms, the terms “bursa” or “precortical pocket
- 20 % of vitreous is liquid in adult and by the age of 80–90 years more than half the vitreous is liquid.
- Changes in collagen or the conformation of HA with subsequent cross-linking of and aggregation of fibrils into bundles

- ***Collapse (syneresis)***
  - Advanced liquefaction with thickening and tortuosity of vitreous fibers
- ***Posterior vitreous detachment***
  - PVD begins at the posterior pole, perhaps in the perifoveal region
  - The attachments of the posterior hyaloid to the foveal center and optic disc are the last to be released
  - Innocuous PVD: clean separation between the ILL of the retina and the cortical vitreous
  - 53% after 50 years and 66% after 60
  - Sudden onset of “floaters” heralds the onset of PVD.
  - Incidence of retinal tears in patients with acute symptomatic PVD varies from 8 to 15%
  - 18% of eyes with retinal breaks developed retinal detachment. Risk factors for progression included fresh, symptomatic, horseshoe-shaped tears; breaks suggestive of the presence of subclinical retinal detachment (RD); and pseudophakia/aphakia.

Anomalous PVD (APVD)

- **Partial thickness:** VITREOSCHISIS (splitting of the posterior vitreous cortex with forward displacement of the anterior portion of the cortex, leaving the posterior layer attached to the retina) → **Macular Hole (centrifugal) or Pucker (centripetal)**
- Full thickness but partial PVD: VMTS, VPT or Retinal tears
- Effects
  - Vitreous: vitreoschisis
  - Retina: Retinal holes
  - Macula: vitreomacular traction syndrome, exudative ARMD, CME, Macular cysts, Macular holes
  - Optic Disc: exacerbating neovascularization in proliferative diabetic vitreoretinopathy
- Macular hole opercula are rarely composed of retinal tissue, hence the name pseudo-operculum.

Vitreoretinal Changes after Lens Extraction

- ***Structural:*** Opacification, APVD, Vitreous incarceration in the wound and vitreoretinal traction
- Reduction of vitreous HA concentration results in decreased viscosity and shock absorption
- PVD:
  - 84% following ICCE
  - 76% following ECCE and surgical capsular discussion
  - 40% following ECCE with an intact posterior capsule

Hereditary and Congenital Diseases

Retinitis Pigmentosa

- Previous terms: tapetoretinal degeneration" (by Leber in 1916), "primary pigmentary retinal degeneration," "pigmentary retinopathy," and "rod–cone dystrophy
- Typical RP: **isolated**
- Syndromic RP: association with systemic disease
- **1 : 5000** worldwide
- Use of the term "retinitis pigmentosa" attributed to **Donders** in 1855

Genetics

- Sporadic 39%, AD 20%, AR 37%, XL 4%
- Consanguinity 30-40%
- Severity: XL> AR> AD
- 45 genes cause nonsyndromic RP
- ***Autosomal dominant RP***
  - 15% and 35% of all cases of RP
  - Codon 23 (Pro23His) of the rhodopsin gene: chromosome 3q
  - P*eripherin*/*rds* gene
  - Mutations in *PIM1*, on chromosome 7p
- ***Autosomal recessive RP***
  - More severe, progress more rapidly, and present earlier than the AD forms
- ***X-linked RP***

Typical retinitis pigmentosa

- **Massof and Finkelstein Types**
  - **type I RP**, which is associated with *early diffuse loss of rod sensitivity* relative to cone sensitivity and childhood-onset nyctalopia
  - **type II RP**, associated with regional and *combined loss of both rod and cone* retinal sensitivity and adult-onset nyctalopia
- **Lyness Types**
  - **Subgroup D** had diffuse loss of rod function and night blindness before the age of 10.
  - **Subgroup R** had regional loss of rod function, and most of these patients were unaware of night blindness until after the age of 20
- Clinical Features
  - Nyctalopia: hallmark symptom, not pathognomonic

- Visual field loss: hallmark, progressive contraction of the visual field, **4.6%** of the remaining visual field was lost per year
- Central vision loss: CME, diffuse retinal vascular leakage, macular preretinal fibrosis, and RPE defects in the macula
- adRP are more likely to retain central vision than arRP or xlRP
- Color vision defects
- Photopsia and other symptoms
- Fundus appearance
  - Attenuated retinal vessels, mottling and granularity of the RPE, bone spicule intraretinal pigmentation, and optic nerve head pallor
  - **RP sine pigmento or paucipigmentary RP**: no longer considered a specific subtype of RP but a stage through which many, if not most, patients with RP pass.
  - Earliest features are attenuation of retinal vessels and the appearance of fine mottling or granularity of the RPE
  - Intraretinal, bone spicule pigment formations represent migration of pigment into the retina from disintegration of RPE cells with accumulation in the interstitial spaces surrounding retinal vessels.
  - Yellowish-white metallic tapetal-like reflex or sheen can occasionally be observed in women who are carriers for the X-linked form of RP
  - **"Golden ring"** or yellowish-white halo can often be seen surrounding the optic disc in early RP. As disease progresses, this golden ring is replaced with peripapillary mottling, hyperpigmentation, and atrophy of the RPE.
  - Presence or absence of macular RPE defects is of significant prognostic importance with regard to retention of visual acuity over the next 5 years
- Vitreous abnormalities
  - Fine, dust-like pigmented cells
  - Complete posterior detachment of the vitreous
  - "Cotton-ball" opacities
  - Interwoven filaments in the retrocortical space
  - Spindle-shaped vitreous condensations
- Anterior-segment abnormalities
  - Cataracts: posterior subcapsular
  - Keratoconus
  - Glaucoma
- Refractive status
  - High myopia and astigmatism

- ***Psychophysical findings***
  - Perimetry

- Most reliable method of quantifying real change in visual deficit
- Relative scotomas in the midperiphery, between 30 and 50°
- Ring scotoma
- **German adaptive thresholding estimation (GATE):** new fast thresholding algorithm, in time limit of SITA, but full field

✣ Dark adaptometry
- Exposure to a strong adapting light → placed in the dark:
  - Cone system, reaching a plateau in about 5 minutes
  - Rod system 2nd plateau at 30 min

✣ Retinal densitometry (fundus reflectometry)
- Difference between light shone into the eye and light reflected out of the eye.

✣ Electrophysiology
- Karpe: 1945: ERG was "extinguished" in RP.
- Arden: 1962 EOG
- Delays in the implicit time for cone-mediated 30-Hz flicker responses

✦ ***Imaging modalities in RP***

✣ Fundus photography/fluorescein angiography
- **Hyperfluorescence in areas of RPE atrophy** and can highlight areas of CME
- Transmission defects

✣ Autofluorescence
- Perifoveal **ring of increased autofluorescence within the macula**, which denotes the border between functional and dysfunctional retina
- Near-infrared autofluorescence (**NIA**) has also been used to image melanin present in the apical tips of the RPE

✣ Optical coherence tomography
- CME, ERM

✣ Adaptive optics scanning laser ophthalmoscopy

✦ ***Classification***

✣ Subdivision by inheritance type
- arRP
- adRP
- X-linked recessive trait (X-linked RP)

✣ Subdivision by molecular defect
- Null alleles
- Dominant-negative alleles
- Toxic gain of function

- Distribution of retinal involvement
  - **RP sine pigmento** – RP without signs of intraretinal pigmentation, can simulate fundus albipunctatus and retinitis punctata albescens
  - **Sector RP**: first described by Bietti,
  - **Pericentral RP**: loss of visual field typically occurs between **5 and 15°** from fixation
  - **Unilateral RP**: mostly acquired rather than genetic unilateral
    - Genetic: carrier state for X-linked RP, somatic mosaicism of a dominant gene for RP
    - In Acquired, MC is diffuse unilateral subacute neuroretinitis or **DUSN**

Complicated retinitis pigmentosa

- ***Systemic associations***
  - Greater than normal risk for **thyroid** disease
  - Mild to severe **hearing loss** as adults
  - Ear infections, sinusitis, and chronic recurrent respiratory tract infections
- ***Usher syndrome***
  - Von Graefe in 1858
  - **Charles Usher** for the appreciation that this condition was familial and represented a distinct entity
  - **Autosomal recessive deafness** (most commonly congenital) with retinopathy indistinguishable from typical RP
  - **Most common of the syndromes** associated with RP and accounts for about 18% of all patients with RP
  - **Type 1**, with profound congenital sensorineural deafness and resultant prelingual deafness or severe speech impairment, vestibular symptoms, and childhood-onset retinopathy
  - **Type 2**, with congenital partial, nonprogressive deafness, absence of vestibular symptoms, and **milder, later-onset** retinopathy.
  - The least common is **type 3** Usher syndrome, which is characterized by progressive deafness starting late in the **second to fourth decades**, adult-onset retinopathy, and hypermetropic astigmatism.
  - Another variant, **Hallgren syndrome**, was defined as congenital progressive deafness, vestibular ataxia, and retinopathy

Differential Diagnosis

- ***Cone–rod and cone dystrophy (CRD)***
  - **Early loss of visual acuity and color vision**, with subsequent progressive peripheral visual field loss (5 and 30° from fixation)

- Marked reduction or absence of cone ERG responses in the presence of quantitatively less reduction in rod responses
- Gene *GUCY2D* for guanylate cyclase-activating protein-1 (**GCAP-1**)

- ***Leber congenital amaurosis/severe early childhood onset retinal dystrophy (SECORD)***
  - Autosomal recessive >> AD
  - 1869, Theodor Leber
  - Severely visually impaired before age 1 year, with nystagmus, poor pupillary reflexes, either normal or abnormal fundus appearance
  - Abnormal or absent ERG
  - **Eye-rubbing – the oculodigital sign** – is a common association
  - Two types
    - **Uncomplicated LCA** is described as congenital blindness, nystagmus, and high **hyperopia** with extinguished ERG responses
    - **Complicated LCA** is used to group together cases of LCA associated with other ocular or systemic features
  - **Retinal abnormalities**: macular coloboma, "salt and pepper" retinopathy, retinitis punctata albescens, and nummular pigmentation
  - 29% keratoconus
  - Systemic: deafness, renal anomalies, infantile cardiomyopathy (**Alström syndrome**), hepatic dysfunction and skeletal abnormalities, Neurologic abnormalities are the most common
- ***Bardet–Biedl syndrome***
  - BBS or Laurence–Moon–Bardet–Biedl syndrome
  - **5 cardinal features**: **retinopathy** 90-100%, **polydactyly** 75%, and **congenital obesity**, **mental retardation** 85% and **hypogenitalism** 50%
  - Macular wrinkling, preretinal membrane formation, and leakage on fluorescein angiogram from paramacular capillaries
  - ERG may show a rod–cone loss
  - Absence of pigmentary deposits
  - Nonocular: renal abnormalities are the most common
- ***Refsum syndromes***
  - **IRD**:
    - Disorder of peroxisomal biogenesis that presents during infancy
    - Nystagmus, poor vision, retinal degeneration with
  - Adult Refsum disease:
    - Disorder of a single peroxisomal enzymatic function
    - Cataract, miosis with poor pupil dilation, and retinopathy

- Phytanic acid levels in blood and urine are always very high due to a deficiency of phytanic acid oxidation

- ***Neuronal ceroid lipofuscinosis (Batten's disease)***

Pseudo-Retinitis Pigmentosa

- ***Retinal inflammatory diseases***
  - Rubella retinopathy
  - Syphilis
  - Infectious retinitis: toxoplasmosis or herpes
- ***Autoimmune paraneoplastic retinopathy***
  - **Cancer-associated retinopathy (CAR):**
    - Small-cell (oat-cell) carcinoma of the lung or small-cell undifferentiated cervical carcinoma
    - First autoantigen in the human retina identified with a CAR is **recoverin**
    - ERG is extinguished
  - **Melanoma-associated retinopathy (MAR):**
    - A-wave amplitude is normal, and the b-wave amplitude is severely subnormal, distinguishing this form of paraneoplastic retinopathy from CAR
    - Night blindness associated with "shimmering lights"
    - Loss of function subserved by magnocellular cells
- ***Drug toxicity***
  - Thioridazine: bind to melanin and concentrate in the uveal tract and RPE, higher than 800 mg/day
  - Chlorpromazine: binds to melanin
  - Hydroxychloroquine: dosage is greater than 6.5 mg/kg per day for > 5 years
  - Quinine:
- ***Pigmented paravenous retinochoroidal atrophy***
  - 1937 as retinochoroiditis radiate
  - Pigmentary changes are closely associated in distribution with retinal veins
  - ERG is generally normal, EOG is abnormal
- ***Traumatic retinopathy***
  - Commonest acquired retinopathy that is confused with RP
- ***Diffuse unilateral subacute neuroretinitis***
  - Previously called "unilateral wipe-out syndrome"
  - Raccoon nematode (*Baylisascaris procyonis*)
  - *Toxocara canis*

- Signs of retinal degeneration (mottling, edema, narrowing of retinal vessels).
- *Management*
  - Retinal laser photocoagulation
  - Vitrectomy with surgical removal of the subretinal nematode
  - Oral tiabendazole or ivermectin is indicated when vitritis obscures retinal detail

- ***Grouped pigmentation of the retina***
  - "Bear-track" pigmentation
  - CHRPE: FAP or Gardner syndrome

Treatment

- ***INCURABLE but not UNTREATABLE***
- appropriate correction of refractive error and access to low-vision aids
- Periodic visual field examinations with compassionate explanation of visual field defects
- Cataract extraction
- CME: CAIs
- **Vitamin A supplements**: 15 000 IU/day of vitamin A
- **Docosahexaenoic acid supplements**: 400 mg/day
- **Lutein supplements**: 20 mg/day
- Improved Cone Function in Retinitis Pigmentosa by Oral *N*-Acetylcysteine:
  - *N*-acetylcysteine (NAC) reduces oxidative damage and increases cone function and survival in an RP model.
  - Patients with moderately advanced RP have suboptimally functioning macular cones that may show improved function with oxidative stress reduction.
- **Vitamin E** should not be given. It has no beneficial effect and may be potentially harmful. (Berson 1993, Survey of ophthalmology)

Ciliopathies

- Ciliopathies are group of rare genetic disorders characterized by dysfunction of a hair-like cellular organelle— the primary cilium. Cilia are microtubule-based structures found on almost all vertebrate cells. They originate from a basal body, a modified centrosome, which is the organelle that forms the spindle poles during mitosis. The cilium-centrosome complex represents nature's universal system for cellular interaction, cellular detection, and management of external signals.
- Primary cilium-related dysfunction can either affect a single tissue or organ, or lead to a full-blown syndromic spectrum of ciliopathy-related manifestations with simultaneous involvement of several organs.
- The retina is a good example of a single-tissue ciliopathy. Primary cilium dysfunction frequently affects photoreceptors (ciliated retinal cells) and causes retinal degeneration.

Mutations in retina-specific ciliary genes lead to isolated nonsyndromic retinitis pigmentosa (RP). These mutations include the most common form of X-linked retinitis pigmentosa, linked to the **RPGR** gene, or subtypes of autosomal recessive Leber congenital amaurosis (LCA) linked to **NPHP6**/**CEP290** and **LCA5**/ **lebercilin**.

- The retinitis pigmentosa phenotype is a common feature of **syndromic ciliopathies**. These include **Usher** syndrome (RP plus sensory-neural deafness with/without vestibular involvement), Bardet-Biedl syndrome (**BBS**), **MORM** (Mental retardation, truncal Obesity, Retinal dystrophy and Micropenis), **Alström** syndrome, Senior-Loken syndrome (**SLS**), Joubert syndrome– related diseases (JSRD), **Jeune** syndrome, and Meckel-Gruber syndrome (MKS).
- Most syndromic ciliopathies are inherited in an autosomal recessive fashion. However, more complex inherited mechanisms (triallelism, modifier effect) have been described. Allelic variability, defined as different mutations in the same gene giving rise to different clinical presentations or syndromes, is common among syndromic ciliopathies. It is well established that NPHP6/ CEP290 mutations may cause a pure retinal phenotype (isolated LCA) to the lethal multisystemic MKS.
- **BBS**
  - The cardinal features of Bardet-Biedl syndrome (BBS) are retinal dystrophy (RD), obesity, polydactyly, hypogonadism, cognitive impairment, and renal failure. Secondary clinical features such as anosmia, diabetes, cardiac anomalies, liver fibrosis, brachydactyly, and Hirschprung disease may also be present. Different types of retinal dystrophy have been reported in BBS. These are mainly a rod-cone dystrophy or a cone-rod dystrophy; however, a choroidal dystrophy and a global severe retinal dystrophy have also been described.
  - BBS is a genetically heterogeneous condition with 16 genes identified to date. These account for about 80% of the cases. All BBS genes have been related to cilium biogenesis and/or function. BBS1 and BBS10 are the two most common culprits. Interestingly, several BBS genes are implicated in other ciliopathies: BBS13 is MKS1 (Meckel Gruber syndrome 1) and BBS14 is the CEP290/NPHP6 gene associated with LCA, JS, and MKS. In contrast, retinal-specific splice variants of BBS3 and BBS8 have been identified and mutations in these transcripts cause nonsyndromic RP.
- **Alström syndrome** manifestations include RP in early childhood, hearing disability, and metabolic defects leading to hyperinsulinemia, type II diabetes mellitus, and obesity in childhood. However, these patients lack polydactyly and cognitive impairment, commonly seen in BBS.
- **Senior-Loken syndrome** is a combination of nephronophthisis (NPH) and retinal degeneration. NPH is characterized by normal kidney size, tubulointerstitial nephritis, and a loss of corticomedullary differentiation leading to cyst formation. The first symptoms are often polyuria and polydipsia caused by a defect in urinary concentration. Three forms of NPH can be distinguished based on end-stage of renal failure: infantile, juvenile, and earlyadulthood. The occurrence of the retinal dystrophy is higher in the juvenile form of NPH. To date, 11 genes (named NPHP 1e11) are known to be causative of SLS.
- **Joubert syndrome** is a combination of cognitive impairment, ataxia, tachypnea, and eye movement abnormalities. Cerebellar vermis hypoplasia is a pathognomonic finding on MRI named molar tooth sign. Multiple other features can be associated with this midbrain-

hindbrain malformation, leading to the denomination of Joubert syndrome–related disorders (JSRD). The retinal phenotype includes macular colobomas and a rod-cone dystrophy.

- **MeckelGruber syndrome** represents the most severe end of the disease spectrum, leading to prenatal or perinatal mortality. It is characterized by occipital encephalocele, kidney cystic dysplasia, hepatic ductal proliferation, liver fibrosis, and polydactyly. Seven genes have been found to be implicated in MKS: MKS1, 2 and 3, CEP290, NPHP3, RPGRIP1L, and CC2D2A.
- The **retinitis pigmentosa** phenotype secondary to dysfunction of the primary cilium can be associated with several other clinical manifestations (syndromic RP) and impacts on clinical practice. It is important to be aware of the target organs for ciliopathies defining well-known and new overlapping syndromes. Therefore, a child with RP/CRD should be assessed for associated features such as obesity, kidney impairment, polydactyly (asking for removal of extra digits during childhood), cognitive impairment, tested for anosmia and diabetes, and checked for bone changes, as the diagnosis of a ciliopathy will influence follow-up.

Hereditary Vitreoretinal Degenerations

- Early-onset cataracts, vitreous anomalies, coarse fibrils and membranes, and retinal detachment.

Snowflake vitreoretinal degeneration

- **Hirose** in 1974
- Autosomal dominant: chromosome 2q36.
- Ocular features
  - Early-onset cataract
  - Fibrillar vitreous degeneration
  - Peripheral retinal abnormalities, including minute crystalline-like deposits called snowflakes
  - Vascular sheathing
  - Retinal detachment
  - Others: guttata, ONH dysplasia
- **Four stages**: (1) extensive white with pressure; (2) snowflake degeneration; (3) sheathing of retinal vessels and fundus pigmentation; and (4) further pigmentation and disappearance of the peripheral retinal vessels
- **Investigations**
  - scotopic b-wave of the electroretinogram (ERG) elicited by dim light is low in amplitude and may be almost extinguished in late stages of the disease
  - electro-oculographic light peak–dark trough ratio is abnormal
- **Differential Diagnosis**
  - Stickler syndrome type I, II
  - Marshall syndrome
  - Wagner syndrome

- Goldmann–Favre vitreotapetoretinal degeneration

- **Management**
  - No specific Management
  - risk of retinal detachment is 20% and cataract surgery of early-onset lens opacification can be difficult due to vitreous liquefaction

The chromosome 5Q retinopathies

- **Wagner syndrome:**
  - Optically empty vitreous with avascular vitreous strands and veils, moderate myopia, presenile cataracts, and retinal degeneration with atrophy
  - Autosomal dominant, VCAN gene, 5q13-14
- **ERVR (erosive vitreoretinopathy)**
  - AD
  - Optically empty vitreous
- **Jansen syndrome**
  - Vitreoretinal and lenticular degeneration associated with retinal detachments
- **Clinical Features**
  - Optically empty vitreous with equatorial avascular vitreous veils.
  - Moderate myopia
  - Typical dot-like cortical cataracts
  - Foveal ectopia
  - Abnormal retinal vessels (inverted papilla)
  - Perivascular pigmentation and sheathing
  - Retinal thinning as well as slowly progressive chorioretinal atrophy.
  - Pseudostrabismus from congenital temporal displacement of the fovea.

Chondrodysplasias associated with vitreoretinal degeneration

- **Stickler syndrome:**
  - MC
  - hereditary progressive arthro-ophthalmopathy
  - Types I: COL2A1 gene encoding type II collagen
  - Type II: COL11A1 gene encoding type XI collagen

- **Marshall syndrome**
  - AD
  - COL11A1 gene of chromosome 1p.

- **Kniest dysplasia**
  - COL2A1 gene which encodes type II collagen,

- **Knobloch syndrome**
  - COL18A1 gene mapped to the long arm of chromosome 21 are supposed to induce the changes in collagen XVIII

- **Weissenbacher Zweymuller syndrome**: aka Pierre Robin syndrome with fetal chondrodysplasia
  - Clinical Features
    - Conductive and sensorineural hearing loss, immunoglobulin deficiency, cleft palate, mid facial underdevelopment, mild spondyloepiphyseal dysplasia, and precocious arthritis
    - congenital high myopia, cataract, and retinal problems, such as vitreous changes, radial perivascular retinal degeneration, and rhegmatogenous retinal detachment

X-linked retinoschisis

- *RS1* gene on Xp22
- Exclusively expressed in the photoreceptors and retinal bipolar cells
- Encodes **retinoschisin** → interact with β2 laminin within the extracellular space and αB crystallin intracellularly
- Most common form of juvenile-onset retinal degeneration in males
- **Clinical Features**
  - Foveal schisis is the characteristic sign of XLRS and is present in 98–100% → **spokewheel** pattern
  - **Peripheral retinoschisis**, It region, 50%
  - **Splitting** occurs in the superficial retinal layers
  - Breaks occur within the inner layer
  - Traction or rhegmatogenous retinal detachment 5–20%
  - Dense vitreous hemorrhage, hemorrhage within a large schisis cavity, and intraretinal splitting involving the macula
  - **Vision loss is the most common** clinical presentation
- **Investigations**
  - OCT:
  - ERG: reduced b-wave amplitude with a relatively preserved a-wave, alteration of the b : a ratio

- Multifocal ERG: reduced amplitudes and longer implicit times in the central macula

- **Differential Diagnosis**
  - RD
  - Cystoid macular edema, degenerative retinoschisis, acquired retinoschisis, amblyopia, Goldmann–Favre vitreoretinal degeneration, ESCS, Eales disease, and *VCAN*-related vitreoretinopathy
- **Management**
  - Genetic counseling
  - CAIs: topical dorzolamide
  - Laser
  - Surgery: patients with severe complications
  - Gene therapy
  - Retina and/or progenitor cell transplantation

NR2E3 related diseases

- Retinal nuclear receptor subfamily 2, group E, member 3
- Expression is uniquely restricted to photoreceptors
- GFS, ESCS, and clumped pigmentary retinal degeneration
- **Goldmann–Favre vitreotapetoretinal degeneration**
  - retina, vitreous body, and crystalline lens
  - early-onset nyctalopia, fibrillar vitreous degeneration, foveal cysts, peripheral retinoschisis, and retinal degeneration with clumped pigment, and an unusual ERG
  - areas of clumped pigment are due to excessive accumulation of melanin granules in retinal pigment epithelial cells
- **ESCS: enhanced S-cone syndrome**
  - increase in the blue cone population with associated variable degeneration of the rod and red and green cone photoreceptors
  - early-onset night blindness, cystic maculopathy, and peripheral retinal degeneration characterized by mild visual field loss
- Clinical Features
  - progressive loss of vision similar to retinitis pigmentosa
  - night blindness
- Investigations
  - ERG: undetectable rod-specific response, similar photopic and scotopic responses to a standard single flash, and a 30-Hz lower-amplitude photopic a-wave response
- Differential Diagnosis
  - X-linked retinoschisis

- Cystoid macular edema

Macular Dystrophies

- Always rule out these 2 before considering macular dystrophy
  - **Neuronal ceroid lipofuscinosis (NCL) aka Batten disease:** fatal systemic disease of children, ERG markedly abnormal, rapidly progressive
  - **Drug toxicity**: CHQ, HCHQ, Thioridazine, Chloropromazine, Tamoxifen, Deferoxamine

- **Mendelian maculopathies**
  - AR Stargardt disease: ABCA4
  - Best disease: BEST1
  - Pattern dystrophy: PRPH2
  - AD Stargardt disease: ELOVL4
  - Sorsby fundus dystrophy: TIMP3
  - Malattia leventinese: EFEMP1
  - Pseudoxanthoma elasticum: ABCC6
  - North Carolina macular dystrophy: chromosomes 5 and 6
  - PROM1-associated macular dystrophy: PROM1
  - Macular dystrophy with diabetes and deafness: mito 3243

Best macular dystrophy

- AD/AR
- Mutations in the *BEST1,* chromosome 11q13
- Friedrich Best in 1905
- 1 in 10 000
- **Pathophysiology**
  - Increased RPE lipofuscin, loss of photoreceptors (often seen over a relatively intact RPE layer), sub-RPE drusenoid material, and accumulation of cells and material in the subretinal space
  - **Bestrophin-1** is expressed in all RPE cells
- **Clinical Features**
  - Known as "**vitelliform**" because of their egg-yolk-like appearance
  - Solitary, round or horizontally oval, yellow, slightly elevated, and are centered on the fovea
  - Larger lesion in childhood, smaller after 20

- **Pseudohypopyon**: the yellow material gravitates inferiorly in the subretinal space
- **Scrambled-egg lesion**: varying amounts of subretinal and sub-RPE fibrosis, RPE atrophy in Addition to hyperpigmentation
- Stages given by some authors, there is not always a predictable progression
- Single or multiple lesion
- **Multifocal Best dystrophy**: multiple vitelliform lesions scattered throughout the posterior pole of both eyes
- Visual acuity is variable but preserved in at least one eye till 6th decade, may decrease due to nodular fibrosis, choroidal neovascularization
- **Hyperopia** due to shortened axial length
- Angle closure
- 4 stages

- **Investigations**
  - EOG: ratio of the light peak to dark trough (**the Arden ratio**) is typically **less than 1.5**
  - ERG: cone and rod aand b-wave amplitudes are usually normal
  - Autofluorescence: increased amounts of lipofuscin
  - OCT: homogenous yellow material, CNVM
  - FA: hydrophobic yellow material, completely excludes fluorescein
- **Additional** phenotypes associated with mutations in BEST1
  - Autosomal dominant vitreoretinochoroidopathy (ADVIRC)
  - Autosomal recessive bestrophinopathy (ARB)
- **Treatment**
  - Recognizing choroidal neovascularization and hastening its regression with anti-VEGF therapy
  - Protective eyewear to protect the other less involved eye

Stargardt disease

- Most common cause of **AR** retinal disease
- ***ABCA4*** mutations
- Disease spectrum is determined largely by the total amount of residual ABCA4 function
- Interplay of three factors:
- The severity of their ***ABCA4* genotype** (and hence the rate at which toxic bisretinoids form in the photoreceptors)
- The relative **sensitivity of the foveal cones** to the genotype
- The relative **sensitivity of the retinal pigment epithelium** to the genotype
- **Pathophysiology**

- Remarkable **lipofuscin accumulation** in the RPE, photoreceptor cell inner segments
- Role of ABCA4 is the clearance of a retinoid intermediate of the visual cycle → Condensation of this retinoid with a second vitamin A moiety, which may occur in the photoreceptor cell or in the RPE following outer segment phagocytosis, results in the formation of A2E, a toxic detergent-like compound that can trigger death of RPE cells

- **Clinical Features**
  - Loss of visual acuity, which can be as mild as 20/30 or as severe as 20/200
  - 5 years or later than 50 years
  - Abnormal fundus appearance that is incidentally discovered
  - Light-colored flecks at the level of the retinal pigment epithelium → more elongated than round,
  - **Pisciform** (fish-tail): two adjacent flecks form an obtuse angle
  - Many different fleck configurations
  - Fairly reliable diagnostic sign: **relative sparing of the peripapillary RPE**.
  - Quite full visual fields for many years after their acuity has fallen below the threshold of legal blindness
- **Investigations**
  - FA/ FAF
    - Accumulation of A2E within the retinal pigment epithelium
    - Dark, silent, or masked choroid
    - Retinal vessels stand out in sharp contrast
  - OCT
    - Anatomic level of flecks with accuracy
  - Full-field ERG: normal ***(Clinical Features: NCL, the ERG is usually severely reduced or extinguished before the age of 10 years)***
- **Management**
  - No proven treatment
  - Drugs that modulate the visual cycle
  - Gene replacement
  - Avoidance of cigarette smoking
  - **Avoidance of high-dose vitamin A supplements**, including AREDS vitamins, because of their potential to increase the formation of bisretinoids in the retina.

Stargardt-like dominant macular dystrophy (SLDMD)

- Autosomal dominant

- Chromosome 6
- *ELOVL4* gene: elongation of very long chain fatty acids-4
- Most-characteristic features of this disease are circular zone of RPE atrophy, a pigmented spot beneath the fovea, and a ring of flecks just beyond the margin of the atrophy
- ERG is usually normal

Pattern dystrophy

- Pigment changes at the level of the RPE.
- Mutations in a single gene, *PRPH2*
- **Pathophysiology**
  - *PRPH2* encodes a structural protein (peripherin) → maintaining the morphology of photoreceptor outer-segment discs
- **Clinical Features**
  - Macular photostress is important feature: central acuity will be slow to recover following exposure to bright light
  - 18% lifetime risk of choroidal neovascularization
  - Butterfly-shaped pigment dystrophy: AD, pigment deposition resembling butterfly
  - Adult-onset vitelliform pattern dystrophy (peculiar foveomacular dystrophy): symmetric, solitary, autofluorescent vitelliform lesions
  - Sjögren reticular dystrophy of the RPE: resemble a fishnet with knots or chicken wire
  - Fundus pulverulentus:
  - Central areolar choroidal dystrophy (central areolar retinochoroidal dystrophy)
- **Investigations**
  - ERG: normal cone and rod amplitudes and implicit times on the full-field ERG
  - EOG light-peak to dark-trough ratios are most frequently normal or only modestly subnormal

Sorsby fundus dystrophy

- **Pathophysiology**
  - Mutations in *TIMP-3* → protein that negatively regulates MMPs
  - Accumulation of lipidic and proteinaceous material between Bruch's membrane and the RPE up to 30 μm in thickness.
- ***Clinical Features***
  - Night blindness
  - Yellow-to-gray material is present at the level of Bruch's membrane
  - Bilateral subfoveal neovascular membranes

- SFD relentlessly extends peripherally beyond arcades

- **Management**: CNVM Management and control

Autosomal dominant radial drusen ADRD

- Doyne honeycomb retinal dystrophy, malattia leventinese
- *EFEMP1* gene, chromosome 2
- ***Pathophysiology***
  - *EFEMP1* gene → protein known as fibulin-3, poorly secreted by RPE cells and its accumulation in the endoplasmic reticulum activates the unfolded protein response
- **Clinical Features**
  - Drusen in the center of the macula and on the nasal edge of the optic disc tend to be large and round, while those at the temporal margin of the macula tend to be smaller, elongated, and radial
  - Central atrophy, scarring, and pigment proliferation that can look similar to SFD
  - Visual acuity in ADRD is typically much better than SFD
  - CNVM less common
- **ERG**: Full-field ERG is usually normal but the pattern ERG is abnormal in most eyes
- **FAF**: Drusen in AMD that tend to be hypoautofluorescent, the drusen in ADRD are hyperautofluorescent

North carolina macular dystrophy

- First described as “dominant macular degeneration and aminoaciduria”
- Chromosome 6
- Clinical Features
  - Lack of progression is one of the most reliable diagnostic features
  - A circular coloboma centered on fixation with a shiny concave base surrounded by a thick, white fibrotic rim

Spotted cystic dystrophy

Dominant cystoid macular dystrophy DCMD

- AD
- leaking perimacular capillaries, whitish punctate deposits in the vitreous, a normal ERG, a subnormal EOG, and hyperopia

Fenestrated sheen macular dystrophy (FSMD)

Glomerulonephritis type II and drusen

- (MPGN) type II (also known as dense-deposit disease) develop subretinal deposits with the clinical appearance of basal laminar drusen

Hereditary Choroidal Diseases

- **Choroidal atrophy phenotypes**
  - Central areolar choroidal dystrophy: mutation in the peripherin/RDS (retinal degeneration slow) gene, AR,
  - Peripapillary choroidal dystrophy: AR
  - Diffuse choroidal dystrophy: AD
- **Gyrate atrophy of the choroid and retina:**
  - AR >> AD
  - deficiency of the enzyme ornithine-delta-aminotransferase (OAT), which results in an increase in the plasma ornithine concentration
  - hyperornithinemia, and reductions in plasma lysine, glutamine, glutamate, and creatine.
  - chromosome 10
  - poor night vision and constricted peripheral vision, usually begins in the second and third decades
  - thinning and atrophic appearance of the RPE in which the underlying choroidal vessels may appear either normal or sclerotic
  - ERG responses deteriorate and may eventually become undetectable
  - EOG light peak to dark trough ratio becomes markedly reduced in the later stages
  - Management
    - arginine-restricted diet
    - rigid low-protein diet, including near-total elimination of arginine with supplementation of essential amino acids
    - Orally administered pyridoxal phosphate
- **Choroideremia**
  - XR
  - CHM gene → Xq21 → Rab escort protein-1 (REP-1)
  - prevalence of 1 in 50 000
  - Clinical Features
    - defective dark adaptation, manifesting as poor visual function in dim illumination is commonly the first symptom
    - fine, peppery-like retinal pigment mottling → salt and pepper mottling → Atrophy of the choroid follows with eventual loss of the entire layer and exposure of bare sclera.

        - midperipheral retina and progress centrally
    - Field: ring scotoma
    - ERG is most often abnormal under both light and dark-adapted conditions
    - EOG recordings show an abnormally low light peak to dark trough ratio.
- **Differential Diagnosis**
    - X-linked retinitis pigmentosa (XLRP)
    - Kearns–Sayre syndrome (KSS)
    - Bietti's crystalline dystrophy
    - Thioridazine (Mellaril) retinal toxicity
    - Stargardt disease
    - Pattern macular dystrophy

Abnormalities of Cone and Rod Function

Cone Disorders

- ***Achromatopsia***
    - 1 in 30 000
    - poor vision from birth and complain of poor color discrimination and photosensitivity
    - monochromatism, are generally considered to lack cones and have vision worse than 20/200
    - because their color vision loss is congenital, even complete achromats may be able to identify colors
    - Clinical Features
        - may have a normal fundus, or have subtle granularity or atrophy of the macula
        - nerve may be normal or show some temporal pallor
    - ERG: completely nonrecordable cone responses in the face of normal or near-normal rod responses
    - pseudochromatic (Ishihara) color plates: Congenital achromats may be able to identify
    - Farnsworth D-15 testing may reveal a scotopic axis between the deutan and tritan axes
    - **Sloan achromatopsia test** uses an achromat's correlation of different shades of gray to various colors in order to distinguish them from normal individuals
    - aptive optics scanning laser ophthalmoscopic imaging of the macular photoreceptor mosaic
    - four genes: *CNGB3>> CNGA3> GNAT2> PDE6C*
    - Management
        - No treatment currently

- Photophobia can be reduced with tinted lenses
- LVA

Cone monochromatism and blue cone monochromatism

Progressive cone dystrophies

Congenital stationary night blindness

- nonprogressive defects in scotopic vision and/or dark adaptation with otherwise normal visual function.
- AD, AR, XR
- ***CSNB with normal fundi***
  - may have normal visual acuity and may not complain of night blindness
  - myopia and can have subnormal vision
  - Dx
    - **Riggs type** (also known as type I)
      - lack a scotopic ERG, lack both an aand b-wave on maximum bright-field stimulation ERG, and lack a rod–cone break on their dark-adaptation curve
    - **Schubert–Bornschein** (also known as type II)
      - possess an a-wave on maximum bright-field stimulation ERG but no b-wave, hence exhibiting a negative waveform.
- ***CSNB with abnormal fundi***
  - ***Oguchi disease***
    - **Mizuo–Nakamura phenomenon**: retina appears normal following prolonged dark adaptation, but on ***exposure to light the retina displays a golden sheen*** with an unusually dark macula
    - Visual acuity and color vision are typically normal
    - dark-adaptation curve with a cone component but no rod–cone break, and exhibit gradual recovery of full rod sensitivity after prolonged dark adaptation of 1–2 hours
    - mutation in rhodopsin kinase (*GRK1*) or arrestin (*SAG*)
  - ***Fundus albipunctatus***
    - White or yellow dots can be seen scattered through the fundus
    - night blindness early in childhood without progression
    - visual acuity and color vision are typically normal
    - scotopic ERG can be recorded but only after unusually long dark adaptation, whereas the cone ERG is usually normal

Coats Disease

- Scottish ophthalmologist **George Coats in 1908**
- Initial classification of group 1,2,3 is now dropped
- Male 3 times more than females
- unilateral in 80–95%
- **Etiopathology**
  - deficiency of **Norrin**, a retinal protein, in the pathogenesis of Coats disease
  - Coats disease may be part of a spectrum of related genetic disorders known as ***retinal hypovasculopathies*** which includes Norrie disease, familial exudative vitreoretinopathy (FEVR), fascioscapulohumeral muscular dystrophy (FSHD), and the osteoporosis pseudoglioma syndrome
  - Norrie disease pseudoglioma (*NDP*) gene on chromosome Xp11.2
- **Clinical Features**
  - **Symptoms:** Decreased visual acuity (43%): variable, strabismus (23%), leukocoria/xanthocoria (20%), pain (3%), heterochromia (1%), nystagmus (1%), no symptom (8%)
  - **Anterior Segment**: 90% normal, rest→ cataract (8%), iris neovascularization (8%), shallow anterior chamber (4%), corneal edema (3%), cholesterol in the anterior chamber (3%) and megalocornea (2%).
  - **Retinal findings:** telangiectasia (100%), intraretinal exudation (99%), exudative retinal detachment (81% with 42% demonstrating partial retinal detachment and 58% with total retinal detachment), retinal hemorrhage (13%), retinal macrocyst (11%), vasoproliferative tumor (6%), and optic disc neovascularization (1%).

- **Shields Staging System (Mnemonic:TEDGP)**
  1. Retinal telangiectasia (T) only
  2. Telangiectasia and exudation (E): Extrafoveal, Foveal
  3. Exudative retinal detachment (D): Subtotal, Total
  4. Total retinal detachment and glaucoma (G)
  5. Advanced endstage disease often with phthisis (P) bulbi

- **Investigations**
  - FA:
    - Telangiectasia, aneurysms, beading of vessel walls, and various vascular communicating channels
    - peripheral retinal nonperfusion
    - early and persistent leakage,

- CT: characterize intraocular morphology, quantify subretinal densities, identify vascularities within the subretinal space through the use of contrast enhancement, and detect other abnormalities
- MRI: distinguished from Coats disease, toxocariasis, and persistent hyperplastic primary vitreous
- Doppler ultrasonography:
- Blood testing: Aqueous and SRF lactic dehydrogenase

- **Coats plus syndrome**: Coats-like picture associated with varied skeletal defects, cerebellar and extrapyramidal movement disorder, epileptic seizures, leukodystrophic changes, and postnatal growth failure

- **Differential diagnosis**
  - **juvenile Coats disease**: Retinoblastoma, RD, Congenital cataract, Norrie disease, PHPV, toxocariasis, hemangiomatosis, FEVR
  - **any stage of coats:** Eales, BRVO, toxoplasmosis
- **Treatment**
  - Mild cases: documentation and observation
  - **Ablative therapies**
    - laser photocoagulation
    - Double freeze–thaw cryotherapy
  - **Pharmacologic therapies**
    - **IVTA**
    - Intravitreal anti-VEGF agents
  - **Surgery**

FEVR: Familial Exudative VitreoRetinopathy

- Potentially active lifelong retinal vascular disease
- Born with avascular peripheral retina and can have varying amounts of exudate and retinal detachment (exudative and tractional)
- Mechanism of the progression of the disease was unknown until widefield fluorescein angiography (FA) showed progressive posterior capillary loss and subsequent VEGF-driven exudative and tractional retinal detachment, which can lead to blindness.
- **Natural History**
  - FEVR is a lifelong disease requiring long-term follow-up and regular examinations.
  - Typically, long periods of disease quiescence are punctuated by episodes of disease reactivation.
  - Retinal detachment may occur up to 20 years following apparent stabilization.

- Prognosis is most guarded in children diagnosed before age 3.
- However, even in adolescence and adults, less severe disease at presentation may progress to more severe disease years later.

- **Clinical Features**
  - Usually bilateral, asymmetric
  - Can present at any age (mean: 6 years; range: 1 month to 50 years)
  - "Findings of retinopathy of prematurity (ROP) in a full-term child"
    - Avascular retinal periphery
    - Vascular buds at junction of vascular and avascular retina
    - Vessel dragging
    - Retinal folds
    - Subretinal, intraretinal, or preretinal exudation
    - Retinal detachment (traction, rhegmatogenous, exudative, or combined)
    - Peripheral retinoschisis
  - Associated findings
    - High myopia
    - Anisometropic amblyopia
    - Cataract
    - (Rare): persistent fetal vasculature syndrome (PFVS), Turner syndrome, Marfan syndrome, neurodevelopmental disorders
- **Genetics**
  - Inheritance can follow autosomal dominant, autosomal recessive, or X-linked patterns. All can have variable penetrance.
  - Four causative genes have been identified (NDP, LRP5, FZD4, TSPAN12).
    - Account for up to 50% of cases of FEVR
    - The type of mutation or the number of genes involved may determine the severity of disease.
    - All genes form part of the Wnt signaling pathway, which is essential for normal retinal vascular growth and development. Thus, genetic abnormality of any part of this pathway may lead to disorders of retinal vasculogenesis.
- **Stages**
  - Stage 1: Avascular retinal periphery
  - Stage 2: Preretinal neovascularization
  - Stage 3: Macula-sparing retinal detachment
  - Stage 4: Macula-involving retinal detachment
  - Stage 5: Total retinal detachment
- **Treatment**

- Laser ablation of avascular retina as determined by clinical exam
- Use of wide field FA allows visualization of areas of capillary loss prior to frank exudation and allows effective laser treatment.
- Use of widefield FA to identify LAPPEL (late FA posterior and peripheral leakage), a newly described lesion that predicts capillary loss and may be treatable with drugs, avoiding the destructive therapy of laser
- Drug treatment that increases intercellular retinal endothelial adhesion molecules claudin-5 and VEcadherin tightens cell junctions and modulates ICAM-1 implicated in leucocyte endothelial adhesion (LEA) and can reverse leakage and prevent capillary loss and the need for destructive laser treatment. Examples of effects in tissue culture and patients of steroid, NSAID, and Norrin will be presented.
- ***Stage-wise Treatment***
  - Stage 1: Observation or peripheral retinal ablation (especially if fellow eye has limited vision)
  - Stage 2: Complete ablation (typically with laser photocoagulation) of all areas of peripheral retinal nonperfusion
  - Stages 3-5: Scleral buckling or vitrectomy or both

Retinopathy of Prematurity

Read details from www.focusrop.com, best concise review.

- First identified by **Terry in 1942** → *retrolental fibroplasia*
- term ROP was coined by **Heath** in 1951.
- 1951, Campbell suggested that toxic effects of uncontrolled oxygen to newborns
- **First epidemic**: 1950, due to use of oxygen
- **Second Epidemic**: 1970-80, due to increased survival of very low birth premature infants
- **Third or Mixed Epidemic**: Asian countries, due to extremes of health cares, combination of first and second epidemic
- 1983: International Classification of Retinopathy of Prematurity, John Flyrm

Epidemiology

- Childhood blindness prevalence of 0.7 (+ 0.3)/1000 in India
- upto 3.35 percent of all premature children.
- Low incidence of ROP in India is due to low or no survival rate of children <1200 gm in rural, unawareness amongst ophthalmologists and neonatologists, and lack of experience and infrastructure for ROP screening.
- Incidence: **2.3% (<1600 gm) [azad et al]**

Pathogenesis

- 6 weeks (5 mm): hyaloid artery enters the globe

- Upto 16 weeks: choroidal vessels alone nourish both outer and inner retina
- 16 weeks: first blood supply to inner retina appears in the form of mesenchymal *"Spindle cells"* arising from the adventitia of the hyaloid artery
- rate of growth of the advancing spindle cells is **0.1 mm/ day** and reaches normal oraserrata by the 7th or 8th month and then temporal ora serrata by the 9th month of gestational
- *The classical theory:*
  - Arhton and Patz
  - Elevated arterial P02 → causes retinal vasoconstriction → vascular closure → if sustained → permanent vascular occlusion occurs → Endothelial cell proliferation → neovascularization.
- *Spindle cell theory*
  - Kretzer
  - spindle cells are exposed to hyperoxic environment due to increased oxygen diffusion through choroidal vasculature → Oxygen free radical: a cytotoxic agent attacks compromised spindle cells, which has deficient anti-oxidative system → prevents migration of cells and canalization.
- Role of VEGF is also proposed.

Differential Diagnosis

- **Bilateral**
  - Retinoblastoma
  - Retinal dysplasia
  - Norrie's disease
  - Waller Warbtug syndrome
  - Trisomy13
  - Fundus coloboma
  - X-lin1ed retinoschlsis
  - Falciform folds
  - Incontinentia pig:rnenti
  - Intrauterine catastrophes
  - Anterior encephaloceles in Asians
  - Cataracts
- **Unilateral**
  - (PHPV) Persistent hyperplastic Primary vitreous
  - Coats' disease
  - Retinal vascular anomalies
  - Parasitic endophthalmitis
  - Prenatal infantile trauma

- Trauma (child abuse syndromes)

Classification

- **Zones**
  - Zone I (Posterior pole or inner zone): The limits of zone I are defined as twice the disc fovea distance in all directions from the optic disc.
  - Zone II: Extends from the edge of zone I peripherally to a point tangential to the nasal ora serrata.
  - Zone III: It is a residual temporal crescent of retina anterior to zone 2.
  - Extent: The extent of the disease is coded by the number of clock hours with ROP. The extent of the disease is further described as contiguous clock hours of ROP or noncontiguous clock hours.
- **ICROP Staging**
  - Stage 1: Demarcation line
  - Stage 2: Ridge
  - Stage 3: Ridge with extraretinal FVP (Mild/Moderate/Severe)
  - Stage 4: Subtotal RD
    - A: Not involving macula
    - B: Involving macula
  - Stage 5: Total retinal detachment (anterior and posterioropen –close types)
- ICROP Revisited
  - **Pre-Plus disease** is defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and venous dilatation than normal and may later progress to plus disease.
  - **Aggressive posterior ROP** is a new term for Rush disease or type 2 fulminant ROP in which there is posterior pole vessels show increased dilatation and tortuosity in all 4 quadrants out of proportion to peripheral retinopathy, progresses rapidly, does not progress through classic stages 1-3 and may appear only as a flat network of neovascularization at the deceptively featureless junction of vascularized and non-vascularized retina
- **Rush disease:** Characterized by engorgement of the posterior pole vessels whose most anterior development was still in the posterior pole and it was associated with broad anterior avascular retina
- **Plus disease:** Schaffer, Quinn and Jhonson recognized this feature when they noted that posterior polar dilation and tortuosity constituted an important sign related to the severity of the disease. Associated with it was the iris vessel dilation and engorgement, which resulted in poor pharmacological dilation of the pupil. This was called the plus disease.
- **Prethreshold ROP:**
  - Any stage of ROP in zone I with plus disease

- ROP stage 3 with plus disease with 3 contiguous or 5 interrupted dock hours of involvement of retina in zone II but less than threshold.

- **ETROP Study (Early Treatment of ROP) Sub-classification**
  - Type 1 ROP defined as zone 1 ROP, any stage ROP with plus disease; zone 1, stage 3 ROP without plus disease; or zone 2, stage 2 or 3 ROP with plus disease-perform retinal ablation.
  - Type 2 ROP defined as zone 1, stage 1 or 2 ROP without plus disease or zone 2, stage 3 ROP without plus disease. These eyes should be considered for treatment only if they progress to type 1 or threshold ROP.
  - Threshold Disease: Zone I or II: ROP stage 3 more than 5 contiguous or 8 cumulative clock hours with plus disease present. This is the stage in which the treatment is mandatory since the chances of progression to retinal detachment are 50 percent if left untreated.

Risk Factors

- Definite and Well Accepted
  - Prematurity /Gestational Age/Birth Weight
  - Oxygen Supplementation
- Associated Factors
  - Light, Vitamin E deficiency, Apnea with bag/mask ventilation, Methyl xanthine administration, Respiratoty distress syndrome, Asphyxia/Hypoxia, Shock, Hypercarbia/Hypocarbia, Acidosis/ Alkalosis, Sepsis, Patent ductus arteriosus/ Indomethacin, Blood transfusions/Exchange transfusions, Intraventricular hemorrhage, Chronic in utero hypoxia, Maternal factors-anemia.
- Scoring for BW and GA available: 0,1,2,3
- **Regressed ROP:**
  - Peripheral and posterior changes
  - Vascular
    - Failure to vascularize peripheral retina
    - Abnormal, nondichotomous branching of retinal vessels
    - Vascular arcades 'With circumferential interconnection
    - Telangiectatic vessels
  - Retinal
    - Pigmentary changes
    - Vitreoretinal interface changes
    - Thin retina
    - Peripheral folds
    - Vitreous membranes with or 'Without attaclunent to retina
    - Latticelike degeneration

- Retinal breaks

Screening

1. Screen all premature infants less than 1500 gram birth weight

2. Screen all babies born at less than or equal to **32 weeks of post-conceptional age or 4 weeks from birth whichever is earlier.**

3. Special criteria (**the THIRD Criteria**, proposed by AZAD et al especially for developing countries like India): Neonatologist is to be cautioned to include all babies for screening who they consider most sickly survivors because of sepsis, multiple blood transfusions, RDS, pneumonitis, Extraordinary oxygen support.

Management

- **CRYOTHERAPY/ LASER**
  - Threshold ROP
  - Prethreshold ROP (Type 1)
- **WHEN NOT TO DO LASER**
  - Less than prethreshold ROP
  - Type 2 prethreshold
  - Lack of consent

ADVANCED STAGES

- Stage 4a: Focal Traction, No RD → follow up
  - Generalised traction, No RD → follow up +buckling
  - Generalized traction with RD → buckling/ lens sparing Vitrectomy
- Stage 4b: Lens sparing Vitrectomy
- Stage 5: Combined lensectomy and vitrectomy or vitrectomy with lens conservation
- **BEAT ROP Study**
  - Anti-VEGF Therapy's Increased Role in ROP
    - Demonstrated efficacy
    - Underestimated systemic exposure

Sequelae of ROP

- **Progressive ROP**
- **Spontaneous regression**
  - Refractive Errors
  - Strabismus and motility defects
  - Changes in ocular dimensions

- Cataract
- Anterior segment change
- Visual field changes

Anti-VEGF Treatment for ROP

- Rationale for Vascular Endothelial Growth Factor (VEGF) Involved in Severe ROP
  - Important in adult diabetic retinopathy, neovascular AMD
  - Preclinical testing of anti-VEGF in adult disease used oxygen-induced retinopathy models that share characteristics with human ROP (stage 3 – intravitreal neovascularization; plus disease – arteriolar tortuosity and venous dilation)
- Caution Regarding Use of Anti-VEGF in ROP
  - VEGF is important in human retinal vascular development.
  - VEGF is neuroprotective. Experimental evidence that optimal anti-VEGF dose thins outer nuclear layer and causes release of neuroprotective factors from Müller cells
  - VEGF necessary to support newly developed retinal capillaries under oxygen stresses similar to human ROP. Experimental intravitreal anti-VEGF:
    - Injures newly developed retinal capillaries
    - Leads to compensatory increases in VEGF
    - Results in recurrent intravitreal neovascularization
  - Anti-VEGF agents enter the bloodstream of preterm infant eyes and reduce serum VEGF; may adversely affect developing organs of premature infant.
- **BEAT-ROP study**
  - Bevacizumab vs. laser for zone 1 or posterior zone 2 ROP with stage 3 and plus disease
  - 0.025 mL of 25 mg/mL (0.625-mg bevacizumab) reduced recurrence of severe ROP to 4% in bevacizumab-treated compared to lasertreated eyes (22%) by 54 weeks postmenstrual age.
- **ROP1 study (Pediatric Eye Disease Investigator Group [PEDIG])**
  - De-escalating dose study of bevacizumab in treatment-naive type 1 ROP in 1 or both eyes found reduced severe ROP at 1 month with 1/20th the dose (0.031 mg).
- **CARE ROP study**
  - Ranibizumab has less systemic absorption and shorter half-life than bevacizumab; ranibizumab at 2 doses (0.12 mg or 0.2 mg) was successful in controlling acute ROP, defined as not requiring rescue treatment at 24 weeks.

Phakomatoses

- oculoneurocutaneous syndromes
- phakoma was first used by **Van der Hoeve** in 1932

- **Hamartia**: is a nontumorous anomaly of tissues normally present at the location where it develops
- **Hamartoma**: is a tumorous malformation of tissues normally present at the location where it develops (eg: VHL)
- **Chorista**: is a nontumorous anomaly composed of elements that are not normally present at the site where they develop
- **Choristoma**: is a tumorous malformation composed of elements that are not normally present at the site where they develop (eg: limbal dermoid)
- Most phakomatoses display an AD inheritance except encephalofacial hemangiomatosis (Sturge–Weber) and racemose hemangiomatosis (Wyburn-Mason) in which germline heredity does not appear to play a role.

Capillary Hemangioblastoma VHL

- Retinal capillary hemangioblastomas RCH = retinal angiomas
- a sign of the systemic condition, **von Hippel–Lindau disease (VHL).**
- AD
- 1 in 36 000
- CNS: brain, spinal cord, inner ear, and retina
- visceral organs: the kidney, adrenal gland, pancreas, epididymis and broad ligament
- **Genetics**
  - germ line mutation in the VHL gene, which is located on the short arm of chromosome 3, **3p25–26**
  - VHL gene's protein degrade particular transcription factors called **hypoxia inducible factors (HIFs)**
  - pVHL, the VHL suppressor gene product, is known to downregulate vascular endothelial growth factor (VEGF) expression. With the absence of pVHL, VEGF is upregulated, resulting in neovascularization on and around these retinal capillary hemangioblastomas
- **Clinical Features**
  - initial appearance: subtle red or grayish dot no larger than a few hundred microns
  - later: proliferation progresses, secondary alterations occur to produce a distinctive clinical appearance that is often nodular
  - tumors are located predominantly in the retinal periphery and less frequently on or around the optic disc
  - tumors are located predominantly in the retinal periphery and less frequently on or around the optic disc
  - retinal hard exudates can develop
- FFA: early leakage and marked hyperfluorescence and this may persist or decrease in the late phases of the study.
- **Treatment**

- laser photocoagulation, cryotherapy, radiation, photodynamic therapy, or by surgical excision.
- **ablatio fugax**: photocoagulation and cryotherapy of peripheral tumors can often lead to massive retinal hard exudate accumulation and retinal edema in the macula, contributing to further decrease in vision following treatment.
- **SU5416**, an intravenously administered inhibitor of VEGF receptor-2,
- **bevacizumab**, a humanized anti-VEGF antibody, was also used systemically, resulting in a transient reduction in exudation, but no improvement in visual outcome

- **Diagnosis of von Hippel–Lindau disease**
  - A positive family history and a CNS hemangioblastoma (including retinal hemangioblastomas), pheochromocytoma, or clear cell renal carcinoma is sufficient for diagnosis
  - if there is no family history, for diagnosis, the individual must have two or more CNS hemangioblastomas, or one CNS hemangioblastoma and a visceral tumor (with the exception of epididymal and renal cysts, which are frequent in the general population

Tuberous Sclerosis

- Bourneville syndrome
- AD
- hamartomatous tumors of the brain, skin, viscera, and eye
- classic triad included seizures, mental retardation, and cutaneous angiofibromas
- Clinical Features
  - ***Neurological:*** infantile spasms" or "salaam attacks
  - ***Cognitive and behavioral disability***
  - ***Skin features:*** butterfly distribution of adenoma sebaceum aka Facial angiofibromas, ash-leaf lesion → **Wood's lamp,** Shagreen patches
  - ***Visceral features:*** Renal angiolipomas, Cardiac hamartomas
  - ***Skeletal features:*** Sclerotic calcified areas
  - **Ocular**
    - ***Retinal***
      - Solitary astrocytic hamartomas: (1) large, whitish (calcified) nodular masses or (2) flat, translucent (noncalcified) smooth tumors
      - vitreous hemorrhage, retinal vascular abnormalities (including telangiectasia, neovascularization, and exudation), and vitreous seeding
    - ***Optic nerve phakomas***
    - ***Ocular adnexal lesions:*** adenoma sebaceum, poliosis
- ***Differential diagnosis***

- Retinal astrocytoma
- Retinoblastoma
- Myelinated nerve fibers
- Coats disease

Neurofibromatosis

- **Type 1**
  - peripheral neurofibromatosis or von Recklinghausen syndrome
  - chromosome 17
  - peripheral and cutaneous manifestations
  - 1 in 3000
  - **at least two of the following seven criteria should be present for diagnosis**
    1. Café au lait
    2. Freckles in axilla or inguinal region
    3. Skin neurofibroma
    4. Optic nerve glioma
    5. Iris Lisch nodules
    6. Osseous lesion
    7. Relative (1st degree) with NF1 by above criteria
- **Type 2**
  - central or bilateral acoustic neurofibromatosis
  - chromosome 22
  - CNS tumors and early onset of posterior subcapsular cataract
  - MISME syndrome, a mnemonic referring to related tumors of MIS (multiple inherited schwannomas), M-meningiomas, and E-ependymomas
  - **at least one of the three**
    1. Bilateral 8th cranial nerve tumors confirmed on magnetic resonance imaging or computed tomography
    2. Unilateral 8th cranial nerve tumor with relative with NF2
    3. Two of following→ Meningioma, Glioma, Schwannoma, Juvenile posterior subcapsular lens opacity with relative with NF2

Sturge–Weber syndrome

- 1 per 50 000 persons
- **Roach diagnostic scale**
  - Classic Sturge–Weber syndrome

- Sturge–Weber syndrome
- Sturge–Weber syndrome forme fruste

Wyburn-Mason syndrome

- Racemose hemangiomatosis
- midbrain and ipsilateral retina
- 30% of patients with the retinal findings have brain findings.
- 8% of patients with brain findings have retinal findings
- **Archer classification**
  1. Abnormal capillary plexus between the major vessels of the arteriovenous malformations
  2. Arteriovenous malformations lack any intervening capillary bed between the artery and vein
  3. Extensive arteriovenous malformations with dilated and tortuous vessels and no distinction between artery and vein

Leber Congenital Amaurosis (LCA)

- Theodor Leber in 1869
- AR
  - 15 genes
  - Numerous genotypes-GUCY2D, RPE65, CEP290, CRB1
- Leber: Tapetoretinale Degeneration mit Amblyopie
- 1957: Franceschetti and Dieterle → severely reduced electroretinogram
- 3 in 100,000 newborn babies.
- 5% of all inherited retinopathies and approximately 20% of children attending schools for the blind
- Clinical features
  - Severe visual loss at or near birth
  - Wandering nystagmus
  - Amaurotic pupils
  - Pigmentary retinopathy
- RPE65 Gene Therapy
  - **LUXTURNA** (voretigene neparvovec-rzyl)
  - RPE65 genetic mutations
  - no-cost genetic testing through Spark
  - Age 1 year or older
  - Viable retina present

PFVS- Persistant Fetal Vascular System

- The name “persistent fetal vasculature syndrome” (PFVS) was suggested by Morton Goldberg in his Jackson Lecture. It replaced an incomplete name, “persistent hyperplastic primary vitreous (PHPV)” The new name, PFVS, addressed all the vascular elements involved in the errors of assembly.
- The fetal vasculature is composed of two parts:
    - Tunica vasculosa lentis: It is situated anteriorly encircling the lens. It has anterior and posterior divisions. Anterior division has Additional attachments to the pupillary frill of the iris. Posterior division has Additional attachments to the ciliary process and continues with the hyaloid artery posteriorly.
    - Hyaloid artery: It is situated posteriorly behind the lens. It is also called primary vitreous. The hyaloid vessel extends from posterior surface of lens to the disc. The vasculature fills the vitreous cavity & has many attachments to the retinal surface
- During development blood flow to the eye is through hyaloid artery. At the 240-mm stage (seventh month), blood flow in the hyaloid artery ceases. Hyaloid vascular regression occurs in following manner:
- The developing lens separates the fetal vasculature from vascular endothelial growth factor (VEGF) producing cells, inducing apoptosis.
    - Initial apoptosis induced by macrophages in a single endothelial cell.
    - Secondary apoptosis induced by synchronous process followed by obstruction of lumen of vasculature.
- Persistence of the hyaloid vascular system occurs in 3% of full-term infants and in 95% of premature infants. There is a spectrum of disorders resulting from persistence of the fetal vasculature.
    - Mittendorf’s dot is a remnant of the former site of anastomosis of the anterior tunica vasculosa lentis and posterior hyaloid artery. It is usually inferonasal to the posterior pole of the lens and is not associated with any known visual dysfunction
    - **Bergmeister's papilla** is the occluded remnant of posterior portion of the hyaloid artery, associated with glial tissue. It appears as a gray, linear structure anterior to the optic disc. It also has no visual dysfunction.
    - **Vitreous cysts** are generally benign lesions that are found in eyes with abnormal regression of the anterior or posterior hyaloid vascular system. It can occur in otherwise normal eyes or eyes with coexisting ocular disease, such as retinitis pigmentosa, retinochoroidal colobomas and uveitis. Vitreous cysts are generally not symptomatic and thus do not require surgical intervention
- It is unilateral approximately 90% of the time.
- PFVS does not progress during the course of the child's life, but tractional intraocular changes can occur later, most likely due to eye growth. The stalk also can cause traction on the posterior lens capsule leading to posterior lenticonus. Traction on the ciliary body can lead to hypotony. Traction on the retina, leads to tractional retinal detachment.
- Retinal Dysplasia: Microscopic and Macroscopic
- There are three types of PFVS:

- **Anterior PFVS**: It has predominant features of persistent anterior tunica vasculosa lentis without much or any posterior hyaloid component.
  - Presentation age 1 – 2 weeks after birth with leukocoria.
  - Microphthalmos.
  - Posterior lens opacity → cataract.
  - Retrolental fibrovascular membrane.
  - Shallow AC → glaucoma.
  - Elongated ciliary process → hypotony.
  - Stalk extending from posterior part of lens to optic disc may or may-not be present
- **Posterior PFVS**: It has predominant features of persistent posterior hyaloid artery without much or any anterior tunica vasculosa lentis.
  - Microphthalmos (may or may-not be present).
  - Posterior lens opacity.
  - Vitreous stalk
  - Retinal fold.
  - Tractional retinal detachment.
  - Hypoplastic optic nerve & macula.
- **Mixed PFVS**: Occurs when both the tunica vasculosa lentis and hyaloid system is present. It has a spectrum of presentations depending on the degree of involution of the hyaloid and tunica vasculosa lentis.

- **Associated diseases**
  - **Norrie disease gene**
  - **oculo-palatal-cerebral syndrome**, intrauterine herpes simplex virus infection, intrauterine exposure to clomiphene, oral-facial-digital syndrome, anterior and posterior colobomas or even cystic globes and tuberous sclerosis
- Differential Diagnosis
  - Retinoblastoma
  - Norrie disease: When bilateral PFV syndrome is present8.
  - Congenital cataract.
  - Walker-Warburg syndrome.
  - Trisomy.
  - Familial exudative vitreoretinopathy.
  - Incontinentia pigmenti.
  - Retinopathy of prematurity
- **Investigations**
  - B scan ultrasound
  - CT-MRI

- Management
    - Anterior PFVS
    - Posterior PFVS
        - Surgery not required if no traction present
        - Lens sparing vitrectomy is the surgery of choice.

Myopia

High Myopia

- 1-5% in different communities
- high myopia: spherical equivalent refractive error exceeds –6 diopters (D) and/or the axial length is longer than 26.5 mm.
- Pathological myopia: high myopia with any posterior myopia-specific pathology resulting from excess axial elongation (posterior staphyloma, CNVM, foveoschisis etc.)
- **The characteristics of the OCT image in these eyes are**
  - a relatively low signal to noise ratio
  - deep posterior staphyloma in the presence of which the peripheral tissue often drops off from the top edge of the image
  - poor fixation due to a large central scotoma from chorioretinal atrophy
  - critical signs that are mostly outside the fovea.
- **pearls for the OCT**
  - better to use spectral domain (SD-) OCT
  - pathology of interest must be located near the top of the OCT image because SD-OCT has the strongest signal at the top
  - large internal fixation or external fixation must be used
  - attention must be paid to pathologies outside the fovea
- **Epidemiology**
  - RRD: distribution of high myopia exceeding –6.0 D is about 16% in overall cases and the lifetime risk is more than 20-fold compared with emmetropia
  - Myopic foveoschisis was identified in 9% of patients with posterior staphyloma
  - In patients with a macular hole and retinal detachment, 8.5% develop the same pathology in the fellow eye within 4 years
  - RRD after LASIK: 0.25%
  - RRD after RLE: 7.3% within 3 years and 8.1% in 7 years
  - RRD after phacoemulsification: 2.2% (0.93% in general population)
- **Etiology and pathophysiology**
  - ***Myopic foveoschisis***
    - foveal cyst in 47%, a lamellar hole in 29%, and a foveal detachment in 29%
    - hypothesis:
      - inner retina is less flexible than the outer retina due to vitreous cortex adhering to the retina, epiretinal membranes (ERMs), internal limiting membrane (ILM), and retinal vessels
    - retinoschisis at multiple levels in the outer plexiform layer, inner plexiform layer, ganglion cell layer, and nerve fiber layer

        - ILM detachments, sometimes recognized as “inner retinoschisis,” are often seen in highly myopic eyes
    - ***Macular hole with or without retinal detachment***
        - persistent traction at the macular hole edge after opening is critical for initiating a retinal detachment
    - ***Posterior retinal detachments from paravascular microholes***
        - incidence rates of retinal cysts and paravascular holes were 50% and 27%,
- ***Clinical Features***
    - central visual distortion
    - relative central scotoma
    - Even if patients present with a macular hole, the Watzke–Allen test is usually negative.
    - OCT
        - split retinal layers normally have a bridge → “**column**” which is presumed to be residual Müller cells
        - ILM detachment, and is an indicator of the tractional force from the ILM
        - IS/OS junction line is typically well preserved in the area of retinoschisis, suggesting that the photoreceptor function is well preserved in this subtype.
    - Two types of macular hole
        - retinoschisis type:
        - detachment type:
    - FAF: accumulated in the RPE and is an indicator of the oxidative stress level
- **Treatment**
    - vision decreased in 69% of patients, a macular hole developed in 31% after 3 years of follow-up, and in 50% of patients with retinoschisis a macular hole or retinal detachment developed after 2 years
    - postponed until the vision decreases to about 20/40 because there is still a chance of visual worsening after vitrectomy.
    - visual improvement after surgery is about 80% in cases with a foveal detachment and 50% with retinoschisis alone
    - ***indications***
        - macular hole with an extensive retinal detachment
        - visual disturbance, turbulence, or visual loss
    - ***prognosis***
        - favorable if no macular hole develops
        - macular hole closure rate with retinoschisis or retinal detachment ranges from 30% to 50% on OCT images
    - ***procedures***
        - Vitreous separation

- Internal limiting membrane peeling
- Tamponade
- Macular buckling: modified silver clip

Myopic Macular Degeneration

- Myopic macular degeneration (MMD), sometimes known as pathologic myopia (PM), myopic maculopathy, or degenerative myopia (used interchangeably here), is a possible consequence of myopia, particularly in eyes with high myopia (typically defined as spherical equivalent of at least -6.0D)
- MMD is characterized by progressive elongation of the globe and abnormal choroidal vasculature (mainly in eyes with posterior staphyloma), with Additional degenerative changes seen in the retina. MMD is estimated to affect up to 3% of the global population and is a particularly frequent cause of vision impairment and blindness in the young working-age population, thus having a considerable social and economic impact.
- **Classification of Myopic Macular Degeneration**
  - There continues to be a lack of a standardized classification system for MMD. Clinically, typical changes in MMD include the following:
    - Peripapillary atrophy
    - Thinning of the retinal pigment epithelium (RPE) and choroid
    - Lacquer cracks in the Bruch membrane
    - Subretinal hemorrhage
    - Posterior staphyloma
    - mCNV
  - Avila et al described a severity pattern (M0 to M5) for MMD, which has been used in some studies to characterize patients.
    - M0: Normal-appearing posterior pole
    - M1: Choroidal pallor and tessellation (Reduced RPE pigmentation means the choroidal vessels can be seen through the retina.)
    - M2: Choroidal pallor and tessellation with posterior staphyloma
    - M3: Choroidal pallor and tessellation with posterior staphyloma and lacquer cracks
    - M4: Choroidal pallor and tessellation with lacquer cracks, posterior staphyloma, and focal areas of deep choroidal atrophy
    - M5: Posterior pole with large geographic areas of deep chorioretinal atrophy and “bare” sclera

Myopic CNV

- One of the most serious complications of MMD is myopic choroidal neovascularization (mCNV), which often leads to a sudden onset but progressive decline in central vision and

is associated with a poor prognosis unless treated. It has been reported that approximately 5%-11% of individuals with MMD will develop mCNV, although this may be an underestimate.

- The interrelationship between the degree of myopia and the development and progression of MMD and mCNV is not fully understood.
- The introduction of intravitreal anti-VEGF therapies for patients with mCNV has had a major impact on the management of these patients, and its efficacy and safety is now supported by 2 Phase 3 randomized clinical trials using ranibizumab andaflibercept.
- **Classification of mCNV**
  - mCNV appears as “classic” pattern of CNV on fluorescein angiography (FA), as a well-defined lesion with hyperfluorescence in the early phases and dye leakage during the later phases. However,not all eyes show fluorescein leakage,and if a hemorrhage is present this can interfere with FA; in these cases, indocyanine green angiography (ICGA) may aid in differentiating the lesion and provide a more accurate location.
  - Spectral domain OCT (SDOCT) can provide useful information on the presence and stage of mCNV. During the active stage, a highly reflective dome-shaped projection above the RPE is typically visible (type 2 CNV), and subretinal as well as intraretinal fluid may be detectable. During the scarring stage, only the surface of the CNV shows high reflectivity. Finally, in the atrophic stage the CNV flattens, but an increase in surrounding choroidal reflectivity is observed due to chorioretinal atrophy.
- FA for diagnosis of mCNV: Some studies show that when compared to FA, SD-OCT alone was found to be inferior in detecting signs of mCNV activity, suggesting that FA should be performed in any suspected case of mCNV. Recent studies have used OCT angiography to characterize presence, severity, and treatment response of mCNV.

Diabetic Retinopathy

Epidemiology

- **Prevalence:** among persons with diabetes, the crude prevalence of **diabetic retinopathy** was **40%** and the crude prevalence of **severe vision-threatening retinopathy** (pre-proliferative and proliferative retinopathy or macular edema) was **8%**.
- **Incidence & Progression: (4 yearWESDR)**

	Younger-onset	Older-onset Taking insulin	Older-onset Not taking insulin
Any retinopathy	59.0	47.4	34.4
Improvement	6.9	15.3	19.8
No change	55.1	58.1	71.0
Progression	41.2	34.0	24.9
Progression to PDR	10.5	7.4	2.3
Incidence of CSME	4.3	5.1	1.3

- **Gender**: no significant difference
- **AGE**
  - Under 13 years of age, diabetic retinopathy was infrequent, irrespective of the duration of diabetes
  - Age at diagnosis was not related to incidence or progression of diabetic retinopathy
- **Duration of diabetes**
  - most consistent relationship
  - 3–4 years after diagnosis of diabetes in the WESDR younger-onset group with type 1 diabetes was 14% in men and 24% in women
  - first 3 years after diagnosis of diabetes, 23% of the type 2 diabetic group not taking insulin had retinopathy, and 2% had proliferative retinopathy (PDR)
- **Glycemic Control**
  - **DCCT and UKPDS**: A1c level **of 7.0% control**, when achieved earlier after diagnosis of diabetes, may have greater long-term benefit in terms of reducing the incidence and progression of retinopathy
  - **NHANES III and the WESDR**: suggest that few persons with diabetes reach this targeted level of glycemic control.
  - **ACCORD and ADVANCE:** further lowering the level of glycemia does not support applying intensive glycemic control with the current technology to achieve such control in patients with long-standing type 2 diabetes who have or who are at risk of cardiovascular disease
- **C-peptide status**
  - most **severe retinopathy** were found in individuals with undetectable or low plasma C-peptide **(<0.3 nM**)
- **exogenous insulin** in itself is unlikely to be causally related to retinopathy in diabetic people with normal C-peptide levels

- **Blood pressure**:
  - **UKPDS**: each 10 mmHg decrease in mean systolic blood pressure, a 13% reduction was found for microvascular complications
  - **WESDR**: a 10 mmHg rise in diastolic blood pressure → **330% increased** 4-year risk of developing macular edema in those with type 1 diabetes and a **210**% increased risk in those with type 2 diabetes
- **Proteinuria and diabetic nephropathy**: association between the prevalence of diabetic nephropathy, as manifest by microalbuminuria or gross proteinuria, and diabetic retinopathy
- **Serum lipids**:
  - **WESDR**: higher serum total cholesterol was associated with higher prevalence of retinal hard exudates in both the younger and the older-onset groups taking insulin but not in those with type 2 diabetes using oral hypoglycemic agents
  - **ETDRS**: higher levels of serum lipids (triglycerides, low-density lipoproteins, and very-low-density lipoproteins) at baseline were associated with increased risk of developing hard exudates in the macula and decreased visual acuity
- **Smoking**: most epidemiologic data show no relationship between cigarette smoking and the incidence or progression of diabetic retinopathy
- **Alcohol**:
  - **UKPDS**: increased alcohol consumption to increased severity of retinopathy
  - **EURODIAB**: alcohol consumption was associated with a reduction in progression of diabetic retinopathy
  - **ADVANCE**: no relation of alcohol consumption to progression of diabetic retinopathy
  - **WESDR**: alcohol consumption was associated with a lower frequency of proliferative retinopathy in persons with type 1 diabetes
- **BMI**: inversely related to the presence or severity of diabetic retinopathy only in persons with type 2
- **Socioeconomic status**: ?? low socioeconomic status was significantly associated with the 6-year incidence of macular edema but not incidence or progression of diabetic retinopathy
- **Hormone** and reproductive exposures in women
  - **WESDR**: menarchal status at the baseline examination was related to the prevalence and severity of retinopathy
  - **Pregnancy**, a condition associated with high levels of estrogens, is associated with more rapid progression of retinopathy.
- risk of developing a *heart attack, stroke, diabetic nephropathy, and amputation* was higher in those with proliferative diabetic retinopathy compared to those with no or minimal nonproliferative retinopathy at baseline

Etiology

- **Anatomic lesions**
  - ***Loss of pericytes***
    - one of the earliest and most specific signs but histological
    - pericytes loss → venous dilation and beading that is visible clinically
    - endothelial cell proliferation resulting in the development of microaneurysms
    - hyperglycemia leads to pericyte degeneration:
      - the aldose reductase pathway
      - platelet-derived growth factor-beta (PDGF-β): deficiency leads to lack of development of pericyte
  - ***Capillary basement membrane thickening***
    - deposition of fibrillar collagen and "Swiss cheese" vacuolization
    - Glycation of basement membrane collagen by enzymatic and nonenzymatic processes
  - ***Microaneurysms***
    - earliest clinically visible sign
    - **hypercellular or acellular**
    - tiny, intraretinal red dots located in the inner retina
    - pericytes have antiproliferative effect, also loss of pericytes leads to weakening of walls
  - ***Capillary acellularity***
    - more advanced microvascular lesion in diabetic retinopathy
    - not unique to diabetes
  - ***Breakdown of blood–retina barrier***
    - development of macular edema
    - opening of the tight junctions between vascular endothelial cell processes
    - VEGF leads to the breakdown of the inner blood–retina barrier appears to involve alteration of endothelial cell tight junctions
    - kallikrein–kinin system: Bradykinin, via nitric oxide, induces vasorelaxation of retinal arterioles

- **Biochemical mechanisms**
  - ***The aldose reductase theory***
    - polyol pathway or the sorbitol pathway
    - enzymes aldose reductase **AR** and sorbitol dehydrogenase **SDH**
    - Elevation of intracellular glucose → **AR (+NADPH)**→ sorbitol → **SDH** → fructose

- When other mechanisms of glucose metabolism becomes saturated, **AR** starts working but **SDH is slow** so sorbitol accumulates
- Also decrease NADPH → decrease the production of nitric oxide

✣ ***Advanced glycation endproduct (AGE) theory***

- nonenzymatic glycation and crosslinking of proteins
- AGEs is the collective name given to proteins, lipids, and nucleic acids that undergo irreversible modification by reducing sugars or sugar-derived products → **Maillard reaction**
- **early glycation**: reversible nonenzymatic binding of a sugar to amino acid groups on proteins, lipids, or nucleic acids. → Schiff bases → more stable **Amadori products** (HbA1c and fructosamine)
- cellular effect of AGEs is mediated by RAGE → of these intracellular kinases can subsequently lead to cell dysfunction
- **Aminoguanidine** is an inhibitor of AGE formation

✣ ***Reactive oxygen intermediates (ROI) theory***

- byproducts of oxidative phosphorylation include free radicals, such as superoxide anion, whose production is increased by high levels of glucose
- damage mitochondrial DNA as well as cellular proteins

✣ ***Protein kinase C (PKC) theory***

- Elevated levels of **DAG and PKC**
- increased vascular permeability, disruption of nitric oxide regulation, increased leukocyte adhesion to vessel walls, and changes in blood flow
- **ruboxistaurin** (LY333531), a PKC-β inhibitor

✦ **Genetic factors**

✣ strong association between proliferative retinopathy and the presence of **HLA-DR** phenotypes **4/0, 3/0, and X/X** (neither 3 nor 4)

✦ **Other ocular factors**

✣ Becker: **glaucoma** was associated with a **decreased** prevalence and severity of diabetic retinopathy in affected eyes.

✣ **Myopia**: decreased prevalence and severity of diabetic retinopathy

NPDR: Non Proliferative Diabetic Retinopathy

✦ **Natural course**

✣ ***Diabetes mellitus without retinopathy***

✣ ***Microaneurysms***

✣ ***Retinal vascular hyperpermeability***

✣ ***Capillary closure, microvascular remodeling, and retinal ischemia***

- ***Alterations of the vitreous gel and vitreoretinal interface***

- **Clinical evaluation**
- ***Duration of diabetes mellitus:***
  - **WESDR**
  - younger-onset group: 13% of those with less than a 5-year duration of DM and in 90% of those with a duration of 10–15 years
  - older-onset group using insulin: 40% of those with less than a 5-year duration of disease and in 84% of those with a duration of 15–19 years
  - older-onset group not taking insulin: were 24% and 53% for <5 years and 15-19 years respectively
- ***Hyperglycemia***
  - retinopathy progression remained significantly **lower in those who had received more intensive treatment in the DCCT** than in those who had received conventional therapy. (Epidemiology of Diabetes Intervention and Complications (**EDIC**) study-its follow up of same patients of DCCT)
  - **UKPDS**: After 12 years, the rate of **retinopathy progression was reduced by 21%** and the use of laser photocoagulation was reduced by 29% in those getting intensive glycemic control compared with those getting conventional treatment.
  - **ACCORD**: In the intensive treatment group, the rate of retinopathy progression was 7.3%, compared with 10.4% in the standard therapy group
- ***Hypertension***
  - **UKPDS:** intensive blood pressure control (<150 SBP with beta blocker or ACEI) resulted in a 37% reduction in microvascular complications of DM, predominantly a reduced risk of retinal photocoagulation, compared with less intensive control (<180 SBP)
  - **ACCORD:** Rate of progression of retinopathy was not significantly different in the two groups 10.4% of those treated intensively (<120 SBP) compared with 8.8% of those treated with standard care (<140 SBP)
- ***Dyslipidemia***
  - Elevated levels of plasma triglycerides were associated with a greater risk of developing high-risk PDR in the ETDRS patients
  - Fenofibrate
  - Statins
- ***Other extraocular factors***
  - Diabetic nephropathy, as measured by albuminuria, proteinuria, or manifestations of renal failure, has been inconsistently associated with progression of retinopathy
  - DR can worsen precipitously in the setting of pregnancy
  - Anemia has been associated with progression of diabetic retinopathy

Ophthalmic evaluation

- measurement of visual acuity and intraocular pressure; evaluation of the anterior segment by slit-lamp biomicroscopy; gonioscopy when warranted (such as in the setting of elevated intraocular pressure, neovascularization of the iris, or glaucoma); and dilated funduscopic examination
- In the **absence of pupil dilation**, only **50**% of eyes are correctly diagnosed for the presence and severity of retinopathy
- stereoscopic evaluation of the posterior pole and visualization of the vitreous gel and peripheral retina
- ***Ancillary ocular imaging***
  - Fundus photography
  - Fluorescein angiography:
    - Nephropathy or renal failure is not a contraindication to testing
    - FA is not indicated for classification of disease
    - not clinically indicated to screen for mild retinopathy
  - Optical coherence tomography
    - Diabetic Retinopathy Clinical Research Network (DRCR.net)
    - pupil dilation, time-domain Stratus OCT, fast macular thickness map, which obtains 128 axial scans
    - Output includes center-point thickness, total macular volume, and mean values for retinal thickness in a grid comprised of a central subfield, four inner subfields, and four outer subfields

Classification ETDRS

- **modified Airlie House seven-field** 30-degree non-simultaneous stereo color fundus photographs
- **Mild NPDR**: At least one microaneurysm, AND criteria not met for more severe retinopathy.
- **Moderate NPDR:** Hemorrhages/microaneurysms ≥ standard photograph 2A; AND/OR cotton-wool spots, venous beading, or IRMA definitely present; AND criteria not met for more severe retinopathy
- **Severe NPDR**: Cotton-wool spots, venous beading, and IRMA definitely present in at least two of photographic fields 4 to 7; OR two of the three preceding features present in at least two of fields 4 to 7 and hemorrhages/microaneurysms present in fields 4 to 7 ≥ standard photograph 2A in at least one of them; OR IRMA present in each of fields 4 to 7 and ≥ standard photograph 8A in at least two of them; AND criteria not met for more severe retinopathy.
- **Early PDR**: New vessels; AND criteria not met for high-risk PDR.
- **High-risk PDR:** New vessels on or within one disc diameter of the optic disc (neovascularization of the disc [NVD]) ≥ standard photograph 10A (approximately 1/4 to 1/3 disc area) with or without vitreous or preretinal hemorrhage; OR vitreous and/or

preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ 1/4 disc area.

Management

- ***Modification of systemic risk factors***
  - **Control of hyperglycemia:**
    - DCCT, EDIC study, UKPDS, and ACCORD
    - hemoglobin A1C of 7.0% or lower
  - **Control of hypertension**
    - UKPDS: <150 is better than <180
    - ACCORD: <120 is not better than <140
  - **Treatment of dyslipidemia**
    - WESDR and the ETDRS: may be beneficial
    - Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: role for fenofibrate in reducing risk of retinopathy progression
- ***Retinopathy screening and surveillance***
  - **FOLLOW-UP**
    - Initial eye examination is recommended 3–5 years following diagnosis of type 1 DM, and at time of diagnosis for those with type 2 DM
    - type 1 and type 2 diabetics with no retinopathy is yearly
    - In the absence of DME, those with mild to moderate NPDR should be evaluated every 6–12 months, and those with severe NPDR should be seen every 2–4 months
    - with DME merit frequent follow-up, generally at least every 2–4 months, and sometimes monthly depending on treatment.
  - **Follow up in Pregnancy**
    - prior to conception and early during the first trimester
    - pregnant patients with no retinopathy, mild NPDR, or moderate NPDR should be individualized based on the severity and recent changes in retinopathy.
    - Pregnant patients with severe NPDR should be evaluated every 1–3 months.
    - Specific circumstances, such as presence of DME, may dictate need for more frequent follow-up
- **ETDRS**:
  - Aspirin (**450 mg** ??) use did not affect the severity of retinopathy or the risk of visual loss over 7 years
  - Aspirin remains an important therapy for control of cardiovascular risk in many diabetics, and no level of retinopathy severity, including PDR, should contraindicate its use.
- **Sorbinil Retinopathy Trial**

- inhibitor of the enzyme **aldose reductase**
- sorbinil or placebo: not significantly different changes

- **Ruboxistaurin**
  - inhibitor of beta-isoforms of **protein kinase C**,
  - participants taking ruboxistaurin (**32 mg/day**) showed a **significant delay in time to moderate vision loss** (doubling of the visual angle) compared with those taking placebo
- **Fenofibrate**: peroxisome proliferator-activated receptor (PPAR) alpha agonist
  - Fenofibrate Intervention and Event Lowering in Diabetes **FIELD study**
    - fenofibrate (200 mg/day) or placebo
    - significantly higher rate of retinopathy progression in the placebo group compared with the fenofibrate group among participants with retinopathy at baseline
  - **ACCORD study**
    - simvastatin plus fenofibrate (160 mg/day) or simvastatin plus placebo

PDR: Proliferative Diabetic Retinopathy

- *nearly 25% with type 1 and 16% with type 2 will develop PDR after 15 years of diabetes*
- four fundamental processes
  1. the cycle of proliferation and regression typical of new vessels
  2. proliferation of fibrous tissue accompanying new vessels
  3. formation of adhesions between the fibrovascular proliferations and the posterior vitreous surface;
  4. contraction of the posterior vitreous surface and associated proliferations
- **The 4–2–1 rule**
  - Severe NPDR (any one of the following)
    - H/MA ≥ Standard photograph 2A in four quadrants
    - VB definitely present in two or more quadrants
    - IRMA ≥ Standard photograph 8A in one or more quadrants
  - Very severe NPDR (two or more of the above)
- Soft exudates usually disappear within 6–12 months.
- H/MA have a half-life of approximately 3 months
- **featureless retina**: after extensive capillary closure, when the number of small vascular branches decreases and some small arterioles become sclerosed with a white thread-like appearance
- New vessels most frequently seen posteriorly, **within about 45 degrees** of the optic disc.
- NVE had been shown to occur most frequently in the superotemporal quadrant, followed in frequency by the inferonasal

- NVD: defined as NV at or within 1 disc diameter of the disc
- For detection of early NVE: 30-degree seven standard fields of the modified Airlie House classification
- Newer Ultrawide field imaging: **Optos 200**
- **distinguishing between NVE and IRMA:**
  - NVE are more superficial location, formation of wheel-like networks, extension across both arterial and venous branches of the underlying retinal vascular network, and accompanying fibrous proliferation.
  - In unusual borderline cases, fluorescein angiography can distinguish between the profuse leakiness of preretinal new vessels and the more competent IRMA.

Natural Course

- treated or untreated, PDR will eventually reach an involutional quiescent stage which may remain stable for decades. Laser photocoagulation induces this quiescent state earlier, usually with less associated retinal damage and visual loss
- ***Development and proliferation of new vessels***
  - PDR with high-risk characteristics is defined by one or more of the following lesions
  - NVD that is approximately one-quarter to one-third disc area or more in size
  - any amount of NVD if fresh vitreous or preretinal hemorrhage is present
  - NVE greater than or equal to one-half disc area in size if fresh vitreous or preretinal hemorrhage is present
- ***Contraction of the vitreous and fibrovascular proliferation***
  - Before the onset of posterior vitreous detachment, neovascular networks appear to propagate primarily on or slightly anterior to the retina
  - beginning of posterior vitreous detachment → localized or diffuse VH
  - Hemorrhage in the formed vitreous tends to lose its red color and become white before absorption is complete. Absorption of a large hemorrhage from the formed vitreous is usually slow, requiring many months.
  - fluid-level or “boat-shaped” hemorrhage
- ***Retinal distortion and tractional detachment***
  - With contraction of an extensive sheet of fibrovascular proliferations, distortion or displacement (“dragging”) of the macula may occur
  - NSR or even RPE may appear dragged
  - Contraction of vitreous or areas of fibrovascular proliferation may also lead to retinal detachment
- ***Involutional or “Quiescent” Proliferative Diabetic Retinopathy***
  - the retinopathy has “burned-out”
  - vitreous contraction has reached completion and the vitreous is detached from all areas of the retina except where vitreoretinal adhesions associated with new vessels prevent such detachment

- Previously dilated or beaded veins return to normal caliber or become narrower and often appear sheathed. Fewer small venous branches are visible

PDR & DM

- **Prevalence**
  - **insulin-taking patients younger than 30:** near zero when duration of diabetes was less than 10 years and then rose rapidly to about 50% in persons with 20 years or more of diabetes
  - **older-onset (30 years or more) insulin-taking:** 2% in persons with less than 5 years of diabetes to about 25% in those with 20 years or more
  - **older-onset, noninsulin-taking (type 2) group:** less than 5% before 20 years to about 5% thereafter
- **Proliferative diabetic retinopathy and blood glucose control**
  - DCCT, EDIC, UKPDS demonstrated conclusively that the long-term risks for the development and progression of DR can be reduced dramatically by improving blood glucose control with intensive treatment
  - ETDRS: HbA1c at baseline was a strong risk factor
- **Early worsening of retinopathy with improved glycemic control**
  - unexpected worsening of DR in the first 3–12 months
  - usually mild (development of cotton-wool spots and/or IRMA) and transient.
  - clinically important early worsening (defined as development of PDR, severe NPDR, or clinically significant macular edema) was not observed in patients with no retinopathy or with microaneurysms involving only one eye, but it occurred in 6 of the 32 patients with moderate NPDR.
  - Panretinal photocoagulation prior to initiation of such treatment may be considered when factors suggest a particular need to protect against advancing severe retinopathy
  - risk factors for early worsening were higher baseline HbA1c and greater reduction of HbA1c after enrollment
  - mechanisms: alterations in retinal blood flow, decreased autoregulation of the retinal circulation, transient ischemia owing to a decrease in nutrient substrate, and insulin-induced changes in retinal homeostasis that lead to an increase in growth factors such as VEGF
- **Systemic medications**
  - glycemic control→ DCCT, EDIC, UKPDS, ACCORD, ADVANCE
  - lipid-lowering medications → ACCORD-EYE, FIELD
  - angiotensin-converting enzyme inhibitors → EURODIAB, EUCLID, ADVANCE
  - angiotensin II type 1-receptor blockers → DIRECT, RASS
  - **Thiazolidinediones (rosiglitazone**): antiangiogenic effects mediated by PPARγ agonist activity

Management

- two principal therapeutic approaches:
  - first, to discourage the proliferation of new vessels → **Medical**
  - second, to prevent or relieve the effects of contraction of the posterior vitreous surface and fibrovascular proliferation → **Surgical**
- ***Pituitary ablation***→ Biasotti and Houssay: hypophysectomy
  - primarily of historical interest because photocoagulation is more effective and is free of the many substantial disadvantages
  - suppression of growth hormone activity and effects on insulin-like growth factor 1

Medical Management

- ***laser therapy***
- mechanisms
  - Ischemic retina, which produces growth factors, is destroyed, thus reducing the angiogenic stimulus.
  - retinal cells may produce growth-inhibiting factors or reduce production of growth-promoting factors in response to photocoagulation injury
  - increase in oxygenation from the choroid to the inner retina that occurs through the laser scars due to the thinning of the retina in the treated area
- The DRS conclusively demonstrated that PRP significantly reduces the risk of severe visual loss (SVL) from PDR, particularly when high-risk PDR is present
  - severe visual loss: visual acuity of <5/200 at each of two consecutively completed follow-up visits, scheduled at least 4-months apart
  - Treatment reduced the risk of severe visual loss by 50% to 65% in all three groups (NPDR, PDR with HRC, PDR without HRC) at both 2 and 4 years, except for the NPDR group at 2 years
  - in the xenon group, laser attributed vision impairment were more than argon group and visual field loss were more than in argon group.
- ***ETDRS and the timing of treatment***
  - scatter treatment not be used in eyes with mild to moderate NPDR but that it be considered for eyes approaching the high-risk stage (i.e., eyes with very severe NPDR or moderate PDR)
  - benefit of prompt treatment is greater in those who have type 2 diabetes or are older than 40 years of age
- ***Scatter photocoagulation and macular edema***
  - Macular edema sometimes increases, at least temporarily, after scatter photocoagulation, and this edema may be followed by transient or persistent reduction of visual acuity

- eyes with DME requiring scatter treatment are at less risk of visual acuity loss when focal or grid treatment to reduce the DME precedes scatter photocoagulation
- VEGF inhibitors combined with either immediate or deferred macular laser have been shown to be more effective at reducing visual loss than laser alone
- scatter treatment should not be delayed when the risks of vitreous hemorrhage or neovascular glaucoma seem high, regardless of the status of the macula

- ***PRP and advanced PDR***
  - high-risk characteristics are definitely present, PRP should usually be carried out, despite the presence of fibrous proliferation or localized traction retinal detachment
  - Extensive neovascularization in the anterior chamber angle is a strong indication for PRP
- **Current techniques of PRP**
- **Regression of new vessels**
  - 3-day post-treatment visit 20% of the 50 eyes had regressed from the high-risk stage; at 2 weeks, 50%; at 3 weeks 72%; and at 6 months, 62%. About one-third of the eyes that were still in the high-risk stage after 3 weeks were no longer high-risk at 6 months.
- **Complications of scatter (PRP)**
  - Loss of visual function
  - Damage to posterior ocular structures
  - Complications related to blood retinal barrier breakdown
  - Complications related to the destructive nature of the procedure
  - Complications related to contraction of fibrovascular tissue
- **High-risk Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema: Results From PANORAMA**
  - PANORAMA (NCT02718326) is the first large prospective trial of eyes with moderately severe to severe (high-risk) nonproliferative diabetic retinopathy (NPDR) in patients without diabetic macular edema (DME) since the Early Treatment Diabetic Retinopathy Study.
  - In the Phase 3 VISTA and VIVID studies, more eyes treated with intravitreal aflibercept injection (IAI) had a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score vs. laser photocoagulation in patients with both diabetic retinopathy and DME.
  - PANORAMA compared the efficacy and safety of IAI vs. sham in moderately severe to severe NPDR in patients without concurrent DME.
  - IAI improved diabetic retinopathy and prevented disease progression in eyes with moderately severe to severe NPDR in patients without DME.

Surgical Management

- **Indications**
- ***Cataract:*** cataract management with Management of PDR by PRP, Anti VEGF
- ***High-risk retinal neovascularization***
  - Fibrovascular proliferations
    - Stable or improved visual function may be achieved in 78%
    - Good prognostic factors include younger age at baseline (<40 years), preoperative panretinal photocoagulation, better visual acuity (>5/200), no iris neovascularizations, and no iatrogenic breaks at surgery
  - Vitreous hemorrhage
    - Waiting, head elevation or intravitreal injection of hyaluronidase
    - Early vitrectomy, defined by the DRVS as within 1–4 months from onset, results in earlier recovery of vision and better functional outcome after 2 and 4 years
- ***Macular traction and macular edema***
  - Vitreomacular traction syndrome, vitreopapillary traction, diabetic macular edema, epiretinal membrane or macular hole
- ***Retinal detachment***
  - Tractional retinal detachment
    - Diabetic tractional macular detachment therefore has been the **most common** indication for Vitrectomy
    - vitrectomy reoperation rates: 24% and 47%
    - Good prognostic factors: age <50 years, preoperative panretinal photocoagulation; visual acuity >5/200; no or few iris neovascularizations or retinal proliferations; macular detachments <30 days, and no iatrogenic breaks
  - Combined TRRD:
    - retina appears convex in contrast to tractional
    - often extending over the ora serrate
    - retinal surface often shows white **hydration lines**, which are diagnostic of retinal holes
- ***Neovascular glaucoma***

Preoperative evaluation

- should be referred to an internist or endocrinologist before surgery
- patient's medical and glycemic status as well as coexistent problems as hypertension, hyperlipidemia, cardiovascular or renal disease
- Anticoagulants as well as antiplatelet medications must be stopped or substituted at the surgeon's suggestion

- Preoperative electrophysiological testing

Surgical procedure

- *Cataract surgery*
- *Glaucoma surgery*
  - Aqueous shunt procedures
  - Cyclodestructive therapy
- *Pars plana Vitrectomy*
  - *Eyes with complete posterior hyaloid separation*
    - hyaloid membrane is incised and the opening enlarged
    - diathermy of neovascularizations or small bleeding sources
    - Full-scatter endophotocoagulation
    - ILM Removal
  - *Eyes with incomplete posterior hyaloid separation*
    - **Segmentation**:
      - tractions between centres of adhesions are removed
      - vertical membrane peeler–cutter scissors
    - **Delamination**:
      - connections between the posterior hyaloid and/or fibrovascular tissue and the internal limiting membrane are cut
      - fibrovascular adhesions to the posterior hyaloid are excised parallel to the retinal surface with horizontal scissors
    - **“en bloc” technique:**
      - removal of the vitreous and associated vitreoretinal membranes as a single unit
      - After an opening is made in the posterior hyaloid adjacent to vascular epicenters, membrane peeler–cutter scissors enter the subhyaloidal space. The unremoved formed vitreous provides anterior traction that helps separate the vitreous and fibrovascular tissue from the retina and helps identify sites of adhesion.
  - *Eyes with subtotal posterior vitreous adhesion*
    - gentle suction can be used to find areas where the vitreous is lesser adherent
    - areas of subhyaloidal hemorrhage or near optic disc
    - centripetal dissection
    - beware of posterior vitreoschisis
  - *Eyes with combined tractional and rhegmatogenous detachment*
    - great care for not to aspirate and cut inadvertently into the retina

- Photocoagulation
- Tamponades
- Wound closure

Complications

- *Intraoperative complications*
  - *Reduced visualization:*
  - Corneal edema:
    - related to intraocular pressure, dryness, duration of surgery, or trauma to the epithelium or endothelium
    - Debridement rate for infusion lenses was 23.8% compared with 13.0% for sew-on lenses and 15.6% for non-contact wide-angle
  - narrow pupil:
    - after prolonged surgery, ocular hypotony or direct surgical trauma
  - lens opacification:
    - postoperative cataract formation after vitrectomy in diabetic eyes was reported to occur in 17–37%
  - Intraocular hemorrhage
  - Retinal breaks and detachment
  - Subretinal perfluorocarbon or silicone oil
- *Postoperative complications*
  - *Conjunctival complications:* Wound dehiscence and stitch abscess may eventually progress to conjunctivitis, scleritis or Endophthalmitis
  - *Corneal complications:* epithelial defects,
  - *Uveitis*
  - *Iris neovascularization and neovascular glaucoma*
  - *Cataract formation*
  - Intraocular pressure elevation: ≥30 mmHg is about 36% in the first 48 hours after surgery
  - Fibrinoid syndrome: 5%, breakdown of the blood–retina barrier
  - Vitreous hemorrhage:
    - single postoperative vitreous hemorrhage occurs in about 65% of patients, whereas 35% will suffer two or more recurrences of vitreous hemorrhage
    - in association with iris or angle neovascularizations, retinal fibrovascular proliferations, or an anterior hyaloidal fibrovascular proliferation (AHFVP).[
    - Only 4–10% of cases will finally require another vitrectomy
  - Anterior hyaloidal fibrovascular proliferation
    - up to 13%

- Risk factors for AHFVP include male gender, type I diabetes, phakic patients, insufficient panretinal photocoagulation, severe ischemia with recurrent neovascularizations, and previous surgery with placement of a scleral buckle
- For treatment, cataract extraction, lensectomy, scleral buckling, extensive laser or cryopexy, and anterior dissection with eventual retinectomy

Diabetic Macular Edema

- **DME** is defined as retinal thickening, assessed by stereoscopic evaluation of the fundus by slit-lamp biomicroscopy or assessment of photographs. ***Hard exudates are a sign of present or past*** retinal thickening.
- In areas of vascular incompetence, DME may result from leakage of microaneurysms, or it may evolve from diffuse leakage of hyperpermeable capillaries. In areas of capillary nonperfusion on angiography, retinal thickening may result from ischemia in the absence of prominent vascular leakage, though hyperpermeable microvascular abnormalities at the borders of such regions may contribute to swelling
- **Classification**
  - **Mild DME**: Some retinal thickening or hard exudates in the posterior pole, **distant** from the center of the macula
  - **Moderate DME**: Retinal thickening or hard exudates **near the center** of the macula but not involving the center
  - **Severe DME**: Retinal thickening or hard exudates **involving the center** of the macula

- **KIM's classification based on OCT:**
  - Pattern I is a **diffuse** increased retinal thickening, with areas of reduced intraretinal reflectivity;
  - Pattern II is **CME**
  - Pattern III shows **posterior hyaloidal traction**, which appears as a highly reflective band over the retinal surface
  - Pattern IV exhibits **serous retinal detachment** not associated with posterior hyaloidal traction, which appears as a dark accumulation of subretinal fluid beneath a highly reflective dome-like elevation of detached retina
  - Pattern V shows **posterior hyaloidal traction and tractional retinal detachment**, which appear as a peak-shaped detachment with a highly reflective signal arising from the inner retinal surface and with an area of low signal beneath the highly reflective border of detached retina

- **Clinical evaluation**
  - ETDRS defined clinically significant macular edema (CSME) as:
    - **thickening** of the retina at or **within 500 *μ*m** of the center of the macula

- **hard exudates** at or **within 500 μm** of the center of the macula, if associated with thickening of the adjacent retina (not residual hard exudates remaining after the disappearance of retinal thickening)
- a zone or zones of retinal thickening **one disc area** or larger, any part of which is within one disc diameter of the center of the macula

- definition for **CSME** was based on observation that retinal thickening or hard exudation involving or threatening the **fovea** frequently leads to vision loss.
- Careful assessment of the distribution of retinal thickening and hard exudates and their relation to the center of the **macula** remains paramount to management of **DME**.

Management

- Focal/grid laser photocoagulation:
  - ETDRS: **At 3 years**, eyes with mild or moderate NPDR plus macular edema at baseline treated with immediate focal/grid laser photocoagulation showed an approximately **50% decrease in the rate of moderate vision loss** (defined as a decrease of three lines or more on a logarithmic visual acuity chart, corresponding to a doubling of the initial visual angle)
  - **FOCAL**: "direct" treatment of all microaneurysms exhibiting leakage of fluorescein dye in regions of retinal thickening between 500 and 3000 μm from the foveal center → 50–100 μm, exposure 0.05–0.10 seconds, and intensity sufficient to whiten or darken large microaneurysms
  - **GRID**: areas of diffuse leakage of fluorescein dye and areas of capillary nonperfusion in regions of retinal thickening between 500 and 3000 μm from the foveal center, with spacing between spots of at least one burn-width → size less than 200 μm, exposure 0.05–0.10 seconds, and intensity described as "mild".
  - **Present standard technique**: **"modified-ETDRS Grid" → DRCR.net**
- Pharmacotherapy with vascular endothelial growth factor (VEGF) antagonists
  - **bevacizumab**, a humanized murine monoclonal **antibody** binding VEGF-A
  - **ranibizumab**, a humanized murine monoclonal **antibody fragment**, also binding VEGF-A
  - **pegaptanib sodium**, an aptamer specifically inhibiting the **VEGF-A 165** isoform
  - **aflibercept**, a human fusion protein incorporating **ligand-binding elements from VEGF receptors and the Fc region of an IgG1 molecule**

  - **DRCR.net comparison** of four strategies for treatment of DME
    1. sham injection with focal/grid laser photocoagulation
    2. intravitreous injection of ranibizumab (0.5 mg) with deferral of early laser
    3. intravitreous injection of ranibizumab (0.5 mg) with early laser (within 3-10 days)
    4. intravitreous injection of triamcinolone acetonide (4 mg) with early laser

- The main outcome measure, best-corrected visual acuity, was evaluated at **one year**, with follow-up planned for 3 years
- **RESULTS**: At one year, mean change in visual acuity was ***significantly better in the ranibizumab plus prompt laser and ranibizumab and deferred laser*** groups compared with the prompt laser plus sham injection group. Mean change in visual acuity was not significantly different from the prompt laser plus sham injection group in the triamcinolone plus prompt laser group

✣ **RESTORE study**

1. intravitreous injection of ranibizumab (0.5 mg) and sham laser
2. injection of ranibizumab (0.5 mg) and focal/grid laser photocoagulation
3. sham injection and focal/grid laser photocoagulation

- At 12 months, the mean change in visual acuity in the group getting ranibizumab alone (+6.1 letters) and in the group getting ranibizumab plus laser (+5.9 letters) was significantly better compared with the group getting laser alone (+0.8 letters; both P <0.0001).

✣ **BOLT study**

- intravitreous injection of bevacizumab (1.25 mg) (3 injection 6 weeks apart→ PRN 6 weekly)
- modified-ETDRS focal/grid laser photocoagulation
- At 12 months, the mean change in visual acuity was significantly better in bevacizumab group (+5.6 letters) than in the laser group

✦ Pharmacotherapy with corticosteroids

✣ **DRCR.net**

1. modified-ETDRS focal/grid laser photocoagulation
2. intravitreous injection of triamcinolone acetonide (1 mg)
3. intravitreous injection of triamcinolone acetonide (4 mg),

- primary outcome measure of mean change in best-corrected visual acuity at two years
- Persistent or new macular edema was retreated every 4 months
- Mean change in visual acuity at two years was **significantly better in laser-treated eyes** than in eyes receiving 1 mg triamcinolone and likewise significantly better than in eyes receiving 4 mg triamcinolone.
- Cataract surgery was performed in **13**% of eyes in the laser group, **23**% of eyes in the 1 mg triamcinolone group, and **51**% of eyes in the 4 mg group.
- Intraocular pressure elevation of 10 mmHg or more from baseline at any study visit was noted in 4, 16, and 33% of eyes in the three groups

✣ **Retisert**: fluocinolone acetonide intravitreal implant

- **0.59 mg pellet** embedded in a **nonbiodegradable** scaffold

- in the vitreous cavity via a **sclerotomy** and anchored by a suture to the eye wall
- releases drug at steady state between **0.3 and 0.4μg/day** for approximately **30 months**

- **Iluvien**: fluocinolone acetonide
  - non-biodegradable cylinder (**3.5×0.37 mm**)
  - injection by **25-gauge** needle
  - **0.2 and 0.5μg/day**
  - **1 year**
- **Ozurdex**: dexamethasone intravitreous implant
  - **60 days**
  - **22-gauge** needle-injector system
  - **350 μg and 700 μg** version

PPV

How PPV Helps

- Pathology at vitreoretinal interface: Eyes with posterior vitreous detachment (PVD) develop DME less frequently than eyes with attached hyaloid.
- Vitreous may harbor inflammatory mediators contributing to DME.
- Relieving tractional forces may help with:
  - Anatomic improvement of vitreomacular traction
  - Oxygenation of tissue may favor arteriolar constriction.

How to do

- With or without internal limiting membrane (ILM) peeling
  - A prospective study indicated that ILM removal, compared to PVD induction with PPV alone for DME, stabilized visual acuity and improved cystoid macular edema
  - ILM removal stabilized BCVA and morphological results.
- ILM plays a role in pathology.
  - ILM is 2 times thicker in DME cases than in macular hole cases.
  - ILM peel may stimulate glial tissue healing.

When to Do?

- Some advocate for PPV for patients who have “persistent DME,”6 defined as:
  - Central macular thickness (CMT) > 250 μm
  - History of 2 sessions of either macular photocoagulation or intravitreal anti-VEGF

- Some studies suggest earlier PPV before unfavorable spectral domain OCT findings . ELM and ellipsoid zone (IS/OS) integrity correlates with post operative outcome

- **Near Infrared Photobiomodulation of Diabetic Macular Edema**
  - Photobiomodulation (PBM) therapy has recently emerged as a potential treatment for a variety of conditions of the central nervous system, including the retina. Tissue is exposed to a low-intensity light at wavelengths ranging from far red to near-infrared (NIR; 600 to 1000 nm).
  - One found anatomical evidence of efficacy of PBM for DME

Subthreshold Laser Therapies for Diabetic Macular Edema

- Subthreshold laser includes all types of laser therapy that show no signs of damage to the examiner.
- **Technologies**
  - ***Micropulse***
    - Chops continuous-wave beam into an envelope of repetitive short pulses
    - Duty cycle = % of time laser is “on” = 5%
    - Micropulse supports foveal therapy for DME
    - Available Models
      - Iridex (Micropulse)
      - Quantel Laser (SubLiminal)
      - Lumenis (SmartPulse)
  - ***Continuous wave***
    - Topcon (Endpoint Management)
      - Endpoint management avoids fovea
      - Arrhenius integral
      - Describes the changes in temperature, in time and space in biologic tissues, in response to laser energy.
      - Short pulse duration results in narrow therapeutic window.
      - Biologic damage proportional to laser power
  - ***Microbubble disruption***
    - Ellex (Retinal Rejuvenation Therapy = 2RT)
      - Microbubble disruption therapy avoids fovea
      - Selective targeting of individual retinal pigment epithelial (RPE) cells
      - Microbubbles around melanosomes expand and result in intracellular damage.
      - Individual RPE cell death
      - Neighboring RPE cells migrate, divide, and produce new RPE cells.

- **Practical Tips**
  - Choose correct Preset
  - Confirm correct treatment mode; make sure you are not using conventional treatment mode.
  - If using Micropulse, confirm 5% duty cycle.
  - Be aware of landmarks and placement of treatment spots.

Telescreening in Diabetic Retinopathy

- **Telemedicine** is the ***exchange of medical data by electronic telecommunications technology*** allowing a patient's medical problems to be evaluated, monitored, and possibly treated while the patient and physician are located at sites physically remote from each other
- **screening programs for diabetic retinopathy:**
  - **ophthalmologist-based** (with actual presence of the ophthalmologist at the site of screening)
  - **ophthalmologist-led** (no ophthalmologist at the site of screening
- Telemedicine for retinopathy screening is an ophthalmologist-led screening model
- American Telemedicine Association (ATA) telehealth practice recommendations for diabetic retinopathy
  - four categories of telescreening programs
    - Category 1: The program allows identification of patients who have **no** or minimal diabetic retinopathy and distinguishes them from those who have more than minimal diabetic retinopathy.
    - Category 2: The program allows identification of patients who do not have **sight-threatening** diabetic retinopathy and distinguishes them from those who have potentially sight-threatening diabetic retinopathy.
    - Category 3: can identify defined levels of non-proliferative DR (mild, moderate, or severe), proliferative DR (either early or high-risk), and the presence or absence of DME. In this category, decisions about appropriate treatment and follow-up can be made with similar certainty to that of a dilated fundus examination by an ophthalmologist.
    - Category 4 has the highest burden of validation. These systems achieve diagnostic accuracy matching or exceeding the gold standard ETDRS photos for identifying and defining DR and DME. A Category 4 program could replace clinical examination or ETDRS photos for clinical or research applications.
- The **gold standard for telescreening** is the **ETDRS 7 mydriatic standard field 35 mm** stereoscopic color fundus photographs
- Picture archiving and communication systems (**PACS**) consists of four major components: the imaging instrumentation, a secured network for the transmission of patient information, workstations for interpreting and reviewing images, and archives for the storage and retrieval of images and reports

Retinal Vascular Diseases

Hypertension

- hypertensive retinopathy, choroidopathy, and optic neuropathy
- also a major risk factor for many other eye diseases, including the development and progression of diabetic retinopathy, retinal vein occlusion, retinal arterial macroaneurysm, and possibly age-related macular degeneration and glaucoma

Retinopathy

- Evolution and Phases
  1. **vasoconstrictive phase**: initial response to elevated blood pressure is vasospasm and an increase in vasomotor tone, with consequent narrowing of retinal arterioles
  2. **sclerotic phase:** Persistently elevated blood pressure leads intimal thickening, media wall hyperplasia and hyaline degeneration leading to manifestation of diffused and localized (focal) retinal arteriolar narrowing, arteriolar wall opacification ("silver" or "copper wiring"), and compression of the venules by structural changes in the arterioles (arteriovenous "nicking" or "nipping").
  3. **exudative phase**: chronically sustained blood pressure elevation→ blood–retinal barrier is disrupted → of the smooth muscles and endothelial cells, exudation of blood and lipids and retinal nerve fiber layer ischemia, which results in microaneurysms, retinal hemorrhages, hard exudates, and cotton-wool spots seen in the retina.
  4. **malignant hypertension phase**: optic disc swelling which may reflect underlying hypertensive encephalopathy with raised intracranial pressure

- **Classifications**
  - **Keith–Wagener–Baker system**
  - **Wong and Mitchell:**
    - **None**: no detectable signs
    - **Mild**: Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, arteriolar wall opacification (silver or copper wiring), or a combination of these signs
    - **Moderate**: Hemorrhages (blot, dot, or flame-shaped), microaneurysms, cotton-wool spots, hard exudates, or a combination of these signs
    - **Malignant**: Signs of moderate retinopathy in combination with optic disc swelling, in the presence of severely elevated blood pressure

Hypertensive choroidopathy

- **Elschnig spots** (round, deep, and gray-yellow patches at the level of the retinal pigment epithelium)
- **Siegrist streaks** (linear hyperpigmented streaks along choroidal arteries)

Hypertensive optic neuropathy

- Ischemia, raised intracranial pressure and hypertensive encephalopathy are all possible mechanisms that can result in papilloedema
- strongly correlated with CVD risk and mortality

Retinal Artery Obstructions

CRAO: Central Retinal Artery Occlusion

- first described in 1859 in von Graefe's report
- 1 in 10 000
- early sixties
- **Clinical Features**
  - monocular, painless, severe loss of vision
  - premonitory episodes of amaurosis fugax
  - CRAO after amaurosis fugax is estimated to be only 1% per year
  - VA: **counting fingers to light perception in 74-90%,** preserved if Cilioretinal Artery supplying macula
  - VA may spontaneously improve in up to 22% of patients with nonarteritic CRAO
  - **afferent pupillary defect** develops within seconds following obstruction of the central retinal artery *regardless of macular sparing*
  - anterior-segment exam is normal initially: **NVI 16%,** mean of 4–5 weeks
  - Fundus: The classic dense, white haze of the central region in the retina with a well-marked clear patch at the yellow-spot was very well shown → **cherry-red spot**
  - **ACUTE**: cherry-red spot (90%), posterior pole retinal opacity or whitening (58%), box-carring of retinal arteries and veins (19% and 20% respectively), retinal arterial attenuation (32%), optic disc edema (22%), and optic nerve pallor (39%).
  - patent cilioretinal artery supplying some or all of the papillomacular bundle is seen in approximately one-third of cases
  - Retinal emboli are the most common cause of nonarteritic CRAO and BRAO
  - yellow, refractile cholesterol embolus (Hollenhorst plaque)
  - **CHRONIC**: optic atrophy (91%), retinal arterial attenuation (58%), cilioretinal collaterals (18%), macular RPE changes (11%), and cotton-wool spots (3%)
- **Investigations**
  - FA: some variable residual retinal circulation with delayed and sluggish filling of the retinal vasculature
  - OCT: irregular macular contour with increased reflectivity of the inner retina.
  - VF: central scotoma, paracentral scotoma, Peripheral constriction
  - ERG: more severe attenuation of the b-wave than the a-wave since the inner retinal layers are more affected

- ***Systemic associations***
  - from carotid artery atherosclerosis is the most common etiology
  - but in < 40 years → cardiac emboli
  - Embolic sources
  - Trauma
  - Coagulopathies
  - Ocular conditions
  - Collagen vascular disease
  - Other vasculitides and inflammatory conditions
  - Miscellaneous associations
- The presence of a **Hollenhorst plaque** or retinal artery occlusion is associated with a ***low prevalence of carotid atherosclerosis requiring carotid endarterectomy***
- **Evaluation**
  - rule out giant cell arteritis in patients older than 50 years
  - embolic source often includes carotid Doppler imaging and echocardiography
  - cardiac evaluation:
  - hypercoagulability evaluation should be considered for patients less than 50 years
- ***Treatment***
  - retina suffers no damage up to **97 minutes** after an acute CRAO but after 4 hours the retina suffers massive irreversible damage
  - recommended within 24 hours of symptom onset
  - ocular massage, sublingual isosorbide dinitrate, intravenous acetazolamide, intravenous mannitol or oral glycerol, anterior-chamber paracentesis, intravenous methylprednisolone, streptokinase, and retrobulbar tolazine.
  - Ocular massage: Goldmann contact lens or digital massage to apply ocular pressure with an in-and-out movement to dislodge a possibly obstructing embolus
  - Mixture of 95% oxygen and 5% carbon dioxide (carbogen) can be provided to induce vasodilation and improve oxygenation
  - purpose of hyperbaric oxygen is to preserve the retina in an oxygenated state until recanalization and reperfusion occur, typically at 72 hours
  - Anterior-chamber paracentesis
  - Nd-YAG laser arteriotomy
  - Corticosteroids should only be used when arteritic CRAO from giant cell arteritis is suspected
  - Intravenously or intra-arterially administered thrombolytics currently in use include streptokinase, urokinase, and tissue plasminogen activator (t-PA).
  - **EAGLE study**: similarity in efficacy between groups and the higher rate of adverse events, namely cerebral hemorrhage, in the intra-arterial t-PA group

BRAO: Branched Retinal Artery Occlusion

- **38%** of all acute retinal artery obstructions
- Clinical Features
  - monocular vision loss, which may be restricted to one part of the visual field
  - field defects include a central scotoma in 20%, a central altitudinal defect in 13%, and sector defects in 49%
  - Fundus: sectoral pattern of retinal opacification, typically occur at vessel bifurcations, and 98% of the time the temporal
  - CHRONIC:
    - sectoral nerve fiber layer loss and arterial attenuation may be seen
    - Artery-to-artery collaterals may also be seen and are pathognomonic for BRAO
- visual prognosis in eyes with symptomatic BRAO is generally good, and acuity usually improves to 20/40 or better in 80% of eyes

CLARA- Cilioretinal artery occlusion

- **5%** of retinal arterial obstructions
- 32% of the time seen in FA and fill concomitantly with the choroidal circulation
- three distinct groups are found:

1. **isolated CLRAO**
   - good prognosis, with nearly 90% achieving 20/40
   - presumably secondary to intact superior and inferior nerve fiber layer bundles supplying the fovea

2. **CLRAO associated with CRVO**
   - 40% of CLRAO
   - 5% of eyes with CRVO
   - Visual acuity correlates with the degree of venous obstruction

3. **CLRAO in conjunction with anterior ischemic optic neuropathy**
   - 15% of eyes with CLRAO
   - Poor visual prognosis, ranging from 20/400 to no light perception

Combined retinal artery and vein occlusion

- CRVO can be seen in association with CRAO, BRAO, and CLRAO
- The visual prognosis is generally poor, with visual acuity in the hand motions range.
- After 6–8 weeks, optic nerve pallor is seen with severe arterial attenuation

Cotton-wool spots

- soft exudates is misnomer
- slightly elevated, small, yellow-white or gray-white, cloud-like, linear or serpentine lesions with fimbriated borders in the superficial retina
- usually restricted to the posterior segment of the fundus
- rarely cause vision loss unless they involve the fovea
- **resolve within 6–12 weeks** though they may last longer in diabetics
- secondary to obstruction of a retinal arteriole with resultant ischemia
- light microscopy of cotton-wool spots in the retina revealed the presence of a cytoid body, a round, dark-staining “pseudonucleus” within a grossly swollen nerve fiber layer
- **Etiologies**
  - Ischemic
  - Embolic
  - Collagen vascular disease
  - Infectious
  - Toxic
  - Neoplastic
  - Miscellaneous
  - Idiopathic

Systemic Management of Retinal Artery Occlusion

- Occlusion of the retinal arteries is considered an ischemic stroke in the central nervous system, according to an updated (2013) definition of a stroke
- Based upon this definition, stroke guidelines apply to the management of retinal artery occlusions
- **Acute OAO, CRAO, BRAO (< 24 hours from onset of symptoms)**
  - Immediate referral to the Emergency Department (ED)
  - Carotid imaging prior to discharge
  - Brain MRI
  - Echocardiogram (preferably transesophageal)
  - Referral to the Transient Ischemic Attack (TIA) Clinic (Neurology)
  - Holter monitor (48 hours in duration) scheduled within 1-2 weeks
- **Subacute OAO, CRAO, BRAO (24 hours to 2 weeks from onset of symptoms):**
  - Referral to TIA Clinic in Neurology
  - If unable to accommodate within 48 hours, send to ED.
  - Studies

        - Brain MRI
        - MRA head and neck
        - Echocardiogram (preferably transesophageal)
        - Holter monitor (48 hour in duration) scheduled within 1-2 weeks
- **Chronic OAO, CRAO, BRAO (> 2 weeks)**
    - Refer to TIA Clinic
    - Begin full-dose aspirin
    - Studies
        - MRI brain
        - MRA head and neck
        - Echocardiogram (preferably transesophageal)
        - Holter monitor (48 hours in duration)

Acquired Retinal Macroaneurysms

- fusiform or round dilations of the retinal arterioles within the **first three orders** of arteriolar bifurcation
- at the site of an arteriolar bifurcation or an arteriovenous crossing
- supratemporal artery is the most commonly **reported**
- Most cases are unilateral, while 10% may be bilateral
- 1 in 9000
- sixth and seventh decades
- F >> M
- Systemic investigations for hypertension and cardiovascular disease should be done
- **Clinical Features**
    - decline in central visual acuity as a result of retinal edema, exudation, or hemorrhage
    - **hourglass hemorrhages** are typical
    - Bleeding from macroaneurysms can occur in the subretinal space, into the retina, beneath the internal limiting membrane, or into the vitreous
    - **Circinate ring of exudates**
- **Investigations**
    - FA: hypofluorescence in case of hemorrhage
    - ICG: allow the light to penetrate the hemorrhage to a greater extent
    - **lesions are pulsatile and contiguous with the arterial wall**, pathognomonic of an insolated retinal artery macroaneurysm
- **Management**

- **yellow dye laser** has been considered for treatment because of its theoretical advantages
- exudative process may progress
- Vitrectomy was performed for clearing the macular hemorrhage
- Pneumatic displacement with or without tissue plasminogen activator
- direct laser photocoagulation of the macroaneurysm

- **Differential Diagnosis**
  - diabetic retinopathy, retinal telangiectasia, retinal capillary angioma, cavernous hemangioma, malignant melanoma, and the hemorrhagic pigment epithelial detachment of age-related macular degeneration

Retinal Vein Occlusions

BRVO: Branched Retinal Vein Occlusion

- M = F
- 60-70 years
- **Risk Factors**
  - Systemic vascular diseases: hypertension and arteriosclerosis
  - smoking, hyperlipidemia, glaucoma, and ocular inflammatory disease
  - Antiphospholipid antibodies, elevated plasma homocysteine levels, and low serum folate levels
  - decreased risk is present in those with higher serum levels of high-density lipoprotein and light to moderate alcohol consumption
  - short axial length
  - **DIABETES is NOT an independent risk factor.**
- **Pathogenesis**
  - mostly occurs at arteriovenous crossings
  - retinal artery and vein share a common adventitial sheath
  - turbulent blood flow at the crossing site causes focal swelling of the endothelium and deeper vein wall tissue, leading to venous obstruction
  - resulting venous obstruction leads to elevation of venous pressure that may overload the collateral drainage capacity → macular edema and ischemia and intraretinal hemorrhage
- **Clinical Features**
  - sudden painless loss of vision or a visual field defect
  - floaters from a vitreous hemorrhage
  - wedge-shaped distribution of intraretinal hemorrhage
  - ischemic BRVO: greater than a total of five disc diameters of nonperfusion on fluorescein angiography

- most common location for BRVOs is in the superotemporal **(larger number of arteriovenous crossings)**

- **Investigations**
  - FA:
    - macular leakage and edema, macular ischemia, and large segments of capillary nonperfusion that may portend eventual neovascularization
    - delayed filling of the occluded retinal vein
  - Wide-field angiography
    - Optos C200MA
  - OCT
    - intraretinal hemorrhages have a minimal effect on the interpretation of OCT
    - cystoid edema, intraretinal hyperreflectivity from hemorrhages, shadowing from edema and hemorrhages, and occasionally subretinal fluid
    - photoreceptor inner-segment–outer-segment junction abnormalities from long-standing macular ischemia and macular edema
- **Complications**:
  - **1) macular edema; (2) macular ischemia; and (3) sequelae of neovascularization**
  - BVOS: 31–41% of patients with ischemic BRVO developed neovascularization or vitreous hemorrhage, compared with 11% of patients with nonischemic BRVO
- **Diagnostic Work-up**
  - Young patient
    - oral contraception in females
    - medications that can promote a hypercoagulable state or thromboembolism
    - infectious causes such as Lyme disease, syphilis, or human immunodeficiency virus
    - complete blood count, prothrombin time/partial thromboplastin time/ international normalized ratio, lipid panel, serum homocysteine, anticardiolipin antibodies, antinuclear antibodies with lupus anticoagulant, protein C/S, and activated protein C resistance (factor V Leiden)
  - Older patient
    - idiopathic or due to hypertension or atherosclerosis.
  - Bilateral or numerous BRVO patients
    - infectious or inflammatory disorder or hypercoagulopathy
- **Management**
- **Medical**: anticoagulants are not recommended
- ***Laser***
- BVOS for macular edema

- Eligibility: fluorescein-proven perfused macular edema involving the foveal center, absorption of intraretinal hemorrhage from the foveal center, recent BRVO (usually 3–18 months' duration), no diabetic retinopathy, and vision reduced to 20/40 or worse after best refraction
- argon laser photocoagulation: 0.1 second, a 100-µm diameter spot size, and a power setting sufficient to produce a “medium” white burn
- APPLICATION: grid pattern, no closer to the fovea than the edge of the capillary-free zone and no further into the periphery than the major vascular arcade
- After 3 years of follow-up, 63% of treated eyes gained two or more lines of vision, compared to 36% of untreated eyes.
- The average gain in visual acuity for treated eyes was one more Snellen line than in untreated eyes.
- **BVOS emphasize waiting at least 3–6 months before considering laser therapy**

- BVOS for neovascularization
  - large areas (>5 disc diameters) of retinal capillary nonperfusion are at risk for developing neovascularization
  - 40% of these eyes develop neovascularization, and of this 40%, about 60% will experience periodic vitreous hemorrhage → at any time within the first 3 years
  - scatter laser photocoagulation can lessen subsequent neovascularization and, if neovascularization already exists, that peripheral scatter laser photocoagulation can lessen subsequent vitreous hemorrhage
  - incidence of neovascularization can be reduced from about 40% to 20% (only after neovascularization is observed), VH from 60% to 30%
  - Iris neovascularization is a rare complication, more if DM is also there
  - APPLICATION: argon blue-green laser to achieve “medium” white burns (200–500 µm in diameter) spaced one burn width apart and covering the entire area of capillary nonperfusion
- ***Steroid treatment***
- inhibit the expression of VEGF and therefore reduce macular edema
- SCORE (triamcinolone) study
  - **Standard care vs Corticosteroid for Retinal vein occlusion (SCORE) BRVO study**
  - 3 groups: **macular grid laser, 1 mg IVTA, or 4 mg IVTA**
  - no significant difference in vision or the reduction of macular edema measured by OCT at the end of 12 months between each group.
  - laser group maintained a significantly greater average increase in vision (12.9 letters) compared with the two IVTA groups
  - RESULT: **IVTA is not recommended as first-line therapy**, considered in patients where macular grid laser or other therapies are ineffective, as the treatment was found to be relatively safe, especially in pseudophakic eyes.
- GENEVA (dexamethasone implant) study

- **Global Evaluation of implantable dexamethasone in retinal Vein occlusion with macular edema**
- Ozurdex for CRVO-BRVO
- Ozurdex is a biodegradable copolymer of poly (D,L-lactide-co-glycolide) acid (PLGA) containing micronized dexamethasone
- **3 groups: ozurdex 0.7 mg, 0.35 mg, and sham groups**
- At 90 days after injection, there was a significant improvement ($P < 0.001$) in central retinal thickness measured by OCT in both Ozurdex groups, compared with the sham group

- ***Anti-VEGF treatment***
- ranibizumab (Lucentis), bevacizumab (Avastin), pegaptanib (Macugen), and aflibercept (Eylea).
- ranibizumab is FDA-approved for the treatment of RVO.
- BRAVO (ranibizumab) study
  - Branch Retinal Vein Occlusion (BRAVO) study
  - 3 groups: sham injection, 0.3 mg ranibizumab, 0.5 mg ranibizumab
  - first 6 months
    - monthly injections
    - At month 3 to 6, a patient was eligible for rescue laser if a gain of <5 ETDRS letters, or improvement of <50 µm
    - both ranibizumab groups gained +**16.6 and +18.3 ETDRS letters** (0.3 mg and 0.5 mg groups, respectively) compared with a gain of +7.3 letters in the control group
  - After the first 6 months
    - All 3 group PRN intravitreal ranibizumab monthly if they had vision ≤ 20/40 or mean central foveal thickness ≥250 µm
    - both ranibizumab groups maintained their vision gain at 12 months
  - ranibizumab is superior to traditional laser
  - current recommendation: **monthly 0.5 mg ranibizumab**
- BRIGHTER: ranibizumab with or without laser was superior to laser alone over 6 months; BCVA gains were similar to those in BRAVO, despite a lower mean number of injections. In Addition, ranibizumab provided similar BCVA gains for ischemic and nonischemic patients.
- Other anti-VEGF inhibitors
  - *Bevacizumab:* 6 months the 1.25 mg group improved by an average +5.1 lines compared with +4.8 lines in the 2.5 mg group.
  - *Pegaptanib:*
  - *Aflibercept:*
    - **COPERNICUS and GALILEO,** 2 mg aflibercept or sham

        - VIBRANT Study: Monthly intravitreal aflibercept injections provided significantly greater visual benefit and reduction in CRT at 24 weeks than did grid laser photocoagulation in eyes with macular edema secondary to BRVO

- ***Experimental treatments***
    - FAVOR (iluvien) study: sustained-release, non-erodable, intravitreal implant of fluocinolone acetonide
- Surgical management
    - *Vitrectomy with or without sheathotomy:* limited clinical use as a first-line therapy.

CRVO: Central Retinal Vein Occlusion

- M = F
- prevalence of CRVO at <0.1 to 0.4%
- **risk in fellow eye is approximately 1% per year**
- **7% of persons with CRVO may develop CRVO in the fellow eye within 5 years**
- **Clinical Features**
    - sudden painless loss of vision
    - VA variable
    - retinal hemorrhages (both superficial flame-shaped and deep blot type) in all four quadrants
    - dilated, tortuous retinal venous system.
    - classic "**blood and thunder**" appearance
    - Optic nerve head swelling, cotton-wool spots, splinter hemorrhages, and macular edema
    - Breakthrough vitreous hemorrhage
    - cilioretinal artery occlusion can occur in association with CRVO
    - presence of an afferent pupillary defect, electroretinography (a negative waveform may be seen), and Goldmann perimetry
    - CHRONIC: hemorrhage may decrease or resolve, RPE Changes, Macular edema often chronically persists, ERM, OC Shunts, NVD, NVE, VH – TRRD
    - **NVA 6-12% cases without any NVI**
    - CVOS used an index of any 2 clock-hours of NVI or any NVA as evidence of significant anterior-segment neovascularization
    - Elevated intraocular pressure associated with NVI/NVA is the hallmark of neovascular glaucoma.
- **Classification**
    - **perfused CRVO** (also termed nonischemic, incomplete, or partial)
        - less than 10 disc areas of retinal capillary nonperfusion

- lesser degree of intraretinal hemorrhage
- better initial and final visual acuity

- **Nonperfused CRVO** (also termed ischemic, hemorrhagic, or complete)
  - 10 or more disc areas of retinal capillary nonperfusion
  - greater degree of intraretinal hemorrhage, macular and disc edema, and capillary nonperfusion
- **indeterminate**
  - sufficient intraretinal hemorrhage to prevent angiographic determination of the perfusion status

Natural history

- In perfused, 10% developed NVI/NVA compared to 35% of eyes initially characterized as nonperfused or indeterminate
- 45% chance of developing neovascular glaucoma after onset of ischemic CRVO at 3 years
- 34% of initially perfused eyes converted to nonperfused status after 3 years
- 83% with an indeterminate CRVO at baseline were ultimately determined to be nonperfused

Pathogenesis

- thrombus occluding the lumen of the central retinal vein at or just proximal to the lamina cribrosa
- CRA-V branches before lamina cribrosa
- common tissue sheath
- compression from mechanical stretching of the lamina, as with increases in intraocular pressure
- compression by an atherosclerotic central retinal artery or primary occlusion of the central retinal vein from inflammation
- **Virchow's triad**: diminished blood flow, increased blood viscosity, and an altered lumen wall
- *hypothesized that a* **less hemorrhagic, more likely nonischemic**, *CRVO may be due to occlusion of the central retinal vein at a* **site further posterior**, *allowing normal collateral channels to provide alternative routes of venous drainage.*
- VEGF from ischemic retina → NV and macular edema

Risk factors

- Systemic vascular diseases: diabetes mellitus, hypertension, carotid insufficiency
- Ocular diseases: open angle glaucoma, ischemic optic neuropathy, pseudotumor cerebri, tilted optic nerve heads, optic nerve head drusen
- Hematologic alterations:
- Inflammatory/autoimmune vasculitis: systemic lupus erythematosus
- Medications: oral contraceptives, diuretics, hepatitis B vaccine

- Infectious vasculitis: HIV, syphilis, herpes zoster, sarcoidosis
- Other: after retrobulbar block, dehydration, pregnancy

- **Evaluation**
  - visual acuity, pupillary reaction, and intraocular pressure. Undilated slit-lamp examination is performed to detect NVI or NVA
  - Undilated gonioscopy
  - systemic workup is not indicated in persons older than 60
  - young patients: systemic thrombotic disease, family history of thrombosis, or other symptoms suggestive of a hematologic or rheumatologic condition, erythrocyte sedimentation rate, antinuclear antibody, antiphospholipid antibody, and fasting plasma homocysteine levels

- **Treatment**
- treating the sequelae of CRVO, particularly macular edema and neovascularization
- ***Treatment of macular edema***
  - CVOS did not recommend grid laser photocoagulation for CRVO-associated macular edema
  - **OBSERVATION** is the standard of care for CRVO-associated macular edema
  - **Standard care vs Corticosteroid for Retinal vein occlusion (SCORE) study**
    - 3 groups: preservative-free IVTA 1 mg and 4 mg, versus standard of care
    - retreated with IVTA every 4 months for 1 year unless CMT, 225, VA > 20/25, adverse event (cataract and glaucoma), Additional treatment needed as no improvement for 2 injections
    - 1 year, 26% (4 mg) and 27% (1 mg) gained ≥15 letters at 1 year compared to 7% of untreated
    - Cataract formation: 26% (1 mg) and 33% (4 mg) IVTA groups compared to 18% in the observation group
    - Elevated intraocular pressure: 20% (1 mg) and 35% (4 mg), 8% in observation
  - sustained-release intravitreal fluocinolone acetonide implant (**Retisert**) for chronic refractory CME
  - GENEVA (dexamethasone implant) study
    - **Global Evaluation of implantable dexamethasone in retinal Vein occlusion with macular edema**
    - Ozurdex for CRVO-BRVO
    - Ozurdex is a biodegradable copolymer of poly (D,L-lactide-co-glycolide) acid (PLGA) containing micronized dexamethasone
    - **3 groups: ozurdex 0.7 mg, 0.35 mg, and sham groups**

        - At 90 days after injection, there was a significant improvement ($P < 0.001$) in central retinal thickness measured by OCT in both Ozurdex groups, compared with the sham group

- Intravitreal anti-VEGF therapy
    - **CRUISE trial**
        - 3 groups: monthly intravitreal injections of 0.3 mg or 0.5 mg ranibizumab to sham-injected controls
        - 0.3 mg and 0.5 mg ranibizumab gained 12.7 and 14.9 letters, respectively, at 6 months compared to a 0.8 letter gain in the sham group
    - Pegaptanib (Macugen)
    - study using a single injection of bevacizumab (OFF LABEL)
    - **LEAVO**:
        - A multicentre Phase III double-masked randomised controlled non-inferiority trial comparing the clinical and cost effectiveness of intravitreal therapy with ranibizumab (Lucentis) vs aflibercept (Eylea) vs bevacizumab (Avastin) for macular oedema due to central retinal vein occlusion. Sponsored by National Institute for Health Research (NIHR), UK and the NIHR Biomedical Research Centre, Moorfields Eye Hospital, UK
        - LEAVO had 4 mandated injections, then investigators followed an algorithm for retreatment. Participants could have injection withheld if no improvement or worsening.
        - LEAVO trial showed that aflibercept is noninferior to ranibizumab, but that bevacizumab is *not* noninferior to either ranibizumab or aflibercept after 2 years of treatment.
    - SCORE2:
        - Study of comparative treatments in retinal vein occlusion 2. Sponsored by National Eye Institute (NEI), National Institutes of Health, U.S. Department of Health and Human Services.
        - SCORE2 had fixed monthly injections until month 5 before primary outcome was measured at month 6; then randomized to monthly or treat-and-extend for good responders through month 11.
        - SCORE2 trial showed bevacizumab to be noninferior to aflibercept at month 6.
    - CRYSTAL was designed to include an expanded CRVO patient population as compared to CRUISE, and allowed patients with both longer disease duration and ischemia to be included. Disease duration was long, and VA gains were affected by disease duration and baseline VA.
- IVTA
- ***Treatment of ocular neovascularization***
- Laser photocoagulation
    - CVOS group N report compared the efficacy of PRP

- 2 groups: early treatment (in 90 days without NVA-NVI) and delayed but prompt treatment (after NVA-NVI)
- CVOS therefore recommended that **PRP be delivered promptly after the development of NVI/NVA but not prophylactically in eyes with nonperfused CRVO**
- Prophylactic placement of PRP may be considered in eyes with nonperfused CRVO and risk factors for developing NVI/NVA (male gender, short duration of CRVO, extensive retinal nonperfusion, and extensive retinal hemorrhage) or in cases where frequent ophthalmologic follow-up is not possible.

- ***Treatment of systemic medical conditions***
  - systemic hypertension and diabetes mellitus
  - **Oral pentoxifylline** is a potent vasodilator: 400 mg three times a day
- ***Alternative treatments***
  - Chorioretinal venous anastomosis
  - Tissue plasminogen activator
  - Surgical treatments
    - *Vitrectomy*
    - *Radial optic neurotomy*

HORV: Hemorrhagic Occlusive Retinal Vasculitis

- Extremely rare condition
- Can occur after any intraocular procedure, usually cataract surgery
- Delayed presentation of sudden, painless, severe visual loss; mean onset of symptoms 1 week after the procedure (range: 1 day to 1 month)
- Strong association with intraocular vancomycin
  - Intracameral bolus
  - Anterior chamber irrigation solution
  - Intravitreal injection
- **Etiology**
  - Exact cause is currently unproven.
  - Immunology experts hypothesize that this may represent a rare type III hypersensitivity reaction to vancomycin. Presumed similar mechanism to leukocytoclastic vasculitis and HenochSchonlein purpura, which are type III hypersensitivity reactions in the skin that have rarely been associated with vancomycin.
- **Timing**
  - If HORV occurs after 1 eye undergoes cataract surgery, it can also occur in the second eye after the second eye undergoes surgery, even if the second surgery is

performed years later (if vancomycin is used). There is evidence that if vancomycin is not used in the second eye, then HORV does not develop in the second eye.

- In bilateral sequential cataract surgery separated by a few weeks, the first eye can be normal until the second eye undergoes surgery, and then HORV can occur simultaneously in both eyes very soon after the second surgery (if vancomycin is used).

- **Clinical features**
  - Visual acuity
    - Usually severely reduced
    - May be normal in mild cases
  - Cornea: Normal or mild corneal edema
  - Anterior chamber
    - Mild to moderate inflammation
    - No hypopyon
  - Vitreous: Mild to moderate inflammation
  - Retina
    - Peripheral retinal involvement in all cases
      - Large patches of intraretinal hemorrhages, often along venules
      - Small dot / blot hemorrhages
      - Sectoral or widespread retinal vasculitis
    - Macular involvement in severe cases: macular whitening
- **Fluorescein Angiography**
  - Severe peripheral nonperfusion; sectoral or widespread
  - Peripheral retinal vasculitis
  - Macular ischemia in advanced cases
  - Intraretinal hemorrhages correspond to areas of vasculitis and nonperfusion.
- **Differential Diagnosis**
  - Acute postoperative endophthalmitis: Pain, hypopyon, and severe vitritis are not present in HORV.
  - Viral retinitis
    - White areas of retinitis are not present in HORV.
    - Viral retinitis is not associated with a recent surgical procedure.
  - Central retinal vein occlusion (CRVO) or combined central retinal artery occlusion (CRAO) / CRVO
    - May be associated with cataract surgery
    - Findings present on postoperative day 1, unlike HORV which typically has a normal exam at this time
    - Severe venous dilation and tortuosity are not characteristic of HORV.

- Medication toxicity
  - Toxic anterior segment syndrome (TASS): TASS has severe corneal edema and findings on postoperative day 1, unlike HORV.
  - Aminoglycoside toxicity: Aminoglycoside toxicity has macular infarction with minimal or no peripheral vascular occlusion, while HORV has severe peripheral vascular occlusion and vasculitis.
  - Cefuroxime toxicity: Intracameral injection of overdoses have associated TASS and retinal hemorrhages.

- **Clinical course**
  - There are some cases of presumed endophthalmitis (cases with retinal findings out of proportion to inflammation and without hypopyon) that in retrospect were probably HORV.
    - These cases were treated with intravitreal vancomycin and had progression of retinal ischemia documented on fluorescein angiography performed before and after vancomycin treatment.
    - These cases that had received vancomycin twice, once during cataract surgery and again for presumed endophthalmitis, and had particularly poor outcomes, with most eyes progressing to no light perception.
  - Visual outcomes are often poor.
    - The majority of eyes are worse than 20/200.
    - Approximately one-quarter of eyes progress to no light perception.
    - A few asymptomatic cases are 20/20. HORV may be under-recognized due to mild involvement in some cases of uniocular or first eye administration.
  - Neovascular glaucoma is common, occurring in approximately 50% of eyes.
  - Eyes that received certain treatments appear to have more favorable outcomes.
    - Steroids (topical, periocular, intraocular, and/or systemic)
    - Early anti-VEGF treatment
    - Early panretinal photocoagulation

Macular Telangiectasia

- **MacTel**
- Coats disease: congenital telangiectasia
- Leber miliary aneurysms
- Gass: idiopathic juxtafoveolar retinal telangiectasis (IJRT)
- **Etiopathology:**
  - AD/ sporadic
  - expression of Müller cell-specific markers in the fovea, which correlated with macroscopically visible pigment depletion in this area
- **Classification (mac tel study group)**

- mac tel type 1:
  - **developmental or congenital**
  - unilateral vascular anomaly
  - part of the larger spectrum of Coats disease
  - M >> F
- mac tel type 2:
  - **presumably acquired bilateral**
  - middle-aged and older 50-60 years
  - M=F
  - macular, juxtafoveal, or perifoveal telangiectasia
  - MC type
- In type 3 MacTel, capillary occlusion is suspected to cause the telangiectasia. These patients are diagnosed with bilateral, easily visible telangiectasia, minimal exudation, and capillary occlusion.

- **Classification GASS**
  - Group 1A and B: Leber miliary aneurysms
  - group 2: **common bilateral disease** seen in older and elderly patients (2A), younger brothers (2B)
  - group 3A: telangiectatic changes, vascular occlusion, and minimal exudation in 3 patients
  - group 3B: similar retinal changes but had Additional neurological changes in 3 patients also
- **Yannuzzi classification:** idiopathic macular telangiectasia
  - aneurysmal telangiectasia: type 1A and 1B
  - type 2A (2b,3a,3b were removed because of lack of subjects)
- **Epidemiology**
  - Prevalence: 0.1%, Beaver dam eye study
  - Incidence 0.0045% to 0.022%: Melbourne collaborative cohort study
- **Clinical Features**
  - Earliest: subtle loss of retinal transparency in the perifoveal region, beginning temporally
  - dilation of the parafoveal capillaries in the temporal parafoveal area
  - retinal hard exudates in type 1 only
  - Crystalline deposits at the vitreoretinal interface
  - Blunted, dilated venules, either as single or multiple vessels, are often associated with ectatic capillaries. As vessels course towards the fovea, they usually decrease in diameter but, in mac tel type 2, they dilate and may make a right-angle turn, diving into the deeper retinal layers

- yellow spot, or vitelliform lesion, in the center of the fovea with slight loss of the foveal depression may become apparent in some eyes
- neovascularization is most commonly seen temporal
- fibrovascular scar with chorioretinal anastomosis can be the endpoint of the pathogenic process

- FAF: loss of the hypofluorescent center seen normally on blue-light FAF due to the depletion of macular pigment in this condition → **diagnostic**
- FA: characteristic telangiectactic capillaries on FA, starting predominantly temporal to the fovea
- OCT
  - temporal enlargement of the foveal pit
  - disruption of the photoreceptor inner-segment–outer-segment junction
  - hyporeflective cavities in the inner retina and these may clinically be described as "pseudolamellar macular holes."
- ***Adaptive optics imaging:*** scanning laser ophthalmoscope, allows evaluation of the cone photoreceptor mosaic
  - Visual function: NEI-VFQ-25
  - Microperimetry

- **Clinical Staging of Macular Telangiectasia Type 2 GASS & BLODI**

1. No biomicroscopic abnormality, no or minimal capillary dilation, mild staining of outer perifoveal retina
2. Slight graying of perifoveolar retina, no or minimal biomicroscopically visible telangiectatic vessels, but capillary telangiectasis of outer capillary network temporally on fundus autofluorescence
3. One or several slightly dilated and blunted retinal venules descending into outer perifovea, typically temporally
4. Pigment hyperplasia, often surrounding right-angle venules
5. Subretinal neovascularization, often in proximity to intraretinal pigment migration

- **Differential diagnosis**
  - Branch retinal vein occlusions
  - Radiation retinopathy
  - neovascular age-related macular degeneration
- **Treatment**
  - no generally accepted therapies
  - Laser photocoagulation or photodynamic therapy
  - Long-term Effects of the Phase 2 **Ciliary Neurotrophic Factor Treatment of Macular Telangiectasia Type 2**

- CNTF treatment delivered by **CNTF Implant NT501** was safe and well tolerated. CNTF had a beneficial effect and reduced the progressive loss of photoreceptors, compared to untreated eyes, persisting up to 36 months and 48 months.

Hemoglobinopathies

- Hemoglobin S: valine substitutes for a glutamic acid at the sixth position within the β-globin
- Hemoglobin C (Hb C) is caused by a glutamic acid to lysine mutation in the β-globin molecule.
- SCD remains the most common inherited blood disorder
- **Pathophysiology**
  - hydrophobic polar valine takes the place of a nonpolar strongly hydrophilic glutamic acid residue
  - polymerization results in the generation of rigid fibers of Hb S
  - Decreased erythrocyte deformability and increased rigidity can cause increased capillary transit time
  - sickled erythrocytes display increased adhesion to vascular endothelium matrix proteins, such as laminin
- **Systemic manifestations**
  - intravascular hemolysis, thrombosis, tissue necrosis, and ischemia, causes a myriad of systemic complications, including cerebrovascular accident, acute chest syndrome, pulmonary hypertension, splenic sequestration, priapism, osteonecrosis, cholelithiasis, pneumonia, leg ulcers, aplastic crisis, renal disease, need for recurrent transfusions, episodic, painful vaso-occlusive crises, and death
  - visual impairment: more in hemoglobin SC (33%) than in hemoglobin SS (3%)
    - **hb SS** may not live long enough to manifest the ophthalmic disease
    - higher hematocrit and cell density, and the lower Hb F, of individuals with Hb SC
- **Ophthalmic clinical features**
  - *Retrobulbar and orbital involvement:* periorbital swelling, lid edema, fever, facial pain, proptosis, restriction of motility, and resultant diplopia
  - *Anterior-segment involvement:*
    - saccular and sausage-like dilatations of the tiniest conjunctival vessels,
    - **Segmental iris atrophy** and pupil abnormalities
    - Hyphema in a patient with SCD and in those with sickle-cell trait represents a sight-threatening emergency, as even modest elevations of intraocular pressure (IOP) have resulted in vision loss from central retinal artery occlusion or macular branch retinal artery occlusion
    - Repetitive use of carbonic anhydrase inhibitors, for example, is **contraindicated** in SCD patients with hyphema

- *Posterior-segment involvement*
- Vitreoretinal interface:
  - peripheral retinal whitening: just like **white without pressure**
  - flat, brown, ovoid lesions in the retinal periphery: **dark without pressure**
- Optic nerve
  - Dark, dilated capillaries at the optic nerve head appear as small red dots → precapillary arterioles plugged with sickled erythrocytes
- Macula
  - **macular depression sign**: oval depression of the bright foveal or parafoveal reflex as a result of macular thinning due to ischemic atrophy
  - enlarged foveal avascular zone (FAZ)
  - "**splaying**," or blunting of the foveal contour on SD-OCT in asymptomatic patients with SCD
- Angioid streaks
  - **1-2%**
  - irregular, reddish subretinal bands → benign course in HbSS
- Retinal vasculature
  - Vascular tortuosity caused by arteriovenous anastomoses may be more commonly observed in Hb SS
  - peripheral retinal nonperfusion
  - Retinal arteriole "**silver-wiring**" represents permanently occluded arterioles

Nonproliferative sickle retinopathy

- *Salmon patch hemorrhages:* blowout" of an occluded arteriole
- *Iridescent spots:* small schisis cavity may develop after the intraretinal portion of the hemorrhage resolves.
- *Black sunburst:* flat, stellate, or round areas of hyperpigmentation, and result when intraretinal hemorrhage tracks into the subretinal space → **sunburst sign**

Proliferative sickle retinopathy

- Resembles marine invertebrate, *Gorgonia flabellum*
- Peripheral retinal arteriolar occlusions→ growth factors→ neovascular fronds
- Sea fans are predisposed to hemorrhage into the vitreous, and to cause vitreous membrane formation, tractional retinoschisis, and tractional or combined rhegmatogenous–tractional retinal detachment

Goldberg classification

1. Peripheral arterial occlusions
2. Peripheral arteriovenous anastomoses
3. Neovascular and fibrous proliferations: Sea-fan fronds are the hallmark of stage III PSR

4. Vitreous hemorrhage: more commonly in the Hb SC than the Hb SS genotype (23% versus 3%)
5. Retinal detachment: TRD

- **Incidence/prevalence**
  - 43% subjects with Hb SC disease and in 14% subjects with Hb SS disease
- **Risk factors**
  - unstable type IIa border (hairpin loop) conferred an increased risk for PSR.
  - Hb SS: high total hemoglobin in males and a low Hb F in both males and females
  - **Hb SC:** High total hemoglobin and high MCHC
- **Progression**
  - Spontaneous regression of PSR may occur in 32%
  - **unilateral PSR** had a **16%** (11% Hb SS, 17% Hb SC) probability of regressing to **no PSR** and a **14%** (16% Hb SS, 13% Hb SC) probability of progressing to **bilateral PSR**.
  - **bilateral PSR** had an **8%** (both Hb SC and Hb SS genotypes) probability of regressing to **unilateral PSR** and a **1%** (0 Hb SS, 2% Hb SC) probability of regressing to a **PSR-free** state
- **Treatment**
  - As per stages

Ocular Ischemic Syndrome

- 1963, Kearns and Hollenhorst**: venous stasis retinopathy**
- Dr. **Larry Magargal**: ocular ischemic syndrome
- 5% of patients with severe carotid artery insufficiency or thrombosis
- 50-80 years
- M:F= 2:1
- 20% bilateral
- **Etiology**
  - 90% or greater stenosis of the ipsilateral carotid arterial system
- **Clinical Features**
  - visual loss: gradual, sudden in 12%
  - VA: variable
  - **cherry-red spot** present on funduscopic examination
  - **Prolonged light recovery**: ischemia of the macular retina
  - Scintillating scotomas:
  - Amaurosis fugax

- Pain: **40% → ocular angina**
- External collaterals:
- ***Anterior segment changes***: **66% cases NVI**, only **50% develop increase IOP** (Impaired ciliary body perfusion)
- ***Posterior segment findings***:
  - retinal arteries are usually narrowed and the retinal veins are most often dilated, but not tortuous
  - Retinal hemorrhages: **midperipheral**
  - **NVD 35%, NVE 8%**
  - **VH 4%**
  - cherry-red spot is seen in approximately 12%
  - cottonwool spots in 6% of eyes, spontaneous retinal arterial pulsations in 4%, and cholesterol emboli within the retinal arteries in 2%.

Investigations

- **FA**:
  - Delayed and/or patchy choroidal filling 60%
  - Prolonged retinal arteriovenous transit time 95%
  - Retinal vascular staining 85%
  - Macular edema 17%
  - Other signs: Retinal capillary nonperfusion, Optic nerve head hyperfluorescence, Microaneurysmal hyperfluorescence
- **Electroretinography**
  - diminution of the amplitude, or absence, of both the aand b-waves
- **Carotid angiography**: typically discloses a 90% or greater obstruction of the ipsilateral internal or common carotid artery
- **VEP**:
- **Ophthalmodynamometry**

Differential Diagnosis

- CRVO
- DR

Treatment

- poor long-term outcome
- if rubeosis: 90% are blind in 1 year
- ***Total carotid artery obstruction:*** extracranial to intracranial bypass surgery → superficial temporal to middle cerebral artery (STA-MCA) bypass
- ***Less than total carotid artery obstruction:*** carotid endarterectomy

Radiation Retinopathy

- Stallard in 1933
- slowly progressive, delayed-onset *occlusive microangiopathy* of the retinal vasculature that occurs with variable latency after exposure of the retina to ionizing radiation.
- **Etiopathogenesis**
  - ionizing radiation of the retina induces an acute transudative as well as a slowly progressive occlusive vasculopathy
  - fundamental abnormality, is retinal vascular endothelial cell injury and loss
  - loss of capillary cellularity leads to the development of microaneurysms, and hemodynamic alterations produce fenestrated telangiectatic retinal vessels.
  - Closure of blood vessels is the single most characteristic finding on FA.
  - In contrast to diabetic retinopathy, in which pericytes are initially affected, RR exhibits an early loss of endothelial cells.
- **Clinical Features**
  - Microaneurysms
  - intraretinal hemorrhages, macular capillary dilation and nonperfusion, and nerve fiber layer infarcts
  - Retinal edema, hard exudates, telangiectasia, and perivascular sheathing
  - FA: presence of severe retinal capillary nonperfusion, capillary dilation, and microaneurysms, frequently in combination with macular edema or ischemia
- **Classification**
  - Nonproliferative radiation retinopathy
  - Proliferative radiation retinopathy
  - Clinically significant macular edema
  - Macular ischemia
- **Finger and Kurli prognosis-related classification**
  1. extramacular ischemic changes
  2. macular ischemic changes
  3. Additional macular edema and retinal neovascularization
  4. vitreous hemorrhage and at least 5 disc areas of retinal ischemia, whether macular or extramacular
- **Horgan OCT-based grading scale**
  1. extrafoveolar, noncystoid edema
  2. extrafoveolar cystoid edema
  3. foveolar noncystoid edema
  4. mild-to-moderate foveolar cystoid edema
  5. severe foveolar cystoid edema
- **Risk factors**

- Internal: concomitant vascular disease
- External: Chemotherapy, pregnancy,

- **Incidence and dosimetry**
  - *Radiation type:* plaque, proton beam irradiation, gamma knife treatment
  - *Treatment modality:* EBRT are less likely than plaque
  - *Total radiation dose:* does not usually occur at total doses <45 Gy
  - *Fractionation schedule:* per fraction below 1.9 Gy/fraction has been shown to decrease the incidence of retinopathy
  - *Volume of retina irradiated:* more than 50 Gy to greater than 60% of the retina have been shown to be more likely to develop RR
  - *Total elapsed time:* most commonly occurs between 6 months and 3 years
- **Differential Diagnosis**
  - diabetic or hypertensive retinopathy
  - Bone marrow transplant retinopathy
  - multiple branch retinal artery occlusions, multiple retinal venous occlusive episodes or retinal telangiectasia from other causes
- **Prevention and treatment**
  - Retinal laser photocoagulation remains the gold standard in the treatment of most forms of ischemic retinopathies.
  - Corticosteroids have both angiostatic and vascular antipermeability properties
  - anti-VEGF agents
  - **Treatment of Radiation Retinopathy (TORR) trial:** intravitreal ranibizumab (0.5 mg) or intravitreal triamcinolone acetonide (4.0 mg) is associated with improved visual acuity at 1 year, as compared to natural history
  - **Ranibizumab for radiation retinopathy (RRR)**: a prospective, multicenter trial of monthly versus prn dosing for radiation retinopathy-related cystoid macular edema.
    - All 3 groups treated with 0.5mg intravitreal ranibizumab had significantly better visual outcomes than historical controls; patients treated with monthly ranibizumab had significant visual gains compared to patients treated with a p.r.n. approach; the Addition of targeted PRP to monthly ranibizumab did not result in visual gain over monthly ranibizumab at the 12-month time point; in year 2, with a treat-and-extend approach, patients in the monthly cohort trended toward their baseline BCVA, although still with improvement over historical controls.
- predictors of poor visual acuity at long-term follow-up following plaque radiotherapy included patient age ≥60 years, tumor base ≥10 mm, tumor thickness >8 mm, radiation dose to the tumor base of ≥33 300 cGy, and increasing radiation dose to the optic disc.

Age Related Macular Degeneration (ARMD)

- Consensus on Neovascular AMD Nomenclature (**CONAN**): experts over the course of 3 years to create consistent definitions of AMD, its components, and its sub-classifications. (It should be noted that there is also the **Beckman** Classification, which was proposed in 2013).
- CONAN defines **AMD** as "a process by which the structure and function of the macula deteriorates over time in association with distinguishing signs and symptoms that typically become evident clinically beyond 50 years of age and do not seem to be secondary to other processes such as pathologic myopia, central serous chorioretinopathy, monogenetic inherited retinal disease, chorioretinal uveitic syndromes or infections, or trauma."
- The group defined macular neovascularization (**MNV**) as "an invasion by vascular and associated tissues into the outer retina, subretinal space, or sub-retinal pigment epithelial (RPE) space in varying combinations," with three subtypes:
  - **Type 1 MNV** is an ingrowth of vessels initially from the choriocapillaris into the sub-RPE space
  - **Type 2 MNV** refers to the proliferation of new vessels arising from the choroid into the subretinal space
  - **Type 3 MNV** refers to a downgrowth of vessels from the retinal circulation toward the outer retina (therefore, the term "choroidal neovascularization" is not accurate for this type of MNV)

Epidemiology

- prevalence and incidence rates differ by race/ethnicity
- different studies available
- Prevalence
  - Total prevalence 6.5% in 40 years or older
  - late AMD 1.6% overall (exudative maculopathy 1.2%, geographic atrophy 0.6%)
  - late AMD 7.1% in persons who were 75 or older.
- Incidence
  - early AMD increased from 3.9% in individuals aged 43–54 years to 22.8% in persons 75 years of age and older
  - overall 5-year incidence of late AMD was 0.9%
- **Quality of life**
  - greater emotional distress, worse self-reported general health, and greater difficulty carrying out daily activities.
  - higher rate of depression
- **Socioeconomic risk factors**
  - ***Age***
    - 30% of individuals 75 years of age or older had early AMD
    - 7.1% had late AMD after 75 years of age

- ***Gender***
  - no overall difference
  - males had lower AMD than females
- ***Race/ethnicity***
  - early AMD is common among blacks and Hispanics than whites
  - Asians have rate comparable to whites
- ***Socioeconomic status***
  - Less education and lower income groups have higher prevalence

Ocular risk factors

- ***Refractive error***
  - association between AMD and hyperopia
- ***Iris color***
  - Higher levels of ocular melanin may be protective against light-induced oxidative damage to the retina
- ***Lens opacities, cataracts, and cataract surgery***
  - history of cataract surgery has been found to be associated with an increased risk for advanced AMD
- ***Cup-to-disc ratio***
  - larger cup-to-disc ratios had a reduced risk of exudative AMD

Behavioral and lifestyle factors

- ***Smoking***
  - 25 or more cigarettes per day had a relative risk (RR) of 2.4
- ***Antioxidants, vitamins, and minerals***
  - vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), and the carotenoids (including alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin)
  - AREDS: zinc supplement included zinc (80 mg) as zinc oxide, and copper (2 mg) as cupric oxide; the antioxidant supplement included vitamin C (500 mg), vitamin E (400 IU), and beta-carotene (15 mg).
  - three or more servings of fresh fruit per day have an RR of 0.64 (95% CI 0.44–0.93) compared to those who consumed less than 1.5 servings per day
- ***Alcohol intake***
  - evidence to date suggests that alcohol intake does not have a large effect
- ***Obesity and physical activity***
  - BMI between 25 and 29 had an RR of 2.32
- ***Sunlight exposure***
  - no significant association??
- ***Medications***

- increased risk of early AMD with use of beta-blockers
- decreased rate of CNV among AMD patients taking aspirin or statins

- **Cardiovascular-related factors**
  - ***Cardiovascular diseases***
    - 4.5-fold increased risk of late AMD associated with plaques in the carotid bifurcation and a twofold increased risk associated with plaques in the common carotid artery
    - positive association between AMD and cerebrovascular disease
    - many CVD risk factors are associated with AMD
  - ***Blood pressure and hypertension***
    - Unclear association
  - ***Cholesterol levels and dietary fat intake***
    - the relationship with dietary fat is more consistent
  - ***Diabetes and hyperglycemia***
    - no significant relationships.
- **Hormonal and reproductive factors**
  - EDCCS showed a marked decrease in the risk of neovascular AMD among postmenopausal women who used estrogen therapy
  - protective effect of estrogen on AMD is possible
- **Inflammatory factors**
  - Inflammation is also associated with angiogenesis and may play a role in the neovascularization seen in the advanced forms of AMD
  - CRP
  - SNPs in the *Clinical FeaturesH* gene
  - **intravitreal compstatin/POT-4**: a C3 inhibitor
  - **Intravitreal use of ARC1905**: C5 inhibitor
  - Systemic administration of the anti-C5 antibody, **eculizumab**, is being investigated for geographic atrophy
- **Genetic factors**
  - Y402H in the *Clinical FeaturesH* gene, chromosome 1q31
  - Variation in the *ARMS2/HTRA1* locus on chromosome 10 has been convincingly associated with AMD
  - *LIPC* and tissue inhibitor of metalloproteinase 3 (*TIMP3*)
  - Data from the Rotterdam study showed that first-degree relatives of affected individuals are at 25% greater risk of developing disease than individuals in the general population without any affected family members.
  - A higher prevalence of AMD is found in identical twins compared to fraternal twins

Pathogenesis

1. RPE

- Primary lesion is in RPE which causes secondary changes in photoreceptors and choriocapillaries.
- RPE cells are responsible for Phagocytosis of membranous discs shed by rods and cones. But Molecular degradation does not always go to completion and Residues of incomplete digestion gradually accumulate—**LIPOFUSCIN GRANULES**
- Incomplete degradation due to → reactive oxygen intermediates
  - High oxygen tension
  - Exposure to irradiation
  - PUFA in cell membranes of photoreceptors
- Accumulated lipofuschin causes →
  - Mechanical distortion
  - Reduces phagocytic ability
  - Reduced activity of catalase, superoxide dismutase
  - Reduces glutathione levels
  - N-retinyl Nretinylidene ethanolamine or A2E a component of lipofuscin induces apoptosis
  - Increases susceptibility of RPE to ROI
- RPE is progressively engorged with lipofuscin and so normal metabolism disrupted
- Altered secretion of materials from basal aspect causing
  - Basal laminar deposits
  - Basal linear deposits

2. Bruch's

- Progressive increase in lipid content
- AGE's
- Change in GAG's ↑Heparan sulfate
- IMPEDANCE OF DIFFUSION → Disrupts RPE function → The abnormal deposits in the Bruch's membrane still have their origin from RPE – Basal Linear Deposits
- Basal laminar deposits: BLamD
  - Between plasma membrane and basement membrane of RPE
  - Widely spaced collagen ,100nm, **most prevalent marker**
- Basal Linear deposits: BLinD
  - In the Inner collagenous layer of Bruch's membrane
  - Widely spaced collagen and lipids, **most specific to AMD**

- Constituents of drusen
  - Denatured mitochondria, cytoplasmic debris, pigment granules, photoreceptor remnants
  - Mucopolysaccharide and lipids.
  - IgG, complement components, complement inhibitor clusterin
- Types of drusen
  - Hard
    - Hyalinized material with membrane bound bodies external to RPE
    - Formed from entrapment sites or microdrusen
  - Hard drusen cluster
    - Amorphous material lines the druse and contains globular material
  - Soft cluster driven
    - Fusion of hard drusen with disruption of amorphous rim
  - Soft membranous
    - Focal accentuation BlinD.
  - Basal Laminar drusen
    - Diffuse accumulation of hyalinized material internal to RPE with nodularity
    - Not a/w AMD

PATHOGENESIS OF CNV

- Surgically excised CNV contains RPE, Bruch's membrane, photoreceptors, vascular endothelium, fibroblasts, stem cells, macrophages, collagen and basal laminar deposits.
- **CNV**
  - VASCULAR COMPONENT
  - EXTRA VASCULAR COMPONENT
- **Stages of CNV**
  - INITIATION:
    - VEGF
    - **Macrophages**
    - **Insulin like growth factor**
    - **Nitric Oxide**
    - **Angiostatin**
    - **Endostatin**
    - **Pigment epithelium derived factor**
    - **CCR3/CD193**
  - ACTIVE INFLAMMATION

- **Matrix Metalloproteinase**
- **Tissue factor**
- **Angiopoietin – 2, Tie1 , Tie 2**
- **b-Fibroblast growth factor**
- **TGF-beta**
- **Activation of complement**
- **PDGF-B**

- INVOLUTION
  - **TGF-BETA**
  - **TIMP-3**
  - **Hyperoxia**

Structural Changes

- ***Choroid***
  - density of the choriocapillaris is decreased with age in eyes without AMD
  - in advanced AMD, loss or narrowing of the choriocapillaris occurs
  - diffusely thickened Bruch's membrane represented a barrier to diffusion of VEGF towards the choroid resulting in changes in the capillary bed

- ***Bruch's membrane***
  - PED: reduction of the hydraulic conductivity of Bruch's membrane would hamper movement of water towards the choroid thus causing it to accumulate in the sub-RPE space
  - There is considerable lipid trafficking through Bruch's membrane and lipids are believed to accumulate as they fail to pass freely through a thickened Bruch's membrane

- ***The retinal pigment epithelium***
  - quadratic relationship exists between age, and both autofluorescence and residual body quantity in RPE
  - those with high autofluorescence levels had a diet high in vitamin A.

- ***Outer retina***
  - photoreceptor cell loss occurs progressively in early AMD

Role of Cytokines

- **Angiogenesis** refers to the creation of new blood vessels from existing blood vessels.

- **vasculogenesis** seen characteristically in utero in which vessels are created de novo.
- VEGF plays a principal role (it's a putative factor X first postulated by Michaelson)
- other cytokines may play an important role as well, including fibroblast growth factor (FGF), pigment epithelial-derived factor (PEDF), the integrins, angiopoietins, and matrix metalloproteinase inhibitors.
- ***VEGF***
  - MOA: increases in hydraulic conductivity of isolated microvessels that are mediated by increased calcium influx and likely changes in levels of nitric oxide caused by induction of nitric oxide synthetase (NOS).
  - **45 kDa**
  - 121, 145, 165, 183, 189, and 206, amino acids respectively after signal sequence cleavage
  - $VEGF_{165}$ exists in both soluble and bound forms
  - 165 is the principal isoform involved in pathologic neovascularization
  - (1) induction of angiogenesis through endothelial proliferation, migration, and new capillary formation, and (2) enhancement of vascular permeability
  - two highly related **receptor tyrosine kinases (RTKs)** VEGFR-1 and VEGFR-2
    - VEGFR-1: important during embryogenesis
    - VEGFR-2: pathologic neovascularization as well as in hematopoietic bone marrow-derived cells and neural signaling
  - VEGF is also suspected to mobilize and augment **endothelial progenitor cells** (EPC) from ***bone marrow***

Angiogenesis

- **Naturally occurring upregulators of angiogenesis**
  - *Fibroblast growth factor and integrins*
  - *Platelet-derived growth factor*
  - *Angiopoietins*
  - *Matrix metalloproteinases and tissue inhibitors of metalloproteinases*

- **Naturally occurring downregulators of angiogenesis**
  - *Pigment epithelial-derived factor*
  - *Other cytokines*
    - Thrombospondin 1 (TSP-1) has been described as both an up-and down-regulator of VEGF
    - Angiostatin, is a 38 kDa internal fragment of plasminogen, it has inhibitory effects on vascular endothelial proliferation

- Endostatin, a cleavage product of collagen XVIII, is structurally related to and shares homology with angiostatin, and inhibits tumor-associated angiogenesis

Non-neovascular AMD

- International Epidemiological Age-related Maculopathy Study Group defined **Early ARM** as
  - Soft drusen (intermediate >63 µm, ≤125 µm; large >125 µm) drusen. When occurring alone, soft, indistinct drusen are considered more likely to indicate AMD than soft, distinct drusen, and drusen over 125 µm have greater importance than smaller drusen.
  - Areas of hyperpigmentation associated with drusen but excluding pigment surrounding hard drusen.
  - Areas of depigmentation or hypopigmentation associated with drusen. These areas, which commonly occur as drusen fade, are most often more sharply demarcated than drusen, but do not permit exposure of the underlying choroidal vessels.
  - Visual acuity is not used to define ARM or AMD because advanced changes may be present without anatomically affecting the fovea.
- Late stages of ARM will be called Age related macular degeneration which can be dry or wet
  - **DRY/EARLY:**
    - A sharply demarcated area of de/hypopigmentation in which choroidal vessels are more visible and the area is at least 175 microns in diameter
  - **WET/LATE**
    - RPE detachments
    - Subretinal/Sub RPE neovascular membrane
    - Epiretinal/Subretinal/Intraretinal/Sub RPE scar or glial tissue
    - Subretinal haemorrhage
    - Hard exudates in macular area with any of the above
- **AREDS CLASSIFICATION**
  - No AMD (AREDS category 1)
    - No or a few small (<63 micrometres in diameter) drusen
  - Early AMD (AREDS category 2)
    - Many small drusen or a few intermediate-sized (63-124 micrometres in diameter) drusen, or macular pigmentary changes
  - Intermediate AMD (AREDS category 3)
    - Extensive intermediate drusen or at least one large (≥125 micrometres) drusen, or geographic atrophy not involving the foveal centre
  - Advanced AMD (AREDS category 4)
    - Geographic atrophy involving the foveal centre (atrophic, or dry, AMD)

- Choroidal neovascularisation (wet AMD) or evidence for neovascular maculopathy (subretinal haemorrhage, serous retinal or retinal pigment epithelium detachments, lipid exudates, or fibrovascular scar).

- Early treatment at the onset of symptomatic exudation from macular neovascularization (MNV) is important for preventing the permanent loss of central vision that results from a delay in treatment. The early detection of nonexudative MNV (NEMNV) in asymptomatic eyes helps to identify those patients at highest risk of exudation.
- shallow, irregular RPE elevation (**SIRE**) above the Bruch membrane (BM) on spectral domain OCT imaging to predict the presence of NE-MNV. In a study, The positive predictive value for a SIRE was 25%, and the negative predictive value was 100%.
- SIRE can be detected on structural OCT imaging and when present indicates a 1 in 4 chance of having detectable NE-MNV on OCT-A imaging. Once NE-MNV is diagnosed, then more frequent follow-up and diligent home monitoring are recommended for early detection of exudation.

Neovascular AMD

- Clinical features & histopathogenesis overall 10% of AMD patients have the wet form of AMD. This includes CNV and associated manifestations like RPED, RPE tears, disciform scarring, and vitreous hemorrhage. Majority of AMD patients with vision, <20/200 have wet form of AMD. Most patients with CNV complain of blurred and/or distorted vision, central scotomas leading to difficulty in reading & recognizing faces. After noting the visual acuity, the scotomas should be mapped on an Amsler grid in order to have a fair idea of the patient's handicap & for planning low vision aids for the patient.
- ***CNV:*** Clinically on slit lamp biomicroscopy CNV appears as grey-green elevation deep to retina with overlying neurosensory detachment, however, this characteristic appearance may not always be present in CNV due to AMD. In such scenarios the presence of CNV is indicated by any one of the following
- Subretinal blood or lipids
- RPED with or without overlying subretinal fluid.
- Occasionally a shallow neurosensory serous RD may be the only presenting sign of underlying CNV.
- The CNV capillary network becomes more apparent after the atrophy of overlying RPE. CNV has been classified into classic and occult depending upon the angiographic appearance (described later). Depending upon its location CNV may be subfoveal, juxtafoveal (between 1&199µm from the centre of FAZ), or extrafoveal (>200µm from FAZ centre). Histologically CNV is growth of abnormal, fragile new vessels between the Bruchs membrane & RPE or between the latter & neurosensory retina. These vessels sprout from the chorio capillaries & proceed inwards through the defects in the Bruchs membrane
- Classic: classic subretinal neovascular membrane (SRNVM or CNVM) presents a fluorescein angiographic picture characterized by early onset of hyperfluorsescence from the arterial phase of the FA, during which a neovascular net may also be seen. This lesion shows progressive increase in the intensity of the hyperfluorescence in the late phase of the FA, with a blurring of the margins of the lesion.
- **Occult CNVM**

- ***three common presentations***
- The first is a late leakage from an unknown source. In these lesions, the early phase of the FA does not show any well defined lesion but by the mid phase of the FA, an area of increasing hyperfluoresence begins to get visualized. The intensity of the hyperfluorescence and even the extent of the lesion increases over time upto the late phase of the FA. In order to be able to make a diagnosis of these lesions conclusively, it is mandatory to take photographic frames during fluorescein angiography from the arterial phase upto at least 8 minutes after the fluorescein injection.
- The second presentation of an occult CNVM is that of a fibrovascular pigment epithelial detachment, which presents with an irregular elevation of the RPF showing stippled hyperfluorescence within 1-2 minutes after fluorescein dye injection, with persistant staining or leakage in the late phase frames of the fluorescein angiogiam.
- The third common presentation of an occult CNVM is of a serous retinal pigment epithelial detachment, which presents clinically as a dark blister type of lesion with a ring halo around it. On fluorescein angiography, this lesion shows hyperfluorescence which is relatively uniform and well defined and starts in the early phase of the FA. The hyperfluorescence become uniform and more intense in the late phase of the angiogram but the margins continue to remain well defined.

- ***RPEDs:*** appear as sharply demarcated, dome shaped elevations of RPE. If filled with serous fluid they transilluminate. Three types of PEDs are seen & can be differentiated on the basis of their Angiographic pattern (described later)
  - Drusenoid PED -does not have CNV
  - Fibrovascular PED-is a form of occult CNV
  - Serous PED-may or may not overlie CNV

- Overlying serous RD, lipid & blood within or surrounding a PED implies the presence of CNV. Sub RPE blood is seen as green or dark red mound.
- ***RPE tear:*** or rip occurs as a complication in serous or fibrovacular PED. It occurs at the border of attached & detached RPE due to stretching forces of the underlying fluid or from the contractile forces of the fibrovacular tissue. Clinically it is seen as area of hypopigmentation with hyperpigmented wavy border on one side due to rolling in of the free edge of torn RPE.
- Massive sub retinal hemorrhage and breakthrough vitreous hemorrhage though unusual complications of AMD, are seen sometimes and result in sudden profound visual loss both central as well as peripheral.
- ***Disciform Scar:*** is the last stage in the evolution of neovascular AMD just as geographic atrophy is in dry AMD. CNV is a fibrovascular tissue; however, the fibrous component is not readily appreciated in the early stages of CNV due to immaturity of the fibrous tissue & also due to the overwhelming signs like serous RD, subretinal lipids and/or blood, of the vascular component. When the fibrous tissue becomes apparent clinically then the fibrovascular complex is called disciform scar. Clinically it appears as white to yellow subretinal scar with intervening areas of hyperpigmentation. If the vascular component has

died its own death then the scar does not grow, however, it can expand with neovascularization occurring along the edges.

Pharmacotherapy

Non-neovascular AMD

1. ***Netraceuticals***
2. ***Prevent photoreceptors and RPE loss***
3. ***Reduce toxic metabolites***
4. ***Suppress or modulate inflammation***

- ***Antioxidants, vitamins, and cofactors***
  - AREDS and related supplements
    - Write trials and results
  - Othera Eye Drops (antioxidant, anti-inflammation and anti angiogenic) – **Omega study**
  - Pills for Dry AMD-**Acucela** (ACU-4429): **ENVISION** Clarity trial in geographic atrophy
  - **Copaxone (glatiramer acetate)**
    - weekly vaccination with the drug Copaxone. This is NOT an injection in the eye.
    - Macular degeneration, Alzheimer's disease and Multiple sclerosis

- ***Visual cycle inhibitors***
  - intended to reduce the accumulation of toxic fluorophores such as A2E in RPE
  - **Fenretinide**: in circulating retinal binding protein (RBP) and retinol by displacing retinol from RBP
  - **Accutane**: inhibits the conversion of all-trans-retinyl esters (in retinosomes) to 11-*cis*-retinol and the conversion of 11-*cis*-retinol to 11-*cis*-retinal
  - most common adverse events
    - dyschromatopsia (32%), unspecified visual disturbance (29%), night blindness (18%), blurred vision (11%), and photophobia (8%).

- ***Complement modulators***
  - Role of CCR3 (chemokine receptor): Anti-CCR3 antibodies may prevent tube formation prior to vascularization and reduce the proliferation of CECs following laser-induced injury.
  - Complement C5aR Inhibition
  - CNTF in Dry AMD

- Protein that effects apoptosis and is classified as a “neuroprotective” agent

✦ ***Cell Based Therapy***

1. **Regenerative**: Isolated Stem cells → expanded differentiated cell therapy product
   - Corneal limbal stem cells for chemical injury
   - Not used for AMD now
2. **Trophic**: Isolate → Expanded but not differentiated (this is now used)
   - **CNTF Implant** for Atrophic AMD (modified allogenic RPE cells secrete CNTF)
   - **First used for RP**
   - Microcathetre guided delivery system: **iTRACK** and iLumin fibreoptic illuminator
   - **Razel pump** for rate-controlled delivery of stem cells

Neovascular AMD

✦ ***VEGF inhibitors***

✦ Direct VEGF inhibitors

✦ *Monoclonal antibody: bevacizumab (Avastin)*

- humanized monoclonal antibody (IgG1) against human VEGF-A
- amino acid sequences which are about 93% human and 7% murine
- **systemic bevacizumab (5 mg/kg)** was shown to reduce leakage from CNV, decrease OCT central retinal thickness measurements, and significantly improve vision in exudative AMD
- intravitreal dose: 0.05 ml (1.25 mg) to 0.1 ml (2.5 mg) [500 times less dose]
- concerns about retinal penetration are now disproved
- **SANA**: Systemic Avastin for Neovascular AMD
  - two to three intravenous infusions of bevacizumab (5 mg/kg)
  - too small to establish the safety
- half-life of 3 days and was likely to provide complete intravitreal VEGF blockade for a minimum of 4 weeks
- **ABC trial**
  - intravitreal bevacizumab (three loading doses every 6 weeks, followed by Additional injections at 6-week intervals as needed) to standard therapy, defined at the time of recruitment as verteporfin PDT for predominantly classic CNV, or pegaptanib injection or sham injection for minimally classic or occult CNV.
  - first level 1 evidence of the efficacy of bevacizumab for the treatment of AMD.
  - bevacizumab group improved by 15 letters compared with the standard therapy group (32% vs 3%, $P < 0.001$)

- Antigen binding fragment: ranibizumab (Lucentis)
  - Ranibizumab is a humanized anti-VEGF-A recombinant Fab fragment
  - **MARINA**
    - assessed the response of minimally classic or occult CNV to ranibizumab.
    - **sham injection:**
    - **0.3 mg ranibizumab**
    - **0.5 mg ranibizumab**
    - 90% of ranibizumab-treated patients had lost less than 15 letters on the Bailey – Lovie (ETDRS) chart as compared to 53% of the sham-injected patients.
  - **ANCHOR study**
    - predominantly classic CNV
    - **verteporfin-PDT plus sham**
    - **sham PDT plus injection of 0.3 mg ranibizumab**
    - **sham PDT plus injection of 0.5 mg ranibizumab**
    - 95% of ranibizumab-treated patients lost less than 15 letters of vision versus 64% in the verteporfin active-treatment control group.
    - Forty percent of patients treated with 0.5 mg ranibizumab gained at least 15 letters vision versus 6% in the verteporfin treatment cohort
  - **PIER**
    - subfoveal CNV
    - **sham injection**
    - **0.3 mg ranibizumab**
    - **0.5 mg ranibizumab**
    - Monthly for 3 months and then 3 monthly upto 12 months
    - injecting patients with ranibizumab every 3 months (after an induction phase of three monthly injections) does not produce the same chance for visual benefit as monthly injection, at least during the first 12 months of therapy
  - **EXCITE study**
    - At month 12, the visual acuity gain in the monthly treatment cohort was higher than that of the quarterly regimens.

PrONTO, SUSTAIN, SAILOR were PRN dosage study.

- **SUSTAIN study**
  - three initial monthly injections of ranibizumab (0.3 mg) and thereafter pro re nata (PRN) retreatment for 9 months
- **PrONTO**: Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intraocular Lucentis

- 0.5 mg ranibizumab at entry, month 1, and month 2
- OCT done monthly, FA every 3 months
- Retreatment with ranibizumab was done only if one or more of the following conditions was observed: (1) CRT increased 100 μm; (2) =5 letter visual loss associated with subretinal fluid (3) new onset classic CNV; (4) new macular hemorrhage; (5) persistent fluid 1 month after the previous injection.
- OCT-guided variable-dosing regimens with intravitreal ranibizumab were capable of achieving visual acuity outcomes comparable

- **SAILOR study**
  - numerically higher rate of cerebrovascular stroke with 0.5 mg ranibizumab compared with 0.3 mg ranibizumab (1.2 vs 0.7%), which was not statistically significant
- **Comparison of Armd Treatments Trial (CATT)**
  - Bevacizumab and ranibizumab
  - 3 questions
    - one treatment offer superior visual outcomes to another?
    - optimal treatment regimen and interval?
    - safety profile of bevacizumab comparable to that of ranibizumab?
  - **ranibizumab 0.5 mg monthly**
  - **bevacizumab 1.25 mg monthly**
  - **ranibizumab PRN**
  - **bevacizumab PRN**
  - 1st year result
    - bevacizumab as needed, when compared to ranibizumab or bevacizumab monthly, yielded inconclusive results, all other groups showed similar efficacy.
    - Rate of systemic adverse events was significantly higher in the bevacizumab group than in the ranibizumab group
  - 2nd year result
    - very similar visual outcomes to patients maintained on as-needed therapy since study enrollment for both medications.
    - Similar about complications also..

- Soluble receptor: **aflibercept (VEGF-TRAP EYE)**
  - ***Regeneron***
  - soluble fusion protein → extracellular components of VEGF receptors 1 and 2 fused to the Fc portion of IgG1
  - 200-fold higher affinity for VEGF
  - also binds VEGF-B and PlGF.

- **CLEAR-IT 1** (CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial)
  - functional and anatomical improvement with a dose of 0.5 and 2 mg
- **CLEAR-IT 2**
  - biologic effects and safety of aflibercept during a 12-week fixed-dosing period in patients with exudative AMD followed by PRN dosing out to 1 year
- **VIEW 1 and VIEW 2:** VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD
  - **aflibercept 0.5 mg monthly**
  - **aflibercept 2 mg monthly**
  - **aflibercept 2 mg every 2 months (following three monthly loading doses)**
  - **ranibizumab administered 0.5 mg every month**
  - at 1 year, no difference in the outcomes when the three aflibercept groups were compared with the ranibizumab group

- **Combination therapy: SUMMIT**
  - evaluate if Visudyne combined with Lucentis was not inferior (with a non-inferiority margin of seven letters) to monthly Lucentis monotherapy
  - **MONT BLANC** is the European study
    - standard-fluence Visudyne with Lucentis 0.5 mg can deliver VA improvements (2.5 letters from baseline) that are non-inferior to a Lucentis monotherapy regimen
  - **DENALI**: USA and Canada
    - both combination therapy and Lucentis monotherapy were well tolerated
  - **EVEREST**: Asia
    - Visudyne therapy, with or without Lucentis, may lead to complete regression of the polyps that can cause vision loss in patients with PCV, a potentially devastating eye disease.

- KH902
- Adeno-associated viral vector (AAV) gene transduction
- Oligonucleotide aptamer (pegaptanib – Macugen)
  - first VEGF inhibitor approved for use
  - aptamer against VEGF isoform 165
  - not used now
- Small interfering RNA (siRNA)
  - Double rather than single-stranded RNA
  - presence of siRNA results in the inhibition of protein synthesis

- phase I study of Sirna-027
- **Bevasiranib** – **Gene Silencing**: Phase I and Phase II trials of Bevasiranib have been completed and a Phase III clinical trial is now recruiting.

- PDGF/PDGFR inhibitors
  - PDGF-B pegylated aptamer, E10030
  - Pazopanib (GlaxoSmithKline) is a tyrosine kinase inhibitor that blocks the action of PDGFR, as well as VEGFR-1, -2, and -3, kit, and FGFR-1
- TrpRS
- Protein kinase C inhibitors
- Complement inhibitors
  - **Intravitreal POT-4 Therapy for Patients With Neovascular Age-Related Macular Degeneration (AMD) (ASaP)**
    - Unrestrained complement activation has been recently identified to be one of the key mechanisms in the pathogenesis of AMD. It has also been demonstrated that complement activation plays a crucial role in the development of CNV. Therefore, the use of intravitreal complement inhibitors may be beneficial in participants subjects with neovascular AMD. This prospective, uncontrolled, non-randomized, dose-escalating, pilot Phase I study will provide initial safety and tolerability information on intravitreal complement inhibitor (POT-4) therapy in AMD patients with subfoveal CNV as a single intra-vitreal injection.
- **PTK787 Pill for AMD:** This Phase I/II study looked at the safety and tolerance of a tablet of Vitalanib, taken over three months and the effect on wet macular degeneration. The study is completed and no data is available as yet.
- **Talaporfin Sodium PDT:** This Phase I trial was undertaken to determine the safety of photodynamic therapy (PDT), using the drug talaporfin sodium (LS11). Twenty-seven patients were enrolled and the study was completed in January 2006
- **Gene therapy in Wet AMD**
  - **AAV2-sFLT01**. This experimental study drug uses a virus to transfer a gene (genetic code) into cells within the eye. The gene codes for a protein that is intended to diminish the growth of abnormal blood vessels under the retina. The duration of the gene's effect is currently unknown, but might last for years. This phase 1, Open-Label, Multi-Center, Dose-Escalating, Safety and Tolerability Study of a Single Intravitreal Injection of AAV2-sFLT01 in Patients With Neovascular Age-Related Macular Degeneration is ongoing.
- EMERALD trial, is designed to evaluate the therapeutic potential of Sirolimus in combination with Lucentis in wet AMD
- **Infliximab, Sirolimus and Daclizumab to Treat Age-Related Macular Degeneration (AMDB1)**
- **HARBOUR Study**
  - **0.5 mg Ranibizumab monthly**
  - **0.5 mg Ranibizumab PRN**

- **2 mg Ranibizumab monthly**
- **2 mg Ranibizumab PRN**
- At 24 months, in view of VA and total number of injections, 2 mg dose was not any better than 0.5 mg standard dose.

- **RADICAL Study**: Reduced fluence PDT AntiVEGF Dexamethasone In Combination for AMD Lesion
  - Its basically a triple Therapy
  - AntiVEGF used was Ranibizumab
  - 4 arms
  - All group has similar result

- **Brolucizumab** is currently being studied for the treatment of wet AMD. It has previously been referred to as "RTH258" and "ESBA1008."
  - It is a humanized microfusion protein with the complementarity-determining regions (CDRs) of VEGF-A.
  - The drug is significantly smaller than other anti-VEGF agents.
  - Bevacizumab is about 150 kilodaltons (KD), aflibercept is about 100 KD, and ranibizumab is about 50 KD, whereas brolucizumab is about 26 KD. Compared to the 0.5-mg ranibizumab dose, a 6.0-mg dose of brolucizumab represents 22x more molar concentration. Broluciuzmab has a higher binding affinity than ranibizumab, which would presumably allow it to last longer in the eye and, in theory, permit less frequent dosing. The dosing interval is being studied in clinical trials.
  - Brolucizumab clinical trials appear to show that it is noninferior to aflibercept at 1 year with an increased dosing interval.
- **Anatomical Predictors of Visual Outcomes After Long-term Anti-VEGF Therapy**
- OCT features that predict worse visual outcome
  - Subretinal hyper-reflective material (SRHM; originally termed "subretinal tissue")
    - Confirmed in 5-year Comparison of AMD Treatment Trial (CATT) results
    - Foveal atrophy/ fibrosis, or "atrosis" (CATT, 7-UP)
      - In neovascular AMD, even areas that appear as atrophy on color photos/exam can demonstrate SRHM, which is also seen with fibrosis.
      - The principal difference between atrophy and fibrosis on OCT is the thickness of SHRM (thicker and brighter with fibrosis).
      - Given similar OCT appearance and similar functional impact due to overlying RPE/photoreceptor loss, "atrosis" may be the best descriptor.
    - Intraretinal fluid (CATT)
  - OCT features associated with better vision (CATT)
    - Subretinal fluid, sub–retinal pigment epithelial (RPE) fluid

- Persistent epithelial defect (PED)/type 1 CNV, especially as CNV apex

- Some evidence to suggest that sub-RPE CNV may be protective, but optimal PED thickness has not yet been defined.
- The presence and thickness of the PED under the fovea was an important predictor of long-term vision in patients being treated for neovascular AMD.
- The best morphology appears to be the absence of SRHM and a thicker PED with intact overlying retinal pigment epithelium.

PDT: PhotoDynamic Therapy

- PDT procedure is relatively contraindicated in patients with severe liver disease, unstable heart disease or uncontrolled hypertension.The dye should not be administered if the patient is allergic to porphyrin, suffers from porphyria or has received any photosensitizing drug within the last two days.
- Photodynamic therapy (PDT) involves the intravenous infusion of a drug (photosensitizer) and the application of a continuous nonthermal laser light directed at the CNVM.The wavelength of the laser light used corresponds to the absorption peak of the drug, but it is not strong enough to produce any thermal (photocoagulation) damage.
- Mechanism of action: The drug gets concentrated in the immature endothelium of CNVM, and light-activation induces a photochemical reaction in the target area that causes immunologic and cellular damage, including endothelial damage of new vessels. Endothelial damage and the resulting platelet adhesion, degranulation, and subsequent thrombosis and occlusion of the vasculature might be the predominant mechanism by which lightactivated drugs work. Since the photosensitizer accumulates predominantly in the CNV, a fairly selective damage to the CNV is expected.
- To date, only PDT with the photosensitizer Verteporfin has been proven to decrease the risk of visual loss in patients with neovascular ARMD. Verteporfin (a benzoporphyrin derivative monoacid, BPD-MA; Visudyne, Novartis AG) is a light-activated drug. The application of photodynamic therapy with verteporfin involves two main steps: intravenous infusion of the drug and activation of the drug by light at a specific wavelength (689 nm) with a low-power, nonthermal laser. The therapy includes retreatment as often as every 3 months if leakage from choroidal neovascularization is detected on follow-up fluorescein angiograms.
- **Procedure**
- The intravenous infusion of verteporfin is given throughout a 10-minute period.
- Then, 15 minutes after the start of the infusion the laser light is applied for 83 seconds. Guidelines for the treatment of patients with ARMD and subfoveal CNV with PDT have been recently published. In these guidelines, treatment with PDT is recommended for patients with predominantly classic CNV and for those with occult and no classic CNV with recent disease progression (e.g., presence of blood associated with the CNV, growth of the CNV, or deterioration of the visual acuity within the past 12 weeks) and a lesion size of four or fewer disk areas or a lesion size greater than four disk areas associated with low levels of vision (i.e., approximately in the level of 20/50 Snellen vision). In these guidelines, it is also recommended to treat juxtafoveal lesions that are so close to the fovea that conventional laser photocoagulation almost certainly would extend under the center of the FAZ, and extrafoveal lesions that are contiguous to the optic nerve provided that treatment spots do not overlie the optic nerve. The recommendations included a 3-month interval follow-up for

at least 2 years from the time of initial treatment in all patients, except in those in whom no treatment was recommended for two consecutive visits (6-month period). Patients should receive retreatments as often as every 3 months if there is any fluorescein leakage from CNV noted.

- Although no data are currently available on the treatment of pregnant or nursing women and patients with moderate or severe liver disease, the guidelines suggest to carefully consider PDT in these patients. Photodynamic therapy is contraindicated in patients with porphyria. Patients must be warned, however, that they will be sensitive to direct sunlight or bright indoor lights for 24 to 48 hours after drug infusion and that they should avoid direct sunlight for about 2 to 5 days after treatment.

- **Macular Photocoagulation Study (MPS)**
- In Patients with well-defined extrafoveal CNVM after a follow-up of 5 years, 64% of eyes assigned to no treatment compared with 46% of eyes randomized to argon laser experienced severe visual loss (six or more lines of visual acuity loss using Bailey-Lovie visual acuity charts). The difference was statistically significant. Although the risk of severe visual loss was reduced in treated patients, a high rate of persistent and recurrent CNVM was observed.
- The recurrence rate observed in treated eyes at 12, 24, and 60 months were of 41%, 51%, and 54%, respectively. Patients with well-defined juxtafoveal CNV were treated with krypton red laser. At 3 years after randomization, 49% of laser-treated eyes experienced severe visual loss compared with 58% of untreated eyes.

Surgical Therapy

- ***Exudative AMD***
  - Removal of the submacular choroidal membrane and/or hemorrhage
  - MTS360: **machemar**
  - LMT: **De Juan**
  - Displacement with TPA and Gas
  - Transplantation of an autologous graft of RPE, Bruch's membrane, choriocapillaris, and choroid: **Peymen**

- Epiretinal Brachytherapy (**NeoVista**)
  - Administred via PPV
  - Strontium 90 device (Epi Rad 90)
  - 24 Gy delivered over 4 minutes
  - Peak dose directly to macula
  - Rapid radiation dissipation
  - 10% drop-off for every 0.1 mm from source
  - **NVI 111 protocol**: Epi Brachytherapy and Bevacizumab

- 74% subjects received no Additional injections
- Mean number of injections: 12months: 2.2; 24months: 2.4
- Major complication was cataract
- This led to another trial CABERNET

- **CABERNET trial (CNV Secondary to AMD Treated with BEta RadiatioN Epiretinal Therapy)**
  - Strontium-90 Beta Radiation Implant Trial
  - CABERNET is a multicenter, randomized, controlled study that has enrolled over 490 subjects at 45 sites worldwide and is evaluating the safety and efficacy of NeoVista's therapy delivered concomitantly with the FDA-approved anti-VEGF therapy Lucentis® (ranibizumab) versus Lucentis alone
- **MERITAGE-I Study**
  - examine NeoVista's novel Epimacular Brachytherapy procedure when used in patients who require chronic therapy with anti-VEGF agents on an ongoing basis to control Neovascular Age-Related Macular Degeneration (Wet AMD
- **Macular EpiRetinal Brachytherapy versus Lucentis Only Treatment (MERLOT) study**

- **External beam radiation**
  - **IRay system** (oraya technologies)
    - Office based radiation
    - 2-3 fractionated dose of 8Gy

- **IMT: Implantable Miniature Telescopes**
  - The Implantable Miniature Telescope (IMT) is implanted into the eye in the same position that an intraocular lens would be placed after a cataract extraction (patients in the study have their cataract or lens removed). It enlarges images up to three times, but only in the center. The peripheral vision of that eye is eliminated by the placement of the telescope. In the clinical trials, the implant is placed in the better eye. The FDA did not approve the device and required more research because of damage to the cornea in some of the patients.
- X ray:
- ***Dry AMD***
  - recreate a functioning RPE underlayer of the macula: autografts versus allografts; cells in suspension versus cell sheets or patches; RPE versus iris pigment epithelium (IPE) cells
  - **Surgery**
  - ***Keyhole approach***

- Paramacular vertical retinectomy (as suggested by **F. Devin**) is currently preferred because this retinotomy has less tendency to enlarge towards the fovea and the graft is inserted more easily

PCV: Polypoidal Choroidal Vasculopathy

- Choroidal abnormality characterized by branching choroidal vascular network (BVN) with surrounding aneurysmal dilatation (polyps) leading to recurrent serous leakage and hemorrhage
- May be considered as a variant of neovascular age-related macular degeneration (AMD)
- Exact pathogenesis is not known
- May share some common genetic factors with AMD, but characteristics and treatment response different
- **Clinical features of PCV**
  - Polyps may be visible as reddish-orange structures beneath retina
  - Pigment epithelial detachments (PED) – exudative or hemorrhagic
  - Subretinal hemorrhage, subretinal exudates, serous retinal detachment
  - Location – subfoveal, juxtafoveal, extrafoveal, peripapillary
  - Peripheral subretinal hemorrhage noted in some countries
- **Masquerading as neovascular AMD**
  - Indocyanine green angiography (ICGA) is essential in the diagnosis of PCV
  - Higher incidence of serous retinal detachment (SRD) (78% vs 53%, $p<0.001$), greater SRD height ($p<0.001$), and less intraretinal edema ($p<0.001$) than exudative AMD. (Ozawa, 2009)
- **Epidemiology**
  - Higher prevalence in Asians and Blacks ape 25% to30%
  - App 20% prevalence in caucasians in USA
- **Difference in PCV Presentation between Asian and Caucasians**
  - Asians
    - mostly males (63%-83%)
    - macular location (85%-93%)
    - unilateral involvement (83%-93%)
    - not as favorable prognosis
  - Caucasians
    - mostly females (53%-85%)
    - mostly macular (64% 80%) but peripapillary scarring can be unusually prominent mostly unilateral (90%), but initial descriptions more bilateral
    - more favorable prognosis
- **Classification of PCV**
  - By location: Macular, Peripapilliary, Extramacular, Peripheral By Clinical morphology
  - Proposed classification for PCV (Adopted from Chan et al, Ophthalmology, 2004)
    - Group 1 (subclinical): asymptomatic polyp

- Group 2 (exudative): serous PED, SRD, exudates, lipids
- Group 3 (hemorrhagic): localized hemorrhagic PED of < 4 disc area
- Group 4 (massive hemorrhage): massive subretinal or sub-RPE macular hemorrhage of more than 4 disc area.

Diagnosis

- Fluorescein Angiography
  - Common FA finding: localized /diffuse stippled hyperfluorescence indistinguishable from the pattern of leakage seen in occult CNV in neovascular AMD
  - Occult FA pattern of leakage is the most common form of PCV
  - Polyps are sometimes depicted as classic FA leakage pattern
- Indocyanine green angiography (ICGA)
  - ICGA is essential to confirm the polyps
  - Single or multiple vascular dilated networks of choroidal vessels seen in early phases of ICGA (usually within one minute) as aneurismal dilatation and/ or polyps
  - Dilated vascular abnormalities can be:
    - Single / solitary
    - String / linear vascular dilatation
    - Cluster /grape like, resembling micro-aneurysmal / large aneurysmal dilations
    - Large choroidal vessel dilation, constriction, looping
  - Abnormal vascular network can be seen (branching vascular network-BVN) associated with terminal polypoidal lesions which is seen as hyperfluorescent plaque in late ICGA
  - Lesions showing choroidal vascular hyperpermeability may be seen
- Optical coherence tomography (OCT)
  - Pathologic vascular lesions of PCV are located under the RPE
  - Polypoidal lesions can be seen as anterior protrusions or dome-shaped elevations of RPE with low-moderate reflectivity beneath the RPE
  - Topographic notch within PED suggests polyp
  - Branching vascular network appears between 2 highly reflective lines, undulated RPE line and a thin straight line representing Bruch's membrane (BM) (**double layer sign** Sato et al. Retina 2007)
  - Thicker choroid can be seen in relatively young patients: PCV may be one of clinical entities of the **pachychoroid spectrum** (Miyake et al. Sci Rep 2015)

Treatment

- Anti-VEGF therapy
  - Advantage of anti-VEGF therapy:

        - Early reduction in the amount of exudation and hemorrhage caused by PCV
        - Lower risks of visual deterioration after injection
    - Disadvantage of anti-VEGF therapy
        - Less effectiveness of polyp occlusion
        - Repeated injections are required
        - Patients presenting as neovascular AMD with treatment refractory to anti-VEGF therapy may be suggestive of PCV
- PDT + Anti-VEGF
    - Up-regulation of VEGF level may occur after PDT and VEGF promotes angiogenesis and may be associated with increased risk of secondary CNV and recurrence of PCV

- **Conbercept** (KH902; Chengdu Kanghong Biotech Co.; Sichuan, China) is the most recent member of the anti-VEGF family of drugs.
    - Recently developed to provide a more potent and prolonged anti-VEGF effect, conbercept was approved by the China Food and Drug Administration (Clinical FeaturesDA) in November 2013.
    - Similar to aflibercept, conbercept consists of the VEGF binding domains of the human VEGFR-1 and VEGFR-2 combined with the Fc portion of the human immunoglobulin G-1.
    - In Addition to having high affinity for all isoforms of VEGF-A, it also binds to placental growth factor and VEGF-B. The structural difference between conbercept and aflibercept is that conbercept also contains the fourth binding domain of VEGFR-2, which is essential for receptor dimerization and enhances the association rate of VEGF to the receptor.
    - As per AURORA trial, Intravitreal injection of conbercept appears to significantly improve visual acuity and anatomic outcomes of patients with PCV.

RPE Tears or Rip

- Retinal Pigment Epithelial (RPE) Tears, also known as RPE tears or rips, is a phenomenon first described in 1981 in which the RPE acutely tears from itself and retracts in an area of retina usually overlying a pigment epithelial detachment (PED) at the junction of detached RPE and flat RPE, leaving the underlying Bruch's membrane and choroid exposed.
- **Classification of Retinal Pigment Epithelial Detachment (PED)**
  - Drusenoid PED
  - Serous PED
  - Serous vascularized PED
  - Fibrovascular PED
- **Imaging of PED**
  - Color fundus photography
  - Confocal scanning laser ophthalmoscopy (cSLO) near-infrared reflectance (NIR)
  - Fundus autofluorescence (FAF)
  - Fluorescein angiography (FLA)
  - Indocyanine green angiography (ICG)
  - Spectral domain OCT (SD-OCT)
  - OCT angiography (OCT-A)
- **Risk Factors for Pigment Epithelial Tears**
  - PED lesion's height and diameter
  - Hyper-reflective lines in near-infrared images
  - Small ratio of CNV size to PED size
  - Subretinal clefts
  - Microrips
  - Duration of PED
- **Mechanism of Pigment Epithelial Tears**
  - Contraction of CNV membranes → shrinkage of the retinal pigment epithelium (RPE) → increased tension on the surface of the cavity
  - Two opposite forces on the marginal RPE: traction forces from CNV contraction and adhesive forces from the RPE still attached
  - The contracted RPE monolayer comes to rest on the side of the CNV; the RPE tear appears on the opposite side of CNV
- **Prediction of Pigment Epithelial Tears**
  - Radial hyper-reflective lines spreading in a funnellike pattern across the PED lesion in NIR images
  - Wrinkles in the RPE on SD-OCT
- **Classification of Pigment Epithelial Tears**

- Small / large
- Central / perifoveal
- Unilobular / multilobular

- **Treatment Status Post Pigment Epithelial Tear**
  - Observation
  - Continued anti-VEGF therapy

Vitreomacular Interface Disease

- **VMI diseases can be broadly classified as:**
  - Full thickness macular hole (FTMH)
  - Lamellar macular hole (LMH)
  - Epiretinal membrane (ERM)
  - Vitreomacular traction (VMT)
- **2012: International Vitreomacular Traction Study (IVTS) Group Classification System.**
  - Vitreomacular adhesion (VMA)
    - Size: Focal (≤ 1500 µm) or broad (>1500 µm)
    - Isolated or concurrent
    - Vitreomacular adhesion (VMA) is defined as perifoveal vitreous separation with continuing vitreomacular attachment within a 3-mm radius of the foveal center, and completely normal retinal anatomic morphology. The posterior vitreous cortex (posterior hyaloid) is visible on or above the retinal surface. It is an OCT finding that is almost always the result of normal vitreous aging. VMA can be subclassified by the diameter of vitreous attachment to the macular surface as measured by OCT, with attachment of ≤ 1500 µm defined as focal and > 1500 µm as broad. If VMA exists without other diseases of the macula, it is “isolated.” When it is associated with other macular disease (eg, AMD, diabetic macular edema, retinal vein obstruction), it is classified as “concurrent.”
  - Vitreomacular traction (VMT)
    - Size: Focal (≤ 1500 µm) or broad (>1500 µm)
    - Isolated or concurrent
    - VMT is characterized by perifoveolar vitreous separation with continued vitreomacular attachment within a 3-mm radius of the foveal center, with abnormal retinal anatomy. Unlike VMA, in which the vitreous separation is virtually always part of the normal aging process, VMT features an anomalous posterior vitreous detachment (PVD). The retinal abnormal changes can include anatomic distortion of the fovea, pseudocysts, macular schisis, cystoid macular edema, and subretinal fluid. Like VMA, VMT can be subclassified by the diameter of vitreous attachment, with attachment of ≤ 1500 µm defined as focal and > 1500 µm defined as broad. If VMT exists without other diseases of the macula, it is “isolated.” When it is associated with other macular disease whose pathology might be adding to the traction-related retinal morphologic changes, VMT is classified as “concurrent.”
  - Full-thickness macular hole (FTMH)
    - Size: Small (≤ 250 µm), medium (> 250 µm to ≤400 µm), or large (> 400 µm)
    - Status of vitreous: With or without VMT Cause: Primary or secondary
    - FTMH is defined as a foveal lesion with interruption of all retinal layers from the internal limiting membrane (ILM) to the retinal pigment epithelium (RPE). FTMH is primary when due to vitreous traction (VMT), or secondary if directly

due to pathology other than VMT (eg, blunt trauma). The term “idiopathic” macular hole should be abandoned.

- FTMH is subclassified by size of the hole as determined by aperture size on OCT. Aperture size is measured using the caliper function on the OCT machine using a single line scan (B-scan) through the center of the hole. A caliper line is drawn parallel
to the RPE at the site of narrowest opening of the hole, usually within mid-retina or at the photoreceptor tips.
- A small FTMH features an aperture size less than 250 µm. The cut-off for small FTMHs at 250 µm is derived from studies that show these holes are associated with a small rate of spontaneous closure, have a very high closure rate with vitrectomy (approaching 100%), and are most responsive to pharmacologic vitreolysis (approximately 60% anatomic success).
- A medium FTMH features an aperture size from 250 to 400 µm. The rate of FTMH closure in these eyes is very high (> 90%) regardless of surgical technique. Pharmacologic therapy can be successful, albeit at a lower rate than for small macular holes (approximately 50% anatomic success).
- Large FTMHs have an aperture size of > 400 µm. Vitrectomy with ILM peel is associated with a high closure rate (approximately 90%) but slightly less than that of small or medium size holes. ILM peeling appears to be of benefit in these holes, as reported series without ILM peel show closure rate of about 75%. So far, no anatomic successes have been reported in eyes with large macular holes that have undergone pharmacologic vitreolysis.
- Finally, the status of the vitreous in FTMH is important. In cases of primary FTMH, either VMT is ongoing (VMT present), or vitreous separation from the macula has occurred (VMT absent – ie, Gass stage 4). Release of VMT is not always associated with a large FTMH, however.

Epiretinal Membranes

- Epiretinal membranes (ERMs) first described by Iwanoff in 1865.
- cellular proliferation on the inner retinal surface
- Prevalence
  - BDES & BMES 7–11.8%, with a 5-year incidence of 5.3%
  - Bilateral in 19.5–31%, with a 13.5% 5-year incidence

- **Classification**
  - Idiopathic
  - Secondary
    - Retinal vascular disease
    - Vascular occlusion, e.g. BRVO, CRVO

        - Diabetic retinopathy
        - Telangiectasias , Macroaneurysm
        - Sickle cell retinopathy
        - Intraocular inflammation
        - Trauma, Retinal detachment and retinal tears, Intraocular tumors
        - Retinitis pigmentosa
    - Iatrogenic
        - Postoperative, Cataract, Retinal detachment, Silicone oil, Retinopexy, Laser or cryotherapy
- **Gass' Grading System**
    - Grade 0 (also termed **cellophane maculopathy**):
        - translucent membrane with no underlying retinal distortion
        - asymptomatic
    - Grade 1: **irregular wrinkling** of the inner retina
        - distorted or blurred vision
        - loss of binocularity, central photopsia, and macropsia
    - Grade 2: **opaque membrane** causing obscuration of underlying vessels
        - marked full-thickness retinal distortion
        - Increasing vascular tortuosity and size of vessel involved
        - CME in 20–40%
- PVD is present in approximately 60–90% of patients at the time of diagnosis

Pathogenesis

- represents a reactive gliosis in response to retinal injury or disease involving inflammatory and glial cells.
- Components
    - **extracellular matrix**: collagen, laminin, tenascin, fibronectin, vitronectin
    - **cells**: glial cells, neurites, retinal pigment epithelium, immune cells and fibrocytes
- secondary ERM: RPE Cells
- Idiopathic ERM: glial cells

Clinical Features

- ophthalmic and general medical history
- distinguish an idiopathic ERM from one that is secondary
- according to gradings as described

Differential Diagnosis

- **Vitreomacular traction**
  - VMT is said to differ from ERM by the degree of vitreous separation in the mid-periphery
  - ERMs may coexist with VMT in 26–83%
  - In VMT with ERM the vitreous in the mid-periphery is detached, whereas in ERM without PVD the vitreous is attached
- **Cystoid macula edema**
  - no distortion of the microvasculature, it is always centered on the fovea and may be seen on fluorescein angiography as a ‘star pattern’ in late pictures

Investigations

- OCT
  - diagnostic capabilities up to 90%
  - hyper-reflective layer on the surface of the retina
  - underlying corrugation of the retinal surface, blunting of the foveal contour, increased retinal thickness and intraretinal cysts
- FFA
  - in cases where an underlying vascular event or choroidal neovascular membrane is suspected.
  - highlight the extent of retinal wrinkling, degree of retinal vascular tortuosity and presence of macular edema

Management

- ***Vital dyes***
  - ICG
    - greater affinity for ILM than ERM and may be more useful when viewed as a negative stain
    - toxicity has been more commonly demonstrated with a solution that has an osmolarity <270 mOsm, a concentration above 0.5% and incubation time >30 seconds
  - Brilliant blue (0.25 mg/mL).
    - stains ILM
    - less toxic
  - Trypan blue
    - highlights ERMs due to its strong affinity for glial cells
    - no evidence of RPE toxicity
- ***Engaging and peeling ERMs***

- **edge visible** → end-grabbing forceps
- **edge not visible** → surgical pick, a bent-tipped microvitreoretinal (MVR) blade or a diamond-dusted scraper
- **ILM peeling along ERM**: controversial issue

Complications

- ***Intraoperative***
  - petechial hemorrhages from the perifoveal capillary bed
  - Peripheral retinal breaks are observed intraoperatively in 4–9%
  - Lens touch
- ***Postoperative***
  - Cataract: most common complication, 6–100%
    - alterations in oxygen tension and glucose concentrations
    - disruption of the anterior vitreous in the retrolental area
    - orientation of the infusion cannula at the time of surgery
  - Retinal detachment
    - 2–14% of eyes
    - unidentified entry site breaks at the time of surgery.
  - Recurrence
    - less than 20%
  - Other rarer complications include endophthalmitis, retinal toxicity from the use of vital dyes, phototoxicity, visual field defects and subretinal neovascularization
- In eyes with ERM and good VA can be safely observed as their visual outcomes are largely stable over an extended follow-up. A small percentage of these patients may eventually progress and be considered for surgery. In patients with phakic ERM, a conservative approach is the best initial management, as many of these patients may report satisfactory vision with cataract surgery alone and this may obviate some of the more significant risks associated with vitrectomy surgery. Key considerations are patient's symptoms and the impact on activities of daily life, which should guide considerations for surgery, not the appearance of the OCT.

Macular Hole

- first described in **1869 by Knapp**
- **Ogilvie** (1900) was the first to use the term hole at the macula
- **Epidemiology**
  - ***Prevalence***
    - 1-3 per 1000
    - female-to-male ratio of 3.3 : 1

        - MH was bilateral in 11.7% of patients
    - ***Incidence***
        - In the fellow eye without PVD is 5% to 16%.
        - No MH in fellow eye with PVD
    - ***Risk factors***
        - age of ≥65
        - female gender
- **Pathogenesis**
    - Vitreomacular traction: **anteroposterior traction** of vitreous fibers on the fovea played a role in the formation of MH
    - Foveal cyst: foveal cyst formation due to vitreous traction was the first step in MH formation
    - Contraction of the premacular vitreous cortex: **GASS, tangential contraction** of the prefoveal "posterior hyaloid membrane" resulted in the detachment of the central photoreceptors and then in the opening of the fovea
    - SD-OCT based theory of pathogenesis:
        - Shows changes substantiate the concept of Stage 0 MH proposed by Chan et al. in 2004

Staging

- Stage 0 MH:
    - slight changes in the foveolar structure long before the occurrence of the early foveal cyst that characterizes Stage 1 MH or impending hole
    - Minor changes in the cone outer segment tips (**COST, or Verhoeff membrane**), line at the foveal center, or subtle changes in the reflectivity of the center of the foveola, along an anteroposterior axis extending from the ILM to the IS/OS junction line
- Stage 1A
    - Impending macular hole
    - central yellow spot and loss of the foveal depression associated with no vitreofoveal separation
    - due to early serous detachment of the foveolar retina
    - inner foveal **cyst**.
- Stage 1B
    - occult hole
    - yellow ring in the fovea, the absence of vitreofoveal separation and the loss of the foveal depression.
    - yellow ring is due to the edematous border of the disrupted outer retina
- Stage 2

- eccentric oval, crescent or horseshoe-shaped retinal defect inside the edge of the yellow ring
- tear in the contracted pre-foveolar vitreous tissue bridging the round retinal hole, with no loss of foveolar retina
- neuronal elements formed a constitutive part of the operculum at least in some cases

- Stage 3
  - central round retinal defect more than 400 µm in diameter
  - with a rim of elevated retina, with or without pre-foveolar pseudo-operculum and without a Weiss's ring
- Stage 4
  - complete PVD with a Weiss's ring.
  - presence of the Weiss's ring on **biomicroscopy** (**not just OCT**) therefore remains the valid indicator for this

Differential diagnosis

- ***Lamellar macular hole***
  - Gass in 1975: opening of the central cyst of a cystoid macular edema.
  - Histology: thinning of the foveal tissue leaving the RPE and photoreceptor layers intact, but causing partial loss of the inner nuclear layer
  - Biomicroscopy:
    - rarely round but rather bior tri-lobulated
    - edge is thin whereas the FTMH edge is thick and elevated
    - Watzke test negative
    - aiming beam test: beam perceived unlike MH
  - OCT: defects in the inner fovea due to the avulsion of the roof of a foveal cyst
- ***Macular pseudoholes***
  - Allen and Gass in 1976
  - OCT: thickening of the macula contracted by an ERM, and the U or V shape of the fovea. There is no loss of retinal tissue at the umbo of the fovea
- Foveal cysts of various origins: cystoid macular edema, X-linked retinoschisis, or foveal cysts of type 2 macular telangiectasia.
- Microholes
  - Cairns 1988
  - dark-reddish lesions in the center of the fovea ranging from 50 to 150 µm in diameter
  - break in the photoreceptor layer at the foveal center. What have been called “microholes” might therefore not be FTMH but in some cases, spontaneously closed FTMH

- **Non-idiopathic (secondary) MH**
  - Orbital trauma and high myopia
  - High myopia
  - Other rare causes

Management

- ***Principles and techniques:***
  - In **1991** the treatment of full-thickness macular holes (FTMH) by pars plana vitrectomy (PPV) and consecutive gas tamponade was first described by ***Kelly and Wendel***, and this technique has been modified since then to improve the functional and anatomical outcome.
  - current standard treatment is by removing vitreous adhesions including the ERMs and the adherent ILM with vitrectomy and in most cases a gas endotamponade.
- Posterior hyaloid detachment
- Extensive Vitrectomy
- Epiretinal membrane peeling
- Internal limiting membrane peeling
  - Eckardt et al. in 1997
  - Maculorrhexis
- **Inverted internal limiting membrane (ILM) flap technique,** first reported by Michalewska et al in 2010, is considered an effective surgical technique for treating large idiopathic full-thickness macular holes (FTMH) and myopic macular holes (MH). In the inverted ILM flap technique, after core vitrectomy and dye staining, the ILM is not removed completely from the retina but is left in place, attached to the edges of the macular hole. This ILM remnant is then inverted upside-down to cover the macular hole. Finally, fluid–air exchange is performed.
- Vital dyes
  - Chromovitrectomy
  - *Indocyanine green and infracyanine*
    - selective affinity for the ILM
    - concentration was reduced to 0.125% and even 0.05%
    - 0.05%, 290 mOsm and no more than 30 seconds with the retina, seems to give no sign of RPE toxicity
    - **Infracyanine**, an **iodine-free** product, diluted in **5% glucose**, results in an iso-osmolar solution, which might be safer for the retina
  - *Trypan blue 0.15%*
    - stains the ERM well but the ILM less effectively
    - must be used after fluid–gas exchange
    - no signs of toxicity for the RPE

- *Brilliant Blue G 0.25%*
  - selective affinity for the ILM
  - iso-osmolar solution of 0.25 mg/mL
- Triamcinolone dusted on macula: Doesn't stain ILM, but allows identification of where ILM has been removed

- Gas
  - most MH close within 3–7 days of tamponade
  - bubble large enough to insulate the macula from intraocular fluid during this period
- Use of silicone oil in MH surgery: anatomic results were no better with silicone oil than with gas
- Use of healing adjuvants: TGF-β, autologous platelet concentrates

- **A nonsurgical treatment**
  - Ocriplasmin (ThromboGenics NV, Leuven, Belgium)
  - Stage 2 MH <400 μm
  - success rate for the ocriplasmin group was 40.6% compared with 10.6% in the placebo
  - MH with a diameter of ≤250 μm, the success rate rose to 58.3%, but for holes with a diameter of 250–400 μm, it was only 24.6%

- **Results**
  - Today the closure rate is currently 85% or more
  - 92% for MH <400 μm but only 56% for MH of ≥400 μm, as measured on OCT
  - Tornambe: 79% success for hole closure without any facedown positioning

- **Complications**
  - ***Retinal detachment:*** under 2%
  - ***Cataract:*** rate of pseudophakia at 3 or 5 years is commonly 85–98%
  - ***Visual field defects:*** attributed to retinal nerve fiber layer damage to the nasal portion of the optic nerve rim, probably due to traction during cortical vitreous peeling, upto 23%
  - ***Reopening of macular holes:*** 5–7% of cases

Macular Hole Indices

- a = base diameter
- b = minimum linear dimension (MLD)
- e = maximal hole height

- f = macular hole inner opening

- **Hole Form Factor (HFF)**
  - Determine extent of Base diameter (a) and MLD (b)
  - Hole Form Factor = (c + d) / a
  - No correlation found between HFF and postop gain in lines
  - HFF:
    - HFF > 0.9: good surgical prognosis
    - HFF < 0.5: 25% MH closure rate
- **Macular Hole Index (MHI)**
  - MHI = e / a
  - MHI was associated with postoperative vision
- **Diameter Hole Index (DHI):** ratio of minimum diameter of MH to base MH diameter
  - indicator of extent of tangential traction
- **Tractional Hole Index (THI):** ratio of the maximal height of MH to minimum diameter
  - indicator of A-P traction and retinal hydration
  - THI = e/b
  - THI correlated significantly with postop vision

- **Closure:**
  - Grade 0 : IS/OS junction absent under the fovea
  - Grade 1 : IS/OS junction present under the fovea; abnormal
  - Grade 2 : IS/OS junction present under the fovea and normal
- OCT imaging preoperatively and postoperatively has provided Additional prognostic data for visual recovery following macular hole surgery. Factors on **OCT predictive of good visual acuity** macular hole surgical outcome are as follows:
  1. Size of macular hole (minimum diameter < 311 µm)
  2. Traction on macular hole edges as defined by various parameters (eg, macular hole height)
  3. Development of a normal photoreceptor inner segment and outer segment junction, which can occur as early as 1 month postoperatively but typically by 6 months postoperatively as shown in the images below.
  4. **MH minimum diameter of <311 micron or a THI >1.41 are predictive factors for a good visual prognosis after MH surgery.**

Refractory Macular Hole

- Definition: Primary failed macular hole surgery

- Risk factors are high myopia associated with or without staphyloma, trauma, or duration of the macular hole.
- Management
  - 2010: Nawrocki et al firstly described the **inverted ILM flap technique,** which also works nicely in very large macular holes or in refractory macular holes
  - The ILM preparation technique can also be achieved successfully in these rare cases, where there is no parafoveal ILM left, in a so called free flap technique, when **extramacular ILM** is used.
  - Another free flap technique is **autologous retinal transplant technique**
  - Difficult large holes with the use of **amnion patches**: Rizzo et al, 2018, promising outcome when the patch size, which is today prepared with a trephine, fits the MH space.
  - Posterior lens capsule and autologous blood patch: Peng et al
  - **Retinal Relaxation Surgery: Carsten Meyer**
    - In preoperated failed (refractory) macular hole cases, there is a secondary alteration between the photoreceptors and the retinal pigment epithelium (RPE), which may induce a firm adhesion between the neuroretina and adjacent RPE-choriocapillaris complex, thus preventing a natural relocation of the retracted (and normally) elastic neuroretina.
    - *As opposed to all techniques mentioned above, a relaxation of the retracted retina might be sufficient to close a MH.*
    - By inducing a posterior retinal detachment with a 41-gauge subretinal catheter and BSS application during a PPV with gas or oil endotamponade, such a retinal relaxation and thus a reproximation and closure of the MH can be achieved.
  - Gonvers, Bove, and Wolfensberger firstly presented a case series of **SR fluid application in FTMH.**

Lamellar Macular Hole LMH

- 1975, Gass first described lamellar macular hole (MH) as a partial-thickness, round, inner foveal defect seen on slit-lamp biomicroscopy using a narrow vertical beam in patients who had pseudophakic cystoid macular edema
- **International Lamellar Macular Hole Study Group: OCT Criteria**
  - major criteria were as follows:
    - irregular foveal contour
    - foveal cavitation
    - apparent loss of foveal tissue.
  - Minor characteristics
    - preretinal macular proliferation (thicker, homogeneous of medium reflectivity),
    - foveal bump

- loss of ellipsoid

- Lamellar MHs with preretinal macular proliferation tend to have greater progression of visual loss, mainly through thinning of the outer foveal layer and disruption of the outer ellipsoid layer.
- material often is observed to have luteal pigment and thought to consist of Müller cells. It has been noted that myopic eyes are more likely to have MHs. Infrequently, lamellar MHs can progress to full-thickness MHs. Surprisingly, full-thickness MHs with a lamellar type of epiretinal proliferation can also close spontaneously.
- Surgery
  - The indications for vitrectomy were a progressive symptomatic loss of visual acuity or disabling metamorphopsia
  - The eyes with lamellar proliferation had a greater prevalence of outer retinal thinning and disruption of the ellipsoid zone.
  - Following vitrectomy, eyes with lamellar MHs had a much smaller degree of visual improvement than eyes with highly reflective premacular membranes or full-thickness MHs with lamellar proliferation

Macular Cystoid Cavity

- Macular cystoid cavities are most often diagnosed on OCT B-scan, while the central macular thickness is assessed and monitored on OCT macular map.
- However, all macular cystoid cavities are not due to blood–retinal barrier (BRB) breakdown and do not require intravitreal treatment.
- Fluorescein angiography (FA), by showing the presence or the absence of dye leakage and pooling in cystoid cavities, helps to differentiate macular edema (ME) due to BRB breakdown from the many other conditions where cystoid cavities are due to other causes.
- It is proposed to use the term **“CME” to name “vasogenic” ME** and to use the term “**cystoid maculopathy” for the conditions not involving the BRB.**

CME-VMT

- The presence of fluid in the macula was first described in diabetic retinopathy by Appolinaire Bouchardat from Paris in 1875. Subsequently, a similar appearance of the retina was noted in a number of other conditions, and in 1950, Hruby drew attention to the occurrence of macular edema after cataract extraction. This was followed 3 years later by Irvine's classical paper on cystoid macular edema (CME), occurring after intra and extracapsular cataract extraction complicated by incarceration of vitreous in the anterior segment. These changes in the macula were further described by Gass and Norton, a decade later, using fluorescein angiography.
- **Pathophysiology**
  - ***cystoid macular edema***
    - **predisposed to develop edema**: extremely high cell count with increased metabolic activity and a central avascular zone, creating a watershed

arrangement between the choroidal and retinal circulation which decreases resorption of extracellular fluid

- In the foveal region, these fibers of the outer plexiform layer demonstrate a loose arrangement allowing accumulation of fluid leaking from perifoveal capillaries
- leakage from the perifoveal capillaries

- ***tractional macular edema***
  - increased water influx into the retinal tissue by decreased fluid clearance through glial and RPE cells
  - **hypothesis of VMT**: Vitreous fibers, which adhere to Müller cell end-feet at sites of vitreoretinal attachments after partial detachment of the vitreous, exert tractional forces onto the cells; this activates Müller cells and results in cell hypertrophy, proliferation, and vascular leakage
  - **breakdown of the BRB**
  - growth factors such as **VEGF, IL-6, PDGF**, and others are secreted in large amounts into the vitreous during proliferative vasculopathies

Clinical Features

- loss in distance visual acuity, contrast sensitivity, color vision, reading acuity to a reduction in reading speed
- marked reduction in central retinal sensitivity with either a relative or absolute scotoma during active macular edema
- cysts are characterized by an altered light reflex
- retroillumination can help to delineate the polycystic spaces
- subclinical foveal edema: 201-300 microns, difficult to identify clinically
- thickness appears to be most closely correlated with visual acuity
- leakage on fluorescein angiography is not directly correlated with reduced visual acuity.

Investigations

- **FFA:**
  - Early: capillary dilation can be detected in the perifoveal region
  - Late: fluorescein pools in cystoid spaces located in the outer plexiform layer (Henle's layer)
  - Foveal area: classic petaloid staining pattern
  - outside the perifoveal area: honeycomb appearance
  - Using fluorescein angiography, the following classification has been suggested:
    - **0 = no edema**
    - **1 = capillary leakage**
    - **2 = partial petalloid ring**

        - **3 = complete petalloid ring**
    - **FAF:** cysts as hyperautofluorescent because of the displacement of macular pigments that naturally attenuate the autofluorescent signal
    - **ICG:** not considered a very useful tool
    - **OCT:**
        - CME: amount of reflectivity within these cystoid spaces is due to higher concentration of protein associated with the breakdown of the inner blood–retinal barrier
        - VMTS: 2 patterns
            - **foveal cavitation** defined as the formation of cystoid cavity located in the inner part of the central fovea secondary to mechanical forces
            - CME that was defined as **intraretinal cyst**-like cavities extending beyond the foveal region
    - **OCT Angiography:** OCT angiography has shown various degrees of capillary perfusion impairment in the etiologies in which it has been studied. The retinal capillary density is usually reduced in vasculopathies such as diabetic retinopathy or retinal vein occlusion, but may be normal in acute pseudophakic ME, or electively altered in the deep capillary plexus such as in RP.
    - **Another classification scheme has been proposed using focal macular electroretinograms.**
        - Eyes with a type I response have reduced amplitudes of the oscillatory potentials with normal aand b-wave responses.
        - In type II, the eyes have reduced amplitudes of the oscillatory potentials and b-waves.
        - In type III reduced amplitudes of the oscillatory potentials, a-waves, and b-waves are observed.
        - The least reduction in visual acuity is seen in type I, while the most severe reduction is present in type III.

- **Management**
    - treatment of tractional macular edema
        - ***Vitrectomy***
        - Tractional origin of macular edema: Newton's third law,
        - Nontractional origin of macular edema:
            - oxygenation of the posterior segment of the eye is increased after Vitrectomy
            - growth factors such as VEGF, IL-6, platelet-derived growth factor, and others are secreted in large amounts into the vitreous which are removed
        - ***internal limiting membrane peeling***

        - diffusion of oxygen from the fluid in the vitreous cavity into the retina would be retarded by a thickened ILM
        - absence of ILM would further speed up this clearance of cytokines
    - **Pharmacologic vitreolysis:** chondroitinase, dispase, hyaluronidase, plasmin, and microplasmin.
        - Plasmin
            - nonspecific serine protease
            - promote PVD acting on a variety of glycoproteins and activating endogenous metalloproteinases
            - anatomic and functional improvement after intravitreal injection
            - Microplasmin is recombinant the agent that shows the greatest clinical potential
            - 125 µg dose that was repeated up to three times, released adhesion in 58% of patients with VMTS, 28 days after the final injection
            - MIVI-IIT trial:
            - MIVI-**TRUST (Traction Release without Surgical Treatment)** trial:
- **Clinical entities with cystoid macular edema**
    - Retinal vasculopathy: Diabetic retinopathy, Retinal vein occlusion, Macular telangiectasia type 1, Radiation retinopathy
    - Inflammation: Pseudophakic macular edema, Birdshot retinochoroidopathy, Retinal vasculitis, Intermediate uveitis
    - Inherited diseases: Retinitis pigmentosa
    - Drug toxicity: Fingolimod, Acitretin (retinoid), Topical latanoprost, topical epinephrine, Vemurafenib
    - Vitreoretinal interface diseases: Epiretinal membrane, Vitreomacular traction
    - Tumors: Choroidal melanoma, Choroidal hemangioma, Vasoproliferative tumor (reactive astrocytic tumor)
    - AMD: Macular new vessels, Peripheral CNV (peripheral exudative hemorrhagic chorioretinopathy)

Cystoid Maculopathy

- Cystoid maculopathy may occur without BRB impairment because the fluid coming from the vitreous cavity may accumulate in the retina under different circumstances—tractional, degenerative, toxic, or other, involving Müller cell or RPE dysfunction, both playing a major role in the hydric transport and regulation in the retina.
- These cells are also involved in vasogenic edemas to eliminate excess fluid. ***Cystoid cavities do not fill with dye during FA***.
- **Causes**

- Inherited diseases: Retinitis pigmentosa, X-linked retinoschisis, Bestrophinopathy, Enhanced S-cone dystrophy, Gyrate atrophy, Bietti crystalline dystrophy, Dominant cystoid macular dystrophy
- Acquired RPE dysfunction: Chronic central serous chorioretinopathy, Cancer-associated retinopathy
- Retinal vasculopathy: Macular telangiectasia type 2 (MacTel2)
- Drug toxicity: Taxanes, Tamoxifen, Chloroquine retinopathy, Nicotinic acid/niacin
- Vitreoretinal interface diseases: Epiretinal membrane, vitreomacular traction, myopic foveoschisis
- Optic nerve diseases: Optic nerve atrophy, optic nerve pit, glaucoma

- CME characterized by BRB breakdown may respond to topical, systemic, or intravitreal steroids; intravitreal anti-VEGF; or oral acetazolamide. Cystoid maculopathies sometimes respond to oral acetazolamide or to treatment discontinuation in case of drug toxicity, or to vitreoretinal surgery in case of epiretinal traction. Distinguishing these two forms of cystoid cavities, which may have the same aspect on OCT, is therefore useful in clinical practice.

Macular Atrophy

- An international group of retinal specialists, experts in anatomy and histopathology, and bioengineers called the CAM (Classification of Atrophy Meeting) Group suggested a new approach for the classification of macular atrophy
- Based on OCT imaging progression and its correlation with histopathology, a different classification was suggested in an attempt to identify new and early stages of macular atrophy.
- **Stages of Macular Atrophy**
  - cRORA: Complete RPE and outer retinal atrophy
    - Presence of hypertransmission of ≥ 250 micrometers
    - Presence of a zone of attenuation / disruption of RPE ± basal laminar (BL) complex of ≥ 250 micrometers
    - Evidence of overlying photoreceptor degeneration whose features include all of the following: outer nuclear layer thinning, external limiting membrane loss, ellipsoid zone / interdigitation zone loss
    - Absence of signs of an RPE tear
  - iRORA: Incomplete RPE and outer retinal atrophy
    - Some hypertransmission must be present, but often discontinuous
    - Some irregularity of RPE ± BL complex
    - Detectable photoreceptor degeneration, signs of which can include “wedge,” “subsidence”
    - Absence of signs of an RPE tear
  - cORA: Complete outer retinal atrophy
    - Continuous loss of ellipsoid zone
    - Severe thinning of outer retina
    - Intact RPE band
  - iORA: Incomplete outer retinal atrophy
    - Subretinal drusenoid deposits with detectable ellipsoid zone
    - Detectable thinning of the outer retina

CNVM/SRNVM

- Choroidal Neovascular Membrane/Subretinal Neovascular Membrane
- Dr. Gass Classification of SRNVM
  - Type I – CNV – between RPE and Bruch's membrane (typical of ARMD)
  - Type II – CNV – under the neurosensory retina and above Bruch's membrane (typical of Histoplasmosis)
  - Type III CNV – RAP – retinal angiomatous proliferation (RAP) intraretinal component with also subretinal, sub RPE and RPED components
- Management wise differences
  - Type I – treatment with anti-VEGF
  - Type II – very sensitive to anti-VEGF
  - Type III – extremely sensitive to anti-VEGF
- PCV – a subtype of Type I subretinal neovascularization with aneurismal dilation
  - Higher incidence of antiVEGF resistance – anti-VEGF resistance is a strong feature of PCV in Asian and in Caucasian populations, much higher incidence than previously thought in Caucasian populations, up to 25% 30%
- ***Submacular surgery trials:*** surgery should not be recommended for ARMD but may be recommended for OH
- ***Current indications for surgical removal of CNV***
  - large peripapillary CNV unresponsive to anti-VEGF agents and/or photodynamic therapy
  - too large for thermal laser photocoagulation

Submacular Hemorrhage

- ***Etiology***
  - most often caused by CNV
  - 80% were due to AMD with retinal arterial macroaneurysms
  - CNV due to histoplasmosis, angioid streaks
  - idiopathic submacular hemorrhage being less common
- ***Natural history***
  - etiology was the most important factor in predicting the final visual outcome
  - 19% of eyes gained two or more lines of vision during follow-up, while loss of two or more lines occurred in 59% and 36% experienced severe vision loss of 6 lines or more
- ***Management***
- Surgical removal of blood and CNV: generally not beneficial
- Vitrectomy, injection of subretinal TPA, and aspiration of liquefied blood
  - tPA (12.5 µg/mL) injected into the subretinal space

- Intravitreal TPA with pneumatic displacement
  - Heriot 1997
  - 50 µg or 100 µg of tPA and injection of a long-acting gas bubble (C_3F_8 or SF_6)
  - intravitreal tPA is controversial
- Subretinal injection of TPA with pneumatic displacement
  - subretinal injection of tPA (25–50 µg/mL) using a bent 36-gauge needle
  - maximal chemical lysis of the clot via subretinal injection of tPA
- Anti-VEGF agents

Giant Retinal Tear

- **Giant retinal tear**: a retinal tear of more than 90° circumferential extent. Since the posterior vitreous is detached, the vitreous gel is adherent to the anterior flap. Hence, the posterior flap has a tendency to fold over.
- **Giant retinal dialysis**: the retina is either torn at the ora serrata or there is a break in ciliary epithelium, with the vitreous being adherent to the posterior retina. Thus, the posterior flap does not have the tendency to fold over, since it is supported by the vitreous gel
- **Etiology**
  - 0.091 patients per 100 000
  - Idiopathic 55%
  - M>>F
  - high myopia
  - Marfan syndrome
  - Stickler syndrome
  - Ehlers–Danlos syndrome, lens coloboma, and aniridia
  - ***Iatrogenic giant retinal tear***
    - During a cataract surgery misadventure
    - During vitreoretinal surgery
    - after pneumatic retinopexy
    - after refractive surgery in the form of LASIK
- **Pathogenesis**
  - Central vitreous liquefaction is associated with condensation in the peripheral vitreous base that leads to traction on the peripheral retina
  - white-without-pressure
  - transvitreal contraction of the cortical gel occurs, tearing the retina along the vitreous base in a zipper fashion
  - multiple horseshoe-shaped tears may form along the posterior vitreous base and coalesce to form a giant retinal tear.
- **Evaluation**
  - corneal problems such as generalized haze due to edema, opacity, Descemet's membrane folds, etc.
  - The lens could be subluxated due to the blunt trauma and could be also cataractous.
  - posterior vitreous will be found to be detached in cases of giant retinal tear, unlike in dialysis.
  - extent of retinal detachment
  - vitreous could be incarcerated in the wound
  - macular hole can coexist

- USG:
  - discontinuity noticed anteriorly in the retinal echo and extending more than one quadrant
  - Double linear echo would be seen near the disc due to the close proximity of the two layers of the retina
- Proliferative vitreoretinopathy
- Role of nonsurgical treatment
  - Laser barrage photocoagulation
  - Outpatient fluid–gas exchange followed by cryopexy or laser photocoagulation
- Role of simple scleral buckling

- **Management**
- **pre-PFCL era**
  - Scleral buckles: shallow, but broad buckle
  - rotate the patient and to reposition the retinal flap with the help of an air bubble
  - retinal tacks or sutures: divide the giant retinal tear into smaller segments by pinning the edge of the tear
  - fluid–air exchange in prone position.
- **PFCL era**
  - **Vitreous surgery**
  - Role of an encircling band: fresh GRT can be managed without band, some degree of PVR should be managed with band
  - Lens management
    - leave it untouched
    - lensectomy and leaving the eye Aphakic
    - lens removal and keeping the posterior capsule intact for future IOL placement
    - lens removal and IOL placement at the same time
  - Management of intraocular lens
  - Visualization
  - Vitrectomy
  - Radical excision of the vitreous base
  - Mobilizing the retina and management of anterior retinal flap
  - Eyes with PVR
  - Conversion to a 360° tear
  - Perfluorocarbon liquids

- During membrane dissection to stabilize the posterior pole
- for facilitating internal limiting membrane removal around macular hole in detached retina
- for reattachment of the mobilized retina without fear of posterior slippage
- for medium-term tamponade.

- Retinopexy
- Internal tamponade
- PFCL–air exchange
- PFCL–silicone oil exchange

- **Results**
  - pre-vitrectomy era: 15-20%
  - Vitrectomy and gas: 43%
  - vitrectomy and silicone oil: 80-90%
- **Management of fellow eye**
  - 14% incidence of giant retinal tear and 36% incidence of other retinal tears
  - High-risk fellow eyes
    - high myopia
    - eyes with progressively increasing white without pressure areas with sharp posterior margin and increased vitreous condensation
    - patients with Wagner–Stickler syndrome
  - prophylactic Management: only cryopexy or laser photocoagulation without scleral buckling
- **Updates on Management**
  - **Medium-term Perfluoro-n-Octane (PFO) Without Scleral Buckle for Inferior Retinal Detachment**
    - Off label
    - No supine or face-down positioning
    - Slow, safe posterior vitreous detachment (PVD) over 14 days; no need for aggressive PVD induction
  - **Medium-term PFO for Inferior, Nasal, or Temporal Giant Retinal Tears (GRTs)**
    - Inject PFO over the optic nerve using a dual bore cannula and viscous fluid control (VFC) at 8 psi; retract tip during injection, keeping tip at PFO–BSS interface to ensure a single PFO bubble.
  - **Superior GRT**
    - PFO–gas exchange *or* PFO–silicone oil exchange for superior GRT. Oil if proliferative vitreoretinopathy.
  - **Autologous Macular Patch Graft**

- Developed by ***Tamer Mahmoud***
- Move graft from donor location to macular hole “under” PFO with DSP internal limiting membrane forceps to prevent scrolling and inversion; do not lift leading edge of graft.
- PFO provides much better graft oxygenation than silicone oil (Steve Charles) because of higher oxygen solubility and extraction ratio
- Remove PFO in 7 days.

Angioid Streaks

- **Doyne in 1889**
- **Knapp's striae** as he first coined the term in 1892
- **1917**: **Kofler** correctly determined that they represented changes at the level of Bruch's membrane
- irregular breaks in calcified and thickened Bruch's membrane radiating outwards from optic nerve in all directions like blood vessels
- peripapillary in 27% of cases when it is confined to two disc diameters from optic nerve or more widespread in 73% of cases where the streaks radiate for varying distances in the fundus, however never going past the equator
- colour of streaks varies from red to dark brown depending on colour of the fundus and overlying retinal pigment epithelial (RPE) atrophy
- associated fundus findings
  - Peau d'orange changes
  - Salmon spots
  - Optic disc drusen They are seen in around 10% of patients.
  - Fresh haemorrhages.
  - Paired red spots along streaks.
  - Cracked egg shell appearance of fundusdiffuse type of angioid streaks.
- **course and complications**
  - Choroidal neovascularisation (CNV) It is the most common and serious complication seen in 72-86% of patients
  - Macular degenerationIt is seen in 72% of these patients
  - Traumatic membrane ruptures
  - RPE tears have also been reported in angioid streaks
- **Systemic associations**
  - pseudoxanthoma elasticum (34%), Paget's disease (10%), hemoglobinopathies (6%). Upto 50% cases are, however, idiopathic
- **Diagnosis**:
  - Clinical examination
    - FFA: window defect' in FA due to RPE atrophy adjacent to them
    - ICG:
    - OCT
- **Management**
  - use eye protection and avoid contact sports
  - Therapy is possible and indicated only whenever a CNV has developed
  - Prophylactic photocoagulation of angioid streaks may stimulate CNV formation and is contraindicated.

- Laser photocoagulation
- Photodynamic therapy
- Anti VEGF
- transpupillary thermotherapy

Choroidal and Retinal Folds

Choroidal Folds

- Choroidal folds involve the choroid, Bruch membrane, and retinal pigment epithelium (RPE).
- **Symptoms**
  - Asymptomatic,
  - Metamorphopsia, or
  - Hyperopia
- **Examination**
  - Due to folding of the choroid and RPE—the RPE stretches and becomes thin over the crest or elevated portion of the fold and becomes compressed or compacted at the trough; location is usually posterior pole; pattern is usually curvilinear and parallel but may be circular and concentric with the disc, radial, or randomly distributed.
  - Ophthalmoscopy
    - Often subtle, alternating yellow and dark bands
    - Crests of the folds appear yellow or less pigmented corresponding to areas of thinned RPE, and troughs appear dark corresponding to areas of compressed RPE.
  - Angiography
    - Usually striking, alternating bands of hyper and hypofluorescence
    - Relatively thin RPE transmits background choroidal fluorescence better than compressed RPE
    - Crests appear hyperfluorescent corresponding to areas of thinned RPE and thickened choroid beneath the crests, and troughs appear hypofluorescent corresponding to areas of compressed RPE.
  - OCT: Folding of the choroid, RPE, and sometimes also the overlying neurosensory retina
  - Ultrasonography may be useful in determining etiology.
- **Etiology/pathophysiology**: Any condition that alters the inner surface of the choroid and/or sclera, such as compression, contraction (shrinkage), or thickening (edema, congestion)
  - Hypotony
    - Characteristic maculopathy
    - Horizontal folds or folds radiating temporally from disc
    - May also have overlying central macular horizontal inner retinal fold
  - Inflammation
    - May have pain, tenderness and/or proptosis
    - Causes include posterior scleritis, thyroid eye disease, uveal effusion syndrome, collagen vascular disease

- Ultrasound useful

- Papilledema
  - Increased optic nerve sheath pressure and/or disc edema can cause adjacent folds.
  - Folds may persist after resolution of papilledema.
- Retrobulbar mass: Intraconal and extraconal masses can indent the globe.
- Choroidal tumor / hemorrhage: Folds may occur at the posterior edge of the lesion.
- Extraocular implants: Scleral buckle can cause folds along posterior slope; also radioactive plaques and orbital implants.
- Choroidal neovascular membrane / disciform scar: Contracted lesion causes focal choroidal shrinkage; radial pattern.
- Idiopathic: Usually have acquired hyperopia; folds often bilateral and symmetric; may rarely develop crowded disc syndrome.

Outer Retinal Folds

- Outer retinal folds involve only the outer neurosensory retina (photoreceptor ellipsoid zone and outer nuclear layer).
- **Associated with rhegmatogenous retinal detachment, usually bullous**
  - Symptoms: Peripheral with or without central visual loss due to retinal detachment
  - Appearance
    - Ophthalmoscopy: Prominent pale lines within outer retina, termed “hydration lines” or “corrugations”
    - OCT: Outer retinal cysts and undulations in area of detached retina, normal smooth inner retinal surface
  - Etiology / pathophysiology: Outer retinal edema associated with extensive subretinal fluid causes large outer retinal folds, likely due to outer retinal ischemia and other causes
- **Associated with repaired rhegmatogenous retinal detachment**
  - Symptoms: Asymptomatic or metamorphopsia
  - Appearance
    - Ophthalmoscopy: Fine pale outer retinal lines
    - OCT: Outer retinal hyper-reflectivity with characteristic “jumping fish” or “flying seagull” appearance
    - Autofluorescence: Hypoautofluorescent lines correspond to outer retinal folds.
  - Etiology / pathophysiology: Outer retinal edema (hydration lines) associated with rhegmatogenous retinal detachment may slowly resolve during postoperative period and appear as fine outer retinal folds.
  - Prevention: None

- Management
  - None
  - Important to distinguish postoperative outer retinal folds from full thickness retinal folds, as outer folds will resolve spontaneously.
- Associated with X-linked juvenile retinoschisis

Inner Retinal Folds

- Inner retinal folds involve only the inner neurosensory retina (nerve fiber layer and internal limiting membrane [ILM]); retinal striae.
  - Symptoms: Asymptomatic or metamorphopsia
  - Appearance
    - Very fine wrinkles of retinal surface
    - No color
    - Not seen on angiography
  - Etiology / pathophysiology: Traction or distortion of the retinal surface
    - Epiretinal membrane: Most common cause
    - Optic disc edema:
      - Termed “Paton’s lines”
      - Pattern is concentric around swollen disc.
    - Hypotony: May have 1 prominent horizontal fold through fovea or multiple small folds that radiate from fovea
    - Inflammation
      - Scleritis and uveal effusion syndrome
      - May radiate from fovea
    - Chorioretinal scar: uncommon, due to contracted scar

Perimacular Retinal Folds

- Along edge of dome-shaped detachment of ILM, usually associated with premacular sub-ILM hemorrhage
- Appearance
  - Ophthalmoscopy
    - a. White oval or round border of dome-shaped detachment of ILM
    - At insertion of detached ILM to nerve fiber layer
    - Usually in association with sub-ILM hemorrhage but fold usually remains after resolution of blood
  - OCT

- Dome-shaped detachment of ILM with or without underlying blood
- Outer retinal hyper-reflective lesion below edge of ILM detachment

- Etiology / pathophysiology: Abrupt rise in intracranial pressure transmitted through perineural sheath results in shearing forces, hemorrhage dissects and separates the retinal layers; when blood resolves, ILM remains detached and perimacular fold usually persists.
  - Nonaccidental trauma
    - Shaken-baby syndrome
    - Perimacular fold was previously thought to be pathognomonic for nonaccidental trauma.
  - Terson syndrome: perimacular fold is a common finding.
  - Valsalva retinopathy: Less likely than other causes to result in perimacular fold

Full Thickness Retinal Folds

- Full-thickness retinal folds involve entire neurosensory retina.
- Falciform fold: May be congenital or acquired
  - Appearance: Usually 1 large linear full-thickness fold from optic disc to inferotemporal periphery
  - Etiology / pathophysiology: peripheral retinal pathology in pediatric patient, such as familial exudative vitreoretinopathy, ROP, toxocariasis, retinoblastoma
- Postoperative full-thickness retinal fold: After repair of rhegmatogenous retinal detachment
  - After vitrectomy for retinal detachment due to giant retinal tear
    - Symptoms: Usually asymptomatic
    - Appearance: Peripheral circumferential fold in area of giant retinal tear
    - Etiology / pathophysiology: Posterior retinal slippage in region of giant retinal tear associated with intravitreal gas and incomplete drainage of subretinal fluid
    - Prevention: Complete drainage of subretinal fluid; perfluorocarbon-silicone oil exchange
  - After vitrectomy for subtotal retinal detachment (without giant retinal tear)
    - Symptoms
      - Decreased vision, distortion, or diplopia
      - Asymptomatic if outside macula
    - Appearance
      - Ophthalmoscopy: Linear or curvilinear fold at inferior edge of prior subtotal retinal detachment
      - OCT: Full-thickness retinal fold without intervening subretinal fluid constitutes a dry fold.

- Etiology / pathophysiology: Inferior retinal displacement associated with intravitreal gas and incomplete drainage of subretinal fluid and possibly also lack of immediate postoperative face-down positioning
- Prevention
  - Complete drainage of subretinal fluid
  - In cases with some remaining subretinal fluid, use steamroll technique at conclusion of surgery and/or immediate postoperative face-down positioning
- Management: Vitrectomy with subretinal saline injection to redetach area involving the fold, then use of perfluorocarbon liquid to displace subretinal fluid peripherally, complete drainage of subretinal fluid, and immediate postoperative face-down positioning

- After scleral buckle for retinal detachment
  - Symptoms: Usually asymptomatic Appearance: Depends on etiology Etiology / pathophysiology
  - Encircling buckle that was placed too high (radial fold on posterior slope)
  - Radial buckle that was placed too far posteriorly (radial or curvilinear folds at posterior edge)
  - External drainage site associated with retinal incarceration (radial folds extending outward from drainage site)

Infectious Endophthalmitis

- Exogenous Endophthalmitis: when the outer wall of the eye sustains a break
- Endogenous Endophthalmitis: less common, when the microorganisms spread to the eye from a source elsewhere in the body, usually through the blood stream
- 90% of all cases are caused by bacteria
- **Etiology**
  - **Postoperative (70%)**
    - ***Acute postoperative (<6 weeks after surgery)***
    - Ninety-four percent Gram-positive bacteria including coagulase-negative staphylococci (70%), Staphylococcus aureus (10%), Streptococcus species (11%); only 6% Gram-negative organisms
    - ***Delayed postoperative (>6 weeks after surgery)***
    - Propionibacterium acnes, coagulase-negative staphylococci, and fungi (Candida species)
    - ***Conjunctival filtering bleb associated***
    - Streptococcus species (47%), coagulase-negative staphylococci (22%), Haemophilus influenza (16%)
  - **Posttraumatic (20%)**
    - Bacillus (B. cereus) species (24%), Staphylococcus species (39%), and Gram-negative organisms (7%)
  - **Endogenous (2–15%)**
    - Rare, usually fungal (Candida species); bacterial endogenous is usually due to Staphylococcus aureus and Gram-negative bacteria. Occurs in debilitated, septicemic, or immune-compromised patients, especially after surgical procedures.
- ***Bacteria***
  - Gram-positive cocci
    - *Staphylococci:*
      - *S. aureus: 2nd MC*
      - *CONS: S. epidermidis is MC (***exopolysaccharide or "slime"**)
    - *Streptococci*
  - Gram-positive bacilli
    - *Bacillus:* IV drug use, sickle-cell disease, foreign bodies including IV catheters, immunosuppression from malignancy, neutropenia, corticosteroid use, AIDS
    - *Corynebacterium diphtheria*
    - *Listeria monocytogenes*
    - *Clostridium species*

- *Propionibacterium:* most common clinical isolate of Gram-positive, nonsporulating bacteria, **chronic granulomatous nature, IOL associated**

- Gram-negative cocci
  - *Neisseria*
  - *Moraxella*
- Gram-negative bacilli
  - *Actinobacter*
  - *Haemophilus influenza*
  - *Pseudomonas*
  - Enterobacteriaceae
  - *Klebsiella*
- Higher bacteria: Mycobacteriaceae, Actinomycetaceae, and Nocardiaceae.

- ***Fungi***
  - Candida
  - *Aspergillus*
  - Histoplasma capsulatum
  - Blastomyces dermatitidis
- ***Helminths***
- ***Protozoa***
- ***Ectoparasites***

- **Clinical Features**
  - ***Postoperative infection***
    - Cataract extraction: 0.03% to 0.1%
      - pain 1–7 days after
      - conjunctival chemosis and increased injection, often with a significant amount of yellowish exudate
      - More severe initial findings suggest infection with Gram-negative bacteria, *Streptococcus* or *Staphylococcus aureus*
      - Postoperative filtering blebs, wound leaks, and vitreous wick are also found more frequently in infected eyes
    - Corneal transplantation: 0.11% and 0.08%
    - Glaucoma filtration surgery:
      - similar to the risk following cataract
      - inferior location to the bleb and use of antifibrotic agents increase the likelihood
    - Pars plana Vitrectomy:

- Intraocular injection: 0.014% up to 0.87%
- Scleral buckling procedure
- Strabismus surgery

✣ ***Post-traumatic Endophthalmitis***

- 20–30% of the cases of endophthalmitis
- 2-17%

✣ Endogenous Endophthalmitis

- 5–7% of cases
- diabetes mellitus or renal therapy, immunosuppressive disease and therapy, IV drug use, or systemic septicemia
- **Bilaterality** is common
- **Fungal** causes are found in 50–62% of cases
- More alarming is the mortality rate, which has been reported to vary from 5% to 29%

✦ **Therapy**

✣ To overcome the problem of poor penetration, intravitreal injection of antibiotics was studied by **von Sallmann** et al and by Leopold with further development by **Peyman** and Forster

✣ Characteristics for ideal drugs

- Bactericidal properties
- Broad spectrum of coverage
- Excellent therapeutic ratio
- Good therapeutic ratio after IV injections
- Favorable pharmacokinetic properties

✣ **Dosing**

- Vancomycin 1 mg/0.1 mL
- Cefazolin 2.25 mg/0.1 mL
- Amikacin 0.2–0.4 mg/0.1 mL
- Ceftazidime 2 mg/0.1 mL
- Dexamethasone 4 mg/0.1 mL
- traumatic endophthalmitis with vegetable matter: Amphotericin B 5 µL/0.1 mL

Retinal Tumors

Cavernous Hemangioma

- **Etiopathology**
  - tumor arising from the inner half of the retina
  - multiple endothelial-lined, thin-walled aneurysms
  - multiple endothelial-lined, thin-walled aneurysms
  - Genotyping for the three known CCM genes can establish its hereditary nature.
- **Clinical Features**
  - clusters of saccular aneurysms filled with dark blood
  - isolated, one to two disc diameters in size, and resembles an intraretinal cluster of grapes
  - pseudohypopyon in retina: layering of the red blood cells within the aneurysms causes a plasma–erythrocytic separation
  - characteristic “cluster-of-grapes” appearance
  - unilateral
  - symptomatic when they are located in or adjacent to the macula which has been reported in approximately 10%
  - can cause simultaneous subretinal, intraretinal, and preretinal hemorrhage
- **Differential Diagnosis**
  - lack of intraretinal exudate distinguishes this tumor from Coats disease
  - Leber miliary aneurysms is a progressive condition
  - capillary hemangioma (von Hippel disease) is a discrete tumor with characteristic feeder vessels
  - Racemose hemangioma (Wyburn Mason syndrome): dilation of the larger retinal vessels with direct arteriovenous anastomosis is seen
- FAF: autofluorescence of the gray-white epiretinal membrane overlying the tumor
- FFA: aneurysms will fill slowly and often incompletely up to 30 minutes after dye injection.
- **Management**
  - Conservative and follow up
  - Laser or cryo in case of VH

Metastases

- 10% of patients who die of cancer have been found to have intraocular metastases
- average age at diagnosis of retinal metastases was 52 years
- **Metastatic cascade**
  - dissociate from the primary tumor
  - invasion of the surrounding connective tissue components

- intravasation
- dissemination: hematogenous or lymphatic
- extravasation and angiogenesis

- **Clinical Features**
  - decreased or blurred vision
  - Floaters
  - pain, diplopia, and red eye
  - can be asymptomatic
  - Metastatic melanoma: pigmented lesion within the retina with irregular borders and flat appearance
  - Carcinomas: non-pigmented, white or yellow
  - Intraretinal/ Subretinal hemorrhage
  - Perivascular infiltrates and exudates
  - subretinal fluid
  - Vitreous cells: “brown spherules” or “globular vitreous opacities” → melanoma
- Differential diagnosis
  - non-pigmented white retinal lesions: carcinoma, the differential includes inflammatory and infectious diseases
  - pigmented lesions: metastatic melanoma, metastatic choroidal tumors, neovascular macular degeneration
- Diagnostic evaluation
  - history and physical exam, with review of systems,
  - metastatic workup
  - Blood work,
  - markers for infectious disease
  - B-scan ultrasonography:
  - FFA: not diagnostic, it is helpful in differentiating metastatic tumors from non-neoplastic conditions
  - OCT
- **Management**
  - systemic chemotherapy
  - Surgical resection for some tumors has been described
  - Plaque radiotherapy
  - Photodynamic therapy

Melanocytoma of the Optic Disc

- Zimmerman
- specific variant of melanocytic nevus, located in the optic disc or anywhere in the uveal tract, characterized clinically by a dark brown to black color, and composed histopathologically of deeply pigmented round to oval cells with small, round, uniform nuclei
- melanocytoma appears to have an equal incidence in all races, whereas uveal melanoma is uncommon in black people
- **Clinical Features**
  - slight visual loss related to the tumor can occur in about 26%, usually due to mild retinal exudation and subretinal fluid.
  - Marcus Gunn pupil 10-30%
  - usually unilateral
  - dark brown to black lesion that is located partly in the optic disc
  - relatively small and confined to the disc in 15%
  - some degree of disc edema (25%), intraretinal edema (16%), subretinal fluid (14%), yellow intraretinal exudation (12%), focal hemorrhage (5%), vitreous seeds (4%), and retinal vein obstruction (3%).

CHRPE

- asymptomatic congenital hamartoma
  - solitary
  - grouped
  - multiple: FAP, Gardner, Turcot
- 3 per 2400 prevalence
- FAP
  - adenomatous polyposis coli (APC) gene
  - chromosome 5
  - Attenuated FAP (AFAP, <100 colorectal adenomas)
  - Severe FAP (>1000 adenomas)
  - intermediate FAP (100–1000 adenomas)
- **Clinical Features**
- ***Solitary CHRPE***
  - flat, round, hyperpigmented lesion with smooth or scalloped margins
  - light gray, brown to black
  - marginal halo of depigmentation may surround the lesion

- punched-out inner lacunae with hypopigmentation
- size may vary
- predominance in the superotemporal and equatorial region

- ***Grouped CHRPE***
  - arranged in a cluster, resembling the footprint of an animal ('bear tracks'),
  - 3–30 lesions, which may vary in size from 100 to 300 µm lesions
  - possible pigmentary mosaicism in both the eye and skin
- ***Multiple CHRPE***
  - generally smaller (50–100 µm in diameter) compared with solitary
  - depigmented halo, mottled RPE
  - More than four widely spaced lesions per eye or bilateral involvement are suggestive of FAP
- **Investigations**
  - FFA ICG: no leaks
  - ERG-EOG: normal

Differential diagnosis

- **choroidal malignant melanoma**: elevated, less homogeneously pigmented and less sharply demarcated compared with CHRPE
- **Choroidal nevi** are flat and located below the RPE
- **Melanocytomas of the choroid**: homogeneously black color
- **sickle cell retinopathy**: Black sunburst lesions

CHRRPE

- Combined hamartomas of the retina and retinal pigment epithelium
- benign tumors that may cause significant visual loss
- solitary, unilateral lesions located at the optic disc or posterior pole.
- mean age at the time of diagnosis was 15
- **Clinical Features**
  - painless visual loss → choroidal neovascularization, vitreous hemorrhage, exudative retinal detachments, retinoschisis, and macular hole formation
  - strabismus, floaters, leukocoria and ocular pain
  - elevated pigmented mass involving the RPE, retina and overlying vitreous with extension of fanlike projections towards the periphery
  - vascular tortuosity within the lesion in 93% of patients, hyperpigmentation in 87%, slight elevation in 80%, epiretinal membrane formation in 78%, and exudation in 7%

- Bilateral CHRRPE lesions have been identified in patient with neurofibromatosis 1

- **Investigations**
  - FFA: degree of hypofluorescence parallels the degree of hyperpigmentation, tortuous vessels usually leak in late phase
  - OCT: elevated lesion with high reflectivity of the inner retina, hyporeflective shadowing of the underlying tissue, and obscuration of the normal retinal layers
- **Differential Diagnosis**
  - Epiretinal membrane
  - Pigmented choroidal lesions
  - Miscellaneous: Morning-glory disc anomaly, retinoblastoma, choroidal neovascularization, retinoschisis, and capillary hemangioma
- **Management**
  - anti-VEGF agents for CNVM
  - surgical removal

Primary Vitreoretinal Lymphoma

- **PCNSL and PIOL**
  - PCNSL is a variant of extranodal non-Hodgkin lymphoma (NHL) that is predominantly a high-grade B-cell malignancy associated with a median survival ranging from 1–8 years depending on factors such as age and Karnofsky performance status
  - Primary intraocular lymphoma (PCNSL-O or PIOL) is a variant of PCNSL with predominantly ophthalmic involvement. In contrast to other ocular lymphomas that affect the orbit, conjunctiva, and uveal tract, PCNSL-O is characterized by vitreoretinal involvement and is therefore referred to as primary vitreoretinal lymphoma (PVRL).
- exact incidence is unknown
- **Etiopathogenesis**
  - originate from late-germinal center or post-germinal center lymphoid cells
- **Clinical Features**
  - painless, decreased visual acuity or floaters
  - bilateral in 80% of cases
  - hallmark: presence of fine vitreous cells or clumps of cells and sub-retinal pigment epithelium (RPE) deposits comprised of aggregated lymphoma cells
  - keratic precipitates, iris nodules, aqueous cells, and flare, focal, multifocal, or diffuse choroidal, retinal, or chorioretinal infiltrates

Autoimmune Retinopathy AIR

- Autoimmune retinopathy (AIR) is an inflammatory retinopathy characterized by vision loss, scotomas, visual field deficits, photoreceptor dysfunction, and the presence of circulating autoantibodies against retinal antigens.
- AIR presumably results from an immunologically mediated attack on the retina by antiretinal autoantibodies, but the mechanisms by which these antibodies cause retinal dysfunction are not entirely understood.
- ***AIR can be studied in two groups: paraneoplastic and non-paraneoplastic.*** Paraneoplastic AIR was described by Sawyer et al in 1976, and the term "paraneoplastic retinopathy" was first used by Klingele in 1984.

Non-Paraneoplastic Retinopathy /AIR

- AIR may be triggered by molecular mimicry between retinal proteins and presumed viral or bacterial proteins
- Patients with AIR typically present with subacute vision loss, scotomas, photopsias, nyctalopia, or photoaversion, and dyschromatopsia. On examination the fundus may appear unremarkable. Despite the heterogeneity in their circulating antiretinal antibodies, common clinical features in AIR patients include retinal vascular attenuation, diffuse retinal atrophy, retinal pigment epithelial (RPE) changes, and waxy disc pallor. AIR is usually bilateral but it can be asymmetric. There is usually minimal or no clinically detectable intraocular inflammation. Visual field testing shows constricted visual fields and central or paracentral scotomas, and electroretinogram (ERG) can show abnormalities in rods, cones, or bipolar cell responses or a combination of these. Visual acuity, particularly in the earlier stages, may be deceivingly good. Ancillary testing with fluorescein angiography (FA) or OCT may show mild retinal vascular staining or leakage, or cystoid macular edema (CME) in some cases.
- Because of the presumed autoimmune nature of AIR, various forms of immunomodulatory approaches have been tried. However, the ambiguity in diagnosis creates an enormous challenge in the management of AIR. Because of limitations in diagnostic testing and lack of our understanding of the underlying mechanisms, immunomodulatory therapy can be considered empiric at this time. Most of the knowledge regarding therapy comes from paraneoplastic retinopathy. Common approaches include systemic or local corticosteroids, intravenous immunoglobulin (IVIG), or plasmapheresis, antimetabolites such as mycophenolate mofetil, azathioprine, and T-cell inhibitors such as cyclosporine. Targeted B cell therapy such as anti-CD20 monoclonal antibody (rituximab), has also been used in the treatment of AIR.

Paraneoplastic Retinopathy

- Effects of Cancer
  - mass effect
  - metastatic
  - due to RT or CT
  - paraneoplastic syndrome

Cancer-associated retinopathy CAR

- **Klingele**: termed this “paraneoplastic retinopathy”
- subacute visual loss resulting from circulating antibodies against retinal proteins in the presence of systemic cancerous tumor growth
- Malignancies associated with CAR
  - Most common solid cancers: lung, breast, gynecologic, prostate, colon
  - Hematological malignancies can also be associated with CAR.
- Etiopathology
  - hormone-like substance ??
  - autoimmune basis ??
  - 23 kDa serum antiretinal ganglion cell antibodies → **recoverin**, a calcium channel photoreceptor protein → recoverin-associated retinopathy
  - 46 kDa antigen identified as human **alpha-enolase**, a glycolytic enzyme
- Clinical Features
  - Acute to subacute visual symptoms can precede the discovery of malignancy by several months.
  - High level of suspicion for CAR should be considered in any patient with acute or subacute vision loss, vascular attenuation, and visual field alterations in the absence of another etiology.
  - Symptoms
    - Decreased vision, particularly under scotopic conditions
    - Glare
    - Photosensitivity
    - Impaired color perception
  - Signs
    - Attenuation of arterial vasculature
    - Variable degrees of optic disc pallor
    - Variable degrees of chorioretinal or retinal pigment epithelial atrophy
    - Subtle vitritis in some cases
  - Test
    - Visual field testing
      - Ring or arcuate scotomas
      - Constriction: Can be generalized or localized to within the central 20 degrees
    - Fluorescein angiography
      - May demonstrate perivascular leakage or staining at the optic nerve head

        - A normal angiogram is observed in a significant number of patients.
    - OCT
        - Thinning of the photoreceptor cell layer
        - Loss of the inner reflective layer

- **Diagnosis**
    - Electroretinography (ERG) and antibody testing are critical steps in the evaluation of a patient suspected to have a paraneoplastic retinopathy based on clinical examination.
    - ERG
        - Classically, ERG demonstrates severely diminished or extinguished a and b waves
        - Electronegative ERG, more typical of MAR, has also been seen
    - Autoantibody testing
        - Over 18 antigens have been implicated in CAR.
        - Recoverin (23 kDa) and α-enolase (46 kDa) are the most commonly detected antigens.
        - Other potentially pathogenic antigens include transducin (40 kDa), carbonic anhydrase II (30 kDa), and interphotoreceptor retinoid binding protein (145 kDa).
- **Treatment**
    - Untreated, CAR can progress to severe vision loss, often to no light perception.
        - Early initiation of therapy is critical for vision preservation.
        - Despite aggressive immunomodulatory therapy, some patients still progress to significant vision loss.
    - The treatment must target the ocular disease, as the removal of cancer alone does not affect the course of CAR.
    - No standardized approach to treatment of paraneoplastic retinopathy exists.
        - Steroids are often tried initially with broadly variable outcomes.
            - Prednisone can control intraocular disease in the short term in some cases.
            - The benefit of local steroid administration in CAR is difficult to assess, as there are limited reports in the literature.
        - Multiple steroid-sparing immunomodulatory agents have been reported in the treatment of CAR, with no single approach showing consistent, long-term efficacy in this disease. Often, multiple agents are used concurrently or sequentially in an attempt to halt visual decline.
            - Intravenous immunoglobulin
            - Plasmapheresis, when used with prednisone
            - newer monoclonal pan-lymphocytic (CD52, alemtuzumab) and B-cell (CD20, rituximab) antibodies in patients failing other therapies.

Cutaneous melanoma-associated retinopathy MAR

- 1984 by Gass as “an acute Vogt–Koyanagi–Harada-like syndrome.”
- Paraneoplastic acquired night blindness
- **Etiopathology**
  - antibodies against **transducin, aldolase A and aldolase C** have also been documented in patients with MAR
- **Clinical Features**
  - differentiated from CAR syndrome by being **nonprogressive, causing central visual loss** (versus ring scotomas), a sensation of shimmering or pulsating light and being associated with vitiligo in up to 20%.
  - In contrast to patients with CAR syndrome and the “acute Vogt–Koyanagi–Harada-like syndrome,” patients with MAR syndrome demonstrate a substantial elevation of rod absolute thresholds and selective reductions in the rod and cone ERG b waves, resembling those of patients with congenital stationary night blindness.
  - The photoreceptor function is intact but signal transmission between the photoreceptors and second-order interneurons appears to be defective.
  - MAR syndrome, unlike CAR syndrome, is more likely to be visually symptomatic in more advanced stages of disease and, in general, does not manifest before the clinical diagnosis of cutaneous malignant melanoma.

Management of paraneoplastic retinopathy

- ERG should be considered in any adult patient who has symptoms of central or paracentral positive visual phenomena (“**shimmering” or “dancing” lights**), photopsias, and minimal retinal findings
- ERG is abnormal or extinguished, then a chest X-ray is a common “next step,”
- panel of autoantibody tests for CAR, MAR
- possible role for immunosuppression therapy

BDUMP Bilateral diffuse uveal melanocytic proliferation

- Development of multiple, slightly elevated (usually only up to 2 mm), pigmented, and nonpigmented uveal melanocytic tumors, as well as evidence of diffuse thickening of the uveal tract
- Multiple, round or oval, subtle, red patches at the level of the RPE in the posterior fundus
- A striking pattern of multifocal areas of early hyperfluorescence on fluorescein angiography corresponding with these patches
- Exudative retinal detachment
- Rapidly progressing cataracts

Paraneoplastic Vitelliform Maculopathy

- Metastatic cutaneous melanoma
- Anti-bestrophin antibodies
- Subretinal location of vitelliform material

Choroidal Melanoma

Epidemiology

- incidence of 5–6 cases per 1 million population per year
- 60-70 years
- only 5% of all melanomas
- most common primary intraocular malignancy
- sunlight has been proposed as an environmental risk factor
- Heavily pigmented individuals rarely get skin or posterior uveal melanoma
- **Risk factors**
  - ***Age:*** median age at diagnosis is 55 years
  - ***Sex:*** slight predominance of males
  - ***Race:*** relative risk for white males compared with African American males of 7.4
  - ***Genetics:***
    - Familial clusters are there but its not common
    - Mutations in G-α proteins
  - **Hormones and reproductive factors**
    - increased risk for women in their childbearing years
    - the seemingly adverse influence of pregnancy on prognosis
    - hormonal effect from estrogens or melanocyte-stimulating hormone ??
  - ***Eye and skin color***
    - blue or gray eyes were found to have three times the risk of disease
    - relative risk of 3.8 comparing light to darker skin color
  - ***History of nonocular malignancy***
    - elevated risk of ocular melanoma among women with a history of invasive ovarian cancer, suggesting a possible common hormonal etiology
  - ***Sunlight exposure:*** possible role
  - ***Diet and smoking:*** smoking and alcohol consumption were not associated with an increased risk for uveal melanoma
  - ***Geography:*** inconclusive about latitude and altitude
  - ***Occupational and chemical exposures:*** associations are weak
  - ***Mobile phone use:*** not associated with risk
  - ***Other environmental exposures:***

Prognosis

- Clinical prognostic indicators:

- Tumor size: 6-year survival rates dropped with increasing tumor diameter from 87% for tumors 10 mm or less, to 30% for tumors larger than 12 mm

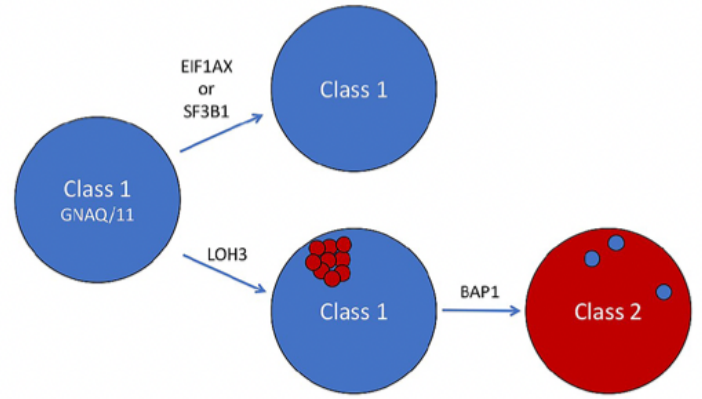
- Histopathologic prognostic indicators
  - The presence of epithelioid cells, extravascular matrix patterns that reflect the arrangement of tumor microcirculation, high microvascular density and large numbers of tumor-infiltrating macrophages in primary uveal melanoma, are independently associated with shorter time to metastatic death
  - ***Histopathology***
  - **Callender** described **five** histologic types: *spindle cell subtypes A and B, epithelioid, fascicular, and mixed cell-type tumors composed of both spindle cells and epithelioid cells*
  - 10-year mortality ranged from 11% to 19% in spindle A tumors; 21–36% in spindle B tumors; 63–79% in mixed-cell tumors, **and 72–100% in epithelioid tumors.**
  - ***Tumor microvasculature***
  - presence of networks of three or more contiguous closed vascular loops was highly predictive
  - 10-year survival was 50.7% when networks were present and 88.3% in the absence of networks.
  - ***Extrascleral extension***
  - 5-year survival rate was 26% in patients with orbital extension and 78% in those without extension.
- Molecular prognostic indicators
  - loss of chromosome 3 is associated with a poor prognosis
  - gains in chromosome 8 are associated with a worse prognosis
  - abnormalities in chromosome 6 are associated with a good prognosis.

Molecular Genetics

- **Cutaneous melanoma**
  - activating mutations in Ras and B-Raf → activation of MEK1/ERK (or the mitogen-activated protein kinase (MAPK) pathway), thereby promoting cell proliferation and survival
- **Uveal melanoma**
- Genes in uveal melanoma
  - half of uveal melanomas exhibit mutations in the gene encoding for $G\alpha_Q$ (GNAQ).
  - other half shows mutation in the gene encoding for the related protein, $G\alpha_{11}$ (GNA11).
  - $G\alpha_{Q/11}$ family → stimulation of phospholipase C-β (PLCβ) → protein kinase C (PKC) → activates downstream intracellular signaling pathways, including the MAPK signaling pathway
- **Later Prognostically Significant Mutations**

- EIF1AX: Low metastatic risk (class 1A)
- SF3B1 and other splicing factors: Intermediate metastatic risk (class 1B)
- BAP1: High metastatic risk (class 2)

- **Chromosome Copy Number Aberrations (CNAs)**
  - Loss of 1p, 3, and 8p
  - Gain of 6p and 8q
- **Hypothesis**: Initiating event occurs in GNAQ/11 or related genes, resulting in benign nevus. Further genomic aberrations drive tumor evolution along one of two major pathways, class 1 or class 2, depending on the later prognostic mutation that occurs.



Pathology

- **Gross appearance**
  - oval or fusiform shape when confined by Bruch's membrane.
  - collar-button/mushroom configuration when the tumor has broken through Bruch's membrane.
- **Histopathologic features**
  - ***Cytologic***
  - Callender classification: spindle cell subtype A; spindle cell subtype B; epithelioid type; fascicular type, and mixed cell type (consisting of mixture of spindle and epithelioid cells)
  - modified Callender classification: Mclean
    - three different types
    - spindle cell melanoma (composed of spindle B cells); epithelioid cell melanoma, and melanoma of mixed-cell type

- Further modification also done with newer proposed classification
  - **Spindle A cells:** fusiform, cohesive cells with poorly defined cell borders
  - **Spindle B cells:** plumper than spindle A cells, most common cell type in choroidal melanoma.
  - **Epithelioid cells:** non-cohesive cells with defined cell borders
  - **Intermediate cells:** small epithelioid cells, are a frequent cell type intermediate between spindle B cells and epithelioid cells
- ***Immunohistochemical***
- Melan A stains melanocytes in general
- HMB45 is predominantly expressed in “activated” melanocytes and is therefore more suggestive of malignant melanocytic lesions
- S100 is expressed in different types of cells including melanocytes and very often used in combination with HMB45 as a marker for uveal melanoma
- Microphthalmia transcription factor (MITF) is essential for the development and survival of melanocytes
- Tyrosinase is an enzyme that is involved in the metabolism of melanocytes and was recently introduced as a melanoma marker
- Ki67 antigen – a proliferation marker expressed in the nucleus – is suitable to detect the proliferative activity in tumors and has prognostic relevance
- ***Electron microscopy:*** cell types can also be differentiated by transmission electron microscopy
- ***Tumor stroma:*** intratumoral vessels and vascular-like structures” – nine different morphologic patterns
- Melanoma-associated spongiform scleropathy (MASS)” is a degenerative, noninflammatory process in the sclera underlying the tumor that occurs in 38% of enucleated eyes harboring uveal melanoma
- ***Tumor extension:***
- ***Degenerative changes:*** Secondary drusen and orange pigment

Special types of uveal melanoma

- Diffuse uveal melanoma
- Multifocal unilateral uveal melanoma
- Bilateral uveal melanoma
- Balloon cell melanoma
- Necrotic melanoma
- Retinoinvasive melanoma

Histologic differential diagnoses

- Nevus
- Melanocytoma
- Other choroidal neoplasms

- Choroidal metastases
- BDUMP (Bilateral Diffuse Uveal Melanocytic Proliferation)
- Choroidal neovascularization (CNV) with hemorrhage

Management

- methods of management today include observation, transpupillary thermotherapy (TTT), radiotherapy, local resection, enucleation, orbit exenteration, and various combinations of these methods

Systemic Evaluation

- **Physical examination**
  - history of weight loss, subcutaneous nodularity or abdominal pain
- ***Serology: liver function tests***
  - gamma-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatases, aminotransferases and bilirubin
  - should be used for metastases screening only as a complement to radiographic imaging
- ***Radiologic assessment: CT, MRI, USG***
  - Contrast-enhanced magnetic resonance imaging (MRI) is considered to be the most sensitive
- ***Positron emission tomography/computed tomography***
  - discrimination between inflammatory and neoplastic tumors
  - those at high risk for metastatic uveal melanoma (e.g., T3 and T4 tumors)

Periodic observation

- small melanocytic tumors are best managed by periodic fundus photography and ultrasonography
- risk factors for metastasis include greater tumor thickness, tumor proximity to the optic nerve, presence of visual symptoms from the melanoma, and prior documented growth

Photocoagulation

- xenon photocoagulation achieved better tumor control but argon laser was associated with fewer complications
- TTT has largely replaced argon laser

Transpupillary thermotherapy

- transpupillary thermotherapy" (TTT) was introduced by **Journée-de Korver**
- thermotherapy is **different from hyperthermia**, which by definition is heating the tumor to a temperature of 42–44°C to enhance the cytotoxic effect of ionizing radiation on tumor cells. In TTT, temperatures of approximately 45–60°C within the tumor are reached with irreversible cytotoxic effects so that Additional radiotherapy may be not required
- delivers heat to the tumor in the infrared range using a modified diode laser delivery system
- Infrared or near-infrared light penetrates deeper into the choroidal tissue than light from argon blue-green lasers theoretically avoiding undesirable coagulation effects in the retina.
- In contrast to other wavelengths, the absorption of ocular media for infrared is very low (approximately 4–7%).
- A laser beam with a spot size of 3 mm and a maximal power density of 12 W/cm^2 is used. At the second half of the exposure time of at least 1 minute, a grayish discoloration of the tumor tissue should be visible, indicating a temperature of the target tissue of 60–65°C
- Indication
  - largest tumor diameter of <12 mm and not more than 4 mm thickness located posterior to the equator
- Leiden Group suggested "**sandwich therapy**" (brachytherapy of the tumor base and TTT of the tumor apex) for the treatment of choroidal melanoma

Radiotherapy/PROTON Therapy

- **two** major radiotherapeutic techniques for the treatment of uveal melanomas: **radioactive plaques** sutured on the sclera over the area of the tumor, and **external beam irradiation** using charged particles such as protons, helium ions and the gamma knife.
- **Brachytherapy**
  - suturing a radiation source to the eye → Moore in 1930
  - Iodine-125 is currently the most commonly used isotope
  - Iodine-125 and Ruthenium-106 plaques have largely replaced Cobalt-60 at most institutions
  - **indications for plaque brachytherapy include:**
    - selected small choroidal melanomas exhibiting growth or malignant transformation
    - medium-sized choroidal (thickness between 2.5 and 10 mm, as well as a maximal basal diameter <16 mm) and ciliary body melanomas in eyes with visual potential
    - large melanomas with dimensions up to 16 mm in diameter and 8–10 mm in thickness;
    - larger melanomas, especially in monocular patients
    - juxtapapillary tumors (touching or located within 1 mm from the optic nerve)

- **Dosimetry**
  - range between 50 and 100 Gy
  - COMS modified the prescription dose to deliver 85 Gy to the tumor apex with a delivery rate of 43–105 cGy/hour
- **Isotope selection**
  - most commonly used: **iodine-125, palladium-103, and ruthenium-106**
  - HVL, half-value layer: thickness of water required to reduce exposure (dose) from the nuclide to 50% (narrow beam).
  - TVL, tenth-value layer: thickness of lead required to reduce exposure (dose) from the nuclide to 10% (broad beam)
  - inverse-square law largely governs the radiation penetration in tissue
- **Plaque design**
  - gold plaque that is approximately 0.4 mm thick with a lip around its perimeter that resembles a smooth bottle cap
  - Within the gold plaque is a soft, pliable plastic (Silastic) seed carrier insert with evenly spaced troughs that accept the iodine-125 seeds

- **charged particle irradiation:**
  - charged particles such as protons, helium ions and the gamma knife.
  - **helium ion irradiation** is no longer in use due to its high cost
  - **gamma knife** do not appear to be as attractive as those of proton irradiation
  - **Protons** are positive, singly charged particles that have minimal scatter and a well-defined, finite, and energy-dependent tissue range
    - positive, singly charged particles
    - well-defined, finite, and energy-dependent tissue range
    - inherent Bragg peak at the end of the beam path
  - ***Patient selection***
    - patients with larger tumors located at the peripheral fundus
  - ***technique***
    - tumor is localized by transillumination, indirect ophthalmoscopy
    - four tantalum rings, 2.5 mm in diameter, are sutured to the sclera at the margins of the tumor
    - patient positioning with a headholder attached to the proton beam collimator
    - standard dose administered for most tumors is 70 cobalt Gy equivalents (CGE) delivered in five equal fractions in 5 days
  - **Results**
    - Disappearance of the lesion, or formation of a flat scar is observed in 15%

Photodynamic therapy

- cytotoxic effect of singlet oxygen radicals by photosensitizers when exposed to visible light
- The first generation of photosensitizers used was hematoporphyrin derivatives (HpD). HpD-based photodynamic therapy, however, had numerous disadvantages, among which was a high rate of recurrences (probably related to the poor tissue penetration of 630 nm laser light into tumor tissue), secondary glaucoma, and severe systemic side-effects (patients had to avoid sunlight for weeks to prevent deleterious phototoxic effects on the skin) which led to rejection of this therapeutic approach
- Benzoporphyrin-derived photosensitizers like verteporfin → better tissue penetration and fewer systemic side effects with regard to skin toxicity and has been proven to be effective in the treatment of choroidal hemangioma

Local resection

- either by **en bloc resection**, through a scleral trapdoor ("**exoresection**"), or in a piecemeal fashion using a vitreous cutter passed transretinally (i.e., "**endoresection**").
- Meyer-Schwickerath: penetrating sclero-uveo-retinectomy
- Foulds and Damato: partial lamellar sclerouvectomy
- **Exoresection**
  - Indications: large tumor size, anterior location, and the presence of exudative retinal detachment
  - Contraindications: (1) a tumor diameter >18 mm; (2) tumor extension to within a disc diameter of the optic disc margin; (3) extensive retinal invasion or any retinal perforation; (4) extraocular extension; (5) involvement of more than 2 clock-hours of ciliary body or angle; and (6) general health precluding hypotensive anesthesia
- **Endoresection**
  - Indications: 1) radiotherapy is unlikely to conserve useful vision, because the tumor has perforated retina or extends close to optic disc, and (2) the patient is highly motivated to retain vision and understands the controversial nature of this operation.

Enucleation

- ***Indications***
  - **primary enucleation** are large tumor size, neovascular glaucoma, optic nerve invasion, blind painful eye, localized extrascleral extension, and patient preference
  - **secondary enucleation** are local treatment failure and ocular pain secondary to radiation-related complications.
- **no touch enucleation**:
  - to minimize the amount of surgical trauma and theoretically to lessen the chance of tumor dissemination at the time of surgery
  - to freeze the venous drainage from the tumor prior to cutting the optic nerve
  - ***recently fallen into disuse***

- ***Implant description***
  - two general categories: solid spheres and porous, integrated implants.
  - Solid spheres include silicone and polymethyl methacrylate (PMMA)
  - porous implants include coralline hydroxyapatite and porous polyethylene
- ***Implant sizing***
  - Most adult patients require at least a 20 mm implant
  - contralateral eye axial length measurements subtracted by 2 mm or by 3 mm for hyperopia
  - Another algorithm subtracts the volume of an ideal 24 mm eye by the volume of sclera and 2 mL to determine implant volume

Orbital exenteration

- in cases of orbital extension

chemotherapy or immunotherapy

- no current method of preventing metastasis in the early stages
- no current evidence that chemotherapy or immunotherapy are effective
- Immune checkpoint inhibitors
  - CTLA-4 inhibitors: ipilimumab (Yervoy)
  - PD-1 inhibitors: pembrolizumab (Keytruda), nivolumab (Opdivo)
- T cell activation
  - Tumor infiltrating lymphocytes (TIL)
  - Immune modulated T cells against cancer (ImmTACs) – IMCgp100 from Immunocore
    - USFDA approved
    - ImmTAC molecule is an engineered T cell receptor that recognizes specific HLA antigens on melanoma and attracts T cells to attack the tumor.

Local Therapy

- Light-activated AU-011 from Aura Biosciences Inc.
- Technology involves:
  - Virus-like nanoparticles modeled on the human papilloma virus that selectively attach to solid tumor without binding normal tissue
  - Nanoparticle coupled with chromophore
  - Laser light applied and chromophore uptakes heat leading to precise cellular destruction of the tumor.

Benefits of PRAME in Prognostic Testing of Melanoma

- PRAME is a testis-specific gene that should not be expressed in normal tissues.
  - PRAME is likely involved in meiosis.
  - Inappropriate expression of PRAME in cancer may cause tumor progression
- PRAME is expressed in a subset of Class 1 and Class 2 uveal melanomas.
  - About 20% of Class 1 uveal melanomas are PRAME+.
  - About 30% of Class 2 uveal melanomas are PRAME+.
- PRAME expression is associated with worse patient outcome.
  - PRAME expression is associate with shorter time to metastasis and melanoma-specific mortality in both Class 1 and Class 2 uveal melanomas.
  - Laboratory research confirms that PRAME promotes uveal melanoma metastasis.
- PRAME expression is associated with specific driver mutations.
  - In Class 1 uveal melanomas, PRAME expression is associated with SF3B1 mutations and inversely associated with EIF1AX mutations.
  - This may allow PRAME to guide the choice of targeted molecular therapy in uveal melanoma.
- PRAME can be recognized as a tumor antigen by the immune system.
  - PRAME-directed T-cell therapies and vaccines are being developed and tested for PRAME-expressing cancers.
  - This may allow PRAME to guide the choice of immune therapy in uveal melanoma.

Choroidal Tumors

Choroidal Nevi

- benign-appearing atypical uveal melanocytes called nevus cells
- **nevus**: benign acquired or congenital tumors of neural crest-derived cells, including atypical melanocytes
- Halo nevus: depigmented annulus that surrounds the central pigmented portion of the nevus
- Giant choroidal nevus: basal diameter greater than or equal to 10 mm
- Nevus cells are believed to be modified, or atypical, melanocytes
- melanization starts between the 24th and 27th weeks of gestation, proceeding anteriorly until birth
- **Melanocytoma**: navus that are composed mostly of uniform, densely pigmented, and plump polyhedral cells (magnocellular nevi)
- **Ocular melanocytosis**: congenital hyperpigmentation of the uveal tract
- **nevus of Ota**: oculodermal melanocytosis, ocular along with trigeminal distribution
- **Prevalence**
  - Nevus: 1-6%
  - Halo nevus: 4.7%
  - Giant choroidal nevus: 1.5%
  - Melanocytoma: 0.05%
  - Ocular melanocytosis: 0.038%
- **systemic disease**
  - neurofibromatosis
  - Dysplastic nevus syndrome: 1) ill-defined or irregular borders; (2) irregular pigmentation; (3) accentuated skin markings, and (4) large size (>5 mm).[1] They tend to occur on sun-shielded skin (e.g., the scalp or bathing trunk area)
  - Bilateral diffuse uveal melanocytic proliferation (BDUMP):
- **Histopathology**
  - Immunohistochemical staining against S-100 antigen is the most sensitive
  - four main cell types
    - Plump polyhedral nevus cells
    - Slender spindle nevus cells
    - Intermediate nevus cells
    - Balloon cells
  - Malignant transformation was described in 4.6% of the reported cases of nevus of Ota and, with rare exception, the melanoma occurred in the pigmented eye
- Clinical Features

- Most nevi are incidental findings
- Visual field defects,
- visual loss
- flat or slightly elevated slate-gray tumors, with defined but not sharply demarcated margins
- Retinal pigment epithelial and Bruch's membrane changes
- Serous detachment
- Choroidal neovascular membrane

- Differential Diagnosis
  - Freckles: flat foci of increased choroidal pigmentation with irregular borders
  - Subretinal hemorrhages:
  - CHRPE
  - Small melanomas: A melanoma should be suspected if
    - the thickness of the tumor is >2 mm
    - there is orange pigment overlying the tumor
    - a neurosensory detachment is present without evidence of choroidal neovascularization,
    - visual symptoms are present
- The presence of any two of the following features is considered evidence of a **suspicious nevus**
  1. largest diameter between two and five disc diameters
  2. thickness >2 mm
  3. significant effects on the overlying structures with most importantly, the presence of orange pigment on the tumor surface
- Shields: The mnemonic **TFSOM UHHD** for the phrase: "To Find Small Ocular Melanomas Using Helpful Hints Daily" correlates to
  - *T*hickness >2 mm
  - subretinal *F*luid
  - visual *S*ymptoms
  - *O*range pigment
  - tumor *M*argin within 3 mm of the optic disc
  - *U*ltrasonographic *H*ollowness
  - absence of a surrounding *H*alo
  - absence of *D*rusen
- Factors predictive of metastases include posterior tumor margin touching the optic disc, documented growth, and greater tumor thickness.
- Management

- Nonsuspicious nevi: observation yearly
- Suspicious nevi: fundus photographs and ultrasound every 6 months
- Serous detachment and CNVM: anti VEGFs

Choroidal Metastases

- most common of adult intraocular tumors
- 10% of cancer patients have ocular metastases
- 20–40% are bilateral
- multifocal involvement of one eye occurs in approximately 20%
- Clinical Features
  - Asymptomatic
  - painless visual loss by involvement of the macular area or peripapillary retina or because of an associated, generally exudative, retinal detachment
  - painful visual loss as a result of neovascular glaucoma or metastatic iritis
  - blurred vision in 80%; pain in 14%; photopsias in 13%; red eye and floaters in 7%; field defects in 3%, and photophobia in 1%
  - **most common location:** posterior pole of the globe
  - present as yellow or white lesions (contrast to choroidal melanomas which are generally darkly pigmented)
  - often flatter than choroidal melanomas
- **primary cancer site**
  - women as follows: **breast**, 68%; **lung**, 12%; unknown, 12%; gastrointestinal, 2%; skin, 1%; renal, <1%; and other, 4%.
  - men, primary sites were: **lung**, 40%; unknown, 29%; gastrointestinal, 9%; prostate, 6%; renal, 6%; skin, 4%; breast, 1%; and other, 4%
- **Investigations**
  - FFA
  - OCT
  - USG
  - FNAB
- ***Differential diagnosis***
  - choroidal melanoma
  - choroidal osteoma
  - choroidal hemangioma
  - choroidal neovascularization with disciform scar
  - posterior scleritis

- **Management**
  - ***Conventional external beam radiation therapy***
    - D-shaped field designed to cover the posterior globe, bony roof, floor of orbit, and a portion of the optic nerve but shield the cornea and lens
  - ***Brachytherapy plaques***
  - ***Stereotactic radiosurgery***
  - ***Protons***

Choroidal Osteoma

- choroid and the retinal pigment epithelium are the most common sites for bone formation within the eye
- Intraocular ossification most often occurs as a dystrophic process
- choroidal osteoma is an unusual form of benign intraocular ossification containing healthy bone
- **healthy** young females in the second or third decades of life
- **pathogenesis**
  - speculated pathogeneses: inflammatory, traumatic, hormonal, metabolic, environmental, or hereditary
  - The mass is composed of dense bony trabeculae with endothelial-lined large cavernous spaces and small capillary blood vessels
- **Clinical features**
  - Asymptomatic
  - mild to severe visual blurring, metamorphopsia, and visual field defects corresponding to the location of the tumor
  - unilateral in approximately 75%
  - tends to be located in the juxtapapillary or peripapillary area, often with extension into the macula
  - location **anterior** to the retinal vascular arcades is **RARE** (**idiopathic sclerochoroidal calcification**: benign multifocal, bilateral process that typically occurs anterior to the retinal vascular arcades)
  - yellow-orange in color
  - Serous subretinal fluid can occur overlying choroidal osteoma
  - Choroidal neovascular membrane overlying osteoma has been found in 31% of cases by 5 years, 31–47% by 10 years, and 46–56% by 20 years
- **Investigations**
  - FFA: mild patchy early hyperfluorescence of the tumor that evolves to a diffuse intense late staining, lacy early hyperfluorescence due to overlying choroidal vessels

- ICGA: early hypofluorescence of the choroidal mass
- USG: high-intensity echo spike, **pseudo-optic nerve appearance**
- OCT
- FAF
- Roentgenography
- Computed tomography: radiopaque plaque of bone density
- Magnetic resonance imaging
- Radioactive phosphorus uptake
- Laboratory studies

- **Differential diagnosis**
  - amelanotic choroidal melanoma
  - amelanotic choroidal nevus
  - metastatic carcinoma to the choroid
  - circumscribed choroidal hemangioma
  - disciform macular degeneration
  - posterior scleritis
  - idiopathic sclerochoroidal calcification
  - choroidal cartilage
- **Management**
  - no known systemic metabolic or hormonal method for altering the growth of the choroidal osteoma
  - PDT
  - Laser
- **Prognosis**
  - prognosis is variable but the systemic prognosis is good.

Circumscribed Choroidal Hemangioma

- benign vascular hamartomas which occur in two forms: circumscribed and diffuse
  - circumscribed form is typically an isolated finding without systemic associations
  - diffuse form generally occurs in association with Sturge–Weber syndrome
- mean age at diagnosis 38 to 47 years
- **Pathology**
  - Hamartomas
- **Clinical features**
  - orange-red elevated masses

- accumulation of lipofuscin pigment (orange pigment) over the lesion, though this is often difficult to distinguish except with fluorescein angiography
- majority are posterior to equator
- usually solitary and unilateral
- Overlying subretinal fluid or serous retinal detachment
- Cystoid macular edema
- exudates, epiretinal membrane, and retinal hemorrhages
- blurred vision in up to 81%, visual field deficits, metamorphopsia, and floaters

- **Differential diagnosis**
  - choroidal nevus, amelanotic choroidal melanoma, choroidal metastasis, choroidal osteoma, and central serous chorioretinopathy
- **Investigations**
  - FFA: mild early lacy hyperfluorescence of the tumor in the pre-arterial and arterial phase, followed by moderate hyperfluorescence during the arteriovenous phase, and increasing hyperfluorescence through the late phase with variable amounts of late leakage
  - ICGA: characteristic pattern of rapid onset of fluorescence around 30 s which occurs much earlier than in other choroidal tumors, “wash out” phenomenon→ in late frames, the tumor demonstrates loss of dye resulting in a hypofluorescent appearance
  - USG: acoustically solid mass, dome-shaped
  - MRI: hyperintensity in contrast to vitreous on T1-weighted images, and hyperintensity or isointensity to vitreous on T2-weighted images
  - OCT: macular edema, epiretinal membranes, and subretinal fluid
  - enhanced depth imaging (EDI) technique:
- **Treatment**
  - Photodynamic therapy
  - Radiation
  - Transpupillary thermotherapy
  - Laser photocoagulation
  - Anti-VEGF injection

Choroidal Tumor Biopsy

- “Biopsy” may be defined as a surgical procedure intended to obtain a representative and sufficient specimen of cells or tissue for pathological or prognostic assessment. At least 4 different types of biopsy can be performed for a clinically identified tumor: excisional, incisional, aspiration, and exfoliative. The particular type of biopsy employed in a given patient depends on factors such as the anatomic site of the tumor, the diagnosis or differential diagnosis of the tumor, the planned analysis of the obtained specimen, and the anticipated benefits and risks of the procedure.

- Aspiration biopsy with small caliber needle is widely used in ophthalmology, especially for choroidal tumors, due to its limited invasiveness. Fine needle aspiration biopsy (FNAB) is becoming widely used because of the development of prognostic testing for uveal melanoma.
- **Indications**
  - **Diagnostic**
  - A diagnostic biopsy is performed primarily to establish a pathologic diagnosis in cases with an uncertain clinical diagnosis; by definition, the clinical diagnosis for the lesion prompting biopsy must be a differential diagnosis that includes at least 1 malignant neoplasm or a microbial intraocular tumor at a reasonably strong level of probability. A biopsy of this type is usually performed as a separate surgical procedure and not generally in conjunction with therapeutic intervention for the tumor; some exceptions to this timing rule occur, including (a) when cytopathologic slides are prepared and reviewed in the operating room by a pathologist and a decision to provide treatment at that time is based on the pathologist's verbal report and (b) the differential diagnosis is between 2 malignant intraocular neoplasms (eg, amelanotic choroidal melanoma vs. non-ophthalmic primary cancer metastatic to choroid) for which treatment by plaque radiotherapy is planned regardless of which tumor type is identified by cytopathology.
  - **Confirmatory**
  - A confirmatory biopsy is performed primarily (a) to convince a skeptical patient about the accuracy of a clinical diagnosis and appropriateness of recommended treatment or (b) to justify patient management that may be complex, expensive, or potentially complicated (eg, intravenous chemotherapy, external beam radiation therapy) to professional colleagues who will have to provide that therapy. By definition, the prebiopsy clinical diagnosis for a confirmatory biopsy must be a single tumor type about which there is no clinically relevant doubt. In Addition, a biopsy of this type is almost always clinical (ie, performed in the in vivo setting prior to any therapeutic intervention as a separate procedure).
  - **Investigational**
  - An investigational biopsy is performed to evaluate some aspect of performance of a particular method or set of instruments in a specific setting. A biopsy of this type may be clinical (in vivo) or performed following enucleation or resection (in vitro) and may be performed for tumors of any clinical diagnosis or differential diagnosis under IRB supervision.
  - **Prognostic**
  - A prognostic biopsy is performed to obtain a representative specimen of a tumor of a particular clinical type for prognostic classification using a validated method of specimen analysis performed in a CLIA-certified laboratory. A biopsy of this type may be clinical or performed after enucleation or resection.
- **Biopsy Techniques**
  - Nowadays, FNABs are mostly performed using 27-gauge, sharp, disposable, hollow lumen needles without an obturator connected to a disposable 20-inch plastic tubing and a 10-mL plastic syringe to obtain biopsy specimens. The needle length depends on tumor location and route.

- Clinical (in vivo) FNAB of posterior segment intraocular tumors whose anterior margin is located at or anterior to the ocular equator are performed trans-sclerally with a short (5/8 inch long) 27-gauge biopsy needle advancing into the choroidal tumor.
- Clinical (in vivo) FNAB of posterior segment intraocular tumors whose anterior margin is located posterior to the ocular equator are performed using a transvitreal approach via a lamellar scleral incision parallel to the limbus in the pars plana region (usually about 3.5 mm from the limbus) in the meridian of the tumor with indirect ophthalmoscopy visualization of the passage of the tip of the biopsy needle through the vitreous and into the visible intraocular tumor. A 27-gauge long (1.5 inch) biopsy needle is used for such biopsies. Tumors < 2 mm thick usually benefit from pending the needle tip to an angle of 45 to 60 degrees relative to the needle shaft to avoid perforating the posterior sclera.
- Clinical (in vivo) FNAB of posterior segment intraocular tumors whose anterior margin is located posterior to the ocular equator may also be performed using a vitrector cutter using a full pars plana vitrectomy approach.
- Post-enucleation and post-transscleral resection (in vitro) biopsies of selected tumors can be performed for investigational or prognostic purposes immediately following surgical excision. Most of the post-enucleation FNABs are performed by direct puncture of full-thickness sclera over the tumor (as localized by post-enucleation transillumination) in the intact eye.

- Intraocular tumors should be biopsied only if there is a substantial likelihood that they are malignant. Clinical FNABs of nonmelanocytic intraocular tumors are rare unless patient management is likely to be influenced by this invasive testing.

Retinal Detachment

Types

- separation of the neurosensory retina from the retinal pigment epithelium
- 3 major types
  - rhegmatogenous retinal detachment
  - traction retinal detachment
  - exudative (serous) retinal detachment

Rhegmatogenous retinal detachment

- one or more full-thickness retinal breaks.
- three factors needed
  1. existence of abnormal mobility of partially liquefied vitreous gel
  2. tractional forces that can precipitate a retinal break
  3. presence of a retinal break that will allow the passage of liquefied vitreous into the subretinal space
- convex, even bullous, surface,
- **Subclinical retinal detachments** are defined as having less than 1–2 disc diameters of associated subretinal fluid and usually do not progress, if asymptomatic
- Dialyses, in general and following trauma, are more common in the inferotemporal quadrant although most of the dialyses in the superonasal quadrant are associated with a definite history of preceding trauma

Traction retinal detachment

- tractional forces that mechanically pull the retina away from the underlying RPE
- diabetic retinopathy, PVR, penetrating trauma, branch retinal vein occlusion, and retinopathy of prematurity (ROP).
- traction is associated with a clinically apparent membrane. Such membranes typically have fibroblasts and glial and RPE cells as cellular constituents
- more concave surface and is likely to be more localized, often not extending to the ora serrata

Combined TR RD

- full-thickness retinal break and a significant tractional component
- often not bullous and have a concave appearance
- Combined tractional–rhegmatogenous retinal detachments are often seen in proliferative diabetic retinopathy, PVR, proliferative sickle-cell retinopathy, and penetrating intraocular injuries.

Exudative RD

- absence of a retinal break or vitreoretinal traction
- secondary to diseases of the choroid and RPE or of the retina itself

Nonrhegmatogenous Retinal Detachment

- three potential sources for fluid accumulation within or under the retina: vitreous fluid, retinal vessels, and choroidal vessels.
    - The main route for vitreous water turnover is by way of the retina, choroid and the vortex veins.
    - Choriocapillaries of the choroidal circulation, a single-layered capillary structure with numerous fenestrations on the vessel walls are freely permeable to the intravascular fluid.
    - The main mechanisms for keeping the retina in a dehydrated state are the presence of inner and outer blood–retinal barriers, and the fluid movement across the retinal pigment epithelium (RPE).

CSCR: Central serous chorioretinopathy

- area of serous detachment of the posterior retina usually in young and middle-aged healthy persons
- mostly self-limiting
- atypical manifestations: acute bullous retinal detachment and chronic CSCR.
- **Bullous retinal detachment**
    - long-term corticosteroid taken for systemic diseases; regular taking of herb drugs or be under steroid treatment for presumed Harada disease
    - acute onset with simultaneous or sequential involvement of the two eyes
    - multiple areas of serous RD in the posterior retina with lower bullous RD
    - multiple RPED
    - FA: shows multiple hyperfluorescent spots or patches with late enlargement; intense fluorescein leakage from the edge of the RPE detachment
    - ICG
    - OCT
    - CX: large RPE tear; broad retinal folding; submacular plaques or fibrotic bands; peripheral paravascular exudates; peripheral retinal telangiectasia, occlusion, or even fibrovascular proliferation
    - Management
        - steroids should be discontinued

- keep the head elevated during sleep
- FA-guided laser to the leaking points
- external drainage of SRF
- pars plana vitrectomy with perfluorocarbon liquid injection
- bevacizumab injection
- Photodynamic therapy (PDT) with reduced fluence

- Differential Diagnosis
  - Harada disease
  - PCV

- Chronic CSCR
  - Aka RPE decompensation, diffuse retinal pigment epitheliopathy
  - chronic steroid usage.
  - poorly defined areas of chronic persistent or recurrent retinal detachment in the posterior pole
  - FA: multiple areas of RPE disturbance with late staining or mild leakage
  - Management
    - Conventional laser or the more recently developed MicroPulse laser
    - PDT with reduced fluence
    - Intravitreal bevacizumab

- **Newer Therapies for CSCR**
  - **Photodynamic Therapy**
    - Evidence of the effectivity of PDT has been shown in a number of studies using various types of PDT, which are classified by fluence of laser and dosage of verteporfin (such as low-fluence PDT or half-dose PDT). In all types of PDT, verteporfin is usually infused over 8 or 10 minutes, followed by laser delivery at 689 nm at 10 or 15 minutes from the start of infusion in the area of the lesion targeted. The photoactivated verteporfin damages the vascular endothelium in the targeted area and leads to reduced choroidal perfusion, thereby decreasing choroidal hyperpermeability, a key factor in CSCR.
    - According to a 2014 meta-analysis, the probability of complete resolution of subretinal fluid when using half-dose PDT is statistically significant, with better results in terms of BCVA and reduction of subretinal fluid when compared to observation, and still significantly better than conventional slit lamp–based threshold laser. With the reduced dose or fluence/dose PDT, the risk of side effects is reduced but still present, with side effects including choroidal ischemia, neuroretinal thinning, choroidal neovascularization, or, very rarely, RPE tears. In Addition, systemic complications have to be considered, including skin damage from excessive exposure to sunlight after treatment.
  - **Microsecond Pulse Laser**

- A micropulse or microsecond pulse (MSP) laser has been introduced recently which uses a pulsed laser of either 810 or 577 nm, with 50-300 µs bursts within a 100-300 ms pulse duration envelope. This is limiting the thermal “injury” to the RPE below the photocoagulation threshold, where an up-and-down regulation of several gene expressions, including PEDF and VEGF and heat shock proteins, is triggered to initiate the treatment response. The MSP lasers generally result in an ophthalmoscopically invisible endpoint, complicating documentation and application in conventional laser systems. Using the navigated laser these shortcomings can be overcome, and a true confluency and a seamless documentation of the procedure can be ensured.

- MSP laser seems to be at least as effective or potentially superior to PDT in the treatment of chronic CSCR. PDT is effective; however, it bears the risk of side effects, such as choroidal neovascularization, and is an invasive procedure, while MSP did not show any side effects. While both conventional MSP lasers and Navilas are laser equivalent, a much lower fluence resulted in a higher rate of complete resolution in concordance with a statistically better BCVA improvement as compared to PDT.

Uveal effusion syndrome

- Middle-aged men with normal ocular size, presenting with unilateral or bilateral serous choroidal, ciliary, and retinal detachment
- Clinical Features
  - episcleral vessel dilatation; the anterior chamber is usually free of cells; intraocular pressure (IOP) is normal; there may be blood in the Schlemm's canal; vitreous cells
  - concentration of the subretinal fluid is 2.5–3 times that of the normal plasma
  - FA: in late stage, the leopard-spot pattern, which was not obvious in fundus examination; choroidal perfusion may be slow, and focal leaking areas in multiple places may be seen
  - UBM can clearly demonstrate ciliochoroidal detachment
- Pathogenesis
  - possibly related to congenital anomaly of the sclera and vortex veins hypoplasia
  - GAG accumulate within the sclera → decreased drainage of extravasated protein through scleral emissary channels
- Management
  - Vortex vein decompression with scleral resection
  - Gass: partial-thickness sclerectomies or full-thickness sclerectomies.
- Other Causes: nanophthalmos, dural arteriovenous fistula, scleritis, Harada disease, diffuse tumors of the uveal tract, prolonged hypotony

Coats disease

- non-familial developmental retinal vasculopathy

- young children-adults, unilateral
- **Clinical Features**
  - All vessels, arteries and veins alike, would be affected, showing telangiectasis combined with a large amount of hard exudates;
  - Exudates
  - hemorrhagic retinopathy is occasionally seen
- other abnormalities such as progressive facial hemiatrophy, facial scapulohumeral muscular dystrophy and deafness, or Alport syndrome
- somatic mutation on the NDP gene on chromosome Xp11.2.
- **Treatment**
  - laser or cryo aiming at the lesions to decrease exudates and preserve vision
  - Scleral buckling
  - Sector panretinal photocoagulation (PRP)
  - intravitreal injection of bevacizumab

Accelerated hypertension and pregnancy-induced hypertension

Proliferative Vitreoretinopathy

Pathogenesis

- complex cellular reaction representing a vitreoretinal wound-healing response that results in a characteristic clinical appearance
- 5–10% of RRD, 10–45% of post trauma cases
- most common cause of ultimate failure of a surgery for RRD
- initially, assumed to be primarily due to changes in the vitreous gel ("massive vitreous retraction", "massive preretinal retraction").
- involvement of cells was recognized, and the condition was re-termed "massive periretinal proliferation"
- **Retina Society Classification 1983:** did not reflect prognosis and surgical difficulty
- **Cologne classification**
- **Silicone Oil Study classification**
- pathological **hallmarks** of the advanced PVR include periretinal membrane formation, causing development of surface wrinkling and single or multifocal star-folds
- retinal break is a prerequisite for the development of PVR.
- it takes 4–8 weeks for PVR development after surgery
- ***Composition of membranes***
  - ***Hallmark:*** formation of periretinal fibrocellular membranes and intraretinal fibrosis
  - retinal glial cells, epithelial cells from the RPE and ciliary body, hyalocytes, blood-borne immune cells, fibrocytes, and finally myofibrocytes
  - ***RPE cells:*** epithelial–mesenchymal transition (EMT), proliferation, and directional migration of transformed RPE cells, resulting in the formation of traction-generating fibrocellular membranes in the vitreous and on both surfaces of the retina.
  - ***Glial cells:*** Müller cell gliosis
  - ***Blood-borne cells:*** Inflammation, macrophages and fibrocytes
- **Stimulation of cellular proliferation and migration**
  - Blood components: Serum, Thrombin, Fibronectin,
  - Platelet-derived growth factor (PDGF): PDGF-C
  - Transforming growth factor-β: tissue contraction
  - Monocyte chemotactic protein-1 (MCP1): migration of RPE cells
  - Basic fibroblast growth factor (bFGF): Fibroproliferative membranes
  - Hepatocyte growth factor (HGF): scattering of retinal cells, chemotaxis and EMT
  - Connective tissue growth factor (CTGF)
  - Epidermal growth factor (EGF)
  - Vascular endothelial growth factor (VEGF): cellular proliferation and vascular permeability
  - Cytokines: IL-6, IL-1β, TNF-α and interferon gamma

- **Biomarkers**
  - MMP-2 and -9
  - α1-antitrypsin, apolipoprotein A-IV, serum albumin, and transferrin
- **vicious cycle of proliferative retinopathy**: The breakdown of the retinal integrity is accompanied by breakdown of the blood–retinal barrier (BRB) and inflammatory tissue reaction. These processes result in an influx of blood-derived cells and soluble factors including growth and inflammatory factors, serum, fibrin, and metalloproteinases into the vitreous and retina. The factors stimulate the scattering, migration and proliferation of the cells of retinal and extraretinal origins followed by periretinal membrane formation. Myofibroblastic transdifferentiation of cells within the fibroproliferative membranes during epithelial–mesenchymal transition and extracellular matrix remodelling cause membrane contraction resulting in fixed (re)detachment of the retina.

Risk factors

- previous retinal detachment repair
- Previous trauma, prolonged inflammation of the posterior segment, viral infections
- retinal detachments with more than two quadrants involved
- coexisting choroidal detachment.
- large retinal breaks or giant tears, vitreous hemorrhage associated with retinal tears, multiple previous eye surgery, previous trauma to the posterior segment and pre-existing signs of localized PVR such as fixed folds
- detachments associated with a variety of systemic conditions such as Wagner disease, Stickler syndrome, Marfan syndrome, and familial exudative vitreoretinopathy
- The greatest risk period is 4–12 weeks after detachment surgery

Clinical Features

- cellular dispersion in the vitreous and on the retinal surface
- localized fibrocellular membranes
- fixed folds
- funnel-shaped detachment

Classification

Retina Society PVR Classification (1983)

A. Vitreous haze, vitreous pigment clumps

B. Wrinkling of the inner retinal surface, rolled edge of retinal break, retinal stiffness, vessel tortuosity

C. Full-thickness retinal folds in

C-1 One quadrant

C-2 Two quadrants

C-3 Three quadrants

D. Fixed retinal folds in four quadrants

D-1 Wide funnel shape

D-2 Narrow funnel shape (anterior end of funnel visible by indirect ophthalmoscopy with 20 diopter lens)

D-3 Closed funnel (optic nerve not visible)

Updated PVR Grade Classification (1991)

A. Vitreous haze, vitreous pigment clumps, pigment clusters on inferior retina

B. Wrinkling of the inner retinal surface, retinal stiffness, vessel tortuosity, rolled and irregular edge of retinal break, decreased mobility of vitreous

C.

CP 1–12 Posterior to equator, focal, diffuse or circumferential full-thickness folds, *subretinal strands

CA 1–12 Anterior to equator, focal, diffuse, or circumferential full-thickness folds, *subretinal strands, *anterior displacement, *condensed vitreous strands

Updated PVR Contraction Type Classification (1991)

- **Focal** → Posterior→ Star fold posterior to vitreous base
- **Diffuse** → Posterior → Confluent star folds posterior to vitreous base; optic disc may not be visible
- **Subretinal** → Posterior/anterior → Proliferation under the retina; annular strand near disc; linear strands; motheaten-appearing sheets
- **Circumferential** → Anterior → Contraction along posterior edge of vitreous base with central displacement of the retina; peripheral retina stretched; posterior retina in radial folds
- **Anterior** → Anterior → Vitreous base pulled anteriorly by proliferative tissue; peripheral retinal trough; displacement ciliary processes may be stretched, may be covered by membrane; iris may be retracted

Demerits of Retina Society Classification

- it ignores antero-posterior epiretinal proliferation and hence the importance of anterior traction in PVR
- says nothing about the degree of cellular proliferative activity at the time of the grading

Prevention

- Laser probably causes less breakdown of the blood–retinal barrier than cryopexy
- signs of early PVR may indicate the need for combined vitrectomy and scleral buckling rather than one or the other

Management

- ***Scleral buckling and PVR***
  - fundamental requirement for most eyes with established PVR
  - it is virtually impossible to remove the whole vitreous base.
- ***Vitrectomy and PVR***
  - vitrectomy to remove all vitreous gel, cellular and inflammatory material, blood, and fibroblastic membranes.
  - relieve all traction by division and peeling or delamination of fixed membranes and to remove as much as possible of the vitreous base
- ***Surgical steps for established PVR***
  - Anesthesia
  - Operative technique
  - Management of the lens in PVR
  - Core vitrectomy and removal of the vitreous base
  - Removal of epiretinal membranes and use of perfluorocarbon heavy fluid
  - Removal of anterior tractional membranes
  - Testing adequacy of relief of traction and relaxing retinotomy: tested by a complete fluid–air exchange
  - Removal of subretinal membranes
  - FAX
  - Creating chorioretinal adhesion and scleral indentation
  - Intraocular tamponade
    - SO: Standard or Heavy
    - GAS
- **Postoperative management**
- **Complications**
  - deliberate relaxing retinotomy for relief of traction was required in 29% of eyes treated in the silicone study
  - ***Intraoperative***
    - bleeding may occur during dissection of dense membranes
    - corneal edema, pupillary constriction, or lens clouding
    - Failure to flatten the retina with internal drainage and fluid–air exchange
    - Choroidal hemorrhagic detachment
    - Serous choroidal detachment
  - ***Early postoperative***

- Elevated intraocular pressure is the most common, occurring in 10–15% of eyes.
- overfill of intraocular gas
- overfill of oil
- persistent corneal epithelial defect
- Endophthalmitis

- ***Late postoperative***
  - regrowth of surface retinal membranes leading to retinal detachment and tractional retinal tears: 25-50%
  - commonest situation is inferior recurrence of retinal detachment with or without a new or reopened retinal break
  - **perisilicone proliferation**: small meniscus of vitreous fluid remains inferiorly when the patient is upright, protein, inflammatory and metaplastic cells and lack of tamponade in this area can lead to further proliferation
  - Macular pucker and discrete tractional membranes: 5-15%
  - prolonged intraocular SO.
    - Emulsification
    - late secondary glaucoma
    - Keratopathy: 27%
  - Cataract
  - late cystoid macular edema with or without preretinal membranes
  - cx associated with a scleral buckle
    - squint and double vision
    - low-grade infection

- **Medical adjunctive therapy**
  - Systemic prednisolone
  - subTenon's injection of long-acting Celestone or triamcinolone
  - Antiproliferative agents including 5-fluorouracil and daunomycin
- **Results**
  - A scleral buckle without vitrectomy successfully reattached up to 50% of milder cases
  - In current practice, up to 90% of all cases of PVR can be anatomically reattached
  - Functional success defined as improved visual acuity is more problematic, as any macula detached for more than a few days is unlikely to recover more than 10–20% of central vision

- **Macular pucker** has some cellular features in common but is usually not classified as PVR. It is not associated with retinal breaks and usually not complicated by retinal detachment.

Macular pucker has a much better overall prognosis compared with PVR, even though it can compromise central vision

- The formation of abnormal membranes on the outer retinal surface is clinically known as subretinal fibrosis. **Subretinal fibrosis** can disrupt the normal intercellular relationship between the photoreceptors and RPE, thus preventing the regeneration of photoreceptor outer segments after reattachment

Optic Pit Maculopathy

- **Cavitary Optic Disc Anomalies Associated with Macular Fluid / Detachment**
  - Typical optic disc coloboma
  - Optic pit and atypical coloboma
  - Morning glory disc anomaly
- **Pathogenesis**
  - Fluctuating pressure gradients along anomalous communications within disc cavitation induce migration of fluid into adjacent retinal tissue.
    - Schisis-like intraretinal fluid connecting with the optic disc is a nearly universal feature.
    - Fluid eventually percolates into subretinal space in most eyes.
    - Rare patients exhibit subretinal fluid alone.
  - Evidence for fluctuating pressure gradients
    - Subretinal migration of vitreous substitutes (gas, silicone oil, heavy liquid)
    - Vitreous gel incarceration into disc cavitation
    - Spontaneous waxing and waning of macular fluid
    - Observation of vitreous debris moving in and out of cavitation with digital pressure on globe
  - Source of macular fluid
    - Depending on pathoanatomy of congenital disc anomaly, macular fluid may be vitreous fluid, cerebrospinal fluid, or possibly mixture of both.
    - Age of patient may be clue (eg, extensive retinal detachment in 1-year-old child unlikely represents liquid vitreous).
- **Management**
  - Macular buckling
    - Posterior scleral indentation may close intraretinal fluid channels.
    - Experienced groups have reported excellent results.
    - Most U.S. surgeons are unfamiliar / uncomfortable with technique.
  - Vitrectomy alone
    - Hirakata and colleagues reported resolution of macular fluid in 90% of eyes.
    - Therapeutic mechanism unclear
    - Long-term recurrence rate unknown
    - Real-world failures and recurrences are common.
  - Titrated juxtapapillary laser photocoagulation followed by vitrectomy and gas tamponade
    - Laser performed at slitlamp immediately prior to vitrectomy

        - Red wavelength laser and contact lens stereopsis for maximum safety
        - Careful titration of power for thermal spread into middle retinal layers, but avoiding nerve fiber layer
    - Vitrectomy with peeling of posterior hyaloid (no internal limiting membrane [ILM] peeling)
- Vitrectomy and plugging of cavitation with autologous sclera
- Proposed vitrectomy adjuncts of questionable value
    - ILM peeling
    - Inner retinal fenestration
    - Vitrectomy with tissue adhesive or ILM flap over disc cavitation

Retinal Diseases in Pregnancy

- **Changes in Pregnancy**
  - Increase in serum cortisol levels
  - Increase in blood pressure, generally during third trimester
  - Increasing insulin resistance (decreasing glycemic control) during second and third trimesters
  - Increase in blood volume; reaches peak in second trimester
  - Hypercoagulability
- **Hypertensive Retinopathy and Choroidopathy**
  - Pregnancy-induced hypertension syndromes
    - Pre-eclampsia: hypertension, peripheral edema, and proteinuria (occurs in 5%-8% of pregnant women)
    - Eclampsia: pre-eclampsia plus seizures
  - Fundus findings
    - Retinal arteriolar constriction, cotton-wool spots, retinal hemorrhages, retinal edema, lipid exudates
    - Subretinal fluid (choroidal ischemia)
    - Ischemic optic neuropathy
  - In most cases, changes are reversible and normalises after delivery.
- **Exudative Retinal Detachment**
  - HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
    - Occurs in up to 15% of women with preeclampsia
    - Infant mortality in up to 25%
    - Bilateral exudative retinal detachment, yellow-white subretinal deposits, vitreous hemorrhage
    - Only effective treatment is prompt delivery.
  - Disseminated intravascular coagulation (DIC)
  - Thrombotic thrombocytopenic purpura (TTP)
- **Retinal vascular occlusive disease**
  - Postpartum Purtscher-like retinopathy
    - Typically occurs within 24 hours of delivery
    - Usually associated with complicated pregnancy
    - Often results in severe bilateral vision loss with only partial recovery
  - Retinal arteriolar occlusions from amniotic fluid embolism; rare, usually fatal
  - Retinal vein occlusion; most often in third trimester and postpartum period
- **Idiopathic central serous chorioretinopathy (ICSC)**
  - Pregnancy is a known trigger for active episodes of ICSC.

- Likely related to hypercortisolemia
- High rate of subretinal fibrin formation (up to 90%)
- Management
  - If no fibrin in or near fovea and patient near term, consider observation and expect resolution after delivery.
  - If fovea threatened by fibrin, consider OCTguided laser treatment (avoid fluorescein angiography and photodynamic therapy [PDT] if possible).

- **Diabetic retinopathy**
  - Retinopathy progression during pregnancy
  - Retinopathy progression occurs at double the rate in pregnant women compared with nonpregnant women.
  - After adjusting for HgA1C, pregnancy itself is associated with progression.
  - Diabetes in Early Pregnancy Study
    - Two-step ETDRS progression occurred in 55% of patients with moderate nonproliferative diabetic retinopathy (NPDR) at baseline.
    - Progression to proliferative diabetic retinopathy (PDR) occurred in 6.3% with mild NPDR and 29% with moderate NPDR at baseline.
  - Risk factors for progression are similar to those in patients who are not pregnant.
  - Diabetes Control and Complications Trial
    - Retinopathy in type 1 diabetes mellitus progresses at a faster rate during pregnancy.
    - Long-term risk of progression of early retinopathy is probably not increased by pregnancy.
    - Recommend increased surveillance during pregnancy and first year postpartum
  - Management
    - Eye examination during first trimester with follow-up visits determined by the severity of retinopathy (moderate NPDR, every 3-6 months; severe NPDR or worse, every 1-3 months)
    - Gestational diabetes does not require eye examination during pregnancy.
    - PDR
      - Recommend panretinal photocoagulation at diagnosis
      - Avoid anti-VEGF therapy
    - Diabetic macular edema
      - If mild, consider observation, since edema may resolve after delivery.
      - If treatment needed, consider focal laser or intravitreal triamcinolone.
      - Avoid anti-VEGF therapy if possible.

- **General Management Tips**

- Intravitreal medications
  - Triamcinolone does not achieve significant serum levels when given intravitreally and is likely safe in pregnancy.
  - Anti-VEGF agents: ranibizumab is cleared from bloodstream most quickly and has least effect on plasma VEGF, but comparative fetal safety data are not available.
  - Use intravitreal anti-VEGF agents in pregnant women only if absolutely necessary.
  - Consider routine pregnancy testing before starting injections in women of childbearing age.
- Angiography
  - Fluorescein angiography dye crosses the placenta and is present in breast milk for 72 hours, but no adverse fetal events reported.
  - Indocyanine green dye does not cross the placenta and is used for non-ophthalmic indications in pregnant women without reports of adverse fetal effects.
  - Where possible, use OCT and/or OCT angiography instead of invasive angiography.
- Verteporfin PDT
  - No data on gestational exposure in humans are yet available.
  - Where possible, use thermal laser instead of PDT.
- VR Surgery
  - It is prudent to avoid elective surgeries during pregnancy.
  - If surgery is absolutely necessary, have obstetrical team involved.
  - Local anesthesia is preferred over general anesthesia.
    - Lidocaine is considered safe for use during pregnancy.
    - Bupivacaine and mepivacaine should be avoided in pregnancy.

Ocular Trauma

- **1996, Ocular Trauma Classification Group**

International Society of Ocular Trauma Standardized classification

- **Eyewall:** Sclera and cornea
- **Closed globe:** The eyewall does not have a full-thickness wound
  - Contusion (no full-thickness wound)
  - Lamellar laceration (partial-thickness wound of the eye wall)
- **Open globe:** The eyewall does have a full-thickness wound
  - Rupture: Full-thickness eyewall wound caused by a blunt object; the impact results in momentary increase of the IOP and an inside-out injury mechanism
  - Laceration: Full-thickness wound of the eyewall, usually caused by a sharp object; the wound occurs at the impact site by an outside-in mechanism
  - Penetrating (single entry wound; no exit wound): Single laceration of the eyewall, usually caused by a sharp object
  - Perforating (separate entry and exit wounds by same agent): Two full-thickness lacerations (entrance + exit) of the eyewall, usually caused by a sharp object or missile
  - Intraocular foreign body (retained foreign object that caused entry wound): Retained foreign object(s) causing body injury and entrance laceration(s)

Closed Globe Injuries

Hyphema

- anterior chamber hemorrhage
- **Complications include:**
  - corneal blood staining
  - ghost cell glaucoma as a result of blocked outflow from clogging of the trabecular meshwork by erythrocytes
  - central retinal artery occlusion from elevated intraocular pressure
- **Investigations**
  - not indicated in most patients
  - blood coagulation tests (partial thromboplastin time, prothrombin time, bleeding time, platelet counts, and liver function tests)
  - sickle cell tests
- **Management**
  - prevention of rebleeding
  - Rebleeding has been reported to complicate up to 35% of cases
  - Corticosteroids, both topical (prednisolone acetate 1% q.i.d.) and systemic (prednisone 0.5–1.0 mg/kg per day), reduce iritis and ciliary spasm, increase

patient comfort, and theoretically stabilize the clot formation, thereby decreasing the rate of rebleed.

- cycloplegics, miotics, aspirin, conjugated estrogens, unilateral or bilateral patching, elevation of the head, and bed rest.
- oral epsilon-aminocaproic acid, both systemic (Amicar, Lederle Laboratories, Pearl River NY, given 50 mg/kg every 4 hours for 5 days) and topical (Caprogel, ISTA Pharmaceuticals Irvine, CA, given every 6 hours for 5 days)
- tranexamic acid (Cyklokapron, Pfizer, New York, NY) in reducing the incidence of secondary bleeding

- **Empiric criteria for surgical evaluation**
  - intractably elevated intraocular pressure (IOP) despite medical therapy (>60 mmHg for 2 days in sickle-negative patients; or >24 mmHg for more than 1 day in sickle patients)
  - total hyphema for more than 5 days with IOP >25 mmHg
  - corneal bloodstaining
  - persistence of hyphema occupying at least one-half of the anterior chamber volume.
- **Surgical techniques**
  - paracentesis
  - anterior chamber washout with a one-needle irrigation or irrigation–aspiration technique
  - washout with a two-needle technique, clot evacuation with a forceps or cryoprobe through a large limbal incision
  - clot evacuation associated with a trabeculectomy filtering operation

Lens subluxation and dislocation

- dislocation or subluxation is not a problem in itself. Patients can have 20/20 vision with a totally dislocated lens and aphakic correction
- Urgent intervention is indicated for cases of pupillary block glaucoma, intractable uveitis, or lens–corneal touch leading to corneal decompensation
- Cataract requires extraction by proper technique as per standard guidelines
- Iridodialysis can be repaired by McCannel suture technique

Vitreous hemorrhage

- from damage to blood vessels in the ciliary body, retina, or choroid
- managed accordingly

Commotio retinae

- seen after a contusive injury to the globe and appears ophthalmoscopically as retinal whitening.
- Edema involving the macula (termed Berlin's edema) can impart an appearance similar to a cherry-red spot.
- vision most often improves as the swelling resolves over a 3–4-week period

Chorioretinitis sclopetaria

Retinal detachment and macular hole

Open-globe injuries

- ***Preoperative evaluation***
  - visual acuity
  - 5/200 or better had a 28 times greater chance of salvaging acuity at this level
  - APD is a strong predictor
  - the “flat tire” sign: flattening of the posterior contour of the sclera, occult rupture, seen on CT
  - CT
  - MRI
- ***Repair of laceration***
- ***Management of IOFB***
  - traumatic endophthalmitis, particularly associated with the *Bacillus cereus*, is more commonly seen with IOFBs
  - Traditionally, IOFB removal within 24 hours of injury
  - **Three instruments** are commonly available for IOFB extraction: external magnets, intraocular forceps, and intraocular magnets
- ***Perforating injury***
  - 4.4% of lacerated globes

Sympathetic ophthalmia

- 0.3% and 1.9%
- High doses of prednisone (up to 200 mg/day) over the first 7–10 days may be particularly critical to the patient's prognosis

Surgical Retina

Vitreoretinal Surgery

History

- introduction of pars plana vitrectomy in the early 1970s by Machemer → 17-gauge (1.5mm diameter)
- 1974, O'Malley → 0.9mm (20-gauge).
- 1990, de Juan → 25-gauge (0.5mm diameter)
- Fuji et al → 23-gauge microcannular system and an array of 25-gauge instruments referred to as transconjunctival sutureless vitrectomy system (TSV)

23G

- **Advantages over 20-gauge vitrectomy**

1. Minimal trauma of the conjunctiva and sclera. No postoperative scleral thinning in the area of the sclerotomy. High postoperative stability of the sclerotomies
2. Less postoperative astigmatism.
3. Less postoperative discomfort.

- **Advantages over 25-gauge vitrectomy**

1. Instruments are less flexible and more effective.
2. Shorter operative time.
3. Brighter endoillumination.
4. Better handling of an acute intraoperative hemorrgae due to the more effective use of the fute needle by its larger inner diameter.
5. Longer durability of the instruments.
6. Lesser learning curve.

Mechanics

- Cutting: separation of a tissue into two parts.
- Peeling: Force along the axis of a collagen fiber bundle causes non-elastic collagen fibers to slightly stretch and ultimately to fail or separate. membrane peeling is inappropriate in diabetic traction retinal detachment cases.
- Shear: when force is applied along two opposing parallel edges moving past each other
- Fatigue failure: when repetitive motion, elongation, and compression weaken tissue structure and cause failure. Ultrasonic cavitation (fragmentation, phacoemulsification) is an example of this mode of cutting.

- Infusion system management
- Vitreous cutter considerations

- Ideal tissue cutting: that producing zero displacement of the tissue to be removed and no vitreoretinal traction
- High cutting rates (≥5000 cuts/minute) increase port-based flow limiting and thereby decrease pulsatile fluid flow and pulsatile vitreoretinal traction

- Minimizing forces required to hold tools increase the surgeon's proprioceptive sense (**Weber–Fechner law**) and decrease fatigue and tremor.
- **Surgical steps**
  - 20G vitrectomy is no longer gold standard (only used to remove intraocular foreign bodies and for a fragmenter to remove dense lens material)
  - no solid evidence that combining a scleral buckle with vitrectomy improves retinal detachment outcomes
  - ***Sclerotomies***
  - ***Vitreous removal***
  - **Lens management**
  - **Epiretinal membrane management:** peeling, segmentation, or delamination
    - Peeling: 25G or 23G, end-grasping ILM forceps
    - Delamination and segmentation: 25G or 23G curved scissors
  - **subretinal proliferation**
    - placoid, band-like, or annular in configuration
    - If the retina cannot be reattached with an undistorted macula due to subretinal proliferation, subretinal surgery is indicated
  - **Extrusion techniques**
    - foot pedal controlled machine-driven aspiration
    - Soft-tip 23/25G cannulas with low suction levels
    - for removing free blood products, PFO (perfluoro-n-octane), oil droplets, or small pieces of lens material from the retinal surface
    - preferable to using the flute cannula
  - **Interfacial surface tension management**
    - Air (gas) interface with aqueous (72 dyne/cm^2)
    - silicone–aqueous interface (40 dyne/cm^2)
    - Force due to interfacial surface tension is far more significant than buoyancy effects provided by air, gas, or silicone
    - purpose → to eliminate trans-hole fluid flow, restoring a transretinal pressure gradient
    - this effect is known as **rhegmatogenous confinement**:
      - addresses missed breaks
      - breaks from subsequent surface proliferation

        - the opportunity for retinopexy avoidance in inflamed eyes (can be performed weeks or months later when retinal edema, subretinal fluid, and inflammation have subsided)
    - Silicone and gases may increase reproliferation by sequestering cells and factors at the retinal surface, and decrease access of therapeutic agents to the retina
    - no scientific evidence that 5000 cSt oil has lower emulsification rates than 1000 cSt
    - best silicone oils are those with the highest electrical resistance, lowest vapor pressure, and 1000 cSt (centi-Stokes) viscosity.
    - ***Fluid–air exchange***
        - An air pump infuses air through the infusion cannula and maintains intraocular pressure while intraocular and subretinal fluid is removed with a proportionally controlled soft-tip cannula
    - ***Air–gas exchange***
        - isoexpansive concentration (25% SF_6 or 18% C_3F_8)
    - ***Liquid perfluorocarbon***
        - repositioning giant retinal breaks and can be used for removal of subretinal fluid as well as stabilization of the retina to offset membrane peeling forces

- **Fogging**
    - room temperature infusion fluid cools the IOL and the infused air is saturated with water vapor
    - capsule defect as well as discontinuity in anterior vitreous cortex is necessary for fogging to occur
    - Silicone IOL >> PMMA IOL >> Acrylic IOL
- ***Air–silicone exchange***
    - fluid–air exchange with internal drainage of SRF to reattach the retina should precede silicone infusion
- ***Perfluorocarbon–silicone oil exchange***
    - preferred over an intermediate step of fluid–air exchange followed by air–perfluorocarbon exchange in giant retinal break cases
    - reduced chance of posterior slippage of the giant break.
- **Retinectomy**
    - performed in conjunction with fluid–air exchange and internal drainage of SRF
- **Hemostasis**
    - Transient (approximately 5 minute) elevation of intraocular pressure
    - Endophotocoagulation
    - bipolar endodiathermy

- Diathermy causes a larger area of retinal necrosis than laser

- **Retinopexy**
  - should be used as little as possible
  - Continuous (painting) laser endophotocoagulation is preferable to rows of spots (results in more uniform tissue destruction and greater tensile strength)
  - PRP should only be used for neovascular retinopathies, never for PVR.
  - Avoid Cryopexy as far as possible.
- **Panretinal photocoagulation**
  - reduces VEGF production
  - causes the RPE to release an antiangiogenesis cytokine
  - increases choroidal oxygen transport to the retina

Complications

- Trochar Insertion: ALWAYS MEASURE
- Suprachoroidal Infusion
- Subretinal Insertion of Endo-illuminator
- Dislocated IOL and Capsular Tension Ring
- Iatrogenic Breaks during the Induction of Posterior Vitreous Detachment
- Iatrogenic Macular Hole during VMT Surgery
- Iatrogenic Breaks during the Delamination of Diabetic Traction Retinal Detachment
- Point Pressure Hemostasis during Diabetic Vitrectomy
- Iatrogenic Retinal Break during ERM Peeling
- Subretinal Brilliant Blue
- Peripheral Retinal Detachment during Macular Hole Surgery
- Subretinal Hemorrhage
- Macular Fold
- Subretinal Perfluorocarbon
- Subretinal Perfluorocarbon Injection during En Bloc Perfluorodissection
- Intraocular Foreign Body Dislodged on the Macula
- Suprachoroidal Hemorrhage
- Hemorrhagic Choroidal Detachment after “One Stitch” Vitrectomy Surgery
- Dislocated Phakic IOL
- Dislocation of the Tip of the Soft Tip Cannula
- Iatrogenic Peripheral Retinal Breaks during IOFB Extraction
- Peri-silicone Proliferation

Hypersonic Vitrectomy

- "Hypersonic vitrectomy" describes a method of vitreous removal in which ultrasonic power is used to drive the vitrectomy probe tip.
- The tip of the hypersonic vitrectomy handpiece oscillates at a frequency of approximately 1.7 million "cuts" per minute, creating a localized region of tissue disruption just within or at the surface of the port.
- This phenomenon is termed "hypersonic liquefaction." The emulsified material is drawn through the probe and out of the eye by conventional vacuum / aspiration methods. However, there exists a phenomenon of low suction that can be induced at the port of the device simply through the action of the hypersonic oscillation.
- Although ***"stroke" (longitudinal oscillation distance) had previously been identified as a key variable***, further research has revealed that ***modifications in ultrasound frequency*** have significant impact on performance.

Primary Vitrectomy

- term "primary vitrectomy" was introduced by **Klöti**
- Traditionally, scleral buckling (SB) was viewed as the gold standard treatment for uncomplicated RRD.
- Advantages
  - view of the retinal periphery is enhanced
  - identification of retinal breaks is rendered easier
  - achievement of complete intraoperative retinal attachment is possible
  - the risks of hemorrhage or retinal incarceration inherent to the external drainage procedure applied during SB is eliminated
  - technique is less likely to cause a refractive change
  - MIVS is less invasive, affords fast recovery, and is sutureless
- **Patient selection**
  - wide and bullous RD
  - older patients with a liquefied vitreous
  - RD with marked traction with different anterior posterior depth of breaks
  - presence of breaks in multiple quadrants
  - absence of an apparent retinal break in a pseudophakic patient
  - preoperative PVR grade C
  - giant tear-induced RD
  - macular hole RD
- **Surgical outcomes**
  - **SOSR (single operation success rate):** primary success rates for RRD repair by PPV range from 64–94%

- 40% of patients will not achieve reading ability, 10–40% will need more than one surgical procedure, and approximately 5% will suffer permanent anatomical and functional failure

- **Prognostic factors**
  - risk factors for surgical failure after PPV in the repair of RRD include
    - duration of symptoms
    - older age
    - extent of RD
    - macular detachment
    - involvement of inferior quadrants
    - absence of detectable retinal breaks
    - high myopia
    - hypotony
    - PVR-related risk factors such as pseudophakia/aphakia, uveitis, vitreous hemorrhage, and preoperative PVR.
    - previous lens extraction is a risk factor for development of PVR
- **Complications**
  - high rates of iatrogenic retinal breakage (0.78–24%)
  - crystalline lens damage (0.03–9%)
  - transient or persistent intraocular pressure increases have been reported in 15–24%
  - nuclear cataracts
  - retinal redetachment, with or without PVR, usually by new or missed breaks, or reopening of former breaks.
  - Several less serious complications include retinal incarceration at retinotomy sites (0.6–2.9%), corneal abrasion (0.6%), scleral rupture (0.2%), and choroidal effusion (0.5%),
  - MIVS: postoperative hypotony and endophthalmitis

Pneumatic Retinopexy

- **Ohm** performed the first intravitreal air injection for retinal detachment in 1911.
- In 1938, **Rosengren** reported the use of intravitreal air with drainage of subretinal fluid.
- 1973, Norton reported intravitreal sulfur hexafluoride (SF6) injection used with SB or vitrectomy for various surgical problems, such as giant breaks, large posterior breaks, and fishmouthing.
- Blodi and Folk treated detachments due to a macular hole using intravitreal gas.
- retinal detachments treated with “repeated insufflations of expansive gas” were described by Dominguez et al.
- Hilton and Grizzard introduced the term “**pneumatic retinopexy**” at the 1985 AAO.

- Lincoff's technique/ ballon: 1979
- SOSR 80%, increasing to 98% after reoperations
- **Basic principles**
  - ***Intraocular gases***
    - Sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8)
    - **three features**:
    - buoyancy: applies upward pressure on the detached retina
    - surface tension: closes the retinal break and prevents the bubble from passing into the subretinal space
    - isolation of retinal tears from intraocular currents
  - Diffusion and Expansion
    - Because of their low solubility in water, SF_6 and C_3F_8 tend to diffuse from the eye very slowly
    - the nitrogen and oxygen that are in solution in the surrounding tissues of the eye are much more soluble and pass relatively quickly into the gas bubble, following the law of partial pressures
    - **0.22 μm Millipore filter** is sufficient to render gas sterile

Gas	Typical dose	Average duration	Largest size	Average expansion
Air	0.8 mL	4 days	Immediate	No expansion
SF_6	0.5 mL	12 days	36 hours	Doubles
C_3F_8	0.3 mL	38 days	3 days	Quadruples

  - ***Retina–gas interface***
    - 0.3 mL gas bubble: 45° of arc of the retina
    - but it takes approximately a 1.2 mL bubble to cover 80–90°
- **Case selection**
  - Indications
  - Exclusion
    - Breaks larger than 1 clock-hour or multiple breaks extending over more than 1 clock-hour of the retina.
    - Breaks in the inferior 4 clock-hours of the retina.
    - Presence of PVR grade C or D.
    - Physical disability or mental incompetence precluding maintenance of the required positioning.
    - Severe or uncontrolled glaucoma.
    - Cloudy media precluding full assessment of the retina.
  - PR is especially advantageous in the management of the following six situations:
    - Macular breaks and other posterior retinal breaks.

- Redetachment or persistent detachment after scleral buckling
- Isolated tears under the superior rectus
- Filtering blebs
- Impending macular detachment
- Bullous detachment

Surgical technique

- one session, with cryopexy applied to the retinal breaks just before gas injection
- two-session procedure, with initial gas injection followed by laser photocoagulation 1 or 2 days later
- ***Anesthesia***
- ***One-session versus two-session procedure***
- ***Cryopexy versus laser***
- ***Applying retinopexy***
- ***Amount and type of gas to inject***
  - PR usually requires a gas bubble large enough to cover all detached breaks simultaneously for about 5 days.
  - moderately larger than the largest retinal break to prevent subretinal gas
  - approximately 1.0 mL
    - which requires an injection of 0.5 mL of pure SF_6.
    - room air at least 0.8 mL
- ***Sterilization of the ocular surface***
- ***Preparation of the gas***
- ***Performing a paracentesis***
- ***Injection of gas***
- ***Assessing intraocular pressure***
  - The patency of the central retinal artery :
    - If it is difficult to tell whether the artery is patent, the eye is compressed with gradually increasing force while monitoring with an indirect ophthalmoscope. If pulsation of the central retinal artery cannot be induced in this manner, it is probably closed
  - indentation tonometry (Schiøtz) gives falsely low IOP
  - 1 mL gas: the error of Schiøtz tonometry is approximately 8 mmHg for intraocular pressures in the range of 10–20 mmHg and approximately 15 mmHg for intraocular pressures in the range of 30–40 mmHg.
  - Do GAT.
- ***Instructing the patient***

- **Special procedures**
  - ***Fish eggs***
    - Multiple small intravitreal gas bubbles
    - To prevent
    1. Make sure that the needle tip is placed shallowly within the vitreous at the time of injection.
    2. Make sure that the injection site is uppermost.
    3. Inject moderately briskly, not too briskly, nor too slowly.
    4. Inject with the needle vertical
    - Management
      - strictly position patient to keep the bubbles away from retinal breaks
      - can be caused to coalesce by flicking the eye with a cotton-tipped applicator or gloved finger
  - ***Gas entrapment at the injection site***
    - probably trapped in the canal of Petit
    - forming a partial ring, variously described as the “bagel,” “donut,” or “sausage” sign
- **Postoperative management**
  - If the fluid is not resorbing
    - there may be a new or missed break
    - traction may be keeping the break open
    - the bubble may be too small
    - patient may not have maintained proper positioning.
  - As long as the fluid is not increasing, there are no detached retinal breaks, and the macula is attached, reoperation is not necessary
- **Results**
  - SOSR: 80% which increased with reoperation to 95%
- **Complications**
  - Operative
    - Incarceration of vitreous
    - Subconjunctival gas
  - Postoperative
    - New or missed breaks: 11-14%
    - PVR: 4%
    - Redetachment
    - Mild macular pucker
    - Persistent subretinal fluid

- Minimal epiretinal membrane
- Reopening of original break
- Vitreous haze, 3–8 days
- choroidal detachment
- anterior gas entrapment
- vitreous hemorrhage
- subretinal gas
- shift of subretinal fluid
- macular hole

Adjuncts to Treatment

Intraocular gases

- **Properties of an ideal intraocular gas**
  - Availability: Readily available, Cheap/not expensive
  - Biocompatibility and safety: Nontoxic, Odorless, Colorless, Inflammable, Not cause lens opacity
  - Variability in terms of longevity and expansile property: Water soluble
  - Stable when mixed with air
- **Gases investigated for intraocular use**
  - Nonexpansile: Air, Xe, N_2, He, O2, Ar, Kr, CO2
  - Expansile: SF_6, Clinical Features$_4$, C_2F_6, C_3F_8
- ***Functions of gas***
  - Internal tamponade:
    - spherical cap is the shape of gas bubble
  - Unfolding and folding of the retina
    - surface tension and buoyancy force of the bubble
  - Postoperative visualization
    - possible to glean a view of the upper fundus by looking through the gas bubble from lower flat surface
  - Replace globe volume
  - Reduces intraocular currents
- ***Dynamics of the gas bubble inside the eye***
  - Different phases of gas resorption:
    1. **Expansion**: most rapid in the initial 6–8 hours, and is similar for all gases
    2. **Equilibration**: maximum size, IOP may rise if the outflow facility cannot cope with the rapid increase, When partial pressure of all gases within the bubble equals that in the fluid compartment, the dissolution phase begins.

3. **Dissolution**: longest phase, tamponade is ineffective and no therapeutic effect can be achieved

- The time taken for complete resorption of the bubble also depends on other factors such as lens status, aqueous turnover, presence of vitreous, presence of periretinal membranes, ocular blood flow, and ocular elasticity. The lifespan of SF_6 and C_3F_8 may be more than twice as *long in phakic nonvitrecomized eyes than in aphakic vitrectomized eyes*.
- Special considerations when under general anesthesia
  - Nitrous oxide (N_2O) is, respectively, 34 times and 117 times more water-soluble than nitrogen and SF_6
  - wristband to wear, indicating clearly the type and time of intraocular gas injection.
- Response to changes in altitude
  - airplane cabin pressure is only equal to atmosphere pressure at an altitude of 8000 feet.
  - Climb rate occurs at roughly 2000–3000 feet per minute during airplane ascent
  - air bubble size may change during scuba diving

Preparation for injection

- Silicone tubing is first connected to the cylinder at one end, and to two 0.22 μm Millipore filters (Millex-GS) at the external end. A 50 mL syringe is then connected to the filters. The syringe is then flushed two to three times to remove air trapped within the tubing and filters. Pure gas is then drawn into the syringe to the desired volume.
- For pure gas injection, the syringe could then be connected to either a needle or the infusion for use.
- For air–gas mixture, the syringe should be disconnected from the cylinder at the junction between the two filters, having one filter still connected on the syringe. Sterile air is then drawn into the syringe to achieve the desired concentration of air-gas mixture.

Clinical applications and surgical techniques

- In vitrectomy for retinal detachments
- In pneumatic retinopexy
- In scleral buckling for retinal detachments
- In macular hole surgery
- In displacement of subretinal blood
- In postvitrectomy gas exchange

Postoperative care

- Head posture after intraocular gas injection
  - If the patient has good compliance to facedown posturing, precipitates could be noted on the central corneal endothelium, which are sometimes referred as “positioning spots”.

- Fundal exam in the postoperative period
- Intraocular pressure measurements
- Laser photocoagulation
- Vision change after surgery
- Changes in altitude

- ***Complications and management***
  - Cataract formation:
  - Raised intraocular pressure: 26–59%
  - Hypotony
  - Subretinal gas
  - Gas in the anterior chamber and corneal decompensation
  - Intraocular lens capture

Perfluorocarbon liquid PFCL

- initially designed for use as a blood substitute
- **Clark and Gollan** first used it as an oxygen transporter
- 1987, **Chang** pioneered its use in humans especially intraoperative use in retinal surgery
- **THIRD HAND of surgeon**
- ***Types and properties***
  - Straight chain: C_5 to C_9
  - cyclic compounds: C_5 to C_{17}
  - Remember, *carbon chain shorter than C5 are gases*
  - odorless, colorless, low viscosity, and have higher specific gravity and density than water
  - stable under high temperatures
  - do not absorb wavelengths of commonly used lasers
  - Molecular weight (g/mol): 438-670
  - Specific gravity: **1.7 – 2.03**
  - Surface tension (dyn/cm at 25°C): 14-20
  - Refractive index: **1.27-1.34**
  - Vapor pressure (mmHg at 37°C):
  - Viscosity (cSt at 25°C): 0.8-3
- **several advantages:**
  1. **optical clarity** allows manipulations under PFCL possible
  2. **high density and specific gravity** allows flattening of the retina and unrolling of folds
  3. avoids the need for a posterior retinotomy to **drain subretinal fluid (SRF)**

4. different refractive indexes from saline allow a **visible PFCL-fluid interface**, which aids intraocular maneuvers, and ease of removal
5. **Higher boiling point** than water and **no interference to laser wavelengths allows** endophotocoagulation under PFCL
6. **low surface tension and high interfacial tension** tends to hold it in a big bubble, and reduce the risk of PFCL migration into subretinal space through the break
7. low viscosity allows **easy injection and aspiration** even with small gauge vitrectomies
8. **immiscibility with water** resists incursion by saline and blood and allows a clear operating field despite intraoperative bleeding
9. **immiscibility with silicone oil allows PFCL–SO exchange**, which is helpful when treating giant retinal tears by reducing risk of slippage

- ***Technique***
  - Injection
    - dual-bore cannula preferred if 20G, not in 23G
    - syringe with a Luer lock is preferred
  - removal
    - PFCL–fluid, PFCL–air, or PFCL–SO exchange
    - flute needle or a soft-tip needle

- ***Indications for use***
  - Proliferative vitreoretinopathy
  - Vitreous base shaving: bimanual technique with the surgeon in control of the indentation
  - Giant tears **(previously Stryker table was used as described by Peyman)**
  - Ocular trauma: Traumatic RD, RIOFB, lens/ IOL removal
  - Dislocated lens
  - Suprachoroidal hemorrhage
  - Other indications
    - Retinal detachment associated with diabetic retinopathy, detachment associated with disc coloboma, detachment from retinopathy of prematurity, vitrectomy for endophthalmitis, displacement of submacular hemorrhage during surgical drainage, and the excision of subretinal membranes
- ***Complications and management***
  - Subretinal PFCL: 1) PFCL breaking into globules; (2) giant retinal tears; and (3) incomplete relief of tractional membranes on the retina.
  - Intraocular toxicity
  - Chemical
    - vasoconstriction of the retinal blood vessel due to high O2 capacity

        - loss of pericytes and endothelial cells of the retinal vessels
    - Mechanical
        - extended compression of inferior retina
        - loss of the outer plexiform layer, displacement of photoreceptor nuclei into the outer segments, and atrophy of the retinal pigment epithelium
        - due to the exclusion of water from the surface of the retina, thus, disrupting the potassium siphoning mechanism of the Müller cells
    - PFCL in the anterior chamber: visual disturbance, corneal endothelial loss, as well as rise in IOP
- **PFO vs. Oil Oxygen Transport**
    - "PFCs can hold as much as 3 times the oxygen as human blood."
    - Lower total oxygen carrying capacity observed for perfluorinated fluid emulsions is balanced by their much higher oxygen extraction efficiencies.
    - "Silicone oil hinders oxygen mass transfer compared to air-water system. Decreases of kLa up to 25% have been noted."
- **Removal of Retained Subretinal PFCL**
    - Surgical approach
        - Direct removal with 39/41/50-gauge needle
        - Inject BSS into subretinal space, followed by aspiration through retinotomy with flute needle.
    - Nonsurgical approach
        - Head tilting in eyes with enough subretinal fluid
        - Head tilting following injection of BSS into subretinal space

Silicon Oil

- first introduced by **Paul Cibis in the 1960s**
- injected into nonvitrectomized eyes as an aid to overcome traction
- ***Chemical properties***
    - repeating units of siloxane
    - Types
        - **Lighter-than-water silicone oils**
            - conventional SOs
            - polydimethylsiloxane PDMS
            - SG 0.97
        - **Heavier-than-water SO**
            - fluorosilicone oils
            - mixture of polymethylsiloxane and semifluorinated alkanes or alkenes

- SG 1.25–1.3
- highly purified.

- ***Physical properties***
  - Specific gravity: 0.97 of PDMS
  - Buoyancy:
    - More Buoyancy: **spherical cap** (sphere with a flat bottom) → larger area of contact, **GAS**
    - **Less Buoyancy**: normal sphere → less contact, SiO
  - Surface tension and interfacial tension
    - **Surface tension** refers to the **Van de Waal forces** between molecules, which always acts to try and reduce the surface for a given volume
    - **Interfacial tension** is a term relating to the surface tension between two immiscible liquids, it is a force that tends to keep a bubble as a whole. It should be above 6 mN/m
  - Viscosity
    - Normally refers to shear viscosity.
    - resistance of a fluid towards being deformed when under shear stress
    - 1000 to 5000 cSt
    - extensional viscosity:
    - dispersion refers to the break up of a large bubble of oil into smaller droplets.
    - Emulsification only occurs when this surface energy is reduced by the presence of surfactants.
- ***Indications***
  - Retinal detachments with proliferative vitreoretinopathy
    - **The Silicone Study**: SO was found to be as effective as C_3F_8, and better than SF_6, in reattaching the retina
  - Giant retinal tears
  - Severe proliferative diabetic retinopathy: stabilized the neovascularization in 83% of eyes, and achieved retinal attachment in 56%
  - Macular hole: lower closure rate with SO, gas is preferred now
  - Viral retinitis: SO tamponade, and ganciclovir implant insertion, 100% reattachment rate was achieved and 80% showed no CMV retinitis progression
  - Complicated pediatric retinal detachments
  - Retinal detachments associated with choroidal coloboma
  - Trauma
  - Endophthalmitis: Azad et al, better visual outcome
- ***Surgical techniques of silicone oil infusion***

- Practical differences between SO of different viscosities are threefold: (1) difficulty in injection is higher as the viscosity goes up; (2) ease of removal is higher as the viscosity goes down; and (3) risk of emulsification. The tamponade effect appears to be similar among SO with different viscosities
- Cataract invariably occurs following SO tamponade, even if SO is removed shortly after surgery (i.e., 6 weeks).
- Air–silicone oil exchange: In aphakic eyes, an inferior peripheral iridectomy (**Ando's PI**) needs to be done
- Perfluorocarbon liquid–silicone oil exchange

- ***Complications***
  - Silicone oil in the anterior chamber: aphakia, loose zonular support, blockage of the inferior peripheral iridectomy, or a break in the posterior capsule.
  - Glaucoma
    - pupil block glaucoma
    - overfill of SO
    - secondary open-angle glaucoma: drainage device is preferable over trabeculectomy (periocular fibrosis)
    - migration of SO into the AC
    - secondary angle closure glaucoma.
  - Chronic hypotony:
    - defined as having IOP ≤5 mmHg in the Silicone Study
    - increased aqueous uveal–scleral outflow and reduced production.
    - hypotony with IOP <10 mmHg is a relatively contraindication to SO removal.
  - Cataract formation
    - Causes: SO, vitrectomy or surgical trauma
  - Recurrent retinal detachment: 360° laser as prophylaxis in high-risk patients could be considered, as an adjunct to enhance the chance of anatomical success after SO removal
  - Emulsification: dependent on rate of eye movement, less with 5000 cSt
  - Keratopathy: 27% at the 24-month follow-up
  - Unexplained visual loss following silicone oil tamponade: sudden change in physiological environment affecting ionic exchange; in particular, potassium pumping by the Müller cells; or phototoxicity may be a potential mechanism

Heavy Temponade

- Agents used
  - perfluorocarbon liquids (PFCL)
  - Fluorinated SOs

- **Double filling**: combining the use of SO and fluorosilicone oil, SO and perfluorocarbon liquid, or SO with perfluorohexyloctane

- The semifluorinated alkanes and alkenes have a **specific gravity of around 1.35** at 25°C.
- force exerted by the heaviest PFCL amounts to 2–3 mmHg
- amphiphilic

Heavy Silicon Oil

- **benefits of heavy silicone oil in complicated retinal detachments are as follows:**
  - Breaks and retinotomy edges in the lower periphery can efficiently be supported in the upright position.
  - The instantaneous interruption of an open communication between the subretinal space / retinal pigment epithelial cells and the preretinal space through the patent break might lower the risks for a PVR development and a reopening break.
  - Displacement of the proliferative mixture of residual aqueous, inflammatory, and retinal pigment epithelial cells away from lower retina and the posterior pole could result in reduction of postoperative PVR and cystoid macular edema.
  - The tamponade effect at the posterior pole may lead to a faster and longer-lasting reattachment of the macula.
  - Redetachments should arise predominantly in the superior periphery where they are easier to treat with gas tamponades.
  - Redetachments should have a higher percentage of “macula on” situations.

- **Oxane HD**
  - Oxane HD (Bausch+Lomb; Toulouse, France) is a mixture of 5700 mPas PDMS and RMN-3 (perfluorooctyl-5-methylhex-2-ene), a mixed fluorinated and hydrocarbonated olefin. The surface tension and the interfacial tension of this agent against water are similar to those of perfluorocarbon liquids (41 mN/m), and its specific gravity is only slightly greater than that of water (1.02 g/cm3). Its high viscosity (3800 mPas) reduces the risk of early emulsification. The rate of inflammatory reactions related to the use of Oxane HD was reported as from 3% to 37% of treated patients.
- **Densiron 68**
  - Densiron 68 (Fluoron; Neu Ulm, Germany) is an mixture of F6H8 (30.5%) and PDMS 5000 mPas (69.5%); thereby, the viscosity was increased to 1387 mPas. This translated into a reduced ability for dispersion and emulsification, consequently irritability to ocular structures.
- **HeavySil (HSIL)**
  - HeavySil (ALCHIMIA srl; Padua, Italy) is made from the combination of high purity 75% silicone oil 5000 cSt (polydimethysiloxane) and 25% perfluoroalkyloxyoctane (C11H11F13o); it has a density of 1032 and a viscosity of 1500 cSt. Its stability and high affinity for silicone oil are due to the presence of a partially fluorinated ether instead of an alkane.

- **Densiron Xtra**
  - Densiron Xtra (Fluoron; Neu Ulm, Germany) is the latest heavy silicone oil on the market. It has improved the properties of Densiron 68 by exchanging the basic silicone. Densiron Xtra no longer uses a Newtonian 5000-cSt silicone oil but the Siluron Xtra with its dynamic viscosity. Siluron Xtra incorporates a mixture of 2 silicone oils with different viscosities; 90% of the Xtra is a 1000-cSt oil, 10% is a high molecular weight silicone oil with a viscosity of 2.500.000 cSt (423000da).
  - The advantages are (1) it is easier to inject, (2) injection time is dramatically reduced compared to Densiron 68, and (3) it could be injected through 25and even 27-gauge cannulas. Explantation is easy due to the bubble effect. Xtra has less emulsification risk compared to Densiron 68, and hence, less inflammation.

VITARGUS

- Phase 1 Trial
- Vitargus is an injectable, transparent, oxihyaluronic acidadipic acid dihydrazide hydrogel, transmitting all wavelengths of visible light. It has a refractive index of 1.34, close to that of human vitreous (1.33), and its injection into the vitreous cavity in liquid form should avoid the shear stress seen in preformed gels, while exerting sufficient compressive strength when it becomes a gel to perform its intended physiological function in holding the retina in place during healing.
- The optical properties allow visualization of the retina in the postoperative period as well as immediate visual rehabilitation for the patient. The gel is nonexpansile, and flying to altitude is possible. The gel does not require removal as it biodegrades.
- Potential applications of Vitargus as a vitreous substitute include retinal detachment repair, management of diabetic retinal hemorrhage with traction retinal detachment, and following repair of penetrating eye trauma, including intraocular foreign body removal.
- The study found that Vitargus was a well-tolerated vitreous substitute. There was no apparent toxicity to ocular tissues or systemic adverse events that could be attributed to the material. Its optical properties allowed the patients to see well, and the fundus was viewed immediately following surgery. Vitargus sets as a stable semisolid gel adhering to the retina and maintains its position without the need of face-down positioning. The unique properties of Vitargus hold promise for its use following vitrectomy surgery.

Scleral Buckles

- In the 1950s, Schepens/Lincoff introduced scleral buckling as a treatment for rhegmatogenous retinal detachments (RD).
- In the 1970s, Machemer developed the pars plana vitrectomy procedure.
- But, Scleral buckling is still the “gold standard” for uncomplicated rhegmatogenous RD.

Effects

Geometry of the eye

- ***Axial length***
  - increases or decreases in axial length, depending on the scleral buckle material, the location of the buckle, and the height of the buckle
  - spherical eye acquires the shape of a prolate spheroid
  - dumbbell shape at very high circumferential buckle heights
  - two effects where 1 >>>2

1. circumferential shortening, increases the axial length
2. invagination of the sclera around a broad encircling element with mattress sutures, contributes to a decrease in the axial length

- ***Refractive errors***

1. Astigmatic errors: high, anterior radial buckle
2. Spherical equivalent errors: caused by changes in axial length and lens position
3. High order abberations

- ***Volume changes***
  - predicted as a function of the following variables: (1) the axial length of the eye; (2) the buckle width measured anterior and/or posterior to the equator; (3) the buckle circumference; and (4) the buckle height.
  - #240: 0.5 ml
  - #276: 1.08-1.13 ml
- ***Scleral buckles and ocular rigidity***
  - measure of the elasticity of the eye
  - change in intraocular pressure for a given change in intraocular volume
- ***Scleral buckles and ocular blood flow***

- **Internal geometry of indentation:**

1. shape of the buckle
2. composition of the buckle (silicone sponge versus hard silicone)
3. suture placement with respect to the dimensions of the buckle
4. suture tension
5. distribution of tension from the suture to the buckle
6. intraocular pressure

- **factors decreasing indentation:**

1. placement of the suture bites too close or too far apart
2. high intraocular pressure

3. short suture bites in the sclera
4. loose sutures
5. use of a half-thickness sponge compared with a full-thickness sponge.

- **Factors that increased scleral indentation:**
  1. low intraocular pressure
  2. tight sutures
- **Fishmouth phenomenon**: circumferential shortening of the eye beneath an encircling buckle, Wedge-shaped buckles and radial scleral buckles minimize the risk.

- **Reattachment forces influenced by scleral buckles**

1. reduction of vitreoretinal traction by displacing the eye wall and retina centrally;

2. displacement of subretinal fluid away from the location of the retinal break and scleral buckle;

3. postoperative increase in the height of the scleral buckle;

4. approximation of the retinal break and adjacent vitreous gel;

5. increase in resistance to fluid flow through the retinal break, with consequent increase in the relative reattachment forces;

6. alteration in the concave shape of the eyeball, resulting in a change in the effect of intraocular currents that encourage liquid vitreous to enter the subretinal space.

RPE and Retina

- ***Forces that lead to retinal tears and detachments***
  - Vitreous traction: perpendicular, tangential, or oblique, radial traction on the retina is more likely to produce retinal breaks than is tangential traction
  - Fluid movement and retinal breaks: The inertia of the vitreous fluid may dissect under the flap of a horseshoe-shaped tear, resulting in retinal detachment.
  - Epiretinal membranes, cellular proliferation, and retinal breaks: Tangential tension in an epiretinal membrane with its associated radial retinal traction may exceed the adhesive force of the retina to the retinal pigment epithelium RPE.
- ***Forces that promote attachment of the retina***
  - Physiologic adhesion between retina and RPE
  - Thermal chorioretinal adhesions
    - **Diathermy**: strength reached upto **2 weeks**
    - **Cryopexy**: minimal change to the sclera compared with diathermy, maximum strength until about **2 weeks**
    - **Laser**: pigmented RPE and choroid, leading to a chorioretinal scar, starts within 24 hours of treatment and increases rapidly within **3 days**
  - Scleral buckles and vitreous traction
    - decrease vitreous traction on the retinal tear in RRD

- decrease vitreous traction in TRD
- **Hook's law**: The force exerted by a stretched spring is greater than a spring with minimal stretch

✣ Scleral buckles and traction on the retinal surface

- two vectors. The first is **tangential to the retina** and is caused by tension in the contractile epiretinal membrane. The second is directed **radially inward**, toward the center of the eye, and is a result of tangential traction on a curved surface
- reverses the direction of the radial inward force on the retina (F1) to an outward force (F2), thereby promoting retinal reattachment of an epiretinal membrane

✣ Scleral buckles and fluid movement

- distance between the RPE and a retinal tear is reduced
- displace vitreous fluid away from the tear
- diminish the flux of vitreous fluid through retinal tears

Lincoff's Rule

✦ Used to locate the primary break from configuration of RD.

	RD	Primary break
1	A shallow inferior RD in which the SRF is slightly higher on the temporal side	points to a primary break located inferiorly on that side
2	Inferior RD with equal fluid levels	A primary break located at 6 o'clock
3	In a bullous inferior RD	the primary break usually lies above the horizontal meridian
4	The SRF will revolve around the optic disc and then rise on the temporal side until it is level with the primary break	If the primary break is located in the upper nasal quadrant
5	A subtotal RD with a superior wedge of attached retina	points to a primary break located in the periphery nearest its highest border
6	When the SRF crosses the vertical midline above	The primary break is near to 12 o'clock, the lower edge of the RD corresponding to the side of the break

Techniques

✦ buckle = deformation of a structure under stress

✦ Explants or Implants

✦ implants are now of purely historical interest.

✦ **Preoperative assessment**

✣ Macular involvement

✣ ***Finding the retinal break:*** **Lincoff's rules**

✣ PVD

✦ ***Anesthesia***

- ***Positioning the head for surgery***
- ***Preparation and draping***
- **Surgical steps**
  - ***Conjunctival peritomy:*** limbal or 2 mm limbal frill
  - ***Slinging rectus muscles***
  - ***Examination under anesthesia and break localization***
  - Parallax errors may be avoided by draining subretinal fluid and then reforming the globe with air: DACE (drain air cryotherapy explant) procedure
  - ***Retinopexy***
    - Cryotherapy
    - Cryotherapy to the disc or macula occurs when the indentation from the shaft of the probe is mistaken for its tip →shaft indentation
    - Diode laser
  - ***scleral explant***
    - solid silicone tires: non-compressible
    - silicone sponges: easily deformable and compressible
    - **Watzke sleeves: cross acting "Watzke" forceps**
  - ***Scleral sutures***
    - durability, biocompatibility and ease of handling
    - Monofilament nylon and polyester
    - ½ to 2/3 of sclera
    - sclera is pseudolamellar: spatulated needle tends to glide
  - ***Subretinal fluid drainage***
    - no consensus on the role of subretinal fluid drainage
    - *Timing: DACE:* Drain air cryotherapy explant
    - *Location of drain sites:* adjacent to horizontal recti, in the bed of the buckle
    - *Drainage techniques:*
      - **Cut down techniques**
      - **Single-stage techniques: Charles,** Hypodermic needle, suture needle
    - Air injection
  - Encirclement
    - Early PVR
    - Very extensive scleromalacia
    - Extensive detachment in which breaks are difficult to detect (for example in some pseudophakic eyes with small anterior breaks and capsular phimosis).
    - Multiple breaks in three or more quadrants

- **Final examination of the retina**
  - **Spontaneous pulsation** of the retinal arteries indicates an intraocular pressure ***between the systolic and diastolic closing pressure***. Intraocular pressure greater than the systolic closing pressure of the retinal arteries causes a pale disc with thready vessels. Reducing the intraocular pressure, typically by paracentesis, is necessary to prevent permanent visual loss.
- **Closure**
  - **"ship to shore" principle**: sutures are passed from more mobile flaps of conjunctiva towards the incised edge

- **Outcomes**
  - success rate of 84% was achieved following a single operation
  - Functional success with recovery of central vision is somewhat lower than anatomical success

Scleral Buckle in Young Phakic RRD

- Excluding pediatric detachments and subsequent hereditary vitreoretinopathies, RRD in younger patients are often attributable to nonpenetrating ocular trauma, retinal dialyses, and high myopia.
- Late presentation is often encountered with high frequencies of macular detachment and proliferative vitreoretinopathy (PVR).
- Although often different at presentation, adolescent RRD has surgical and visual outcomes as promising as those of senile RRD.
- Scleral buckling remains the mainstay for repair of retinal dialysis. Single operation success rates (SOSR) of 87%.
- **Young patients with PVR**
  - PVR grade A: Reported SOSR after scleral buckling ranges between 80% and 87.5%.
  - PVR Grade C or higher: SOSR after scleral buckling reaches 58%.
- **Advantages**
  - Scleral buckling confers the distinct advantage of avoiding excessive vitreous manipulation.
    - The elevation of the hyaloid and complete removal of vitreous poses a challenge in this subset of patients who are often phakic.
      Incomplete vitreous dissection can engender or exacerbate PVR, causing redetachment.
    - It is easier to fix a scleral buckle failure than a PPV failure.
      A large series found that eyes that failed initial treatment with scleral buckling required approximately 30% fewer secondary retinal procedures, and a third less use of silicone oil, compared with those who underwent initial PPV or PPV plus scleral buckling.

- Scleral buckling preserves the crystalline lens and accommodation in adolescent patients.
- Scleral buckling provides circumferential support of a firmly adherent vitreous base in adolescents.
  - Highly myopic eyes: These eyes carry an increased lifelong risk of detachment.
  - Eyes that suffered nonpenetrating trauma: Subsequent retinal breaks can occur much later.
  - In both scenarios, the buckling effect reduces the risk of late tractional forces causing redetachment, whereas vitrectomized eyes with incomplete vitreous base dissection can have untoward outcomes.
- Scleral buckling may reduce positioning needs.
  - Adolescent patients may have unique rehabilitative needs (ie, early return to work, school, caring for others).
  - Less reliance on silicone oil tamponade and subsequent removal
- Scleral buckling in younger patients does not induce significant myopia and anisometropia.
  - One study found that the mean refractive change was only –0.6 D at follow-up of up to 4 years.
  - In younger patients still in the amblyogenic period, the myopic change after scleral buckle was found to be less than in the subsequent nonoperated eye, indicating reduced progressive scleral elongation.

Complications

- ***Recurrent retinal detachment:***
  - Inadequate buckle
  - Missed retinal break
  - Misplaced buckle
  - Fishmouthing
  - Proliferative vitreoretinopathy
- ***Glaucoma***
  - steroid response
  - buckle-related angle closure glaucoma occur without pupil block
- ***Epiretinal membranes***
  - commonest cause of visual loss after successful scleral buckling
- ***Extrusion/infection***
- ***Band migration***
- ***Diplopia***
- ***Anterior segment ischemia***

Prevention of RD

- Following anatomically successful surgery, visual acuity returns to 20/50 or better in only approximately 50% of cases
- initial surgical attempts to reattach the retina currently fail in approximately 10–20% of cases, and reoperations are unsuccessful in as many as 5% of cases
- **retinal detachment might be avoided by:**
  1. ***preventing vitreous liquefaction and associated PVD:*** no treatment yet
  2. ***relieving vitreoretinal traction***: by vitrectomy or by scleral buckling
  3. ***creating a chorioretinal adhesion around vitreoretinal adhesions and retinal breaks:*** laser and cryo

- **Risk factors for rhegmatogenous retinal detachment**
  - **Hereditary/congenital/developmental/degenerative:** Male, Hereditary vitreoretinopathies, Myopia, Lattice, Cystic retinal tuft, Degenerative retinoschisis, Retinal breaks
  - **Prior ocular surgery:**
  - **Prior ocular trauma:**
  - **Inflammatory:** CMV retinitis, ARN
  - **Other:** Fellow-eye nontraumatic retinal detachment

- **Symptomatic eyes**
  - photopsia and/or increased vitreous floaters associated with an acute posterior vitreous detachment
  - 15% of eyes with a symptomatic PVD develop retinal tears of various types
  - ***Tears with persistent vitreoretinal traction***
  - Horseshoe-shaped tears
    - cause retinal detachment in 33–55% of cases
    - do cryo or laser
  - Round tears
    - Operculated
    - persistent vitreoretinal traction on a nearby retinal vessel
    - treat or not ?? not given clearly
  - ***Tears unassociated with persistent vitreoretinal traction:*** no need to treat
  - ***Retinal holes and precursors of retinal detachment:*** pre-existing
- **Asymptomatic eyes without high-risk factors**
  - Lattice degeneration

- 30% of retinal detachments
- 94% of these detachments occur in primary (nonfellow) eyes
- 8% of the population
- **Subclinical retinal detachments**: subretinal fluid extending more than one disc diameter (Differential Diagnosis) from the break but not posterior to the equator

✣ Cystic retinal tufts
- 10% of clinical retinal detachments has tear near retinal tufts
- not worthy of prophylactic therapy

✣ Degenerative retinoschisis
- 6% of consecutive detachment
- prophylactic therapy is indicated only in the presence of obvious significant progression of subretinal fluid posterior to the equator

✣ Asymptomatic Retinal Breaks
- phakic nonfellow eyes is usually not recommended

✦ **Asymptomatic nonfellow eyes with high-risk factors**

✣ ***Myopic nonfellow eyes***
- Lattice degeneration associated with retinal holes did not correlate with degree of myopia
- Cystic retinal tufts and degenerative retinoschisis are not more common in myopic eyes
- Asymptomatic retinal breaks are more common in myopic eyes

✣ ***Aphakic and pseudophakic nonfellow eyes***
- HST is treated, no data for asymptomatic retinal holes

✣ ***Family history of retinal detachment***
- Stickler syndrome

✦ **Asymptomatic patients with retinal detachment in the fellow eye**

✣ Incidence is 9% to as high as 40%

✣ ***Phakic fellow eyes***
- Lattice degeneration
- Retinal breaks: horseshoe-shaped tears that are discovered in asymptomatic fellow eyes is sometimes recommended
- Giant retinal tears: increased vitreous liquefaction, and “white-with-pressure” in other eye is treated

✣ ***Asymptomatic aphakic and pseudophakic fellow eyes***
- 14–41%

- Precursors of retinal breaks
- Retinal breaks
- Giant retinal tears

- **Prophylactic therapy in eyes undergoing vitreoretinal surgery**
  - During silicone oil removal in previously operated eyes: 360 EL recommended
  - During primary vitrectomy for nonretinal detachment: subsequent RD in 11.4% of the nontreated cases and in 3.5% of those that were treated
  - During pneumatic retinopexy

Retinotomies and Retinectomies

- **Retinotomy**: cutting the retina, vary from a small hole created for drainage of subretinal fluid or removal of a subretinal membrane to a 360° cut to release massive peripheral traction
- **Retinectomy**: excision of retina, may mean limited excision of the fixed edge of a retinal flap or total excision of peripheral fibrotic retina.

- **Drainage retinotomy**
  - retinal hole created to allow removal of subretinal fluid
  - posterior drainage retinotomy is less frequently used today
  - after as complete a removal as possible of periretinal membranes
  - unimanual, bipolar endodiathermy probe: complete hemostasis and whitening
  - **Technique**
    - Surgical technique in conjunction with perfluorocarbon liquid (PFCL)
    - Surgical technique without PFCL

- **Retinotomy to gain access to the subretinal space**
  - Subretinal foreign body
  - Removal of subretinal PFCL
  - Retinal or subretinal mass
- **Retinotomies to mobilize retina: macular translocation**
  - Retinotomies to obtain abnormal retinal tissue: retinal biopsy
  - Retinectomy for treatment of intractable glaucoma
- **Relaxing retinotomy and retinectomy**
- ***Indications***
  - Retinal incarceration in traumatic or surgical wound

- Proliferative vitreoretinopathy
  - Focal contraction (star fold)
  - Diffuse contraction
  - Circumferential contraction
  - Intrinsic retinal contraction
  - Anterior retinal displacement
  - Extensive fibrous periretinal proliferation
  - Contraction and fibrosis of flap of giant retinal tear
- Proliferative vascular retinopathy
- Inner wall of congenital retinoschisis

Anterior retinal displacement

- important cause of retinal detachment with PVR and is primarily found in patients who have undergone a previous vitrectomy.[
- vitreous base pull peripheral retina anteriorly to the pars plana, pars ciliaris, or even to the posterior iris

Complications

- Hemorrhage
- inability to unfold and reattach the retina
- hypotony, visual field loss
- recurrent fibrous proliferation from the retinectomy site
- persistent traction leading to retinal detachment when the retinectomy is too small.

Retinectomy

- Retinectomy (Charles 1978) is defined as removing all retina, vitreous, and epiretinal membrane anterior to a circumferential so-called relaxing retinotomy (Machemer 1978).
- Retinectomy produces less hypotony than relaxing retinotomy, probably because it involves debulking of proliferating retinal pigment epithelium (RPE) and glial cells as well as elimination of substrate (scaffold), extending from the posterior edge of the vitreous base anteriorly to the ciliary body.
- If lensectomy is required, rather than leaving the capsule so a sulcus IOL can be implanted at a later date, a total capsulectomy should be performed using end-grasping forceps. Leaving capsule results in adherence to the iris, concave iris, epiciliary membranes and hypotony, and closure of inferior peripheral iridectomy by fibrous proliferation. Residual lens epithelial cells associated with remaining capsule can be highly reactive and cause inflammation, which leads to ciliary body membranes and resultant hypotony and concave iris.

- Debulking of proliferating RPE and glial cells also reduces recurrent proliferative vitreoretinopathy (PVR). All silicone oil reoperations should be performed under oil; forceps membrane peeling, subretinal surgery, and retinectomy work very well under oil. There is no need to remove oil and use liquid perfluorocarbons and then replace the oil at the end of the case in PVR reoperations with oil present. These Additional unnecessary steps add time and cost as well as increasing inflammation. Liquid perfluorocarbons often become subfoveal in PVR cases. Further, there is no need for buckles in PVR cases. Buckles cause, on average, a 2.75 D myopic shift—they damage the conjunctiva and episclera, making glaucoma surgery less effective; cause strabismus, pain, slight ptosis, and ocular surface disorder; and increase operating time and cost.
- Many surgeons currently perform retinectomy under BSS or, even worse, under liquid perfluorocarbons. Retinectomy should be performed under air as a final step in the reattachment experiment as a subset of interface vitrectomy.
- The steps in the reattachment are as follows: (1) remove all apparent vitreous traction, including anterior loop traction, (2) perform inside-out forceps membrane peeling for all apparent, peelable epiretinal membranes, (3) remove or segment subretinal bands causing retinal elevation using punch-through retinotomy without using diathermy or cutter retinotomy, (4) initiate drainage of subretinal fluid through existing retinal breaks or a posterior drainage retinotomy if needed, (5) start fluid–air exchange when the height of the retinal detachment stops decreasing, (6) perform simultaneous drainage of subretinal fluid and fluid–air exchange until the retina reattaches, subretinal air appears, or the reattachment process stalls, (7) perform vitrectomy under air if residual vitreous traction is identified, (8) perform forceps peeling of epiretinal membrane under air if Additional membrane is identified, (9) use punch-through retinotomy and end-grasping forceps to remove subretinal bands under air if bands are preventing reattachment, and (10) if the retina remains partially detached, use incremental retinectomy under air, using diathermy or endolaser hemostasis only to large vessels. If 270-degree retinectomy is needed, extend to 360 degrees because experience has shown the remaining 90 degrees will typically contract later.

Macular Translocation

- 1983, Lindsey first proposed
- **Machemer** published the first human surgical cases in 1993.
- original MTS360 technique: PPV with transscleral injection of subretinal fluid with 360° retinectomy, removal of subretinal blood and choroidal neovascularization (CNV); partial fill with silicone oil; retinal translocation; complete silicone oil fill, and finally laser retinopexy.
- retinal rotation results in significant cyclotorsion, extraocular muscle surgery to counter-rotate the globe is used routinely to manage the cyclotropia
- **limited macular translocation (LMT):**
  - **De Juan**: shorten the sclera following detachment of the superotemporal retina across the macula
  - variable and limited distance of macular displacement, this procedure has decreased in use
- **Principles**

- relocate the fovea to a new location of healthier subretinal tissues in order to preserve and maintain foveal function to maximize visual acuity
- MTS360: average foveal displacement of 3500 µm
- LMT: maximum translocation distance of 1500 µm
- translocating the macula upward off:
  - position the blind spot in the superior visual field
  - to position the macula in an optimal superior location for silicone oil tamponade
  - to avoid placing the macula over RPE that has been in an area of chronic exudate or hemorrhage, which is more likely inferior to the macula
  - to allow for the most effective surgery for the cyclotropia since advancing the inferior oblique produces more torsional effect than advancing the superior oblique.

Indications

- Bilateral disease
- Severe loss of central vision in second affected eye for no more than 6 months*
- Best-corrected Snellen visual acuity between 20/50 and 20/400 in the surgically treated eye

Contra-Indications

- No light perception visual acuity
- Previous thermal laser treatment of fovea
- Other ocular disease

Surgical technique

MTS360

- Complete pars plana vitrectomy with elevation of the posterior hyaloid
- close shaving of the vitreous base 360
- Retinal detachment is induced with subretinal fluid injection through peripheral retinotomy
- After total RD → peripheral retinotomy
- PFCL to stabilize
- Relocation
- typically approximately 45° off the CNV bed, which equates to the center of the old CNV bed under the inferotemporal arcade
- laser

Limited macular translocation

- Rectus traction sutures are placed prior to vitrectomy under the LR, SR or IR according to desired location
- 5-6 sutures

- creates chorioscleral infolding

- ***Positioning***
  - face-down positioning or alternating side-to-side positioning
- ***Extraocular muscle surgery following macular translocation***
  - translocation that occurs during MTS360, often 30–45° in an upward direction, the amount of torsion exceeds the maximum amplitude of cyclofusion (typically around 15°)
  - Freedman technique: surgery 8 weeks after the MTS360
  - Eckardt technique: Simultaneous extraocular muscle surgery is performed during the initial MTS360 procedure
  - windmill technique:
- **Complications**
  - RD is the most common complications with a prevalence of 7.8–42.8%.
  - Recurrence of CNV: 0-27%
  - CME:0-40%
  - ERM: 6-28%
  - Macular Hole
  - Hypotony
  - Keratopathy

Diagnostic and Therapeutic Vitrectomy

Indications of diagnostic Vitrectomy

- Infectious uveitis: Endophthalmitis, Vitritis, Retinitis, Choroiditis, Retinal vasculitis
- Noninfectious uveitis: Autoimmune uveitis, Primary intraocular lymphoma, Carcinoma metastasis, Choroidal melanoma
- ***Techniques***
  - Preoperative preparation: Standard
  - Vitreous sampling
    - 3-port pars plana vitrectomy (PPV)
    - vitreous cutter connected directly to a 3 or 5 mL syringe: 1.5 mL can be obtained
    - using continuous air or perfluorocarbon liquid (PFCL) infusion:

Indications for Therapeutic Vitrectomy

1. media opacity causing significant visual loss
2. intractable cystoid macular edema (CME)

3. other vitreoretinal complications, including tractional retinal detachment, rhegmatogenous retinal detachment, macular pucker, hemophthalmos, hypotony, or macular hole

Common indications for biopsy

- Vitreous: Endophthalmitis (bacterial or fungal), Intraocular lymphoma, Retinitis with associated vitritis
- Retinal: Retinitis (atypical or not responsive to empiric therapy)
- Choroidal: Tumor, Choroiditis (atypical or not responsive to empiric therapy

Treatment of Persistent Hypotony in Post-VR Surgery

- Major causes
    - Ciliary body abnormalities
        - Anterior fibrous proliferation/PVR
        - Ischemia
        - Trauma
    - Choroidal detachment
    - Surgical or traumatic filtering bleb
    - Uveoscleral outflow abnormalities
- **Long-term Effects of Chronic Hypotony**
    - Macular edema
    - Choroidal folds
    - Optic nerve edema
    - Uveal edema
    - Reduced vision
    - Phthisis
- **Management**
    - Ibopamine: Sympathomimetic prodrug of epinine; dopamine 1 receptor agonist
        - Increased aqueous production leads to increased IOP.
        - Severe ocular irritation limited completion of trials and clinical usage.
    - Viscoelastic in the anterior chamber Viscoelastic in the vitreous cavity Fluid–gas exchange
      Silicone oil
    - Steroids: Increase IOP by 25%-75%
        - Topical
            - Difluprednate > dexamethasone, prednisolone > fluoromethalone, hydrocortisone, rimexolone

        - 25%-30% increase in IOP
    - Periocular: triamcinolone (40 mg), 25%-50% > 5 mmHg ↑ IOP
    - Intravitreal
        - Triamcinolone: 20%-50% > 5 mmHg ↑ IOP
        - Dexamethasone implant: 25+% > 10 mmHg ↑ IOP
        - Fluocinolone implant: 75% needed IOP-lowering meds; 36% needed incisional surgery

Subretinal Delivery for Gene and Cell Therapy

- Subretinal delivery gives direct surgical access to target retinal pigment epithelial cells (RPE) and retinal cells/photoreceptors.
- FDA approval in 2017: subretinal delivery of ***voretigene*** for RPE65 Leber congenital amaurosis and RPE65 retinitis pigmentosa
- **Types**
    - **Transvitreal Subretinal Delivery After Pars Plana Vitrectomy**
        - Used for most retinal gene and cell therapy studies
        - good safety profile, familiar procedure, and direct visualization, improved precision with MicroDose Injection kit, which is performed with surgeon foot pedal control via viscous fluid injection (VFI) system
        - ***41-gauge cannula*** to subretinal space with simultaneous foot pedal injection (optional intraoperative OCT)
        - MicroDose syringe allows measured subretinal volume, typically 100-250 µl
    - **Transvitreal Subretinal Delivery Without Pars Plana Vitrectomy**
        - A subretinal delivery method that may reduce complications of pars plana vitrectomy (for example, cataract progression) is transvitreal injection to the subretinal space without vitrectomy.
        - This technique is being considered in a gene therapy clinical trial. Instrumentation is in development.
    - **Ab Externo Subretinal Delivery**
        - The retina and RPE are accessible target tissues, with vitreous surgery techniques for delivery of therapies to the subretinal space; however, transvitreal approaches necessitate a retinotomy.
        - Ab externo approaches to the subretinal space may be less invasive, may avoid vitrectomy and vitrectomy complications like progressive cataract, and may deliver more precise subretinal dosing.
            - **New FDA-approved instrumentation:** flexible, dual bore catheter with ***38G microadjustable*** advancing microcatheter and positioning system
            - Ab externo suprachoroidal to subretinal procedure
- Preoperative and Intraoperative Imaging Technology May Improve Subretinal Delivery

- Suprachoroidal Injection Is Being Explored to Simplify Delivery of Gene And cell and Other Retinal Therapies
- **Since 2012, the US FDA has approved > 1100 gene therapy trials.**
  - Achromatopsia: CNGA3
  - Achromatopsia: CNGB3
  - Choroideremia
  - Leber congenital amaurosis (LCA) RPE65
  - LCA: CEP290
  - Stargardt: ABCA4
  - Ushers: MYO7A
  - ProQR USH2A
  - X-linked retinitis pigmentosa (XLRP): RPGR
  - X-linked retinoschisis (XLRS): RS1
- **Complications of Gene and Cell Therapies**
  - Presurgery: Manufacturing, Pharmacy
  - Injection: Position, fluid, Foveal detachment
  - Immune response: Immune privilege, Immunosuppressives
  - Wound healing: Mechanical issues, Cell reaction

Pharmacology at Surgery

Pharmacologic vitreolysis

- PVD involves both syneresis (liquefaction) and synchysis (separation).
- spontaneous PVD is very often incomplete
- concept initially introduced by **Sebag** in 1998
- ***Enzymatic vitreolysis***
- Microplasmin
  - recombinant protein that contains the catalytic domain of human plasmin
  - nonspecific serine proteases cleaving a variety of glycoproteins such as fibronectin, laminin, fibrin and thrombospondin
  - 125 µg microplasmin was associated with a greater likelihood of induction and progression of PVD than placebo injection
- Plasmin
  - Autologous plasmin
  - transient reduction of the b-wave amplitude in the electroretinogram
- Hyaluronidase
  - potential to liquefy the vitreous, but does not induce a PVD in animal models

- Dispase
  - preferentially cleaves fibronectin and type IV collagen
  - retinal bleedings, epimacular membrane formation, abnormalities in the electroretinogram responses and ultrastructural retinal damage
  - not evaluated further

Antiproliferative agents

- colchicine, daunomycin and 5-fluorouracil
- alkylphosphocholines (APCs)

TPA

- Read from ARMD chapter

Dyes

- Read from Macular Hole chapter

VEGF

- Michaelson first suggested that a diffusible "Factor X" from the retina stimulated the retinal and iris neovascularization seen in diabetic retinopathy
- In 1989, **Napoleone Ferrara** and colleagues identified a molecule in the conditioned media from bovine pituitary follicular cells that promoted the proliferation of endothelial cells; they called it vascular endothelial growth factor (VEGF)
- Write other things from ARMD/DME Chapter.

Artificial Vision

- Foerster, a German neurosurgeon, observed that electrical stimulation of the visual cortex caused his subject to detect a spot of light (**phosphene**).
- **Giles Brindley**: 80-electrode device onto the visual cortex of a blind patient
- 625 electrodes implanted in a 1 cm^2 area near the foveal representation in the visual cortex could produce a phosphene image with a visual acuity of approximately 20/30 and reading rates near 170 words/minute with scrolled text and 100 words/minute with fixed text. Further, a degree of learning was noted as walking speeds increased five-fold during 3 weeks of training
- **The Argus II Retinal Prosthesis System (Second Sight Medical Products)**
  - CE Mark was obtained in 2011, allowing the commercialization of the Argus II System in the European Economic Area.

- Over 150 commercial patients have been implanted worldwide, and including clinical trial subjects, Argus II has demonstrated acceptable safety in this blind population and proven reliability with longterm functionality beyond 8 years.

Nano-Retina

- The creation and use of materials and devices at the size scale of intracellular structures and molecules; involves systems and structures on the order of < 100 nm

Optogenetics

- Concept: Virus-induced expression of lightactivated molecules linked to ion channels in neurons allows the neurons to generate an electrochemical signal when exposed to light.
- Method of delivery: Either intravitreal injection or subretinal injection, depending on the virus used to deliver the photosensitizer DNA to the target neurons
- Device: Molecule whose shape changes when exposed to light; this molecule may activate ion channels directly (eg, channelrhodopsin-2) or through second messenger systems (eg, OptomGluR6, rhodopsin).

Photoswitches

- Concept: Light-stimulated change in configuration (eg, light-induced trans-cis transition) causes molecules to block / open native ion channels in neurons when exposed to light.
- Device: A photochromic ligand that uses an azobenzene photoswitch to enable light-induced isomerization from the trans to the cis configuration, which alters binding to native ion channels in retinal neurons

Quantum dots (QDs)

- Concept
  - Light generates electric current in nanoscale semiconductor.
  - Local electrical field stimulates adjacent retinal neurons (eg, by activating voltage-gated ion channels).
- Method of delivery: Intravitreal injection of colloidal suspension of cadmium-selenium zinc oxide-biotin QDs (~10^{13})

The Role of Neuroprotection in Retinal Diseases

- **Basics of Apoptosis and Cell Signals**
  - **Apoptosis is Cell Suicide.**
  - Normal process of genetically programmed cell death that destroys cells that are injured or unneeded
  - Apoptotic cell morphology
    - Shrinkage of cellular nucleus and cytoplasm
    - Chromatin condensation
    - Formation of apoptotic bodies
    - Internucleosomal DNA fragmentation
  - Debris from apoptotic cells is eliminated through phagocytosis; no inflammatory response.
  - Normally an important homeostatic function
    - Excessive or uncontrolled apoptosis is implicated in the pathogenesis or poor outcome of many ocular diseases, including glaucomatous optic neuropathy, diabetic macular ischemia, chronic macular edema, retinitis pigmentosa, retinal detachments, and geographic atrophy (GA).
    - Apoptosis also implicated in CNS diseases such as Alzheimer and Parkinson diseases.
  - **Cell death signals include the following:**
    - Apoptosis: programmed cell death
    - Glutamate excitotoxicity/NMDA receptor activation
    - Intracellular Ca++
    - Caspases
    - Mitochondrial cytochrome c leakage
    - Expression of apoptosis-promoting genes (eg, *bax*)
    - Underexpression of apoptosis-inhibitory genes (eg, *bcl-2, bcl-xL*)
    - Inflammatory cytokines (eg, TNFα, interleukins)
    - Nitric oxide and reactive oxygen species (free radicals)
  - Cell survival signals include the following:
    - Neurotrophins, or growth factors (eg, CNTF, BDNF, bFGF)
    - Expression of apoptosis-suppressing genes (eg, *bcl2, bcl-xL*)
    - Endogenous antioxidants (eg, glutathione, catalase, SOD)
    - Adrenergic alpha2-receptor–mediated pathways (eg, *bcl-2, bcl-xL*)
- **The goal of neuroprotective therapy is to tip the balance in favor of cell survival.**
  - Block cell death signals
  - Enhance cell survival signals

- **Multiple potential pathways merit exploration as targets for neuroprotection.**
  - **Brimonidine, a selective α-2 receptor agonist**
    - In vitro, cytoprotective effects have been demonstrated in retinal pigment epithelial and Müller cells.
    - In vivo, cyto/neuroprotective effects have been demonstrated across a variety of models of retinal disease
    - In humans, topical use of brimonidine (as compared with a β-blocker) prevented visual field loss in glaucoma patients, with similar degree of IOP lowering in the Low-Pressure Glaucoma Treatment Study.
    - Brimonidine drug delivery system (Brimo DDS) investigational product; generation 1 used in Phase 2a Study 190342-032D
  - Complement inhibition
    - Apellis (C3 inhibition): FILLY Trial
    - Eculizumab (C5 inhibition)
    - ARC1905 (C5 inhibition)
    - Genentech lampalizumab (complement factor D inhibition)
    - FClinical FeaturesD4514S (TNX-234; factor D inhibition)
    - Replacement of complement factor H
  - Integrin peptide inhibition
    - Integrins are cell surface receptors. Cell adhesion (structural) and Cell signaling (functional)
    - Integrins are upregulated with cellular oxidative stress. Integrins downregulate the extracellular matrix and molecules that activate downstream stress pathways.
    - **Risuteganib** was found to be safe, with no reported drug related serious adverse events.
  - Stem cell neurotrophic products
    - Human Retinal Progenitor Cells for Retinitis Pigmentosa
    - Allogeneic progenitor cells (proprietary to jCyte)
    - Biology: *Not* pluripotent; predifferentiated; low immunogenicity; no tumor formation
    - Mechanism of action: Neurotrophic; treats disease, not underlying mutation (non-gene specific)
    - Intravitreal injection (the only cell therapy program using intravitreal injection of an ocular cell type, vs. subretinal)
  - CNTF (ciliary neurotrophic factor)
  - Memantine (NMDA antagonist)
  - Corticosteroids

Miscellaneous

Macular Infarction

- pharmacological (aminoglycoside toxicity)
- vascular stasis (sickle cell disease)
- prothrombotic states (thrombotic thrombocytopenic purpura, disseminated intravascular coagulation).

Hydroxychloroquine (HCQ) Retinopathy

- **Risk factors: (Updated as per 2016 AAO)**
  - daily dose > 5.0 mg/kg actual body weight (ABW) (Daily dose is the most important risk factor)
  - duration of use > 5 years
  - subnormal glomerular filtration rate (GFR)
  - concomitant use of tamoxifen
  - pre-existing macular disease
- If none of these risk factors are present, the guidelines advise a **baseline fundus examination** within the first year of starting HC.
- Baseline standard **automated perimetry** with testing protocol based on the patient's race and spectral domain OCT (**SD-OCT**) are termed "always useful" but "not critical."
- If any major risk factors are present, the guidelines recommend that these tests be done at baseline and then annually from the start. If no major risk factors are present, it recommends that annual screening begin after 5 years of HC use.
- If changes consistent with retinopathy are detected on standard automated perimetry and/or SD-OCT and are confirmed by repeat testing or supplemental testing with fundus autofluorescence (FAF) or multifocal electroretinogram (mfERG), cessation of HC "should be made in conjunction with the patient and the prescribing medical physician."
- **Some points**
  - There is rationale to obtaining baseline SD-OCT and 10-2 VFs in all patients.
  - There is rationale for avoiding reliance on the 24-2 and 30-2 VFs for Asian patients. There are too few test points centrally. Instead, there is rationale for focusing attention on the 8-10 degree annulus of the 10-2 and to supplement, but not replace, the 10-2 VF with a 24-2 and/or 30-2 VF. A good way to screen Asian patients is with broader length SD-OCT line scans, and placing added weight on FAF imaging, which covers the perifovea as well as the parafovea.
  - Asian patients have a higher rate of pericentral rather than paracentral retinopathy.
  - 10-2 white VF and SD-OCT tests used together will pick up almost all patients early enough to avoid sight-threatening retinopathy.
  - Renal disease is a major risk factor.

- Skills in interpreting necessary ancillary testing need to be learned.
  - For the 10-2 VF, a cluster of scotoma points in the high-risk zone 2 to 8 degrees from fixation for white and black patients or 8 to 10 degrees from fixation in Asian and black patients; a scotoma that persists and grows in breadth or depth; and the appearance of new scotomas should lead to further investigation. The 10-2 VF with a white test object has less noise than the version using a red test object and the advantage of the pattern standard deviation display.
  - For the SD-OCT, be aware that a decrease in reflectivity of the parafoveal or perifoveal ellipsoid zone and/or external limiting membrane relative to the foveal reflectivity is an early sign of retinopathy. Complete absence of the ellipsoid zone and/ or external limiting membrane (the flying saucer sign) is a sign of more advanced disease. Thinning of the outer nuclear layer over a succession of SD-OCTs should be looked for ("spread of the red" on the ETDRS display of comparisons to population norms).

Pentosan Polysulfate Maculopathy

- unique pigmentary maculopathy in patients with chronic exposure to pentosan polysulfate sodium
- this condition resembles other maculopathies such as AMD and pattern dystrophy, many affected patients may currently be misdiagnosed
- **PPS**
  - trade name: **Elmiron**; Janssen Pharmaceuticals; Titusville, NJ
  - Pentosan polysulfate sodium is a glycosaminoglycan-like macromolecule that is widely used to treat interstitial cystitis (IC).
  - First used in the mid-20th century, it received FDA approval for management of IC in 1996, and remains the only FDAapproved oral treatment for this condition.
  - PPS provide symptomatic relief to individuals with IC by coating and protecting the bladder epithelium
- **Incidence**: Not known yet
- **Clinical Features**
  - blurred vision (49%) and prolonged dark adaptation (43%)
  - PPS exposure (median: 14.5 years; range: 3-21.9 years)
  - Color fundus photography revealed relatively nondescript fundus changes, typically with paracentral pigment clumps amidst a background of yellow-orange subretinal deposits.
  - Fundus autofluorescence imaging revealed striking abnormality, typically with a densely packed pattern of hyperand hypo-autofluorescent spots that were centered on and involved the fovea. Fundus alterations were typically confined to the posterior pole, although they occasionally extended to the retinal periphery.

- OCT demonstrated nodular lesions at the level of the retinal pigment epithelium that corresponded to the hyperpigmented macular spots.

- **Management**
  - drug cessation and coordination with the prescribing physician to explore alternative regimens for IC management
  - perform a baseline examination with comprehensive fundus imaging (color fundus photography, OCT, and fundus autofluorescence imaging).
  - repeat screening 5 years after PPS initiation and annually thereafter.
  - Patients with potentially elevated risk, including those with an atypical dosing regimen, those with a history of smoking or macular disease, as well as those with comorbidities involving renal, hepatic, or splenic function, may benefit from more frequent screening examinations, or drug avoidance altogether.