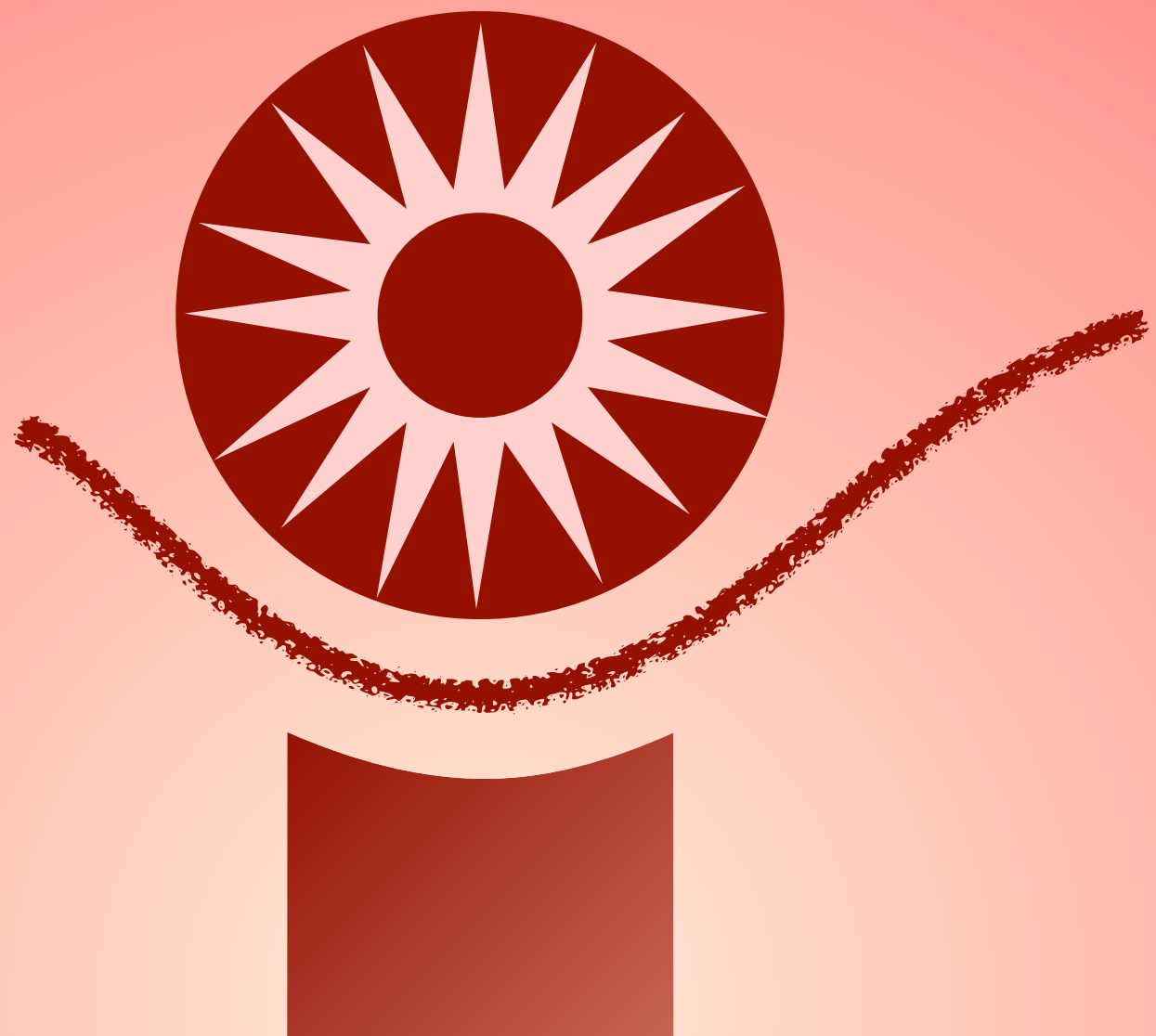
Ophthalmology PG Exam Notes



NOTES

2020

Glaucoma

Dhaval Patel MD

I notes 2020

(Ophthalmology PG Exam Notes)

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by inotesforPG.blogspot.com

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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 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

Glaucoma

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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History of Glaucoma

- The term ***glaucoma originally meant cataract*** and distinction between glaucoma and cataract was not understood till 1705. “glaukos” means “watery blue” or gray color which is actually appearance of typical cataract.
- “The scientific history of glaucoma began the day on which cataracts were put in their correct place” (**Albert Terson**, 1867–1935, French ophthalmologist).
- The correct **anatomic location of cataracts** is credited to **Pierre Brisseau** (1631–1717) in 1707.
- Elevation of intraocular pressure as a sign of glaucoma was first mentioned in Breviary (1622) by **Richard Banister** (1570–1626, English ophthalmologist).
- Discovery of the ophthalmoscope in 1851 by Hermann von Helmholtz (1821–1894, German ophthalmologist) and its subsequent use by **Edward Jaeger** (1818–1884) led to the belief that the optic nerve was also involved.
- **Cupping of the optic nerve** as a sign of glaucoma was confirmed by anatomist **Heinrich Muller** in the late 1850s.
- **Von Graefe** is credited as having first described contraction of the **v**isual field and paracentral defects in glaucoma in 1856.
- Sir **William Mackenzie** (I835) was the first to describe raised intraocular pressure (**IOP**) in glaucoma.
- Following the introduction of the ophthalmoscope, the presence of glaucomatous cupping was soon recognised (**Jacobson**, I853; Jaeger, I854; von Graefe, 1854; Weber, 1855; and others) and was confirmed histopathologically by Muller (1856).
- **Mackenzie** (1854) also described flattened and atrophic nerves in glaucomatous eyes.
- Nerve fibre bundle defects were first described by **Landesberg** (1869) and later by **Bjerrum** (1889).
- Cavernous degeneration of the optic nerve in glaucoma was noted by **Schnabel** (1892).
- **Jonas's ISNT rule**: 1991, inferior > superior > nasal > temporal (ISNT) Neuroretinal rim area rule
- **Modern definition**: a pathologic condition in which there is a progressive loss of ganglion cell axons causing visual field damage that is related to IOP.
- On a molecular level, glaucoma of diverse aetiology is linked by the presence of endothelial leucocyte adhesion molecule-1 (**ELAM-1**), which indicates activation of a stress response in trabecular meshwork cells.

History of Glaucoma Medicines

Year	Drug Class	Route	Generic Name	Remark
1876	Cholinergic agonists	Topical	Physostigmine	The first glaucoma drug, derived from the West African calabar bean, which caused pupils to become smaller, was initially used for miosis in iridectomy cases, then found to lower IOP and break angle-closure attacks.
1877	Cholinergic agonists	Topical	Pilocarpine	Pilocarpine was introduced just a year later, while it wasn't until 1946 that the first indirectacting cholinergic agonist, diisopropyl fluorophosphate, was discovered, followed by echothiophate iodide (Phospholine iodide) in 1957.
1897	Crystalline alkaloids	Systemic	Strychnine	Strychnine is a rat poison, administered hypodermically in large doses to relieve the "mental and physical depression" of glaucoma
1904	Osmotic agents	Systemic	Hypertonic saline	hypertonic saline was joined by glucose, urea, mannitol, and glycerol.
1948	Adrenergic antagonists	Systemic	Dibenamine	Patients given intravenous dibenamine often experienced IOP levels dropping below 25 mm Hg for up to 24 hours.
1954	Carbonic anhydrase inhibitors	Systemic	Acetazolamide	
1955	Adrenergic agonists	Topical	Epinephrine	Topical epinephrine lowered IOP but led to both topical and systemic side effects. In one study, 80% of patients had to discontinue therapy.
1978	Beta-Adrenergic Inhibitors	Topical	Timolol	discovered in 1967, but problems such as decreased tear production, corneal anesthesia, and tachyphylaxis stalled commercial use until timolol was found to be both effective and well tolerated a decade later.
1987	Alpha-Adrenergic Agonists	Topical	Apraclonidine	Apraclonidine, a derivative of clonidine, was initially used with laser iridotomies to control bleeding.
1995	Carbonic anhydrase inhibitors	Topical	Dorzolamide	
1995	Adrenergic agonist prodrug	Topical	Dipivefren	
1996	Prostaglandin analogue	Topical	Latanoprost	Xalatan was the first prostaglandin analog to receive FDA approval
2017	Rho-kinase Inhibitors	Topical	Netarsudil	In March 2019, Aerie announced FDA approval of netarsudil/latanoprost ophthalmic solution 0.02%/0.005% (Rocklatan) for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension.

Anatomy & Physiology

Development of Anterior Chamber

- The anterior chamber structures are derived from the **mesenchyme and the ectoderm**.
- The chronological development is:
- 5-6 weeks: Cells of neural tissue origin migrate anteriorly.
- 6-8 weeks: Three waves of mesenchyme migrate anteriorly.
    - Wave 1: Forming the corneal endothelium.
    - Wave 2: Forms the iris stroma
    - Wave 3: forms the keratocytes.
- 3-4 months: Angle defined, trabecular meshwork develops, and aqueous production begins
- 5-7 months: Differentiation and perforation of trabecular meshwork enables it to communicate with the anterior chamber
- Birth: Iris and ciliary body are aligned with the scleral spur
- 1 year: angle recess develops

Trabecular meshwork

- The trabecular meshwork is functionally classified into:
    - Anterior non filtering portion
    - Posterior filtering portion.
- The ultrastructure of the trabecular meshwork shows the following divisions:
    - Uveal meshwork
    - Corneoscleral meshwork
    - Juxtacanalicular meshwork
- The trabecular meshwork comprises of sheets of connective tissue lined by endothelium and fenestrated with pores of size ranging from **5 to 75 *μ***
- The extra cellular matrix comprises of endogenous metalloproteinases which are responsible for ECM turnover and maintenance of aqueous outflow
- The juxtacanalicular layer offers maximal resistance to aqueous outflow.

Ciliary Body

- The ciliary body is composed of:
    - Bilayered epithelium
    - Ciliary vasculature
    - Ciliary muscles
- The two layers of the epithelium are:

- Outer pigmented epithelium
- Inner non pigmented epithelium

- The twin layers show the presence of three types of intercellular junctions:
  - Desmosomes: maintain cell adhesion
  - Gap junctions: inter cellular transfer of solutes occur.
  - **Tight junctions: form the blood aqueous barrier**. They play an important role in the formation of aqueous humour
- The ciliary body derives its blood supply from the major arterial circle formed by:
  - Long posterior ciliary arteries
  - Anterior ciliary arteries
  - The capillaries of the ciliary circulation are highly fenestrated and form the site for ultrafiltration
- The ciliary body comprises of three types of muscle fibres:
  - Longitudinal
  - Circular
  - Radial
- The longitudinal muscle fibres terminate in three types of tendons:
  - Type A Terminates in the cornea
  - Type B – Terminates in the sclera
  - Type C Terminates in the trabecular meshwork

Aqueous Humor Dynamics

- **Goldmann Equation** [P0 = (F/C) + Pv], P represents the IOP, F is the rate of aqueous formation, and C is the facility of outflow, which roughly corresponds to the inverse of the total resistance to outflow.
- Uveoscleral outflow is relatively insensitive to changes in pressure
- So Goldmann equation can be modified as: P = (F U)/C + Pv, where P represents the IOP, F is the rate of aqueous formation, U is the rate of aqueous outflow through the pressure insensitive uveoscleral pathway, and C is the outflow facility. Each of these parameters can be measured except U which must be calculated from IOP and the remaining variables.
- Outflow facility is typically between **0.23 and 0.33 *μ*L/min/mm Hg**
- Mean aqueous humor production rate is typically found to range from 2.2 to 3.1 μL per minute.
- Episcleral venous pressure is currently the most difficult parameter to measure in aqueous humor dynamics. (episcleral venomanometer)

- **Formation**:

- Ultrafiltration: Involves entry of plasma constituents into ciliary stroma
- Active secretion: Involves secretion of Na and bicarbonate ions
- Diffusion: Involves movement of fluid oxygen and glucose across the gradient

- **Aqueous humor outflow:**
  - Trabecular pathway: TM → SC → CC → Episcleral vein → ciliary circulation
  - Uveoscleral pathway: loose tissue between fibres of long ciliary muscles → flow through suprachoroidal space → trans-scleral emissary vein
  - Posterior pathway

Mechanism of Glaucoma

- The **Mechanical** theory:
  - 1858, **Müller**
  - Proposed that the elevated IOP led to direct compression and death of the neurons
- The **Vascular** theory:
  - **Von Jaeger**, 1858
  - Suggested that a vascular abnormality was the underlying cause of the optic atrophy
- **Schnabel cavernous atrophy**:
  - 1892, Schnabel
  - Atrophy of neural elements created empty spaces, which pulled the nerve head posteriorly

Lymphatic like pump & Glaucoma

- As per recent research, A Lymphatic-like Pump Controls Aqueous Outflow. It has impact on POAG Management and MIGS Implications.
- **Direct Observation of the Aqueous Veins suggest that**
  - Aqueous outflow is pulsatile!
  - Pulsatile aqueous outflow stops in glaucoma.
  - Pilocarpine restores pulsatile aqueous outflow.
- **Lymphatics & Cardiovascular physiology**
  - Like veins and lymphatics, the aqueous outflow system returns fluid to the heart.
  - Venous blood and lymph flow by pulsatile mechanisms.
  - Veins and lymphatics use displacement pumps to move fluid.
  - Displacement pumps have unique requirements:
    - A chamber, inlet valves, and outlet valves
    - Segments between the vein and lymphatic valves act as miniventricles.
    - Walls of the miniventricle compartments must move to propel fluid forward.

- A driving force is present resulting from the cyclic cardiac pulse and transient tissue motion.
- The outflow system has **Prox 1**, known to be a marker for lymphatic valves.
- Defective Prox 1, necessary for lymphatic valve development, causes a glaucoma.

- **Available knowledge before OCT Advancements**
  - The trabecular meshwork (TM) is the wall of a vessel called the Schlemm canal (SC).
  - The SC is a chamber. SC chamber volume changes with IOP.
  - Aqueous-containing endothelial-lined conduits arise from the SC inner wall.
  - The conduits attain a tube-like shape, cross the SC, and attach to the external wall.
  - The conduits act as SC inlet valves (SIVs), allowing flow and preventing blood reflux.
    - Light, scanning, and transmission electron microscopy document SIV structure.
    - Microsphere and RBC tracer studies document SIV function as conduits.
    - During SC unroofing, SIVs break and discharge aqueous.
  - During gonioscopy, SIVs discharge oscillating waves of aqueous into the SC.
- **Insights from Ex Vivo High-Resolution OCT**
  - Collector channel (CC) valves
    - CC entrances have collagen flaps attached only at one end.
    - The CC hinged flaps undergo pressure-dependent changes in position.
    - Position changes allow the hinged flaps to open and close CC.
    - Position changes enable the flaps to act as SC outlet valves (SOV).
    - SIV provides connections between the TM and the SOV hinged flaps.
    - SIV elongate as SC pressure increases, placing tension on the hinged flaps.
  - Circumferentially oriented deep scleral plexus (CDSP) channels are adjacent to the SC.
    - Thin septa separate the CDSP from the SC and move by pressure-dependent mechanisms.
    - The CDSP opens and closes like a second pressure-dependent chamber.
  - Evidence from real-time imaging of tissue motion
    - The TM beams, SIV, SOV, and CDSP all undergo rapid cyclic pulsatile movement.
    - The amplitude and speed of motion can account for all of the aqueous outflow.
    - Motion of TM, SIV, and SOV, as well as the SC and CDSP volume Δs, are all synchronous.

        - Cellular attachments between the structures can explain the synchrony of motion.

- **Insights from Human In Vivo Phase Sensitive OCT (PhS-OCT):**
    - Trans-scleral OCT in human subjects is challenging because of motion and light scattering.
    - Commercial spectral domain OCT systems using an 810-nm wavelength have limited sensitivity.
    - A purpose-built 1310-nm PhS-OCT system resolves motion of ~20 nm.
    - The PhS-OCT system quantitates TM velocity and displacement.
    - A recent report finds significant motion differences between normal and glaucoma eyes.
- **Benefits for Motion Monitoring by PhS-OCT in Medical Management of Glaucoma:**
    - Infrequent office IOP measurements are of poor predictive value for IOP peaks and fluctuation.
    - IOP is measured 3 to 4 times a year, thus sampling IOP for ~12 seconds/year.
    - Patients look straight with no blinking or eye movement, preventing the capture of transients.
    - As a pump, the outflow system requires movement to function properly.
    - Poor TM movement may predict early aqueous outflow abnormalities.
    - PhS-OCT measurement of TM motion may be an alternative to brief, infrequent IOP sampling.
    - TM movement deterioration may be a sensitive indicator of a need for medication escalation.
    - Improved TM movement following outflow drugs may assess their effectiveness.
- **Aqueous Outflow Pump Behaviour on MIGS Effects**
    - Real-time OCT imaging of motion following insertion of a MIGS-like cannula into the SC
    - Pressure introduced into SC simulates AC pressures and transients after MIGS.
        - A SC pressure increase at device end causes TM movement and SC dilation ≥5 mm distally.
        - SC pressure changes cause collector channels to open and close distal to the insertion area.
        - SC and CC dilation is sufficiently rapid to permit pulsatile aqueous flow.
        - CDSP channels in the deep scleral plexus open and close with SC pulsatile pressure.
- **Pump Function Improvement and IOP Reduction After Cataract Extraction**
    - Pilocarpine briefly restores pump function by improving scleral spur (SS) traction.
    - High-resolution MRI demonstrates improved spur vectors and traction after cataract surgery.

- Reports propose that cataract surgery improves pump function by improved SS traction.

- **Awareness of the Pump Function and New Therapies:** Restoration of pump function without frequent meds or invasive surgery.
  - Pilocarpine temporarily restores pulsatile flow but with many side effects.
  - Trans-scleral micropulse laser (TMP) simulates pilocarpine effect on outflow system.
  - Optimisation of TMP delivery systems may provide a persistent effect.

Genetics of Glaucoma

- 1.8% of the Indian population is blind and 0.15% suffers from glaucoma (Balasubramanian et al.)
- Glaucoma affects 15 million Indians and around 25 million are at risk
- 1938, Barkan: deep-chamber and shallow chamber glaucoma
- **Primary open-angle glaucoma**
  - 11 genetic loci designated GLC1A to GLC1K
  - The first gene identified from GLC1A is myocilin (MYOC)
    - Chromosomal region 1q23-24
    - Codes for a protein that was initially named trabecular meshwork inducible glucocorticoid response protein (TIGR) → now myocilin
  - Second gene for POAG was identified from GLC1E as optineurin
    - Chromosome 10p15-p14
    - Interacts with different proteins that are involved in apoptosis, inflammation, and vasoconstriction.
  - The third gene for POAG was recently characterized as the WD repeat domain 36 (WDR36)
    - Uniquely involved in T-cell activation and highly co-regulated with interleukin 2
  - NTF4 gene on chromosome 19q13.3.
- **Primary angle-closure glaucoma**
  - Presence of MYOC mutations in a few individuals
  - CYP1B1 gene is located on chromosome 2 at position 2p21. CYP1B1 is a member of cytochrome P450 superfamily
- **Congenital glaucoma**
  - Primary congenital glaucoma
    - 22.2% of congenital glaucomas
    - Anomaly of trabecular meshwork and anterior chamber angle
    - Autosomal recessive
    - 3 genes loci: GLC3A to GLC3C
    - 2p21 (GLC3A), for which the responsible gene is CYP1B1, 1p36 (GLC3B) and 14q24 (GLC3C), for which the genes are not yet identified.
    - Familial in 10 to 40% and bilateral in 80%

Tests for Disease-Causing Glaucoma Genes

- Primary open-angle glaucoma (POAG): Myocilin (MYOC), WDR36
- POAG with nail-patella syndrome: LManagement1B

- Normal-tension glaucoma (NTG): Optineurin (OPTN), TBK1
- Juvenile open-angle glaucoma: Myocilin (MYOC)
- Primary congenital glaucoma (PCG): CYP1B1, LTBP2
- Aniridia: PAX6
- Axenfeld-Rieger syndrome: PITX2, FOXC1
- Peters anomaly: PAX6 PITX2 FOXC1 CYP1B1
- Peters plus: B3GALTL
- Anterior segment dysgenesis panel: **B3GALTL**, BCOR, BMP4, COL4A1, **CYP1B1**, **FOXC1**, FOXE3, FRAS1, FREM1, FREM2, GRIP1, HCCS, MFRP, OTX2, **PAX6**, **PITX2**, PITX3, SMOC1, SOX2, STRA6, VAX1, VSX2.

Intraocular pressure

- Direct: **Manometric** technique (needle insertion in AC, most accurate but invasive → not used)
- Indirect: **Tonometric**, eye's response to an applied force
  - Palpation → digital pressure (only gross alterations of IOP)
  - Tonometry
    - Applanation: force necessary to flatten a small, standard area of the cornea
    - Indentation: amount of deformation or indentation of the globe in response to a standard weight applied to the cornea.
    - Contour matching
    - Transpalpebral phosphene induction
    - Indentation/rebound
    - Intraocular implantation of pressure sensors.

Classification

- **Contact tonometers (instruments that touch the eye):**
  - *Static instruments*
    - Applanation tonometers: flatten a portion of the cornea
      - Constant area:
        - ✓ Goldmann
        - ✓ Hand-held versions of Goldmann's instrument: Perkins and Drager tonometers
        - ✓ Pneumatonometry
        - ✓ Mackay – Marg
      - Constant force
        - ✓ Maklakoff: a highly displacement tonometer, requires a supine subject
    - Indentation tonometers indent the cornea with a shape other than a flat surface
      - Schiotz a highly displacement tonometer that nearly doubles IOP during measurement.
  - *Dynamic instruments*
    - Ballistic tonometers
      - Impact acceleration
      - Impact duration: **Pascal Dynamic Contour Tonometry (DCT)**: digital tonometer that uses the principle of contour matching instead of applanation to measure IOP. Theoretically this tonometer can measure IOP independent of CCT or corneal biomechanics

- Rebound velocityiCare rebound tonometer
- Vibration tonometer: Krakau a low displacement tonometer

- **Noncontact tonometry (NCT)**
  - **Nidek NT 4000** synchronizes air discharge with the cardiac cycle.
  - **Topcon NT** discharges air automatically when the corneal dome is in focus and discharges only the amount air needed to applanate the cornea (older units discharged a fixed amount of air each time).

Applanation Instruments

Goldmann tonometer

- **Constant-area applanation**: **3.06 mm** (because Theoretically, average corneal rigidity and the capillary attraction of the tear meniscus cancel each other out when the flattened area has the 3.06 mm diameter contact surface of the Goldmann prism)
- Force necessary to flatten (or applanate) an area of the cornea
- **Imbert–Fick principle**, which states that for an ideal, dry, thin-walled sphere, the pressure (P) inside the sphere equals the force (F) necessary to flatten its surface divided by the area (A) of flattening (i.e. P = F/A).
- Displaces only about **0.5 uL** of aqueous humor, which raises IOP by about **3%**
- Because the volume displaced is so small, ocular rigidity, or the 'stretchability' of the globe, has little effect on the pressure readings.
- When the inner margins of the two semicircles are aligned in a smooth S curve at the midpoint of their pulsations, the proper degree of applanation has been achieved
- Disposable tonometer tip designed to fit over Goldmann prism → **Tonosafe**, acrylic better than silicone
- Tension knob is set **at 1 g.** If the knob is set at 0, the prism head may vibrate when it touches the eye and damage the corneal epithelium. The 1 g position is used before each measurement. As a rule, it is more accurate to measure IOP by increasing rather than decreasing the force of applanation.
- More than 3 D of corneal astigmatism →elliptical mires, prism should be rotated to about 45° from the long axis of the ellipse – that is, the prism graduation corresponding to the least curved meridian of the cornea should be set at the red mark on the prism holder: **FLAT AXIS AT RED MARK**
- Fluorescein rings should be approximately 0.25–0.3 mm in thickness – or about one-tenth the diameter of the flattened area.

- **Potential errors of applanation tonometry**
  - Thin cornea
  - Thick cornea
  - Astigmatism >3 diopters
  - Inadequate fluorescein

- Too much fluorescein
- Irregular cornea
- Tonometer out of calibration
- Elevating the eyes >15°
- Repeated tonometry
- Pressing on the eyelids or globe
- Squeezing of the eyelids
- Observer bias (expectations and even numbers)
- Wide pulse pressure. It is normal for there to be a small oscillation in IOP in time with the rhythm of ocular perfusion. If this 'pulse pressure' is substantial, the mid-point is taken as the reading.

Perkins tonometer

- The Perkins tonometer is similar to the Goldmann tonometer, except that it is portable and counterbalanced, so it can be used in any position.

Draeger tonometer

- Similar to the Goldmann and Perkins tonometers, except that it uses a different biprism

MacKay-Marg tonometer

- Movable plunger 1.5 mm in diameter, that protrudes slightly from a surrounding footplate or sleeve. The movements of the plunger are measured by a transducer and recorded on a paper strip.
- Tonometer measures IOP over a brief interval, so several readings should be averaged to reduce the effects of the cardiac and respiratory cycles.
- Tip of the instrument is covered with a plastic film to prevent transfer of infection

Tono-Pen™

- Small portable applanation tonometer that works on the same principle as the MacKay-Marg tonometer
- Community health fairs, on ward rounds
- Depends on an electronic end point → more accurate
- Disposable latex cover

Pneumotonometer

- OBF pneumotonometer (Ocular Blood Flow OBF)
- Sensing device that consists of a gas chamber covered by a polymeric silicone diaphragm

- As the diaphragm touches the cornea, the gas vent is reduced in size, and the pressure in the chamber rises
- Some properties that are more like an indentation tonometer
- Scarred, irregular, or edematous corneas

Non-contact tonometer

- Applanates the cornea by a jet of air, so there is no direct contact between
- When an area of the cornea 3.6 mm in diameter is flattened, the light reflected to the photocell is at a maximum.
- Useful for screening programs, non-medical person can operate, no TA

Ocular Response Analyser™

- Reichert Ophthalmic Instruments, Depew, NY, USA
- Air puff tonometer that directs the air jet against the cornea and measures not one but two pressures at which applanation occurs
- When the air jet flattens the cornea as the cornea is bent inward and as the air jet lessens in force and the cornea recovers. The first is the resting intraocular pressure.
- The difference between the first and the second applanation pressure is called corneal hysteresis and is a measure of the viscous dampening and, hence, the biomechanical properties of the cornea

The Ocuton™ tonometer

- ✦ Hand-held tonometer that works on the applanation
- ✦ Very light probe, for home tonometry

Maklakow tonometer

- ✦ Differs from the other applanation instruments in that a known force is applied to the eye, and the area of applanation is measured – a technique known as **constant-force** rather than constant-area applanation
- ✦ The instrument consists of a wire holder into which a flat-bottom weight, ranging from 5 to 15 g, is inserted.

Indentation instruments

- Known weight is placed on the cornea, and the IOP is estimated by measuring the deformation or indentation of the globe.

Schiøtz tonometer

- Metal plunger that slides through a hole in a concave metal footplate.

- The plunger supports a hammer device connected to a needle that crosses a scale. The plunger, hammer, and needle weigh **5.5 g**. This can be increased to **7.5, 10, or 15 g** by the addition of appropriate weights.
- Lower the IOP, the higher the scale reading. Each scale unit represents a **0.05 mm** protrusion of the plunger
- Portable, sturdy, relatively inexpensive, and easy to operate.

✦ **Friedenwald nomogram**

  - An important concern is that placing the heavy tonometer (total weight at least 16.5 g) on the eye raises IOP. This ocular rigidity is not taken into account.

Electronic Schiotz tonometer

- Continuous recording of IOP that is used for tonography.

Impact–rebound tonometer

- Updated version of an indentation tonometer
- Very light, disposable, sterile probe is propelled forward into the cornea by a solenoid; the time taken for the probe to return to its resting position and the characteristics of the rebound motion are indicative of the IOP
- Comparable to the Goldmann in both normal and post-keratoplasty human eyes.

Transpalpebral tonometry

1. **TGDc-01** (Envision Ophthalmic Instruments, Livonia, Michigan, USA) was developed in Russia → weight falling within the instrument onto the closed eyelid and the amount of indentation it causes.
2. **DIATON** TONOMETER: IOP through the Eyelid
3. **Proview** (Bausch & Lomb, Rochester, NY, USA) → pressure on the eyelid required to induce these phosphenes is proportional to the intraocular pressure.

Dynamic contour tonometry

✦ Kanngiesser

✦ **Principle**: by surrounding and matching the contour of a sphere (or a portion thereof), the pressure on the outside equals the pressure on the inside.

✦ Measures transcorneal pressure with minimal deformation of the cornea. This principle measures pressure instead of force.

✦ Concave pressure-sensing tip (**10.5 mm** radius of curvature) is slightly flatter than that of the average human cornea.

✦ The **1.7-mm piezo-resistive pressure sensor** at the center of the concavity measures the intraocular pressure at the cornea 100 times per second with less than 1 g of appositional force.

- Requires **measuring periods of 4–5 s** and is difficult in the noncompliant patient or in nystagmus.
- Dynamic contour tonometer (DCT) (**Pascal™**, Zeimer, Zurich, Switzerland)
- Not affected by pachymetry, previous refractive surgery
- Measures IOP in real time, the actual measurement, like the IOP, is pulsed
- Less dependent than applanation tonometry on central corneal thickness, corneal curvature, astigmatism, anterior chamber depth, and axial length.
- It is possible to measure both the diastolic and the systolic intraocular pressures and determine the difference between the two, that is, the ocular pulse amplitude. **Ocular pulse amplitude** is an indirect measure of choroidal perfusion and may have a role in the pathophysiology of glaucoma.

Continuous monitoring of IOP

- Intraocular pressure (IOP) has long been known to be variable, with Sidler-Huguenin first reporting diurnal variations in 1898.
- Modes
  - Contact lens or suction cups
  - Sonic resonance of the eye
  - Infrared spectroscopy
  - Miniature pressure sensor
- **Sensimed Triggerfish**
  - The Triggerfish contact lens sensor (CLS, Sensimed AG; Lausanne, Switzerland) is the first device to enable noninvasive, continuous, 24-hour monitoring of IOP patterns.
  - Uses a sensor which is a **soft hydrophilic single use contact lens**, containing passive and active strain gauges embedded in the silicone to monitor fluctuations in diameter of the corneo-scleral junction
  - FDA cleared in March 2016 as a de novo device

Factors influencing intraocular pressure

- ***Demographic***
  - Age: Mean IOP increases with increasing age
  - Sex: Higher IOP in women Effect more marked after age 40 years
  - Race: Higher IOP among blacks
  - Heredity: IOP inherited
- ***Systemic***
  - Diurnal variation: Most people have a diurnal pattern of IOP Quite variable in some individuals.

- Seasonal variation: Higher IOP in winter months
- Blood pressure: IOP increases with increasing blood pressure
- Obesity: Higher IOP in obese people
- Posture: IOP increases from sitting to inverted position Greater effect below horizontal
- Exercise: Strenuous exercise lowers IOP transiently Long-term training has a lesser effect
- Neural: Cholinergic and adrenergic input alters IOP
- Hormones: Corticosteroids raise IOP; diabetes associated with increased IOP
- Drugs: Multiple drugs alter IOP

- ***Ocular***
  - Refractive error: Myopic individuals have higher IOP
  - Eye movements: IOP increases if eye moves against resistance
  - Eyelid closure: IOP increases with forcible closure
  - Inflammation: IOP decreases unless aqueous humor outflow affected more than inflow
  - Surgery: IOP generally decreases unless aqueous humor outflow affected more than inflow

Corneal Hysteresis

- Corneal hysteresis is a **measurement of the viscoelastic properties** of the cornea. It can be likened to the spring effect of the cornea.
- Corneal elasticity is affected by corneal thickness, collagen composition, hydration, and extracellular matrix.
- Corneal hysteresis appears to have a greater effect on measured IOP than on CCT or corneal radius of curvature.
- Corneal hysteresis is measured by the **ocular response analyzer**.
- Low CH may underestimate IOP and high CH may overestimate IOP.
- **Average normal CH is around 12.5 mmHg.**
- Normal children have CH values similar to normal adults.
- Decreased CH values are associated with glaucoma.
- Glaucoma patients with lower CH values have greater progressive visual field worsening.
- The **dynamic contour tonometer (DCT)** is least affected by corneal biomechanics of all instruments used to estimate IOP.

Target IOP

- Past efforts to lower intraocular pressure in the 'normal' range of 21 mm Hg or lower may be inadequate and that "control" really means an intraocular pressure of less than 15 mm or 16 mm of Hg especially in advanced glaucoma.
- Target pressure may be defined as a pressure, rather a range of intraocular pressure levels within which the progression of glaucoma and visual field loss will be delayed or halted. The goal should be to lower the intraocular pressure to a level that is 'safe' for that particular eye. Because individuals vary in their susceptibility to IOP independent damage, **there is no 'Safe' intraocular pressure that can be guaranteed** to prevent further glaucomatous damage. The optic nerve that has already been damaged appears to be more susceptible to pressure mediated injury, so patients with advanced glaucomatous neuropathy may require very low target pressure to halt the disease.
- In determining the appropriate target pressure for an individual, the ophthalmologist must take into account several major factors, the IOP level at which the nerve damage occurred (damaging IOP), the extent and rate of progression of glaucomatous damage, if known; the presence of other risk factors for glaucoma; and the patient's age, expected life span, and medical history.
- Specific IOP ranges may be recommended as a starting point. The **AAO guidelines** suggest:
  - For patients with **mild** damage (optic disc cupping but no visual field loss), the initial target pressure should be 20-30% below baseline.
  - For patients with **advanced** damage, the target pressure range may be a reduction of 40% or more from baseline.
  - For patients with **NTG**, a 30% reduction is recommended.
- A target intraocular pressure that is appropriate when you first see a patient may not be a safe pressure 10 years later when he/she may have developed systemic hypertension, diabetes or some other condition, that may affect the person's susceptibility to glaucomatous progression. The clinician should always revaluate each glaucoma patient at regular intervals to determine if the target intraocular pressure originally selected is still valid.

Effect of Anti-VEGF Agents on IOP

- **Acute Effect: Transient Elevation**
  - ***Factors influencing post-injection IOP spikes***
    - Pre-injection IOP
    - Injection volume
    - Phakic vs. pseudophakic state (higher in phakic eyes)
    - History of glaucoma
    - Axial length and patient age are poor predictors of IOP spike.
    - Needle bore size (higher with smaller needle gauge, reduced reflux)
  - ***Management of post-injection IOP spikes***

- Observation (IOP usually < 25 mmHg within 30-60 minutes)
- Pre and postoperative medical therapies
- Paracentesis (rarely needed)

- **Chronic Effect: Sustained Elevation**
  - ***Risk factors***
    - Higher number of intravitreal injections
    - Shorter interval between injections
    - Pre-existing glaucoma
    - Family history of glaucoma
    - History of intravitreal or topical steroids
    - Possibly higher with compounded bevacizumab
    - Possibly lower with aflibercept
  - ***Potential mechanisms***
    - Impaired outflow due to microparticles (silicone, protein aggregates)
    - Mechanical trauma: Impaired outflow due to repeated IOP spikes
    - Pharmacologic effect of VEGF blockade on:
      - Trabeculocytes
      - Trabecular meshwork extracellular matrix
      - Episcleral venous pressure
      - Uveoscleral outflow
    - Inhibition of nitric oxide synthase (decreased outflow)
    - Inflammatory mechanism / trabeculitis
    - Idiopathic
  - ***Management***
    - Manage pre-injection IOP
    - Reduce injection volume
    - Use lower needle gauge (more reflux)
    - Give fewer injections
    - Lengthen interval between injections
    - Choice of anti-VEGF agent

Gonioscopy

- Optical principles
  - **Total internal reflection**: angle of the anterior chamber cannot be visualized directly
  - Refractive index of a goniolens is similar to that of the cornea, it eliminates total internal reflection by replacing the tear film-air interface with a new tear film-goniolens interface.
- Two important parameters of anterior chamber depth & angle width.
- When the angle formed between the iris and the surface of the trabecular meshwork is between **20° and 45**°, the eye is said to have a **wide angle (= scleral spur visible)**. Angles smaller than 20° are termed narrow angles (= scleral spur not visible).

Interpretation

- Pupil
- Iris:
  - Contour: flat, concave, convex
  - Site of iris insertion: apparent and actual
  - The *angulation* between the iris insertion and the slope of the inner cornea in the angle, in approximate steps of 10°.
  - Last, abnormalities such as neovascularization, hypoplasia, atrophy, and polycoria should be noted.
- Ciliary Body:
- Iris process and PAS
- Scleral Spur
- Schwalbe's line, pigmented **Sampaolesi's** line
- Trabecular meshwork and trabecular pigment band
- The angle recess represents the posterior dipping of the iris as it inserts into the ciliary body.
- Any blood vessel that crosses the scleral spur onto the trabecular meshwork is abnormal.

In most eyes the inferior quadrant is widest, the lateral quadrants narrower, and the superior narrowest. In eyes with narrow angles, the temporal quadrant may be narrowest.

Methods

- **Direct method: Koeppe lens, Medical workshop, Barkan, Swan-Jacob**
  - Allows the observer to look directly at the angle
  - 1.5x magnification

- Barkan hand illuminator or fiber optic light source also used along with microscope having 1.6x objective lenses and 10x ocular lenses → 24x magnification of trabecular area

- **Indirect method: Goldmann and Zeiss lenses**
  - Mirrors by which the angle is examined with reflected light
  - Light and magnification of the slit lamp and corneal microscope.
  - The mirrored arrangement of both of these types of lenses causes the observed image of the angle to be reversed but not crossed.
- **Indentation (compression) gonioscopy: Zeiss, Posner, Suzzman**
  - Tear-coupled indirect (e.g., Zeiss) contact lens, the physician can observe the effects on angle width.

Grading of chamber angle

- **Shaffer Grading:**
  - 0 – 0,
  - S – no obvious iridocorneal contact but no angle structures can be identified,
  - 1 –10 degree
  - 2 –20 degree
  - 3 –25-35 degree
  - 4 – 35-45 degree
- **Scheie Grading** → like Shaffer but in reverse order
- **Spaeth Grading:**
  - Three-dimensional information in coded form
  - Indirect goniolenses (e.g., Zeiss four mirror) that allow for indentation

1. **The site of insertion of the iris root in the eyewall**
   A. Anterior to trabecular meshwork (i.e., Schwalbe's line)
   B. Behind Schwalbe's line (i.e., at level of trabecular meshwork)
   C. Centered at the level of the scleral spur
   D. Deep to the scleral spur (i.e., anterior ciliary body)
   E. Extremely deep in the ciliary body.
2. **Width or geometric angle of the iris insertion**
   - Like Shaffer: 10-40
3. **The contour of the peripheral iris near the angle**
   - Initially 3 contours
     - s = 'steep' or convexly configured (e.g., plateau iris)
     - r = 'regular' or flat (the most common contour seen)

- q = 'quixotic' or 'queer' for deeply concave (e.g., pigment dispersion syndrome).

- Now 4 contours
  - b = 'bows 1 to 4 plus' (usually indicative of optically-appearing closure, altering with indentation)
  - p = 'plateau' (comparable to older 's' designation)
  - f = 'f lat approach': the commonest iris appearance (comparable to the older 'r' designation)
  - c = 'concave' as in posteriorly bowed iris (comparable to the older 'q' designation).

4. **Intensity of the trabecular pigmentation**
   - Trabecular meshwork pigmentation (TMP) is labeled from 1 to 4: minimal or no pigment is graded 1, and dense pigment deposition is indicated as grade 4, with lesser degrees between.
5. **Presence or absence of abnormalities such as mid-iris bowing, peripheral synechiae, and so on.**

- **RPC Classification (R.P.Center, AIIMS, New Delhi, India)**
  - Grade 0: Closed
  - Grade 1: Dipping of light
  - Grade 2: Schwalbe's line visible
  - Grade 3: Anterior trabecular meshwork
  - Grade 4: Posterior TM scleral spur
  - Grade 5: Ciliary body band visible
  - Grade 6: Root of iris visible

- **Van Herick estimate of angle width**
  - Grade 4 angle→ Anterior chamber depth = Corneal thickness
  - Grade 3 angle→ Anterior chamber depth = 1⁄4 to 1⁄2 corneal thickness
  - Grade 2 angle→ Anterior chamber depth = 1⁄4 corneal thickness
  - Grade 1 angle→ Anterior chamber depth = Less than 1⁄4 corneal thickness
  - Slit angle→ Anterior chamber depth = Slit-like (extremely shallow)
  - Closed angle→ absent peripheral anterior chamber

Visual Field

- Normal visual field: an island of vision in a sea of darkness →**Traquair**
- 60° superiorly and nasally, 75° inferiorly, and 100° temporally
- Visual field testing is usually done in the photopic (light-adapted) or mesopic (partially light-adapted) state
- Visual acuity → resolving power of the retina
- Static visual field → tests differential light sensitivity
- **Central field: within 30 degrees**
- **Peripheral field: 30 degrees to far periphery**
- **Bjerrum's area (arcuate area):** within the central 25°, extending from the blind spot and arcing above or below fixation in a broadening path to end at the horizontal raphe nasal to fixation.
- **Kinetic perimetry:** stimulus location is moved.
- **Static perimetry:** stimulus intensity is varied
- **Isopter:** an area outlined by a given stimulus in kinetic perimetry
- **Threshold:** At a given retinal point, the intensity of a stimulus that is perceived 50% of the times it is presented.
- **Short-term fluctuation:** variability within a field during the time of its measurement.
- **Long-term fluctuation:** variability between two visual fields performed sequentially on the same eye that cannot be attributed to pathologic change.
- **Candela per square meter (cd/m2):** The international unit of luminance.
- **Apostilb:** 0.1 milli-lambert = 3.183 cd/m2.
- **Log unit:** Logarithm base 10 of the luminance in apostilbs.
- **Decibel:** One-tenth of the log unit.

- **Kinetic perimetry**
  - Confrontation
  - Tangent screen
  - Goldmann perimeter.
  - Non-seeing periphery and moved at approximately 2° per second toward fixation
  - 15° intervals around 360° of the visual field

- **Static perimetry**
  - Full-threshold testing: each point in the visual field is evaluated by positioning the stimulus at a test point and varying the intensity until the threshold for that particular retinal location is defined
  - Slopes and scotomas are shown better by static than by kinetic perimetry.

- Automated achromatic static visual field (**AASVF**) testing is the gold standard for the evaluation of optic nerve function.
- There are many makers of AASVF machines, among them are Humphrey (Allergan, Irvine, CA), Octopus, and Dicon
- Modifications:
  - Threshold-related testing: Each retinal location has a statistically determined 'normal' sensitivity range
  - Zone testing: normal, relative defect, or absolute defect.
  - Algorithms that use less precise bracketing to estimate the threshold: Swedish Interactive Testing Algorithm (SITA) program in HFA
  - Noise-field perimetry = white-noise perimetry = **campimetry**: TV screen – normal abnormal areas
  - Optokinetic perimetry

Combined static and kinetic perimetry

- Uses the speed of kinetic perimetry and the sensitivity of static testing
- With manual perimetry, a threshold stimulus is chosen for testing the central field. This stimulus is chosen by a variety of methods, but commonly it is the weakest stimulus visible at the point either 15° above or 15° below the horizontal meridian 25° temporal to fixation.

Reasons for Computerized Perimetry

- Reproducible testing conditions.
- Data-storage capability:
- More sensitive testing: Many researchers claim static perimetry to be superior to kinetic.
- Easy operation and menu driven software make automated perimetry easy to learn and to use.
- **STATPAC analysis: HFA STATistical PACkage**

Techniques

- Mean sensitivity of the visual field decreases approximately **0.58–1.0 dB per decade**
- If the patient generates fixation losses more than 20–30% of the time, the test can be considered only an approximation of the true visual field
- Learning curve
- Pupillary diameter of less than 3 mm can cause generalized depression of the visual field
- Humphrey, Goldmann, and more recent Octopus perimeters use **31.5 apostilbs** of background illumination.

- Temporal summation, the ability of the visual apparatus to accumulate information over time, can influence visual field testing for stimulus exposure times less than 0.5 seconds

- **Variables**
  - Patient variables
    - Age
    - Fixation
    - Reliability
  - Ocular variables
    - Pupil size
    - Media clarity
    - Refractive correction
  - Testing variables
    - Technician
    - Background illumination
    - Stimulus size and intensity
    - Stimulus exposure time
    - Area tested

- The 30-2 program is better for recognizing change along horizontal and vertical meridians such as those that occur in patients with glaucoma and neurologic deficits.
- **Fixation Target**
  - **Central**—Yellow light in the center of the bowl
  - **Small diamond** —It is located below the central target and should be used if the patient cannot see the central fixation light (e.g: macular degeneration). The patient should look in the center of the diamond formed by the four lights.
  - **Large diamond**—It is located below the central target and is used for patient with central scotoma who cannot see either central fixation light or small diamond.
  - **Bottom LED**—Some tests have points in the superior visual field that require a lower fixation light than the central target. The target used is the bottom LED of the large diamond. When testing with the superior 64 or superior 36 screening speciality tests, the bottom LED is the default fixation target. It is automatically illuminated at the beginning of a test.
- **Size of the stimulus:** The standard size of the stimulus is size III for all routine tests. But in situations like advanced glaucoma, the test will be conducted with size V to know the status of macular split.

Visual field interpretation

- Generalized or localized defects
- In an absolute scotoma, the brightest stimulus of the machine is not perceived. In a relative scotoma, the brightest stimulus is visible, but dimmer stimuli are not.
- In glaucoma:
  - 29% of their patients had paracentral scotomas
  - 20% had nasal steps
  - 18% had simple arcuate defects as the predominant diagnostic field abnormality
- HFA vs OCTOPUS
  - MD : Octopus → mean defect, Humphrey → Mean Deviation
  - Humphrey: PSD Pattern Standard Deviation; Octopus: loss variance
  - Important thing to remember is that in both instruments has reverse off nomenclature.

- **Glaucomatous visual field defects**
  - Generalised depression
  - Irregularity of the visual field
  - Nasal step or depression: nasal portion of the visual field is often affected early in glaucoma, and defects may persist until the last stages of the disease. The horizontal raphe is the anatomic basis for this appearance.
  - Temporal step or depression: more commonly found as a component of late-stage disease
  - Enlargement of the blind spot: nonspecific, The normal blind spot is about 7° vertically and 5.5° horizontally, with sharp borders.
  - Seidel's scotoma: If the blind spot enlarges in an arcuate manner.
  - Isolated paracentral scotomata: 20% of glaucomatous visual fields
  - Arcuate defects (nerve fiber bundle defects): begins at the blind spot, arcs around fixation, and ends at the horizontal nasal raphe, classically known as Bjerrum's defect
  - Central and temporal islands: end stage field, only the Papillomacular bundle and some nasal fibers left.
  - Temporal Wedge:
  - Split fixation: only fibers from half of the papillomacular bundle remain, these patients more susceptible to central vision loss at surgery
  - Clover leaf pattern that can accompany fatigue (Four primary points around fixation are checked and confirmed)

- **Nerve fiber bundle associated visual field defects**
  - Chorioretinitis

- Myopic retinal degeneration
- Refractive scotomata
- Trauma
- Retinal laser damage glaucoma
- Optic nerve ischemia
- Optic nerve compressive lesions
- Optic neuritis
- Drusen of optic nerve head

- **Esterman disability rating**: ***Binocular*** assessment used by government and industry is described more fully in the AMA *Guides to the Evaluation of Impairment* and the *Physicians' Desk Reference for Ophthalmology.*

- **Reliability indexes**
  - *False-positive responses* occur when the patient indicates that he or she has seen a stimulus when one was not presented. This is usually a reaction to random noise generated by the perimeter. <20-30%
  - *False-negative responses* occur when the patient fails to respond to a stimulus that is at least as bright or brighter than one that he or she had previously recognized in that position. <20-30%
  - Fixation reliability: <20-33%
  - **Heijl-Krakau technique**: blind spot may be stimulated periodically
  - Technician can offer a subjective assessment of the patient's fixation
  - Computer may stop the test if a video or infrared fixation monitor indicates that the eye has shifted

- **Short-term fluctuation:** the intra-test variation, result of checking several loci in the visual field twice. Deviation should exceed about 5 dB to be considered abnormal.
- **Long-term fluctuation:** the inter-test variation
- **Global indexes**
- **Mean sensitivity**
- **Mean deviation or defect**
- **Standard deviation or variance (PSD/ LV)**
- **Corrected SD (CPSD/ CLV)**

Algorithms

- First described by **Lynn** in 1968.

- **1st Generation-**Threshold determination simply by altering stimulus intensities from infra-or supra luminal until threshold was crossed
- **2nd Generation-**Staircase methods (Standard Full Threshold Testing Algorithm)
    - Predetermined rules for stimulus sequences, Step wise, Number of reversals
    - Used in Humphrey Field Analyzer
    - White, size III stimulus

✦ **3rd Generation**

✣ **FASTPAC**

- Introduced in 1991,it changes stimulus intensity in ***3 dB steps***
- When sequences crosses threshold (i.e. either from seeing to nonseeing or vice versa) ***,testing stops without reversing direction in smaller steps***
- More vulnerable to pt. response because it defines threshold only on the basis of single crossing of threshold

o **Swedish Interactive Threshold Algorithm (SITA) (SITA Standard/ SITA Fast)**

- Test starts by measuring thresholds at 4 primary points, one each quadrant,12.7 degrees from point of fixation
- Conventional up-down staircases using **4-2 step** sizes is used in these 4 points
- Threshold values at these points are used to calculate threshold values in adjacent points
- ***Testing stops if the confidence in a threshold value at a point is (compared to a predetermined value)***
- ***If confidence is low another staircase is initiated***
- **The SITA strategy does not determine Short term Fluctuation.**
- **SITA uses information gained throughout the program to determine the threshold strategy for adjacent points. SITA measures the response time of each patient and uses the information to set the pace of the test.**
- Types-
    - ***30-2***-Central 30 deg with tested points 6 deg apart(offset 3 deg from both horizontal and vertical axes)-total **76** locations
    - ***24-2***-Central 24 deg with grid spacing same like 30-2 i.e. 6 deg total **54** locations
    - ***10-2***-**68** locations spaced on a 2 deg within 10 deg of fixation
    - MACULA TEST: it tests a square grid of **16** points 2 degrees apart centred around the point of fixation. It is used to monitor the central field in advanced glaucoma
    - 60-2/60-4
    - 120 point test
    - Nasal Step Pattern

- Throughout the test **3 types of catch trials** performed-
  1. Fixation loss
  2. False +ve response
  3. False –ve response

- **WEBER'S LAW:** When the threshold visibility is a matter of contrast alone then the threshold sensitivity is a constant expressed as the ratio between the stimulus and background intensity. This constant is termed as the Weber's fraction.
  - Thus if Weber's law is operating any change in the background intensity is reflected in the stimulus intensity maintaining a constant threshold sensitivity. Hence variables like pupillary size do not affect the threshold sensitivity.
- **TEMPORAL SUMMATION:** The visibility of a stimulus varies directly with the duration upto a critical period of 0.3 s
- **SPATIAL SUMMATION:** If the intensity of a stimulus remains the same then its visibility varies directly with the size.

How to Read

- **Zones Independent of normative data and STATPAC analysis**
  - Zone 1: Patient data / test data
  - Zone 2: Reliability indices / foveal threshold
  - Zone 3: Raw data
  - Zone 4: Gray scale
- **Zones Dependent on normative data and STATPAC analysis**
  - Zone 5: Total deviation numerical plot,
  - Zone 6: Total deviation probability plot
  - Zone 7: Pattern deviation numerical plot,
  - Zone 8: Pattern deviation probability plot
  - Zone 9: Global indices—Mean Deviation Index in dB value and with its P value. Pattern Standard Deviation (PSD) in dB value and with its P value, Corrected Pattern Standard Deviation (CPSD) in dB value and with its P value. Short-term Fluctuation (SF) in dB value.
  - Zone 10: Glaucoma hemifield test :
    - a. Out side normal limits
    - b. Border line
    - c. Abnormally low sensitivity,
    - d. Abnormally high sensitivity,
    - e. Within normal limits.

- **How to decide Eye??** → The blind spot is to the left side of mid line so this is a print of a left eye.
- In 24-2 pattern, the outermost ring is omitted from the test except the two nasal points ***(because they are MC involved)***, the will reduce tested locations from 76 locations in the 30-2 test to 54 locations in the 24-2 test, thus reducing the number of tested locations by 29%.
- Reliability indices include fixation loss, false positive and false negative: should be <33%
- Short term fluctuation less than 2.5 means a test of good accuracy
- **Blind spot**: at temporal side of point of fixation, having a size of 5 X 7 and its centre is located 12.5 from point of fixation and slightly below the horizontal line.
- **Fixation loss** is the number of times a patient responds to a target placed in the blind spot.
- **False positive error**: is the number of times a patient responds to the audible click of the perimeter's shutter when no target is presented.
    - Typical areas of white scotomas
    - Trigger happy patients
    - Remember, this can show abnormality in pattern deviation, but pure localized defects should also appear exactly on the total deviation area.
- **False negative error**: is the number of times a patient fails to respond to a suprathreshold target placed in a seeing area of the visual field.
    - Clover leaf pattern
    - Fields should not be considered unreliable solely upon a false negative response rate, particularly if there is a great deal of pathology. In patients with advanced glaucomatous optic nerve damage we may get more than 50% false response which can be attributed in small shifts in fixation.
- **Gray Scale (Halftone):** used to explain to the patient, only points are actually tested (54 -76 points), and at the same time 2000 symbolic representations are used to draw the gray scale.
- **Total Deviation**: the difference between the **measured threshold** of each individual test location & the age corrected normal value for that location.
- Visual field thresholds decline with age at a rate of 0.5-1.0 dB per decade.
- Generalized depression is seen in cases of cataracts and miosis.
- **Pattern deviation** is derived from the total deviation via ***adjustment of the measured thresholds*** upward or downward by an amount which reflects any generalized change in the threshold of the least-damaged portion.
- **The graphic probability plots of total deviation or pattern deviation**: how frequently a value at a particular test location is found in the normal population.
- **Global indices:**
    - **Mean Deviation (MD):**
        - Average departure of each test location from the age-corrected normal value.

    - Severity of damage is considered ***mild if the value of MD is below 6, moderate if the value is between 6-12 and severe if the value is more than 12***
  - **Pattern Standard Deviation (PSD):**
    - Measure of focal visual loss
    - Higher PSD suggests greater localized field damage, In advanced glaucoma, PSD can actually decrease because damage is no longer focal
    - SD calculated for the differences of each test location of that patient and that of the normal of the same age.
    - Remember that MD points toward the height of the field while PSD indicates the shape of the field
  - **Corrected Pattern Standard Deviation (CPSD):** deviation from normal reference hill after adjusting for short term fluctuation
  - **Short Term Fluctuation (SF):** Variability of the threshold for test location when determined within the same session. 1.5 db in young and 2.5 db in old.

- **Long term fluctuation**: variability present between the tests.
- **Glaucoma Hemifield Test (GHT)** evaluates five zones in the superior field and compares these zones to their mirror image zones in the inferior field.
  1. Outside normal limits
  2. Borderline
  3. Generalized reduction in sensitivity
  4. Abnormally high sensitivity
  5. Within normal

- **GAZE TRACKER:**
  - Present in the newer machines.
  - Follows the patient's cornea and records the movements.
  - More spikes and taller spikes indicate greater deviation. Downward spikes represent the situation when fixation was unrecordable.

- **Anderson's Criteria**
  - 3 or more contiguous, non edge points in an expected location of the field that have p<5% on the PD plot, one of which must have p<1% in 30-2.
  - GHT outside normal limits.
  - CPSD values seen in < 5% of population.

Visual Field Progression

- **Procedures used for progression**
  - Clinical evaluation: Determination of improvement, progression, or stability by experienced practitioners
  - Classification systems: Divide the range of visual field stages from normal to blind into discrete segments
  - Event analysis: Determines the change in visual field properties for the current visual field in comparison to baseline values
  - Trend analysis: Determines the best fit of visual field sensitivity over time (regression). In most instances this is a linear fit, but exponential Tobit, polynomial, and spline fits have also been employed.
- **New methods**
  - Bayesian procedures: Forecasting techniques that use prior probabilities and other useful information that are modified by the responses of the individual being tested
  - Support vector machine: A heuristic method of using a machine classifier that develops a model based on a small learning set to classify different groups using a variety of mathematical techniques (eg, quadratic discriminant analysis, Gaussian kernels)
  - Classification and regression trees (CART): A decision tree procedure that uses recursive partitioning of numerical and categorical data to classify groups (eg, normal vs. glaucoma, progressors vs. nonprogressors). It is a forecasting model.
  - Kalman filters: A dynamic model that continually updates knowledge about an individual's visual field status and clinical findings to forecast future outcomes
  - Cluster analysis: This procedure uses clusters of points in the visual field that correspond to the arcuate nerve fiber bundle patterns that are characteristic of the distribution of optic nerve fiber patterns that enter the optic disc.
  - Polar trend analysis: Performs linear regression of visual field sensitivity values that are contained in various sectors of the visual field. It is used as a method of determining visual field progression for various local regions of the visual field, and as a simple means of comparing functional visual field changes with structural variations produced by glaucoma.
  - ANSWERS (Analysis with Non-Stationary Weibull Error Regression and Spatial Enhancement): A linear regression model that incorporates the nonstationary variability at different levels of visual field sensitivity determined as mixtures of Weibull functions, and that also includes the spatial correlation measurements obtained at neighboring locations
  - Permutation analysis: Permutation of pointwise linear regression (PoPLR) is a linear regression procedure that performs a random permutation of the order of visual fields to find the best estimate of visual field progression
  - Least absolute shrinkage and selection operator (LASSO): Uses robust regression and several other methods to provide the best prediction of future visual field status
  - ***Visual field index (VFI):***

- A scale from 0 to 100 that classifies glaucomatous visual fields on the basis of mean deviation (MD) neighboring points, provides more weight to central points, and includes other information.
- It has a ceiling and a floor effect, which limits its use for early or advanced glaucomatous visual field loss.
- Component of the GPA suite
- Each point on the pattern deviation map is scored as a percent.
- Normal sensitivity are given a score of 100% and points with absolute defects are given a score of 0%.
- Points with depressed sensitivity ($p < 0.05$) receive a score calculated by a formula that includes total deviation and age-corrected normal threshold.
- The center of the visual field is then weighted more highly.
- Resulting percentage is displayed on a graph

✦ **Used Methods in Clinical Trials**

✣ Clinical assessment: Clinical evaluation of Goldmann kinetic visual fields was used in the Collaborative Normal Glaucoma Tension Study (CIGTS). To achieve good sensitivity and specificity, progression was determined by 2 out of 3 visual fields within 6 months demonstrating progression followed by 2 out of 3 showing progression in the following 6 months.

✣ Classification: In the Advanced Glaucoma Intervention Study (AGIS) and CIGTS multicenter trials, a 20-point glaucoma visual field severity scale was used, and a 4-point deterioration was an endpoint. Advantages: quantitative. Disadvantages: Not sure whether differences from one point to another are the same across the whole scale.

✣ Event:

- The Early Manifest Glaucoma Trial (EMGT) used event analysis, which consisted of determination of a change in the current visual field from baseline (average of 2 visual fields). To improve specificity, confirmation of a minimum number of abnormal points were required on 2 subsequent tests. This formed the basis for the **Glaucoma Progression Analysis (GPA).**
- Identifies each point as stable, deteriorating, or improving
- **possible progression**: When three test points are significantly progressing ($p < 0.05$) in the same location over two consecutive tests
- **Likely progression**: when three test points are significantly progressing in three consecutive tests.
- Can be used in following all glaucoma patients and glaucoma suspects.

✣ Trend: Linear regression analysis (the Progressor program) was used in the Primary Treatment Trial (Moorfields Eye Hospital). Progressor performs linear regression analysis of individual test locations and has procedures for minimizing the influence of “outliers” (measures that are inconsistent with the remainder of the data).

- ANSWERS: By analyzing several large visual field datasets, ANSWERS demonstrated superior performance when compared to linear regression and permutation analysis (PoPLR).

- **Comparison of Different Methods**
  - Clinical vs. trend: Trend analysis performs better than highly trained clinicians' evaluations.
  - Event vs. trend: Event analysis usually detects progression earlier (sensitivity), but trend analysis has higher specificity.
  - Criteria for identifying progression: Depending on what criteria are used for any of the analysis procedures, there are large differences in sensitivity to detect change, specificity for distinguishing stable from changing visual fields, and the time required to detect change. Agreement among the various methods occurs only about 50%-60% of the time.
  - Continuous vs. discrete functions: Continuous functions contain more information that discrete functions (eg, classification systems).

Newer Perimetry Techniques

- **Why??**
  - To identify glaucomatous damage prior to conventional white-on-white perimetry
  - Because traditional Automated Perimetry will not reveal a scotoma until 25-40 % of nerve fibers are damaged
  - Motion attributes of vision are involved early in glaucoma and not picked up by conventional perimetry
- **Techniques**
  - Short wave automated perimetry (S.W.A.P)
  - High pass resolution perimetry (H.P.R.P)
  - Frequency doubling perimetry (F.D.P)
  - Flicker perimetry
  - Motion perimetry
  - Detection and resolution perimetry

- **Retinal Ganglion Cell Types**
  - Parvocellular (80%):
    - Smaller diameter axons
    - Slower conduction
    - Sensitivity to higher spatial freq(details)
    - Projection to parvocellular layer

        - Concentrated in the central fields
    - Magnocellular (15%):
        - Larger diameter axons
        - Faster conduction
        - Sensitivity to higher temporal freq (ficker, motion)
        - Projection to magnocellular layer
        - Found throughout the retina
    - Koniocellular (5%):
        - 5% of cells project to the koniocellular interlaminar layer of the L.G.B.
        - Involved in the blue-yellow opponent information

Short Wave Automated Perimetry

- Developed by Stiles
- Also called Blue on yellow perimetry
- Software incorporated into Humphrey's Field Analyser II (30-2, 24-2 programs)
- Now available using the SITA strategy (SITA-SWAP), which reduces testing time.
- Intense yellow background with blue stimulus
- **The Principle:**
    - Concept of reduced redundancy
    - Stimulate one colour-vision mechanism
    - Large blue target stimulate short wave sensitive mechanism
    - Isolate the short–wave sensitive pathways
- Stimulus Goldman size V, blue light (440 nm), 200 ms duration
- Background100 cd/m2 intensity yellow light (500-700 nm)
- Instrumentation and software same as W-W-perimetry
- **Advantages**
    - Detect glaucomatous visual field loss prior to conventional white-on-white (W-W) perimetry (3-5 yrs in advance)
    - Predict future visual field defects for standard W-W
    - More rapid glaucomatous progression seen, earlier
    - Correlate well with early optic nerve head changes
    - SWAP shown more extensive visual field loss than W-W perimetry in optic neuritis and in diabetic macula oedema(blue cones are more susceptible to damage in diabetes)
    - SWAP pathway deficits precede luminance pathway deficits in age-related maculopathy, central serous choroidopathy and retinitis pigmentosa.
- **Disadvantages:**

- Affected by absorption of short wavelength stimuli by the aging lens
- Influenced by macular pigment absorption causing a depression in the foveal peak
- Takes approx 15% longer than W-W perimetry , 30-2 using the Full Threshold strategy and approx 17% with the FASTPAC strategy
- Between-subject normal variability is greater for SWAP than for conventional perimetry

Frequency Doubling Perimetry (FDP Matrix)

- Portable small tabletop unit
- **Principle**
  - M-cell neuron sub-set comprising a third to a half of the M-cell neurons (called "non-linear" My-cells) are first involved in glaucoma, basis for frequency doubling testing (25%)
  - When a low spatial frequency sinusoidal grating with alternating wide light and dark bars undergoes high temporal-frequency counterphase flicker, (i.e., the black bands reverse to become white and the white bands reverse to become become black in rapid sequence) gratings appear twice as many light/dark bars (spatial frequency appears doubled) called the "**frequency doubling illusion"**
  - Non-linear M-cell neurons transmit signals related to this illusion. These neurons are the first involved in glaucoma, tests presenting alternate grating stimuli attempt to identify neuron loss earlier
- Greater than 90% sensitivity and specificity when compared to the HFA standard achromatic perimetry as the gold standard
- FDT perimetry tolerates up to 6 D of refractive error
- Not affected by external room illumination
- Not affected by variations in the pupil size, the pupil diameter should be greater than 2 mm
- Instructions to the patient are also quite simple: look at a black dot in the center of the screen and press a button any time a grating pattern is seen
- A 10-degree square pattern is presented at 17 different locations within the **central 20** * 20 degrees visual field
- Test options include a screening field (Screening C-20-1) in which 5-degree gratings with three contrast levels are show at 17 locations in the central 20 degree field
- Abnormal when
  - Any defect in the central five locations
  - Two mild or moderate defects in the outer 12 squares
  - One severe defect in the outer 12 squares
  - Screening test time greater than 90 seconds per eye
- **Advantages:**
  - Short test duration(4-5 min for full threshold)
  - Quick, inexpensive, easily administered, and highly sensitive and specific.

- Not affected by blur upto 6 D
- Not affected by pupil size
- Minimal training required

- Limitations:
  - Fewer spots with larger area (19 spots, each subtending 10 degrees of visual arc, in the N-30 glaucoma testing program)

High-Pass Resolution Perimetry (HPRP)

- **Principle**
  - Ringshaped stimuli are presented on a computer screen
  - The inner and outer borders of the ring are darker, and the area between is lighter, than the background. the average contrast of the stimulus is identical to that of the background, and is maintained at a constant level while stimulus size is altered
  - The computergenerated stimuli are "high pass filtered"; that is, all low spatial frequency information is removed. This technique forms a stimulus type known as the "vanishing optotype"
  - The thresholds for the detection of an object as present and for recognition of what it is become simultaneous if the target cannot be recognized, it will not even be seen
  - Stimulus design is thus chosen because it corresponds to center-surround arrangement of retinal ganglions receptive field
- Test available in **Ophthimus** (High Tech Vision)
- 14 target sizes in 1 db steps are available
- Parameters obtained are Global deviation, Local deviation, neural capacity index, etc
- The Ophthimus provides global indices and statistical analyses conceptually similar to those produced by the Humphrey. In addition, the Ophthimus provides, as a unique parameter, the estimated neural capacity
- Ophthimus provides a printout that includes the ring target sizes seen graphically as well as data about the overall deviation and fluctuation of the responses
- Subject reliability is also assessed
- Central 30 degrees visual field is examined, 50 locations tested
- Adapts automatically to the patient´s reaction time as well to responses to fixation control tests and "blank" and "catch" targets
- **Advantages**
  - Quicker examination (5 min duration)
  - Excellent test-retest reliability
  - Earlier detection of progression
  - Continuous feedback helps to improve concentration

- Early detection and monitoring of glaucomatous damage
- Useful for neurophthalmologic conditions

- **Disadvantages**
  - Limited commercial distribution and representation
  - Requires near correction of 6D greater than patients distance correction , special trial lens needed
  - Use of ring targets makes it difficult to show the linear nature of defects such as a hemianopia that respects the vertical midline or a nerve fiber layer defect that splits fixation
  - The exact location and dimensions of the blind spot are not delineated, this is rarely a significant problem

Flicker Perimetry

- Detection of rapidly flickering stimuli depends on the magnocellular mechanisms(M-cells)
- Tyler suggested that deficits in flicker sensitivity (for high temporal freq) was lost early in glaucoma and ocular hypertensives
- Three different methods are employed for flicker perimetry
- Employs light emitting diodes
- Uniform background of 50 cd
- Stimuli are briefly flickered, patient is asked to respond if flicker detected
- Temporal frequency of flicker is varied to determine highest rate at which it is detected (CFF, critical flicker fusion)
- Advantages:
  - Normal ageing appear later than in HFA
  - More resistant to optical degradation (from Blur, cataract, etc)
- Disadvantages:
  - Still experimental
  - Lack of standardisation
  - Not too patient friendly

Motion Perimetry

- **Principle**:
  - M-cells and large neurons may be damaged early in glaucoma leading to degradation in motion perception
  - Involves detection of direction of motion of small dot / line stimulus
  - Detects the min displacement required to detect movement (Motion displacement thresholds are found elevated in pt at risk of glaucoma with normal visual fields)

- Another technique for motion perimetry uses random pattern of light and dark dots, 'snow pattern', this portion is than moved in a particular direction, pt detects the direction of movement
- Minimum percentage of dots (coherence) needed to detect the direction is determined
- The central 21 degrees of the visual field are tested
- To complete a test takes 3-8 minutes
- Moving stimuli are vertical bars as described in detail by Fitzke *et al*
- Test randomly examines 16 locations with one displacement distance (amplitude) and then the procedure is repeated five times
- Motion sensitivity score are based on the percentage of response from a total of 84 movements over 14 locations (excluding two close points to the blind spot)

Multifocal Electroretinography

- Objectively establishes the loss of retinal function
- Focal responses are obtained from a large number of retinal patches, and topographic maps of dysfunctional areas are derived.
- All focal areas are independently and concurrently stimulated as the ERG signal is derived from the cornea by means of a contact lens electrode.
- 103 hexagonal patches displayed on a video monitor stimulate the central 50 degrees of the patient's visual field
- Focal stimulation consists of pseudorandomly presented flashes.

Home Monitoring of Visual Field

- Moorfields Motion Displacement Test (MBT) on laptop
- Experimental head-mounted perimetry to detect multifocal steady-state visual evoked potentials
- Melbourne Rapid Fields (MRF) on tablet
- Six-month longitudinal comparison of tablet perimeter with Humphrey Field Analyser

Optic nerve

- Optic nerve head is defined as the distal portion of the optic nerve that is directly susceptible to intraocular pressure (IOP) elevation.
- Average disc area: 2.56 mm^2 (different studies)
- Diameter: mean of 1.88 mm vertically and 1.77 mm horizontally
- Diameter of the nerve expands to approximately 3 mm just behind the sclera, where the neurons acquire a myelin

- Three major alterations of glaucomatous damage are
    a. Thinning of the retinal NFL
    b. Posterior excavation and enlargement of the central cup
    c. Posterior outward rotation of the lamina cribrosa with cupping.

- **ONH vasculature**
    a. **Surface layer**: arteriolar branches of the central retinal artery
    b. **Prelaminar region**: Peripapillary choroidal vessels
    c. **Laminar region** : Arterial circle of Zinn-Haller/ SPCA
    d. **Retro laminar region**: contributions from the retinal and ciliary circulation

- **Circle of Zinn-Haller**: Medial and lateral perioptic nerve short posterior ciliary arteries anastomose to form an elliptical arterial circle around the optic nerve, only in 75%

- **Supportive structures of the optic nerve head:**
    - **Internal limiting membrane of Elschnig:** continuous with the internal limiting membrane of the retina
    - Central meniscus of Kuhnt: central thickening of the internal limiting membrane
    - Intermediary tissue of Kuhnt: separates the nerve from the retina (muller cells)
    - Border tissue of Jacoby: separates the nerve from the choroid
    - Border tissue of Elschnig: rim of connective tissue occasionally extends between the choroid and optic nerve tissues, especially temporally
    - Lamina cribrosa
    - **Meningeal sheaths:** posterior to globe

- **Factors influencing ONH circulation**
    - The blood flow depends upon three parameters: (1) vascular resistance (2) blood pressure, and (3) IOP.
    - To calculate the ONH blood flow, the following formula is used: **BF= PP/ R**

- Perfusion Pressure **PP= MABP – IOP** [MABP= DBP + 1/3(SBP-CBP)]
- Vascular Resistance
  - *Auto-regulation of blood flow* is to maintain a relatively constant blood flow, capillary pressure and nutrient supply in spite of changes in perfusion pressure. Evidences show that blood flow in both the retina and ONH is autoregulated by neural, endothelial and myogenic mechanisms.
  - *Vascular endothelial vasoactive agents* play an important role in modulating the local vascular tone. The vascular endothelial cells release various known endothelial vasoactive agents, which include prostanoids, nitric oxide, endothelins, angiotensins, oxygen free radicals, smooth muscle cell hyperpolarization, thromboxane A2 and other agents.
- Retinal circulation has autoregulation while choroidal circulation has neural control.

Clinical evaluation

- Increasing evidence that alterations in the ONH are the earliest signs of primary open-angle glaucoma (POAG), and that visual field studies are more useful later in the disease process
- Slit-lamp fundoscopy
- Monocular examination direct ophthalmoscope
- Photographs of the ONH
- Clinician's disc drawings
- **Disc Damage Likelihood Scale (DDLS)** [Spaeth and co-workers]
  - Radial width of the neuroretinal rim measured at its thinnest point. The unit of measurement is the rim/disk ratio,
  - Average size 1.5-2.0 mm2
- **Armaly** back in 1970 introduced the idea of cup disc ratios (CDR).

- **Optic disc changes in glaucoma**
  - **Intrapapillary disc changes**
    - ***Eight***: two aspects of the optic disc (its size and shape); two aspects of the NRR (its size and shape); three aspects of the optic cup (its size and configuration, and the cup:disc ratio); and the relative position of the central retinal vascular trunk.
      1. **Optic disc size:** 2.1–2.8 mm2, smallest 5° aperture
      2. **Optic disc shape:** only correlates with the extent of corneal astigmatism
      3. **Neuroretinal rim size:**
      4. **Neuroretinal rim shape:** characteristic vertical oval shape of the optic disc and the horizontal oval shape of the optic cup. Neuroretinal rim loss manifests earliest in the inferotemporal and superotemporal regions, followed by the temporal sector, and lastly the nasal rim.
      5. **Optic cup size:**

6. **Optic cup configuration and depth**
7. **Cup:disc ratios:** vertical cup:disc ratio increases faster than the horizontal ratio
    - Quigley found up to 40% of some nerves' axonal mass could be lost without having any recognizable field defect on Goldmann perimetry.
8. **Position of central retinal vessels and branches**

- **Peripapillary disc changes**
    - ***Four***: optic disc splinter hemorrhages; changes in the RNFL; variations in the diameter of retinal arterioles; and patterns of peripapillary choroidal atrophy (PPCA).
        1. **Optic disc hemorrhage**
        2. **Nerve fiber layer defects:** Hoyt and co-workers, visible loss of optic nerve axons from any form of optic atrophy.
        3. **Diameter of retinal arterioles:** Diffuse narrowing of the retinal vessels
        4. **Peripapillary choroidal atrophy:**
            - more peripherally *zone alpha* is characterized by irregular hypopigmentation/hyperpigmentation. It suggests superficial retinal pigment epithelial changes.
            - *Zone beta* is located closer to the optic disc border and is usually more distinctive because of its visible sclera and visible large choroidal vessels. It chorioretinal atrophy. When both zones are present, zone beta is always internal.

- **Subtypes of glaucoma by optic nerve head appearance**
    - High myope
    - Focal normal pressure (focal ischemic)
    - Age-related atrophic POAG (senile sclerotic)
    - Juvenile OAG
    - POAG (generalized enlargement)
- **Specific subtypes of glaucomatous damage**
    - Type 1 – focal ischaemic
    - Type 2 – myopic
    - Type 3 – senile sclerotic
    - Type 4 – concentrically enlarging

- **The Disc Damage Likelihood Scale (DDLS)**
    - Way to describe quantitatively and simply the changes that occur in the Optic Nerve Head (ONH) (the disc).

- It is used to quantify the health of the optic disc, specifically as it relates to glaucoma.
- Two characteristics of the disc: (1) the width of the neuroretinal rim and (2) the size of the optic disc. The DDLS scale goes from 1 to 10, 1 being the most normal and 10 the most pathologic.
- First, one measures the size of the optic disc and classifies the disc as small, average, large, or very large. Small is less than 1.5 mm in height, average between 1.5 and 2.0 mm in height, large between 2 and 3 mm in height, and very large greater than 3 mm
- Next, one looks for where the neuroretinal rim is the narrowest. *("thin" is the wrong word) The narrowest rim would be 0 and the widest rim possible would be .5.*
- Discs with DDLS of 6 or more are never normal.

Optic nerve imaging

- **Structural** glaucomatous changes which usually **precede** functional deterioration (visual field loss)
- **Pre-perimetric diagnosis**
- Progression
  1. Confocal scanning laser ophthalmoscopy (CSLO)→**HRT**; **ONH**
  2. Optical coherence tomography **OCT**: **ONH, RNFL, Macula**
  3. Scanning laser polarimetry (SLP) → **GDX**; **RNFL**

Stereophotography

- Most widely used imaging technique and is considered the gold standard for documentation of glaucomatous optic neuropathy (GON)
- Two photographs in sequence
  - Manually repositioning the camera
  - Using a sliding carriage adapter (Allen separator)
  - By taking two photographs simultaneously with two cameras that utilize the indirect ophthalmoscopic principle (Donaldson stereoscopic fundus camera)
  - A twin-prism separator can be used
- Digital stereochronoscopy
- Advantage
  - Ability to document parameters that cannot be quantified → disc hemorrhages, peripapillary atrophy, and pallor
- Disadvantage
  - Interpretation remains subjective
  - Increased variability and limited usefulness over time

- Media opacities, such as cataracts, or a poorly focused photograph can inhibit optimal analysis

Confocal scanning laser ophthalmoscopy (CSLO)

- In 1980, **R. H. Webb**; created a laser light source device to illuminate the fundus and produce an image of it on a television monitor---**Flying Spot TV ophthalmoscope**. It was later termed as scanning laser ophthalmoscope (**SLO**)
- To improve the contrast and resolution of the SLO, the **confocal mode** is used. Confocality of the system is achieved by placing a pinhole in front of the detector, which is conjugate to the laser focus.
- Heidelberg retina tomography has three generations: **HRT (1991), HRT II (1999) and HRT 3.**
- Three-dimensional images of the optic disc
- **Principle**:
  - ***Spot illumination and spot detection***
  - Diode laser is aimed through a pinhole onto the retina. The light reflected passes through a second pinhole into a detector, which transfers the maximum intensity of light at a given point to create an image
  - The instantaneous volume of tissue from which reflected light is accepted by the confocal aperture is called a **voxel**, and the smaller the aperture, the smaller the voxel and the higher the resolution of the image.
- **670 micron** diode laser
- Bi-dimensional image (15 x 15 degrees); **total of 64 sections**, each done **with 1/16 mm** of depth
- Optical section is composed of 384 x 384 points
- Transverse resolution is **10 microns** and the axial resolution is **300 microns**.
- 3 sets of scans done → data are combined to produce a pseudo-three-dimensional image of the nerve head
- Image is taken → Optic nerve disc delineation by operator → ***'best-fit' ellipse***
- The **reference plane** is located 50 microns posterior to the mean height along a 6° arc of the contour line at the temporal inferior sector.
- Data based on **OHTS**
- Classification of the eye is done with **Moorefield's regression analysis** in HRT or other **discriminating method in HRT II**, or with **neural network analysis in HRT 3**.
- Printout formats currently available: *initial report, follow-up report and OU report*
- **Components of the HRT report**
  - Patient data
  - ***Topography image***: red indicates the cup, green and blue indicate neuroretinal rim tissue. Blue indicates sloping rim.
  - ***Reflectance image****:* it is overlaid with Moorfields analysis

- ***Retinal surface height variation graph****:* retinal height along the contour line and of the thickness of the nerve fiber layer. double-hump → superior and inferior nerve fiber layer
- ***Vertical and horizontal interactive analysis:*** disc steepness, presence of sloping,
- ***Stereometric analysis****:* 14 nerve parameters in HRT II
- *Moorfields regression analysis (MRA):*
- Red x: below the 99.9% prediction interval
- Yellow checkmark: between the 95% and 99.9%
- Green checkmark: within the 95%
- ***Glaucoma probability score (GPS): in HRT 3***

- **Evaluating scan quality**: Image quality is expressed by a "topography standard deviation (TSD)" value. **do not** analyzing scans with a **SD value greater than 40**.
- **Strengths:**
  - Rapid and simple operation
  - Specificity from 75% to 95% and sensitivity from 51% to 97%.
- **Limitations:**
  - Contour line drawn by the operator.
  - Overestimate rim area in small optic nerves and to underestimate rim area in large nerves
- ***Change analysis with HRT***
  - Trend analysis
  - Topographic change analysis (TCA): automatically done at 3rd scan
- **Top five Parameters in HRT II**: Rim area, Rim volume, Cup shape measure, Height variation contour, Mean RNFL Thickness
- **HRT 3:**
  - Larger ethnicity-specific normative database.
  - Reduces technician dependence by producing automated results of the contour line as described by Swindale et al

Optical coherence tomography (OCT)

- Carl Zeiss, 1991
- ONH, RNFL and macula
- **Principle**: intensity and echo time delay of back-scattered and back-reflected light from the scanned tissues
- Super luminescent **810 or 850 nm diode laser**
- Best axial resolution: **3–4 microns**
- OCT 1, OCT 2, OCT 3 or Stratus OCT, and OCT 4/ Spectral domain & OCT fourier domain

- 1.73 mm radius circle

- **Peripapillary scan**
  - 3.4 mm circular scan
  - Thickness values are provided for the four quadrants
- **Macular scan**
  - Six linear scans in a spoke pattern configuration.
  - The linear scans are spaced 30° apart
- **ONH scan**
  - 'Star' or 'Spoke' pattern scan, 4 mm
- **Components of the oct report**
  - RNFL thickness
    - NFL thickness was the first parameter developed and validated for glaucoma diagnosis and for following glaucoma. Peripapillary RNFL cross-sectional thickness and area maps should both be evaluated to assess RNFL loss.
    - Optic disc parameters are intuitive and familiar but do not replace in vivo and photographic assessment of the optic nerve head since things like optic disc hemorrhages and pallor cannot be assessed with OCT.
  - Ganglion cell layer (GCL) thickness
    - Measurement of the GCL in the macula is a more recent parameter used in glaucoma assessment.
    - Approximately 54% of the ganglion cell bodies reside in the macula, so measuring this layer perhaps does not provide as much information as RNFL or ONH measurements since the latter measure 100% of their structures. The boundary between the GCL and the underlying inner plexiform layer (IPL) is difficult to segment, so these two layers are measured together even though the inner plexiform layer is not affected in glaucoma.
    - The instrument from Optovue includes the RNFL, GCL, and IPL in its Ganglion Cell Complex (GCC) measurement, while the instrument from Zeiss does not include the RNFL in its Ganglion Cell/Inner Plexiform Layer (GCIPL) measurements.
    - As long as one is not comparing across OCT manufacturers, this has no impact on clinical judgment.
  - Optic nerve head (ONH) parameters
  - Total macular retinal thickness (TRT)
    - Finally, the Spectralis OCT provides measurements of total retinal thickness (TRT) in the macula and relies on symmetry analysis comparing TRT between the right and left eyes of a patient and between upper and lower hemifields in the same eye. Good sensitivity and specificity have been reported for these OCT parameters.

- **Quality assessment**
  1. *Peripapillary circular scan centration*
  2. *Signal strength value:* **not lower than 5**
  3. *Homogeneity of the RNFL scan*
  4. *OCT algorithm*
- **Strengths:**
  - Most versatile
  - Best axial resolution
  - *The only technology capable of imaging the RNFL, macula and ONH.*
- **GCC of Macula**: The higher speed and resolution of FD-OCT improved the repeatability of macular imaging compared with standard TD-OCT. Ganglion cell mapping and pattern analysis improved diagnostic power**. The improved diagnostic power of macular GCC imaging is on par with, and complementary to, peripapillary NFL imaging. Macular imaging with FD-OCT is a useful method for glaucoma diagnosis and has potential for tracking glaucoma progression.**
- Sensitivity ranging from 61% to 84% and specificity from 85% to 100%.
- **Limitations:**
  - Its normative database
  - Transverse resolution
  - Originated from one set of scans and **not a series (three) of sets of scans as in HRT**
  - **Not yet developed robust programs for the longitudinal evaluation** of glaucomatous progression
  - Multiple factors can cause **"red disease," or false positive** results, or **"green disease," or false negative** results.

Scanning laser polarimetry

- GDX
- Latest: **GDX VCC** → GDX variable corneal compensator
- Measure peripapillary RNFL thickness
- **Principle of birefringence**: In the retina, the parallel arrangement of the microtubules in retinal ganglion cell axons causes a change in the polarization of light passing through them. The change in the polarization of light is called **retardation**, which can be quantified by a built-in **ellipsometer**. The retardation value is proportionate to the thickness of the RNFL.
- 2.8 mm and 3.2 mm diameter circle, 0.4 mm band
- Diode laser 780 nm
- VCC: to account for the variable corneal birefringence in patients, it uses the birefringence of Henle's layer in the macula as a control for measurement of corneal birefringence

- ECC: enhanced corneal compensator
- **Components of the GDX report**
  1. **Patient data and quality score***:* ideal quality score is from 7 to 10
  2. ***Fundus image****:* reflectance image of the posterior pole 20 x 20 degrees
  3. *RNFL thickness map*
  4. *TSNIT graph*
  5. *TSNIT symmetry graph*
  6. *TSNIT comparison graph and serial analysis graph*
  7. *Deviation from normal map:*
  8. *TSNIT parameters*
  9. ***Nerve fiber indicator (NFI):*** proprietary value, origin not published, [range 1 (normal) to 100 (glaucoma)]
     - <30: low likelihood of glaucoma
     - 30–50: glaucoma suspect
     - >50: high likelihood of glaucoma.
- **Strengths**
  - Rapid and simple imaging of peripapillary RNFL
  - Sensitivity ranging from 80% to 92% and specificity from 66% to 98%
  - Progression in the GDx is documented using **guided progression analysis**
- **limitations**
  - Only provide RNFL data
  - Corneal surgery will induce error
  - Macular pathology is likely to impede GDX scanning

Retinal Thickness Analyzer

- RTA; Talia Technology, Mevaseret Zion, Israel
- Computes **macular thickness** and displays 2D-3D images
- Green, 540-nm HeNe laser slit beam to image the retina.
- Nine scans with nine separate fixation targets are taken. The compositions of these scans cover the central 20 degrees (measuring 6 × 6 mm) of the fundus.
- Highest concentrations of retinal ganglion cells reside in the macula, and retinal ganglion cells are significantly thicker than their axons (which comprise the NFL), macular thickness may be a good measure of glaucoma.
- RTA and OCT may both be used for macular thickness assessment.
- Limitations
  - Requires a 5-mm pupil size and is limited by eyes with numerous floaters or significant media opacity.

- More sensitive to nuclear sclerotic cataract

Posterior Pole Asymmetry Analyser

- Latest in sprectalis.
- Macular vulnerability area.
- Looks like corneal topography colour maps..!!
- **Considered to be most most most sensitive..!!**

Blood Flow in Glaucoma

- Other than IOP, Vascular risk factors, including systemic blood pressure, ocular perfusion pressure, disc hemorrhage, and migraine, have been linked to glaucoma.

Scanning Laser Ophthalmoscope Angiography

- Replacing the incandescent light source with a low-power argon laser beam to achieve better penetration through lens and corneal opacities
- Laser frequency according to FA or ICG
- Measurements such as arteriovenous passage time (AVP) and mean dye velocity.
- **Fluorescein SLO Angiography**
  - Evaluation of retinal hemodynamics
  - AVP allows localization of measurements to a specific retinal quadrant
  - Mean dye velocity: evaluates the average speed of blood flowing through large retinal vessels
  - Mean transit time (MTT): measures the amount of time that blood spends in the retinal vasculature
- **Indocyanine Green SLO Angiography**
  - Evaluation of choroidal hemodynamics
  - Two areas adjacent to the optic disk and four areas surrounding the macula, each 25 × 25 pixels, are selected
  - Area dilution analysis: measures the brightness of these six areas and determines the time required to reach predefined levels of brightness (10% and 63%)

Color Doppler Imaging

- Retrobulbar vessels, specifically the ophthalmic, central retinal, and posterior ciliary arteries.
- B-scan with superimposed color representation of blood flow velocity
- Velocity data are graphed against time, and the peak and trough are identified as the peak systolic (PSV) and end diastolic (EDV) velocities.

- **Pourcelot's resistive index** (RI) is a measure of downstream resistance that is derived from the PSV and EDV.

Measurement of Ocular Pulsation

- Modified pneumotonometer or a dynamic contour tonometer is used to assess pulsatile ocular blood flow (POBF)
- POBF device provides real-time measurement of IOP approximately 200 times per second

Confocal Scanning Laser Doppler Flowmetry

- Heidelberg retinal flowmeter (HRF) is a commonly utilized confocal scanning LDF device
- 790-nm laser to scan each pixel within the targeted area of the retina.

Spectral Retinal Oximetry

- Measurement of the oxygen saturation of hemoglobin in retinal vessels

Doppler Ocular Coherence Tomography

OCT-Angiography

- OCT angiography (OCT-A) is a novel imaging modality that uses the motion of blood cells to detect blood flow and map blood vessels down to the capillary level. No extrinsic contrast agent, such as intravenous fluorescein, is needed. OCT-A is a software extension of standard OCT technology and does not require any hardware modification of widely available OCT devices.
- OCT-A can be used to visualize and measure the blood vessels in these structures and measure vessel density. In the optic disc, OCT-A has been used to show that glaucoma reduces perfusion both in the superficial disc and in the deeper lamina cribrosa.
- In the peripapillary retina, vessel density (VD) is significantly reduced in glaucomatous eyes compared to normal eyes, and measuring this could be used to diagnose glaucoma with excellent accuracy
- In the macula, glaucoma damages the ganglion cells supplied by the superficial vascular complex (SVC). OCT-A measurements of the SVC-VD had an excellent diagnostic accuracy for distinguishing glaucoma from normal controls
- Advantages
    - OCT-A may be able to detect dysfunctional nerve fibers or ganglion cells before cell death and tissue thinning occurs—which would allow for earlier diagnosis of glaucoma.
    - In the later stages of glaucoma, OCT-A may be able to monitor progression better than conventional structural OCT measures such as the NFL thickness. The relationship between NFL thickness and VF is highly nonlinear.

Primary angle-closure glaucoma

- Congestive/non-congestive and compensated/uncompensated.
- Acute, subacute, and chronic
- **International Society of Geography and Epidemiology of Ophthalmology (ISGEO) Terminology**
  - Facilitates meaningful comparison
  - Addresses both the prognosis for progression, and the stage-appropriate need for treatment.
- PAC disease relies on three simple categories: IOP measurement, gonioscopy, and disc and visual field evaluation.
  - **PAC suspect:**
    - Greater than 270° of irido-trabecular contact
    - Absence of PAS
    - Normal IOP, disc, VF
  - **PAC**
    - Greater than 270° of irido-trabecular contact
    - PAS
    - Increased/ normal IOP
    - Normal disc, VF
  - **PACG**
    - Greater than 270° of irido-trabecular contact
    - PAS
    - Increased IOP
    - Abnormal disc, VF

Mechanisms

- RECENT TRENDS: Angle closure is characterized by iris apposition to the trabecular meshwork. The mechanisms of this anatomic abnormality can be categorized at four structural levels:
  - The pupillary margin (e.g., pupillary block)
  - The ciliary body (e.g., plateau iris and iridociliary cysts)
  - The lens (e.g., phacomorphic glaucoma)
  - Posterior to the lens (e.g., malignant glaucoma)

1. Pupillary block glaucoma

- **Demographic risk factors**
  - Age: greatest frequency in the sixth and seventh decades
  - Gender: 2–3 times more commonly in women

- Heredity: sporadic, AD, AR
- Refractive error: much higher in individuals with hyperopic eyes
- Miscellaneous factors: winter, low levels of illumination, increased cloudiness, changeable weather, and low sunspot activity

- **Ocular risk factors and mechanisms**
  - Shallow anterior chamber both centrally & peripherally
  - Decreased anterior chamber volume
  - Short axial length of the globe
  - Small corneal diameter
  - Increased posterior corneal curvature
  - Decreased corneal height.
  - Anterior position of the lens with respect to the ciliary body
  - Increased curvature of the anterior lens surface
  - Increased thickness of the lens
  - More anterior insertion of the iris into the ciliary body, giving a narrower approach to the angle recess, and possible anomalies of iris histology.
  - Thinning of the ciliary body is reportedly associated with anterior movement of the lens, increased lens thickness and decreased anterior chamber depth.
- **It is estimated that central anterior chamber depth decreases 0.01 mm/year**

2. Plateau Iris

- **Barkan**: 20% of eyes with 'noncongestive' forms of angle-closure glaucoma were atypical in that they had normal central anterior chamber depths, little bombé, and minimal pupillary block
- **Shaffer and Chandler**: *plateau iris*
- **Wand**: plateau iris configuration and plateau iris syndrome
- **Plateau iris configuration**
  - Narrow angles or angle closure in an eye with a 'normal' central anterior chamber depth on slit-lamp examination, and a flat iris plane from pupil to periphery
  - **Tornquist**: plateau, on gonioscopy, iris appears flat from the pupillary margin to the periphery
  - ***Double hump* or *S-sign***: peripherally elevated roll of iris
    - Best seen in ***Koeppe gonioscopy***, where the forwardly positioned ciliary processes prevent the peripheral iris from falling backward in the supine
    - ***On–off indentation*** maneuver of compression gonioscopy at the slit lamp
  - In many cases, plateau iris configuration is accompanied by some degree of pupillary block, which exacerbates the problem. Therefore, it is often not possible

on clinical grounds to differentiate between a pupillary block PAC and a plateau iris configuration embarrassing the angle **until after an iridotomy** has been performed. In conditions precipitated by **pupillary block, iridotomy will cause the iris to fall back and the peripheral chamber to deepen; whereas in plateau iris, the peripheral angle remains unchanged**

- Mydriasis if required: one drop of 0.5% tropicamide or 2.5% phenylephrine. Always reverse with **dipiperazole**.

- **Plateau iris syndrome**
  - Angle closure in the presence of plateau iris configuration following a patent iridotomy
  - Angle closure occurs because the ciliary processes are rotated forward (UBM is the mainstay Dx)
  - **Lowe and Ritch**: incomplete form of PIS → iris is not as far forward as in the complete syndrome;
  - **Diagnosis is usually not made until after a successful iridotomy**; at that point, little significant opening of the chamber angle and elevated IOP (especially after pharmacologic dilation) may signal its presence
  - Differential diagnosis
    - Extensive PAS due to any cause
    - Imperforate or occluded iridotomy
    - Multiple cysts of the iris or ciliary body
    - Ciliary block glaucoma (aqueous misdirection or malignant glaucoma)
  - Treatment
    - Laser iridotomy
    - Peripheral iridoplasty: ALPI is useful to open appositionally closed angle. Typical treatment includes approximately 20 to 30 spots of argon laser placed in the far periphery over 360 degrees. Filtration surgery may ultimately become necessary in some patients.
    - Miotic agents can be tried to minimize pupillary dilation
- **Pseudoplateau iris**
  - Primary cysts of the iris and ciliary body

3. phacomorphic mechanism

- Abnormal lens either compromises the lens–iris channel (pupillary block) or mechanically pushes the peripheral iris forward into the angle structures.
- Age-related cataract or rapidly with a traumatic, swollen cataract.
- The definitive treatment for this condition is cataract extraction.
- **Angle-closure glaucoma from a swollen lens**

- Idiosyncratic response to a variety of systemic medications: sulfonamide drugs and their derivatives, the carbonic anhydrase inhibitors, thiazide diuretics, tetracycline, prochlorperazine, spironolactone, phenformin, acetylsalicylic acid, and the anticonvulsant topiramate (Topamax)
- Blurred vision at distance, and are noted to have acquired bilateral myopia, with shallow anterior chambers and angle closure

- **Clinical Features**
  - Unilateral blurring and ocular pain to extreme ocular or periocular pain, headache, nausea, vomiting, and diaphoresis.
  - Acute attacks may be precipitated by pharmacological mydriasis, dim illumination, stress, or prolonged near work.
  - Conjunctival injection, corneal epithelial edema, mid-dilated pupil, a shallow anterior chamber
  - Intraocular pressure may be as high as 70
  - Glaukomflecken: flecks of anterior subcapsular opacities.
- **Treatment**
  - Topical beta-blocker, cholinergic agent, and carbonic anhydrase inhibitor, and systemic acetazolamide (i.v. 250 to 500 mg
  - Osmotic agent (e.g., i.v. mannitol 1 to 2 g per kg over 45 minutes)
  - Argon laser peripheral iridoplasty (ALPI) can be applied from 180 degrees to 360 degrees
  - Once the corneal edema has cleared, a laser peripheral iridotomy (LPI) can be performed to prevent recurrent attack.
  - LPI of the fellow eye

Acute Angle Closure

- Precipitating factors: Emotional stress, near work in dim lit conditions, watching a movie in a dark theater, acute hyperglycemia, pharmacological dilation, general anesthesia, and rarely ciliary body tumors/cysts, trauma, uveal melanoma and secondaries to the eye, can precipitate an acute angle closure attack.
- Drug induced angle closure glaucoma : Drugs like topiamate (antiepileptic) and paroxetine (antidepressant) can induce bilateral angle closure attacks probably due to cilio retinal effusion.
- Symptoms : Blurred vision with haloes around lights, severe pain in eyes with redness and frontal headache on the affected side, nausea vomiting and rarely palpitations with abdominal cramps. In some patients the attack may be associated with minimal pain and no congestion.
- Signs : Elevated IOP > 45mmHg, corneal edema, shallow or flat anterior chamber, circum ciliary congestion, pupil is mid dilated with reduced or no reactivity. Fundus shows disc edema, with venous congestion and splinter hemorrhages or it may be a normal disc or may show glaucomatous excavation. There may be some inflammation and rarely a hypopyon if the attack is long standing.

- **Differential diagnosis**
  - Phacomorphic glaucoma
  - Neovascular Glaucoma
  - Glaucomatocyclitic Crisis:
  - Acute anterior uveitis:
- **Management**
  - Mannitol is used as 20% solution. It acts over ½ 1hour (5-7 ml/kg body wt)
    - Actions via osmoreceptors in the brain and the local actions of shrinking the vitreous and pulling back the iris – lens diaphragm.
  - Syrup glycerol used as 50% solution. Lime juice is added to make it palatable.
  - Intravenous acetazolamide should be considered if available. Oral acetazolomide 500 mg is given followed by three times a day
  - Pilocarpine drop installation
  - Special Maneuvers
    - compression gonioscopy
    - alternative is to indent the central cornea with cotton tipped applicator
    - Argon laser iridoplasty
  - Definitive Management
    - Iridotomy
    - prophylactic iridotomy in the fellow eye
    - Trabeculectomy
    - surgical iridectomy

Secondary angle-closure glaucoma

- **Narrowing of the angle due to Pulling**
  - Contracture of membranes in:
    - Neovascular glaucoma
    - ICE syndrome
    - Posterior polymorphous dystrophy
    - Penetrating and non-penetrating trauma.
- **Narrowing of the angle due to pushing**
  - With Pupillary Block
    - Phacomorphic glaucoma
    - Ectopia lentis
    - Posterior synechiae due to uveitis.
  - Without Pupillary Block
    - Ciliary block glaucoma
    - Phacomorphic glaucoma
    - Ectopia lentis
    - Intraocular tumours like malignant melanoma/ retinoblastoma
    - Anterior rotation of the ciliary body following scleral buckling/PRP.

Phacomorphic Glaucoma

- Angle closure secondary to a mature or hypermature lens
- Pathophysiology
  - Crowding of the anterior segment structures→ pupillary block may cause high IOP. Later, the growing size of the lens presses forward on the iris in the periphery, blocking off outflow through the trabecular meshwork.
  - Mapstone hypothesis of pupillary block.
- Only 57% of 49 patients with phacomorphic glaucoma attained visual acuity of 6/12 or better
- Clinical Features
  - Pupil may be mid-dilated with or without iris bombé, and gonioscopy reveals angle closure.
- Management
  - Medical therapy to suppress aqueous formation
  - **NO MIOTICS**
  - Iridotomy may open up the angle, lower the IOP, and allow the eye to quiet before cataract removal
  - Definitive treatment for phacomorphic glaucoma is removal of the intumescent lens

Neovascular Glaucoma

- Neovascular glaucoma (NVG), is a type of secondary glaucoma which results due to growth of new blood vessels on the iris and the anterior chamber angle. It is one of the most intractable types of secondary glaucoma, and if not recognized and managed early, can rapidly lead to vision loss.
- **Pathogenesis:**
  - In 97% of cases the cause for the development of new blood vessels in the anterior segment, is underlying retinal ischemia. Only in 3% of cases, other causes like chronic anterior segment inflammation, can contribute to the new vessel development.
  - 4 stages
    1. Release of angiogenesis factors (PRE RUBEOSIS STAGE) (FGF, VEGF, angiogenin, TGF, interferon, tumor necrosis factor-a, and platelet derived growth factor)
    2. New blood vessels on the iris and angle (RUBEOSIS IRIDIS/PRE GLAUCOMA STAGE)
    3. Open angle but occlusion of aqueous outflow (NVG-OAG)
    4. Fibrosis with NV, closed angle, Ectropion uveae (NVG-ACG)
- **Underlying retinal causes for NVG:**
  - ***Vascular disorders***
    - Central retinal vein occlusion: The most common cause for NVI. The overall incidence of NVI in all CRVO cases is 12% to 30%. NVI also more commonly occurs in the ischemic type of CRVO. One thirds of CRVO cases are ischemic, and of them two thirds develop NVG. NVG usually develops after three months of the vein occlusion.
    - Diabetic retinopathy: one third of patients with NVI have Diabetic retinopathy. More common in aphakic eyes, and pseudophakic eye with posterior capsule opening.
    - Central retinal artery occlusion
    - Branch retinal vein occlusion
    - Carotid occlusive disease
    - **Ocular ischemic syndrome (OIS)** encompasses the ocular signs and symptoms that result from chronic vascular insufficiency. Severe atherosclerotic disease of unilateral or bilateral internal carotid arteries, or, at the bifurcation of the common carotid arteries, results in OIS. 5% of severe carotid artery stenosis cases present with OIS.
  - ***Ocular disease***
    - Uveitis
    - Retinal detachment
    - Persistent hyperplastic vitreous

- ***Surgery and radiation therapy***
  - Retinal detachment surgery
  - Vitrectomy
  - Radiation
- ***Trauma***
- ***Neoplastic diseases***
  - Retinoblastoma
  - Melanoma of the choroid

- **Clinical findings:**
  - ***Symptoms***: In the early stages of NVG, where NVI and or NVA are present but IOP is not raised, the patient does not have any symptoms. Once the IOP is increased, symptoms attributable to the raised IOP, and its sequelae are seen. The patient may have pain, and redness in the involved eye, accompanied by a decrease in vision. Corneal epithelial and stromal edema if present can give rise to photophobia and watering, in the affected eye.
  - ***Signs:*** Undilated anterior segment examination under high magnification can help detect fine NVI at the pupillary border. This should be compulsorily done in all cases of CRVO, PDR, and when other systemic or ocular diseases which can cause NVI are present.
  - Gonioscopy in the affected eye in crvo can reveal presence of NVA. Gonioscopy should also be done in all cases of PDR, to detect fine NVA if present. NVA can be distinguished from normal angle vessels by the fact that these are fine and cross the Trabecular meshwork, unlike normal angle vessels which do not cross the scleral spur.
  - In advanced cases, synechial closure of the angle, may be present, with none of the angle structures being seen.
  - Ectropion uveae may be seen as a result of the contraction of the fibro vascular membrane , which pulls the iris pigment epithelium, anteriorly.
  - Pupillary reaction may be sluggish and a RAPD may be seen in eye with coexistent retinal pathology, or if extensive glaucomatous disc damage has occurred.
  - Dilated retinal exam in all cases with NVI/NVA is mandatory as the underlying cause can be detected, in most cases by fundus examination.
  - In advanced stages of NVG, IOP is raised, and secondary to the raised IOP, one may see corneal stromal, and epithelial edema. Visual acuity is grossly reduced.
  - Anterior segment flare may be present, because of the compromised blood ocular barrier, due to the presence of NVI.
  - Pupil is fixed in the mid dilated position, with Ectropion uveae, and does not react to light.
  - Hyphaema may also be seen due to bleeding into the Anterior chamber due to the NVI.
- **Investigations**:

- Fundus fluorescein angiogramto assess retinal ischaemia
- Electroretinogram – to assess for retinal ischemia. The electroretinogram measures a mass electrical response of the retina, allowing for assessment of the retinal periphery, which cannot be seen with fluorescein angiography.
- Iris angiography in cases of doubtful NVI, to confirm the diagnosis
- B scan ultrasound if view of retina not possible due to media opacity/ corneal edema.
- Systemic:
  - FBS and PPBSto r/o Diabetes Mellitus.
  - Carotid Doppler in case OIS is suspectedNVG in absence of either PDR, or CRVO.

- **Differential Diagnosis:**
  - Fuchs Heterochromic Cyclitis.
  - Acute Angle closure Glaucoma.
  - Other Inflammatory Glaucomas.
- **<u>The management of NVG</u>**, is two pronged.
  - Management of the underlying condition which led to development of NVI/NVA e.g. CRVO, PDR, OIS, etc.
  - Management of the NVG per seIOP and Pain management.
  - **Management of the underlying condition is crucial to effectively control IOP, and preserve vision in NVG.**
    - ***Pan Retinal Photocoagulation:***
    - Ablation of retinal tissue is known to cause a decrease in the release of angiogenesis factors, and leads to regression of NVI/ NVA. If done early in the natural history of the disease, before synechial closure develops, PRP itself can help in reduction of IOP. The presence of extensive synechiae will warrant additional medical/ surgical methods to control the IOP.
    - In some instances where media is hazy, PRP may still be performed with the use of an indirect ophthalmoscopic delivery system. When adequate PRP (1200–1600 laser spots) is not achievable, other modalities should be considered, including panretinal cryotherapy and transscleral diode laser retinopexy.
  - **Management of the IOP:**
    - Medical management of raised IOP in cases of NVG, involve use of
    - Topical antiglaucoma medicationsBeta blockersTimolol maleate 0.5%, or Betaxolol 0.5% bd, or Brimonidine, or Dorzolamide eye drops.
    - Prostaglandin analogues and Pilocarpine are contraindicated in the setting of NVG, as they tend to further compromise the blood ocular barrier, and are not effective in NVG to bring down IOP

- Systemic antiglaucoma medicationsAcetazolamide 250 mg upto qid, and use of Oral Glycerol, or Intravenous Mannitol can help in decreasing IOP, and clearing up the cornea to enable pan retinal photocoagulation.
- Atropine 1% bd, can stabilize the blood ocular barrier, and decreases pain associated with NVG.
- Topical steroids can also help stabilize the blood ocular barrier, and reduce pain.

- **Initial medical management helps control IOP, and enables performing PRP.**
  - In case of raised IOP despite adequate PRP/ other retinal ablation, the treatment options are as follows:
  - Supplemental medical management with topical anti glaucoma medications.
  - If uncontrolled despite this,(maximal medical management)
    - Trabeculectomy with MitomycinC
    - Implantation of Glaucoma Drainage devicesAhmed Glaucoma Valve, Molteno Valve, Baerveldt valve etc.
    - Cyclodestruction:
      - Cyclocryotherapy.
      - Trans scleral cyclo photocoagulation.
      - Endoscopic cyclophotocoagulation.
- **Anti VEGF treatment** with various Intravitreal drugs e.g: Bevacizumab, Pegatanib, VEGF trap, Ranibizumab can cause regression of NVI/ NVA. *The use of these anti angiogenic agents, is to obtain a therapeutic window, in which one can perform PRP, or other forms of retinal ablation*.

ICE Syndrome

- Classically unilateral ***(if bilateral, first think of Reiger's syndrome with late presentation)***
- **Epidemiology**
  - Most often unilateral; rarely bilateral or familial
  - Seen most often in early to middle adulthood
  - More common in women
  - Chandler syndrome is the most common variant.
  - Glaucoma is most common with essential iris atrophy.
- **History**
  - Essential or progressive iris atrophy was first described by Harms in 1903.
  - Chandler syndrome was reported in 1956.
  - Cogan Reese syndrome was described by Cogan and Reese in 1969.
  - Campbell in 1978 suggested that the syndrome resulted from abnormal corneal endothelium.

- In 1979, Yanoff coined the term “iridocorneal endothelial” (ICE) syndrome, which has been the accepted term used to describe this group of disorders.

- **Pathogenesis and Pathology**
  - The underlying abnormality in ICE syndrome is an abnormal corneal endothelium that is dysfunctional but also proliferates to extend over the anterior chamber angle and over the iris surface with production of basement membrane material by these cells.
    - In Chandler’s variant, the abnormal corneal endothelium is attenuated, demonstrating pleomorphism and epithelium like features by EM and immunohistochemical labeling and associated with a thickened collagenous basement membrane.
  - In progressive iris atrophy, “stretch holes” are formed; the cellular membrane, which is often prominent where the pupil is up drawn, is away from the area of atrophy, which is where the iris is stretched. “Melt holes” of the iris are also seen.
  - In Cogan-Reese syndrome the iris nodules are caused by contraction of the iris surface cellular membrane, which bunches normal iris stroma, resulting in stromal nodules that resemble nevi.
  - The stimulus causing proliferation of endothelial cells is not clearly identified. Alvarado and colleagues described the presence of HSV DNA in 16/25 corneal buttons from ICE syndrome, suggesting a viral etiology.

- **Clinical Features**
  - Patients may present with unilateral visual loss that can occasionally be painful or may present with complaints of an abnormal pupil or a spot on the iris.
  - The diagnosis may often be overlooked.
  - The clinical findings of the 3 variants can be described separately, but there is often an overlap between the variants, the extent of which can be quite variable
    - **Chandler syndrome:** Corneal edema occurs more frequently. Iris changes are mild. Elevated IOP might be present. Specular microscopy shows a beaten silver/ metal appearance of the corneal endothelium. Corneal endothelial cells show pleomorphism, loss of hexagonal features, and dark areas within the cells. Confocal microscopy shows pleomorphic epithelial-like endothelial cells with hyperreflective nuclei. In the United States one series describes this to be the more common variant of the syndrome. In a series from Thailand, Cogan Reese syndrome was the most common form and was strongly associated with glaucoma.
    - **Progressive (essential) iris atrophy:** Iris atrophy may be multifocal and progressive. The iris atrophy is often diagonally opposite to the area of corectopia. Ectropion uvea may be seen. Peripheral anterior synechiae on gonioscopy. Corneal edema may be present concurrently. Glaucoma is common and more severe than that seen in Chandler syndrome.
    - **Cogan Reese (iris-nevus) syndrome:** The variant is characterized by nevus-like nodular pigmented lesions on the iris surface, which can be progressive. Peripheral anterior synechiae are noted. May be associated with corneal edema, iris atrophy, and glaucoma. The glaucoma tends to be

severe. The contralateral eye may show subtle endothelial cell abnormalities in some patients.

- Glaucoma in ICE syndrome is secondary closed-angle type glaucoma. Prevalence of glaucoma in patients with ICE syndrome ranges from 46% to 80%. Glaucoma tends to be more severe and progressive in progressive iris atrophy and in Cogan Reese syndrome, but this figure is also variable, depending on the series. The risk factors that determine which patients develop glaucoma are not clear.

- **Testing**
  - Ophthalmic evaluation
  - Gonioscopy shows high peripheral anterior synechiae, especially in the quadrant where the pupil is up drawn.
  - Visual field testing
  - Specular or confocal microscopy of both eyes
  - Anterior segment photography may be useful to follow iris changes.
- **Differential Diagnosis**
  - Corneal findings: Posterior polymorphous dystrophy and Fuchs endothelial dystrophy
  - Iris atrophy: Axenfeld Rieger syndrome, aniridia, iridoschisis
  - Iris nodules: Iris melanosis, melanoma, granulomatous uveitis with iris nodules, neurofibromatosis.
  - The features differentiating ICE syndrome cases from iris melanoma include guttata-like changes in the cornea, peripheral anterior synechiae, iris atrophy, iris transillumination defects, and ectropion uvea or corectopia. Features that favored a melanoma included tumor compression of angle, iris seeding of tumor extra scleral extension of tumor. IOP elevation was seen in only 10%.
- **Management**
  - Medical treatment is the initial mode of management. Among those patients that do develop glaucoma eventually, 80% required a surgical procedure in one series.
  - In those patients that develop glaucoma, medical treatment will eventually fail. The period between medical treatment failure and the need for surgery is highly variable.
  - Surgical success
    - Trabeculectomy: Success rate with 5-fluorouracil and mitomycinC is reported at 45% and 53% at 2 years and 5 years, respectively. Trabeculectomy failure is attributed to formation of peripheral anterior synechiae and membrane overgrowth covering the ostium. YAG laser can disrupt membranes occluding the ostium.
    - Glaucoma drainage devices
    - Cyclodestructive procedures
    - Corneal transplantation

Aqueous Misdirection Syndrome (Malignant Glaucoma)

- Usually occurs following penetrating surgery of the eye
- **History**
  - Von Graefe 1869
    - Malignant glaucoma first described
    - Seen in 2% of patients undergoing surgery for angle-closure glaucoma
    - 1870s: posterior sclerectomy, lens extraction for malignant glaucoma
  - Shaffer, 1954
    - Aqueous diverted posteriorly secondary to relative block causes condition.
    - Vitreous loss during lens extraction relieves condition.
  - Chandler/Grant 1962
    - Miotic therapy ineffective
    - Cycloplegia indicated
  - Chandler, 1964: Surgical puncture and aspiration of vitreous
  - Epstein, 1979
    - Vitreous allows fluid flow at normal IOP.
    - Elevated IOP leads to reduced permeability of vitreous to aqueous.
    - May lead to sequestration of fluid, forward shift of vitreous and lens/iris, and further IOP elevation
  - Epstein, 1984: Nd:YAG hyaloidotomy for malignant glaucoma
  - 1951, Chandler: 4% incidence after glaucoma surgery, now decreased
- **Pathophysiology**
  - Traditional conception
    - Anterior rotation of ciliary body triggered by shallow anterior chamber, choroidals, miotics, etc.
    - Ciliary body processes misdirect fluid into vitreous cavity.
    - Ciliolenticular or ciliovitreal block ensues: allows fluid to flow posteriorly but not anteriorly.
    - Vitreous becomes increasingly hydrated, pushes lens and iris forward, shallowing chamber, closing angle, increasing pressure.
  - Newer conception
    - Fluid retention within vitreous
      - Normally, fluid moves back and forth between vitreous and posterior chamber.
      - At elevated IOP, vitreous less permeable to fluid

        - An event that triggers a shallow chamber or moves the vitreous forward may trigger malignant glaucoma.
    - Multiple mechanisms may contribute to fluid retention and shallowing of anterior chamber.
        - As vitreous moves forward, especially in small eyes, more of vitreous face covered by lens/ciliary body insertion, leaving less area (smaller posterior chamber-vitreous interface) available for diffusion of aqueous.
        - As vitreous moves forward, lens moves forward, increasing relative pupillary block, further shallowing chamber.
        - As lens and iris move forward, angle is closed, elevating IOP, reducing movement of aqueous across vitreous face, further exacerbating the sequence of events which is elevating pressure and shallowing the chamber.
        - Increased choroidal volume for any reason may also trigger same sequence of events.
        - Smaller eyes have smaller area of vitreous face exposed to posterior chamber (more covered by insertion of ciliary body and lens) and may be more at risk for reduced aqueous movement across vitreous face.
        - Smaller eyes have thicker sclera, which reduces transscleral fluid movement, putting them at greater risk for swelling of the choroid (eg, choroidal effusions) which can trigger above events.

- **Essential features**
    - Shallow anterior chamber (AC): central shallowing as well as peripheral shallowing
    - Moderately to severely elevated IOP
    - Absence of posterior segment space occupying lesions to account for AC shallowing
- **Clinical Features**
    - Blurry vision, pain, Increased IOP
    - Shallow AC, NO IRIS BOMBE
    - Bleb is usually low with no evidence of wound leak.
    - Corneal edema
    - The hallmark of the disease is that there are no choroidals.
    - UBM shows flattening of the ciliary body processes
- **Associations/Risk Factors**
    - Hyperopia
    - Shallow anterior chamber/shorter eyes
    - Miotic therapy
    - Cessation of mydriatics

- Following iridectomy, laser or surgical
- Following trabeculectomy or other penetrating ocular surgery, including (uncomplicated) phaco/IOL
- Following cyclophotocoagulation

- **Differential Diagnosis**
  - Pupillary block: Peripheral chamber shallowing greater than central with bowing of iris
  - Suprachoroidal hemorrhage
    - Usually associated with pain and often specific activity at onset (eg, bending over)
    - Characteristic dark elevation on exam or echogenic elevation on B-scan ultrasound
  - Serous choroidals
    - Usually but not always associated with low IOP
    - More common with higher IOP after vigorous panretinal photocoagulation
    - Light orange dome-shaped elevations if posterior; echo-lucent on B-scan ultrasound
  - Anterior serous choroidals may be detected only by ultrasound biomicroscope (UBM): anterior serous choroidals with moderately elevated IOP clinically indistinguishable from malignant glaucoma without UBM.
  - Central retinal vein occlusion (CRVO)
  - Tumors/cysts of iris, ciliary body, or retina
  - Subretinal hemorrhage (massive)
- **Management**
  - Medical therapy: historically reported as 50% success rate, but much lower in recent reports
    - Atropine 1% and phenylephrine 2.5% q.i.d.
    - Aqueous suppressants, topical with or without oral
    - Oral or intravenous hyperosmotic therapy
  - Laser therapy
    - Peripheral Iridotomy (PI)
    - Nd:YAG hyaloidotomy: via PI (phakic or pseudophakic) or behind IOL
    - Argon laser shrinkage of ciliary processes (selected cases)
    - Argon laser iridoplasty (selected cases)
    - Cyclophotocoagulation (selected cases)
  - Surgical Therapy
    - Drainage of choroidal detachments if present
    - Vitrectomy with disruption of hyaloid face

- Pars plana or anterior approach (if pseudophakic): Passage of the vitrector from posterior segment through iris into anterior chamber is thought to be helpful in creating a functionally unicameral eye and reducing the potential for recurrence.
- Phakic patients may have better prognosis if lens is removed: Essential issue may be opening of vitreous face, which is more difficult in phakic patient when attempt is made to spare the lens.

Primary open angle glaucoma

- Chronic, progressive, anterior optic neuropathy that is accompanied by a characteristic cupping and atrophy of the optic disc, visual field loss, open angles, and no obvious causative ocular or systemic conditions.
- 60–70% of the cases seen in the United States.
- Prevalence: 0.5–1% of the population
- Incidence: 1.2% in the 40–49 age group to 4.2% in those over 70
- Genetics
  - Mutations at 15 loci in the human genome have so far been identified as associated with POAG and are designated primary open angle glaucoma-1A (GLC1A) to GLC1O.
  - Four susceptible genes have been identified: the MYOC gene (chromosome 1q21-q31), coding for the glycoprotein myocilin that is found in the trabecular meshwork and other ocular tissues, the OPTN gene on chromosome 10p, which codes for optineurin, the WDR36 gene on chromosome 5q22, and the NTF4 gene on chromosome 19q13.3. Among them MYOC is the most frequently mutated gene in POAG
- **Variables**
  - **Intraocular pressure**
  - **Age**
  - **Gender:** males had a higher prevalence
  - **Race:** more prevalent in blacks than in whites
  - **Socioeconomic factors**
  - **Refractive error:** Myopia has been associated with POAG
  - **Corneal thickness:** thin cornea is a risk factor for conversion from ocular hypertension to open-angle glaucoma
  - **Heredity:**
    - If a parent has POAG, the risk of the child developing POAG is 4%
    - But if a sibling has POAG, the chance of the other **sibling** developing POAG is **10%**
  - **Systemic factors:** diabetes mellitus (Blue Mountains Eye Study in Australia, the Rotterdam Study, and the Beaver Dam Eye Study in Wisconsin)
- **Pathophysiology**
  - Diminished aqueous humor outflow facility
    - An obstruction of the trabecular meshwork by foreign material
    - A loss of trabecular endothelial cells
    - A reduction in pore density and size in the inner wall endothelium of Schlemm's canal.
    - A loss of giant vacuoles in the inner wall endothelium of Schlemm's canal.

        - A loss of normal phagocytic activity.
        - Disturbance of neurologic feedback mechanisms
    - Altered corticosteroid metabolism
    - Dysfunctional adrenergic control
    - Abnormal immunologic processes
    - Oxidative damage
    - Other toxic influences: TGF beta2
    - Optic nerve cupping and atrophy
    - The final common pathway in all the primary open-angle glaucomas is the death, sometimes by necrosis, but usually by apoptosis, of the retinal ganglion cells.

- **Symptoms**
    - Notices a scotoma when performing a monocular visual task
    - Corneal edema, halo vision, and discomfort
    - *Marcus Gunn's sign*
    - The angles are open in patients with POAG

- **Differential Diagnosis**
    - Exfoliative syndrome
    - Pigmentary dispersion
    - Trauma
    - Anterior segment inflammation
    - Subacute or chronic angle closure
    - Elevated episcleral venous pressure
    - Axenfeld's and Rieger's syndromes
    - Corticosteroid administration

Glaucoma suspect

- **Definition of a Glaucoma Suspect**
  - Open angle by gonioscopy and one of the following in at least one eye:
    - IOP consistently >21 mm Hg by applanation tonometry
    - Appearance of the optic disc or retinal nerve fiber layer suggestive of glaucomatous damage
    - Diffuse or focal narrowing or sloping of the disc rim
    - Diffuse or localized abnormalities of the nerve fiber layer, especially at superior and inferior poles
    - Disc hemorrhage
    - Asymmetric appearance of the disc or rim between fellow eyes (e.g., cup-to-disc ratio difference > 0.2), suggesting loss of neural tissue
    - Visual fields suspicious for early glaucomatous damage

- **High-Risk Glaucoma Suspects**
  - High-risk glaucoma suspects include patients who have one or more of the following:
    - IOP consistently >30 mm Hg
    - Thin central corneal thickness (dependent on ethnicity)
    - Vertical cup-to-disc ratio >0.7
    - Older age
    - Abnormal visual field, e.g., increased pattern standard deviation on Humphrey Visual Field test
    - Presence of exfoliation or pigment dispersion syndrome
    - Disc hemorrhage
    - Family history of glaucoma or known genetic predisposition
    - Fellow eye of patient with severe unilateral glaucoma (excluding secondary unilateral glaucoma)
    - Additional ocular (e.g., suspicious disc appearance, myopia, low optic nerve perfusion pressure, steroid responder) or systemic risk factors that might increase the likelihood of developing glaucomatous nerve damage (e.g., African ancestry, sleep apnea, diabetes mellitus, hypertension, cardiovascular disease, hypothyroidism, myopia, migraine headache, vasospasm)

Ocular hypertension

- Individuals with IOPs of 21 mmHg (the statistical upper end of the 'normal' range) or greater
  - Normal visual fields
  - Normal optic discs
  - Open angles
  - Absence of any ocular or systemic disorders contributing to the elevated IOPs
- 4–10% of the population over age 40
- 0.5–1% of ocular hypertensive patients per year develop visual field loss as detected by kinetic perimetry

- **Risk factors in ocular hypertension**
  - **Prospectively proven risk factors**
    - Thin corneas (<535 microns)
    - Elevated intraocular pressures
    - Increasing age
    - Vertical cupping of the optic nerve (>0.6)
    - Increased pattern standard deviation on threshold perimetry
    - Abnormalities in the optic nerve with the scanning laser ophthalmoscope
    - Pseudoexfoliation
  - **Pfizer Corporation (STARR II Risk Calculator)**
    - The STAR (Scoring Tool for Assessing Risk) calculator is based on a model derived from a collective assessment of key risk factors
    - The STAR calculator has been around since 2005, and was designed by Dr R Weinreb and Dr F Medeiros.2 There are two versions, STAR I and II. The earlier version uses six variables for risk calculation whereas the newer version's calculation is based on just the **five risk factors** as follow.
      - Age, IOP, CCT, CD Ratio, PSD (dB)
- **Management**:
  - 9.5% cumulative risk of developing POAG after 5 years; treatment (which aimed to reduce IOP by 20% or more and to reach 24 mmHg or less) reduced this to 4.4%.
  - Drug choice is the same as for POAG, although a less aggressive pressure-lowering approach is frequently taken

Normal Tension Glaucoma

- In 1857 Von Graefe noted Nerve head excavation without a palpable increase in IOP
- Progressive optic neuropathy with optic nerve damage and visual field loss with IOP consistently <21 mmHg
- In the Collaborative Normal-Tension Glaucoma Study, IOP reduction of 30% or more stopped visual field progression in 80% of eyes.
- With low pretreatment IOP, treatment goals are often <12 and sometimes below episcleral venous pressure (EVP).
- **Pathogenesis**
  - Ischemic theory
    - Ischemia causes retinal ganglion cell death by neurotrophic deprivation
    - Poor optic nerve perfusion initiates the cascade that ends in cell death
  - Mechanical theory
    - Increased IOP distorts the lamina cribrosa
    - Get compression of the axons
    - This interferes and disrupts axoplasmic flow
    - This may lead to cell death
  - Hypoperfusion theory
    - Postural hypotension
    - Nocturnal hypotension with optic nerve hypoperfusion
    - Sleep apnea contributing to optic nerve hypoperfusion
    - Increased resistance to blood flow in the ophthalmic and retinal arteries
  - Apoptosis theory: Ischemia causing a chain of events leading to programmed cell death.
  - Genetic Theory:
    - OPA 1 GENE
    - GENOTYPE IVS+4 C/T;32T/C
    - May be strongly associated with NTG
- **Clinical Features**
  - Signs of optic nerve damage in a characteristic glaucomatous pattern.
  - An open anterior chamber angle.
  - Visual field loss as damage progresses, consistent in pattern with the nerve appearance.
  - No features of secondary glaucoma or a non-glaucomatous cause for the neuropathy.
  - While optic nerve cupping is the hallmark of glaucomatous optic neuropathy, it is not pathognomonic for LTG, as cupping can result from any disease process that

causes injury of ganglion cell axons leading to loss and thinning of the neuroretinal rim.

- **Risk factors**
  - Older age (60-70 years)
  - Female
  - Japan > Europe
  - Family History of POAG
  - Lower CCT
  - Abnormal vasoregulation
  - Systemic hypotension
  - Obstructive sleep apnoea syndrome
  - Autoantibody levels
- **Differential Diagnosis**
  - **Glaucoma**
    - Elevated intraocular pressure (IOP) not detected
      - Undetected wide diurnal variation
      - Low scleral rigidity
      - Systemic medication that may mask elevated IOP (e.g., recent B-blocker treatment)
      - Past systemic medication that may have elevated IOP
      - Elevation of IOP in supine position only
    - Glaucoma in remission
      - Past corticosteroid administration
      - Pigmentary glaucoma
      - Associated with past uveitis or trauma
      - Glaucomatocyclitic crisis
      - Burned-out primary open-angle glaucoma
  - **Optic nerve damage**
    - Congenital optic nerve conditions: Pits, Colobomas, Tilted discs
    - Ischemic optic neuropathy: Arteritic, Non-arteritic
    - Compressed lesions: Tumors, Aneurysms, Cysts, Chiasmatic arachnoiditis
    - Optic nerve drusen
    - Demyelinating conditions
    - Inflammatory diseases
    - Hereditary optic atrophy
    - Toxic drugs or chemicals

- **Ocular disorders**
  - Myopia
  - Retinal degeneration
  - Myelinated nerve fibers
  - Branch vascular occlusions
  - Choroidal nevus or melanoma
  - Choroidal rupture
  - Retinoschisis
  - Chorioretinal disease
- **Systemic vascular conditions**
  - Anemia
  - Carotid artery obstruction
  - Acute blood loss
  - Arrhythmia
  - Hypotensive episodes
- **Miscellanenous**
  - Hysteria
  - Artifact of visual field testing

Management

- Medical Management with Ocular hypotensive drugs
  - Start with a prostaglandin or beta blocker
  - Switch before adding, keeping number of drops to a minimum to improve compliance
  - Alpha agonist or topical CAI consider next
  - Keep adding and subtracting until the drops are efficacious and tolerated
- Oral calcium channel blocker stabilize the visual fields in NTG **nilvadipine** with laser-Doppler flowmetry, showed decreased vascular resistance (Used in JAPAN)
- Filtering surgery: Trabeculectomy is traditionally used to achieve ultra-low IOP targets in NTG
  - Risks
    - Hypotony maculopathy
    - Serous/hemorrhagic choroidal effusions
    - Flat anterior chamber
    - Cataract progression
- MIGS as First-line Surgical Treatment in NTG
  - Advantages:

- Microinsional, ab interno approach
- Augment physiologic outflow/inflow pathways
- At least modest efficacy
- Very high safety profile
- Rapid patient recovery

- Variety of approaches
  - Angle based:
    - ✓ Goniotomy/trabeculotomy: Kahook dual blade, Trabectome, gonioscopy-assisted transluminal trabeculotomy, Trab360
    - ✓ Bypass stents: iStent, iStent Inject, Hydrus
    - ✓ Canaloplasty: ab interno canaloplasty
  - Cyclophotocoagulation: Endoscopic cyclophotocoagulation (ECP), micropulse cyclophotocoagulation (MP-CPC)
  - Subconjunctival: Xen gel stent
- **When to Consider MIGS in NTG**
  - IOP goal > 10 mmHg
  - High risk for filtration surgery (high myope, monocular, conjunctival scarring, prior complications)
  - Mild to moderate disease
  - Coexisting cataract
  - Treatment goal is medication replacement.
- **When Not to Consider MIGS in NTG**
  - IOP goal < 10 mmHg
  - Advanced disease approaching fixation
  - Elevated EVP

Combined and Mixed Glaucoma

- **Combined mechanism glaucoma** refers to situations in which both open-angle and angle-closure components are present. Most commonly, angle-closure glaucoma is treated successfully with iridotomy, eliminating all appositional closure, and IOP still remains elevated, with or without the presence of PAS of any extent.
- **Mixed mechanism glaucoma** refers to the term to describe an eye with angle-closure due to more than one contributory mechanism. When pupillary block is eliminated by iridotomy and the angle opens to a greater degree than before the iridotomy, an appositional closure remains on the basis of plateau iris, phacomorphic glaucoma, or malignant glaucoma, a mixed mechanism may be present.

Secondary open angle glaucoma

- Secondary open-angle glaucoma can be subdivided on the basis of the site of aqueous outflow obstruction as follows:
  - **Pre-trabecular glaucoma**
    - Fibrovascular membrane in neovascular glaucoma
    - Epithelial ingrowth
    - Fibrous downgrowth
    - Proliferation of the endothelium
    - Posterior polymorphous dystrophy
    - Penetrating and non-penetrating trauma
    - Inflammatory membrane
  - **Trabecular glaucoma**
    - *Clogging of the trabecular meshwork*
      - RBC's in Haemorrhagic/ ghost cell/ sickled cell glaucoma
      - Macrophages in hemolytic/phacolytic/melanomalytic glaucoma
      - Neoplastic cells in primal)' ocular tumours/juvenile xanthogranuloma
      - Pigment particles in pigmentary glaucoma/ exfoliation syndrome/ malignant
      - Protein in uveitis/lens induced glaucoma
      - Viscoelastic agents.
    - Alterations of the trabecular meshwork
      - Steroid induced glaucoma
      - Uveitis
      - Scleritis
      - Alkali burns
      - Trauma
      - Intraocular foreign body
  - **Post-trabecular glaucoma**
    - Collapse of the Schlemm's canal
    - Elevated episcleral venous pressure
      - Carotid cavernous fistula
      - Cavernous sinus thrombosis
      - Retrobulbar tumours
      - Thyroid ophthalmopathy
      - SVC obstruction
      - Mediastinal tumours

- Sturge Weber syndrome

Pigmentary glaucoma

- Pigment dispersion syndrome (**PDS**) has **no** Glaucoma, When associated with glaucoma, it is called Pigmentary Glaucoma.
- **1.0–2.5%**
- Young adults
- Male > female
- Most often in white
- Strong association between pigmentary glaucoma and myopia
- Significant linkage between the disease phenotype and genetic markers located on 7q35-36.
- **Pathophysiology**: release of pigment particles from the pigment epithelium of the iris. These particles are carried by the aqueous humor convection currents and then deposited on a variety of tissues in the anterior segment of the eye, including the corneal endothelium, trabecular meshwork, anterior iris surface, zonules, and lens.
  - Campbell's Mechanical Theory: concave shape of the peripheral iris allows it to rub against the zonules, causing pigment release and dispersion.
  - Anderson's Genetic Predisposition Theory: conditions resulted from mutations in genes encoding melanosomal proteins. They postulate that pigment production and mutant melanosomal protein genes may contribute to human pigmentary glaucoma.
- Jarring exercise, strenuous physical activity, or rarely dilation may lead to dramatically increased pigment dispersion, a so-called **pigment storm**, leading to sudden elevations of IOP.
- **Clinical Features**
  - Spokelike, midperipheral transillumination iris defects
  - Very deep anterior chambers
  - Concave appearance of the peripheral iris, and mild iridodonesis
  - ***Krukenberg's Spindle****:* deposition of pigment on the corneal endothelium. (extracellular as well as intracellular pigment granules phago-cytized by the corneal endothelium)
  - ***Sampaolesi's line****:* pigment line anterior to Schwalbe's line
  - **Zentmayer's ring or Scheie's stripe**: Pigment deposition on the zonules, posterior lens surface and anterior iris surface
  - Resembles POAG in IOP, ON, VF changes
  - Pigment release and marked IOP elevation after exercise can be blocked by topical pilocarpine therapy
  - UBM of patient with PDS, showing backward-bowing peripheral iris in contact with lens surface
- **Differential diagnosis**

- Normal eyes with aging
- POAG
- Uveitis
- Cysts of the iris and ciliary body
- Pigmented intraocular tumors
- Previous surgery (including laser surgery)
- Trauma
- Angle-closure glaucoma
- Amyloidosis
- Diabetes mellitus
- Herpes zoster
- Megalocornea
- Radiation
- Siderosis and hemosiderosis

- **Management**
  - Like POAG: medical therapy to argon laser trabeculoplasty (ALT) to filtering surgery.
  - Miotic agents reduce IOP in pigmentary glaucoma and are theoretically appealing because they increase pupillary block and lift the peripheral iris from the zonules. However, cholinergic drugs are generally poorly tolerated by these young patients
  - Thymoxamine, an A-adrenergic antagonist, might be useful in this situation because it constricts the pupil without inducing a myopic shift in refraction
  - Laser peripheral iridotomy also may reduce pigment shedding, because it allows the posteriorly bowed iris to move anteriorly as any built-up fluid pressure in the anterior chamber is then normalized with the posterior chamber (relief of so-called **reverse pupillary block**). This may help prevent glaucoma in individuals at higher risk but have not yet developed uncontrolled pressure.
  - ALT: done with relatively low energy settings

Exfoliation syndrome (XFS)

- 1917, Lindberg: inherited microfibrillopathy
- Previously or classically known as pseudoexfoliation syndrome (PXF)
- MC type of Secondary POAG
- MC identifiable cause of glaucoma
- 40% of patients with exfoliation syndrome may have associated glaucoma.
- Ranges in prevalence from near 0 in Eskimos to near 30% in people in Scandinavian countries.
- Prevalence: **Framingham study**: 0.6% in patients younger than 65 years of age, 2.6% in patients 65–74 years of age and 5.0% in patients 75–85 years of age.

- Syndrome: Female> Male
- Glaucoma: Female = Male
- The cumulative risk of glaucoma in eyes with PXF is **5% at 5 years and 15% at 10 years**.
- **Pathogenesis**
  - Genetics: polymorphism in exon 1 of the **LOXL1 gene (lysyl oxidase like 1)**, chromosome **15q22 → extracellular matrix formation and stability:** LOXL1 is one of a family of lysyl oxidase enzymes essential for the formation of elastin fibers. It has an important role in modifying tropoelastin, the basic building block of elastin, and catalyzing process for monomers to cross-link and form elastin.
  - Exfoliation material: random 10 to 12 nm fibrils, arranged in a fibrillogranular matrix and occasionally coiled as spirals
  - Affects the rigidity of the lamina cribrosa
  - Increased inhibitors of MMPs
  - Environmental and gene-environment interactions also appear to play a role in the development of XFS, including UV light exposure, latitude of residence, increased caffeine intake, and decreased folate intake.
- **Clinical Features**
  - **Target Sign**: classic pattern on the anterior lens surface consisting of a central translucent disc surrounded by a clear zone, which in turn is surrounded by a granular grey-white ring with scalloped edges
  - Dandruff-like flakes of exfoliation material are deposited on the corneal endothelium, trabecular meshwork, anterior and posterior iris, pupillary margin, zonules, and ciliary processes as well as the anterior hyaloid face in aphakic eyes.
  - Peripupillary iris has an irregular, **moth-eaten pattern** of transillumination
  - Sampaolesi's line: An accumulation of pigment may also be seen along the Schwalbe line
  - Most eyes with exfoliative glaucoma have an open-angle mechanism, although acute angle-closure glaucoma also occurs in a small number of cases
  - Systemic Associations: material has also been demonstrated in tissues throughout the body of patients with the exfoliation syndrome, including lung, heart, liver, gallbladder, skin, kidney, and cerebral meninges, Alzheimer Disease
- **Management**
  - Narrow Angles with XFS: 2.2%
    - Consider laser peripheral iridotomy
    - Consider lensectomy if visually significant cataract
  - Open Angles or OHT with XFS
    - Medical therapy is relatively less effective
      - PG Analogues
      - Beta adrenergic antagonists
      - Alpha agonists

- Carbonic anhydrase inhibitors
- ALT has maximum benefit
- **Filtering surgery** has a high rate of success
  - MIGS (microinvasive glaucoma surgery) procedures
    - ✓ Trabecular bypass stent
    - ✓ Ab interno trabeculotomy
    - ✓ Suprachoroidal shunts
    - ✓ Combined gel stent and cataract surgery
  - Trabeculectomy
  - Combined trabeculectomy and cataract surgery
  - Aqueous drainage devices
  - Combined endoscopic cyclophotocoagulation and cataract surgery

Steroid Induced Glaucoma

- **Epidemiology**
  - Bimodal distribution: Children less than 6 years of age and older people, usually more than 70 years
- **Steroid Responders**
  - 4-6% of patients may demonstrate a rise of IOP more than 30mmHg after 4 weeks application of potent topical corticosteroids-these are the patients at maximum risk
  - A third of the population have a moderate elevation of IOP (22-30mm Hg)
  - Non responders have virtually no change in IOP
  - Open angle glaucoma patients have a higher rate of steroid response than the general population
  - Diabetics, myopes, eyes with angle recession, patients with collagen vascular disease have a higher rate of steroid responsiveness
  - Other factors like potency, duration and dose of the steroid also influence the rise in IOP.
  - Topical administration, periocular and systemic administration are the ones most commonly implicated.
  - Onset of IOP elevation can occur within days, weeks, months or even years of administration. With topical corticosteroids it typically occurs over 2-6 weeks
  - Lelorier et al., noted that high doses of inhaled corticosteroids (defined as > 1500μg flunisolide or > 1600μg of beclomethasone, budesonide or triamcinolone) was associated with a significantly increased risk of ocular hypertension or open-angle glaucoma.
  - The odds ratio was 1.44 after 3 months of corticosteroid use.
  - Use of lower doses of inhaled steroids or use of nasal corticosteroids was not associated with a rise in intraocular pressure

- **Pathogenesis**:
  - Increased deposition of extracellular material in the trabecular beams, fingerprint like deposits in the uveal meshwork and fibrillar deposits in the juxtacanalicular tissue of the TM
  - **TM cell function**: inhibition of proliferation, migration and phagocytosis.
  - **TM cell extracellular matrix:** increased deposition of ECM material in TM. Increased expression of fibronectin, laminin, collagen and elastin. Decreased expression of t-PA and MMPs.
  - **TM Cell morphology:** activation of TM cells (increased endoplasmic reticulum, Golgi complexes, and secretory vesicles), increased biosynthesis
  - **Heritability** of the steroid response and its relation to glaucoma: expression of the protein myocilin (previously known as TIGR and GLC1A) in cultured TM cells is *greatly enhanced* by treatment with glucocorticoids.
- **Pathophysiology (*read STEROID mnemonic from Ophthalmonics*)**
  - Stabilization of lysosomal membranes and leading to accumulation of polymerized glycosaminoglycans(GAG).
  - Alteration of the composition of the extracellular matrix through which aqueous flows (such as the proteoglycans or glycosaminoglycans), thereby increasing resistance to outflow (Biological edema).
  - Increased expression of collagen, elastin, laminin and fibronectin within the trabecular meshwork, as a result of which there is increased trabecular meshwork resistance.
  - Inhibition of phagocytosis by endothelial cells lining the trabecular meshwork thereby leading to accumulation of debris in the trabecular meshwork.
  - Decreased expression of extracellular proteinases including fibrinolytic enzymes, stromolysin, matrix metalloproteinases.
  - Steroids increase the expression of TIGR gene and decrease the MMP.
  - Inhibition of the production of outflow-enhancing PGs (such as PGF2α).

- **Relative risks of various steroids**
  - The risk generally parallels the potency
  - The most potent include betamethasone, dexamethasone and prednisolone
  - Some steroids like rimexolone, loteprednol etabonate and fluorometholone have less tendency to raise IOP but are also less potent
  - Different preparations of the same corticosteroid may have different antiinflammatory effects with similar IOP raising tendency e.g., 0.1% dexamethasone phosphate and acetate
  - Topical NSAIDS have little tendency to raise IOP
  - IVTA: 50% of cases starting at 1-2 months > 30 mmHg
  - PST: > 5 mm Hg

- **Difluprednate**
  - Rapidly penetrates corneal epithelium and then deacetylates into its active form
  - 6x more powerful than prednisolone
  - Unpredictable and dramatic IOP elevations have been reported; increased IOP in post-vitrectomy eyes vs. prednisolone.
- **TYPE OF RESPONDER (Armaly-Backer)**
  - LOW: <20 mmHg (58%)
  - INTERMEDIATE: 20-31 mmHg (36%)
  - HIGH: >31 mmHg (6%)

	INCIDENCE OF STEROID RESPONSIVENESS		
RESPONDERS	HIGH(%)	INTERMEDIATE(%)	NONRESPONDER(%)
General Population	5	35	60
POAG	90	10	0
Siblings Of POAG	30	50	20
Offsprings Of POAG	25	70	5

- **Risk factors**
  - Patients with primary open angle glaucoma. About 30% of the glaucoma suspects and 90% of patients with POAG might have an ocular hypertensive response to a 4 week course of topical Dexamethasone 0.1%.
  - First degree relatives of POAG patients.
  - Children below 10 years
  - High myopia
  - Diabetes Mellitus
  - Connective Tissue Disorders (Rheumatoid Arthritis)
  - Eyes with Traumatic Angle Recession
  - Pigment Dispersion Syndrome
  - Endogenous Hypercortisolism.

- **Steroid formulation and glaucoma**

	Topical ocular preparation	Oral and intravenous steroids(equivalent doses in mg)	Skin preparations
High potent	Prednisolone Acetate 1% Dexamethasone 0.1% Betamethasone 0.1%	Betamethasone –3 Dexamethasone-3	Clobetasole propionate Betamethasone Dipropionate
Intermediate	Prednisolone Sodium Phosphate 0.5%	Triamcinolone-12 Methylprednisolone-15 Prednisolone-15	Diflucortolone Valerate Mometasone furoate Flucinolone acetonide
Low potent	Fluoromethalone 0.1% Loteprednol Etabonate	Hydrocortisone-60	Hydrocortisone

- **Duration and dose of steroids**

Route	Average dose	Average Time taken for IOP rise
Oral	25 mg hydrocortisone/ day 50 mg prednisolone/day	1 year 2-15 months
Inhalational	1500 μg flunisolide 1600μg beclomethasone, budesonide, triamcinalone 200 μg fluticasone	3 months 1 year
Pulse steroids	140mg repeated 4 weekly	6 months
Dermatological	Betamethasone cream (0.1%)	3 months
Topical	QID dose of a potent steroid	2-6 weeks
IVTA	4mg of triamcinolone acetonide	4-8 weeks
PST	40 mg of triamcinolone acetonide	5-9 weeks

- **Differential diagnosis**
  - POAG
  - Uveitic glaucoma
  - Glaucomatocyclytic crisis
  - Normal tension glaucoma
  - Primary juvenile open angle glaucoma
- **Management**
  - Stop the responsible steroid preparation
  - Switch to lower potency steroids like phosphate forms of prednisolone and dexamethasone, rimexolone, loteprednol etabonate, flurometholone, medrysone
  - Substituting with non steroidal anti inflammatory drugs like diclofenac, ketorolac, bromfenac, nepafenac that act as cyclooxygenase inhibitors and reduce inflammation.
  - Steroid sparing drugs are the immunosuppressants like tacrolimus ointment/ cyclosporin for vernal keratoconjunctivitis or methotrexate for systemic condition or uveitis
  - Selective Laser Trabeculoplasty or argon laser trabeculoplasty can be considered
  - Medical and laser therapy fails → surgery (esp in Age≤ 20 years, Higher base line IOP, Greater glaucomatous optic neuropathy)
  - Anecortave acetate (AA): potent inhibition of blood vessel growth but with no evidence of glucocorticoid receptor mediated bioactivity

Lens-induced glaucoma

- ***Phacomorphic glaucoma***: a swollen lens causes increased pupillary block and secondary angle closure.

- ***Phacotopic Glaucoma:*** a dislocated lens causes increased pupillary block and secondary angle closure.
- ***Phacolytic glaucoma:*** lens protein leaks from an intact cataract and obstructs the trabecular meshwork.
- ***Lens-particle glaucoma:*** lens material liberated by trauma or surgery obstructs the outflow channels.
- ***Phacoanaphylaxis:*** sensitization to lens protein produces granulomatous inflammation and occasionally secondary glaucoma.

Phacolytic Glaucoma/ Lens Protein Glaucoma

- Protein composition of the lens is altered to components with heavier molecular weight. If these soluble molecules leak through micro leaks what grossly appears to be an intact capsule, they can obstruct the trabecular meshwork, also macrophages engulf the lens protein and may further obstruct the outflow channels.
- **Pathophysiology**
  - Heavy-molecular-weight (HMW) proteins (greater than 150 × 106 Da) obstruct trabecular meshwork outflow, causing a rise in IOP.
- **Clinical Features**
  - Acute onset of monocular pain, redness, and perhaps a further decrease in vision
  - Intense flare, may be yellow
  - White particles on the anterior lens surface and in the aqueous; these particles are thought to be cellular aggregates or clumps of insoluble lens protein
- Aqueous humour is examined by phase-contrast microscopy or Millipore filtration and staining.
- **Management**
  - IOP and inflammation control
  - Cataract extraction is the definitive treatment

Lens-Particle Glaucoma

- Disruption of the lens capsule by penetrating trauma or surgery
- glaucoma has its onset a few days after the precipitating event.
- **Pathophysiology**
  - Lens particles obstructing the trabecular meshwork
  - Inflammatory cells
  - Peripheral anterior synechiae and angle closure related to the inflammation
  - Pupillary block from posterior synechiae
- **Clinical Features**
  - Elevated IOP can cause corneal edema, and inflammation can be marked, as evidenced by flare and cell.

- Hypopyon

Phacoanaphylaxis - Lens Associated Uveitis

- When patients become sensitized to their own lens protein
- After penetrating trauma or extracapsular cataract extraction
- **Pathophysiology**
  - Alterations in immune tolerance to lens proteins
  - Indolent bacteria such as Propionibacterium acnes that are found in lens material or that bacteria instigate a loss of immune tolerance in the eye.
  - Autoimmune theory (yet to be proven)
  - Zonal granulomatous inflammation with three populations of cell types
    - Zone 1—Neutrophils closely surround and infiltrate the lens.
    - Zone 2—A secondary zone of monocytes, macrophages, epithelioid cells, and giant cells surround the neutrophils.
    - Zone 3—A nonspecific mononuclear cell infiltrate forms the outer zone of inflammation.
- **Clinical Features**
  - Low-grade anterior segment inflammation
  - Panuveitis with a hypopyon
  - Associated with hypotony rather than with elevated IOP, although high IOP can occur

Glaucoma after cataract surgery

- A transient rise in IOP has been reported in 33% to almost 100%
- **Mechanism of IOP rise**
  - Inflammation with the release of active substances, including prostaglandins and the formation of secondary aqueous humor
  - A watertight wound closure with multiple fine sutures limiting the ‘safety valve’ leak of aqueous humor.
  - Deformation of the limbal area, reducing trabecular outflow
  - Obstruction of the trabecular meshwork by pigment, blood, lens particles, inflammatory cells, and viscoelastic substances

- **Open-angle glaucoma**
  - **Early onset (within first postoperative week)**
    - Pre-existing chronic open-angle glaucoma
    - Alpha-Chymotrypsin-induced glaucoma
    - Hyphema/debris

- Viscoelastic material
- Idiopathic pressure elevation

- **Intermediate onset (after first postoperative week)**
  - Pre-existing chronic open-angle glaucoma
  - Vitreous in the anterior chamber
  - Hyphema
  - Inflammation
  - Lens particle glaucoma
  - Corticosteroid-induced glaucoma
  - Ghost-cell glaucoma
- **Late onset (more than 2 months postoperatively)**
  - Pre-existing chronic open-angle glaucoma
  - Ghost-cell glaucoma
  - Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy
  - Vitreous in the anterior chamber
  - Late-occurring hemorrhage
  - Chronic inflammation

Angle-closure glaucoma

- **With pupillary block**
  - Anterior hyaloid face
  - Posterior lens capsule
  - Intraocular lens
  - Posterior synechiae
  - Silicone oil
- **Aqueous misdirection (malignant glaucoma)**
- **Without pupillary block**
  - Pre-existing angle-closure glaucoma
  - Inflammation/hyphema
  - Prolonged anterior chamber shallowing
  - Iris incarceration in cataract incision
  - Intraocular lens haptics
  - Neovascular glaucoma
  - Epithelial ingrowth
  - Fibrous ingrowth
  - Endothelial proliferation

- Proliferation of iris melanocytes across the trabecular meshwork

Glaucoma after Vitrectomy

- Pre-existing glaucoma
  - Angle recession
  - Ghost cell
  - Primary open-angle glaucoma
  - Pigmentary glaucoma
- Associated with intraocular hemorrhage
  - Hyphema
  - Ghost cell
  - Hemolytic
  - Hemosiderosis
- Related to lens material
  - Phacolytic
  - Lens particle
  - Phacoanaphylactic
- Neovascular
- Inflammatory
- Corticosteroid induced
- Intraocular gas or liquid
  - Air
  - Viscoelastic substances
  - Perfluorocarbons
  - Silicone
  - Band/ buckle

Glaucoma with uveitis

- Aka inflammatory glaucoma, uveitic glaucoma, or glaucoma secondary to uveitis
- In patients with uveitis and no demonstrable “glaucomatous” optic nerve damage or “glaucomatous” visual field defects: → uveitis-induced ocular hypertension, ocular hypertension secondary to uveitis
- **Epidemiology**
  - Uveitis may account for 5% to 10% of legal blindness
  - 25% of all patients with uveitis will develop increased intraocular pressure
  - More common in cases of granulomatous

- **Pathophysiology**
  - Open Angle Mechanisms
    - Abnormal Aqueous Secretion
    - Aqueous Humor Proteins
    - Inflammatory Cells
    - Prostaglandins
    - Trabeculitis
    - Steroid-induced Ocular Hypertension
  - Closed-Angle Mechanisms
    - Peripheral Anterior Synechiae
    - Posterior Synechiae
    - Forward Rotation of the Ciliary Body
    - Uveal effusion
    - neovascularization
- **Management**
  - Control of uveitis
  - Beta-blockers, carbonic anhydrase inhibitors, adrenergic agents, and hyperosmotic agents
  - Miotic agents and prostaglandin-like agents are generally avoided
  - Pupillary block: YAG PI (multiple PI might be needed, in 4 quadrant PI, inferior PI should be done first)
  - Goniosynechialysis
  - Trabeculodialysis
  - Trabeculectomy with and without the use of antimetabolites:
    - Success rate 62-81%
    - Trabeculectomy performed in patients with uveitis has a higher risk of both early hypotony and late failure. Early hypotony may be prevented by tight suturing of the scleral flap and selective postoperative suture release, whereas late failure is more easily avoided by careful case selection.
  - Tube shunt procedures such as the Ahmed, Baerveldt, and Molteno implants
    - In those with chronic severe uveitis from early childhood, it is preferable to use a single-plate Molteno implant, finding that other, larger-plate implants may result in chronic hypotony.
    - On the other hand, many of those with less severe, but chronic uveitis in adulthood require a Baerveldt 101-350, the Ahmed valve being insufficient to achieve long-term pressure control.
  - Nonpenetrating glaucoma surgery
  - Ciliary body destructive procedures

- Secondary acute angle closure from a secluded pupil is very different from that in primary angle-closure glaucoma. Laser iridotomy is often inadequate or even counterproductive, and incisional surgery is frequently required. There are a number of methods for performing surgical iridectomy, and these may be combined with visco-goniosynechiolysis.

Fuchs' Heterochromic Iridocyclitis

- Chronic but relatively mild form of anterior uveitis associated with cataract and glaucoma
- 90% of the cases are unilateral
- 1.2% to 3.2% of all uveitis cases
- Third and fourth decades
- Male = Female
- **Clinical Features**
  - Minimal cell and flare
  - Fine round or stellate keratic precipitates
  - Fine filaments on the endothelium between the keratic precipitates
  - A patchy loss of the iris pigment epithelium
  - Hypochromia
  - Grey-white nodules on the anterior iris
  - A few opacities in the anterior vitreous
  - Chorioretinal scars that resemble toxoplasmosis.
  - Heterochromia in 25-70%
  - Gonioscopy reveals fine vessels that bridge the angle and
  - Can bleed with minimal trauma, such as paracentesis – **AMSLER'S SIGN**
  - Increased IOP has been reported in 13–59%
  - Despite the chronicity of the intraocular inflammation in these patients, peripheral anterior synechiae and posterior synechiae almost never form
  - Cataract formation has been reported in more than 80%
- **Etiology**
  - Rubella virus and antibodies against rubella virus ??
- **Differential Diagnosis**
  - Herpetic uveitis, the Posner–Schlossman syndrome, sarcoidosis, syphilis, and, in those cases with posterior pole lesions, toxoplasmosis
- **Management**
  - Cataract
  - Glaucoma Medical management

Glaucomatocyclitic Crisis

- ***Posner-Schlossman syndrome***
- First described in 1929, it carries the eponym of Posner and Schlossman who reported the syndrome in 1948
- Young to middle-aged adult
- Clinical Features
  - Recurrent episodes of mild anterior uveitis and marked elevations of IOP.
  - Unilateral >> bilateral
  - Slight discomfort, slight blurring of vision, or halo vision.
  - 0.4% of all uveitis
  - Mild ciliary flush
  - A dilated or sluggishly reactive pupil
  - If pressure is significantly elevated, the pupil may be slightly dilated; however, peripheral anterior synechiae and posterior synechiae do not occur.
  - Corneal epithelial edema
  - IOP in the range of 40–60 mmHg
  - Decreased outflow facility
  - Open angle
  - Faint flare
  - 1–20 fine keratic precipitates.
- **Etiology**
  - Cytomegalovirus or herpes simplex virus (HSV) in at least some cases
  - Increased prostaglandins → breakdown of BAB
- **Differential Diagnosis**
  - Fuchs' heterochromic iridocyclitis, herpes simplex or zoster uveitis, sarcoidosis, HLA-B27–associated anterior uveitis, and idiopathic anterior uveitis.
- **Management**
  - Self-limited ocular hypertension that resolves spontaneously regardless of treatment.
  - Topical corticosteroids to control the anterior uveitis.
  - Mydriatic and cycloplegic agents are not commonly needed as ciliary muscle spasm is uncommon and synechiae rarely form
  - Glaucoma:
    - Miotics and argon laser trabeculoplasty are generally not effective

Traumatic Glaucoma

Hyphema

- Blood in AC can be either due to Blunt or Penetrating injury, in blunt trauma there is antero-posterior compression and equatorial expansion leading to damage to ciliary body and TM. There are shearing forces acting on the angle structures and the ciliary body leading to damage to the anterior face of ciliary body and damage to major arterial circle causing the hyphema, Penetrating injury leads to hyphema by damaging the blood vessels and due to hypotony.
- Certain conditions lead to **HYPHEMA even in MINOR TRAUMA** – Rubeosis iridis, juvenile xanthogranuloma, iris melanoma, iris leiomyosarcoma, myotonic dystrophy , vascular iris tufts blood dyscrasias.
- Hyphema resorption occurs by anterior surface of the iris and TM. Uncomplicated hyphemas are cleared within **1 week.**
- **Grading**
  - Grade 1: < 1/3th of AC
  - Grade 2: 1/3dth -1/2 of AC
  - Grade 3 > ½ of AC
  - Grade 4: total or eight ball hyphema
- **Complications of Hyphema**
  - Increased IOP: various causes of high iop in hyphema are:
  - Occlusion of trabecular meshwork by clot, inflammatory cells, erythrocytic debris.
  - Pupillary block due collar button shaped clot.
  - Peripharal anterior synechiae: PAS are formed if hyphema persists for more than a week .
  - Optic atrophy : optic atrophy in hyphema can occur because of high IOP , contusion to the optic nerve, secondary to damage to short posterior ciliary arteries. Risk of optic atrophy increases when th IOP is > 50 mmHg for 5 days or 35 mmHg or more for 7 days. Patients with sickle cell disease have optic atrophy even at normal or slightly raised IOP.
  - Corneal blood staining: Factors which influence corneal blood staining include: rebleeding, prolonged clot duration, sustained increase in IOP and corneal endothelial dysfunction. Two main risk factors of corneal blood staining include IOP>25mmHg and >6 days duration.
  - Accommodative impairment
- Earliest sign of corneal blood staining is a straw coloured discoloration of *deep stroma*, presence of tiny yellow granules in posterior 1/3rd of the cornea.
- In sunlight the haemoglobin gets converted in to porphyrins, which toxic to the corneal endothelium therefore patching might have a role in management of hyphema.
- Corneal blood staining can cause decreased visual acquity and deprivation amblyopia in children.

- Secondary haemorrhage: rebleed occurs because of clot retraction on and after day 4. signs of rebleed incude increase in size of hyphema, layer of free RBCs over previous clot, change of colour from dark red to bright red.
- Chances of rebleed are more with black race and children
- **Medical Management:**
  - Anti fibrinolytic agents: epsilon amina caproic acid(EACA) and Tranexamic acid are used to prevent rebleed in cases of hyphema
    - EACA (amicar) binds to lysine molecules in the clot via lysine binding site and inhibits fibrin clot digestion. Its dose is 100mg/kg every 4 hours to a maximum dose of 30g/day by mouth for 5 days.
    - Side effects include nausea, vomiting, diarrhea, postural hypotention, pruritis, muscle cramps, rash, nasal stuffiness, arrhythmia, confusional state. Rhabdomyolysis and myoglobinuria are rare. Contraindications include drug allergy, active intravascular clotting, history of thrombosis, hematuria, renal failure and hemophilia.
    - Tranexamic acid also has similar mechanism. Side effects are lesser as compared to amicar The results of various studies indicate that both amicar and tranexamic acid have beneficial effect on rate of secondary haemorrhage but none of them had improved the final visual outcome.
  - Corticosteroids: by stabilizing the blood-ocular barrier and by directly inhibiting fibrinolysis corticosteroids decrease the incidence of secondary haemorrhage.predinislone in dase of 40mg/day or 0.6 mg/kg in children is effective in reducing the incidence of rebleed statistical analysis indicates that corticosteroids decreased the incidence of rebleeding without having any effect on the longterm visual outcome.
  - Studies advocate use of mydriatics as they relieve ciliary spasm and prevents formation of PAS. Aspirin should not be given in cases of hyphema
- **Outpatient management:**
  - Can be considered in following Cases (Walton et al):
    - No associated injury
    - Hyphema< ½ of AC volume
    - Satisfactory IOP
    - No blood dyscrasia
    - Safe home environment
    - Good patient compliance
    - Good follow up (no time delay at presentation)
- **Indications for surgical management**
- Irrigation, vitrectomy, trabeculectomy-walton et al:
  - Microscopic corneal blood staining
  - Risk of optic atrophy/ CRAO

- Sickle cell disease/trait, IOP avg >25 mmHg> 24 hours or spikes repeatedly > 30mmHg
- IOP >60mmHg for 2 days OR 50mmHg for >4 days
- Presence of pre-existing glaucomatous optic atrophy and “unacceptable” IOP.
- Risk of corneal blood staining(e.g 4 days after the onset of glaucoma, > ½ total hyphema with IOP > 25mmHg > 6 days
- Risk of synechiae formation (e.g > 50% hyphema for > 8 days.

Angle Recession/ Glaucoma

- **COLLINS** was the first person to describe angle recession due to blunt trauma in 1892. **Wolf and Zimmerman** in 1962 linked angle recession to development of Glaucoma. tear in the ciliary body between the longitudinal and circular muscle layers.
- Angle recession occurs in 20-94% cases of eye trauma. Studies indicate that incidence of glaucoma in angle recession ranges from 7-9%.
- Clinically, there is abnormal widening of the ciliary body band on gonioscopy
- Blunt or penetrating trauma to the anterior segment
- Risk of developing glaucoma: proportional to the extent of ciliary body damage, with an incidence as high as 10% in eyes with greater than 180 degrees of damage.
- 50% of these patients will develop elevated pressures in the contralateral eye.
- **Pathophysiology**
  - Pathologically angle recession is a separation between the circular and the longitudinal fibers of the ciliary body, longitudinal muscles remain attached to the scleral spur. There might be associated cyclodialysis, iridodialysis, damage to the lens manifested as cataract, subluxation ,dislocation , hyphema. Later the inner layer of ciliary body atrophies leading to broad and fusiform ciliary band appearance on gonioscopy.
  - Impaired outflow may occur as the result of direct damage to the trabecular meshwork
  - As the result of a Descemet-like endothelial proliferation over the trabecular meshwork.
- **Clinical Features**
  - Grading is done according to **Howard’s Classification** as Grade I (shallow), grade II (moderate), grade III (deep)
  - Pain, photophobia, and decreased vision as the result of elevated intraocular pressure
  - Evidence of previous trauma: Corneal scarring or blood staining, cataract, phacodonesis, iris sphincter tears, or tears at the iris root (iridodialysis)
  - Gonioscopy demonstrates an irregular widening of the ciliary body band
  - Choroidal ruptures, retinal detachments, or vitreous hemorrhage may be present.
- **Treatment**

- Bilateral simultaneous gonioscopy is a very effective way detecting even the subtle changes in the angle.
- Angle recession on gonioscopy following trauma need to be followed indefinitely for the development of glaucoma
- Medical
  - Aqueous suppressants, Hyperosmotics
  - Miotics often make angle recession worse, because they decrease uveoscleral outflow in eyes that rely on uveoscleral outflow for intraocular pressure control.
  - Laser trabeculoplasty has limited success in eyes with angle recession.
- A guarded filtration procedure or implantation of a glaucoma drainage device is often required to control intraocular pressure in these patients.

Cyclodialysis Cleft

- Term was first used by Heine in 1905
- Separation of the meriodinal ciliary muscle fibers from its attachment to the scleral spur and ciliary body band
- **Hypotony**
  - Direct communication between drainage of aqueous from the anterior chamber to the suprachoroidal space.
  - Decreased aqueous humor production due to diminished blood supply to the ciliary body.
- **Etiology**
  - Traumatic, caused by contusion injuries, or iatrogenic, caused by anterior segment surgeries, like extracapsular cataract surgery, phacoemulsification, etc.
  - Occasionally, there can be traumatic cyclodialysis cleft that remains dormant and is later potentially opened during anterior segment surgery leading to postoperative hypotony
- **Clinical Features**
  - Corneal folds, shallow AC, cataract formation, optic disk edema, hypotonous maculopathy, choroidal effusion, retinal striae and choroidal folds resulting in severe visual loss. The magnitude of hypotony is not proportionate to the size of the cleft
- **Diagnosis**
  - Deep angle recess with a gap between the sclera and the ciliary body band.
  - Surgical gonioscopy with chamber deepening with OVDs is a useful method in cases of shallow AC that precludes proper angle visualization.
  - UBM is a contact procedure used to identify and localize the cleft when direct visualization is difficult. The UBM transducer tip emits high frequency pulses and detects the reflection from the ocular tissue interfaces giving a detailed

representation of the anterior chamber, angle and the ciliary body. It can accurately diagnose and delineate the cyclodialysis cleft.

- AS-OCT is a noncontact procedure. The technique is accurate and reproducible allowing the visualization of the angle in great detail. It has a higher resolution than UBM.

- **Management**
  - Spontaneous closure of cyclodialysis rarely occurs in smaller clefts
  - *Medical therapy* is the first line management in all the cases. It consists of topical cycloplegics (atropine sulphate 1%) twice daily for 6 to 8 weeks
  - *Laser photocoagulation* can be delivered via transcorneal , transscleral route or by endophotocoagulator probe. It may be effective in small clefts.
  - *Transconjunctival cyclocryopexy* is another noninvasive procedure to achieve adhesion between the choroids and the sclera.
  - *Transscleral ciliochoroidal diathermy* after creating a partial thickness scleral flap.
  - *Surgical management* is effective in moderate-to-large sized clefts.
  - *Direct cycloplexy*
  - *Cataract surgery with PCIOL in sulcus*
  - *Cataract Surgery with CTR*

Elevated episcleral venous pressure

- Episcleral venous pressure is raised 1 mmHg, IOP increases approximately 0.8 mmHg
- Concept of pseudofacility ?? → pressure-related reduction in aqueous humor formation
- **Signs**
  - Chemosis
  - Proptosis
  - Orbital bruit
  - Pulsating exophthalmos
  - Episcleral veins are dilated, tortuous, and have a corkscrew appearance
- Can be confused with conjunctivitis, episcleritis, scleritis, and general orbital inflammation.
- **Etiology of elevated episcleral venous pressure**
  - ***Obstruction of venous drainage***
    - Episcleral
      - Chemical burns
      - Radiation
    - Orbital
      - Retrobulbar tumors
      - Thyroid eye disease

        - Pseudotumor
        - Phlebitis
    - Cavernous sinus thrombosis
    - Jugular vein obstruction
    - Superior vena cava obstruction
    - Pulmonary venous obstruction
- ***Arteriovenous fistulas***
    - Orbital
    - Intracranial
        - Carotid-cavernous fistula
        - Dural fistula
        - Venous varix
        - Sturge-Weber syndrome
- ***Idiopathic***

Carotid-Cavernous Fistula

- **Classification**
    - Direct CCF in which highly pressurized blood from the carotid artery is directly shunted into the venous CS: HIGH FLOW → trauma
    - Indirect CCF, which develops as a result of communication between smaller, low-pressure arterial branches and veins of the CS: LOW FLOW → congenitally, during pregnancy, or spontaneously in post-menopausal women.
- **Pathophysiology**
    - CCFs alter ocular hemodynamics in a way whereby the high-flow, high-pressure profile of the carotid artery is transmitted to orbital and ocular structures
    - Classic clinical triad
        - Unilateral exophthalmos: pulsatile
        - Ocular or cephalic bruit
        - Injection and chemosis of the conjunctiva
- **Clinical Features**
    - Direct: headaches, diplopia, epistaxis, and visual loss
    - Indirect: ocular redness and swelling, loss of Visual acuity and color vision
    - Arterialized and tortuous, corkscrew conjunctival vessels
    - IOP is often elevated and wide mires
- **Management**
    - Orbital imaging with CT or MRI
    - Carotid angiography

- Endovascular embolization using balloons or detachable coils or stenting for both types of fistulas
- Indirect CCFs: spontaneous regression can occur
- Filtration surgery is to be avoided in eyes with CCFs if at all possible.

Sturge-Weber syndrome

- Encephalotrigeminal angiomatosis
- Triad of neuropsychiatric, dermatological, and ophthalmological manifestations
- Often referred to as the "fourth phacomatosis" but unlike the other phacomatoses, it has no known inheritance pattern.
- Neurocutaneous disorder with angiomas involving the leptomeninges (leptomeningeal angiomas [LAs]) and skin of the face, typically in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve. The cutaneous angioma is called a port-wine stain (PWS).
- **Roach Scale for classification**
  - Type I Both facial and leptomeningeal angiomas; may have glaucoma
  - Type II Facial angioma alone (no CNS involvement); may have glaucoma
  - Type III Isolated LA; usually no glaucoma
- **Pathophysiology**
  - During development there is an abnormal vascular plexus adjacent to the neural tube during development. This vascular nexus fails to regress and is dragged to various surface ectodermal and neuroectodermal locations during development. These loci of aberrant vascular tissue contribute to the clinical manifestations in SWS.
- **Clinical Features**
  - The facial hemangioma "port wine stain" is usually unilateral but may be bilateral. These skin lesions do not necessarily respect a strict dermatomal distribution
  - Conjunctival, episcleral, and choroidal hemangiomas are also common abnormalities. Diffuse uveal involvement has been termed the "tomato-catsup" fundus.
  - Glaucoma more often occurs when the ipsilateral facial hemangioma involves the lids and conjunctiva.
  - **30% to 70%** of individuals with SWS develop glaucoma, with 60% of cases reported at birth or in infancy and 40% reported in adolescence or young adulthood
  - The glaucoma that occurs in infancy looks and behaves like glaucoma associated with isolated trabeculodysgenesis and responds well to goniotomy.
  - The glaucoma that appears later in life is probably related to elevated episcleral venous pressure from arteriovenous fistulas.
  - Serous retinal detachment from large choroidal vascular malformations and homonymous hemianopsia.

- **Management**
  - **Pulsed dye laser photocoagulation**: for cosmetic effects of cutaneous port wine lesions
  - Older children medical therapy should be attempted first. However, if this is not successful, trabeculectomy should be considered in > 3years
  - Prophylactic posterior sclerotomy is often recommended to prevent perioperative choroidal hemorrhage in SWS ??
  - Filtering surgery has an increased risk of choroidal hemorrhage, resulting in shallowing or flattening of the anterior chamber related to the diminution of the intraocular pressure at the moment of surgery. This probably occurs when the intraocular pressure level falls below that of arterial blood pressure and results in effusion of choroidal fluid into surrounding tissues
  - Cyclodesctruction and glaucoma drainage device implantation

Idiopathic Elevated Episcleral Venous Pressure

- **IEEVP** is a diagnosis of exclusion.
- **Clinical Features**
  - Dilated, tortuous episcleral vessels with onset occurring subacutely typically in the third or fourth decade of life.
  - UL/ BL/ Asymmetric
  - Blood in Schlemm's canal which is a generalized sign of elevated episcleral venous pressure

Developmental and childhood glaucoma

Definitions

- ***Childhood glaucomas***
  - **Congenital glaucoma**, in which the developmental abnormality of the anterior chamber angle is not associated with other ocular or systemic anomalies
  - **Developmental glaucomas** with associated anomalies, in which ocular or systemic anomalies are present
  - **Secondary glaucomas** of childhood, in which other ocular pathologies are the cause of the impairment of the aqueous outflow
- **Definitions**
  - **Childhood**: Based on national criteria: < 18 years of age (United States); ≤ 16 years of age (U.K., Europe, UNICEF)
  - **Glaucoma**: IOP-related damage to the eye (2 or more of the following required for diagnosis):
    - IOP > 21 mmHg (discretion if examination under anesthesia data alone)
    - Optic disc damage: Progressive increase in cupdisc ratio, cup-disc asymmetry of ≥ 0.2 when the optic discs are similar in size, or focal rim thinning
    - Corneal findings: Haab striae or diameter ≥ 11 mm in newborn, > 12 mm in child under 12 months of age, > 13 mm any age
    - Progressive myopia or myopic shift coupled with an increase in ocular dimensions out of keeping with normal growth
    - Reproducible visual field defect consistent with glaucomatous optic neuropathy without other observable cause
  - **Glaucoma suspect**: No IOP-related damage and at least one of the following:
    - IOP > 21 mmHg on 2 separate occasions, or
    - Suspicious optic disc appearance for glaucoma (ie, increased cup-disc ratio for size of optic disc), or
    - Suspicious visual field for glaucoma, or
    - Increased corneal diameter or axial length in setting of normal IOP

Classifications

- **International Classification of Childhood Glaucoma (International Consensus)**
- ***Primary childhood glaucoma***
  - **Primary congenital glaucoma (PCG)**
    - Isolated angle anomalies (± mild congenital iris anomalies)
    - Meets glaucoma definition (usually with ocular enlargement)
    - Subcategories based on age of onset

        - Neonatal or newborn onset (0-1 month)
        - Infantile onset (> 1-24 months)
        - Late onset or late-recognized (> 2 years)
    - Spontaneously arrested cases with normal IOP but typical signs of PCG may be classified as PCG.
- **Juvenile open-angle glaucoma (JOAG)**
    - No ocular enlargement
    - No congenital ocular anomalies or syndromes
    - Open angle (normal appearance)
    - Meets glaucoma definition

- ***Secondary childhood glaucoma***
    - **Glaucoma associated with nonacquired ocular anomalies**
        - Includes conditions of predominantly ocular anomalies present at birth that may or may not be associated with systemic signs
        - Meets glaucoma definition
        - List common ocular anomalies (eg, AxenfeldRieger anomaly/syndrome, Peters anomaly/ syndrome, aniridia, ectopia lentis without systemic association, etc.)
    - **Glaucoma associated with nonacquired systemic anomalies**
        - Includes conditions of predominantly systemic disease present at birth that may be associated with ocular signs
        - Meets glaucoma definition
        - List common systemic syndrome or disease (eg, Down syndrome, Marfan and other connective tissue disorders, Lowe syndrome and other metabolic disorders, neurofibromatosis, Sturge-Weber, and other phacomatoses, etc.)
    - **Glaucoma associated with acquired condition**
        - Meets glaucoma definition after the acquired condition is recognized. An acquired condition is one that is not inherited or present at birth but that develops after birth.
        - Glaucoma developing after cataract surgery is excluded from this category to highlight its frequency and differences from other conditions in the acquired condition category.
        - List common acquired conditions (eg, uveitis, trauma, steroid-induced, tumors, ROP, post non-cataract surgery)
        - Based on gonioscopy results:
            - Open-angle glaucoma (≥ 50% open) or
            - Angle-closure glaucoma (< 50% open or acute angle closure)
    - **Glaucoma following cataract surgery**

- Meets glaucoma definition after cataract surgery is performed and subdivided into three categories:
  - Congenital idiopathic cataract
  - Congenital cataract associated with ocular anomalies / systemic disease (no previous glaucoma)
  - Acquired cataract (no previous glaucoma)
- Based on gonioscopy results:
  - Open angle glaucoma (≥ 50% open) or
  - Angle-closure glaucoma (< 50% open or acute angle closure)

✦ Shaffer-Weiss Syndrome classification of congenital glaucoma

1. **Primary congenital glaucoma**, in which the developmental anomaly is restricted to a maldevelopment of the trabecular meshwork
   - ✣ Congenital open-angle glaucoma
   - ✣ Autosomal dominant juvenile glaucoma
2. **Glaucoma associated** with specific ocular or systemic congenital anomalies
   - ✣ Glaucoma associated with systemic abnormalities
   - ✣ Glaucoma associated with ocular abnormalities
3. **Glaucoma secondary** to miscellaneous pediatric conditions involving the eye, such as inflammation,trauma, or tumors.
   - ✣ Traumatic glaucoma
   - ✣ Glaucoma secondary to intraocular neoplasm
   - ✣ Uveitic glaucoma
   - ✣ Lens-induced glaucoma
   - ✣ Glaucoma after congenital cataract surgery
   - ✣ Steroid-induced glaucoma
   - ✣ Neovascular glaucoma
   - ✣ Secondary angle-closure glaucoma
   - ✣ Glaucoma with increased episcleral venous pressure
   - ✣ Glaucoma secondary to intraocular infections

✦ Hoskins Clinical anatomic classification of developmental glaucoma

1. **Isolated trabeculodysgenesis** (malformation of trabecular meshwork in the absence of iris or corneal anomalies) 50% of infants and juvenile,
   A. Flat Iris Insertion
      - Anterior insertion
      - Posterior insertion

        - Mixed insertion
    B. Concave (wrap-around) iris insertion
    C. Unclassified
2. **Iridodysgenesis** (Iris anomalies are usually seen with trabeculodysgenesis)
    A. Anterior stromal defects
        - Hypoplasia
        - Hyperplasia *(a/w Sturge-Weber syndrome)*
    B. Anomalous iris vessels
        - Persistence of tunica vasculosa lentis
        - Anomalous superficial vessels
    C. Structural anomalies
        - Holes
        - Colobomata
        - Aniridia
3. **Corneodysgenesis** (Corneal anomalies are usually seen with iridodysgenesis)
    A. Peripheral: posterior embryotoxin, Axenfeld's anomaly
    B. Midperipheral: Rieger's anomaly
    C. Central: Peter's anomaly, posterior ulcer of von Hippel, and posterior keratoconus
    D. Corneal size
        - Macrocornea: microphthalmos, nanophthalmos, Rieger's anomaly, persistent hyperplastic primary vitreous, and congenital rubella syndrome
        - Microcornea: Axenfeld's syndrome or in X-linked recessive megalocornea.

Features & EUA

- **Clinical presentation**
    - Epiphora, photophobia and blepharospasm
    - Enlargement mainly at the corneoscleral junction
    - Breaks in Descemet's membrane (Haab's striae)
    - Progressive myopia
- **Examination under anesthesia (EUA)**
    - IOP:
        - Applanation (Goldmann or hand-held Perkins)
        - Indentation (Schiøtz)
        - Indentation-applanation hybrid (pneumotonometer)
        - Non-contact air-puff (Keeler Pulsair)

- Electronic (TonoPen or Mackay-Marg)

- Corneal diameters
  - Newborns 9.5–10.5
  - 1 year 10–11.5
  - 2 years 11.5–12
  - >2 years 12
- Corneal thickness
  - Applanation IOP readings are profoundly affected by the CCT (*viz.*, thicker CCTs 'overestimate' and thinner CCTs 'underestimate' true IOPs)
  - Is a significant risk factor for developing glaucoma damage, independent of IOP corrections, with thinner CCTs.
- Gonioscopy:
  - Smooth-domed Koeppe 14to 16-mm lens, with a Barkan light and hand-held binocular microscope
  - Although the angle is usually avascular, loops of vessels from the major arterial circle may be seen above the iris ("**Loch Ness Monster phenomenon**").
  - In addition, the peripheral iris may be covered by a fine, fluffy tissue ("**Lister's morning mist**").
- Ophthalmoscopy:
  - Optic disc cupping larger than 0.3, especially if asymmetric between both eyes, is strong evidence that the disc is under pressure and probably glaucomatous. Dilated fundus examination and disc evaluation are essential in the diagnosis and follow up of congenital glaucoma
  - Optic disc cupping in infants
    - Steep walled
    - Central
    - Circumferential (oval) enlargement, with the nerve retaining its pink rim until advanced stages of cupping
  - Changes in the optic disc occur readily with changes in IOP in infants.
    - Early appearance of cupping
      - ✓ Mechanical distortion in the disc supporting elements and posterior bowing of the lamina cribrosa
      - ✓ Stretched out globe
      - ✓ Neuronal loss then ensues
    - Reversible Cupping
      - ✓ Remarkable decrease in cupping can be observed as early as one week after normalization of IOP
      - ✓ The younger the child, the faster the reversibility

- ✓ So consistent that it can be used as the main criterion for control of glaucoma in infants rather than using the level of IOP
- ✓ Probably related to mechanical changes rather than neural damage

- *With successful control of the IOP, the cup will either remain stable or its size will decrease*

- Axial length measurements
- Ultrasonic biomicroscopy
- Cycloplegic retinoscopy

Primary congenital glaucoma

- 1 in 10 000 live births in western literature, 1 in 4000 in India
- 40% at birth, 70% between 1 and 6 months, and 80% before 1 year.
- Most cases sporadic, 10% autosomal recessive
- Most common form of infantile glaucoma, representing 50% of all cases of congenital glaucoma
- 75% bilateral
- Clinical Features
  - Epiphora, photophobia, and blepharospasm form the classic triad
  - Buphthalmos
  - Horizontal corneal diameter greater than 12 mm in an infant is highly suggestive of congenital glaucoma.
  - Corneal cloudiness, tears in Descemet's membrane (Haab's striae), deep anterior chamber, intraocular pressure greater than 21 mm Hg, iris stroma hypoplasia, isolated trabeculodysgenesis on gonioscopy, and increased optic nerve cupping.
  - Cup-to-disc ratios greater than 0.3 are rare in normal infants
  - Asymmetry of optic nerve cupping > 0.2
  - Anterior chamber angle
    - Flat iris insertion
    - Concave iris insertion
- **Differential diagnosis**
  - **Other glaucomas**
    - Glaucoma associated with congenital anomalies
    - Secondary glaucoma
  - **Other causes of corneal enlargement or clouding**
    - Megalocornea

        - Primary megalocornea: X-linked form from mutation in CHRDL1 (MIM *300350) and other forms
        - Primary megalocornea with zonular weakness and secondary lens-related glaucoma: recessive mutations in LTBP2 (MIM *602091)
    - Sclerocornea
    - High myopia
    - Metabolic diseases
    - Posterior polymorphous dystrophy
    - Congenital hereditary endothelial dystrophy: recessive mutations in *SLC4A11* (Online Mendelian Inheritance in Man [MIM] *610206)
    - Obstetric trauma
    - Inflammation (keratitis, iridocyclitis)
- **Other causes of epiphora or photophobia**
    - Nasolacrimal duct obstruction
    - Conjunctivitis
    - Corneal abrasion
    - Meesman's corneal dystrophy
    - Reis-Buckler's dystrophy
- **Other causes of Posterior Corneal Breaks**
    - Birth trauma
    - Primary corneal ectasia/fragility (brittle cornea syndrome): recessive mutations in ZNF469 (MIM *612078) or PRDM5 (MIM *614161)
- **Other causes of optic nerve abnormalities**
    - Pit
    - Coloboma
    - Hypoplasia
    - Tilted disc
    - Large physiologic cup

Medical Management

- Beta Blockers, such as timolol 0.25% or betaxolol suspension 0.25%
- Prostaglandin anaologs are usually well tolerated, without demonstrable toxicity in pregnant mothers or children
- *Brimonidine should be avoided*, as it may produce bradycardia, hypotension, hypothermia, and apnea in infants.

Surgical Management

- Early surgery is essential
- **Old Angle Surgeries:** ab-interno approach (goniotomy) or an ab-externo approach (trabeculotomy)

- Advantages: Familiar techniques, very long followup reported
- Disadvantages: Repeat surgery necessary for 15%40% of cases as only 1/3 to 1/2 of the angle is treated.

- **New Angle Surgeries**: Circumferential suture trabeculotomy, Circumferential microcatheter trabeculotomy
  - Advantages: Can treat the entire angle with one procedure with better reported outcomes than old angle surgeries.
  - Disadvantages: More time consuming and technically challenging than old angle surgeries. Microcatheter approach is more expensive than the suture technique. Subretinal suture misdirection has been reported with the suture technique. Follow-up duration is not as long as old angle surgeries

- **Goniotomy**
  - Developed in the 1930s by Barkan
  - Goniotomy spares the conjunctiva but requires a clear cornea to visualize the irido-corneal angle, while trabeculotomy can be performed in most cases regardless corneal clarity.
  - Goniotome and direct gonioscopy lens
  - Barkan's goniolens
  - Modified Swan–Jacob lens
  - Titratable Goniotomy for Glaucoma
    - 90-120 degree treatment, Kahook Dual Blade
    - Gonioscopy-assisted transluminal trabeculotomy (GATT) and HEMI GATT modification
    - Demonstration of 360 blanching from 180 treatment of GATT

- **Trabeculectomy**
  - Standard technique with metal probes developed in the 1960s (Harms most commonly used)
  - Cloudy or opacified corneas
  - Trabecular meshwork is broken using a trabeculotome
  - Trabeculectomy is not recommended as a first line treatment in PCG, because of the extensive postoperative scarring, thin sclera/low scleral rigidity, stretched limbus and most importantly because of the life-long risk of infection associated with the bleb.

- **Circumferential suture trabeculotomy:**
  - Smith published a suture approach in 1960 with adaptations by Fellman, Lynn, and Lynch for circumferential surgery in the 1980s.
  - Suture (usually propylene) through Schlemm's canal (**Lynch procedure**).
  - Fiber optic catheter (iCath, iScience), which has the advantage of an illuminated tip that identifies the location of the catheter

- **GATT** (gonioscopyassisted transluminal trabeculotomy) and **TRAB360** ab-interno trabeculotomy and both have shown promising results.

- **Circumferential microcatheter trabeculotomy:** iTrack microcatheter developed for canaloplasty used for trabeculotomy in the last 10 years.

Glaucoma Associated with Congenital Anterior Segment Anomalies

- **Classification:**
  - Opaque cornea
    - Congenital glaucoma
      - Primary
      - Secondary: Mnemonic: **ReNTALS** (Rubinstein-Taybi, NF1, trisomy 18, Axenfeld-Rieger, Lowes, Sturge-Weber)
    - Peters anomaly
    - Congenital hereditary endothelial dystrophy
  - Unusual iris, chamber and angle
    - Aniridia
    - Pachyphakia, microcornea, angle closure (**PMAC**)
    - Axenfeld-Rieger syndrome
    - Ectropion uveae
  - Lens-related issues: aphakia/pseudophakia
  - Whole globe issue
    - Microphthalmia
      - Simple: less common, 1/3 of microphthalmia cases, 50% associated with developmental anomalies
      - Complex: more common, 2/3 of microphthalmia cases, lack of secondary vitreous production
    - Early onset High Myopia
- **Management**
  - Medications
  - Surgical
    - Cornea clear, angle open: goniotomy and related ab interno angle surgery
    - Cornea cloudy, angle open: ab externo trabeculotomy
    - Cornea clear, angle closed: lensectomy, goniosynechialysis, ± endocyclophotocoagulation
    - Cornea cloudy, angle closed: many options

Aniridia

- Rudimentary iris stump
- Two-thirds of cases are dominantly transmitted with a high-degree penetrance. Twenty percent are associated with Wilms' tumor.
- Short arm of chromosome 11
- Foveal and optic nerve hypoplasia, keratopathy, cataract (60% to 80%), and ectopia lentis
- Photophobia, nystagmus, decreased vision, and strabismus
- Progressive corneal opacification and pannus
- **AN1:** 85%
  - Familial aniridia (most cases in this category)
  - Autosomal dominant with incomplete penetrance and expression
  - Isolated ocular defect, foveal hypoplasia, corneal "dystrophy", glaucoma, etc.
- **AN2:** 13% (**Miller's Syndrome,** WAGR)
  - **Sporadic nonfamilial aniridia and Wilms' tumor**
  - Deletion or mutation in short arm of chromosome 11 **(11p-)**
  - Associations include:
    - Wilms' tumor of kidney (nephroblastoma),genitourinary abnormalities, mental
    - Retardation, craniofacial dysmorphism, hemihypertrophy
    - Incidence of aniridia in patients with Wilms' tumor is 1/73 (1.4%)
    - Incidence of Wilms' tumor in sporadic aniridia is 34%
- **AN3:** 2% (**Gillespie's Syndrome**)
  - Autosomal recessive aniridia, Mental retardation, cerebellar ataxia
- Glaucoma:
  - Late childhood or early adulthood.
  - Result of trabeculodysgenesis or of progressive closure of the trabecular meshwork by the residual iris stump
  - Early goniotomy or Trabeculectomy if early presentation
  - Late presentation: medical therapy, filtering procedure, Cyclodestructive procedures

Axenfeld's Anomaly

- Bilateral
- AD
- Peripheral cornea, anterior chamber angle, and iris anomalies.
- Prominent Schwalbe's line, referred to as posterior embryotoxon
- Iris strands attaching to the posterior embryotoxon and hypoplasia of the anterior iris stroma may be present.

- **Axenfeld's syndrome**
  - Includes glaucoma and occurs in 50% of patients with the anomaly

Rieger's Anomaly

- Bilateral
- AD
- Advanced degree of angle dysgenesis
- Marked iris hypoplasia is observed with polycoria and corectopia.
- >50% glaucoma
- Rieger's Syndrome
  - Dental abnormalities include a reduction of crown size (microdontia), a decreased but evenly spaced number of teeth, and a focal absence of teeth (commonly the anterior maxillary primary and permanent central incisors
  - Facial bones defect: maxillary hypoplasia
- All are collectively known as anterior chamber cleavage syndrome and mesodermal dysgenesis of cornea and iris. They are also referred to as Axenfeld–Rieger syndrome.

Peter's Anomaly

- Major degree of anterior chamber developmental disorder
- Corneal opacity associated with a posterior stromal defect → **Von Hippel's corneal ulcer**
- Iris is adherent to the cornea at the collarette
- Bilateral and frequently associated with glaucoma and cataract.

Neurofibromatosis

- Primarily affects tissue derived from the neural crest, particularly the sensitive nerves, Schwann's cells, and melanocytes.
- Ophthalmic involvement
  - Iris hamartomas, clinically observed as bilateral, raised, smooth-surfaced, dome-shaped lesions
  - Plexiform neurofibromas of the upper lid, which appear clinically as an area of thickening of the lid margin with ptosis and an S-shaped deformity
  - Retinal tumors, most commonly astrocytic hamartomas
  - Optic nerve gliomas, which manifest as unilateral decreased visual acuity or strabismus and have been observed in 25% of cases
  - Ipsilateral glaucoma is also occasionally seen and is usually associated with plexiform neurofibroma of the upper lid.

Glaucoma After Pediatric Cataract Extraction

- 15%-30% after cataract surgery during infancy; rare after cataract surgery in children > 6 months of age
- **Etiology**
  - Cataract surgery interferes with the maturation of the trabecular meshwork.
  - "Collapse" of the immature angle after cataract surgery
- **Risk Factors**
  - Cataract surgery during infancy
  - Reoperations
  - Nuclear cataracts
  - Persistent fetal vasculature
  - Microphthalmia
  - Chronic inflammation and retained lens material
  - Bilateral cataracts
- **Protective Factors:** IOL implantation
- Different Studies and their Summary
  - **Infant Aphakia Treatment Study**
    - The risk for glaucoma 4.8 years after cataract surgery was 17%.
    - The risk for glaucoma + glaucoma suspect 4.8 years after cataract surgery was 31%.
    - Risk of glaucoma was the same with or without IOL
  - **IOLunder2 Study**
    - Cumulative incidence of glaucoma: 13%
    - All patients who developed glaucoma underwent cataract surgery < 6 months of age.
    - Microphthalmia was an independent predictor of glaucoma with unilateral (OR, 12.1), but not bilateral cataracts.
  - **Melbourne Study**
    - Cumulative incidence of glaucoma: 32%
    - Mean time to glaucoma diagnosis: 7.2 years (IQR, 2.0-9.5 years)
    - Age at cataract surgery was the only factor independently associated with increased risk of glaucoma.
  - **Emory Longitudinal Study**
    - Cumulative incidence of glaucoma: 14.5%
    - Estimated probability of an eye developing glaucoma by age 10 years: 19.5%
    - Estimated probability of an eye developing glaucoma or glaucoma suspect by age 10 years: 63%

Medical management of Glaucoma

Few Concepts

- **Glaucoma Suspect**
  - Glaucoma suspect type I: Normal intraocular pressure, no damage
  - Glaucoma suspect type II: Normal intraocular pressure, possible damage
  - Glaucoma suspect type III: High intraocular pressure, no damage
  - Glaucoma suspect type IV: High intraocular pressure, possible damage
- **Possible glaucomatous damage**
  - **Visual field**
    - Generalized depression
    - Baring of blind spot
    - Nasal step < 10°
    - Relative scotoma < 5°
    - Statistical field loss index *P* = 0.05–0.10
  - **Visual function**
    - Reduced color vision
    - Reduced temporal contrast sensitivity
    - Abnormal pattern electroretinogram
  - **Optic nerve head**
    - Cup-to-disc ratio > 0.5
    - Asymmetry of disc cups > 0.2 cup-to-disc ratio
    - Disc hemorrhage
    - Disc pit
    - Rim area < 1.10 mm2
    - Vertically oval cup
    - Diffuse or localized nerve fiber layer defect
  - **Chamber angle**
    - Peripheral anterior synechiae

- **Risk factors for progression from ocular hypertension to manifest glaucoma**
  - Corneal thickness under 535 microns
  - Elevated IOP
  - Increasing age
  - Enlarged vertical cup-to-disc ratio
  - Increased pattern standard deviation on static threshold perimetry

- **Risk factors for progression of manifest glaucoma**
  - **Established**
    - Elevated IOP
    - Over 18 mmHg any of the time
    - Increased fluctuation of IOP
    - Increasing age
    - Exfoliation of the lens capsule
    - Advanced cupping
    - Advanced visual field loss
  - **Putative**
    - Sleep apnea
    - Thin corneas
    - Nocturnal systemic hypotension

Target pressure

- An IOP of 21 mmHg or lower – the previously sought goal – may not be low enough for many glaucomatous eyes.
- AGIS: 18mmHg
- Lower the IOP to a level that is 'safe' for that particular eye
- Depends on
  - Initial IOP
  - Degree of existing damage
  - How hard the patient has to work to achieve the goal
  - The realities of adherence expectations for that individual
  - What potential side effects, complications, and cost that particular regimen might entail.
- Many formulae available (may refer reference books for details)

Mechanisms to Decrease IOP

- Decrease Aqueous Production
  - Beta-blocker
  - CAI
  - Alpha 2-agonist
- Increase Aqueous outflow
  - Trabecular/Conventional outflow: Cholonergics

- Uveoscleral/Unconventional outflow:
  - Prostaglandin analog
  - Alpha 2-agonist
- Combination of Pathways
  - NATARSUDIL 0.02% (Rho kinase inhibitors)
    - Unlike PGA's, CAI's, alphaagonists or beta blockers, **ROCK** inhibition relaxes TM1, increases TM outflow
    - **NET** (Norepinephrine Transferase) inhibition reduces fluid production
    - Lowers Episcleral Venous Pressure (EVP)

Trabecular Meshwork–Targeted Drugs

- Juxtacanalicular TM as the primary site of aqueous outflow resistance
- Trabecular outflow is impaired due to oxidative stress and cellular debris in TM cells.
- Mechanisms of Novel TM-Targeted Drugs
  - Latanoprostene bunod, a nitric oxide–donating prostaglandin analogue (PGA)
    - Increased uveoscleral outflow (PGA)
    - Trabecular relaxation and increased trabecular outflow (NO)
  - Netarsudil, rho kinase (ROCK) and norepinephrine transporter (NET) inhibitor
    - Increased trabecular outflow (ROCK inhibitor)
    - Decreased episcleral venous pressure (ROCK inhibitor)
    - Decreased aqueous production (NET inhibitor)
- Side Effects of New Outflow Drugs
  - Latanoprostene bunod: eye pain and hyperemia
  - Netarsudil: hyperemia, conjunctival hemorrhages, and corneal verticillata

Routinely used Agents

Alpha Adrenergic agonists

- 1900: Darier treated glaucoma patients with subconjunctival injections of epinephrine
- 1920: Hamburger: epinephrine topically to reduce intraocular pressure
- Five major types are recognized: alpha 1 & 2, beta 1,2,3
  - **Alpha 1 stimulation**: mydriasis, vasoconstriction, elevation of IOP, and eyelid retraction
  - **Alpha 2 stimulation:** decreased aqueous humor formation and, probably, increased outflow of aqueous
  - ***Combined Alpha and Beta agonists:*** epinephrine

- ***Alpha2 agonist:*** brimonidine
- ***Alpha1 Alpha2 agonist:*** apraclonidine

Mechanism of action

- Epinephrine: increases both conventional and unconventional outflow
- Dipivefrin: Prodrug → converted to epinephrine by esterase enzymes in the cornea
- Norepinephrine
  - Decrease in IOP by increasing the trabecular outflow facility+
  - Too modest for clinical effectiveness
- Alpha1 Adrenergic agonists
  - Phenylephrine
  - Acts predominantly on alpha 1-adrenergic receptors
  - 0.125–10% Vasoconstriction or mydriasis or to break posterior synechiae
- Alpha 2 Adrenergic agonists
  - Clonidine
    - 0.125% and 0.05%,
    - Central and peripheral adrenergic mechanisms to reduce aqueous humor formation
  - Apraclonidine
    - Reduces the risk of systemic hypotension
    - May reduce episcleral venous pressure and, unlike clonidine, may increase trabecular outflow
    - Peak effect in 1-2 hours, do used before lasr PI etc.
  - Brimonidine
    - Selective for alpha
    - Decreases IOP by reducing aqueous formation; in addition, it acts by increasing uveoscleral outflow.
    - Effectiveness may be reduced by concomitant administration of non-steroidal anti-inflammatory agents;
    - 0.2%. 0.15% & 0.1%
    - Cardiovascular instability in infants and is therefore contraindicated in the first 5 years of life.
    - Sleepiness and lethargy in <15 years age
- Beta Adrenergic agonists
  - Isoproterenol
  - Salbutamol
- Dopaminergic agonists
  - Nonadrenergic activators of adenylate cyclase

- Plant derivative forskolin (non-proprietary name colforsin).

Drugs in clinical use

Non-selective

- Epinephrine
  - Hydrochloride, bitartrate, and borate
  - 0.5%, 1%, and 2%
  - IOP begins to fall in 1 hour, reaches a minimum in 2–6 hours, and returns to baseline in 12–24 hours
- Dipivefrin (Propine)
  - 0.1%
  - Less external irritation, burning, and systemic side effects than does epinephrine
- Side Effects
  - **Lid and conjunctiva:** Hyperemia, Burning/stinging, Tearing, Blepharoconjunctivitis, Skin blanching, Adrenochrome deposits, Madarosis, Ocular pemphigoid
  - **Lacrimal system:** Lacrimal stones
  - **Cornea:** Epithelial edema, Endothelial toxicity, Epithelial erosion from tarsal adrenochrome deposits, Adrenochrome deposits, Soft contact lens staining
  - **Iris and uveal tract:** Mydriasis and angle closure, Visual distortion/blurred vision, Photophobia, Iridocyclitis
  - **Retina:** Cystoid macular edema
  - **Systemic:** Headache/browache, Tachycardia/dysrhythmia, Premature ventricular contractions, Palpitations/Anxiety/nervousness/pallor/faintness, Tremor, Increased blood pressure, Cerebrovascular accident, Myocardial infarction, Death
- Contraindications
  - Severe hypertension
  - Cardiac disease
  - Thyrotoxicosis

Alpha 2 Agonists

- Clonidine
- **Side Effects**
  - **Systemic:** Dry mouth, Fatigue, Drowsiness, Headache, Hypotension, Bradycardia in neonates, Hypothermia in neonates
  - **Ocular:** Allergy, Blurred vision, Burning/stinging, Follicular conjunctival response, Hyperemia, Itching, Photophobia

Beta Adrenergic antagonists

- 1967: Phillips, IV propranolol decreases IOP → topical
- **Mechanism of action**
  - B-Adrenergic receptors are found in the ciliary processes which produces aqueous
  - Five different topical B-blocking agents are available for clinical use in the United States: timolol, levobunolol, betaxolol, metipranolol, and carteolol.
- **Timolol maleate**
  - Nonselective B1 B2 adrenergic antagonist
  - Mild local side effects (decrease corneal sensation, allergic reaction, cicatricial conjunctivitis)
  - Severe systemic side effects (pulmonary bronchospasm, brady- cardia, hypoglycemia)
  - Common systemic side effects (lethargy, decreased libido, depression)

Prostaglandins

- First identified in seminal fluid in the 1930s
- 1955, Ambache identified a substance in iris tissue that he called irin → Irritation
- **Mechanism of action**
  - High doses: signs of inflammation & INCREASED IOP
  - Low doses: DECREASES IOP
  - Receptor types have been positively identified; **DP**, EP, ***FP***, IP, and TP.
  - Currently available clinical agents: activity at a FP receptor
    - **Functional**: increase in outflow facility without significant effect on aqueous formation, trabecular outflow facility, or episcleral venous pressure
    - **Structural**: extracellular matrix remodeling, widening of intermuscular spaces along the longitudinal ciliary muscle bundles, and dissolution of collagen types I and III.
    - Ciliary muscle relaxation which also widens the connective tissue spaces. This is responsible for the initial fall in IOP with topical prostaglandins
  - Latanoprost & Travoprost: FP receptor → increases uveoscleral outflow
  - Bimatoprost – **prostamides** → increases uveoscleral and trabecular outflow
  - Unoprostone – **docosanoids**
  - Tafluprost: DP receptor agonist
- **Drugs in clinical use**
  - First prostaglandin analog: PF F2-**tromethamine salt** (PGF2-TS)

- First usable prostaglandin: Japan. Isopropyl unoprostone (Rescula)
- PHXA34
- PHXA41= Latanoprost= Just R epimer of PHXA34

Latanoprost (xalatan, phxa41)

- 0.005%
- Persist over 24 hours
- No evidence of tachyphylaxis
- Prodrug
- NTG, pigmentary glaucoma, steroid induced glaucoma

Bimatoprost (Lumigan)

- 0.03%
- Prostaglandin F2 alpha analog
- Slightly improved pressure control or works in a greater percentage of patients
- Most potent of these agents but with a concomitant increase in local side effects
- Higher incidence of hyperemia

Travoprost (Travatan)

- 0.004%
- Isopropyl ester of a potent prostaglandin F2 alpha agonist
- Prodrug
- Greater duration of action – over 40 hours from a single dose
- The only with a different preservative than BAK → Travatan Z™

Isopropyl unoprostone (uf-021,rescula™)

- No longer available now, Docosanoid, BID dosage
- Prodrug derived from a pulmonary metabolite of PGF2.
- 0.06% or 0.12%
- Side effects: conjunctival hyperemia, corneal epithelial defect, and headache. Increased iris pigmentation

Tafluprost

- Is a new difluoro prostaglandin analog undergoing clinical trials in Japan.
- Prostanoid EP3 receptor
- It is approved in some countries (Demark since April 2008 and Germany since May 2008)
- Preservative free 0.0015% solution for once daily dosing.

Side effects

- Conjunctival hyperemia **B >> T >> L >> U**
- Foreign body sensation
- Eye irritation
- Superficial punctate keratopathy
- Activation of latent herpes simplex
- Periocular hyperpigmentation B >> L
- Darkening and increase in length of the eyelashes ***(able to induce resting follicles to enter the growth phase and prolong it)***
- Vellus hairs & poliosis
- Anterior uveitis
- CME: 1–2% of Aphakic or pseudophakic eyes. ***(Management: NSAID can be given along with it) ,*** should be discontinued before surgery and resumed after 6-8 weeks of surgery
- Choroidal effusions
- Darkening of iris color (stimulate the formation of extra melanin granules in the individual iris stromal melanocytes due to increase in tyrosinase transcription associated with latanoprost administration)
- Systemic: joint or muscle pains, dry mouth, backache, bitter taste, and allergic skin reactions, wheezing, Urge incontinence

Carbonic anhydrase inhibitors

- **MOA**
  - $CO_2 + OH \rightarrow CA \rightarrow HCO_3$
  - Direct Effect: decreases CA activity in non-pigmented epithelium of the ciliary processes
  - Indirect Effect:
    - Interfere with this buffering system and indirectly reduce aqueous humor formation.
    - Vasoconstriction in the anterior uveal tract
    - Decreased episcleral venous pressure
- CA is present in renal cortex, gastric mucosa, red blood cells (RBCs), lung, pancreas, and central nervous system (CNS).
- In the eye: corneal endothelium, non-pigmented iris epithelium, pigmented and non-pigmented epithelium of the ciliary processes, Müller cells, and retinal pigment epithelium
- Mostly its **type 2** in the eye, (3,4 also present)
- CAI in full doses reduce aqueous humor formation by about 40%. This means that at least 60% of aqueous humor formation is independent of the enzyme CA.

- More than 99% of the enzyme activity must be inhibited before aqueous production is reduced

- **Topical carbonic anhydrase inhibitors**
  - Original agent (ethoxzolamide gel) → not successful
  - Finally, dorzolamide & brinzolamide came
  - **Dorzolamide**
    - Trusopt
    - Free sulfonamide group and a second amine group
    - Isoenzymes II and IV > I
    - RBC CA is depressed to 21% of normal level
    - 2% solution is the most effective, BD or TDS
    - Also in pediatrics
    - Cosopt (with timolol)
  - **Brinzolamide**
    - Azopt
    - 1% TDS or BD

- **Systemic carbonic anhydrase inhibitors**
  - **Acetazolamide**
    - Diamox
    - 125 and 250 mg tablets and as a 500 mg sustained-release (SR) preparation
    - Oral: IOP begins to drop in 1–2 hours, reaches a minimum in 2–4 hours, and returns to baseline in 4–12 hours.
    - IV/IM: IOP begins to fall within minutes, reaches a minimum in 15–30 minutes, and returns to baseline in 4–6 hours.
    - 5–10 mg/kg every 6 hours
    - Serum half life: 4 hours
    - Plasma acetazolamide concentrations of 4–20 microgram/ml
    - Actively secreted by the renal tubules and then passively resorbed by non-ionic diffusion.
  - **Methazolamide**
    - 50-100 mg BD
    - Not actively secreted by the kidneys,
    - Less bound to plasma protein
  - **Ethoxzolamide**
    - Most potent of the clinically used CAIs

        - 62.5–250 mg every 4–8 hours
    - **Dichlorphenamide**
        - 25–200 mg every 6–8

- **Side effects**
- **Side effects with TOPICAL**
    - Ocular
        - Stinging → 10%
        - Allergy
        - Dryness
        - Superficial punctate keratopathy → 10%
        - Induced myopia
    - Systemic
        - Metallic taste
        - Urticaria
        - Neutropenia
        - Headache
        - Gastrointestinal distress
        - Dizziness
        - Paresthesias
        - ?Aplastic anemia
        - ?Stevens-Johnson syndrome
- **Side effects with ORAL**
    - Myopic shift*
    - Paresthesias of fingers, toes, circumoral region: Decreased dexterity
    - Electrolyte disturbances: Metabolic acidosis, Potassium depletion associated with concomitant use of diuretics or corticosteroid, Chloride depletion associated with use of dichlorphenamide, Uric acid retention
    - Gastrointestinal: Abdominal cramping/discomfort, Metallic taste to carbonated beverages, Nausea, Diarrhea*, Anorexia, Weight loss*, Constipation
    - Genitourinary: Nocturia, Urolithiasis*, Impotence, Frequency with polydypsia* (especially in the first week of treatment), Hypersensitivity nephropathy*
    - Central nervous system: Malaise*, Excitement, Elevated cerebrospinal fluid pressure, Fatigue, Confusion, Depression*, Drowsiness*, Headache, Decreased libido, Vertigo, Irritability*, Insomnia, Tremor
    - Blood dyscrasias: Thrombocytopenia*, Agranulocytosis*, Hyperchromic anemia, Aplastic anemia*, Neutropenia, Interference with anticholinesterase treatment of myasthenia gravis, Exacerbation of effect of diphenylhydantoin on bone

demineralization, Dyspnea*, Leg cramps, Hearing loss, Birth defects, Hypersensitivity hepatitis

- Dermatologic: Rash, Exfoliative dermatitis* (Stevens-Johnson syndrome), Pruritis, Hair loss, Flushing, Hirsutism
- If you want to start Diamox in a patient with HTN, just check they are not on HCTZ, as it will accentuate hypokalemia.

- ***Non Glaucoma use of CAI***
  - Chromic macular edema
  - BIH
  - Mountain sickness

Cholinergics

- Oldest effective medical treatment
- Laqueur: physostigmine
- Weber: pilocarpine
- MOA
  - Effect on parasympathetic receptors in the iris and ciliary body.
  - **Angle-closure glaucoma**
    - Constrict the pupillary sphincter, tighten the iris, decrease the volume of iris tissue in the angle, and pull the peripheral iris away
    - Ischemic pupil may not respond
  - **Open-angle glaucoma**
    - Increasing the facility of outflow
    - Stimulate the ciliary muscle, putting traction on the scleral spur and the trabecular meshwork, which separates the trabecular sheets and prevents Schlemm's canal from collapsing

- **Direct-acting cholinergic agents**
  - **Acetylcholine**
    - Not used for the treatment of glaucoma because it penetrates the cornea poorly and is destroyed rapidly by cholinesterase.
  - **Pilocarpine**
    - More potent at muscarinic than at nicotinic receptor sites
    - 0.25–10% QID
    - Reduction in IOP that begins in an hour and lasts for 4 to 8 hours
    - Binds to melanin in the iris and ciliary body, iris color may influence IOP response.

- *Alternative drug delivery systems*
  - Pilocarpine in 1.6% polyvinylpyrrolidone (Adsorbocarpine)
  - ***Soft contact lenses***
  - ***Membrane-controlled delivery (Ocusert):*** 20 ug per hour or 40 ug per hour,
  - ***Pilocarpine gel (Pilopine HS gel)***
  - ***Pilocarpine polymer (Piloplex)***

- **Methacholine**
  - Unstable in solution
- **Carbachol**
  - 0.75–3% and is administered 3–4 times
  - As a substitute for pilocarpine

Indirect (anticholinesterase) agents

- Echothiophate iodide (phospholine iodide)
- Demecarium bromide (Humorsol, Tosmilen)
- Isoflurophate
- Physostigmine (eserine)
- Neostigmine (prostigmine)

Side effects

- More with indirect acting
- **Ocular**
  - Miosis, decreased vision in dim illumination
  - Ciliary muscle spasm, fluctuating vision, headache
  - Orbicularis muscle spasm, lid twitching, periocular pain
  - Vascular dilation, conjunctival and iris hyperemia
  - Increased vascular permeability, formation of posterior synechiae,
  - postoperative inflammation
  - Production or enhancement of angle-closure glaucoma
  - Temporary increase in IOP
  - Cataract formation
  - Stinging, irritation
  - Tearing
  - Allergic blepharoconjunctivitis
  - Cyst of the iris pigment epithelium

- Retinal hole, retinal detachment, vitreous hemorrhage
- Lacrimal obstruction, ocular pseudopemphigoid
- Corneal epithelial staining, vascularization
- Atypical band keratopathy caused by phenylmercuric nitrate preservative

Systemic

- Bronchial spasm, asthma, pulmonary edema
- Nausea, vomiting, abdominal pain
- Weakness, fatigue, muscle spasm – may mimic myasthenia gravis
- Paresthesia
- Prolonged respiratory paralysis after general anesthesia including succinylcholine
- Toxic reactions to local anesthetics containing an ester linkage group
- Sweating, salivation, lacrimation
- Hypotension, bradycardia
- Nightmares, depression, delusions
- Exacerbation of myasthenia gravis and interference with its drug treatment

Contraindications

- Intraocular inflammation or known hypersensitivity
- Chronic obstructive airway disease, peptic ulcer, Parkinson's disease, bradycardia, hypotension, myasthenia gravis, peripheral retinal degeneration, high myopia, and a history of retinal detachment.

Hyperosmotic agents

Mechanisms of action

- Drawing water from the eye into the circulation via the blood vessels of the retina and uveal tract
- Decrease aqueous humor production via a central nervous system (CNS) pathway involving osmoreceptors in the hypothalamus.

Oral agents

Glycerol

- 50% solution
- Dose of 1.5–3 ml/kg
- Lower IOP in 10–30 minutes, reaches a maximum effect in 45–120 minutes, and has a duration of effect of 4–5 hours
- Intense, sweet taste
- Given in an iced unsweetened fruit juice or cola base

- Disadvantage
  - Associated nausea and vomiting
  - Produces 4.32 kcal/g of energy
  - Not suitable in DM

- **Isosorbide**
  - 45% solution
  - 1.5–4 ml/kgs
- **Ethyl alcohol**
  - 1.0–1.8 ml/kg of absolute alcohol (about 1–2 ml/kg of a 40–50% solution (80–100 proof)).

Intravenous agents

- **Mannitol**
  - 2.5–7.0 ml/kg of the 20% solution
  - Lower IOP in 15–30 minutes, reaches a maximum effect in 30–60 minutes, and has a duration of action of approximately 6 hours.
  - Disadvantages
    - Cellular dehydration: dementia and disorientation
    - Intolerable load on patients with congestive heart failure
- **Urea**
  - 30% solution
  - Dose of 2.0–7.0 ml/kg
  - Lower IOP in 15–30 minutes, reaches a maximum effect in 60 minutes, and has a duration of action of 4–6 hours

Side effects

- GI: Nausea, Vomiting, Diarrhea, Abdominal cramping
- Cardiovascular: Angina, Congestive heart failure, Pulmonary edema
- Central nervous system: Headache, Backache, Confusion, Disorientation, Chills, Fever, Subdural hematoma
- Renal/genitourinary: Diuresis, Loss of potassium, Urinary retention, Anuria46
- Miscellaneous: Arm pain, Skin slough, Thrombophlebitis, Acidosis, Diabetic ketoacidosis, Hyperosmolar non-ketotic coma, Urticaria, Laryngeal edema, Anaphylactic reaction, Hyphema, Suprachoroidal hemorrhage

Preservative Free Available Drops

- **Clinical Effects on Chronic Glaucoma Medications**
  - Decreased mucus layer of the tear film
  - Reduced tear secretion, basal Schirmers and TBUT
  - Increased Rose-Bengal staining of cornea
  - Foreshortening of the inferior conjunctival fornix
  - Inflammatory cell infiltration in trabecular meshwork

- **Currently Available "Preservative Free" Glaucoma Medications**
  - Zioptan (tafluprost 0.0015)
  - Cosopt PF (dozolamide/timolol)
  - Timoptic in Ocudose (timolol)
  - Timolast
  - Timolet OD
- **Currently Available "BAK Free" Glaucoma Medications**
  - Travatan Z (travoprst)
  - Xovatra
  - Alphagan P (brimonidine)

Sustained Release Upcoming Agents

- **Bimatoprost SR (Allergan)**
  - Biodegradable implant (anterior chamber)
  - Same underlying technology as the Ozurdex dexamethasone
- **iDose (Glaukos)**
  - Nondegradable titanium implant containing a 6to 12-month reservoir of travoprost.
- **Bimatoprost Ring (formarly HELIOS Allergan)**
  - Peri-ocular ring (conjunctival cul-de-sac)
  - 6-month reservoir of bimatoprost
- **OTX-TP** (Ocular Therapeutix): Punctal plug (PGA)
- **Evolute** (Mati Therapeutics): Punctal plug (PGA)
- **Travoprost XR – ENV 515 (Envisia Therapeutics)**
  - Biodegradable implant (anterior chamber)
- **The topical ophthalmic drug delivery device TODDD** is a soft flexible device that floats on the tear film and can simultaneously deliver several different ocular hypotensive medications. An early phase clinical trial has demonstrated efficacy through 180 days. A contact lens containing a drugpolymer film that elutes latanoprost is under development. A

small trial in glaucomatous monkeys demonstrated IOP efficacy greater than or equal to topical latanoprost over 8 days of wear.

- The **Bionode** is a contact lens that has been fitted with a gold trace. The gold trace receives an electromagnetic field from a specially equipped pair of glasses. The electromagnetic field is converted into a current that stimulates the muscles around the Schlemm canal, somewhat analogous to pilocarpine, and enhances trabecular outflow. In a small number of glaucoma patients IOP reductions were rapid and maintained with the Bionode system.

Upcoming Agents in Glaucoma

- **Nitric oxide (NO) donating PGF2 alpha analog**
  - **Latanoprostene Bunod 0.024% (LBN)** AAO approved a few days before AAO 2017 and likely to show up in your office in December 2017
  - Was named Veseneo now **Vyzulta**
  - NO offers a “rich biology” that is not fully explored just like the rho kinases and the adenosine class
  - Good basic science evidence of vasodilatory effect including optic nerve (Work of Hernandez and Neufeld presented at American Society for Cell Biology
  - First in class – NO donating PGF2 alpha analog
  - Other NO donators under development
  - Hydrolyzed by corneal esterases to Latanoprost acid and Butanediol mononitrate (BDMN)
  - NO donating moiety is released from BDMN in sufficient quantities to be pharmacologically effective
- **Rho-kinase inhibitor / NET Inhibitor**
  - Inventor, **Dave Epstein**
  - Natarsudil = Rhopressa (AR-13324); ROCK/NET inhibitor – dual, possibly triple mechanism
  - Roclatan (PG-324): possibly quadruple mechanism
  - What does Rho-kinase do?
    - Rho kinase regulates cell contraction, cell motility
      - Promotes actin:myosin contraction
      - Increases actin stress fibers, focal adhesions
      - Increases secretion of extracellular matrix (ECM)
    - In 3D tissue (non-motile cells), Rho kinase activity causes contraction, stiffness
      - Blood vessels → vasoconstriction, elevated BP
      - Trabecular meshwork → reduced flow, elevated IOP

- Mechanism of Rho-kinase Inhibitors
  - Rho activation increases contractility of TM cells
    - Induces myosin light chain phosphorylation
    - Results in formation of actin stress fibers and focal adhesions – increased contractility
    - Reduces outflow of aqueous humor
  - Rho kinase inhibition relaxes TM cells
    - Reduces actin stress fibers/focal adhesions
    - Increases outflow of aqueous humor
  - Rho kinase inhibition may also:
    - Increase ocular blood flow
    - Increase retinal ganglion cell survival

- **Expanded Prostaglandins**
  - Sharif showed long ago that Latanoprost and Travaprost mostly bind FP receptors
  - Bimatoprost binds both FP and EP and the EP binding is associated with both increased hyperemia, increase efficacy and increased MMP changes in the outflow pathway.
  - FP/EP3 Dual Receptor Agonist and other new PG Drugs
    - ONO-9054
    - Santen EP2 receptor drug comes onto the horizon at AAO 2017 (New Orleans)
- **Adenosine mimetic: Now won't likely develop further**
  - Trabodenoson, INO-8875
  - Withdrawn due to bad outcome of phase 3 trial
- **Bimatoprost SR Implant**
  - Biodegradable sustained-release bimatoprost intracameral implant
  - Designed to provide slow release of bimatoprost for 3 to 4 months
  - One 10-µg implant contains the same amount of bimatoprost as 1 drop of bimatoprost
- **SiRNA targeting beta2 receptors:** Bamosiran (SYL040012, Sylentis SA; Tres Cantos, Madrid, Spain): A naked siRNA that blocks by gene silencing the β2-adrenegic receptor (ADRB2), thus reducing the aqueous humor production at the ciliary body
- **Latrunculin**: Macrolides from marine sponges that inhibit actin polymerization. Studies in nonhuman primates and post-mortem: increased TM outflow via a mechanism that disrupts actin cytoskeleton of the TM.

Neuroprotection in Glaucoma

- In glaucoma, retinal ganglion cells (RGCs) and their axons in the optic nerve degenerate.
- Current glaucoma research aims to find complimentary therapies to decreasing IOP to promote neuroprotection, regeneration, and neuroenhancement of RGCs and their axons in the optic nerve.
    - "Neuroprotection" refers to keeping retinal ganglion cells alive.
    - "Regeneration" refers to promoting the regrowth of axons from damaged RGCs down the optic nerve.
    - "Neuroenhancement" refers to augmenting or enhancing the function of residual RGCs.
- **Kerr's concept of neuronal death→** Neuronal death can be conjectured to occur in three stages: axonal injury, death of the injured neuron and injury to and death of the neighbouring intact neurons through secondary degeneration.
- **Yoles and Schwartz:** explain progression of glaucomatous damage despite reduction of intraocular pressure and the fact that patients with severe pre-existing damage are more likely to deteriorate despite lower IOPs than those who do not have visual field loss at the time of diagnosis.
    - Neurotrophin factor deprivation
    - Insufficient blood perfusion to the optic nerve head
    - Glial cell activation may also be an important factor contributing to RGC death in glaucoma.
    - Glial fibrillary acidic protein is significantly increased in glaucoma by astrocytes and Muller's cells.
    - Neuronal damage through release of Cytokines, Reactive Oxygen species or Nitric oxide.
- **Neurotrophic factors:** Nerve growth factor (NGF), brain-derived neurotrophic factor (BNDF), and ciliary neurotrophic factor (CNTF) are prosurvival factors. Axon damage apoptosis can be blocked with caspase inhibitors. Intercellular signaling of axonal damage can be interrupted with dual leucine zipper kinase (DLK) inhibitors. Reduction in reactive oxygen species can also be neuroprotective.
- **Tozasertib**: Inhibits the work of DLK, which provides a major injury signal and might be neuroprotective, being found to be highly protective against glaucoma in rats.
- **Calcium channel Blockers:**
    - Inhibit the entry of Calcium ions into vascular smooth muscle
    - Protect the optic nerve head by improving vascular perfusion especially in Normal tension glaucoma.
    - Nimodipine has been found to have significant improvement in both visual field indices and colour vision.

- However, systemic hypotension prohibits extensive use of the drug. Nocturnal hypotension secondary to antihypertensive medications have been associated with visual field loss in patients with Normal tension glaucoma.
- Flunarizine, a potent Calcium channel blocker has been found to enhance RGC survival after optic nerve transaction in mice.

- **Antiglaucoma medications:**
  - Betoxolol possesses both calcium channel blocking activity resulting in vasodilatation and also exerts actions on retinal ganglion cells by reversibly blocking glutamate gated currents and subsequent firing of RPG cells.
  - Brimonidine has also been demonstrated to neuroprotective action in animal studies by its ability to reduce rate of RGC loss and also to increase endogenous Brain derived neurophin factor.
- **N-methyl-D-aspartate Antagonists:**
  - The NMDA receptor is an ion channel that gets activated when glutamate and glycine bind to the receptor complex thus allowing calcium to enter the cell. Excessive activation of the NMDA signaling cascade leads to “Excitotoxicity” wherein intracellular calcium overloads neurons and causes cell death by apoptosis. This excessive calcium activates destructive pathways in the mitochondria, stimulates nitric oxide production and certain mitogen activated protein kinases.
  - An NMDA antagonist **Memantine** has shown great promise as an effective agent for the prevention of GON progression. Memantine is a noncompetitive NMDA receptor antagonist derived from Amantidine which blocks the toxic effects of glutamate without significant effects on normal cellular function.
  - **Eliprodil** is another noncompetitive antagonist which provides protection from glutamate mediated cytotoxicity to retinal ganglion cells.
- **Nitric oxide synthetase inhibitors:**
  - Local production of nitric oxide may play a significant role in the development of multiple neurodegenerative diseases. It is produced by the enzyme nitric oxide synthetase. It has been seen that production of nitric oxide at the ONH has a role in the pathogenesis of glaucoma. Therefore pharmacological agents that inhibit NOS-2 may have therapeutic value.
  - Aminoguanidine, a selective inhibitor of iNOS (inducible nitric oxide synthetase) has been seen to reduce retinal ganglion cell loss by about 70% in a rat ocular hypertension model. A prodrug of an iNOS inhibitor, L-N (1-iminoethyl) lysine 5tetrazole amide has also been found to have similar results.
- **Antioxidants**:
  - These agents neutralize other suicide triggers like reactive oxygen species emanating from the glutamate cascade. Free radical scavengers like Catalase, superoxide dismutase and vitamins C and E mop up loose byproducts during secondary degeneration.
- **Neurotrophins**:
  - These agents increase retinal ganglion cell survival and are capable of being produced by retinal cells. Delivery of this agent by means of a viral vector has been

tried in animal models. Another method of delivering this agent to the eye could be repeated intravitreal injections which may not be well tolerated. Systemic administration will be difficult as these are large protein molecules and cannot readily cross the blood-retinal barrier. Implantation of a sustained release intraocular implant or a transscleral delivery are other modalities of drug delivery but none of these strategies have proved to have any value.

- **Angiotensin II type 1 receptor agonists**
  - Olmeartan: Ability to lower IOP by increasing outflow
  - Losartan: An angiotensin-converting enzyme inhibitor that inhibits activation of TGF-ß in patients with Marfan syndrome. In an animal model, mice treated with oral losartan lost 10% of ganglion cells, while mice treated with only water lost 30% of ganglion cells.
- **AL-8398B:** Topical selective agonist of the 5-hydroxytryptamine 1A receptor (5-HT_{1A}) showed neuroprotection in animal models. Suggested mechanisms: activation of the MAPK signaling pathway that activates anti-apoptotic factors and inhibition of caspase 3.
- **Vaccination**:
  - T lymphocytes localize in damaged neural tissue in case of injury. It has been found in animal models that a subset of these T lymphocytes have receptors specific to proteins of the myelin sheath, such as MBP, which have a protective effect on ganglion cell death ,suggesting thereby that a vaccine based on myelin sheath antigens may have therapeutic value in treating optic nerve damage and possibly glaucoma. However, MBP immunization and T cells specific for MBP induce a severe paralytic condition known as EAE thereby preventing its use as a vaccine. A vaccine called COP-1 has shown to reduce ganglion cell death in animal models and therefore this vaccine may play a role in glaucoma therapy as it does not have side effects like MBP immunization.
- **Ginkgo Biloba extracts:**
  - Ginkgo Biloba influences a number of biological processes including intracellular signaling and neutralizing reactive oxygen species .It is claimed to be effective in a variety of disorders associated with ageing and has also been found to improve both peripheral and cerebral blood flow.
  - Therapy with Ginkgo biloba extracts has shown to improve preexisting visual field defects in normal tension glaucoma in one clinical trial.
- **Ciliary neurotrophic factor (CNTF)**
  - Ciliary neurotrophic factor (CNTF) is a protein normally expressed at low levels in the visual system.
  - CNTF has been shown in preclinical research to improve survival and regeneration of RGCs in a variety of optic neuropathies.
  - CNTF has been tested in human patients with retinitis pigmentosa, macular degeneration, and, in two Phase 1 open label trials, nonarteritic ischemic optic neuropathy and glaucoma.
  - Data from human patients suggest that CNTF can increase retinal thickness and may stabilize or reverse visual dysfunction.

- Based on Phase 1 data, CNTF is hypothesized to prevent loss of vision (neuroprotection) and/or improve visual function (neuroenhancement) in patients with diagnosed glaucoma.

- **Optic Nerve Regeneration**
  - **Oncomodulin (Ocm):** An 11 kDa Ca2+ binding protein. Appears to mediate most of the inflammatory effect of optic nerve regeneration. Zymosan elevates the levels of oncomodulin and other trophic factors.
  - **Suppressors of regeneration:** Combining pten and scos3 (2 suppressors of regeneration) deletion combined with CNTF promoted regeneration. C-myc transcription factor overexpression in RGCs augments long-distance regeneration induced by deleting pten and socs3 combined with CNTF.
  - **Cell-extrinsic inhibitors of axonal growth:** The Nogo receptor (NgR) and PirB receptors are a common site of binding to molecules inhibitory to axonal growth. Many cell-extrinsic inhibitors of axon growth converge on GTPase RhoA, and RhoA inactivation was studied for axonal regeneration. Additional factors: Taxol is another pro-regenerative treatment that stabilizes microtubules.

Gene Therapy in Glaucoma

- Target structures or cell types for glaucoma gene therapy include trabecular meshwork (TM), ciliary epithelium (CE), ciliary muscle (CM), Retinal ganglion cells, and Müller cells (MC).
- **Delivery systems: six**
  - Adenoviruses (Ads)
  - Adenoassociated viruses (AAVs)
  - Herpes simplex viruses (HSVs)
  - Lentiviruses (LVs; feline immunodeficiency virus [FIV] & HIV)
  - Liposomes (LPs)
  - Naked DNAs
- The final common outcome of glaucoma is retinal ganglion cell death. Repeated intraocular injections of neurotrophic factors temporarily rescue RGCs from axotomy-induced death.
- Ad-mediated intravitreal delivery of brain-derived neurotrophic factor (BDNF) has been shown to protect RGCs in a rat optic nerve transection model. AAV-mediated TrkB gene transfer into RGCs combined with exogenous BDNF administration markedly increases neuronal survival. Isenmann et al also found protection of the RGCs after Ad-mediated delivery of BDNF, and protection was increased by the combined systemic administration of the free radical scavenger N-tert-butyl-(2-sulfophenyl)-nitrone (S-PBN). Similar RGC survival results were obtained recently with Ads containing the ciliary neurotrophic factor (CNTF).
- **Trabecular meshwork targeting to lower IOP**
  - Single nucleotide polymorphisms (SNPs) associated with glaucoma. Examples: SNP between caveolin-1 (CAV-1) and caveolin-2 (CAV-2).

- Genes that have their expression under glaucomatous conditions: 50 genes that might be potential targets for further gene therapy. Examples: angiopoietin-like 7 (ANGPTL7, alias CDT6) that encodes for a glycoprotein with direct influence on the organization of the extracellular matrix. An experiment with the MMP1 (metallopeptidase 1) cDNA into an adenoviral vector under the expression only when steroid is present could prevent steroid-induced elevated IOP in a large animal model (58 gene therapy). Another gene shown to be downregulated by steroids is plasminogen activator tissue.
- SiRNA for silencing genes such as ANGPTL7 and MYOC is a method to be further explored.
- Genes that are involved in pathways regulating outflow are potential targets for gene therapy. Six potential pathways: RhoA-Rho kinase, adenosine 1 agonists, nitric oxide donors, phosphodiesterase inhibitors (PDE), prostaglandin EP4 agonists, potassium channel openers.
- Additional genome-wide association candidate genes: growth arrest-specific 7 (GAS7), transmembrane and coiled-coil domains 1 (TMCO1), multivascular body subunit 12B (MVB12B/ FAM 125B), caveolins 1 and 2 (CAV1, CAV2), fibronectin type III domain containing 3B (FNDC3B), ATB binding cassette subfamily A member 1 (ABCA1), Rho guanine nucleotide exchange factor 12 (ARHGEF12), B blood group (ABO), and a region of chromosome 11 containing multiple genes

- **Potential for neuroprotection**
  - Neurotrophins such as BNDF that act by the tyrosine kinase receptor B (TrkB) were demonstrated to delay RGC death in a model of optic nerve transection. A recent study showed that injection of AAV2-BDNF in rat eyes with elevated IOP showed less loss of RGC and improved F-VEP parameters.
  - Anti-apoptotic genes—Example: inhibitor of the apoptotic caspase-3, beculoviral IAP repeatcontaining-4 (BIRC4), had positive impact on RGC in vivo. Other genes: B-cell lymphoma extra-large [Bcl-X(L)], p53.
  - Antioxidants—Examples: a catalase gene (CAT), a reactive oxygen species detoxifying enzyme vector (AAV2.CAT)
  - Other genes: mitogen-activated protein kinase 1 (MAP2K1), PEDF (protection of RGC survival)

Stem Cells in Glaucoma

- Two types of pluripotent stem cells have been investigated.
  - Embryonic stem cells (**ESC**) are harvested from the inner cell mass of the blastocyst of an embryo.
  - A newer type of pluripotent stem cell, the induced pluripotent stem cell (**iPSC**), first made the news in 2006. Takahashi and Yamanaka, working with somatic mouse fibroblasts, overexpressed 4 transcription factors to develop this pluripotent adult stem cell type in the laboratory, and repeated this in human fibroblasts
- Advantages of IPSC
  - Can be made patient-specific, thereby limiting immune rejection concerns

- Not generally subject to ethical concerns.
- Can be harvested from a patient by a simple skin biopsy and then de-differentiated into iPSCs

- How to use?
  - There is a loss of trabecular meshwork (TM) cells in glaucomatous patients.
  - Increasing the TM cellularity in glaucomatous human eyes could be an effective method to ameliorate the cellular loss
  - Differentiated TM-like iPSCs, when transplanted into anterior segments (in vitro), were able to restore IOP homeostatic functionality, while several other cell types, including normal iPSCs, HUVECs, and fibroblasts, were unable to do so.
- There is promising future for using TM-like iPSCs as an innovative, patient-specific treatment for glaucoma.

Role of Marijuana in Glaucoma

- Traditional Glaucoma Therapy includes Prostaglandins, Beta blockers, Alpha agonists, Carbonic anhydrase inhibitors and Cholinergics
- Complimentary Therapy in Glaucoma
  - 50% of patients believe in complementary medicine.
  - 5% of glaucoma patients use complementary medicine.
  - Herbal: Ginkgo biloba, Bilberry, **Marijuana/Cannabis**
  - Vitamins
  - Diet
  - Exercise
- **Cannabis:**
- Plant contains >100 individual (phyto)cannabinoids in addition to tars, teratogens, carcinogens (greater amounts than tobacco), pesticides?
- Predominant cannabinoids: Tetrahydrocannabinol (THC), Cannabidiol (CBD)
- Merritt et al and Helper, Frank, et al evaluated cannabis in normal and glaucoma patients; IOP reduction 20%-30%.
- Inhalation, intravenous, oral are effective.
- Topical not effective (lipophilic); poorly crosses corneal epithelium
- Cannabis Effects
  - Hypotension/orthostatic changes
  - Tachycardia
  - Emphysematous lung changes
  - Motor coordination
  - Abuse

- Psychotropic effects: Altered mood, Paranoia, Hallucinations, Difficulty thinking, problem solving, Memory

- Cannabis Inhalation
  - Heat/vaporization needed for activation
  - Quickest onset (10 minutes)
  - Shortest duration (3-4 hours)
  - Processed by liver
  - Stored in brain, vascularized organs, and fatty tissue
- Cannabis Dosing: 6-8 cigarettes daily
- Endocannabinoid System
  - CB1: psychoactive receptor, primarily stimulated by THC
  - CB2: immune modulation, primarily stimulated by CBD
- Endocannabinoid System in the Eye
  - CB1 receptors in various parts of the eye; anterior segment
  - CB2 receptors in the retina and trabecular meshwork
  - Natural and synthetic molecules can interact with endocannabinoid system.
    - IOP reduction
    - Neuroprotection
- Endocannabinoid System and Neuroprotection
  - Glutamate excitatory neurotransmitter
  - Elevated levels of glutamate found in vitreous of glaucoma patients
  - Elevated level triggers excitotoxic cascade, leading to retinal ganglion cell (RGC) death.
  - Glutamate receptor antagonists conferred neuroprotection (including diminished RGC apoptosis).
  - Studies show CB receptor activation inhibits glutamate release.
  - Maintaining agonists of CB important neuroprotective effect in preventing RGC death

Laser therapy for Glaucoma

Tissue effects of laser

- **Thermal effects (photocoagulation, photovaporization)**
  - Long exposures by lasers at relatively low energy → coagulative effect that shrinks collagen
  - Higher energy → can vaporize tissue.
- **Photodisruption**
  - Optical breakdown of molecules
  - Short-pulsed
- **Photoablation**
  - Excimer lasers (excited dimer)
  - Intense ultraviolet energy beams
  - 193 micron: argon fluoride
  - 308 nm: xenon chloride
- **Photochemical**
  - Photodynamic therapy:
  - Destruction of tumors previously sensitized by hematoporphyrin derivatives and precise chorioretinal thermal damage for subretinal neovascularization

Laser treatment for internal flow block

- The technique of creating laser holes through the trabecular meshwork is known as laser trabeculopuncture (trabeculotomy). This technique is the earliest attempt to treat glaucoma using laser technology, but it has not been successful in people or in animal models.

Laser peripheral iridotomy (LPI)

- Meyer-Schwickerath in 1956: xenon
- ***Firm indications***
  - Acute angle-closure glaucoma
  - Chronic angle-closure glaucoma with peripheral anterior synechiae
  - Intermittent angle-closure glaucoma with classic symptoms of angle closure
  - Aphakic or pseudophakic pupillary block
  - Anatomically narrow angles and signs of previous attacks
  - Narrow-angle eye with acute angle-closure glaucoma in the fellow eye
  - Incomplete surgical iridectomy
  - Luxated or subluxated crystalline lens
  - Anterior chamber lens implant

- Nanophthalmos
- Pupillary block from silicone oil after vitrectomy
- Mixed-mechanism forms of glaucoma when filtering surgery might not be necessary for adequate pressure control

- **Relative indications**
  - Critically narrow angles in asymptomatic patients
  - Younger patients, especially those who live some distance from medical care or who travel frequently
  - Narrow angles with positive provocative test
  - Iris–trabecular contact demonstrated by compression gonioscopy
- **Lenses**
  - Abraham iridotomy lens
  - Wise lens modifications
  - Pollack lens

- **Location**:11 to 1 o'clock, avoid 12 o'clock **(air bubble can block view, if bleeding occurs then visual axis can be spared)**
- **Size:** minimum iridotomy size of **150 µm** should be recommended
- **Good sign of complete perforation**
  - Direct observation of the anterior lens capsule
  - Transillumination
  - Direct the aiming beam into the depths of the iridotomy, If the opening is through-and-through the iris, the aiming beam will disappear
- **Complications**
  - **Iritis**
  - **Pressure elevation:** commonly occurs 1–4 hours after
  - **Cataract:** lens capsule perforation, or localized cataract
  - **Hyphema:** common after Nd:YAG,
  - **Corneal epithelial injury**
  - **Endothelial damage**
  - **Corneal stroma:** if poorly focused, spectacular effect called *corneal emphysema*
  - **Failure to perforate:** second treatment required in 1–3 days.
  - **Late closure: 15 micron** hole is adequate for aqueous flow through the eye. To prevent subsequent closure, it is best to have an opening of at least **100 micron**.
  - **Retinal burn**
  - **Aphakia and pseudophakia with pupillary block**

Argon Laser Peripheral Iridoplasty ALPI (Gonioplasty)

- ALPI is a simple and effective method of opening an appositionally closed angle when laser peripheral iridotomy (LPI) either cannot be performed (acute angle closure, or AAC) or does not eliminate appositional angle closure because mechanisms other than or in addition to pupillary block are present (plateau iris syndrome or lens-related angle closure).
- **Indications**
  - Breaking an attack of AAC
    - ALPI is a safe and effective alternative to antiglaucoma medications for initial treatment of AAC.
    - No longer necessary to treat medically prior to performing ALPI
    - Circumferential treatment of the iris opens the angle in those areas in which there are no peripheral anterior synechiae (PAS).
    - Appositional closure is eliminated immediately and IOP is almost always normalized within one hour in eyes without extensive PAS. Even when extensive PAS are present, the IOP is usually normalized within an hour or two.
    - All published series have reported virtually 100% success.
  - Eliminating continued appositional closure if elimination of pupillary block by LPI is insufficient to open the angle
    - Plateau iris
    - Lens-related (phacomorphic) angle closure
    - Malignant glaucoma
- **Contraindications**
  - Severe and extensive corneal edema or opacification
  - Flat anterior chamber
  - Total PAS
    - ALPI is ineffective at breaking PAS despite two publications claiming this.
    - However, even in eyes with extensive PAS, ALPI can open the angle in areas where it is appositionally closed and result in lowering of IOP.
    - It is ineffective in eyes with angle closure originating anterior to the iris (“pull” mechanisms), such as in iridocorneal endothelial syndrome.
- Since ALPI does not eliminate pupillary block, a peripheral iridotomy is still required in eyes with AAC once IOP is controlled and the cornea has cleared sufficiently.
- **Laser Parameters**
  - 0.50.7 second, 500 microns, starting at 240 mW and increasing the power until contraction of the peripheral iris stroma is noted.
  - An Abraham lens is used.
  - Burns must be placed in the far periphery of the iris in order to achieve successful opening of the angle. Burns placed more centrally will have no effect.

- The patient must feel the burns or there is a good chance that insufficient contraction will occur; they should be told in advance and questioned about this early in the procedure.

- ALPI may open sufficient portions of the angle for laser trabeculoplasty to be performed.
- If extensive PAS are present after ALPI, goniosynechialysis (GSL) may be performed, surgically stripping PAS from the angle wall to restore aqueous access to the trabecular meshwork.
    - GSL is thought to be useful only if the PAS have been present for < 1 year.
    - Combined cataract extraction and GSL was reported more effective than GSL alone.

Lasers in malignant glaucoma

- If ciliary processes are visible through an iridotomy, 2–4 ciliary processes can be shrunk with an argon or solid-state laser using 200–800 mW for 0.1 second with a 100–200 micron spot size
- Disruption of ciliovitreal compression: Nd YAG hyaloidtomy

Laser treatment for outflow obstruction

Argon Laser trabeculoplasty (ALT)

- **Krasnov**: temporary lowering of intraocular pressure (IOP) after 'trabeculopuncture'
- In 1979 by Witter and Wise
- **Mechanisms**:
    - The first theory suggested that these contraction burns over the angle mechanically helped adjacent trabecular beams open wider, thus allowing easier aqueous outflow.
    - The second theory suggested that the laser irradiation stimulated trabecular endothelial cells to replicate
    - Laser spot is aimed at the junction of the pigmented and nonpigmented trabecular meshwork.
- **50 micron spot is used with 0.1 second exposure time, 400–500 mW,** 3–4° apart so that approximately 20–25 spots are created per quadrant
- Argon Blue-Green Laser: 488-514 nm wavelength
- Initial treatment of 180 degrees, 50 spots → 4-6 weeks
- **Success**
    - Positive predictors of a favorable response include heavy pigmentation of the trabecular meshwork, age (older patients), and diagnosis (pigmentary glaucoma, primary open-angle glaucoma, and exfoliation syndrome).
    - Typically reduces 20% to 30% below baseline levels with ALT.

- 77% success rate at 1 year, to 49% at 5 years, and to 32% at 10 years
- Argon LTP is effective in most forms of open-angle glaucoma
- **Retreatment:** Repeat argon LTP is often not advised.

Selective laser trabeculoplasty (SLT)

- Pulsed-frequency doubled neodymium (Nd):YAG laser was introduced in 1998 by Mark Latina
- Selectively target pigmented tissue and minimize any collateral effect.
- Selective photothermolysis, relies on selective absorption of a short laser pulse to generate and spatially confine heat to pigmented targets within trabecular meshwork cells.
- Short pulse durations of 3–10 ns
- Mechanism
  - SLT results in a stretching of the trabecular meshwork beams, their mobility is increased following SLT
  - Targeted only the pigmented cells → Recruitment of macrophages → chemical mediators that regulate the outflow rate → Elevated interleukin levels
  - Stimulates endothelial cell replication
- 400 micron spot size **(Significantly larger spot size of SLT)**
- Energy level for SLT treatment is set initially at 0.8 mJ → decreased in 0.1-mJ intervals until minimal bubble formation
- **Success**
  - ALT and SLT have equivalent efficacy
  - Lowers the intraocular pressure by 24% to 35%
  - Positive predictors of success include higher baseline intraocular pressure and the 2-week postlaser pressure response.
  - No apparent structural damage with SLT, repeat SLT is generally safe
- **Contraindications**
  - Inadequate visualization of the trabecular meshwork
  - Hazy media
  - Closure of the iridocorneal angle
  - Corneal edema
  - Uveitic glaucoma
  - Juvenile glaucoma (usually)
  - Patient age of 35 years or less
  - Need for IOP-lowering greater than 7–10 mmHg.
- **Complications**
  - Intraocular pressure elevation

- Sustained intraocular pressure increase
- Hyphema
- Peripheral anterior synechiae
- Iritis
- Uveitis

Excimer laser trabeculostomy (ELT)

- First used clinically in 1998
- Xenon-chloride (XeCl) 308-nm wavelength excimer laser energy is fiber-optically transmissible and became the wavelength of choice for these types of ab-interno fistulizing procedures
- Delivers photoablative energy to precisely remove the tissue which obstructs fluid outflow with minimal thermal damage to adjacent tissue
- Inner wall of Schlemm's canal without damaging the outer wall of Schlemm's canal or the collector channels. It creates no filtering fistula or bleb.

Laser sclerostomy

- Better results than repeat trabeculectomy in eyes that have undergone prior filtering surgery

Cyclodestructive Procedures

- Started as **Cyclocryotherapy**
  - 1950 Bietti: Freezing the ciliary body resulted in lower IOP.
  - Quigley demonstrated histologically that cryo destroyed the epithelial cells and capillaries of the ciliary body, resulting in a decrease in aqueous production and a breakdown of the blood–aqueous barrier.
  - Complications: pain, uveitis, extensive posterior synechiae, pupillary block, cataract, chronic flare, choroidal detachment, 52% decreased vision, phthisis 12% overall, with neovascular glaucoma, 22%
- **Cyclophotocoagulation (CPC)**
  - 1961 Weekers, first to use light energy as a means of cyclo destruction. Trans scleral xenon arc photocoagulation over ciliary body lowered IOP.
  - 1985 Beckman used ruby laser than Nd:Yag which ushered in the present era of cyclophotocoagulation (CPC)
  - Nd:Yag CPC is 1064 nm in the infrared spectrum (2-6 joules)
  - Placed 2 to 3 mm from the limbus with 30 to 40 applications
  - Pulsed mode: produces mechanical photodisruption of the ciliary processes with homogeneous lesions

- Continuous mode: energy 1000 times greater than for YAG iridectomy; full thickness burn to ciliary body and a mild thermal effect in the sclera. IOP decreases 44%-68%. A contact lens delivers the energy for 360°.

- **Indications**
  - Reserved for use in patients who have failed previous treatment with medicines or surgeries.
  - Beneficial in controlling pain in blind, painful eyes, and may allow the patient to avoid removal of the eye as long as visualization or ultrasound reveals no intraocular tumor.
  - Types of glaucoma
    - Refractory med & surgically uncontrollable gl.
    - Post PK glaucoma.
    - NVG.
    - Cong glaucoma.
    - Aphakic/pseudophakic OAG.
  - Who are not willing to undergo filtration surgery, those who cannot undergo surgery owing to medical conditions, and patients in underdeveloped countries.
- **Contraindications**
  - Phakic patient with good vision
  - Marked uveitis
  - Blind nonpainful eye as this includes risk of SO in other eye
- **Principle**: light absorption by melanin pigment
- **Various wavelengths**
  - Ruby laser (694)
  - Argon laser(514)
  - Nd YAG Laser(1064)
  - Continuous wave diode laser(804)
- **Types**
  - Noncontact transscleral CPC
  - Contact transscleral CPC
  - Cyclocryotherapy (CCT)
  - Transpupillary CPC
  - Endocyclophotocoagulation ECP
  - Micropulse TSCPC
- Avoid the 3 and 9 o'clock meridians in order to avoid coagulating the long posterior ciliary arteries and causing anterior segment necrosis.

1. Noncontact Transscleral CPC

- Nd YAG
- Contact lens developed by Bruce Shields may or may not be used
- Eight to ten burns are placed 1.5 mm from limbus
- Energy levels of 4 to 8 J

2. Contact Transscleral CPC

- Most popular
- contact diode laser probe that is relatively small and portable (**G-Probe of Gaasterland**; IRIDEX Corporation, Mountain View, CA).
- Krypton and Nd:YAG lasers can also be used
- ***Diode:*** 1.5-2.0 W, 1.5-2.0 SEC, 25-30 spots
- The energy level is titrated to be slightly below (250 mW lower) the audible pop, because audible pops are associated with greater inflammation and hyphema.
- **Grading of gross lesions**
    1. NO EFFECT:
    2. MILD: Inconsistent, just noticeable shrinkage.
    3. Moderate: Just noticeable shrinkage, slight tissue blanching.
    4. Good: Obvious shrinkage & tissue blanching, pig dispersal,occ. popping
    5. Excessive: Hole formation with large burn.
- **Success rate of DLCP** –38 to75%.
    - Re treatment required in 42% of pt.
    - Average IOP reduction—35-50% of pre-treatment levels.

3. Cyclocryotherapy

- Nitrous oxide cryosurgical unit is used to cool the 2.5-mm probe to -80 °C, which is placed approximately 1 mm posterior to the limbus for 60 seconds.

4. Transpupillary CPC

- Continuous-wave argon laser is delivered via a biomicroscope.
- Goldmann-type gonioprism and scleral depression are necessary to visualize ciliary process
- Laser settings of 50to 100-µm spot size, 700 to 1000 mW, for 0.1 second

5. Endoscopic Cyclophotocoagulation

- 1991: ECP first available by Endo Optiks

- 2005: ECP has own CPT code; 2 units available in the United States
  - E2: endoscope + diode laser (pulsed continuouswave energy 810-nm laser, video camera, helium-neon laser aiming beam, and xenon light)
  - E4: Endoscope only (video and xenon light) for vitrectomy
  - Uses a 1.5to 2.0-mm incision. Expand posterior chamber with ophthalmic viscosurgical device
- **Laser settings**: Treat 180 to 360 degrees (make a second incision 1.5-2 mm, 120 degrees away)
  - Continuous settings, about 3 seconds for slow whitening
  - 250-900 mW (up to a maximum of 2.0 W)
  - No popping, gas bubbles, or pigment dispersion
- Uses of ECP: phaco/ECP for mild to moderate glaucoma; target mid-teens
- Advanced refractory glaucoma with prior trabs/ tube shunts
- Eyes that cannot undergo a filtering procedure (chronic ocular surface disease or high risk of complications [history of pars plana vitrectomy, aphakia, suprachoroidal])
- Can use at same time or after other angle surgeries (Trabectome, iStent) as it lowers IOP via a decrease in inflow
- Good for anterior segment disease where view is poor or in plateau iris as the ECP causes the ciliary processes to shrink and deepen the angle

6. Micropulse Transscleral Cyclophotocoagulation

- (Micropulse TSCPC, MP-TSCPC, IRIDEX IQ810 Laser Systems; Mountain View, CA)
- Micropulse transscleral diode laser CPC uses micropulse technology to denature the target tissue while further minimizing collateral tissue damage.
- The device applies a series of short (microsecond), repetitive bursts of energy that effectively confines the thermal effect to the absorbing tissue.
- The micropulse delivery mode includes on and off cycles, allowing energy to build up in the targeted pigmented tissues, eventually reaching the coagulative threshold.
- The adjacent nonpigmented structures have time to cool off during the off cycle, thus never reaching the coagulative threshold, which minimizes collateral tissue damage.
- Only a few studies have described the outcomes of this novel treatment for glaucoma. They showed micropulse transscleral cyclophotocoagulation (MP-TSCPC) to have comparable efficacy with fewer side effects when compared with traditional continuous wave mode diode laser delivery.
- This more favorable side effect profile has the potential to make MP-TSCPC an earlier therapeutic option instead of reserving it for end-stage refractory eyes.

- **COMPLICATIONS**
  - Common: Conjunctival burn, AC inflammation, transient IOP rise
  - Uncommon: conjunctival inflammation, severe uveitis, anterior vitritis >10 IOP rise

- Rare:
  - Sterile hypopyon
  - Hyphema
  - Vitreous Hemorrhage
  - Hypotony<2mm
  - Phthisis bulbi
  - Vision loss (2 lines or more)
  - CME/macular pucker
  - Malignant glaucoma
  - Neurotrophic corneal ulcer
  - Pupillary distortion/ staphyloma formation
  - Scleral perforation

Surgical Management of Glaucoma

- Glaucoma Outflow Procedures
- Incisional surgery to relieve outflow block:
  - External filtration (e.g., trabeculectomy or full-thickness filtering procedures)
  - Internal filtration (e.g., cyclodialysis)
  - It may essentially disrupt the trabecular meshwork from the outflow pathway (e.g., trabeculotomy ab externo and goniotomy).
- Lowest IOP that can be tolerated by the eye is generally ***above 5 mmHg.***

External Filtration Surgery

- Filtration surgery has historically been the gold standard procedure for the surgical treatment of glaucoma
- Creation of a hole through the sclera into the anterior chamber so that aqueous flow can occur into the subconjunctival space, thus lowering IOP.
- **15 micron diameter** hole that (theoretically) is adequate for total aqueous flow out of the eye.
- Two basic types
  - **1. Full-Thickness Procedures (Scheie procedure)**
    - Thermal sclerostomy, posterior or anterior lip sclerectomy, or Elliott's trephination
    - Not used now.
  - **2. Guarded Procedures**
    - **Trabeculectomy**: the filtering sclerostomy is protected from excessive flow either by partially closing it with a scleral flap or by suturing techniques.

1. Full-Thickness Filtration Procedures

- Thermal sclerostomy (scheie Procedure)
- Sclerectomy: Posterior lip sclerectomy, Anterior lip sclerectomy
- Trephination
- Unregulated early flow was managed by full-time patching of the eye and the use of devices, such as the Simmons shell, that would apply pressure to the ostium and slow flow temporarily.
- **Iridencleisis**: Historical procedure, from observation that that inadvertently incarcerated iris in the wound after intracapsular cataract extraction or surgical iridectomy sometimes resulted in IOP lowering

2. Guarded Filtration Procedure: Trabeculectomy

- 1960: Cairns, modern-day trabeculectomy (modification of Sugar's procedure)

- Most commonly used surgical procedure in patients with glaucoma
- Standard technique
- **Moorfields Safer Surgery System technique**
  - Fornix-based conjunctival flap, Lewicke anterior chamber maintainer, a standardized punch technique, and a combination of adjustable and releasable sutures.
- **Success rates:**
  - 80% in first 2 years in POAG (without antimetabolites)
  - 50 % in 5 years (without antimetabolites)
  - 65% at 5 years and (with antimetabolite)
  - 40% over 10 years (with antimetabolite)
- **Preoperative considerations**
  - Chronic topical medication usage: Effect on conjunctiva and subsequent trabeculectomy filtration surgery site documented; potential role for cessation of medicines
  - Neovascular glaucoma: Intravitreal bevacizumab critical for success, coupled with panretinal photocoagulation
  - Inflammatory glaucomas: Use of topical/subconjunctival/systemic steroids
- **Surgical Technique**
  - Any type of regional anesthesia
  - Fixation or traction suture is used to keep the eye in down
    - Corneal traction suture in the quadrant of the planned surgery
    - Superior rectus traction suture
  - Conjunctiva mobilization
    - Site:
      - Superior limbus, because inferiorly high rate of infections
      - Guided by conjunctival motility. Avoid significant nasal or temporal shift if possible.
    - Fornix vs. limbal (Westcott scissors)
      - Fornix-based flap: Fast, effective, facilitates broad application of antimetabolite, particularly useful for scarred conjunctiva. More prone to bleb leaks.
      - Limbal-based flap: Effective, reduced bleb leaks, facilitates earlier laser suture lysis and digital massage, keeps conjunctival sutures away from sclerectomy site. Takes longer to mobilize and possibly more localized cystic blebs
    - Dealing with Tenon fascia: New instruments for dissection and role of tenonectomy

- Cautery: Minimize underwater diathermy to achieve satisfactory hemostasis. Avoid perforating, scleral emissary vessels.
- Antimetabolite use: Broad application zone, consistent vehicle, fixed concentration; vary time of application

- Scleral flap
  - Shape, size, thickness, tightness of closure all important; tightness of closure most important
  - Position of sutures: Minimize tight radial sutures, which might induce astigmatism.
  - Releasable sutures
  - Consider deep sclerectomy flap mobilization and unroofing of Schlemm canal to permit possibility of Schlemm canal viscoexpansion.
  - Scleral flap dissection: thickness should be between one-half and two-thirds, approximately 1 mm into clear cornea-to cross scleral spur
- Corneal paracentesis is made before opening the globe
- Sclerectomy creation
  - Site: Anterior to avoid peripheral anterior synechiae
  - Size: Bigger is not necessarily better; less than or equal to 0.5 mm may be adequate.
  - Two radial incisions into cornea extending 1 mm behind, then rectangular piece of tissue is removed or Kelly or Gass punch used to enter AC
- Peripheral iridectomy
  - "Always" perform in phakic eyes; however, not performed with Ex-Press shunt, which is another form of filtration surgery
  - "Required?": Pseudophakic eyes/combined procedures
  - Recommended in patients with shallow AC
- Scleral flap is sutured initially with two interrupted 10–0 nylon sutures
- Anterior chamber is filled through the paracentesis, and the flow around the scleral flap is observed
- Externalized releasable sutures
- Conjunctival closure
  - Multiple techniques possible for fornix and limbal-based closure
  - Premise: Avoid leaks, minimize suture material near sclerectomy, minimize transmitted scleral compression forces that might induce astigmatism.
- Fill the anterior chamber BSS through the paracentesis track to elevate the conjunctival bleb and test for leaks

Conjunctival Flaps

- Limbal based vs Fornix based

- IOP control is comparable with both techniques
  - **Fornix Based**
    - Advantages : intraoperative benefits and better bleb morphology
    - Disadvantage : increased incidence of early bleb leaks
  - **Limbus Based**
    - Advantage : more secure wound closure
    - Disadvantages : late complications of leaks & infection
- Wise closure
- Khaw closure

- **Post operative Care**
  - Topical steroids, antibiotics and cycloplegics
  - Digital ocular compression applied to the inferior sclera or cornea through inferior eyelid
  - Focal compression with a moistened cotton tip at the posterior edge of the scleral flap
  - In early failure (e.g., vascularized and thickened blebs): subconjunctival 5-FU (5 mg in 0.1 mL solution) and anti-VEGF therapy
- **Laser suture lysis**
  - Necessary when there is a high IOP, a flat filtration bleb, and a deep anterior chamber.
  - Without magnification with the edge of a four-mirror Zeiss gonioprism or with the Hoskins laser suture lens
  - High-magnification suture lysis contact lenses are commercially available (e.g., Mandlekorn lens or Blumenthal lens)
  - Gonioscopy must be performed prior to the laser treatment to confirm an open sclerostomy with no tissue or clot occluding its entrance

- **Anti-VEGF Therapy for Bleb Vascularization**
  - Potentially lead to a healthier bleb with less scarring and better long-term IOP control.
  - Subconjunctival anti-VEGF (bevacizumab 1 mg) after glaucoma surgery
  - Proximal to blebs after trabeculectomy at the earliest sign of vascularization

- **Bleb Needling**
  - In cases of subconjunctival–episcleral fibrosis an external revision or bleb needling can be tried
  - 27 or 25-gauge needle is used to cut the edge of the scleral flap and restore aqueous outflow.

- Entry of the needle tip into the anterior chamber beneath the flap is important but should be undertaken with extreme caution in phakic eyes
- Repeated subconjunctival injections of 5-FU after revision increases the probability of success.

Antimetabolites

- Antimetabolites are usually used during trabeculectomy surgery to prevent bleb failure due to scarring by the wound healing process. The most commonly used antimetabolites are 5-fluorouracil (5-FU) or mitomycin C (MMC).
  - BAPN (beta-aminoproprionitrile), an inhibitor of lysyl oxidase, blocks collagen cross-linking
  - 5-FU inhibits fibroblast proliferation by acting selectively on the **S phase** of the cell cycle
  - Mitomycin-C is an alkylating agent that decreases DNA synthesis by causing DNA cross-linking
  - Colchicine affects collagen cross-linking and thereby decreases scar formation.
- **5-Fluorouracil (5FU)**
  - Pyrimidine analogue which blocks DNA synthesis.
  - Sponge may be removed after 30 seconds to 5 minutes.
  - Can be injected into the subconjunctival space intraoperatively or in the early postoperative period.
  - **Advantages**
    - Inexpensive
    - No dilution or dosage calculations required
    - Stable at room temperature
    - Better safety margin than MMC
  - **Disadvantages**
    - Less effective than MMC
    - Multiple injections
    - High incidence of corneal toxicity
- **Mitomycin C (MMC)**
  - Introduced in the mid 1980s
  - It was a major step forward improved the success rate of filtration surgery through controlling subconjunctival fibrosis
  - Antitumor antibiotic isolated from Streptomyces **c**aespitosus.
  - DNA cross-linker which inhibits fibroblast proliferation.
  - **Advantages**
    - More potent than 5-FU

- Results in lower intraocular pressures

- **Disadvantages**
  - Expensive
  - Reconstituted from powder
  - Not stable at room temperature
  - Possibly more complications

Implantable Collagen Matrix

- **Ologen** (Optous, Roseville, California) collagen-matrix implant
- Marketed initially as OculusGen™ and currently as Ologen™ and iGen™
- Consists of a collagen-based scaffold containing thousands of microscopic pores. The implant is placed directly over the scleral flap and influences the healing process by forcing fibroblasts and myofibroblasts to grow into the pores and secrete connective tissue in the form of a loose matrix
- Decreased scar formation and improved surgical success over trabeculectomy performed without the adjunctive use of antifibrotic agents

Releasable Sutures

- Introduced by Schaffer et al, but popularized by Cohen and Osher.
- Minimized the incidence of shallow anterior chamber and hypotony in the early postoperative period
- Combines the benefits of partial thickness filtration surgery by allowing a formed anterior chamber in the immediate post operative period along with those of full thickness filtration surgery by allowing a freer flow of aqueous and consequently lower intraocular pressures (IOP) once the sutures are removed in the later post operative period.
- Seventy percent of eyes had a reduction in IOP more than 5 mm Hg if released within the first week compared to 20% after the third week
- Astigmatism
- **Technique**
  - start sclera → end cornea
  - start cornea → end cornea

Filtering Bleb

- Filtration surgery creates a fistula between anterior chamber & subconjunctival epithelium. Successful filtration surgery is associated with a blister-like elevation of the conjunctiva over the sclerostomy site "**a filtration bleb**". The appearance of filtration bleb is an important factor in evaluating the outcome of glaucoma filtering surgery.
- The **ideal bleb** is diffuse with microcystic conjunctival changes, mildly elevated, with moderate thickness of wall AND with relative paucity of vessels.
- Types:

I. Well Filtering: Thin, polycystic, Transconjunctival flow of aqueous
II. Shallow ,diffuse: Thin-walled with relatively avascular appearance, Microcysts usually seen
III. Poor Filtering: Flat with engorged surface blood vessels, No microcystic spaces, Episcleral fibrosis
IV. Encapsulated: Localized dome shaped elevation, Hypertrophied tenon"s capsule, 2-8 weeks post-op

- **Histology**
  - While subepithelial connective tissue appears thin in normal persons ,failed blebs show a large amount of collagen with hypercellular response ,mainly of activated fibroblasts.
- **Causes of failure**
  - Extraocular: Subconjuctival\ episcleral fibrosis, encapsulated bleb
  - Scleral: tight suturing, scarring of scleral bed
  - Intraocular: blockage of sclerostomy, blockage of internal opening
  - **EARLY FAILING BLEB-** bleb within the first postoperative month.
    - Internal obstruction by blood, fibrinous clot, vitreous, iris, scleral tissue, fibrosis, membrane
  - **LATE FAILING BLEB:** Those with a history of good bleb function with adequate IOP control for at least 1 month
    - Subconjunctival and episcleral fibrosis most common cause
- **Prevention of Failure**
  - **Topical steroid** used routinely in the post-operative period& then tapered after 6-8 weeks
  - **Adjunctive anti-metabolites**Adjunctive mitomycin-C or 5-FU inhibits fibroblast proliferation & subsequent scar tissue formation
- **Management:**
  - **Conservative**
    - Topical steroids
    - Digital compression-if compression is effective, IOP will fall & bleb will appear inflated
    - Focal compression-at the edge of scleral flap under slit-lamp
    - **Suture manipulation**(7-14 days post-operatively)Releasable sutures cut or released, Argon laser suture lysis
    - **Needling** of encysted blebusing Mitomycin-C or 5 FU using a tuberculin syringe
    - **ND Yag laser** can be used as internal (gonioscopic reopening of blocked ostium) or External (trans-conjunctival revision of a late failing bleb dye to episcleral fibrosis)
  - **Surgical**

- **Where conservative measures alone are not enough to treat the condition**
- **In grade III shallow AC– ie in cases of lens-corneal touch urgent surgery is indicated**
- External conjunctival cryopexy
- Thermal coagulation by cautery,argon laser,N-D Yag laser
- Direct suturing of the conjunctival hole
- Patching with corneal scleral graft
- Free and pedunculated conjunctival graft

✦ **Complications**

- Flat AC and endothelial decompensation
- Endophthalmitis
- Peripheral anterior synechiae formation
- Hypotony
- Choroidal detachment
- Blebitis
- Hypotonic maculopathy

Moorfields Bleb Grading System

✦ Height and to vascularity in three zones: central bleb, peripheral bleb and non-bleb

1. **Central bleb area:** an estimation into five categories of percentages (0%, 25%, 50%, 75%, and 100%) is made of the relative size of the central demarcated area of the bleb relative to the visible conjunctival field superiorly. Often this is confined to the area over the scleral flap; in a uniform bleb, central and peripheral estimations are congruent.
2. **Peripheral bleb area**: the maximal extent of the bleb is assessed using a similar scale of five percentage estimations. This parameter assesses the maximal diffusion area of the bleb, as evidenced by slight bogginess or guttering at the edges.
3. **Bleb height:** in reference to the standardized photographs, the maximal central bleb height is scaled as flat, low, moderately elevated, or maximally elevated.
4. **Vascularity**: considered the most important prognostic parameter for bleb failure, this scale is applied to three areas: the central demarcated bleb, the bleb's peripheral extent of diffusion, and the surrounding non-bleb conjunctiva. Five grades of vascularity are used: avascular, normal, mild vascularity, moderate vascularity, and severe vascularity. Subconjunctival blood is also notated.

Indiana Bleb Grading System

1. **Bleb height:** this describes the maximal vertical elevation of the bleb: flat, low, medium, or high.

2. **Horizontal extent:** the maximal horizontal extent is described relative to limbal clock hours: <1 hr, 1–2 hr, >2–<4 hr, and >4 hr.
3. **Vascularity**: five simple categories are elaborated: white and avascular, cystic and avascular (with microcysts), mild vascularity, moderate vascularity, and extensive vascularity.
4. **Seidel leakage:** in the testing for a bleb leak with a fluorescein strip at the slit lamp, the bleb is categorized as showing no leak, multiple pinpoint leaks without streaming, or brisk streaming within 5 seconds.

Complications of Filtration Procedures & Management

- **Intraoperative**
  - ***Conjunctival Buttonhole:*** Purse-string suture with 10–0 or 11–0 needle on a rounded ("vascular") needle.
  - Trabeculectomy Scleral Flap Tear/Disinsertion
  - Vitreous Loss
  - Intraoperative Bleeding
  - Choroidal Effusion: Observation, cycloplegics, steroids. Drainage is considered if effusions are appositional and associated with flat anterior chamber.
  - Early overfiltration: If AC is shallow or flat with no lens–cornea touch, use cycloplegics, restriction in activity, and avoidance of Valsalva maneuvers. If there is lens–corneal touch, perform urgent reformation of AC. If complication persists, resuture scleral flap.
- **Early Postoperative Complications**
  - Underdrainage
  - Shallow Anterior Chamber
    - Spaeth classification
      - grade 1 : peripheral iris and cornea touching
      - grade 2: mid iris and the cornea
      - grade 3: complete contact of the iris and the pupillary space with the posterior surface of the cornea
    - High Intraocular Pressure and Flat Chamber
      - Aqueous misdirection syndrome (i.e., malignant glaucoma)
      - Suprachoroidal hemorrhage
      - Pupillary block
    - Low Intraocular Pressure and Flat Chamber
      - Overfiltration caused by insufficient flap resistance
      - Uveal–scleral outflow tract due to choroidal detachment
      - Cyclodialysis cleft

        - A true flat chamber with lens–cornea or intraocular lens–cornea touch (should be fixed immediately)
    - Choroidal Effusions
    - Corneal Epitheliopathy
- **Late Postoperative Complications**
    - Late Bleb Failure
    - Tenon's Cyst Formation: Initial observation. Aqueous suppressants if IOP is elevated. Consider needling with 5-fluorouracil or surgical revision. Topical lubrication. Compression sutures (Palmberg's).
    - Late Bleb Leaks: If leak is not brisk, initial observation and topical antibiotics. If it persists, surgical revision (conjunctival advancement or autograft).
    - Blebitis Versus Late Endophthalmitis:
    - Late Hypotony: If there is decreased vision or maculopathy: transconjunctival flap sutures or revision of the scleral flap
    - Drainage Setons

Hypotony and Bleb Revision

- Hypotony is usually diagnosed when the IOP is less than **3 standard deviations (SD) below the population mean**. Less than **6 mmHg** is typically used as a cutoff. Ideally, hypotony should not be diagnosed unless the IOP is consistently below this cutoff (eg, measured below 6 mmHg on at least 2 consecutive clinic visits), unless the IOP level is very low (eg, less than 3 mmHg).
- **Clinical Features**
    - Astigmatism (typically with the rule)
    - Intermittent blurring due to compression of the globe on blinking
    - Mild shallowing of the anterior chamber or axial length reduction
    - Sequelae of severe hypotony (consistently very low IOP of < 3 mmHg)
        - Hypotony maculopathy: Hypotony maculopathy is more common in myopes and requires prompt correction of the IOP in order to restore the correct choroidal and retinal morphology.
        - Marked anterior chamber shallowing
        - Choroidal effusions: Choroidal effusions will generally resolve without draining if the IOP is restored to levels above 6 mmHg, though occasionally IOP levels in double figures are required to achieve resolution.
- **Management**
    - In the early postoperative period, one or more anterior chamber injections of viscoelastic may provide a temporary solution to protect against the sequelae of hypotony while waiting for healing to occur. Viscoelastic may be injected into the anterior chamber at the slit lamp if a temporal corneal paracentesis has been made at the time of the original surgery.

- Bleb revision may be required for Late Hypotony
  - **Semiconservative methods**
    - Autologous blood injection into or around the drainage bleb
    - Bleb delimitation or compression suturing
    - Cautery to shrink the bleb
  - **Diagnosis of Over-draining Bleb (Pseudophakic eye only)**
    - Intracameral injection of a nonexpansile concentration of a gas such as 20% SF6 or 12% C3F8.
    - Later appearance of gas bubbles under the conjunctiva over the subsequent 24 hours will confirm the cause of the hypotony to be an over-draining bleb
  - **Formal bleb revision**
    - When hypotony is due to scleral flap insufficiency alone (ie, a loose flap, a very thin flap, or a flap that has degenerated over time), either flap resuture or reinforcement with a donor scleral or commercially available pericardial patch graft may be all that is required.
    - Hypotony in association with an unsatisfactory bleb morphology or a leaking bleb may require bleb excision and conjunctival advancement or replacement in addition to scleral flap resuture / reinforcement.

Choroidal Effusion & Management

- **Choroidal Swelling Causes**
  - ***Choroidal Effusion***
    - Transudate from hypotony (eg, glaucoma surgery), ophthalmic venous obstruction (eg, thick sclera [nanophthalmos]), vortex vein obstruction during scleral buckling, superior ophthalmic vein, cavernous sinus thrombosis or carotidcavernous fistula, severe anterior capsular / zonular contraction after cataract surgery
    - Exudate or other mechanism from inflammatory disease or drugs
      - Posterior scleritis, Vogt-Koyanagi-Harada (VKH)
      - Topiramate, acetazolamide, methazolamide, pergolide, hydrochlorothiazide
  - ***Hemorrhage***
    - Drugs (eg, anticoagulants)
    - Trauma – choroidal rupture
    - Surgery – retina, cataract, glaucoma (filtration or cyclophotocoagulation), penetrating keratoplasty
    - Spontaneous, subarachnoid hemorrhage

- Rarer – melanoma, disseminated intravascular coagulation eg, thrombotic thrombocytopenic purpura, polypoidal choroidal vasculopathy, laser to retinal vascular disorders

- **Risk Factors**
  - Sturge-Weber
  - Hypotony
  - Myopia
  - Coagulation disorders (eg, hemophilia)
- **Diagnosis**
  - Clinical appearance
  - Ultrasonography
- **Differential Diagnoses**
  - Choroidal hemorrhage may be misdiagnosed as malignant melanoma or vice versa.
- **Management**
  - Effusions in the presence of hypotony resolve quickly on correction of the hypotony, avoiding the need for drainage.
  - Effusions that have resulted from a period of hypotony occasionally persist after the hypotony has been corrected. Drainage of the effusion is then indicated.
  - Effusions in the presence of high IOP from secondary angle closure are usually small and more easily detected by imaging than clinical examination. Drainage is not usually a practical consideration. Treatment:
    - Aqueous suppressants for the IOP, avoiding acetazolamide and other sulphas if secondary to topiramate.
    - Treat the cause, eg, effusion with inflammatory disease – VKH, scleritis – treat inflammation, effusion with drugs (eg, topiramate) – withdraw.
  - Choroidal hemorrhage – correct hypotony, corticosteroid treatment to minimize inflammation and drain.
    - Timing of drainage is very important. Traditional teaching is to drain immediately before the hemorrhage clots or after 7-10 days when the clot has lysed.
    - Unless the hemorrhage occurs in the operating room, it is usually not possible to drain immediately.
    - On the other hand, delaying drainage in a hemorrhage involving the macula may result in a very poor visual outcome. Good results have been reported from drainage as early as 5 days, and the author will illustrate this talk with a good result from drainage after 6 days.
  - Intraocular gas tamponade is often recommended when draining choroidal effusions or hemorrhage. The author prefers to use an anterior chamber infusion in combination with correction of the cause of hypotony, resorting to gas when the IOP cannot be successfully maintained.

- Vitrectomy / silicone oil if vitreous hemorrhage / retinal breaks or failure of previous drainage
- Tissue plasminogen activator has been used to lyse subretinal and suprachoroidal hemorrhages in isolated reports.

- **Drainage Techniques**
  - Identify area of largest effusion / hemorrhage, usually by B-scan ultrasonography, before surgery. This will usually be an inferior quadrant.
  - In the operating room, first correct the hypotony (eg, close over-draining trabeculectomy flap or ligate overdraining aqueous shunt).
  - Use an anterior-chamber infusion to maintain the IOP and provide tamponade.
  - Create a sclerostomy at the lower-most point of the globe that is surgically accessible. This will have to be either inferonasal or inferotemporal to avoid inferior rectus and should also avoid the vortex veins.
  - A *V*-shaped sclerostomy, with the apex of the *V* pointing anteriorly, is easier to fashion and drain fluid from than a slit. Begin with partial thickness grooves and deepen slowly until the sclera is just breached. Then lengthen with the blade upward, away from choroid.
  - At the point when the suprachoroidal space is entered, there should be a gush of fluid / blood. In the case of hemorrhage, the blood will be a dark dusky color in contrast to any bleeding from the scleral wound.
  - Gently depress choroid just at the scleral entry with a flat blunt instrument (eg, iris repository), repetitively. It is worth continuing this activity repetitively for a significant period of time (eg, 15-20 minutes) to ensure that all blood has drained.
  - Leave the scleral wound unsutured.
  - Close conjunctiva with sutures or fibrin glue.
  - Repeat the procedure in the contralateral inferior quadrant.
  - An alternative method of drainage has been suggested using 23-gauge or other vitrectomy cannulas as a method of avoiding the risk of choroidal and retinal incarceration in the scleral wound.

Bleb Leaks

- Occur in approximately 4%-30% of trabeculectomies with antimetabolites
- Majority occur within the first 3 months after surgery
- **Clinical Features**
  - Can be asymptomatic
  - May present with ocular discomfort, tearing, and/or decreased acuity from maculopathy, hyperopic shift, or increased astigmatism
  - Hypotony with corneal striae, shallow anterior chamber, disc edema, and maculopathy may be present.

- Positive Seidel testing: Paint area with moistened fluorescein strip under cobalt blue light. Carefully assess wound edge, possible sites of buttonholes, and cystic/thin areas for leaks.

Early Bleb Leaks

- **Definition**: Leak occurring within 1 month following trabeculectomy
- **Prevalence**: Reported rate varies widely.
- **Location**
  - Wound site or other site of surgical trauma (ie, conjunctival buttonhole)
  - May be more common in fornix-based than limbal-based trabeculectomies
- **Impact on surgical outcome**: Conflicting reports as risk factor for bleb failure
- **Prevention**
  - Meticulous attention to wound closure and careful assessment for leaks at the end of case
  - Incorporation of Tenon capsule into wound closure (single or double-layer closure)
  - Check with Weck-cell sponges or fluorescein strip
  - Verify ability to elevate / maintain formed bleb with deep anterior chamber by applying gentle pressure or by instilling BSS into anterior chamber through paracentesis.
  - Close buttonholes with 9-0 poly-glactin suture on tapered needle (BV or VAS) using purse-string suture.
  - Use lower concentrations of mitomycin, 5-fluorouracil, or no antimetabolite in patients with very thin conjunctiva.
- **Management**
  - Non-Surgical
    - Observe
    - Medications
      - ✓ Prophylactic antibiotic use controversial; may not be effective in preventing blebitis
      - ✓ Aqueous suppressant (ie, timolol, dorzolamide, or brimonidine)
      - ✓ Gentamicin to promote scarring
      - ✓ Reduce frequency of topical steroid
      - ✓ Increase frequency of ointment to reduce friction against eyelid
      - ✓ Topical application of autologous serum
      - ✓ Topical application of trichloroacetic acid
    - Mechanical treatments
      - ✓ Bandage contact lens with prophylactic antibiotic

- ✓ Pressure patching
- ✓ Symblepharon ring/Simmons shell

- Procedures
  - ✓ Cyanoacrylate or fibrin glue
  - ✓ Autologous blood injection
  - ✓ Suture wound at slitlamp or in minor procedure room
  - ✓ Laser, cryotherapy, or cautery

- Surgical: Wound closure / bleb revision

Late Bleb Leaks

- **Definition**: Leak occurring 1-3 months or more following trabeculectomy
- **Prevalence**: 3.7%-9% of patients undergoing trabeculectomy with mitomycin C
- **Location**: avascular, cystic thin-walled area of bleb Risk factor: use of mitomycin-C Recurrence: 36% represent recurrent leaks
- **Frequency of infection**
  - 22% had blebitis upon diagnosis of leak.
  - 5% had endophthalmitis upon diagnosis of leak.
  - 5% had subsequent endophthalmitis following diagnosis of leak despite initiation of antibiotic prophylaxis.
- **Management**
  - Goal: resolution of leak
    - 77% resolved with conservative, office-based management.
    - 18% resolved after surgical revision.
    - 5% had a persistent leak with conservative therapy.
  - Nonsurgical
    - As above (ie, observation, medications, mechanical treatments, and procedures)
    - Needle bleb to expand filtration area in localized bleb (can be done in the office or OR)
  - Surgical
    - Conjunctival advancement or transplantation
    - Scleral or corneal patch
    - Amniotic membrane transplantation
    - Bleb closure with implantation of glaucoma drainage device

Bleb-Related Infection

- Reported to occur in 0.2%-9.6% of patients after filtering surgery
- **Common organisms:** Staphylococcus, Streptococcus, Haemophilus influenzae

- **Risk factors**
  - Bleb leak
  - Prior history of blebitis
  - Blepharitis
  - Nasolacrimal duct obstruction
  - Contact lens use
  - Use of antimetabolites
  - Inferior bleb placement
  - Pediatric patients
- **Management**: First aggressively treat infection, then plan surgical revision following complete resolution of infection.
  - Blebitis: mucopurulent material in or around bleb with mild anterior chamber inflammation
    - Hourly or every 30 min alternating topical antibiotics (ie, fluoroquinolone and/ or fortified antibiotics)
    - Topical steroids added once there are signs/ symptoms of improvement
    - Tap and inject if no improvement or worsening over the first 24-48 hours following initiation of topical antibiotics
  - Endophthalmitis: moderate-severe anterior chamber inflammation, hypopyon, or the presence of vitritis
    - Tap and inject with intravitreal antibiotics
    - Vitrectomy in severe cases (may have lower threshold compared to Endophthalmitis Vitrectomy Study (EVS) guidelines, which evaluated endophthalmitis following cataract surgery)
    - Topical steroids

Glaucoma Drainage Devices (GDD)

- The first attempt to implant a drainage device was made by Rollet and Moreau in 1907 when they performed a double paracentesis and used horse hair
- Molteno in 1969 → functioning implant with an episcleral plate and tube
- **Basic design:**
  - Plastic tube that extends from the anterior chamber to a plate
  - Explant: disc or encircling band beneath conjunctiva and Tenon's capsule
- Posterior explant stimulates fibrovascular encapsulation and allows aqueous to passively flow across a pressure gradient, across the capsule wall to be subsequently absorbed by conjunctival capillaries and lymphatics
- **Types of implants:**

1. Non-valved / non restrictive implants: Molteno, Baerveldt, Schocket.
2. Valved / restrictive implants: Ahmed, Krupin, Joseph, Optimed, White.

- **Indications:**
  - Previously failed filtration procedures in acquired or congenital glaucoma
  - Neovascular glaucoma.
  - Silicone-oil glaucoma.
  - Aphakic / Pseudophakic glaucoma.
  - Complicated glaucomaeg Aniridia/ICE/ Uveitis
  - Traumatized eyes with conjunctival scarring
  - Dryness which precludes standard glaucoma surgery

- **Non Restrictive Implants**
  - **Molteno** implant variations
    - Polypropylene plates, including single-plate (133 mm^2), double-plate, pressure ridge, and pediatric
    - Molteno implant is a flexible, larger, singleplate design (175 mm^2 or 230 mm^2 plates)
  - **Baerveldt** implant introduced in 1990
    - Larger (250 mm^2 and 350 mm^2) silicone plates
    - Intraluminal occlusion sutures and external ligation of the tube avoided postop hypotony.
  - While the **Schocket** implant is not commercially available, clinicians have attached tubes to previously implanted encircling bands to treat patients with elevated IOP after scleral buckle
- **Flow-Restrictive Implants**
  - Flow-restrictive implants were developed in order to avoid problems associated with early postoperative hypotony after drainage implants.
  - An implant with a pressure-sensitive slit opening was described in 1976 by **Krupin**.
    - The slit “valve” was prone to variability of efficacy and obstruction by debris.
    - The Krupin (Eagle Vision) implant is no longer commercially available.
  - Various other flow-restrictive implants, including the **Joseph, White, and Optimed** implants, were developed but did not remain commercially available.
  - **Ahmed Glaucoma Valve** was introduced in 1993.
    - The valve is comprised of 2 thin silicone elastomer membranes positioned in a Venturi-shaped chamber.
    - Different models include polypropylene plates (single-, double-plate, and pediatric), silicone plates (single-, double-plate, and pediatric), and a porous polyethylene plate.

- The silicone single-plate model (FP-7) has been popular among clinicians.
- The Ahmed Glaucoma Valve is the only available resistance glaucoma drainage device.

Ex-Press Mini Glaucoma Shunt

- Small stainless-steel implant that is inserted through the limbus into the anterior chamber under a 4 to 5-mm–wide partial-thickness scleral flap
- Several models with different shapes and sizes (length range from 2.4 to 2.9 mm).
- Internal lumen diameter varies between 50 µm (most commonly used) and 200 µm.
- Outer 250-350 um
- More uniform, consistent, and reliable postoperative course than standard trabeculectomy
- Can be placed either subconjunctivally or under a scleral flap. Owing to an unacceptably high rate of choroidal effusion and SCH subconjunctival placement is no longer recommended.

Complications of GDD

- **Early Complications: occurring within few days**
  - Hypotony / choroidal detachment: Can be prevented by temporarily obstructing the tube lumen. Manage by reforming anterior chamber via the paracentesis, ligating or even removing the tube. Cause is excessive flow of aqueous through the tube, rarely leakage around the tube arising from too large an entry incision.
  - Hyphematransient and usually resolves, in cases of neovascular glaucoma it may be massive enough to cause IOP rise and tube blockage. The latter maybe prevented by anterior retinal cryopexy in NVG cases prior to surgery.
  - Corneal endothelial touch – usually seen when the tube has not been placed accurately or the bevel has not been cut in the proximal orifice. The other reason for this complication is shallow anterior chamber. This maybe exacerbated by blinking or eye rubbing.
  - Elevated IOP: Early post operative IOP elevation may be due to obstruction of tube by fibrin, blood, iris tissue, or vitreous. This occurs in 5-11% of cases. Laser tube revision by Nd:YAG/ Nd:YLF is on temporary benefit. But still this non invasive procedure should be attempted first. Intracameral injection of tissue plasminogen activator is an expensive option, but may work. The ultimate solution is tube revision. Late IOP elevation, is usually due to an excessively thick fibrous capsule. This can be dealt by removing a portion of the capsule beneath the conjunctival flap.
  - Hypotony Maculopathy
  - Suprachoroidal Hemorrhage
  - Flat AC
  - Aqueous Misdirection

- **Late complications: occurring within weeks or months**
  - Increased IOP cause may be tube blockage, non functioning bleb, resurgence of disease eg uveitis, rubeosis, fibrous ingrowth.
  - Endothelial touch intermittent or constant leads to endothelial decompensation. If progressive tube repositioning and tight anchorage maybe indicated.
  - Tube exposure/ migration/ extrusion Tube exposure incidence varies from 015%. To prevent it prophylactic use of donor sclera to cover it in areas of scleral thinning, adequate anchorage to scleral bed by sutures, the superficial flap must be evenly dissected. Treatment of this complication may be initially by rotating an adjacent partial; thickness flap to cover the tube but ultimately a fresh site needs to be selected. Tube migration is usually due to slippage of anchoring sutures.
  - Insufficient aqueous absorption inspite of patent tube – thickened fibrous capsule over the distal end of the tube or less surface area of drainage. Persisting inflammation is a common culprit and a stringent antifibrotic regimen consisting of steroids and non steroidal anti inflammatory
  - Others Cataract progression in almost 36%/ Endophthalmitis/ Retinal detachment.
  - Ocular Motility Disturbance : Exotropia, hypertropia, or limitation of ocular rotation, usually occurs with larger, plates eg; Baerveldt and Krupin implant but can also occur with smaller plates. This is usually due to bulk effects or from direct impingement on or scarring of the rectus/ oblique muscles. Diplopia occurring commonly with Baerveldt's implants led to the discontinuation of 500 mm sq. explant and its redesigning with fenestrations to allow fibrous ingrowth, thereby reducing the bleb height. Placing the implant in the spacious supero-temporal quadrant minimizes this complication
  - Loss of visual acuity: Occurs due to hypotonous maculopathy, retinal detachment, vitreous hemorrhage and cystoid macular edema.
  - Epithelial down growth in fornix based conjunctival flaps careful closure of conjunctiva keeping the epithelium facing away from the tubes is advocated. This complication is minimized by limbal based flaps.

NPGS: Non-penetrating Glaucoma Surgeries

- **Principle**: Removal of deep scleral flap, external wall of SC, corneal stroma behind the anterior trabeculum and the DM, thus creating a scleral lake →Aqueous leaves the AC through the intact Trabeculo-Descemet's membrane (TDM)
- **Indications**:
  - When conventional trabeculectomy has failed:
    - OAG
    - High myopia
    - PDG
    - PXG
    - Aphakic/ pseudophakic Glaucoma
  - Where NPGS are safer

        - Congenital and juvenile glaucoma
        - SWS
        - Aniridia and anterior segment dysgenesis
        - Post uveitis glaucoma
- **Contraindications**:
    - Narrow angle glaucoma
    - Post-trauma angle recession glaucoma
    - Post-laser trabeculoplasty
    - NVG (absolute contraindication)

- **Advantages of non-penetrating glaucoma surgery (compared to trabeculectomy)**
    - No sudden decompression of anterior chamber
        - Suprachoroidal hemorrhage less likely
        - Serous choroidal detachment less likely
    - Reduced risk of prolonged hypotony
        - Less likely to get filtering bleb
        - Less chance of bleb leak – early or late
        - Less chance of blebitis, endophthalmitis
        - Contact lens wear less likely to be problematic
        - Bleb dysthesia rare
    - Less intraocular inflammation
    - Less chance of intraocular bleeding
    - Fewer postoperative visits
    - More rapid visual rehabilitation postoperatively
- **Disadvantages of non-penetrating glaucoma surgery (compared to trabeculectomy)**
    - Technically more difficult
    - Takes longer in the operating room
    - Requires some specialized instrumentation
    - About 10% have actual perforation into anterior chamber requiring iridectomy
    - Intraocular pressure less likely to be lowered sufficiently in advanced glaucoma
    - Pressure lowering may not last as long

Deep sclerectomy

- Aka nonpenetrating trabeculectomy and external trabeculectomy.

- Epstein and Krasnov in the late 1950s
- Deep sclerectomy involves creating two partial-thickness scleral flaps with the second, deeper flat at 99% depth. During the procedure, the inner flap is removed, creating an intrascleral lake.
- **MOA**:
  - Aqueous flow through Trabecular-Descemet's Membrane (TDM): The resistance offered by TDM is significantly low enough to ensure low IOP and high enough to maintain deep AC
  - Aqueous reabsorption:
    - Subconjunctival filtering bleb
    - Intrascleral bleb
    - Suprachoroidal passage
    - Episcleral drainage via schlemn canal
- **Advantage**
  - Minimal intraocular inflammation
  - Risk of flat anterior chamber is very low
- **Postoperative Care**
  - Infection prophylaxis and treatment of inflammation
  - Steroids
  - Trabeculodescemetic membrane is so thin that it can break and the implant can enter the anterior chamber if at all, so do gonioscopy in follow up
  - The bleb can become encapsulated and can benefit from needling.

Schlem's Canal-based Surgery

- **Indications**
  - Canal-based procedures have been used successfully in the full spectrum of open-angle glaucomas from congenital to adult primary open angle including pigmentary and pseudoexfoliation.
  - Open angles are the only prerequisite.
  - Clear media is necessary for the ab interno-based Trabectome and iStent.
  - Canaloplasty is performed ab externo and can be performed in the presence of hazy media or scarred cornea.
- **Canaloplasty**
  - The first nonpenetrating procedure to utilize a microcatheter ***iTrack***
  - Mechanism of Action
    - canal is dilated, the TM is tensioned, and after removal of the deep scleral flap, a Descemet's window is created

        - primarily by enhancing conventional circumferential outflow through the canal and the collector system
    - Hypotony, choroidal detachment, and bleb infections were reported in less than 1% of all cases. The most common side effect is transient hyphema.
    - Safer than trabeculectomy.
    - 200-µm–diameter catheter with a 250-µm tip is attached to a battery-powered light source with a second attachment to facilitate injecting viscoelastic to dilate the canal upon removal
- **Trabectome**
    - Minimally invasive ab interno procedure
    - Mechanism of Action
        - ablate the juxtacanalicular area to eliminate the area of resistance, creating direct flow into the canal and collectors.
    - The presence of blood reflux at the conclusion of the procedure is confirmation of reduced outflow resistance. This is a transient complication that usually resolves within 1 to 2 weeks.
    - Allows sparing of the conjunctiva; thus, future filtering or drainage device surgery will not be compromised.
- **iStent**
    - The iStent was developed by Glaukos (Glaukos Corp.; San Clemente, CA), and the first implantation in the United States was performed in 2005.
    - The stent is designed to fit into and remain within the Schlemm canal. Made from non-ferromagnetic titanium, it consists of an inlet (or “snorkel”) connected at a 40-degree angle to the half-pipe portion that is implanted within the canal. The stent comes preloaded, attached to the tip of a 26-gauge disposable insertion instrument that has been sterilized by gamma radiation.
    - The leading, pointed end of the device facilitates entry into the canal, and the direction of this point corresponds to the designation of a right or left-handed model. Depending on the preference of the surgeon, both “right” and “left” iStents have been developed to ease implantation, although there are no data to suggest that one orientation is more efficacious than the other.
    - Surgeons are encouraged to use whichever design is more comfortable to implant. The left design is implanted with a forehand maneuver for right-handed surgeons, while the right design is implanted with a backhand maneuver.
    - The segment residing within the canal includes a half cylinder opening, which, combined with heparin coating, helps to prevent blockage or fibrosis. Three retention arches help to ensure that the device will be held in place within the canal.
    - The implant is 1.0 mm in length, 0.33 mm in height, and has a weight of 60 micrograms. The snorkel has a length of 0.25 mm and bore diameter of 120 micrometers.
- **iStent inject**

- The iStent inject system (Glaukos Corp.; Laguna Hills, CA), a second-generation device, consists of an apical head connected to a narrow thorax that is attached to a wider flange.
- Currently the smallest medical implant approved for use in the human body, the implant is 360 microns in length, with a diameter of 230 microns. The head is inserted directly into the canal without the need to adjust the angle for implantation or direct it circumferentially.
- It resides within the canal and contains 4 inlets for fluid passage. The 23-gauge stainless steel injector contains 2 stents for implantation in the nasal angle, at a distance of approximately 30 to 60 degrees.
- The multifocal placement improves the chance of implanting close to a collector channel, reducing the need for "intelligent placement" (the process of selecting specific anatomic locations within the canal for implantation in the proximity of a collector channel). The iStent inject was approved for use in Europe in 2006 and by the US FDA in June 2018, although it has not yet been commercialized in the United States.

Hydrus

- The Hydrus Microstent (Ivantis, Inc.; Irvine, CA) is an aqueous drainage device, laser cut from a nitinol (nickel-titanium alloy) tube and thermally set to a curvature consistent with the Schlemm canal. The device is designed for ab interno placement through the TM.
- While most of the 8-mm device resides within the canal, a portion of the stent remains in the anterior chamber.
- The device provides a direct inlet to the canal but also scaffolds and tensions the canal. Studies have suggested that such tensioning improves facility of outflow.
- The fact that Hydrus spans 8 mm, or nearly 3 clock hours, virtually eliminates the need for "intelligent placement" within the canal as it provides access to multiple collector channels. Excellent material biocompatibility has been demonstrated in 2 different in vivo models.
- Laboratory studies in human cadaver tissue have demonstrated increased outflow facility compared to controls who did not receive the device. The Hydrus implant received European CE mark approval in 2011, and prior clinical studies demonstrated significant reductions in IOP and topical hypotensive medication usage among eyes that received the device, either in combination with cataract surgery or as a stand-alone device, for as long as 2 years postoperatively.
- The results of the HORIZON Trial were recently published and demonstrate safe and efficacious reduction of IOP that is statistically superior to PE alone, sustained throughout the 2-year study period.

Viscocanalostomy

- Proposed by Robert Stegman 1991.
- Surgical steps being the same as in Deep sclerectomy upto Schlemm's canal being deroofed. Then by a paracentesis the IOP is lowered, the 2 cut ends of the SC are cannulated by a 165 um blunt needle and a high molecular sodium hyluronate is

slowly injected into the canal. Upto 1-2 clock hrs of the canal is a-traumatically dilated. The slow injection is repeated 6-7 times on each side. A 2nd site of injection is between superficial scleral flap and deep scleral bed to display the potent anti-inflammatory properties of the high viscoelastic device. The outer scleral flap is tightly secured with 10-0 nylon sutures to ensure that the intra-scleral chamber is created. Conjunctiva and the Tenon's capsule are then sutured in a similar fashion with 8-0 nylon sutures.

- **Early Postoperative complications:**
  - ***Wound leak :*** rare
  - ***Hyphaema:*** rare. May be d/t rupture of a small iris vessel.
  - ***Inflammation:***if penetration of TDM occurs causing breakdown of blood-aqueous barrier
  - ***Hypotony:*** Mean IOP can reach upto 5mmHg on 1st post-op day,a progressive increase in the IOP occurs over the next few days without specific treatment.
  - ***Shallow or flat AC:*** rarely occurs. Large drop in IOP with shallowing of AC maybe associated with choroidal detachment.
  - ***DOV:*** d/t re-adaptation of the retina and the choroidal circulation to the new low level of IOP. Visual acuity may fall by a mean of 2 Snellen's lines for the 1st post-op week, returning to pre-op levels within next 2weeks.
  - ***Cataract:*** no such reports of surgically induced cataract are found on account of the constant maintenance of AC
- **Late Post operative complications:**
  - ***Fibrosis of sub-conjunctival bleb:*** common. But the presence of intra-scleral bleb reduces the need for a sub-conj bleb. If IOP is adequate, then flat bleb need not be treated otherwise needling with 5FU or revision surgery may be required.
  - ***Increased IOP:*** late rise may be d/t steroid response or fibrosis of TDM, sub-scleral or subconjunctival fibrosis. UBM assessment may be useful to denote the exact site. A Nd-Yag goniopuncture, medical therapy or revision are the treatment modalities.
  - ***Late rupture of TDM:*** usually does not occur, unless secondary to ocular trauma.

MIGS: Minimally Invasive Glaucoma Surgery

- The cardinal features of MIGS, as proposed by Saheb and Ahmed in 2012, are:
  - Ab interno, micro-incisional approach (InnFocus MicroShunt uses an ab-externo approach.)
  - Minimal trauma/disruption to normal anatomy and physiology
  - Demonstrable/reliable IOP lowering
  - Extremely high safety profile
  - Rapid post-op recovery, with minimal need for follow-up

- As per USFDA and American Glaucoma Society definition, MIGS is characterized by the implantation of a surgical device intended to lower IOP via an outflow mechanism with either an ab interno or ab externo approach, associated with very little or no scleral dissection.

MIGS: **Increase Trabecular Outflow**	**Specifics / Procedure:**
iStent Micro-Bypass	Heparin-coated, non-ferromagnetic titanium stent; 1.0 mm x 0.3 mm. Ab interno insertion into Schlemm's canal
Gonioscopy-assisted transluminal trabeculotomy (GATT)	Ab interno trabeculotomy using illuminated microcatheter (iTrack; Ellex) or prolene/nylon suture passed through a 1-2 mm goniotomy into Schlemm's canal 360° and lysed through the trabecular tissue
Trabectome	Ab interno trabeculectomy using combination of electrocautery, irrigation and aspiration
TRAB 360 Trabeculotomy	Ab interno trabeculotomy using disposable, non-powered device from which a flexible nylon-like trabeculotome is advanced into Schlemm's canal for 180° and then lysed (x2 to perform up to 360° trabeculotomy)
Kahook Dual Blade	Ab interno trabeculotomy using a single use, tapered, stainless steel blade
Ab interno canaloplasty	Illuminated microcatheter (iTrack; Ellex) and viscosurgical device used to cannulate and viscodilate Schlemm's canal
Hydrus Microstent	Crescent-shaped scaffold (8-mm long) composed of nickel-titanium alloy, Ab interno insertion into Schlemm's canal
Increase Uveoscleral / Suprachoroidal/ Supraciliary Outflow	
CyPass Micro-Stent	Fenestrated micro-stent, composed of biocompatible, polyimide material (6.35 mm x 510 mm, 300 mm lumen) Ab interno insertion between anterior chamber/sclera and suprachoroidal space
iStent Supra	Heparin-coated stent (4mm long, 0.16-0.17mm lumen) composed of polyethersulfone (PES) with a titanium sleeve. Ab interno insertion between anterior chamber/sclera and suprachoroidal space
Increase Subconjunctival Outflow	
XEN Glaucoma Treatment System	Tissue-conforming tube implant (6-mm long) composed of gelatin and glutaraldehyde material Ab interno insertion from the anterior chamber, through sclera into the subconjunctival space, bleb forming
InnFocus MicroShunt	Flexible microshunt (8.5 mm x 0.350 mm, 70 µm lumen) composed of SIBS (poly(styrene-block-isobutylene-block-styrene)) Ab-externo, subconjunctival (via peritomy) insertion through scleral needle tract into anterior chamber, connecting it to sub-Tenon's space, bleb forming
Decrease Aqueous Production	
Endocyclophotocoagulation	Ab interno cyclodestruction of ciliary body epithelium using continuous energy (810nm wavelength)

Newer Surgical modalities

Small incision trabeculectomy (SIT)

- The supratemporal quadrant of the eye is exposed with a traction suture; 2.5mm conjunctival peritomy is performed without cutting the tenons capsule near the limbus. A 1/3-1/2 partial thickness incision is made at the limbus & a scleral pocket is dissected posteriorly.The sub-conjunctival space is entered with an Alcon Crescent knife (bevel up) passed through the scleral pocket and balanced salt solution (BSS) is injected forming a sub-conjunctival bleb. The anterior chamber is entered at the initial limbal incision and the Vannas scissors is used to excise a 1.5mm x 1mm fragment of the floor of the pocket followed by peripheral iridectomy. The scleral wound as well as the conjunctiva is closed with separate 10-0 running / interrupted sutures.
- **Advantages**:
  - Places the incision between the insertion of the conjunctiva and Tenon's capsule avoiding manipulation of the latter and the subconjunctival space.
  - Thus obviates the stimulus for episcleral fibrosis without using pharmacological wound modulation
  - Minimal cautery is used thus avoiding further stimulus for post-operative scarring.
  - Low cost and highly efficacious.
  - As the cornea is not dissected, there occurs no visual disturbance d/t astigmatism or corneal oedema.

Intrastromal Holomium Laser Keratostomy:

- **Procedure**: A laser (Holomium) canal is created intrastromally in the cornea anterior to Scwalbe's line in the floor of corneo-scleral tunnel incision, made with a knife from the corneal site which acts as a valved mechanism. Mitomycin C is used intra-operatively by subconjunctival injection over the proposed surgical site to prevent sub-conjunctival fibrosis.
- **Advantages**: Post-op blebs are pale, diffuse and low-lying. No occurrence of flat AC is seen. Similarly low incidence of transient shallowing of AC (25%) while achieving IOP < 20mmHg without medication and re-operation in 63% cases over a mean follow up of 22.5months
- **Dis-advantages**: Need for expensive laser equipments with costly probes that should not be used more than 5 times.

Glaucoma surgery using Fugo blade

- Dr. Richard Fugo invented the Fugo Blade, which employs plasma energy for ablating incisional pathways in tissues in such a manner that it creates a smooth wall along the ablation pathways. Long-term results however remain unknown.Following procedures can be done:
  - Transciliary Filtration
  - Transconjunctival filtration
  - Adjunct in filtration surgery

E-PTFE Membrane Implant for refractory glaucomas

- The most common causes of failure of filtration surgery are-blockage of fistula by tissue in-growth, adhesion of scleral flap to the scleral bed, fibrous breakdown of conjunctival filtering bleb. Thus in order to halt this process, mechanical barriers have been tried out. A reservoir portion made of rigid materials is needed to facilitate aqueous outflow and prevent prevent blockage of distal end of the tube, which requires a large incision through the conjunctiva and Tenon's tissue for its insertion. Promising results have been seen with the use of double layered Expanded polytetra-fluroethylene (E-PTFE) membrane, a newer implant, soft and malleable as a reservoir portion. This obviates the need for a large incision and the related complications such as wide scar, erosion ad extrusion of implant and extra-ocular muscle movements.

Retinectomy for intractable glaucoma

- In a recent study, retinectomy was performed to lower IOP in pts. With uncontrolled IOP (> 35 mm Hg for more than 4 months) despite conventional filtration surgery and drug treatment. Pars plana vitrectomy was performed and the peripheral retina was surgically excised to various degrees. The procedure was concluded by an intraocular gas temponade of 60% C3F8. Retinotomy may be alternative to enucleation in otherwise intractable glaucoma. It has the advantage of a lack of initial post operative hypotony together with a sufficient long term drainage effect. The posterior aqueous routing via retinectomy depends on the integrity of the choroids and thus the size and area of retinectomy should be chosen accordingly. The reduction in systemic and topical medications after retinectomy is considered beneficial for the patients.

Surgical Management Cataract & Glaucoma

- **Risks and complications** greater with cataract surgery in glaucomatous eyes than in non-glaucomatous eyes due to:
  - CACG: miotic pupil, posterior synechiae, PAS
  - Congested eye bleeding, previous surgery scarring or pre-existing bleb
  - Associated systemic diseases diabetes,
  - Associated eye conditions –myopia;
  - Crowded anterior chamber – high hyperopia, nanophthalmos increased incidence of post-op IOP rise, increased incidence of suprachoroidal hemorrhage.
  - CME may increase with use of multiple glaucoma meds incorporating BAK (benzalkonium chloride) preservative.
  - Pseudoexfoliation (PXE) underappreciated as a risk factor: higher risk of zonular dehiscence, vitreous loss, anterior capsule contraction, IOL dislocation/decentration
- **IOP Effect ON Cataract Formation:**
  - Elevated IOP may increase risk of nuclear cataract and use of glaucoma meds could magnify this risk (Blue Mountain Eye Study).

- Low IOP after trabeculectomy is a risk factor for cataract progression

- **IOP Effect OF Cataract Surgery:**
  - Small incision phacoemulsification has a statistically significant, but small, IOP lowering effect in normal eyes and glaucoma suspect eyes extending one to five years post-op.
  - Preop IOP level and angle status important.
  - Medication requirements may be reduced in eyes with glaucoma. However, IOP spikes may occur in the first 24-hours post-operatively and occasional patients may have long-term IOP elevation

- **Visually significant cataract in presence of glaucoma: *5 options***

1. Phaco alone

- **Advantages**
  - Restore vision promptly
  - Single procedure
  - Technically easiest short surgical time
  - Reduced operative and post-op complications related to wound.
  - Facilitate post-op assessment of optic nerve and visual field
  - Opportunity for glaucoma operation later if needed – multiple options conjunctiva can be spared
  - Small incision phacoemulsification itself can yield improved long-term IOP control
- **Disadvantages**
  - Early post-op IOP rise: 1-8 hours post-op and POD #1
  - Reduced long-term IOP control compared to combined surgery
  - Future filtration surgery success potentially compromised if conjunctiva violated
  - Cannot depend on beneficial effect of cataract surgery for IOP control
  - Early (30 min – 1 hour) post-operative hypotony may be more frequent
- **Indications**
  - Acceptable IOP control on 3 or less medications
  - No significant glaucomatous visual field loss or cupping
  - Higher preop IOP/narrow angles with healthy nerve
  - Older age

2. Phaco "Plus" MIGS

- **Indications**
  - Reasonable optic nerve
  - Modest IOP reduction requirement

- Reduced medication requirement desired
- Multiple stents may have advantage over single stent

- **Advantages**
  - IOP reduction slightly more than phaco alone
  - Reduction in glaucoma medication requirement greater than phaco alone
- **Multiple Variations**
  - Ab interno – no conjunctival incision
    - Normal pathways:
      - New conduit/opening into Schlemm's canal (iStent, Hydrus, ECT)
      - Reopen synechial angle closure (goniosynechialysis (GSL))
        - ✓ The **GSL technique** was first reported in1984 by Campbell and Vela and performed in conjunction with cataract surgery
        - ✓ Greater success in IOP control was found when the apposition had not been present for a long period of time (less than one year).
        - ✓ The technique is to use viscoelastic to open the angle and maintain the chamber for adequate view while physically teasing away the PAS from the TM under direct gonioscopic visualization utilizing a spatula or microforceps. When performed in conjunction with cataract surgery, GSL can address the root problem by opening a physical obstruction blocking outflow, while the cataract extraction debulks the crowded anterior chamber (AC) for maintenance of outflow.
        - ✓ Good Candidate: A phakic patient with PAC, PACG, or chronic ACG with elevated IOP and at least 50% of the angle sealed with PAS done with or without cataract surgery
      - Ablate TM and inner wall of Schlemm's canal (trabectome)
    - Alternate pathways: new conduit into suprachoroidal space (CyPass); subconjunctival space (AqueSys)
    - Inflow System: ciliary processes (ECP)
  - Ab externo – no conjunctival incision: ciliary processes (diode cyclophotocoagulation)
  - Ab externo – small conjunctival incision: alternate pathway via subconjunctival space (InnFocus Midi Arrow → InnFocus MicroShunt)

3. Combined phaco and glaucoma surgery

- **Advantages**
  - Restore vision promptly
  - Single procedure

- Reduced glaucoma medication requirements post-op
- Good early post-op IOP control
- Better long-term post-op control with phacotrabeculectomy than cataract extraction alone (Friedman et al)
- Antimetabolites possible enhanced success with possibility of more complications
- Multiple glaucoma surgical options
- Facilitate post-op assessment of optic nerve and visual fields quality of life

- **Disadvantages**
  - More complications than cataract extraction alone shallow AC, bleb leak, choroidal effusion/hemorrhage, hypotony, infection, dellen, astigmatism, postoperative myopic shift, tube issues
  - Longer surgery time than cataract extraction alone
  - More intensive post-op care requirements than cataract extraction alone – important for patient and surgeon
  - ? less IOP control than 2-stage procedure?
  - Glaucoma meds often required post-op
  - Against-the-rule (ATR) astigmatism – may be exacerbated with larger superior incisions/antimetabolites
- **Indications**
  - More than 3 medications required for good IOP control
  - Medication use limited by allergy or medical contraindications
  - Presence of significant glaucomatous visual field loss and cupping.
  - Age factor may favor combined procedure for younger patients; cataract surgery alone for older patients.
  - Presence of other significant risk factors for glaucoma (e.g. pseudoexfoliation, pigment dispersion, angle recession) may favor combined procedure.
  - Monocular status may favor combined surgery.
  - Unable to tolerate 2 separate operations.

4. Two-Stage: Glaucoma Procedure First, Phaco Second

- **Advantages**:
  - Best for immediate IOP control.
  - ? best for long-term IOP control?
  - Reduced glaucoma medication requirements post-op
  - Successful filter/tube eliminates need for miotics – occasionally improves vision post-operatively in patient with cataract
  - Opportunity for glaucoma enhancement procedure at time of cataract surgery – multiple options

- **Disadvantages**:
  - 2-stages delayed visual recovery
  - Subsequent cataract surgery.
    - Lose some IOP control – controversial
    - More challenging in presence of bleb – multiple issues
- **Indications**:
  - Glaucoma immediate threat to vision
  - Difficult glaucoma where IOL not indicated in acute situation – active uveitis, active NVG
  - Success with subsequent phaco makes this option reasonable

5. Pseudophakic Filter

- Express mini-glaucoma shunt – under flap; shunt to site near limbus, create bleb equivalent to filter
- Tube/shunt to site remote from limbus (e.g. Molteno, Baerveldt, Ahmed, Krupin): all types possible
- Ciliary body endophotocoagulation (ECP) Uram and others; beware chronic inflammation postop characteristic of all external cycloablative therapies; such inflammation appears to be much less with ECP

Miscellaneous Topics

Systemic Hypotension and Glaucoma

- **Increased Prevalence of Glaucoma With Low Diastolic Perfusion Pressure**
  - Low ocular perfusion pressure (OPP) is associated with an increased prevalence of glaucoma in population-based studies.
    - Barbados Eye Study: Low diastolic OPP (<55mmHg) was a risk factor for the development of glaucoma (relative risk: 3.2).
    - Baltimore Eye Survey: Subjects with low diastolic OPP (<30mmHg) had a 6x increased open-angle glaucoma (OAG) prevalence.
    - Singapore Malay Eye Study: Low diastolic blood pressure (BP), low mean OPP, and low diastolic OPP are independent risk factors for OAG development.
  - Glaucoma prevalence decreases as diastolic perfusion pressure increases (Egna Neumarkt study).
  - Low diastolic and high systolic BP are associated with an increased prevalence of primary OAG (POAG) (J-shaped curve) in the Los Angeles Latino Eye Study.
- **Increased Progression of Glaucoma and Low OPP:** Early Manifest Glaucoma Trial: Low OPP (<125 mm Hg) significantly increased the risk of progression of glaucoma, and higher OPP (>160 mmHg) was protective. Follow-up: 11+ years.
- **Nocturnal Hypotension and NTG:**
  - Ramin et al NTG study:
    - Low nocturnal diastolic OPP is an independent predictor of glaucomatous visual field (VF) progression in NTG patients.
    - No difference in comorbidities such as systemic hypertension, diabetes, or medication class of hypertension treatment
    - The progressing group had significantly lower diastolic BP and diastolic perfusion pressure (day, evening, and night).
    - No significant difference detected in 24-hour IOP
    - No difference in the nocturnal dip percentage in the progressing group
  - Nocturnal dips of BP are a result of diminished sympathetic nervous system activity during sleep and are physiologic. They are protective against cardiovascular mortality (MI, CVA, CHF).
  - Approximately 10% of people have <10% decrease in BP at night and are labeled "***nondippers***." Nondippers have an increased risk of cardiovascular mortality, particularly if they are hypertensive.
  - Even though IOP increases with supine position, true OPP increases by approximately 15 mmHg when changing from standing to supine position as the eye aligns horizontally with the heart. Typical nocturnal dips of BP of 10-20 mmHg should not result in ischemic injury in normal eyes.
- **Glaucoma progression and nocturnal BP:**
  - Greater dips in nocturnal BP may be related to glaucoma progression.

- Nocturnal OPP and diastolic and systolic BP were lower in NTG vs. Controls
- NTG and HTG patients with VF progression had lower nocturnal BP and greater nocturnal dips of BP.
- Nondippers and extreme dippers were more likely to progress than those with a normal dipping pattern.
- Nocturnal overdipping was more likely to result in VF progression in patients with normal BP rather than hypertensives.
- POAG patients with nocturnal BP dips demonstrated reduced retrobulbar blood flow parameters.
- **Disc hemorrhages and Blood pressure:** Nocturnal overdippers have an increased risk of optic disc hemorrhages.

- **Causes of Systemic Hypotension:**
  - Overtreatment of systemic hypertension
  - Poor hydration
  - Natural phenotype: cold hands and feet, migraine, thin, young to middle-aged women
  - Impaired Auto-regulation:
    - Longstanding hypertension may lead to atherosclerosis, increased vascular resistance, and impaired vascular autoregulation.
    - Impaired autoregulation may also develop in many situations including medication use, diabetes, and glaucoma.
    - The Baltimore Eye Survey demonstrated that young hypertensives had a lower prevalence of POAG than nonhypertensives, while older hypertensives with assumed impaired autoregulation had higher prevalence compared to nonhypertensives.
- **Management of OPP:**
  - **Circadian OPP Measurement**: 24 hours
    - Triggerfish contact lens device
    - Ambulatory BP measurement: Medtronics
  - Lowering IOP is our best-studied mechanism for increasing OPP.
  - Avoid extreme nocturnal dips.
  - Avoid nocturnal peak response of antihypertensives.
  - Consider alternatives to calcium channel blockers in the treatment of hypertension.
  - Encourage patients to stay hydrated.
  - Consider alternatives to topical beta blockers in patients with systemic hypotension, encourage punctal occlusion and eyelid closure for 3 minutes after dosing topical beta blockers.
  - Treatment of Systemic Hypertension May Increase Glaucoma Progression

- Aggressive BP lowering in glaucoma patients may cause a drop in OPP and ischemic injury, which was also found to be a significant risk factor for glaucoma in large epidemiologic studies.
- Treatment may lower BP below a level that can autoregulate, resulting in a drop in OPP and ischemic injury.

Sleep Apnea (OSA) and Glaucoma

- Moderate association seen in the clinical studies and administrative databases
- Mechanism ***unclear***
  - IOP: Evidence suggests IOP drops during apneic episodes.
  - Hypoperfusion
  - Hypoxia
- No evidence that treating sleep apnea retards glaucoma progression
- **Types of Sleep Apnea**
  - Obstructive: Most common, Caused by a blockage of the airway when soft tissue in the back of the throat collapses during sleep
  - Central: Much less common, Unstable respiratory control center
- **Prevalence**: Adult prevalence: 3%-7% have OSA with daytime somnolence, but over 1/4 of individuals have multiple episodes of apnea on sleep studies, 2%-3% of kids (10%-20% with chronic snoring)
- **Risk factors**
  - Male
  - Over 40
  - Overweight
  - Large neck size: 17 inches in men, 16 inches in women
  - Large tongue or tonsil relative to jaw
  - Family history of sleep apnea
  - Nasal obstruction (deviated septum, allergies, sinus disease)
- **Impact of sleep apnea on general health:** High blood pressure, Stroke, Heart failure, arrhythmia, infarction, Diabetes, Depression, Exacerbation of ADHD, Headaches, ***Glaucoma***

Gonioscopy vs OCT in Angle Closure

- **Gonioscopy for Angle closure**
  - Widely used, various approaches, Goldmann-style lenses vs. 4-mirror lenses
  - **Advantages of gonioscopy**
    - Allows visualization of peripheral anterior synechiae
    - Allows pigment to be seen

        - Compression is fairly straightforward.
    - **Disadvantages of gonioscopy**
        - Patient discomfort
        - Possible infection, corneal abrasion
        - Subjective, significant variation between observers and possibly intraobserver variation
        - Difficult to document in the medical record photographically
        - Need for illumination and eye contact
            - Light falling on the pupil can result in opening of the angle.
            - Touching the eye can compress the angle open, even with Goldmann lenses.
- **OCT for Angle closure**
    - Many devices, no clear standard imaging approach
        - Spectral domain OCT
        - Swept source OCT
    - **Advantages of OCT**
        - Minimal illumination required, so angle maximally closed
        - No compression required
        - No drops needed
        - Potentially automated assessment of angle structures
        - Allows for categorization of principle causes of angle closure
            - Pupil block
            - Peripheral iris crowding
            - Lens vault
            - Others
        - Highly reproducible
        - Images are able to be stored; could be integrated into artificial intelligence algorithms
    - **Disadvantages of OCT**
        - Difficult to image superior angle
        - Costly
        - Currently seems to over diagnose
- **Conclusion**: Currently, gonioscopy remains a reference standard for angle closure diagnosis. As the field evolves further, future looks promising for OCT-based angle assessment.

Cornea & Glaucoma Dilemma

- **Complex Interaction**
  - Glaucoma medication can thin the cornea, causing a slight underestimation of IOP.
  - Ocular surface disease is common in the age group that develops glaucoma.
  - Glaucoma medication exacerbates ocular surface disease.
  - The preservatives in glaucoma medication exacerbate ocular surface disease.
  - Glaucoma medication can cause ocular surface disease (drug allergies and pseudopemphigoid).
  - Elevated IOP reduces the corneal endothelial cell count.
  - Glaucoma surgery may exacerbate corneal endothelial cell loss.
  - Early laser may protect the ocular surface and endothelium against the long-term effects of medical therapy.
  - In recalcitrant cases, laser may be an alternative to incisional surgery.
- **Corneal problems after Glaucoma**
  - Delle
  - Infections: keratitis from sutures
  - Astigmatism
  - Corneal endothelial decompensation
  - Corneal Edema After Glaucoma Surgery: Surgical insult, Hypotony, Disrupting natural flow inside anterior chamber, Damage from tube
- **Glaucoma after Corneal Surgery**
  - Medically treated glaucoma is worse due to angle closure or reduced outflow or because of steroid response.
  - Surgically treated glaucoma is worse due to occlusion, angle closure or steroids.
  - PKP: distorted angle structure or closure
  - DALK: distorted angle structure
  - EK: pupillary block or steroids
  - Keratoprosthesis: Angle closure or steroids

Glaucoma in Marfans

- Glaucoma in Marfan's syndrome is due to angle anomaly including thickened trabecular sheets, decreased outflow facility along with scleral-TM collapse (Low rigidity); anterior iris insertion and iris processes make up the juvenile angles. Associated ectopia lentis and lens induced glaucomas contribute.
- Incidence of glaucoma in Marfan's syndrome is about 5%. Suggested first treatment is Goniotomy/ Trabeculotomy in newborn glaucoma variant and Augmented Trabeculectomy in juvenile variant.

- Glaucoma Drainage Device (GDD) is the current preferred practice for a patient with juvenile age with failed trabeculectomy and aphakia.

Weinreb's 5 R

Weinreb's 5 R for Disc Assessment

1. Observe the scleral **Ring**
2. Identify the size of the **Rim**: ISNT Rule
3. Examine the Retinal nerve fiber layer **RNFL**
4. Examine the **Region** of parapapillary atrophy
5. Look for **retinal** and optic disc hemorrhages

Weinreb's 5 R for Visual Field

1. **Right** test
2. **Reliability**
3. **Review** probability plots
4. **RNFL** pattern of loss
5. **Re-affirm** the diagnosis

True Exfoliation Syndrome

- Capsular delamination
- Elschnig: condition in glassblowers, leading to the term glassblower cataracts, and it was subsequently found that extended exposure to infrared radiation in a variety of occupations
- Glaucoma is not a common feature

Glaucoma versus red disease

- Imaging: Optical coherence tomography (OCT), confocal scanning laser tomography (CSLT), scanning laser polarimetry (SLP) and photographic imaging of the optic nerve head (ONH) data are green or red suggesting normal or abnormal. Because of normative database limitations, a small population of normal patients is excluded from the normative database because they are not completely 'normal'. These patients may have abnormal test results on imaging yet might have no disease.

Pregnancy and Glaucoma

- All anti-glaucoma medications are categorised as class C by the Food and Drug Administration, except brimonidine and nonspecific adrenergic agonists, which belong to class B.
- **Intraocular Pressure and Pregnancy:**
- Pregnancy has been associated with about a 10% decrease in IOP in healthy eyes.

- **Mechanism**
  - Uveoscleral outflow increases as a result of changes in hormone levels.
  - Acidosis during pregnancy could theoretically alter aqueous humor production, but aqueous humor flow rate remains consistent during pregnancy.
  - Increased measurement error: softening of corneoscleral envelope to produce reduced corneoscleral rigidity
- ***Visual Field in Pregnancy***: bitemporal contraction, concentric contraction, and enlarged blind spots.
- In patients with narrow angles, angle-closure glaucoma may be precipitated during labor.
- **FDA Use-in-Pregnancy Ratings (A-X)**
  - "A": Controlled studies show no risk.
  - "B": No evidence of risk in humans
  - "C": Risk cannot be ruled out.
  - "D": Positive evidence of risk.
  - "X": Contraindicated in pregnancy
- **MEDICAL THERAPY**
- **BAK**: minor sternal defects occurred in fetuses exposed to a single dose of 100 and 200 mg/ kg.
- **Topical beta-blockers: Pregnancy Category C**
  - Betaxolol is the only relatively beta-1 selective beta-blocker commercially available. It is safer to use than the
  - Nonselective beta-blockers during late pregnancy.
  - Nonselective: bradycardia, cardio-respiratory symptoms
- **Prostaglandin analogs: Pregnancy Category C**
  - Bimatoprost 0.01%, 0.03% (Lumigan) Latanoprost 0.005% (Xalatan)Tafluprost ophthalmic solution 0.0015% (Zioptan) Travoprost 0.004% (Travatan Z)
  - Same class of medication used to induce labor at much higher doses
  - Embryocidal at high doses in animals. No human studies.
- **Carbonic Anhydrase Inhibitors: Pregnancy Category C**
  - Oral Carbonic Anhydrase Inhibitors: forelimb anomalies, SCT
  - Topical Carbonic Anhydrase Inhibitors: decreased weight gain
- **Cholinergic agents: Pregnancy Category C**
  - Pilocarpine HCl 1%, 2%, 4% and pilocarpine HCl gel 4%
  - Carbachol 0.75%, 1.5%, 3%
  - Teratogenic and adverse fetal effects in animals
  - Use of systemic cholinergic drugs in the first 4 months of gestation found no association with congenital abnormalities.
- **Sympathomimetics: Pregnancy Category B**

- Sympathomimetics: category B
- Congenital cataract with epinephrine

- **Alpha-2 agonists: Pregnancy Category B**
  - Apraclonidine HCl 0.5%, 1% (Iopidine)
    - Not used for chronic treatment due to development of tachyphylaxis and allergy
    - High doses in animals are embryocidal.
  - Brimonidine tartrate 0.1%, 0.15%, 2% (Alphagan)
    - High doses in animals did not reveal fetal damage.
    - Nursing mothers: Brimonidine is secreted in breast milk and causes apnea in infants. It should be discontinued at delivery in patients planning to breast feed.
- **5-Fluorouracil: Pregnancy Category X**
  - Known teratogenic effects-birth defects and miscarriage reported with topical use of 5-FU on mucus membranes
- **Mitomycin C: Pregnancy Category X**
  - Known teratogenic effects in animals. Safe use in pregnant women has not been established.

- **SURGICAL MANAGEMENT**
  - Laser trabeculoplasty
    - May be a good choice for temporary control during pregnancy
    - Usually not a long-term solution in this age group
  - Trabeculectomy and other procedures
    - Best done prior to pregnancy to minimize risk
    - Most local anesthetics have not been shown to be teratogenic
    - Exposure to antifibrotic agents
    - If patient is or may be pregnant at the time of surgery avoid antifibrotic agents.

Improving Daily Life of Glaucoma Patients

- Five “D”
- **Daily Activities**
  - Recommend increased lighting in the home
  - Low vision managements
  - iPhone/iPad applications for low vision patients (eg, Magnifier, Ariadne GPS, LookTel Money Reader, Voice Brief, VoCal)

- Strategies to maximize reading skills (eg, eccentric viewing, scanning)
- Environmental modifications (eg, organization and marking strategies, contrasting colors)

- **Driving**
  - Increased risk of motor vehicle collisions compared to drivers without glaucoma
  - Consider restricted driving for select patients (eg, daytime driving only).
- **Disability from Falls**
  - Glaucoma patients have almost a 4-fold increased risk of fall
  - Consider changing bifocal or progressive corrective lenses to separate distance and reading glasses.
- **Dual Sensory Loss**
  - The compounded effects of hearing and vision impairment increase a patient's risk for depression and poor overall well-being compared to single sensory loss alone.
- **Depression**
  - Along with glaucoma, other additional factors for depression, including older age, chronic comorbidities, disability, retirement, and bereavement

Environmental Risks & Modifications in Glaucoma

- Black currant anthocyanins reduce risk of glaucoma compared to conventional therapy alone
- Oral antioxidant supplements with or without omega-3 fatty acids are not a useful adjunctive treatment for mild / moderate glaucoma in the short term
- Ginkgo biloba had no effect on mean defect or contrast sensitivity in normal-tension glaucoma patients
- **Dietary patterns / food groups**
  - Mediterranean diet: Improves insulin resistance, which may be important in some glaucoma subtypes
  - Ketogenic diet (low carbohydrate, high protein, high fat, with the latter 2 sourced from vegetables): Improves energy biogenesis in the optic nerve head
  - Leafy green vegetables: Excellent source of nitrates, which may improve nitric oxide signaling in glaucoma
- **Nutrients / supplements**
  - Resveratrol: Multiple mechanisms implicated in experimental glaucoma
  - Niacin: Improves mitochondrial dysfunction in experimental glaucoma
  - Coenzyme Q10: Along with vitamin E, showed improved pattern electroretinogram function in open-angle glaucoma
  - Ginkgo biloba: Improves vascular function
- **Other lifestyle factors**

- Sleep: Keep head elevated and avoid sleeping with worse eye in dependent position; this lowers IOP and reduces visual field progression.
- Exercise: Lowers IOP; may depend on the type of exercise (aerobic vs. isometric vs. toning)
- Maintain oral hygiene: Reduces neuroinflammation
- Maintain a healthy weight for age, sex, and height: Mechanism unclear
- Protect the eyes from solar exposure: May be important in exfoliation glaucoma

- **Environmental Exposures for Glaucoma Patients to Consider Avoiding**
  - Head-down yoga postures are documented to produce marked elevation of IOP.
  - Prolonged playing of high wind instruments increases IOP transiently during play.