This lecture consists of a detailed review of primary open angle glaucoma and analysis of the glaucomatous disc. While acknowledging that many audience members will have some familiarity with this material from prior training and clinical experience, it is imperative that the most up-to-date information be conveyed to all audience members. Please remember that there is nothing in this presentation that supersedes interactive discussions with the audience or answering questions that arise during the lecture. Please join in our discussions, and refer to this information later as a resource or as a way to solidify your understanding of the various conditions.

Playing the Glaucoma Game

Goal: To delay the progression of the disease so that the patient still has vision when they die.

What was glaucoma?

- High IOP: At one time, everyone with IOP>21 mm Hg was diagnosed with glaucoma and medicated ad infinitum. There still people medicated for years who truly do not have glaucoma.
- Optic nerve anomalies: ONH hypoplasia, coloboma, buried drusen, optic pit, tilted disc, obliquely inserted disc, congenitally full disc, chubby disc, etc. Misdiagnosis.
- Neurological diseases: optic atrophy, chiasmal syndromes, compressive lesions of the anterior visual tract. Another misdiagnosis.
What is Glaucoma?
1. Glaucoma represents a group of ocular conditions in which the level of intraocular pressure damages the optic nerve causing a loss of visual function.

2. An optic neuropathy characterized by a pathological process called cupping. Cupping is a type of optic atrophy which produces nerve fiber layer defects which results in visual field defects often associated with elevated IOP.

3. Primary open angle glaucoma is a progressive, chronic optic neuropathy in adults where intraocular pressure and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This is associated with an anterior chamber angle that is open by Gonioscopic appearance.

How Does Glaucomatous Damage Happen?

Theories
- Mechanical compression
- Ischemic vascular
- Excitotoxicity of neural cells
- Genetically pre-programmed cellular suicide

Mechanical Compression:
- Pressure related distortion of the fibers themselves.
- Glaucoma usually presents with vertical cupping patterns from damage at the superior and inferior aspect of the optic disc. Differing degrees of physical support to the fibers passing through the lamina at the superior and inferior aspect of the disc would be expected to give this type of cupping pattern.
- Increased IOP causes stretching of lamina connective tissue. This, in itself, is not bad. However, in glaucoma, it leads to other possible disturbances of the optic nerve, which are pathological.
- Glaucoma is a disease where the connective tissue collapses on itself.
- Elevated IOP and/or defects in the extracellular matrix cause compression and distortion of the lamina cribrosa. This impedes the axoplasmic flow of neurotrophins (“survival factors”) to retinal ganglion cells.

Ischemic Theory
- Short posterior ciliary arteries (SPCA) feed the anterior optic nerve.
- Vascular stasis could cause ischemia to the optic nerve head and cause death of tissue and cupping.
- If a patient is vascularly compromised though atherosclerosis and arteriosclerosis, then the SPCA could be compromised leading to ischemia and loss of neural tissue. This is supported by the fact that most glaucoma patients are older and vascularly challenged.
• Axonal transport is interrupted by ischemia
• Increased IOP compresses vessels with lower intraluminal pressure
• Blood flow is maintained in the face of elevated IOP by autoregulatory mechanisms in most people.
  • When IOP is high, arterioles and capillaries dilate
  • When IOP is low, arterioles and capillaries constrict
  • All mechanisms keep blood flowing in the face of variable IOP
• In glaucoma, there may be faulty autoregulatory mechanisms which results in blood flow impedance.
• Optic nerve head perfusion may be affected by increased IOP and dysfunctional autoregulatory mechanisms of blood flow.
• Localized ischemia may result in decreased metabolic activity and accumulation of extracellular exotoxins such as glutamate.
• Localized ischemia may also result in deprivation of neurotrophins and retinal ganglion cell death due to disruption of axonal transport.

Excitotoxicity Theory
• Amino acid glutamate is an excitatory neurotransmitter in CNS & retina
• Glutamate, at low levels, is a neurotransmitter in the retinal ganglion cells
  • At high levels, it is a neurotoxin to retinal ganglion cells
• High levels of glutamate may occur due to neurotrophin deprivation, neuronal vascular compromise, and/or improper Muller cell metabolism secondary to elevated IOP
• Traumatic and ischemic neuronal injury can be mediated by excessive levels of excitatory neurotransmitters, including glutamate
• Glutamate acts on glutamate receptors (N-methyl-D-aspartate) in the neurons, which opens sodium channels, which increases the intracellular calcium levels to toxic levels by opening calcium channels in cell membrane. This activates the enzyme nitric oxide synthase, which leads increases in nitric oxide and to the formation of destructive free radicals. This results in retinal ganglion cell death. This is an early step in the sequence that programs a cell to die.
  • There are human and animal studies indicating excessive glutamate in glaucoma
• Glutamate may be released from retinal ganglion cells in a mechanical or pressure induced phenomenon
• Glutamate blockers (NMDA) are being investigated to stem retinal toxicity
• When cells die, glutamate is released into retinal extracellular space, which kills adjacent healthy cells.
• Excess glutamate may be a cause of glaucoma or and epiphenomenon of glaucoma

Cellular Suicide: Apoptosis
• Apoptosis: “To prune”
  • At 3 months gestation, there are 3 million ganglion cells. At one year, there are only 1-1.2 million axons. What happened?
  • The cells spread back to the brain. Only 1 million reach the lateral geniculate
nucleus and receives, via retrograde flow, neurotrophic growth factors, which allow survival, and prevents these cells from ‘committing suicide’. The other 2 million ganglion cells do not reach their goal, do not receive neurotrophic growth factors that allow survival, and, as a result, commit suicide. In this case, apoptosis cleans up the nervous system. Apoptosis is programmed cell death.

- Nerve growth factor tells the cells to stay alive. If nerve growth factor is not present, the cell undergoes apoptosis. Neurotrophin deprivation (and/or glutamate toxicity) seems to be the inciting event in apoptosis.
  - Brain-derived neurotrophic factor (BDNF) nourishes retinal ganglion cells via retrograde axonal transport to the retina
  - Glaucoma interrupts axonal transport (either through ischemia or compression or both)
  - Elevated IOP blocks axoplasmic transport
  - Ischemia also blocks axonal transport
- Cells don’t get nerve growth factor
- Cells commit suicide
  - There is secondary collateral damage
  - Cells shrink
  - Nucleus condenses
  - Cell utilizes energy in order to die
  - The cell itself expresses the genetic components necessary for its own demise. This appears to be an active process. It is also fast; < 8 hours.
    - Cellular damage activates a protein called p53
  - This protein controls cellular levels of 2 key genes, bcl-2 (inhibiting apoptosis) and bax (promotes cell death)
    - Overexpression of bcl-2 inhibits apoptosis
    - These genes affect a protein called cytochrome c, which is released by mitochondria, causing activation of internal proteases called caspases, which digest cellular components
  - Nothing is extruded into extracellular matrix, thus no inflammation.
  - Macrophages digest the dead cellular components
- Retinal ganglion cells undergo apoptosis during fetal development and throughout life to ensure homeostasis and proper retinal development. Glaucoma is an abnormal expression of apoptosis.

**Genetics: TIGR/myocillin gene**
- The TIGR/myocillin protein influences extracellular flow mechanics in the meshwork.
- TIGR (trabecular meshwork inducible glucocorticoid response) is an olfactomedin-related glycoprotein that is localizable to the inner portion of the trabecular meshwork and appears to exhibit increased expression in glaucoma.
The Pathophysiology of Glaucoma as We Know it Best Today:

Elevated intraocular pressure affects the optic nerve in two ways. First, it deforms the lamina cribrosa, which may directly physically impinge ganglion cells or blood vessels (or both). Second, it impairs blood flow to the optic nerve head in susceptible individuals who have poor blood flow compensatory autoregulatory mechanisms. This will all block axonal transport from the brain to the ganglion cells. This deprives the ganglion cells of nerve growth factor (brain derived neurotrophic growth factor). When this deprivation of a vital nutrient occurs, the cell doesn’t receive the signal to ‘stay alive’ and the cell expresses its genetic potential for apoptosis. This causes internal enzymes to be turned on (in an energy-dependant process) which causes the ganglion cell to ingest its own DNA and phagocytize itself. Thus, it commits suicide. Also, the dying cells release excess amounts of glutamate into the extracellular space. This excess glutamate binds with receptors, which opens calcium channels on adjacent ganglion cells. This causes an excessive influx of calcium into the adjacent, healthy cells, which kills them. Additionally, through a pressure and/or ischemic phenomenon, there may be further release of glutamate (with intracellular calcium accumulation) with subsequent accumulation of nitric oxide (with formation of destructive free radicals), which are both toxic. This also stimulates additional cells to undergo apoptosis, and kill other healthy cells.

While these are all called ‘theories’ they are better termed ‘puzzle pieces’ which, when put together correctly (along with some other pieces that we do not yet have) give the picture of glaucoma. While historically, experts have embraced one theory or another, it is now seen that everything fits together and is not mutually exclusive.

Enough of the Research Theories: Let’s Get Clinical!

Glaucoma: Clinical

- A constellation of risk factors in addition to loss of neural tissue with progressive disc damage
- Progressive loss of visual field
- Risk factors make this a multifaceted disease.
- While technically glaucoma is a disease characterized by progressive disc damage and progressive field loss, diagnostic dilemmas and contradictions exist. In early cases, the progressive nature is crucial in making the diagnosis. Therefore, in these cases, sequential visual field examinations and optic nerve head photos are often required in order to demonstrate the progressive nature of the disease. However, in advanced cases, where the patient presents with elevated IOP, optic nerves with obvious glaucomatous changes, and advanced visual field defects consistent with glaucoma, the diagnosis is often made upon the initial visit (without waiting to demonstrate progression). Also, there are a number of conditions (e.g. inflammation, pigment dispersion, etc.), which produce an elevation in IOP and are termed
secondary glaucomas, though there may be no field defect or optic nerve defect at the time of diagnosis. So, while not technically glaucoma based on the definition of progressed field loss and ONH damage, they are termed glaucoma because, in our best medical opinion, these pathological changes will likely occur if the IOP is not reduced.

Clinical Pearl: When dealing with diseases such as uveitis and the IOP elevates to abnormal levels, the condition is typically called glaucoma (in this case, uveitic glaucoma) even though all the criteria for diagnosing true glaucoma may not be yet present.

Ocular Hypertension (OHTN)
- Ocular hypertension is defined as IOP of 21 mm hg or more in the absence of structural and functional changes
- The Myth of 16 and 21
- The Ocular Hypertension Treatment Study (OHTS) has recently shown that approximately 10% of patients with ocular hypertension convert to true glaucoma over the course of 5 years
- There are far more patients with OHTN than glaucoma
- Prevalence increases with age
  - 75% of ocular hypertensives are over 60 yrs.
  - 24% of people over 70 yrs may be ocular hypertensives

Glaucoma Suspect
- Elevated IOP
- Suspicious disc appearance
- Family history of glaucoma
- Age
- Race
- Suspicious visual field loss
- Suspicious nerve fiber layer (NFL)

Epidemiology of Glaucoma
- 0.41-0.86% of Americans over 40 years have glaucoma (1-3 million Americans)
- 1 million undetected
- 95,000/yr lose sight
- #2 cause of blindness
- #1 cause in non-whites
- Approximately 4% of glaucoma patients become blind
  - However, not everyone with glaucoma has a 4% risk of becoming blind – some may be much higher or lower
- Prevalence of ocular hypertension is always greater than glaucoma
- Prevalence of glaucoma increases with age
Primary Open Angle Glaucoma (POAG)
- Most prevalent type of glaucoma
- Idiopathic
- Poor outflow of aqueous
- Typically elevated IOP (decreased outflow, not increased inflow)
  - Level of IOP is inconsistent with health of optic nerve in that individual
  - Ability to tolerate a certain level of IOP varies between patients and within the same patients as they age
- Characteristic glaucomatous neuropathy
  - Rim notching
  - NFL defects
- Characteristic visual field loss
- Angles open by gonioscopy
- No secondary cause: this must be established before POAG can be diagnosed. There still are cases where there is a secondary cause that has not correctly been identified.

Histopathology of Glaucoma
- Anterior Segment
  - Accelerated and exaggerated normal aging changes in anterior chamber angle.
  - Affects both Schlemm’s canal and uveoscleral outflow pathways.
- Posterior Segment
  - Early Changes
    1) Compression of laminar sheets
    2) Distortion of laminar pores
    3) Blockage of axonal transport
       a. IOP induced (?)
       b. Vascularly induced (?)
    4) Death of ganglion cells
    5) Deepening and enlargement of optic cup
  - Later Changes
    1) Additional compression of laminar sheet
    2) Posterior and lateral displacement of laminar sheet

POAG: Pathophysiology
- Truly unknown and likely to involve mechanical features, ischemia, excitotoxicity, genetic apoptosis expression, neurotrophin deprivation, oxygen free radicals, nitric oxide generation, and lipid peroxidation (as discussed above).

POAG: Diagnosis
- ONH and nerve fiber layer damage consistent with glaucoma
- Visual field loss consistent with glaucoma
- Progression
- IOP inconsistent with optic nerve health
- Other risk factors
  - Age, race, family history
POAG: Visual Field Defects

- Increased short term fluctuation
- Small, shallow, fluctuating scotoma
- Nasal step
- Arcuate depressions
- Sensitivity depression
- Paracentral scotomas
- Superior-inferior asymmetry
- 90-93% of all field loss in glaucoma occurs within the central 30 degrees
- Visual field defects are reflected by damage to the optic disc and nerve fiber layer

Clinical Pearl: Glaucoma is not a disease where the patient loses peripheral vision as most doctors describe. In fact, most field losses are within the central 30 degrees.

Clinical Pearl: A patient can be ocular hypertensive due to IOP above 21-mm hg with normal nerve functions. A patient can also be a glaucoma suspect due to elevated IOP, large C/D ratio or otherwise suspicious optic nerve appearance, loss of nerve fiber layer, positive family history, race, or a combination of other risk factors.

Risk Factors for Developing POAG:

- Elevated IOP: This is the most significant risk factor overall
- Age
- Race (1/8 blacks over age 60 develop glaucoma)
  - Earlier onset
  - More aggressive course
  - Especially aggressive in patients of Caribbean descent
- Corneal thickness (i.e., thin central cornea)
  - Thick corneas overestimate true application pressure and thin corneas underestimate true application pressure. However, beyond errors imparted by application, patients with thin corneas have greater risk of converting to glaucoma from ocular hypertension, are more likely to progress in glaucomatous damage, and are more likely to have structural and functional changes.
  - Possibly indicative of other structural weaknesses within the eye predisposing to glaucoma, but this is only speculative and not proven
  - Don’t know if thin cornea in normal populations is risk factor alone, thus checking corneal thickness on every patient is not indicated
- Family hx.
- Diabetes(?)
  - Recently questioned by the OHTS study
- Hypertension (HTN)
  - Causing vascular compromise
- Hypotension
  - Causing poor ONH perfusion
- Carotid artery disease
  - Causing poor ONH perfusion
- Cardiac disease

**Risk Factors (Elevated IOP): Development of Glaucoma**

- Mean IOP 16 +/- 2.5 mm hg
- IOP which is statistically abnormal is not necessarily physiologically abnormal for an individual eye
- There is no clinically useful level of IOP to differentiate all normals from all people with glaucoma
- Patients with advanced glaucoma may not be able to tolerate even moderate levels of IOP
- Ocular hypertension is a risk factor for glaucoma, not a prerequisite
  - The level of IOP which causes damage to an optic nerve varies significantly between individuals and even in the same person as she/he ages
- 1/3-1/2 of all glaucoma patients shows IOP below 21 mm hg on a single visit. If you do nothing other than measure IOP for the detection of glaucoma, you will miss 1/3-1/2 of the glaucoma cases in your office.
- Pressure above 30 mm hg should be reduced due to a greater risk of developing glaucoma (popular thinking)
  - However, this is debatable in patients with thick corneas
- IOP increases with age
- IOP decreases with exercise (transiently)
- Increased blood osmolarity decreases IOP (mannitol, glycerin, alcohol)
- Must consider corneal thickness (OHTS study)
  - Thinner corneas have been associated with an increased risk of developing glaucoma
    - Factor of underestimating true IOP by Goldmann applanation?
    - Problems with connective tissue making eye more susceptible
    - It has been shown that a thin cornea is itself a risk factor for the development of glaucoma independent from its impact on applanation tonometric measurement

**Clinical Pearl: Elevated IOP is the single greatest risk factor for the development of glaucoma.**

**Elevated IOP**

- Drainage problem
  - Outflow resistance at trabecular meshwork and Schlemm’s canal.
- Closed angle
- Idiopathic
- Angle debris: inflammation or pigment dispersion
- Increased episcleral venous pressure: carotid cavernous fistula, cavernous sinus thrombosis, or idiopathic
- Almost never due to increased aqueous production (except for glaucomatocyclitic
Diurnal Variation of IOP

- < 5 mm = normal
- > 5mm = abnormal; but only a risk factor
- Ocular hypertensives: 9 mm
- Glaucoma patients: 15 mm or more
- In glaucoma patients, a high diurnal variation was seen as a risk for progression
- It was once thought that IOP peaked in the morning and decreased throughout the day. It was also thought that IOP dropped during sleep due to aqueous production suppression; however, we have recently learned that the highest IOP may well be when the patient is sleeping in the supine position.

Clinical Pearl: COMBINED ASSESSMENT OF IOP, ANTERIOR CHAMBER ANGLE ANATOMY, OPTIC NERVE, NERVE FIBER LAYER AND VISUAL FIELD FUNCTION IS ESSENTIAL FOR THE DIAGNOSIS AND MANAGEMENT OF OCULAR HYPERTENSIVE AND GLAUCOMA PATIENTS.

POAG: Final Rules

- Take the appropriate amount of time and collect the appropriate amount of information prior to making a diagnosis. Do not rush to make a diagnosis.
  - Don't rely on a single field
  - Don't rely on a single tonometry
- Insist that the nerve match the field
- Don't forget gonioscopy
- Don't neglect other causes
  - Undiscovered secondary glaucoma
  - Meds - both past and present
  - It may not be glaucoma!

Clinical Pearl: You cannot accurately diagnose or categorize any glaucoma unless you do gonioscopy.

Clinical Pearl: Glaucoma is generally a disease of months and years, not days and weeks. Do not rush to a diagnosis without collecting the appropriate amount of information.

Update on Glaucoma Clinical Trials:

Advanced Glaucoma Intervention Study (AGIS)¹

- To determine the long range outcomes of glaucoma surgery in advanced cases that have failed medical therapy. Enrolled 776 eyes of 581 patients
- Looks at both trabeculectomy and trabeculoplasty
- ATT vs TAT protocols
  - Argon Trabeculoplasty- Trabeculectomy- Trabeculectomy or
Results:
- Black patients with advanced glaucoma should receive laser first.
- White patients with advanced glaucoma should receive surgery first.

Side arm of study looked at role of IOP reduction
- Patients were grouped into categories based upon the percentage of study visits where the IOP was below 18 mm Hg. In each group, an average IOP was determined.
- Patients with average IOP > 17.5 mm Hg had more worsening of visual fields than those with average IOP < 14 mm Hg.
- Patients who presented with 100% of study visits below 18 mm Hg had, on average, little deterioration of their visual fields over six years. The patients in this group had an average IOP of 12.3 mm Hg.
- Patients who had fewer than 50% of study visits in which IOP was below 18 mm Hg had much more significant visual field deterioration. These patients had an average IOP of 20.2 mm Hg.

Conclusion: Low IOP is associated with reduced progression of visual field defects.
- Recently, it was seen that a high diurnal variation was the most significant factor in predicting progression of the disease in this study.

Clinical Pearl: While the below 14 mm Hg group experienced visual field changes that were nearly zero, this represents an average change which incorporates patients who actually had improvement in their visual fields throughout the study. This means that there were also patients in this low-IOP group who did experience visual field deterioration. Please be aware that an IOP of 12-14 mm Hg does not guarantee that the patient will not experience further glaucomatous losses.

Early Manifest Glaucoma Trial (EMGT)\textsuperscript{1-4}
- Major Purpose of Study: To determine the most appropriate initial management for newly diagnosed, early stage glaucoma patients.
- The Early Manifest Glaucoma Trial -- followed 255 patients, aged 50-80 years, with early stage glaucoma in at least one eye.
- One group (129 patients) was treated immediately with medicines and laser (standard treatment of betaxolol plus argon laser trabecuoplasty) to lower eye pressure, and the other group (126 patients) -- the control group -- was left untreated.
- Both groups were followed carefully and monitored every three months for early signs of advancing disease, using indicators that are extremely sensitive for detecting glaucoma progression. Any patient in the control group whose glaucoma progressed was immediately offered treatment.
• After six years of follow-up, scientists found that progression was less frequent in the treated group (45 percent) than in the control group (62 percent), and occurred significantly later in treated patients. Treatment effects were also evident in patients with different characteristics, such as age, initial eye pressure levels, and degree of glaucoma damage. In the treated group, eye pressure was lowered by an average of 25 percent.

• Many of the patients remained stable over time, even those in the control group
• Despite the clear effect of treatment, glaucoma progressed in as many as 30 percent of treated patients after four years
• Worst representation of patients in any major study
  • All were Scandinavian
• The time it took for glaucoma to progress varied greatly among patients and was sometimes rather short, even in treated patients.
  • In many patients with rapidly progressing glaucoma, the treatment used in this study was insufficient to halt progression of the disease
  • Treatment for early, newly diagnosed glaucoma should be individualized and carefully balanced. Before deciding on the best treatment option, eye care professionals should consider several unique patient factors, such as age, eye pressure levels, and disease severity.
  • One option could include no initial treatment, but subsequent treatment if the disease progresses. Many glaucoma medicines have side effects, so the decision not to treat the disease in its early stage -- but closely monitor patients -- can postpone or obviate the need for medications.
• Progression was also increased with higher baseline IOP, exfoliation, bilateral disease, worse mean deviation, and older age, as well as frequent disc hemorrhages during follow-up.
• It was seen that each mm Hg pressure reduction imparted approximately a 10% reduced risk of further glaucomatous damage
  • Forces us to rethink treatment goals and what constitutes a clinically significant pressure reduction
• After longer follow up at the end of the EMGT study (up to 11 years, 8 years median)- cardiovascular disease (self reported), lower ocular systolic perfusion pressure in patients with higher IOP, lower systolic BP in patients with lower IOP, thinner CCT in higher IOP patients were seen as risk factors for progression.3,4
• At the very end of study, 67% of patients overall progressed (59% in treated patients vs. 76% in control patients)
• While disc hemorrhages were predictive of progression, IOP-reducing treatment was unrelated to the presence or frequency of disc hemorrhages. Disc hemorrhages were equally common in both the treated and untreated groups of patients. The results may suggest that disc hemorrhages cannot be considered an indication of insufficient IOP-lowering treatment, and that glaucoma progression in eyes with disc hemorrhages cannot be totally halted by IOP reduction. The results also suggest that disc hemorrhages do not occur in all patients with glaucoma.
• Of the 136 patients who showed evidence of progression
  • 86% reached endpoint by Visual Field changes alone
13% showed optic disc and visual field changes together
1 patient showed optic disc change

1. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression. Results from the early manifest glaucoma trial.

Ocular Hypertension Treatment Study (OHTS)1-2

- **Major Purpose of Study:** To determine if lowering IOP in patients with ocular hypertension delays or prevents development of glaucoma.
- **Notable feature:** OHTS is the first and only NEI funded ophthalmologic study that uses an optometrist as a principal investigator (G. Richard Bennett, O.D.)
- **The Ocular Hypertension Treatment Study (OHTS) is a long-term, randomized, controlled multicenter clinical trial. Ocular hypertensive subjects judged to be at moderate risk of developing primary open-angle glaucoma are randomly assigned to either close observation only or a stepped medical regimen. Medical treatment consists of all commercially available topical antiglaucoma agents. 1636 patients**
- In univariate analyses, baseline factors that predicted the development of primary open-angle glaucoma (POAG) included older age, race (African American), sex (male), larger vertical cup-disc ratio, larger horizontal cup-disc ratio, higher intraocular pressure, greater Humphrey visual field pattern standard deviation, heart disease, and thinner central corneal measurement. In multivariate analyses, baseline factors that predicted POAG included older age, larger vertical or horizontal cup-disc ratio, higher intraocular pressure, greater pattern standard deviation, and thinner central corneal measurement.
- Notably, the study concluded that that lowering IOP in patients with ocular hypertension reduced the risk of developing glaucoma in five years from 9.5% to 4.4%).1 Thus, IOP reduction in ocular hypertension did benefit some patients. However, it is also easy to see that initiating therapy on every patient with ocular hypertension would result in gross over-treatment.
- Topical ocular hypotensive medication was effective in delaying or preventing onset of POAG in individuals with elevated IOP. Although this does not imply that all patients with borderline or elevated IOP should receive medication, clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG.
- OHTS also attempted to identify which patients would most likely benefit from treatment.2 There were some surprising results. Surprisingly, the presence of diabetes seemed to protect patients from the development of glaucoma. Not unexpectedly, older age, larger initial cup-to-disc ratio, and higher IOP were predictive of glaucoma.
- However, the factor that was most predictive was the presence of a thin central cornea. Patients with a central corneal thickness of 555 µm or less had a three-fold greater risk
of developing POAG than those with a central corneal thickness of 588 µm or greater. The theory holds that the rigidity of a thick cornea artificially elevates the Goldmann applanation measurement of IOP and a thin cornea consequently lowers the reading of the true IOP, though other unknown factors may contribute to this finding.

- Central corneal thickness appears to be a powerful predictor of the progression from ocular hypertension to POAG. The study shows patients with thin central corneas are likely to benefit most from IOP reduction. Rarely are the conclusions of a landmark study so emphatic: At this time, measurement of central corneal thickness is necessary to accurately manage patients with ocular hypertension.

- It was recently reported in a follow-up paper that, in African American individuals with ocular hypertension, topical ocular hypotensive agents are effective in delaying or preventing the onset of POAG. Among African Americans in the study, 16.1% of the control group developed glaucoma while 8.4% of the treated group progressed.

- African Americans in the study had twice the risk of developing POAG despite similar baseline and treated IOPs

- Studies looking at glaucoma development or progression need study endpoints.
  - Typically, study endpoints are progression of visual field damage or progressive damage to the optic disc. The majority of patients in glaucoma studies reach the study endpoint with progressive damage to the visual field. Very few patients reach a study endpoint by demonstrating progressive damage to the optic disc. The OHTS study was unique in that the majority of patients reached the study endpoint by having progressive damage to the optic disc rather than progressive damage to the visual field.
    - Patients who converted to glaucoma
      - 55% had optic disc changes only
      - 35% had visual field changes only
      - 10% had both disc and field change

- A recent report from OHTS compared the rates of detection of optic disc hemorrhages by clinical examination and by review of optic disc photographs at the Optic Disc Reading Center. Further, an attempt was made to assess the incidence of and the predictive factors for disc hemorrhages in an effort to determine whether optic disc hemorrhages were predictive of the development of POAG.
  - Remarkably, 16% of disc hemorrhages were detected by both clinical examination and review of photographs, and 84% were detected only by review of photographs following clinical examination.
    - Thus, review of stereophotographs was more sensitive at detecting optic disc hemorrhage than clinical examination.
    - The occurrence of an optic disc hemorrhage was associated with an increased risk of developing POAG (as defined by the OHTS end points), though it must be acknowledged that 86.7% of eyes in which a disc hemorrhage developed have not converted to POAG to date.
      - Note: The development of a disc hemorrhage was not an endpoint or a signal of conversion to glaucoma (but it did increase the risk of conversion).

- Currently, OHTS II is underway. Essentially, the original patients will be followed until death. Additional features include genetic analysis and serologic studies.
Because of the risk of progression to glaucoma seen at 7-8 years, all patients are now being treated. One goal is to see if there is any difference between those patients treated early compared to those treated at the end of OHTS. Currently, all patients from the initial study are being treated.

- Problems with the OHTS: Certain eyes and patients should never have been included.
  - CCT was not initially considered. Thus, a lot of thick cornea eyes were enrolled and when applanation artifacts are considered, likely these eyes didn’t truly have elevated IOP. That is the reason that the thin cornea group (>555) is thicker than what is considered to be a population average (545).
  - There were eyes that had normal fields and were included, but actually had glaucomatous discs and not really OHTN

- The European Glaucoma Prevention Study was essentially the same study as OHTS, except that treatment was either 1 medication (dorzolamide) or placebo. Though the medication significantly lowered IOP, there was no difference in the conversion to glaucoma between the medication group and the placebo group.


Collaborative Normal Tension Glaucoma Study (CNTGS) 1-4
- Major Purpose of Study: To determine if IOP reduction affects the outcome of eyes with normal tension glaucoma (NTG)
- Randomized, controlled 5 year clinical trial (144 eyes) of the effectiveness of IOP reduction in slowing the progression of field loss in pts. with NTG.
- Inclusion criteria
  - Showed documented progression, high risk field defects that threatened fixation, or appearance of new disc hemorrhage
- Goal: 30% reduction from IOP baseline
  - Due to potential (theoretical) impact to optic nerve perfusion, adrenergic drugs such as beta blockers and epinephrine weren’t used. Alphagan and prostaglandins weren’t invented yet. Essentially, the only way that IOP was reduced in this study was with pilocarpine, laser trabeculoplasty, and trabeculectomy. Surprisingly, over half of the treated patients achieved the goal IOP reduction without having to undergo trabeculectomy.
- Results: 35% of control eyes (untreated) showed progression (glaucomatous optic disc progression or visual field loss) whereas only 12% of treated eyes showed progression.

Conclusion: Intraocular pressure is part of the pathogenic process of NTG. Therapy that reduces IOP and is free of side effects would be expected to be beneficial in patients who are at risk of disease progression.
Problems: 1. Which patients are at risk for disease progression? 2. While 35% of untreated eyes showed progression, 65% of untreated eyes did **not** progress.

Further Conclusions from CNTGS: Lowering IOP without producing cataracts is beneficial. Because not all untreated patients progressed, the natural history of NTG must be considered prior to embarking on IOP reduction with therapy apt to exacerbate cataract formation unless NTG threatens serious visual loss.

- According to the CNTGSG, those at risk of progression include:
  - Females
  - Those with history of migraines
  - Those manifesting disc hemorrhage
- Factors that were not associated with an increased risk of progression include:
  - Older age
  - Higher mean IOP
  - Field defects threatening fixation
- Factors associated with treatment benefit include:
  - No disc hemorrhage
  - Female gender
  - Family history of glaucoma
  - No family history of stroke
  - No personal history of cardiovascular disease
  - Less initial disc damage (C/D < 0.7/0.7)
- Factors not associated with treatment benefit include:
  - Male gender
  - Disc hemorrhage
  - Severely damaged discs
  - Migraine
- Clinical notes and curiosities:
  - Asian patients have less severe disease than Caucasians
  - Disc hemorrhage is strongly predictive of progression, yet doesn’t benefit from treatment
  - Females gender is strong factor for having NTG, progression of disease, and benefit of treatment
  - Female gender does NOT show up as risk factor in Ocular hypertension


**Glaucoma: The Optic Nerve Head Evaluation**

Despite the multifaceted nature of glaucoma and the array of diagnostic technologies available, the single most important aspect of glaucoma diagnosis and management is stereoscopic evaluation of the optic disc and nerve fiber layer. It is the goal of every good glaucoma practitioner to be able to diagnose glaucoma and judge disease progression based solely upon the appearance of the optic disc.

**Optic Nerve Head:**
- 1 million retinal ganglion cell axons
- Blood supply: mostly short posterior ciliary arteries (SPCA)
  - Central core blood supply is the small branches of the central retinal artery.
  - Peripheral prelaminar supply is the centripetal branches of the peripapillary choroid arising from the short posterior ciliary arteries.
  - The laminar portion is nourished by the Circle of Zinn-Haller, an anastamoses arising within the sclera of adjacent SPCA’s.
  - The peripheral part of the retro-laminar nerve is supplied by branches from the pia mater’s vascular plexus. This plexus is formed by branches from muscular arteries, the ophthalmic artery, and recurrent branches from the peripapillary choroid and the Circle of Zinn-Haller. SPCA supplies some extent of all portions of the nerve; the CRA supplies only the NFL and central core of the nerve.

**The Glaucomatous Nerve:**

**ONH: Cupping**
- Neural tissue vs. non-neural tissue (donut vs. hole)
- Axon, glial tissue, capillaries
  - Direct ophthalmoscopy has limited value due to magnification and monocularity.
  - Current teaching: the point of deviation of small blood vessels on the surface of the ONH should be used to determine the size of the cup (contour technique) rather than the area of pallor in the center of the disc (color-contrast technique)
  - Reality: the area of pallor in the center of the disc frequently corresponds well with the area of the cup. Use both techniques together. However, contour always wins out over color
- Average cupping: 0.4
  - As disc area increases, so does the average size of the C/D ratio
  - Due to inter-individual variation in disc size and cup size, the C/D ratio in normal patients can range from 0.0 to 0.9
• Symmetrical C/D ratio in 99.5% of normal population
• Progressive, concentric excavation in most glaucoma cases
  • Symmetrical increase in C/D ratio not common in glaucoma
    • Indicates diffuse ganglion cell loss from glaucomatous process
    • May not be associated with early visual field loss
    • Difficult to distinguish from physiological cupping
    • Considerable overlap in C/D ratio of normals, physiological cups, and glaucoma patients.
• Rim thinning: generalized loss of tissue
• Notching: focal loss of tissue. Corresponds exquisitely with field loss
• Saucerization: shallow enlargement of cup- very hard to detect in some cases, hence the need for contour judging rather than color judging.
• Bean potting
• No rim pallor - if this occurs, it is not glaucoma

Other diseases can cause “cupping”, though there will be other features inconsistent with glaucoma such as central acuity loss and disc pallor. Non-glaucomatous cupping include:
  • AION
  • Compression
  • Inflammation
  • Trauma
  • Hereditary
• Inferior, Superior, Nasal, Temporal (ISNT) rule. Any disc that breaks this rule of rim thickness is suspect.

**Clinical Pearl:** Increasing excavation and enlargement of the optic cup occurs most commonly in glaucoma, but can occur in arteritic anterior ischemic optic neuropathy and compressive lesions of the optic nerve such as sphenoid wing meningioma. However, in these last two cases, the neuroretinal rim typically will have pallor whereas glaucoma will not.

**Clinical Pearl:** If you think that you see a relative afferent pupil defect and the visual acuity is 20/20, you are likely wrong. If you are sure that you see a relative afferent pupil and the vision is 20/20, then it is likely to be asymmetric glaucoma. The reason is that glaucoma is the optic neuropathy most likely to preserve good vision.

**Clinical Pearl:** The appearance of the optic disc will most likely give you the greatest amount of information as to whether or not the patient has glaucoma.

**ONH: Rim Tissue**
• Pink coloration due to axons and capillaries
• Glaucoma: rim is always pink
• Pale cupping (pallor exceeding cupping): compressional lesion, ischemic vascular accident, neurological event.

Ode to a Cupped Disc:

Oh, to have a cupped disc pink,
That, my friend, hath a glaucomatous stink.
But to have a cupped disc pale,
Call this glaucoma and you will fail.

ONH: Notching
• Focal loss of tissue
• Vertical elongation
  • Axons loose in inferior and superior lamina- this is the reason for vertical elongation
  • Look for narrowing of neuroretinal rim superiorly and inferiorly
    • Inferior temporal or superior temporal (usually)
      • Inferior or superior in 2/3rds of cases
• NFL defect often associated
• Hemorrhage may be present or an antecedent event
• Typically associated with (dense) field defect
• 87% specific for glaucoma
• Occurs only from inside cup to inner rim. There may be patients who have an irregularity of the outer rim-this is not notching
• Nothing notches a rim like glaucoma

Clinical pearl: Notching does not occur commonly on the temporal or nasal aspect of the disc. Temporal thinning of the disc is most commonly an anomaly of disc insertion and not glaucoma. The term “temporal thinning”, in the absence of other glaucomatous disc changes, is meaningless.

ONH: Hemorrhages
• NFL, splinter, Drance, disc
• Typically occurs where notches occur
• Ischemic or mechanical
  • Probable infarction of the blood supply to the ONH
• Occurs 2-23% of glaucoma cases
• Resolves within 6 weeks. This is the reason that the incidence is difficult to determine.
• Can be recurrent and, if it recurs, it typically is in the same place on the disc each time
• Precedes notching, NFL defect, field loss. Perhaps the earliest change in glaucoma (if it happens)
• More common in patients with large IOP variations
Indicates a need to change therapy (more aggressive)
Seems to indicate progression of the disease
Meaning is unclear- probably bad stuff

ONH: Baring
- Circumlinear vessels
- Possibly represents loss of neural tissue
- Often occurs normally- not pathognomonic of glaucoma

ONH: Bean Potting
- Undermining of margin
- Vessels covered by scleral lip
- Excavation and bowing outwards and backwards of lamina cribrosa
  - Due to pressure dependent deformation of the lamina cribrosa
- Commonly occurs in normal patients as well
- Can indicate focal loss of tissue (notching)

Clinical Pearl: Baring of a circumlinear vessel and beanpotting are pathological changes that can occur in glaucoma but can also present in a non-pathological normal nerve.

ONH: Nasalization of the retinal vasculature
- Nasal displacement of the vasculature
- Non-specific
- Weak finding

Peripapillary Observations
- A ratty looking atrophic peripapillary retina should make you suspect glaucoma
- Often due to tissue misalignment
- Possible shifting of tissues
- May change over time
- Susceptibility to damage or the result of damage
- Unclear if this is a cause of glaucoma or an epiphenomenon of glaucoma
- Zone beta
  - Adjacent to nerve
  - Scleral tissue
  - More associated with glaucoma
- Zone alpha - pigment adjacent to zone beta

Nerve Fiber Layer Evaluation
- Normal NFL- striate appearance- underlying vessel obscured as if transparent tape was over them
- Alteration in appearance of normal striated pattern of NFL around ONH
• Diffuse or focal
• Selective damage
• Precedes field loss (in one study, 50% showed NFL loss 5 years prior to field loss)
• NFL loss is 85% specific for glaucoma (in certain patterns)
• Precedes disc changes

**NFL Defects**
• Slit
• Wedge (bigger than slit)
• Diffuse
• NFL defects must meet two criteria
  • They are at least the same caliber as an arteriole
  • They must extend to the disc
  • Anything that doesn’t meet these criteria are pseudodefects

**Predictive Value of Nerve Head Evaluation for Glaucoma:**
If done properly, evaluation of the optic nerve head and nerve fiber layer should allow an experienced clinician to predict correctly:

1) Which patients do not have glaucoma 95% of the time and
2) Which patients have glaucoma 85% of the time
   • The reason for this is that 85% of the time, glaucoma presents with ONH changes prior to visual field changes.

**Clinical Pearl:** The goal of glaucoma management is to be able to identify glaucoma and judge disease progression by disc appearance alone.

**Final Thoughts: Not All –Omas are Glaucoma:**
“-Omas”
• Pituitary adenoma
• Craniopharyngioma
• Meningioma
• Glioma
• Metastatic carcinoma
• “Ischemioma”
  • Anterior ischemic optic neuropathy (AION)
  • Both arteritic and non-arteritic

“-Omas” and Glaucoma Share:
• Isolated
• Painless
• Progressive
• Visual dysfunction
• Cupped discs
“-Omas” and Glaucoma Differ:

- Visual acuity
- Color vision
- RAPD
- Visual field defects
- Disc appearance
  - Pallor of the rim is 94% specific for non-glaucoma
  - Obliteration of the rim is 87% specific for glaucoma

Clinical Pearl: While other conditions can cause increased cupping, nothing notches the neuroretinal rim like glaucoma.

Summary: “-Omas” vs. Glaucoma

<table>
<thead>
<tr>
<th>-Omas</th>
<th>Glaucoma</th>
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<tbody>
<tr>
<td>Reduced VA</td>
<td>Normal VA</td>
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<tr>
<td>Color defect</td>
<td>Normal color</td>
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<tr>
<td>RAPD more likely</td>
<td>RAPD less likely</td>
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<tr>
<td>Field doesn’t match disc</td>
<td>Field matches disc</td>
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<tr>
<td>Rim pallor</td>
<td>Rim defect</td>
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<tr>
<td>Central and cecocentral scotoma</td>
<td>Arcuate defects</td>
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Clinical Pearl: Glaucoma is over diagnosed in patients with large disc area and under diagnosed in patients with small disc area. Size does matter.
This lecture consists of a detailed review of the role of gonioscopy, visual field analysis, and new technologies in the diagnosis and management of patients with glaucoma. While acknowledging that many audience members will have some familiarity with this material from prior training and clinical experience, it is imperative that the most up-to-date information be conveyed to all audience members. Please remember that there is nothing in this presentation that supersedes interactive discussions with the audience or answering questions that arise during the lecture. Please join in our discussions, and refer to this information later as a resource or as a way to solidify your understanding of the various conditions.

The Gonioscopic Evaluation

**Gonioscopy Facts**

- Must be done on every glaucoma patient and suspect. You cannot accurately diagnose any glaucoma until you know the anatomic status of the angle.
- Perform at least yearly. Do not assume that the configuration of the angle remains the same. As the patient ages, cataracts develop, the pupil becomes blocked, and the angle becomes shallower (or closes).
- Use of Goldmann gonioscopic lenses artifactually opens closed angles by creating a suction cup effect, stretching the scleral-corneal ring and displacing the iris and ciliary body backwards.
- Indentation with a Zeiss 4-mirror lens can open closed angles. Called depression gonioscopy and dynamic gonioscopy.
  - Pressure from lens forces aqueous into angle and opens angle
  - If no peripheral anterior synechiae (PAS), angle will change configuration (more open)
- Can give a false impression of angle (more open than it truly is)
- In reality, depression will warp the cornea and negatively impact your ability to visualize the angle
- If light is allowed to pass through the pupil during gonioscopy or if the patient is fixating on a near target, the pupil will constrict and an angle that is actually closed in the dark may open. Said another way, excess light or near fixation may make an angle appear more open than it typically is by nature. Gonioscopy is best performed both in light and dark. You can also widen and narrow the biomicroscope beam during gonioscopy to open and close angles.

**Clinical Pearl:** Gonioscopy should be done at least yearly on all glaucoma patients.

**Clinical Pearl:** Because some gonioscopy lenses will displace aqueous, you should check IOP prior to performing gonioscopy as the pressure may be falsely lowered otherwise.

**Drainage of Aqueous:**
- TM to Schlemm’s canal (80%)- conventional
  - Giant vacuoles
  - Scleral venous plexus or aqueous veins
  - Episcleral venous plexus
  - Anterior ciliary veins
- Uveoscleral outflow pathway (20%)- non- conventional
  - Vortex veins
    - Influenced by contraction of ciliary muscle
    - Decreases outflow with contraction

**Gonioscopic Findings: Posterior to Anterior**
- Iris
- Angle recess
- Ciliary body
- Scleral spur
- (Schlemm’s canal) not truly seen on routine gonio unless it is full of blood
- Trabecular meshwork
- Schwalbe's line

**Gonioscopic Findings: Angle Recess**
- Iris dipping to ciliary body with concave approach (Queer)
- Flat approach (Regular)
- Plateau iris with convex approach (Steep)
- Iris processes

**Clinical Pearl:** The iris approach is important in determining the optimal management of any patient with glaucoma.
Gonioscopic Findings: Ciliary Body
- Brown to gray
- Variable presence
- Pigmentation insignificant

Clinical Pearl: The ciliary body can be distinguished from the iris based upon color and texture.

Gonioscopic Findings: Scleral Spur
- Short extension of sclera
- Ciliary body insertion
- Thin white line above (anterior to) ciliary body
- May be obscured anatomically or by liberated pigment

Clinical Pearl: The scleral spur is an excellent anatomic landmark. Once it is identified, remember that everything anterior to it is trabecular meshwork and everything posterior to it is ciliary body.

Gonioscopic Findings: Trabecular Meshwork
- Sieve-like fibrocellular sheets
- Clinically significant pigmentation- should be graded
- Possibly the site of all glaucoma development
- Important treatment structure- miotics and argon laser act upon the TM
- Posterior 2/3rds filters aqueous actively and is more pigmented than the anterior 1/3rd
- Schlemm's canal somewhere behind TM

Clinical Pearl: Degree of pigmentation of the ciliary body is unimportant. However, degree of pigmentation of the trabecular meshwork is important. Degree of pigmentation should be described as mild, moderate, or heavy.

Gonioscopic Findings: Schwalbe's line
- White, opaque, raised
- Axenfeld's syndrome/ posterior embryotoxin
- End of Descemet's membrane
- Sampaolesci’s line: pigmentation buildup on Schwalbe’s line

Clinical Pearl: Sampaolesci’s line is highly indicative of a pigment dispersion syndrome and is important to note.

Gonioscopic Landmarks: Scleral Spur and Corneal Wedge
- The scleral spur, when present, is an excellent anatomic landmark. Everything posterior is ciliary body and everything anterior is trabecular meshwork
• The corneal wedge is a useful technique to identify the trabecular meshwork in eyes that are either nonpigmented or excessively pigmented. It can be difficult to determine whether one is looking at a wide-open and nonpigmented angle or a totally closed angle where one is looking at the internal cornea.

• The slit beam is made very thin and bright and offset from the oculars. Through the gonioscopy lens the light beam will be seen to travel across the iris and the angle. Where it travels across the cornea one will notice two lines, one sharp and bright line that is contiguous with the line that travels across the iris and trabecular structures and another line that is broader and fuzzier on the outside of the cornea. If one follows the outside line from the cornea towards the angle it will continue until the cornea ends. It then illuminates the curved interface between the cornea and sclera at the limbus and joins the brighter inner beam at Schwalbe’s line.

• Try to use a bright and narrow beam of light in a dark room. Also, if the patient looks slightly away from the examining mirror it will allow the examiner to look at the cornea and make the wedge easier to find.

Iris Processes
• Non-regressed mesodermal structures
• Present in 1/3 of normals
• Iris to CB or TM
• Benign, unless profuse and confluent

Peripheral Anterior Synechiae (PAS)
• Permanent adhesion between the iris and trabecular meshwork (or cornea)
  • Inflammation
• Angle closure
• Neovascularization
• Trauma/hyphema/surgery
• Congenital
• Superior angle PAS is diagnostic of chronic angle closure glaucoma (CACG)
• Indentation gonioscopy helps differentiate between PAS and appositional closure
• IOP increases with closure

**Angle Recession**
• Blunt trauma
• CB tear
• TM scarring
• Angle appears very open
• Need contralateral comparison
• The antecedent trauma usually included hyphema

**Clinical Pearl:** The angle recess is the area between the iris and cornea. Angle recession refers to a traumatic dialysis of the iris from the ciliary body.

**Clinical Pearl:** Gonioscopy is actually a poor screening tool to predict which patients will undergo angle closure. It is a static view of a dynamic phenomenon.

**Clinical Pearl:** The angle status changes upon the amount of ambient lighting. The angle is more open when room lights are on and less open when the room lights are dim due to pupil constriction and dilation. When doing gonioscopy, be aware that the angle status can change if light from the biomicroscope actually goes through the pupil and induces miosis. I personally like to do gonioscopy with the light beam both in and out of the pupil.

**Clinical Pearl:** When a patient presents with either very high IOP or an acute pressure elevation, practitioners are often quick to reach for pressure lowering medications. By instinct, you should first reach for a gonioscopic lens so that you understand the mechanism of IOP elevation.

**Clinical Pearl:** Do not get lazy. Do not try to diagnose and manage glaucoma without doing gonioscopy. You are just going to Forrest Gump your way through a case if you try to do so.

**Automated Visual Field Analysis**

**Visual Field Changes in Glaucoma**
• Damage may be widespread or focal
• Relative scotomas
• Fluctuating scotomas
• Absolute scotomas
• Paracentral scotomas (5-15°)
• Nasal steps
• Arcuate scotomas (Bjerrum’s scotomas)
• Altitudinal defects
• General depression and in sensitivity “diffuse loss” is actually very rare in glaucoma and more indicative of cataract, miosis, or other media/refractive issues.

Clinical Pearl: The earliest visual field defect in glaucoma is increased short term fluctuation. The next is a shallow fluctuating scotoma.

Clinical Pearl: The majority of automated threshold field tests performed today test only the central 24°. This implies that you can miss up to 7% of initial glaucoma defects. However, careful examination of the disc, IOP, and other risk factors should elevate your suspicion and lead you to utilize more peripheral field tests and thus raise your sensitivity to nearly 100%.

Clinical Pearl: You can do a field on a dilated or non-dilated patient, but you cannot do a field while the patient is dilating.

Sensitivity:
• Up to 50% of the optic nerve fibers can be destroyed in a glaucoma patient who may demonstrate full fields
• It may take 4-6 years before ganglion cell damage will be detectable on conventional visual fields

Threshold test strategies:
• Threshold testing strategies can be full threshold, SITA Standard (SS), or SITA Fast (SF) These are all names of threshold strategies designed to identify the retinal sensitivities at predetermined points in the visual field.
  • 30-2 (30 degrees tested)
  • 24-2 (24 degrees tested)
  • 10-2 (10 degrees tested)

Swedish Interactive Thresholding Algorithm (SITA)
• New(ish) threshold strategy which reduces threshold test time down to 3-5 minutes without sacrificing accuracy
  • SITA standard threshold field is a good routine test for diagnosing and following glaucoma
  • SITA Fast is a good screening test and for those patients who can not maintain attention for long
    • Faster thresholding algorithm
    • May be slightly less accurate
  • Methods to enhance testing time
• Asks smart questions
• Normal age-corrected values
• Patterns of loss typical in disease
• Patient responses in test thus far
• Patient responses at nearby points
• Normal frequency of seeing curve
• Estimated patient frequency of seeing curve vs. location
• Patient false answer rates
• Smart pacing
  • Presentations based on patient response time
• Knows when to quit
• Uses all available information- not just last test point seen
• Uses better methods for determining false positive and false negative responses
• Error Related Factor (ERF)
  • SITA algorithms employ ERF.
  • Perfect determination of threshold (that is, the sensitivity where the patient will see the stimulus 50% of time) is impractical. SITA allows for some “error” based upon known data and patient responses. SITA fast differs from SITA Standard in that there is decreased test time because the ERF is greater. That is, SF allows for a greater degree of uncertainty about threshold when deciding to end the test.

Reading and Interpreting the Printout: Single Field Analysis

Reliability Parameters:
• Fixation losses (FL):
  • Presentations are made in the plotted blind spot. If the patient responds, it is assumed that the patient lost fixation and the blind spot is no longer in the original location. Expressed as the ratio of the number of times the patient responded to a stimulus presented at the presumed blind spot location over the total number of such presentations. High values occur if:
    • The patient's gaze had often drifted from fixation so that the stimulus falls on a seeing point of the retina
    • The presumed location of the blind spot is incorrect (pseudo-loss of fixation).
    • The patient readjusted head position after the blind spot had been plotted, yet still maintains good fixation (pseudo-loss of fixation). Fixation losses > 20% are considered a sign of possible unreliability and a caution message will appear. However, SITA strategies have no published criteria that indicate when a field is unreliable. But the field may be reliable due to pseudo-loss of fixation.
  • Eye tracking system (gaze monitor) in SITA tells, by deviation above or below a horizontal line, the exact instances when a patient closes their lids (excluding blink) or makes a saccadic deviation from fixation.
    • Deviation upward indicates that the patient’s gaze was not on the fixation target. The magnitude of the deflection indicates the extent of the errant fixation.
• Large deviations downwards indicates a blink while small downward deviations indicates that the computer cannot tell the direction of the patient’s gaze
• A pattern that resembles a city skyline indicates dubious reliability.
• The gaze tracking system can be employed simultaneously with the FL catch trial

**Clinical Pearl:** Fixation losses are performed early in the test. The eye tracking system can better indicate when a patient loses fixation or becomes fatigued later in the test.

**False Negative Rate (FN):**
• This may indicate that the patient is fatigued and falling asleep, has changed personal criteria for response, or is a true indicator of actual field loss where sensitivities are variable.
  • The patient failed to respond when a presumably visible stimulus is presented. In a normal field, a high FN rate results from patient inconsistency in responses. In an abnormal field, a high FN rate occurs because there is highly variable visibility during the test in abnormal regions.
• SITA strategies use information already determined in the actual threshold testing
  • It uses all responses gathered during the testing of a point
  • It identifies all responses that should have been clearly visible based on the final determined threshold value. These are determined to be false negative responses
  • No increase in time spent retesting points with brighter stimuli
• SITA strategies have no published criteria that indicate when a field is unreliable based upon false negative responses

**False Positive Rate (FP):**
• A high false positive rate indicates an unreliable field. This is seen as the patient becomes "trigger happy". **High FP rate is most devastating to interpretation.** High FP rates will be accompanied by:
  • Suprathreshold levels
  • MD has a high (+) value
  • Fixation losses high
  • Patchy loss on grayscale
  • White scotoma
  • Pattern Deviation is worse than Total Deviation
• SITA: The computer knows how long that it minimally takes in order to respond to a stimulus. A response faster than the preset criteria is determined to be an aberration and is considered a false positive response
• Likewise, the time of the patient’s responses are monitored. The average time to respond is determined as is the range of response time. It determines an “acceptable interval” of response time. Any response falling beyond this interval is perceived as a response to something other than the stimulus and is deemed a false positive response
• SITA strategies have no published criteria that indicate when a field is unreliable based upon false positive responses
Clinical Pearl: False positive responses in the SITA strategies on the HFA-2 (Humphrey Field Analyzer-2) are determined by responses that occur too soon or too late.

Clinical pearl: Patients with a high degree of false negatives are typically becoming inattentive. However, if the patient seems attentive, then this could be indicative of true visual field defects.

Clinical Pearl: A patient can have a significant number of fixation losses and false negative responses and yet the field may still be valid. However, a high degree of false positive results makes a field invalid.

Clinical Pearl: A recent study has shown that the reliability parameters are not a reliable indicator of reliability.

Clinical Pearl: There are no published criteria on percentage of FP or FN that make a field unreliable. However, fields demonstrating a false positive response rate of 10% or more should be discarded.

Visual Field Analysis

- **Raw data:** threshold sensitivity values (in decibels – tenth of log unit)
- **Grayscale:** interpolated raw data
- **Total deviation:**
  - General depression
  - Numeric values: deviation from normal values for age.
  - Probability display symbols indicate frequency of that particular value within a normal population, derived as a percentile by non-Gaussian statistics.
- **Pattern deviation:**
  - Localized depression
  - Deviation is corrected for the overall height of the hill of vision (if the best portion of the field tends to be above or below the average normal values by virtue of normal variation or depression). The computer ranks the total deviation values from best to worst and then looks at the value of the point that represents the 85th percentile of non-edge points (also excluding some points around the optic disc/physiological blind spot). This point is used to determine the “general height indicator”. The difference between the obtained threshold value for the general height indicator and its expected value is then added to all points in the visual field. If the point used for the general height indicator is depressed, all threshold values in the visual field will be raised. By raising the values of the patient’s actual threshold, the effects of cataracts or miosis can be minimized, allowing for the detection of focal defects. Conversely, the general height indicator may be elevated rather than depressed. This will occur in patients who have truly supersensitive threshold values (rare). This will lower the hill of vision and reduce the visual field threshold values.
measurements by a few decibels. This is important because shallow scotomas may
be missed otherwise. This will also occur in those who have a high degree of false
positive responses and the field may be lowered by some absurd factor, which is
physiologically impossible and a sign of unreliability.

- Probability display is provided equivalent to the total deviation probability plot after
removing any deviation from normal that affects the entire field equally. This
subtracts out the field defects that occur from aging, i.e., cataracts, media opacity,
etc.

- For both the total deviation and the pattern deviation probability displays, the
low probability refers to the probability of the value at that point, i.e., the
occurrence of that particular sensitivity value in a normal population. However,
when points are analyzed, a normal field may contain a few scattered points that
have, by chance, an abnormal value. The finding of an abnormal point is not
sufficient to conclude that a field is abnormal, especially if the clinical picture
does not correlate. Abnormality of a field as a whole must be judged on the
basis of finding sufficient abnormality in a cluster of points in a pattern that is
typical of the associated clinical findings.

- The probability symbols are probably the most important feature of the single
field analysis. This analyzes the deviation from normal of the patient's threshold
values and displays then individually as probability symbols. Each symbol
corresponds to the occurrence of that threshold value in a normal individual
within a normal population. It allows us to see the degree of departure from
expected values in a normal population and the pattern of field loss (as it is).

**Clinical Pearl:** The Pattern Deviation is the best representation of the true retro-
lenticular visual field defect.

**Global Indices:**

- **Mean deviation (MD):**
  - *Weighted Average* of the numbers on the total deviation plot each value weighted
    according to the magnitude of the normal range at that point (points with low
    variation, i.e., closer to fixation, are weighted more heavily).
  - Signifies the overall severity of the field loss, interpreting the severity of the field
    loss at individual locations and the area of the field involved. Thus, a MD of -4 db
depression may indicate a 4 db depression everywhere in the field or a depression of
-8 db over half of the field.
  - A positive number indicates that the average sensitivity is above the normal for age,
    and a negative number indicates that the average sensitivity is below the average
    age-matched normal.
  - If the MD is outside the normal range, the probability that such a value would occur
    in a normal population is given, determined by non-Gaussian stats stored in a
    computer look-up table.
  - Abnormalities may indicate:
    - Widespread damage
    - General depression
- Many small depressions

- **Pattern standard deviation (PSD):**
  - Weighted standard deviation of the difference of each sensitivity value from the value expected, based on normal values and the MD index. This is a measure of how different points are from one another within the field. This is the “averaged” amount that each point in the field deviates from the expected STAT-PAC value after it has been adjusted for a general depression or suprasensitivity. This is a weighted average of the pattern deviation. Conceptually, the PSD is supposed to indicate how evenly the visual loss is spread across the visual field. It is minimally influenced by cataract. One would expect similar values in adjacent points in a normal field. In an abnormal field, contiguous points may vary widely as a sign of field loss. In a normal field, or a field in which all points are equally abnormal, the PSD will be low. The PSD becomes larger as some points become more affected, and is thus an index of localized change in the field. If the PSD is outside the normal range, the probability that such a value could exist in a normal person is given.

| Clinical Pearl: The PSD is the global index that indicates focal field loss. |
| Clinical Pearl: An abnormal MD with a normal PSD indicates diffuse loss, likely from cataract (but possibly from glaucoma, though not likely). |
| Clinical Pearl: Initially, if the MD worsens, but the PSD remains (relatively) the same, then there is a worsening cataract. If the MD remains stable and the PSD worsens, then the glaucoma is progressing. If both parameters worsen simultaneously, the both glaucoma and (likely) cataract are progressing. |
| Clinical Pearl: For early and moderate glaucoma, an increasing PSD indicates worsening with greater focal defects. However, as glaucoma advances, the PSD will decrease and return to “normal” as all points are equally defective and there are no longer any “focal” defects. |

- **Glaucoma Hemifield Test (GHT):**
  - In glaucoma, the upper and lower hemispheres of the field are often significantly different.
  - Points within the visual field are grouped together into 5 smaller zones with mirror images of one another above and below the horizontal meridian. Probability values are used rather than threshold values. The mirror images are compared to one another. There are 5 possible interpretations of the results that are printed.

1. **GHT outside normal limits:** A score is assigned to each member of the pair of mirror image matched zones based on the percentile deviation from normal. This message will appear if one of the matched zones that are compared yields a score that is found in less than 1% of normals, or if each zone in a matched pair is outside the 0.5% level of probability. Put another way, if the difference between the mirror image zones would be expected in less
than 1% of the normal age-matched population, this message will appear. If both mirror image zones are depressed more or less equally, but to a degree found in less than 0.5% of the normal age-matched population, this message will appear.

2. **GHT borderline:** Zone pairs differ by a degree greater than that seen in less than 3% of the normal population (but doesn’t meet the criteria for “Outside Normal Limits”).

3. **General reduction of sensitivity:** The GHT looks at the "elevator" factor (the general height indicator as described above) used in the analysis of pattern deviation. If the value is positive and occurs in less than 0.5% of normals, this message will appear. Criteria for a localized depression are absent and the general height adjustment yields a result in which the best part of the field is depressed to a degree that would be expected in less than 0.5% of the age-matched population. This message will be superseded by either of the above two messages if those conditions are met.

4. **Abnormally high sensitivity:** If the patient's threshold values are higher than those occurring in less than 0.5% of age-matched normals, this message will appear. The best part of the field is more sensitive than that of 99.5% of the normal age-matched population. This will supersede all other messages and indicates that the patient's responses are unreliable.

5. **Within normal limits:** None of the above criteria are met

**Clinical Pearl:** The GHT is the most widely accepted standard for computer-assisted interpretation of a visual field.

**Diagnosing Glaucoma with Visual Fields: Anderson Criteria**
- GHT outside normal limits on 2 consecutive fields
- Cluster of 3 or more non-edge points on the pattern defect at p < 5% with 1 point at p < 1% over 2 consecutive fields
- CPSD < 5% over 2 consecutive fields
- Moderate loss defined as MD between 6 and 12 dB
- Severe loss defined as > 12 dB defect on MD
- A value of “0” within the central 5% of fixation is considered severe

**Diagnosing Glaucoma with Visual Fields: Sowka Criteria**
- Visual field depression (in the same quadrant) that is statistically significant and present on 3 consecutive visual fields or 3 out of 4 consecutive visual fields.

**Always demand that the field matches the nerve and retina and that the findings are reproducible on another day.**

**Clinical Pearl:** You cannot make a diagnosis based solely on a visual field printout.

**Clinical Pearl:** In diseases that are chiasmal or retrochiasmal, you cannot make a diagnosis or localization based upon the field results of one eye only.
Clinical Pearl: It has been shown that it takes at least three visual field examinations (and, according to some studies, up to six or seven) in order to document true progression. Always confirm suspected progression with a second (or third) field.

Challenges to Interpretation:
- Artifacts:
  - Trial lens rim artifacts
  - Eyelids and brows
  - Refraction scotoma
  - Wrong fixation target
  - Dim light bulb
  - Inexperienced perimetrist
    - “Dim bulb”
  - Inexperienced patient and learning curve
  - Cataract progression
  - Long-term fluctuation

Clinical Pearl: Often, the first series of automated visual field tests that a patient performs are invalid due to a high degree of artifact and the patient’s inexperience with the test. However, after 3 fields, there will be no more improvement from learning to take the test.

Clinical Pearl: The greatest challenges to judging stability or progression on a visual field are cataract development and long-term fluctuation.

Clinical Pearl: If you could look at just one aspect of the visual field printout, it should be the pattern deviation.

Clinical Pearl: One diopters of blur (under-correction) can cause a 1 dB depression in retinal sensitivity.

Clinical Pearl: A 3-dB decrease in retinal sensitivity generally represents a 50% loss of vision.

Glaucoma Progression Analysis (GPA)
- Used with Humphrey HFA perimeter
- Uses algorithm developed for Early Manifest Glaucoma Trial
- Designed to help identify clinically significant progression of visual field loss in patients with glaucoma
- Highlights changes from selected baseline examinations that are larger than typical clinical variability in patients with similar degrees of glaucoma.
- Identifies consistent and repeated patterns of loss
- Corrects for ocular media effects
• Analysis based upon detailed empirical knowledge of variability found at all stages of glaucomatous visual field loss
• Can be used on full threshold (baseline only), SITA Standard, and SITA Fast strategies
• Visual fields that repeatedly and consistently show changes exceeding what is known to represent typical variability are identified as having “possible” or “likely” progression

GPA: Clinical Considerations
• Baseline is established
  • Either by machine or by operator
    • Machine picks two earliest similar strategies
• Small triangles on printout (following baseline) identify statistically significant change
• Open triangles
  • Denotes a point that has progressed at least one time
  • Identifies any point that has worsened by an amount that exceeds the variability expected in all but the most variable 5% (p<0.05) of glaucoma patients having similar visual fields status. This symbol is shown if the change is greater than 95% of the variability seen in that exact test location in fields having a similar mean threshold deviation from normal values. This can occur on the first follow-up (after baseline) exam
• Half-filled triangle
  • Identifies points changing as described above (p<0.05) in two consecutive follow-up (after baseline) exams. (Possible Progression)
• Filled triangle
  • Identifies points changing as described above (p<0.05) in three consecutive follow-up (after baseline) exams. (Likely Progression)

GPA Alert: Possible and Likely Progression
• Combines the knowledge of clinical variability with the demand that the change be consistent and repeatable.
• Judging progression should involve all clinical data
  • However, if solely using perimetric data, the significant change should be present in at least two follow-up tests and must be found consistently in the same area of the visual field
  • Before changing therapy based upon this information, care should be made to ensure that the baseline exams are appropriate and the follow-up exams are reliable.
• When significant degradation is present in the same three or more points (on the same side of the horizontal meridian) on two consecutive follow-up exams, the GPA software will alert you to “Possible Progression”. If this trend is present on three consecutive follow-up exams, the GPA software with alert you to “Likely Progression”
• Slope of Mean Deviation from all exams is determined using a regression analysis. This allows one to determine the rate of progression
- In general, a minimum of 4 exams (2 baseline and 2 follow-up exams) is required in order to judge “Possible Progression”. In order to get a message of “Likely Progression”, 5 exams (2 baseline and 3 follow-up) are necessary.

**Clinical Pearl:** A 2-dB decrease in the Mean Deviation can be associated with disease progression.

**Short Wavelength Automated Perimetry (SWAP)**
- Also known as Blue-Yellow perimetry. Utilizes a yellow background and large blue stimulus to stimulate a different (lower population) retinal ganglion cell than conventional white light perimetry.
- Yellow light bleaches out red and green sensitive fibers and isolates blue sensitive fibers. Because of the lower population of tested cells, field defects are being identified much sooner than conventional white light perimetry. Visual field defects are being identified in ocular hypertensives that are not demonstrated by conventional perimetry.
- Defects have been isolated on SWAP up to 5 years earlier than on conventional perimetry. Conventional perimetry requires that approximately 25% of fibers need to be wiped out before identifiable defect occurs.
  - Blue-yellow color vision defects present in patients with glaucoma and ocular hypertension.
  - SWAP field loss progresses faster than conventional perimetry field loss
  - When SWAP field matches conventional field, then the patient is probably stable
  - Blue sensitive fibers are wiped out at (-) 10 dB and SWAP is no longer useful
  - Cataract with vision < 20/40 will adversely affect the accuracy of SWAP
  - SWAP testing takes much longer, which reduces the reliability due to patient fatigue
  - SITA SWAP has recently been developed and is coming to clinical practice

**Frequency Doubling Technology (FDT)**
- Flickers a linear background until the patient sees a doubling of the background
- Not yet shown to be more sensitive than conventional perimetry
- Does appear to correlate with conventional perimetry.
- Resistant to environmental factors such as blur, refractive error, room illumination.
- Isolates macrocellular cells- tests only 3-5% of all axons
- Screening tests run 45 secs. To 3 min.
- Threshold tests run 2 ½ to 4 ½ minutes
- 82% sensitive and 95% specific for mild defects
- 96% sensitive for moderate defects
- 100% sensitive for severe defects

**Clinical Pearl:** You cannot compare results from different test strategies and testing algorithms.
New Technology in Glaucoma Diagnosis and Management:

Scanning Laser Polarimetry: GDx:
- GDx technology
- Images 16,000 points
- Laser double passes the retinal nerve fiber layer (NFL) and is split into 2 parallel rays by the birefringent fibers. Laser light enters eye at specific orientation. As it goes through tubules (ganglion cells), it returns at a different orientation/axis. This delays return and this difference (called retardation) is the measurement of thickness. Parallel light passes through at a different speed than perpendicular light.
- Near infra-red wavelength
- Measurement time is 0.7 seconds
- Total chair time less than 3 minutes for both eyes
- Completely objective
- Must have clear corneal surface with good tear layer
  - Do nothing to cornea prior to taking test
  - Undilated pupils work best

GDx: Normative Values
- Normative data base from healthy volunteers
  - Sampling of races represented in US included
  - Strict inclusion criteria
    - At least 18 years old
    - No ocular medications
    - No ocular hypertension, glaucoma, or retinal disease
    - BVA 20/40 or better
- Comparison of patients to age- and race-matched normals

GDx: Just the Facts
- Once patient is examined, the GDx shows how patient compares to normal patients of same age range and race category
- Each quadrant is analyzed and actual deviation from normal, in microns, is displayed
- Key parameters which were determined to be most effective in differentiating glaucoma from normal are listed with the results for the patient
  - Deviations from normal are highlighted
  - All normal values are shown in green
  - Probability represents the likelihood that this value would been seen in a normal, healthy patient

Corneal Compensation
- GDx measures the birefringence of the NFL
- To an extent, the cornea (as well as the lens) has birefringent properties as well
  - This introduces artifact in that not everything measured by the GDx is NFL
• The early versions of GDx compensated for this aberrant birefringence in the majority of the population with a standard axis and magnitude of polarization – fixed corneal compensator (FCC)
  • Some patients are not compensated for by the device
  • Present with significant artifact
• Variable Corneal Compensator adjusts for all patients by first imaging the macula
  • At the macula, there should be no birefringence due to the anatomy of the NFL
  • If there is an uncompensated bowtie appearing retardance image in the macular region, this indicates that the artifact showing through is from the anterior segment (cornea) because there is an absence of NFL at that region.
    • This is used by the device to adjust for the amount of cornea-induced artifact showing through.
    • Thus, for all new patients, a macular scan must be completed first
    • On subsequent exams, macular scanning is not performed and stored data are used. However, if the patient has a significant change in a cornea (e.g., corneal transplant, refractive surgery), then this process must be done again.

GDx: The Printout
• Fundus image
  • Nerve size, focus
• NFL Thickness map
  • Looking for bright red and yellow superiorly and inferiorly, corresponding to thick, healthy NFL
• Deviation (from normal) map
  • Shows how the patient’s NFL: thickness compares with values derived from the normative database
  • Small color coded squares indicate the amount of deviation from normal at each given location and are presented on a black and white image
  • Color legend defines the degree of statistical significance for each point using p-values
• TSNIT Average
  • The average thickness values within the calculation circle (measuring ellipse)
• Superior average
  • Average of all pixels in the superior 120 degrees of the calculation circle
• Inferior Average
  • Average of all pixels in the inferior 120 degrees of the calculation circle
• TSNIT Standard Deviation
  • Standard deviation of the values contained in the calculation circle. The higher the number, the greater the modulation of the double hump pattern
    • That is, the higher the superior and inferior peaks
• Inter-Eye Symmetry
  • The correlation of corresponding points in the TSNIT data for the right and left eyes. The closer the ratio is to 1.0, the more symmetric the NFL.
• **Nerve Fiber Indicator (NFI)**
  • A single number meant to indicate whether or not the patient has glaucoma (i.e., the likelihood that the patient has glaucoma.
  • As the number is still experimental, it does not have a color to indicate significance or deviation from normal. The following guideline should be used:
    • 0-30 normal (low likelihood of glaucoma)
    • 31-50 glaucoma suspect
    • 51-100 high likelihood of glaucoma
  • Not an indication of severity or progression, but only if disease is present
  • New research involving patients with glaucomatous optic neuropathy, yet normal visual fields has better defined this range:
    • > 15: Virtually guaranteed that the patient was normal*
    • < 35: 9-fold more likely to get these values in patients with glaucoma*  
    • 16-34: borderline range.*
    * In this study

**Clinical Pearl:** I find that symmetry between the two eyes is perhaps the greatest indicator of glaucoma or normalcy.

**Optical Coherence Tomography (OCT)**
- Non-invasive diagnostic imaging technique first described in 1991 by Huang et al
- Provides high-resolution cross-sectional and topographic images of retinal and optic nerve tissues
- Stratus OCT (Carl Zeiss Meditec, Dublin, CA) is the 3rd generation machine, which received FDA approval in May 2002
- Newer designs such as Spectral Domain OCT are being approved and marketed currently

**How OCT works**
- A superluminescent diode (830-850 nm and 200uw-1mw) serves as the light source
- Imaging technique that compares the coherence between this near-infrared light reflected off the retina and light reflected off a reference mirror
- Distance information concerning ocular structures is extracted from time delays of reflected signals
  - Interferometry
    - Light beam is simultaneously sent to the eye and a reference mirror
    - The light penetrates through the ocular tissue layers and is reflected back
    - The returning light is compared to the reference light and allows a computer reconstruction of the underlying tissue

**Principles of OCT**
- OCT computes tomographic images based on the amount of incident light which is reflected for a given tissue (or indices =n)
• OCT is particularly sensitive to light that has only one back-scattering event
• Light returns without more scattering or absorbing events
• This property makes the OCT highly precise

Retinal Examination by OCT
• OCT beam is directed to eye via fiber optic sampling arm using 2 galvanometer-driven mirrors
  • Allows for scanning the beam of light across the retina – image time 2.5 sec
  • Allows for direct visualization of the fundus
• Via visible light or IR Videoscopy
  • Provides Cross-sectional images of retinal structures
  • Allows clinical correlation
  • Better anatomic perspective
  • Supplements other diagnostic testing

How OCT measures RNFL?
• The OCT is able to distinguish precisely the interface between the vitreous cavity and retinal nerve fiber surface anteriorly and the retinal nerve fibers and the retinal ganglion cells posteriorly
• Measurements are taken at 768 points in a 3.37 mm diameter circle around the optic disc. Results are analyzed to calculate average RNFL thickness

OCT in Glaucoma
• Retinal nerve fiber layer analysis
• Optic nerve head analysis
• Bilateral Comparisons
• Serial Comparisons
• Comparisons to normative database

Clinical Pearl: When using the OCT, the Fast RNFL Thickness is the program that the vast majority of clinicians use for glaucoma diagnosis.

OCT for Glaucoma: Reading the Printout

RNFL Thickness Charts:
• Graphic display of RNFL thickness in circular peripapillary region for right and left eyes
  • Colored bands demonstrate range of normative data

Sector Averages
• Displayed numerically
  • Comparison to normative data in each sector is indicated by color coding

Quadrant Averages
• Numerical display
• Color coded comparison to normative data in each quadrant

OD/OS Graph
• TSNIT line graph of RNFL Thickness average in both eyes

RNFL Normative Data
• White – 5% fall within the white band
• Green – 95% fall within or below the green band; 90% fall within the green band
• Yellow - 5% fall within or below the yellow band; considered “borderline”
• Red - 1% fall within the red band; considered “outside normal limits”

Optic Nerve Head Analysis
• Radial scanning across optic nerve head
• Six 4mm scans are taken

Normative Database
• Normative database provides age-matched reference values for retinal nerve fiber layer thickness measurements
• FDA approved July 2003
• Fast RNFL thickness scans (256 points)
• More than 300 subjects
• Aged 18 – 85; mean age 47
• 6 sites in the US
• Broad representation of ethnic types
• No correction for other demographic factors (ethnicity, gender)

Limitations of OCT
• Denser media opacities can lead to unreliable readings
• Produces artificial results for peripapillary staphyloma (flat line)
• Normative database limited to 328 patients
• Need pupil dilation greater than 3 mm

Confocal Scanning Laser Ophthalmoscopy

Heidelberg Retinal Tomograph II (HRT II/III)
• Scanning laser Tomograph
• Confocal laser scanning microscope
• Objectively measures the optic nerve and surrounding topography
• Acquisition and analysis of three-dimensional images of the posterior segment
• Quantitative assessment of topography
• Follow-up of topographic changes
• Very sensitive in detecting change over time
• Operator subjectively uses image to plot the contour line (edge of the disc)
• This is one source of introduced error
• Focused laser beam
• Sequential scanning in two dimensions
• Confocal pinhole
• Suppression of out-of-focus light
• Depth resolution
• Optical section images
• Series of optical section images at different locations
• Layer-by-layer three-dimensional image
• Laser scanning tomography
• Similar to CT scan technology

**Reading the Printout**

**Topography Image**
• False color image
• Bright colors represent depth
  • Red is the cup
• Dark colors represent elevation
  • Blue is sloping
  • Green is the neuroretinal rim

**Vertical Height Profile**
• Height profile along a while line in topography image
• Reference plane (line) in red indicates the location of the reference plane (separation between the cup and neuroretinal rim)
  • Selected location based on histological study
  • Bundle which remains intact through disease progression
  • Average thickness of papillo-macular bundle located 350º-356 found to be 50 µm
  • The separation of rim from cup is set 50 µm below the average thickness of this area
  • This is another source of introduced error
  • Two black lines perpendicular to the height profile denotes the borders of the disc as defined by the contour line

**Horizontal Height Profile**
• Height profile along the white horizontal line in the topography image
• Red reference line indicates the location of the reference plane (separation between cup and rim)
• Two black lines perpendicular to height profile denote the borders of the disc as defined by the contour line

**Reflection Image**
• False color image
The brighter the color – more light being reflected from this region
ONH is divided into six sectors
  Sectors are compared to a normal database and then classified
Moorefield’s regression Analysis means that the rim (green and blue) and the disc area (green, blue, and red) for each sector are compared to the normal database.
  The sectors are classified as “within normal limits”, “borderline”, or “outside normal limits”.

Mean Height Contour Graph
Red line represents the location of the reference plane (separation between the cup and rim)
  Approximately at the base of the NFL
Green line is the retinal surface height profile
  Corresponds to the retinal NFL thickness along the contour line

Moorefield’s Regression Analysis
Each column represents the total optic nerve head area for each specific sector
  Rim is green and cup is red
Predicted: 50% of the ONH in the database have a larger rim area than this limit
Low 95.0%: 95% of the ONH in the database have a larger rim area than this limit
Low 99.0%: 99.0% of the ONH in the database have a larger rim area than this limit
Low 99.9%: 99.9% of the ONH in the database have a larger rim area than this limit
If the percentage of the rim is larger than or equal to the 95% limit, the sector is classified as “within normal limits”
If the percentage of the rim is between the 95% and 99.9% limits, the sector is classified as “borderline”
If the percentage of the rim is lower than the 99.9% limit, the sector is classified as “outside normal limits”
1st column is global and the rest are labeled

Stereometric Analysis ONH: The 5 Most Important Parameters
  Rim Area: Area of neuroretinal rim (green and blue). Area enclosed by the contour line and above the reference plane.
  Rim Volume: Volume of neuroretinal rim. Volume enclosed by the contour line and above the reference plane.
  Cup Shape Measure: Measure for the overall three-dimensional shape of the optic disc cupping.
  Height Variation Contour: Height variation of the retinal surface along the contour line: height difference between the most elevated and most depressed point of the contour line.
• **Mean NFL Thickness**: Mean thickness of the retinal NFL along the contour line (measured relative to the reference plane).

• Possible classifications:
  - Within Normal Limits
  - Borderline
  - Outside Normal Limits

**Differences in the Follow-up Report**

- Beginning with 2nd follow-up exam
- Regions with significant changes are color coded
  - Green: increased height
  - Red: decreased height
- Topography follow-up is black & white for better contrast

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**Clinical Pearl: The contour line (which is a subjective determination of the edge of the disc) and the reference plane set by the device to delineate cup from rim, are the two main sources of error in this technology. Because these determinations may be incorrect, this makes the HRT II not a good on-the-spot diagnostic device. However, in sequential analyses, these sources of error remain constant and the device is good to measure change over time.**

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**Clinical Pearl: The GDx, OCT, HRT are not a Silicon Valley Rumplestilskins. You can not put in straw and expect to get out gold. Garbage in – garbage out. No amount of technology will replace your clinical acumen.**

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**Clinical Pearl: Interpretation of any diagnostic laser is a three part process. 1. Understand that the printout identifies how the patient’s measured data differs from the normative data base and to what statistical degree, 2. Use personal clinical experience to determine if the results are consistent with normal or abnormal anatomy and, 3. Incorporate everything into the entire clinical picture.**
Diagnostic and Therapeutic Review of the Glaucomas III: Medicines; Angle Closure Glaucoma

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This lecture consists of a detailed review of the role of therapeutic medications used in the management of patients with glaucoma. Additionally, there will be a detailed discussion of the pathophysiology and management of patients with angle closure glaucoma. While acknowledging that many audience members will have some familiarity with this material from prior training and clinical experience, it is imperative that the most up-to-date information be conveyed to all audience members. Please remember that there is nothing in this presentation that supersedes interactive discussions with the audience or answering questions that arise during the lecture. Please join in our discussions, and refer to this information later as a resource or as a way to solidify your understanding of the various conditions.

Medical Therapy of Glaucoma

Despite all of the new knowledge in glaucoma pathophysiology and all of the new therapies under study, our only therapeutic option currently available is intraocular pressure reduction.

Ocular Parasympathetic receptors
- Iris: miosis
- Ciliary body: accommodation and trabecular meshwork opening
- Trabecular meshwork: aqueous outflow increase
- Ciliary meshwork (uveal meshwork-uveoscleral pathway)- aqueous outflow decrease

Systemic Parasympathetics
- Glands: increased activity
- Heart: reduced activity
• Blood vessels: vasodilation
• Lung: bronchiole constriction
  • Because these organs are more controlled by the sympathetic system, there is less systemic affects by parasympathomimetic drugs than would be expected.
• Gastrointestinal tract: increased motility
• Urinary tract: increased motility
• Stimulation of parasympathetic system often results in increased sweating, bradycardia and syncope, vomiting, and incontinence. You will eventually see these reactions when a patient undergoes vasovagal syncope from over stimulation of the vagus nerve. This can result from evertting an eyelid or instilling medications into an eye. True anaphylaxis is extremely rare with ocular medications. If a patient has a medical situation following diagnostic medication instillation, consider vasovagal syncope as the cause.

Parasympathetic Agents: Pilocarpine
• Direct acting cholinergic agonist
• Miotic
• Ciliary body contraction
• Increases outflow of aqueous through trabecular meshwork (conventional pathway). Tends to decrease outflow through uveoscleral pathway (unconventional pathway).
• Accommodation- myopic shift
• Cholinesterase independent
• 4-8 hrs IOP effect
• Oldest anti-glaucoma medication
• Generic and inexpensive

Pilocarpine Forms
• 0.25%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 8%, 10%
• 1%, 2%, 4% most commonly used
• QID dosing
  • Very unfriendly dosing dschedule
• Green cap
• 4% Pilopine Gel HS: side effects occur during sleep and may be better tolerated

Pilocarpine: Ocular Adverse Effects
• Miosis
• Brow ache: ciliary body (CB) contraction
• Globe and orbital pain
• Allergic reactions
• Increased myopia due to accommodative spasm: CB contraction
• Vision reduction: especially with cataracts
• Posterior synechiae in some cases
• Retinal detachment: CB contraction- not common, but be aware of the potential
• Angle closure: Due to pupil block with a changing cataractous lens
• Field constriction
Clinical Pearl: Due to miosis, pilocarpine can mimic the blinding effects of glaucoma.

### Pilocarpine: Systemic Effects

<table>
<thead>
<tr>
<th>Minimal</th>
<th>Bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Slight respiration decrease</td>
</tr>
<tr>
<td>Sweats and salivation</td>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>Muscle weakness</td>
</tr>
</tbody>
</table>

### Other Parasympathetic Agents:
- Carbachol
- Physostigmine (Eserine): Indirect acting
  - Occasionally used to treat crab louse infection of the eyelashes
- Echotothiophate iodide (phospholine iodide-indirect acting)
- Demarcarium bromide (Humersol): Indirect acting
- These agents are virtually never used and should be considered clinically insignificant

### Miotics: Contraindications
- Uveitic glaucoma
  - Any significant ocular inflammation
- Neovascular glaucoma
- Aphakia (relative contraindication)
- Retinal breaks, RD
- Posterior subcapsular cataract present
- Pre-presbyopia
- Concurrent use of prostaglandin analogs (relative contraindication)

Clinical Pearl: NEVER USE MIOTICS ON ANY CASE OF UVEITIS OR INFLAMMATORY GLAUCOMA!

Clinical Pearl: Miotics are losing popularity as glaucoma treatment, due mostly to local side effects and the advent of newer medications. Miotics are rarely used today in modern glaucoma therapy. However, any patient with primary angle closure glaucoma should be on this medication prior to laser surgery.

Clinical Pearl: Occasionally, to reduce IOP in acute situations, doctors will liberally use pilocarpine. This strategy only works if the mechanism is acute angle closure. If the patient has uveitis, the outcome can be disastrous. In reality, pouring pilocarpine into a patient is likely only to give them diarrhea.
Sympathetic Agents
- Adrenergic agonists
- Sympathomimetic
  - Norepinephrine based
- Adrenergic antagonist
  - Sympatholytic

Sympathetic System
- Alpha 1
  - Blood vessels of ciliary body: vasoconstriction, which reduces blood flow and aqueous production.
- Epinephrine-like drugs
- Alpha 2
  - Nerve terminal
  - Stimulation results in diminished release of norepinephrine
    - Stimulation here result in decrease in norepinephrine release, thus a reduction in sympathetic tone and reduction in aqueous production
- Alpha-2 adrenergic agonist (Brimonidine)
- Beta 1
  - Heart: increased
- Beta 2
  - Lungs: relaxed- increased breathing ability
- Beta 1 & 2 on ciliary body
  - Stimulation increases aqueous production
  - Blocking B1 & 2 receptors reduces aqueous production
  - Beta blockers

Adrenergic Agonists: Epinephrine
- Epinephrine contraindications
  - Narrow angles
  - Aphakia/pseudophakia
  - Cardiovascular disease, HTN, arrhythmias, recent myocardial infarction
  - Use of MAO inhibitors: enhances the affects of adrenergic drugs and can trigger a catecholamine induced hypertensive crisis

Clinical Pearl: Epinephrine is practically never used in current glaucoma therapy.

Adrenergic Agonists: Dipivefrin 0.1%
- Propine
- BID dosing
- Pro-drug- concentration in anterior chamber equal to traditional epinephrine 1%
- Mild effect
- Lower side effects than epinephrine
- Avoid in aphakes and pseudophakes due to cystoid macular edema (CME)
Clinical Pearl: Propine has lost a great deal of popularity. It is used more commonly than epinephrine, but today most doctors avoid this medication due to its weak actions in lowering IOP. Today, Propine is virtually never used.

Adrenergic Agonists: Apraclonidine 1% & 0.5%
- Iopidine 0.5% (ophthalmic bottle), 1% (single use containers)
- Alpha 2 agonist: acts presynaptically to inhibit release of norepinephrine and reduces adrenergic receptor stimulation. The reduced sympathetic activity in ciliary body reduces aqueous production. Inflow reduction
- 1% used during laser surgery to prevent IOP spike
- Has been used for acute angle closure
- 0.5% concentration- used for POAG management
  - TID dosing
  - Initially was not viewed for long-term treatment (beyond 3 mos) due to tachyphylaxis.
  - 20-30% incidence of allergic ocular reactions requiring discontinuation.

Clinical Pearl: Apraclonidine is virtually never used in modern glaucoma therapy.

Adrenergic Agonists: Brimonidine tartrate (Alphagan)
- Alphagan 0.2% (available generically only)
- Alphagan P
  - Brimonidine tartrate 0.15% and 0.1% preserved with Purite®
  - Comparable effectiveness to Alphagan
  - Reduced (by 40%) incidence of local toxic adverse effects
    - Does not affect headache, somnolence or other problems associated with the medication, not the vehicle
  - 30 fold more selective for alpha 2 receptors than apraclonidine
- Decreases aqueous production (and possibly increasing uveoscleral outflow- not a big component of action)
  - Selective alpha-2 agonist
    - Seems to work via inhibition, thus no effects on heart and blood pressure as seen with sympathomimetics
- IOP reduction of approximately 4-6 mm hg (25-30%)
- TID dosing
  - Often used initially BID.
    - BID dosing can leave the patient with uncontrolled IOP at certain times of the day.
      - This is significant for monotherapy
      - Patients on polytherapy may be able to get away with BID dosing
- Purple cap
- Approximately 7% of patients have toxic allergic responses that require discontinuation of the drug
- The most significant side effects are drowsiness and fatigue, and dry mouth
• These effects are most significant in smaller patients and children
• This medication has induced fatigue, drowsiness and even coma in children
• Other side effects: conjunctivitis, blurring, burning, headache
• There are some vasoconstriction effects in 20% of patients
• No effect on blood pressure, pulse, or pulmonary function
• Minimal cardiovascular and pulmonary responses - not frankly contraindicated in patients with cardiovascular disease, but use caution in patients with ischemic heart disease or prior MI
• Concurrent use of MAO inhibitors (anti-depressants) are a strict contraindication to the use of Alphagan
• Has been said to have a neuro-protective effect.
  • In rabbit eyes, traumatized nerves release glutamate, which kills healthy nerve tissue. Alphagan may suppress glutamate (not proven to be the mechanism) and protect healthy nerves. Whether this is true or not is unknown. Looking at nerve-crush and ischemic models, Brimonidine can prevent nerve cell death. Clinical trials are underway to test neuroprotective properties in humans. Also, Brimonidine seems to have the capacity to increase fibroblast growth factor (FGF), which stimulates a cell to live in the apoptosis theory. At this point, Alphagan is not proven to be nor is considered to be neuroprotective.
• This is currently a popular and important medication (both as primary and adjunctive therapy)

Clinical Pearl: Alphagan is a more popular alpha 2 agonist than Iopidine and is one of the most popular glaucoma medications in use.

Clinical Pearl: Do not use Alphagan in smaller patients or children.

Clinical Pearl: No currently approved medication has been proven to be neuroprotective. You should not use any medication for this reason.

**Beta Antagonists (Blockers):**
- All forms block norepinephrine and thus blocks aqueous formation- considered aqueous suppressants
- May be selective
  - Beta 1 specific (blocks only beta 1 receptors)
  - Most are non-specific
- Reduced sympathetic activity
- Aqueous suppressant
- Bilateral effects when using in only one eye due to systemic absorption
- Short term escape
  - After an initial decrease in IOP from several days to weeks, a rise in IOP will occur. After an additional 2-4 weeks, the IOP will stabilize, often below pre-treatment levels.
- Long term drift
• A slow steady rise in IOP after months to years of treatment.
• Medications become ineffective
• Common problem with beta blockers

**Beta Blockers: Adverse Effects**
• Ocular allergic reactions (generally insignificant magnitude, but may necessitate discontinuation of the medication)
  • Burning/stinging
  • Hyperemia
  • Punctate keratitis
  • Corneal hypoaesthesia
• BP decrease (beta 1)
• Bradycardia (beta 1)
• Pulmonary bronchiole contraction (beta 2)
• Depression
• Confusion
• Anxiety
• Fatigue
• Malaise
• Irritability
• Somnolence
• Confusion
• Death
  • Approximately 40 deaths from topical beta blocker use have been reported in the literature
• Syncope
• Palpitations
• Impotence
• Diarrhea, nausea, cramps
• Altered lipid profiles
  • Decreased high density lipoproteins
  • Increased triglyceride levels
• Most common effects are depression and impotence

**Beta Blockers: Contraindications**
• Sinus bradycardia (pulse less than 60 BPM)
• Congestive heart failure
• COPD
• Asthma
• Emphysema
• Brittle diabetes
• Myasthenia gravis
  • Can worsen myasthenia gravis
• Cerebrovascular insufficiency
• Greater than 1st degree heart block
• Hypotension (<100/60)
• Beta blockers are bad for athletes as it prevents heart rate from exceeding 135 BPM. Athletes cannot train through this block.
• Every patient considered for a topical beta blocker needs baseline blood pressure and resting pulse measurement in addition to review of medical history.

Clinical Pearl: Topical beta blockers have the same systemic effects as 20 mg of oral beta blocker therapy.

**Beta Blockers: Shattering the Myths**
• Can be used in hypertensive patients
• Can be used even if the patient is on systemic beta blockers for hypertension
  - However, systemic beta blockers reduce effectivity of topical beta blockers
  - Those on both forms experienced a greater degree of bradycardia

**Beta Blockers: Timolol maleate**
• Timoptic
  - 0.25% (blue cap)
  - 0.50% (yellow cap)
• Considered to be the gold standard against which all other anti-glaucoma medications are measured
• BID dosing
• Beta 1 & 2 blocker (non-selective)
• 30% decrease in IOP
• Timoptic XE: forms a gel for better contact and penetration. Same concentrations, but is designed to be used QD. However, new understanding of diurnal pressure variations make QD AM dosing suspect
  - 0.25%, 0.5% concentration in gelrite
  - Longer corneal contact time
  - AM dosing preferred
  - Same cost as timoptic BID soln.
  - Can cause transiently blurred vision
  - Same cap colors as solution
  - Reduced systemic absorption with reduced systemic adverse effects
• Generic
• Istalol: timolol maleate 0.5%: QD dosing approval
  - New and not especially impressive

Clinical Pearl: Beta blockers are still popular glaucoma medications and Timoptic is the most popular beta blocker.

**Beta Blockers: Timolol hemihydrate**
• Betimol 0.25% and 0.5%
Beta Blockers: Levobunolol
- Brand name Betagan no longer available. Only available as generic
  - 0.25% (blue cap) and 0.5% (yellow cap)
- Clinically equivalent to Timoptic
- Originally designed for QD dosing
- Generally BID dosing
- Same side effects and contraindications as Timoptic

Beta Blockers: Betaxolol
- Betoptic S 0.25% suspension – blue cap
- Beta 1 selective
- Pulmonary friendly (but not perfect)
  - May still exacerbate asthma- caution required
- Affects heart as does previous beta blockers
- Weaker than previous beta blockers
- BID dosing
- May have action to increase optic nerve perfusion and is favored by many practitioners for this reason- controversial
  - May exhibit calcium channel blocking activity through a secondary receptor stimulus and thus may be neuroprotective. Absolutely unproven

Beta Blockers: Metapranolol
- Optipranolol 0.3%
- Non-selective
- BID
- There may be an association in the development of granulomatous uveitis
- Generic

Beta Blockers: Carteolol 1%
- Ocupress
- Has intrinsic sympathomimetic activity and transient agonist activity and is the beta blocker least likely to cause bradycardia even though it is non-selective. There remains some agonal tone, which allows for more normal cardiac rhythm. There appears to be incomplete beta 2 receptor blockages. Less likely (of non-selective beta blockers) to cause bronchospasm and bradycardia.
- Less dyslipidemia
- QD dosing
- Generic

Clinical Pearl: Beta blockers work well and are generally safe in children. Beta blockers tend not to work well in cases of uveitic glaucoma.
Clinical Pearl: Beta-blockers should not be dosed at bedtime for two reasons. Some patients have nocturnal hypotension and this may lower blood pressure further. Also, aqueous formation decreases in the evening during sleep and topical beta-blockers have less effect.

**Carbonic Anhydrase Inhibitors**
- Carbonic anhydrase catalyzes the hydration of carbon dioxide to carbonic acid that then dissociates into bicarbonate ions and hydrogen.
  \[
  \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-
  \]
- Bicarbonate diffuses into the eye, making it hypertonic in relation to plasma, and fluid flows osmotically into the eye from plasma.
- Blocking carbonic anhydrase blocks bicarbonate formation - Blocks osmosis into posterior chamber
- Blocks aqueous formation by slowing production of bicarbonate in secretory neuroepithelial cells of ciliary body

**Carbonic Anhydrase Inhibitors: Side Effects**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis</td>
<td>Paresthesia</td>
</tr>
<tr>
<td>Metallic taste</td>
<td>Malaise</td>
</tr>
<tr>
<td>Calculi formation</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Depression</td>
<td>Impotence</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Confusion</td>
<td>Anorexia and weight loss</td>
</tr>
<tr>
<td>GI upset</td>
<td>Polyuria</td>
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<tr>
<td>Bone marrow toxicity and suppression of</td>
<td>Loss of libido</td>
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<tr>
<td>formed blood elements</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

**Carbonic Anhydrase Inhibitors: Systemic Contraindications**
- Sulfur allergies
- Sickle cell disease
- Hypokalemia
- Renal disease
  - Predisposition to form kidney stones
- Liver disease

**Oral Carbonic Anhydrase Inhibitors: Acetazolamide**
- Diamox - Oral
- 125mg, 250mg, 500 mg SR (Diamox sequels)
- 1000mg QD PO
- 6-week tolerance, in most cases.
- Indicated post-surgically and for acute angle closure (250 mg tabs)
Oral Carbonic Anhydrase Inhibitors: Methazolamide
- Neptazane
- 25mg, 50mg
- Dosing: 25 mg BID up to 50 mg TID maximum
- Side effects and contraindications similar to acetazolamide, but is much better tolerated.

Topical Carbonic Anhydrase Inhibitors: Dorzolamide
- Trusopt 2%
- Orange cap
- 10-26% IOP reduction
- Reduces aqueous production
- Poor lipid solubility and doesn’t penetrate cornea well
- Tends to be an irritating medication to use (low pH)
- Dosing TID
- Binds to melanin, so it is slightly less effective in dark irides.
- Can be combined with other families of medications.

Dorzolamide: Side Effects
- Hyperemia
- Bitter taste
- Toxic allergy (significant)
- Aplastic anemia
- Bone marrow suppression with reduction of WBC’s, RBC’s, platelets
- Renal stone development
- Onset of corneal edema in patients with compromised corneal endothelium

Topical Carbonic Anhydrase Inhibitors: Brinzolamide Ophthalmic Suspension 1%
- Azopt
- Orange cap
- Reduces IOP 20%
- TID dosing
- Formulated at physiological pH
- Significantly more comfortable and better tolerated than Trusopt
- Less incidence of allergic reactions
- Clinically equivalent to Trusopt

Clinical Pearl: Topical CAI’s work very well in cases of uveitic glaucoma. Also, they work very well and are well tolerated in children.

Clinical Pearl: While dosing is TID, many prescribe topical CAIs BID. This is probably acceptable as part of polytherapy, but is not advised for monotherapy.
Clinical Pearl: Avoid using topical CAI’s in patients with compromised corneal endothelium, an allergy to sulfa medications, and a history of renal stones.

Clinical Pearl: Due to the safety of topical CAI’s compared to oral CAI’s, the therapeutic index indicates that orals CAI’s are no longer appropriate in the chronic care of glaucoma.

Prostaglandins and Prostaglandin-like Medications

- Prostaglandins are chemical mediators of inflammation which have the ability to reduce IOP by increasing uveoscleral outflow
- One of the newest and most heralded medications in glaucoma management. Is considered by some to be revolutionary
- Dosing QD HS
- Independent of episcleral venous pressure (drug of choice in glaucoma secondary to idiopathic elevated episcleral venous pressure and carotid cavernous fistula and dural arteriovenous shunt/malformation within the cavernous sinus).
- Ocular adverse and side effects: hyperemia, periorbital skin darkening, punctate keratopathy, increased eyelash and nose hair growth, blurred vision, dry eye, increased iris coloration, anterior chamber cells/flare (anecdotal evidence of uveitis). Increased iris coloration and the potential to cause uveitis are reasons that FDA has not typically viewed prostaglandins as first line therapy (See clinical pearl below). Only now are they being approved as first-line agents. Unilateral usage should be used with caution due to iris color changes. Anecdotal evidence of cystoid macular edema (CME) in aphakes and pseudophakes. Prostaglandins been associated with pseudodendritic keratopathy as well as inducing recurrence of herpes simplex dendritic ulcers.
- About 10-20% of population does not respond. For those that do respond, IOP reduction can be dramatic.
- Systemic side effects: none
- Systemic contraindications: none
- Additional thoughts: avoid prescribing miotics (pilocarpine) in combination with prostaglandins in that miotics reduce uveoscleral outflow and may potentially interfere with the efficacy of prostaglandins
- Prostaglandins are not indicated in secondary inflammatory glaucoma or any clinical entity that has anterior segment inflammation as a component

Clinical Pearl: Prostaglandins are important in that they flatten the diurnal IOP curve as well as giving lingering IOP reduction even as much as 80 hours after dosing. Thus, they are more forgiving of patients that miss dosages.

Clinical Pearl: The most commonly encountered adverse effects from prostaglandin usage are hyperemia, eyelash growth, and periorbital skin darkening.
Clinical Pearl: Hyperemia is reversible with medication cessation. Iris color changes appear to be irreversible. Periorbital skin darkening may be reversible if the medication is stopped soon enough, but may indeed be permanent.

Prostaglandin Analogs: Latanoprost 0.005%
- Xalatan
- Mean IOP reduction: 27-33.7%
  - Can exceed 50%
- Latanoprost is very oculoselective
- Peak action: 8-12 hours after instillation
- Should be refrigerated in storage, but for clinical usage, refrigeration may not be necessary. Shouldn’t be exposed to high temperature or intense light
- Half-life is 17 minutes, thus very low degree of systemic effects
- Initial short-term response to Xalatan is likely due to PF-2 receptor stimulation. Later response may be due to Xalatan actually changing the ground substance in the cellular matrix of the ciliary meshwork.
- Long term IOP control is excellent with Xalatan and may be better than other meds, even if patients miss dosages.
  - Xalatan is as effective at 24 hours as at 4 hours.

Clinical Pearl: It takes about 5 weeks to appreciate the full pressure lowering effects of Xalatan. Don’t check IOP too early after starting therapy.

Travoprost 0.004%: Travatan and Travatan Z
- New bottle design
  - No streaming
  - Smaller drop size
  - More drops/bottle
- Refrigeration not required
- Full FP agonist
- More effective than Timolol 0.5% BID
- 7 – 8 mm Hg reduction over full diurnal
- 33% reduction in IOP
- No significant drift over time
- 56% have IOP reduction > 30% or IOP < 17 mm Hg
- QD dosing
- Peak activity 20 hrs post dose
- Excellent safety profile – well tolerated
- Original Travatan is preserved with benzalkonium chloride and Travatan Z is preserved with Sofzvia, which may be more gentle to the ocular surface
Clinical Pearl: It takes about 2 weeks to see the full IOP lowering effect of Travatan.

Bimatoprost 0.03%: Lumigan
- Allergan hypotensive lipid
- Not true prostaglandin (?) – Different receptors
  - Synthetic prostamidie technically
  - Occurs naturally in ocular tissues
- Regulates aqueous flow and IOP
- Strong IOP lowering activity
- Well tolerated by patients
- Lumigan QD PM most effective dosing
- Lumigan QD lowers IOP better than Timoptic 0.5% BID
- Lumigan is the prostaglandin most likely to cause hyperemia, likely due to the FP receptors that it stimulates.

Clinical Pearl: IOP lowering effects of Lumigan are appreciated very fast, usually within a few days.

Clinical Pearl: Many drugs promote the fact that they increase ocular blood flow. This is nearly meaningless. Any medication that reduces IOP will increase perfusion by reducing blood flow impedance. Further, these studies are all in normal patients or animal models that likely have no bearing on glaucomatous patients.

Clinical Pearl: Every prostaglandin analog and prostaglandin-like drug has the same potential adverse effects and contraindications.

Clinical Pearl: Avoid using prostaglandins in cases of uveitis and avoid using with miotics (not that you would anyway).

Clinical Pearl: Prostaglandins are the drug of choice in IOP rise secondary to carotid cavernous sinus fistula and other cases where the episcleral venous pressure is elevated.

Clinical Pearl: Hyperemia from prostaglandin use is not an allergic reaction, but a response to the prostaglandin, which mitigates inflammation.

Clinical Pearl: Due to chemical differences, each prostaglandin behaves differently. If a prostaglandin reduces IOP, but causes unacceptable redness, try another prostaglandin. Further, if the desired IOP reduction is not optimal with one prostaglandin, try another. Caveat- don’t expect dramatic pressure reductions from switching prostaglandins. For example, if IOP is reduced to 18 mm Hg with a one prostaglandin and your target is 16 mm Hg, then switching prostaglandins may work. Don’t expect much more.
Clinical Pearl: While uveitis and cystoid macular edema have occurred from prostaglandins usage (notably in patients who have had previous bouts of uveitis and CME), these side effects are unlikely to occur in a previously normal patient.

Clinical Pearl: Travatan, Xalatan, and Lumigan account for the vast majority of prescriptions for glaucoma written today.

Clinical Pearl: While prostaglandins are not wholly approved for first line therapy, standard of care indicates that they are the preferred category of medication today.

Sorting Out the Prostaglandins: The XLT study
- XLT (Xalatan-Lumigan-Travatan) study by Parrish and associates, was the first study performed that simultaneously compared the clinical outcomes associated with the use of latanoprost, bimatoprost, and travoprost. This multi-center, randomized, masked-evaluator prospective study compared not only the effectiveness of IOP reduction of the three medications, but also examined the adverse effects and tolerability of the medications.
- In terms of efficacy of pressure reduction, at the conclusion of the study, the IOP was significantly reduced from baseline for all three medications. The magnitude of the reduction was not statistically significant between the medications.
- This indicated that all three prostaglandins performed equally in their ability to reduce IOP, with equal persistence and stability of pressure reduction.
- There were fewer reported symptoms of hyperemia in the latanoprost treated group. The intensity of the hyperemia was also less in the latanoprost group compared to the travoprost and bimatoprost groups.
  - While the latanoprost treated group had less hyperemia, it must be noted that the mean hyperemia score of all three medications was less than Grade 1. Thus, it was seen that all three medications were well tolerated ocularly. All three medications were well tolerated systemically as well.

Combination Agents: Topical Beta Blocker/Carbonic Anhydrase Inhibitor: Cosopt
- Combination of 0.5% Timoptic and 2% Trusopt
- Yellow/orange cap & label
- BID dosing
- Slightly less effective than using each separate drug in combination
- Better convenience and compliance
- This is a popular and important medication currently

Combination Agents: Topical Beat Blocker/Alpha Adrenergic Agent: Combigan
- Combination of 0.5% Timoptic and 0.2% Alphagan
- Approved for several years in Canada; recently approved in USA- availability unknown
Medically Managing Glaucoma:

The goal of treatment in open angle glaucoma is to reduce IOP to a level below which optic nerve and visual field damage will not occur or progression of existing damage is prevented.

- Based upon diagnostic evaluation, weighing risk factors, and considering risk-to-benefit ratio of treatment, the decision to initiate medical therapy is made. Once the decision to treat is made, a target pressure is chosen. This pressure is the one that is felt to be a safe level for a given patient.
- Glaucoma suspects/ocular hypertensive patients who have normal discs and fields and no other associated risk factors could be followed without medical treatment. As numbers of risk factors increase, then the decision to treat may be initiated.
- Treatment is recommended when visual field and/or optic nerve changes occur which are consistent with glaucoma independent of the IOP level.
- Based upon age, expected life span, and degree of damage, some patients may be followed without therapy.
- Once patient is controlled, examine Q3months. Always record the exact time that the patient used the medications on the day of follow-up (a surprisingly high number of glaucoma patients believe that they should skip their medications on the day that they are scheduled to come in for a visit).
- Always measure pulse rate and BP if patient is using beta blockers
- Use a flow sheet to facilitate care
- Noncompliance is the biggest cause of treatment failure
- Never change therapy based upon one bad IOP reading

Therapeutic Considerations

- Medical contraindications necessitate your choosing different therapeutic paths.
- Synergy/non-synergy
  - Each family of glaucoma medications can potentiate pressure-lowering effects.
  - There is no synergy within families, only increasing side effects.
  - You can't mix 2 beta blockers or two prostaglandins together and expect a better effect than with either one alone.
- If IOP is lowered with a drug, but not sufficiently, add another drug to the initial drug. If the initial drug fails to reduce IOP (i.e., is ineffective), discontinue the initial drug and move on to another.
- Sequential monotherapy- a practice where each medication family is tried independently to see which one works best in each individual patient and if one medication can control IOP adequately
  - Time consuming
  - Never add more than one drug at a time!
    - Can’t tell if a single drug is effective or not

Climbing the Therapeutic Ladder

1. Start with one of the commonly used medications (typically a prostaglandin
analog)
2. If IOP not controlled, add beta-blocker or a topical carbonic anhydrase inhibitor or alpha-2 agonist
3. If IOP not controlled, add another choice from #2 and continue until IOP acceptable

- If CAI and beta blocker are both effective, they can be both discontinued and replaced with Cosopt
- Pilocarpine and oral CAI’s, while available, are not great choices and are not typically used
- Some practitioners will not put patients on any more than two medications and others will use three or four
- Laser trabeculoplasty is an option if medications are insufficient
- Surgery is an option if medications and/or laser fail

Clinical Pearl: There is not “standard” medical regimen that is appropriate for every patient.

Clinical Pearl: While Alphagan, a beta blocker, a prostaglandin analog, and a topical CAI are considered maximal medical therapy, many practitioners will not use this much medication. Some practitioners consider three medications and sometimes two medications to be the maximal tolerable therapy for patients and feel that laser or surgery should be used beyond that point.

Treatment Guidelines
Target Pressure Re-examined
- The myth of 21
  - There is no guarantee that IOP less than 21 will preserve a patient’s vision.
  - The greater the degree of damage, the lower the IOP needs to be due to fragility of the already damaged nerve.

Clinical Pearl: Some experts have developed complex algorithms with which to develop a target pressure. Frankly speaking, the most complicated algorithm in the world is no more accurate than guessing.

Clinical Pearl: Target pressure can be considered a range of IOP level, which must not be consistently breached if optic nerve damage is to not occur. This has been seen with zero tolerance. This is not necessary. Any pressure reduction will buy the patient some time.
Clinical Pearl: Glaucoma is not like pregnancy. You can have a ‘little’ glaucoma. You must take into account the detrimental effects on a patient’s life that IOP lowering is likely to have, especially when compared to a small visual field loss that the patient doesn’t notice. You must take into account the side effects of the medications as well as other factors such as cost that reduce the quality of life when treating a patient when you pick a target pressure. The quality of the patient’s life can go down as you force the IOP lower.

Clinical Pearl: What if you don’t reach the target IOP? Did you fail? The most important mm Hg is not the last mm Hg, but the first mm Hg, and the second…and so on.

So, what is the most important thing that we can say about target pressures? A target pressure is that pressure at which the sum of the impact of the glaucomatous vision loss upon the patient and the impact of treatment upon the patient is minimized. Once treatment is started, the goal is not to make the IOP ‘normal’, but safe for the patient.

Clinical Pearl: There is absolutely no reason to heroically lower IOP in office in patients with chronic glaucoma.

Angle Closure Glaucoma

A malignant type of glaucoma caused by the apposition of the iris to the trabecular meshwork obstructing the outflow of aqueous.

Terminology
- Primary angle closure suspect
- Primary angle closure
- Primary angle closure glaucoma
- Primary angle closure attack

Primary angle closure suspect
- Pigmented trabecular meshwork blocked by iris
  - Extent of blockage not clear
- No peripheral anterior synechiae (PAS)
- Disc and IOP normal
- Probe for symptoms of intermittent closure
- Not clear if laser peripheral iridotomy (LPI) or observation is better

Primary angle closure
- Pigmented TM is blocked by iris for 180°
- Have either PAS or elevated IOP
- No disc damage or field loss
• Considered pathologic
• LPI recommended

**Primary angle closure glaucoma**
• Pigmented TM is blocked by iris for 180\(^0\)
• Have either PAS or elevated IOP
• Glaucomatous neuropathy and field loss
• LPI recommended

**Primary angle closure attack**
• Near complete apposition of iris to pigmented TM
• Classic signs and symptoms
• Injection, vision loss, nausea, emesis, halos, corneal edema, elevated IOP, inflammation, mid-dilated fixed pupil
• Medical therapy, iridotomy, iridoplasty, trabeculectomy

**Classes of Angle Closure Glaucoma**
1. Primary angle closure glaucoma (ACG) with pupil block
   • Acute
   • Subacute (intermittent)
   • Chronic
2. Primary angle closure without pupil block
   • Plateau iris syndrome
3. Secondary angle closure with pupil block
4. Secondary angle closure without pupil block

**1. Primary Angle Closure with Pupil Block: Mechanism**
• Irido-lenticular apposition
• Mid dilated state causes most problems
• Absent egress of aqueous to anterior chamber
• Pressure buildup
• Iris bombé: bowing forward of iris due to posterior pressure buildup.
• Irido-corneal apposition
• Closure of angle- Peripheral anterior synechiae (PAS) formation
  • Permanent synechial closure if contact remains too long
• Alleviated by altering the irido-lenticular apposition (pupil block). Can be done with either dilation or miosis: Miosis has long been the standard to pull the iris out of the angle, but anything that alleviates the irido-lenticular apposition should benefit.
  • Very few doctors will dilate a patient in angle closure
• IOP rise (40-70 mm hg or higher)
  • Possible central retinal artery or vein closure due to elevated IOP
  • NFL damage can occur within 24 hrs- tissue cannot adapt to sudden pressure rise
  • Permanent
• Surgical therapy: Laser peripheral iridotomy (LPI) reestablishes communication between the anterior and posterior chamber, thus relieving posterior pressure and
allows the iris bombé to relax and the angle to ultimately open. Every case of angle closure due to primary pupil block should have LPI as part of management. Iridectomy is done surgically as part of trabeculectomy and is much more invasive than iridotomy.

- Prevalence: 0.09% - higher in Asian and Eskimo population
- Anatomic features:
  - Small corneal diameter
  - Small axial length
  - Axial length 5% shorter
  - Moderate hyperopia
- Thick lens
  - 7% thicker
- Greater propensity for lens to move forward
- Shallow anterior chamber:
  - AC depth > 2.5 mm-almost never see ACG
  - AC depth 2.0-2.5 mm-sometimes see ACG
  - AC depth < 2.0 mm-frequently see ACG
  - 75% of ACG has AC depth < 1.5 mm
  - 24% shallower and 37% less volume

**DO NOT MISTAKE ANGLE CLOSURE GLAUCOMA FOR UVEITIC GLAUCOMA AND VICE-VERSA!**

**Clinical Pearl:** Acute angle closure glaucoma can appear superficially similar to acute uveitic glaucoma. In fact, uveitis can cause a secondary angle closure. However, in acute uveitic glaucoma, there will be a very heavy anterior chamber reaction that will be absent in acute angle closure.

**Angle Closure Glaucoma: Patient Profile**
- White > Black
- Asian: ACG > POAG
- Females > males
- Older > younger
- Hyperopes > myopes
- Eskimo population has the highest incidence of angle closure
- Angle closure is uncommon in patients of African descent

**Clinical Pearl:** The typical profile of an angle closure glaucoma patient is an older, hyperopic female. Asian descent increases the risk greatly.

**Acute Primary Angle Closure Glaucoma:**
- Entire angle involved
- Vision loss in days
• NFL damage by 48 hours
• Profound signs and symptoms
  • Red eye
  • Photophobic
  • Halos- corneal edema
  • Blurred vision
  • Nausea/emesis
  • Elevated IOP
    • IOP 45 mm Hg (or greater) common
  • Mid-dilated pupil
  • Mild anterior chamber reaction
  • Cloudy, corneal edema
  • Vision loss can occur from glaucomatous atrophy, ischemic neuropathy, or vascular occlusion. Retinal NFL damage has been documented to occur beyond 48 hours of angle closure attack
• May result in chronic IOP elevation after breaking attack and alleviating angle closure due to TM damage.

**Acute Primary Angle Closure Glaucoma: Management**
• Relieve corneal edema-glycerin topically
• Corneal indentation: Force aqueous into the angle, thus draining it and forcing the angle open.
• Beta blocker (i gtt, no more than 2 drops)
• Pilocarpine 2% (if IOP < 40 mm hg. If IOP > 40 mm hg, it is theorized that ischemia to the iris and ciliary body will prevent miotic effects).
• Be sure that your diagnosis is correct before you start pouring pilocarpine into the patient’s eye
• This is becoming a dangerous strategy because too many doctors have a knee-jerk reaction to elevated IOP and pour in the pilocarpine when the diagnosis isn’t even angle closure.
• Concentrations greater than 2% should be avoided as it may increase ciliary body congestion and lead to greater pupil block
• Iopidine or Alphagan x 2
• Pred forte q15 min.
• Diamox 500 mg (2x250mg tabs)
  • Topical CAI may be used if oral not available or contraindicated. However, it will not be as effective.
• Osmoglyn cocktail (Glaucola)
• Isosorbide if the patient is diabetic
• **Always:** laser PI (pupil block)
• Argon laser iridoplasty has been seen recently as a successful way to break angle closure attacks
• Trabeculectomy in some unresponsive cases
Clinical Pearl: Most doctors believe that you should be pouring pilocarpine into eyes undergoing angle closure. In reality, all that you are likely to do is give your patient diarrhea.

Brain Teaser: What do you do if the cornea is too cloudy to visualize the angle with gonioscopy and won't clear with glycerin? What do you do?

Clinical Pearl: When managing patients in acute primary angle closure, remember that your goal is not to reduce the IOP, but to change the angle anatomy. Pressure reduction is merely part of the process.

Primary Angle Closure Glaucoma: Subacute (Intermittent)
- Recurrent attacks
- Dim lighting leads to pupil dilation and block
- Opens during sleep as pupil mioses- Subsides spontaneously
- Lesser symptoms
- Partial angle closure
- PAS, particularly superiorly
- Cataract and iris atrophy
- Episodic blurred vision
- Halos
- Incorrectly called narrow angle glaucoma
  - Angle chronically narrow
- Often discovered on routine exam
  - IOP often normal in office- misdiagnosed as NTG
  - ONH cupping and field loss are often first indication of this disease

Primary Subacute Angle Closure Glaucoma: Management
- Laser iridotomy first followed by iridoplasty, if necessary
- Long term medical management not appropriate
  - False security-allows PAS to form
- Filtering surgery

Primary Angle Closure Glaucoma: Chronic
- Most common type of primary angle closure
  - 80% are chronic, 20% are acute
- Asymptomatic- Mistaken for POAG- do gonio
- PAS - zippering shut of angle, especially superior angle
- Discovered on routine exam
- Iridotomy first, then medications and filtering surgery if not controlled
- Often will require topical medications following iridotomy to control IOP due to chronic trabecular damage
- Stable visual fields and good long term IOP control were seen in 90% of chronic primary angle closure glaucoma eyes on medical/surgical therapy over 6 years. (Acta
So now we understand angle closure glaucoma … or do we?

Angle Closure Glaucoma Revisited

- ACG – angle opens less dynamically in response to light and pilocarpine
- Patients of Chinese descent – 5 fold more ACG, yet incidence of small eyes not 5 fold
  - Factors other than small eye size must contribute to ACG
  - The factor appears to be the choroid
- Choroidal expansion seen on UBM in ACG

ACG: Role of the Choroid

- Choroid expansion likely contributes heavily to ACG
- Choroidal expansion takes up volume
  - Choroidal expansion by 20% takes up 96 uL
  - Normal anterior chamber is only 100 uL
- Choroidal expansion leads to forward movement of lens and iris and chamber flattening with ACG
- Change in choroidal vessel permeability leads to choroidal expansion
  - Scleritis

Factors Affecting Choroid: Associated with ACG in otherwise normal eyes

- Hypotony
- Choroidal detachment
- CCSF
- Suprachoroidal hemorrhage
- Scleritis
- Choroidal tumors
- Extensive pan-retinal photocoagulation (PRP)
- Fresh CRVO
- Drug-induced choroidal effusions (sulfa based)

Drugs Causing ACG

<table>
<thead>
<tr>
<th>Acetazolamide</th>
<th>Hydrochlorothiazide</th>
<th>Trimethoprim-sulfamethoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indapamide</td>
<td>Promethazine</td>
<td>Spironolactone</td>
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<tr>
<td>Isosorbide dinitrate</td>
<td>Bromocriptine</td>
<td>Tetracycline</td>
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<tr>
<td>Corticosteroids</td>
<td>Penicillamine</td>
<td>Quinine</td>
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<tr>
<td>Metronidazole</td>
<td>Isotretinoin</td>
<td>Aspirin</td>
</tr>
<tr>
<td><em>Topiramate (Topamax)</em>*</td>
<td>Viagra</td>
<td></td>
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</tbody>
</table>

Choroidal Involvement in ACG

- Choroidal expansion in ACG associated with shallowing of chamber
• Malignant glaucoma may not be aqueous misdirection, but poor fluid permeability and choroidal expansion
• Atropine may work by moving ciliary body and improving forward diffusional area for fluid
  • Atropine may be a better choice than pilocarpine

**Primary Angle Closure Glaucoma: Treatment Revisited**
• Medical treatment for acute and only to prep for laser
• Medically treating chronically can worsen condition as angle continues to close
• Laser PI for pupil block
• PAS indicates that laser procedures are likely to be ineffective and trabeculectomy may be needed

**Acute Angle Closure: Pupil Block vs Choroidal Expansion**
• Acute angle closure secondary to pupil block: iris bombe
• Acute angle closure secondary to choroidal expansion: flat anterior chamber without iris bombe
• Acute angle closure secondary to pupil block: beta blocker, pilocarpine, alpha-2 agonist, CAI, topical steroids; LPI
• Acute angle closure secondary to choroidal expansion: topical steroids, cycloplegic (atropine), beta blocker, alpha-2 agonist, d/c precipitating medication (e.g. Topamax); No LPI

**Primary Angle Closure Glaucoma: Steps Toward Angle Closure**
• Small eye
• Nanophthalmos
• Tendency to choroidal expansion
• Poor fluid conductivity in vitreous
• Physiology, not anatomy, leads to ACG
• Need provocative tests to identify choroidal expanders
• Atropine may be better than pilocarpine

2. **Primary Angle Closure without Pupil Block**
• Plateau iris configuration vs syndrome
  • Gonioscopic description of any eye with deep anterior chamber and narrow angle due to large last role of the iris
    • Last roll of the iris is draped over forward displaced ciliary processes
    • Forward rotation of the ciliary processes- usually occurs anatomically
  • The above description applies to plateau iris configuration. Plateau iris syndrome can only be diagnosed following LPI. The angle remains either closed or potentially occludable following LPI
  • Treatable with pilocarpine
• Laser PI
  • Necessary for diagnosing plateau iris syndrome, but does not change the status of
the angle
- Argon laser iridoplasty
  - Seen as quite effective
- Affected by dilation-crowds angle. Can have angle closure with dilation despite patent LPI
- Permanent PAS may form

Clinical Pearl: The presence of a patent LPI does not necessarily mean that the patient is automatically safe to dilate. Don’t forget about plateau iris syndrome.

3. Secondary Angle Closure with Pupil Block
- Phacolytic
- Uveitic
- Phacomorphic
- Aphakia
  - Vitreous prolapse
- Pseudophakia
  - Reverse pupil block with AC lens
- Subluxated lens

4. Secondary Angle Closure without Pupil Block
- Either the peripheral iris is pulled or pushed into the cornea.
- Neovascular glaucoma
- Neoplastic disease
- Iridocorneal endothelial syndromes (ICE): syndromes where corneal endothelial cells over-secrete leading to Descemet’s membrane migrating and extending over the trabecular meshwork. As this membrane contracts, PAS forms. Theses are typically unilateral and more commonly affect women.
  - Essential iris atrophy- gonioscopy shows progressive angle closure by PAS. The pupil is displaced towards the PAS and the iris shows mild-to-moderate ectropion uveae, stromal atrophy, and full thickness iris hole formation opposite the PAS
  - Chandler’s syndrome- changes in the iris are mild to absent while corneal edema presents at normal IOP level
  - Iris nevus (Cogan-Reese) syndrome- the angle changes are the same as in essential iris atrophy, except that an iris nevus covers the anterior iris
  - Treatments include filtering surgery and often penetrating keratectomy. Medical therapy tends to work for a short while and ALTP is ineffective
  - Some inflammatory cases/ uveitic

Clinical Pearl: Many cases of angle closure, such as aphakic (vitreous) pupil block, can be best managed by dilating the patient.

Clinical Pearl: Knowing whether to dilate or miose an angle closure separates doctors from technicians.
Clinical Pearl: After successful laser treatment for angle closure glaucoma, the IOP may still be elevated. The cause typically is compromise to the angle structures (meshwork) from the angle closure. Many doctors don’t realize this and use the term, “mixed mechanism” glaucoma to denote a case where the patient has been successfully treated with laser for angle closure, yet still has elevated IOP. The doctor who uses the term, “mixed mechanism glaucoma” is really saying, “The pressure is high and I don’t know why”.

Primary Open Angle Glaucoma and Primary Angle Closure Glaucoma
- Changing angle configuration- age
- Gonio on a yearly basis on all POAG patients to determine if a conversion from open to closed angle is occurring, especially if a previously well-controlled POAG patient begins to show signs of progressing field loss.
- Laser PI

Primary Angle Closure Glaucoma: Prophylaxis
- Laser PI
  - Especially if AC < 2.0 mm
- Gonio to identify areas of reversible closure
- Provocative tests

Clinical Pearl: Gonioscopy is a static view of a dynamic process and a poor predictor of which patients will undergo angle closure. Better provocative tests are needed to identify those at risk for choroidal expansion and angle closure. Physiology and not merely anatomy explains angle closure glaucoma.
Diagnostic and Therapeutic Review of the Glaucomas IV: Secondary Glaucomas and Childhood Glaucomas

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This lecture consists of a detailed review of the role of the pathophysiology and management of patients with secondary glaucoma. Additionally, there will be a detailed discussion of the pathophysiology and management of patients with childhood glaucomas. While acknowledging that many audience members will have some familiarity with this material from prior training and clinical experience, it is imperative that the most up-to-date information be conveyed to all audience members. Please remember that there is nothing in this presentation that supersedes interactive discussions with the audience or answering questions that arise during the lecture. Please join in our discussions, and refer to this information later as a resource or as a way to solidify your understanding of the various conditions.

Secondary Glaucoma

- Secondary to another condition
  - Inflammation, neovascular disease, etc.
  - 1/3 of all glaucoma cases
  - Patient is typically younger than POAG
  - Angle may be closed or open

Secondary Glaucoma

- Pigmentary (angle open)
- Pseudo-exfoliative (angle open, rarely closed)
- Early and late traumatic (angle open or closed)
- Steroid induced (angle open)
- Lens induced (angle open or closed)
- Neovascular (angle closed)
- Inflammatory (angle open or closed)
- Miscellaneous causes (angle open or closed)

**Pigmentary Glaucoma**
- 1-1.5% of glaucomas in the Western world
- Heredity
  - Autosomal dominant
    - Chromosome 7 (35Q, 36Q)
- Secondary Open angle
- Can occur in patients of African descent
  - Often women 45-53 years
  - Distinctly different appearance
- Bilateral, but may be asymmetric
- Pigment dispersion syndrome (PDS) is the precursor
  - 50% conversion rate to pigmentary glaucoma over lifetime
- High diurnal IOP fluctuations

**Pigmentary Glaucoma: Pathophysiology**
- Irido-zonular contact
- Posterior bowing of mid-peripheral iris (Queer configuration on gonioscopy)
  - Aqueous is trapped in anterior chamber
  - Valve-effect is created
  - Possible relationship with blink and/or accommodation
  - Reverse pupillary block created
  - Constant rub between iris and lens zonules
- Pigment release
- Development of Krukenberg’s spindle (KS)
  - Doesn’t always have to be a spindle formation
- The presence of Krukenberg’s spindle or endothelial pigment should lead you to transilluminate the eye.
- Transillumination defects (radially located in mid-peripheral iris)
  - The presence of transillumination defects should lead you to perform gonioscopy
  - Transillumination defects not always present
    - Dependent upon iris thickness
    - Not directly related to IOP
- Declines with age as the irido-zonular contact decreases as the eye ages and the lens status changes
  - Relative pupil block raises iris off the zonules.
- Heavy pigment accumulation in trabecular meshwork
  - Not directly related to IOP
- The TM endothelial cells phagocytize the pigment. Eventually, digested pigment as well as the increased activity breaks down the TM cells which lift off the trabecular beams. The overall result is a breakdown of the TM secondary to having to process
the pigment. The subsequent inability to process aqueous causes IOP elevations. Physical blockade is only part of the reason for the pressure rise. Trabecular meshwork may have pigment deposition w/o IOP increase- depends on the ability of TM to process and phagocytize pigment

- Pigment release with dilation and exercise (anecdotal)- pts may have IOP spike after exercise
  - Look for pigments in anterior chamber following dilation
- Pigment on lens equator – Scheie line: pathognomic for PDS/PG
  - More common in Black patients
  - Need wide dilation to see it

**Pigmentary Glaucoma: Presentation**

- Endothelial pigment
- Transillumination defects
  - Midperipheral and corresponding to zonular packets
- Trabecular meshwork pigment (seen on gonioscopy)
  - Especially heavy inferiorly, due to gravity
  - In some cases, there will be greater pigment superiorly than inferiorly. This is termed, “pigment reversal sign” and indicates a case of pigment dispersion that is “burning out” with trabecular processing returning to better activity.
- Backward bowed iris, especially in Caucasians (rare in patients of African descent)
  - Iris has concave approach
- Pigment dispersion/pigmentary glaucoma in African descent:
  - Rare endothelial pigment
  - No transillumination defects
  - Heavy meshwork pigment
    - Typically overlooked and considered “normal” in darkly pigmented patients

**Pigmentary Glaucoma: Management**

- Treat PDS as a risk factor for glaucoma development. Initial fields, disc, and NFL analysis is indicated to assess what status of damage may have already occurred. Diagnosis can be missed
- Tx similar to POAG
  - Beta blockers, CAI, adrenergic agonist, prostaglandins
    - There is an argument that because prostaglandins increase the size of the pigment cells, it may exacerbate the blockage. This concept is unproven, however and many patients have been successfully managed with these medications
  - Pilocarpine 1% or Pilopine gel 4%HS (for younger pts.)
    - However, the risk of retinal detachment in these patients on miotics is 6.6%
    - While pilocarpine will stretch the iris, the risk of RD is there
    - Patients the pigment dispersion syndrome/pigmentary glaucoma have a higher incidence of retinal pathology such as lattice degeneration and retinal detachment
  - Argon laser trabeculoplasty (ALT) or selective laser trabeculoplasty (SLT)
    - Heavy pigment makes this treatment effective as laser is pigment dependent
ALT success in pigmentary glaucoma:
- 80% @ 1 yr.
- 62% @ 2 yrs.
- 45% @ 3 yrs.

Trabeculectomy
For PDS- f/u Q3-6mos for IOP check. There is a significant diurnal IOP variation and you may miss change if you are cavalier. Perform DFE and fields
There is new thinking that indicates that iridotomy may be indicated even though it is not a closed angle presentation because the iridotomy will lead to a shallowing of the anterior chamber, which may be enough to reduce irido-zonular apposition. There is theorized to be a reverse pupil block occurring whereas increased pressure occurs in the anterior chamber and forces the iris backwards into apposition with the lens zonules. Some feel that there is no effect on IOP, just a decreasing of the etiology, while others say that it takes at least 5 years in order to realize IOP lowering effect of this procedure. At this point, this manner of treatment is falling into disfavor.

Clinical Pearl: There are many patients with pigment dispersion who do not develop glaucoma. However, be aware that there is a significant diurnal variation in IOP with PDS/PG and you must monitor PDS patients frequently.

Clinical Pearl: Pigmentary glaucoma (and PDS) is different in Black patients. There may not be transillumination defects or endothelial pigment. In fact, this is often overlooked as a cause of glaucoma in Black patients.

Pseudoexfoliative (PXE) Glaucoma
- Exfoliation: peeling of anterior lens capsule due to heat/radiation (glass blowers disease). This is truly rare.
- Pseudoexfoliation: deposition of abnormal basement membrane (fibrillar extracellular material) on anterior lens capsule and in trabecular meshwork. Abnormal basement membrane comes from lens, iris, ciliary body, and uvea. This is the predominate form of the disease.
- Sixth to eighth decade
  - Rare under age 40
- 3:1 bilateral, but may be asymmetric
  - Unaffected “normal” eye will have subtle histopathologic changes
- Open angle
- High prevalence in northern Europeans
  - Scandinavia, Ireland, USA
  - Rare in patients of African descent
- Peripupillary transillumination (may be seen in absence of clinically detectable pseudo-exfoliative material)
  - The presence or development of peripupillary TID is a very important indicator of PXE

Pseudoexfoliative Glaucoma: Pathophysiology
• Exfoliative material
  • Abnormal basement membrane
    • Disturbed basement membrane metabolism
      • Lens epithelium and other tissues as source
  • Deposited on anterior lens capsule, not from lens
  • Pigment released from pupil border
    • Peripupillary transillumination defects – very important finding
  • Heavy pigment (and exfoliative material) found in trabecular meshwork and may block trabecular meshwork, but the mechanism is not well understood
    • Liberated pigment may cause blockage
    • Material likely causes trabecular cell dysfunction
      • Essentially functions the same as pigmentary glaucoma
  • Lens ectomy is not curative—material will deposit on IOL
  • Now recognized as a generalized disorder of the extracellular matrix
    • May have relationship with TIA’s, stroke, and heart disease

Pseudoexfoliative Glaucoma
• All tissues affected
• Ocular HTN develops in 22-81% of pseudoexfoliative cases
  • Overall, about 40% likelihood of developing glaucoma within 10 years
• When glaucoma develops, IOP is usually higher than in POAG
  • More rapid progression than POAG
  • IOP very labile
  • Difficult to control
  • More likely to need surgery
  • More complications with cataract surgery
    • Due to loss of zonular support
    • Can allow for angle closure
• Highest IOP is typically occurring outside normal office hours.
• IOP rise after dilation
  • Pigment dispersion

Pseudoexfoliative Glaucoma: Management
• Treat as POAG
  • Beta blockers
  • Prostaglandins
  • Adrenergic agonists
  • CAI’s
• ALT/SLT - good modality
• Trabeculectomy

Clinical Pearl: Pseudoexfoliative glaucoma is more severe than primary open angle glaucoma. More medications and surgery are needed to control pseudoexfoliative glaucoma than POAG
**Clinical Pearl:** Pseudoexfoliation is easily missed without a dilated lens evaluation.

**Clinical Pearl:** Pigmentary glaucoma and pseudoexfoliative glaucoma may be within the spectrum of the same disease process.

**Clinical Pearl:** The transillumination defects in pigmentary glaucoma are mid-peripheral and are peri-pupillary in pseudoexfoliation syndrome.

**Clinical Pearl:** Pseudoexfoliation syndrome is now generally considered to be a widespread systemic condition of abnormal extracellular matrix that manifests most clearly in the eye.

**Traumatic Glaucoma**
- Early and late effects
- Angle recession
- Hyphema
- Inflammation
- Lens dislocations
- Perforation

**Early Traumatic Glaucoma**
- Hours to days
- Inflammation
- Hyphema
- Trabecular meshwork changes

**Late Traumatic Changes**
- Weeks to years
- Angle recession
- Peripheral anterior synechiae (PAS)

**Traumatic Glaucoma: Hyphema**
- Tear in ciliary body (usually longitudinal muscle)
- Occurs within 7 days of injury
- Range from barely detectable to 8 ball hemorrhage
- Rebleed may occur within 5-7 days
- 50-90% of these pts. develop angle recession
- Prognosis based upon size of initial hemorrhage
  - 1/3rd - good
  - 2/3rd - fair
  - > 2/3rd - poor
- IOP rise related to blood in anterior chamber, pupil block secondary to clot; hemolytic; sideritic; blockage by normal, ghost, or sickled red blood cells.
**Traumatic Glaucoma: Hyphema Management**
- Bed rest (bathroom privileges only)
- Atropine 1% bid
- Pred forte q1h
- Aqueous suppressants
- Avoid prostaglandin analogs and miotics
- Avoid aspirin
- Sickle positive patients - 24/24 rule: If IOP > 24 mm hg for 24 hours, needs paracentesis

**Ghost Cell Glaucoma**
- Follows traumatic hyphema or vitreous hemorrhage
- Ability of RBC's to traverse TM depends upon ability to bend
- Deformability is dependent on natural biconcave shape
- RBC’s undergo senescence in 120 days
- Hemoglobin leaches out and biconcave shape is lost (ghost of its former self)
- Trapped within TM-secondary open angle mechanism
- Tx: paracentesis

**Traumatic Glaucoma: Angle Recession**
- Cleavage of ciliary body muscles
- Widening and deepening of angle
- Fellow eye comparison is necessary because this is not obvious
- Problems occur years after antecedent trauma
- This should be your first thought when encountering unilateral glaucoma
- Etiology is thought to be trabecular meshwork scarring/sclerosis
- 10-20% angle recession pts. develop secondary glaucoma
- Severity of glaucoma related to extent of recession

**Traumatic Glaucoma: Angle Recession Management**
- Observation if IOP, discs normal. Always remember that glaucoma can develop years later and these patients are forever at risk.
- **Fair to poor response to medication**
  - Aqueous suppressants
    - Beta blockers, CAI's, Alphagan
  - Miotics very questionable due to changes in meshwork
  - Prostaglandin analogs seem to work well
- LT very questionable- poor response if recession > 180°
- Trabeculectomy works well
- POAG more common in fellow, uninjured eye. These patients may have predisposition to glaucoma
Clinical Pearl: Always consider angle recession when encountering unilateral glaucoma. This is the number one cause of unilateral glaucoma.

Clinical Pearl: When diagnosing angle recession, you must often compare gonioscopic appearance to the fellow eye, as angle recession can appear normal.

Clinical Pearl: Approximately 40% of cases of angle recession glaucoma are made by imagination only when a doctor can find no other cause for a unilateral or asymmetric case of glaucoma.

**Traumatic Glaucoma: Penetrating Injuries**
- Flat anterior chamber
  - Synechiae (both posterior and anterior)
  - Angle closure
- Metallic foreign body- siderosis
  - Iron in the ferrous form is toxic to TM endothelium
- Fibrous connective tissue ingrowth
- Epithelial ingrowth
  - Blocks TM
- An ophthalmic train wreck (generally, there are no survivors)
- Manage with aqueous suppressants, surgery, etc., - Whatever works. Aggressiveness of management dictated by the level of remaining vision. Glaucoma management is secondary to management of open globe injury.

**Secondary Glaucoma: Steroid Induced**
- Outflow difficulty- steroids are thought to change the TM ability to process aqueous.
- Glycoaminoglycan accumulation is though to be the underlying difficulty
- TM endothelium decreases phagocytotic ability
  - Steroids may prevent release of enzymes that normally depolymerize gags
- Increased difficulty of outflow
- Topical or oral corticosteroids can cause IOP rise
  - Ointment or creams periorbital and inhaled steroids can cause IOP increase
- May be seen in patients endogenously producing excess steroids (e.g., Cushing’s syndrome)
- 2 week onset (often longer)
- About 2/3 of population are steroid responders
- Response is dependent upon:
  - Frequency of application
  - Dose
- Genetic predisposition
  - Genetic relationship - TIGR/Myocillin gene
    - The incidence points to an autosomal recessive inheritance pattern
- Those at risk include:
  - Myopes
- Pts with POAG
- Children
- Treatment:
  - D/C meds
    - After prolonged use, IOP may not lower with medication cessation
  - Aqueous suppressants
  - Prostaglandins
  - LT/ filtering surgery

**Steroid Response in Normal Patients: Dexamethasone 0.1% QID x 4-6 weeks**

<table>
<thead>
<tr>
<th>Degree</th>
<th>Incidence</th>
<th>IOP response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low responders</td>
<td>60-66%</td>
<td>&lt; 20 mm Hg</td>
</tr>
<tr>
<td>Moderate responders</td>
<td>30-33%</td>
<td>21-30 mm Hg</td>
</tr>
<tr>
<td>High responders</td>
<td>4-6%</td>
<td>&gt; 30 mm Hg</td>
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</tbody>
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Armaly & Becker 1970
Urban & Dryer 1990.

**Steroid Response in POAG Patients: Dexamethasone 0.1% QID x 4-6 weeks**

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<td>6%</td>
<td>&lt; 20 mm Hg</td>
</tr>
<tr>
<td>Moderate responders</td>
<td>48%</td>
<td>21-30 mm Hg</td>
</tr>
<tr>
<td>High responders</td>
<td>46%</td>
<td>&gt; 30 mm Hg</td>
</tr>
</tbody>
</table>

Armaly & Becker 1970

**Clinical Pearl:** Steroid induced pressure elevations only occur in approximately 2/3rds of the population and it typically takes 2 weeks (minimum) to 5 weeks (typically) in order for IOP elevations to become apparent. Less than 10% of the population ever becomes a significant problem.

**Clinical Pearl:** The patients most likely to steroid respond are those with glaucoma and children.

**Clinical Pearl:** The most dramatic steroid responses that I have seen (both magnitude and rapid onset) have been in children.

**Secondary Glaucoma: Lens Induced Glaucoma**
- PhacoLYTic
- Lens particle
- Phacoanaphylactic
- Phacomorphic
Subluxated lens

**Lens Induced Glaucoma: Phacolytic**
- Uveitis and elevated IOP in association with hypermature cataract
- Acute onset of pain and redness in an eye that is non-seeing
  - Vision typically is in light perception range
- Hypermature cataract- lens leaks out internal proteins, which are antigenic. Capsule ruptures and extrudes lens proteins into anterior chamber
- Antigen/antibody reaction and subsequent A/C reaction
  - Provokes macrophage response
  - Heavy molecular weight proteins become soluble
  - Proteins can leak out through an intact capsule
- Liquefaction of lens cortex and attenuation of lens capsule
- White flocculent material in chamber and on lens surface
- Bloated macrophages with lens material within them found in anterior chamber
  - PMN’s, plasma cells, and lymphocytes are typically absent
- Variable anterior chamber reaction, heavy flare typical, hypopyon and KP’s rare
  - If inflammation is bad enough, there can be posterior synechiae and pupil block with angle closure or angle closure without pupil block. Not likely, though
- Outflow blockage
- Trabecular meshwork effects (open angle)
- Cured by lensectomy and vitrectomy
  - Some surgeons have had success without vitrectomy
    - Possibility of capsular rupture with subsequent vitrectomy required
- Medical therapy initially to temporize IOP and quell inflammation
  - Corticosteroids q15min to Q2H, depending upon severity
  - Cycloplegia (unless there is zonular damage and danger of subluxation): homatropine 5%, scopolamine ¼%, atropine 1%
  - Beta blockers, alpha adrenergic agonists, CAI’s
  - Avoid prostaglandins and miotics

**Clinical Pearl:** Phacolytic glaucoma occurs more commonly than most practitioners realize. Always consider this in patients with advanced cataract, inflammation, and glaucoma.

**Lens Induced Glaucoma: Lens Particle Glaucoma**
- Broken lens capsule (trauma/surgery)
- Essentially the same pathophysiology as phacolytic glaucoma, except that there is antecedent trauma rupturing the capsule rather than lens hypermaturity.

**Lens Induced Glaucoma: Phacoanaphylactic Uveitis**
- Uveitis following cataract extraction
- Inflammatory secondary glaucoma
• Angle open or closed
• Autoimmunity to lens antigens, which may be left in anterior chamber following procedure.
• Essentially identical to uveitic glaucoma, but is associated with lensectomy complications.
• Occurs as a severe uveitis following cataract extraction- may be confused with endophthalmitis.

**Lens Induced Glaucoma: Phacomorphic Glaucoma**
• Unilateral or asymmetric cataract associated with asymmetric shallowing of the anterior chamber not explained by other factors
• Difficult to differentiate from primary angle closure
• Acute to intermittent red, painful eye, typically at night
• Blurred vision from corneal edema
• Often have rapidly developing cataract from trauma or inflammation
• Mild anterior segment inflammation
• Typically, vision is greatly reduced (<20/400)
• Due to increasing lens thickness: irido-lenticular apposition from growth of the lens cortex and intumescence of the lens.
  • May be associated with short globe axial length
  • Occasionally, phacomorphic glaucoma will occur not due to mature cataract formation, but due to spherophakia in Weill-Marchesani syndrome
• Pupil block and posterior chamber pressure increase
• Secondary iris bombé
• Angle closure with possible PAS formation

**Phacomorphic Glaucoma: Management**
• Initial management should address the acute nature of the angle closure
  • Beta blockers
  • CAI’s
  • Alpha 2 adrenergic agonists
  • Pilocarpine 2%
  • Corticosteroid
• Secondary management begins with iridotomy to relieve pupil block, and perhaps iridoplasty to retract iris out of angle
  • Acceptable only if no significant PAS
  • Be aware that angle closure can occur without pupil block and therefore, LPI is ineffective
• Optimal management is cataract extraction with IOL implantation
  • LPI should be first performed as mydriasis for surgery can exacerbate the condition
  • Cataract extraction in these patients has a high rate of exudative detachment of the choroid and ciliary body with rhematogenous retinal detachment. It is safer to do LPI and iridoplasty with medical therapy, especially if visual potential poor.
Clinical Pearl: Consider phacomorphic glaucoma in cases with glaucoma, angle closure, shallow chamber, and asymmetric advanced cataract.

Lens Induced Glaucoma: Ectopia Lentis
- Trauma
- Marfan's syndrome
- Pupil block with angle closure—may be reverse pupil block
- Complicated cataract extraction when lens is dislocated. Often better to leave it alone.
- Iridotomy to relieve angle closure and pupil block. Can have pupil block from other side if lens lies back against the pupil in the anterior chamber.

Clinical Pearl: Any time the crystalline lens is displaced, there is the potential for pupil block and angle closure.

Neovascular Glaucoma
- Neovascularization of the iris and angle (NVI/NVA)
- Many possible causes
  - CRVO*
  - Diabetic retinopathy*
  - Carotid artery disease (ocular ischemic syndrome)*
  - BRVO, HRVO
  - CRAO
  - Giant cell arteritis
  - Coat’s disease
  - Eale’s disease
  - Sickle cell retinopathy
  - Uveitis
  - Retinal detachment
  - Ocular neoplasia
*Most common causes

Neovascular Glaucoma Pathophysiology
- Hypoxia from above conditions
- Vasoproliferative substance (Vascular Endothelial Growth Factor – VEGF) diffuses to viable tissue
- Neovascularization
- Rubeosis
- Angle neovascularization
  - Vessels bridge scleral spur and arborize on trabecular meshwork
- Fibrovascular membranes
- Synechial closure of angle
  - Tent-like PAS initially, later broad areas of angle closure
- Inflammation and high IOP
• Poor prognosis
  • Poorly responsive to medical treatment
• 90 day glaucoma- usually occurs within 90 days of antecedent vascular occlusion
  • This is unique in that the mechanism is secondary angle closure without pupil block

**Neovascular Glaucoma Management**
• Medical tx: atropine and Pred forte used for inflammatory component. May also temporarily use aqueous suppressants.
  • Generally, you do not medically treat this type of glaucoma.
• Trabeculectomy if not too much of the angle is compromised
• Pan-retinal photocoagulation (PRP) to destroy the ischemic retina and reduce the vasoproliferative substance and induce regression of neovascular vessels. Generally successful (90% success) in diabetic retinopathy if <270 degrees of closure. Much less successful in ocular ischemic syndrome. Cryotherapy may be used in place of PRP.
• A newer modality to manage refractory NVG involves trans-scleral diode laser cyclophoto-coagulation. This reduces aqueous production through the laser-induced ablation of the ciliary processes.
• A still newer modality (used in conjunction with methods mentioned above) involves ocular injection of Avastin, an anti-vasogenic drug
• Overall poor prognosis- blind painless eye.

| Medically treating neovascular glaucoma is like arranging deck chairs on the Titanic |
| Clinical Pearl: Neovascular glaucoma is typically the worst glaucoma that a patient can have. |
| Clinical Pearl: Always obtain an ESR and C-reactive protein on patients over the age of 60 years who have anterior segment neovascularization. |

**Glaucoma Associated with Elevated Episcleral Venous Pressure**
• Flow of aqueous:
  • TM to Schlemm’s canal to aqueous veins to anterior ciliary veins to episcleral veins to superior and inferior ophthalmic veins to cavernous sinus to inferior petrosal sinus to jugular vein
  • Increasing episcleral venous pressure will reflexly increase IOP
  • Elevated episcleral venous pressure can be indirectly diagnosed gonioscopically by blood in Schlemm’s canal
• Possible causes:
  • Carotid cavernous sinus fistula
  • Low flow dural sinus fistula of the cavernous sinus
  • Sturge-Webber syndrome
  • Cavernous sinus thrombosis
- Retrobulbar tumors
- Thyroid ophthalmopathy
- Idiopathic elevated episcleral venous pressure
- Most glaucoma meds can only reduce gap between IOP and episcleral venous pressure and are thus very ineffective. Only one medication family will work independent of episcleral venous pressure: Prostaglandins

**Clinical Pearl:** Whenever a patient comes in with a unilateral red eye and ipsilateral IOP elevation, always consider acute angle closure, uveitic glaucoma, and low-flow carotid cavernous sinus fistula.

**Clinical Pearl:** Blood seen in Schlemm’s canal on gonioscopy should increase your suspicion for elevated episcleral venous pressure and lead you to use a prostaglandin medication.

**Clinical Pearl:** You will always misdiagnose your first case of low-flow carotid cavernous sinus fistula. This statement applies also to neurologists, ophthalmologists, and primary care physicians.

**Uveitic Glaucoma**
Glaucoma secondary to uveitis may occur by one or by a combination of several different pathophysiological mechanisms. Careful delineation of the pathophysiology involved is the cornerstone of successful management.

**Clinical Appearance: Two Types**
- "Hot" eye with pronounced episcleral injection, profuse anterior chamber reaction, high IOP, and variable patient discomfort (sometimes excruciating agony).
- Quiet and insidious IOP elevation in patients with chronic iridocyclitis
  - More likely to cause glaucoma

**Classifications and Mechanisms**
- Angle closure with pupil block
- Angle closure without pupil block
- Open angle
- Combination involving all of the above
- Specific uveitic/ocular hypertensive syndromes

**Angle Closure with Pupil Block**
- In acute anterior uveitis, there is a large amount of inflammatory cells, debris fibrous proteins, and aqueous proteins being released into the anterior chamber. Adhesions between the iris and the anterior lens face result in posterior synechiae leading to iris bombé.
- Posterior synechiae forms
- Posterior chamber pressure rises
• Iris bombé occurs
• Peripheral iris-meshwork apposition
• Peripheral anterior synechiae (PAS)

**Angle Closure without Pupil Block**
• Deposition and subsequent contraction of inflammatory debris within the angle may pull the peripheral iris over the trabecular meshwork and cause a progressive closure by PAS. While this may occur without pupil block, there is often some degree of posterior synechiae present. Don’t be fooled. This is common and can happen even if the anterior chamber is deep.

**Open Angle**
• Trabecular meshwork outflow can be impeded both by the accumulation of inflammatory cells as well as the inherent outflow infacility of proteinacious aqueous humor in patients with excessive flare.
  • Flare may be more of a factor in the development of IOP elevation than the amount of inflammatory cells as outflow facility is greatly reduced in patients with excessive amounts of flare, irrespective of the number of inflammatory cells
  • Increased protein content and increased aqueous viscosity. This, combined with other factors leads to a reduction in outflow through the trabecular meshwork
• Acute trabeculitis decreases processing ability
  • Though unsubstantiated by histological evaluation, there may be direct inflammation of the trabecular meshwork itself (trabeculitis), leading to a decreased ability to filter aqueous
• Corticosteroids may also contribute to the IOP rise
• The pressure rise may or may not be proportional to the severity of the inflammation. Secretory hypotony (and increased uveoscleral outflow due to elevated levels of prostaglandins in the anterior chamber) may mask decreased trabecular function. Pressure spike may occur if ciliary aqueous function returns before trabecular function.

**Clinical Pearl:** In most cases of uveitic glaucoma, there will be a combination of factors causing pressure elevation.

**Glaucoma Associated with Acute Anterior Uveitis: Medical Therapy**
• **Aggressively** reduce inflammation
  • E.g. Pred forte (prednisolone acetate 1%) Q15min x 6H, then Q1H while awake
    • May require steroid injections in very severe cases
      • Can be handled topically if treatment begins early enough
      • This is absolutely essential to prevent disaster. Do not worry about steroid response glaucoma. Under-treating inflammation due to concerns about steroid impact on pressure is false economy.
  • Cycloplegia:
    • Atropine 1% or scopolamine ¼%
  • Prevent PAS with aggressive anti-inflammatory therapy above
• Break/prevent posterior synechiae
  • In the early stage, prevent or break posterior synechiae with potent cycloplegics
  • If this doesn't break synechiae, additionally use 10% Phenylephrine (Neosynephrine) in office.
    • Pledgets of 10% neosynephrine in cul-de-sac
    • Steroids help dissolve fibrin and adhesions
• Lower IOP
  1. Beta-blockers, alpha-2 adrenergic agonists, and CAI's (topical or oral)
  2. Avoid miotics - miotics exacerbate the condition because it causes movement to a damaged tissue, leading to further breakdown of the blood-aqueous barrier and an increase in inflammation and inflammatory cell in the anterior chamber. This can lead to disastrous consequences
  3. Avoid prostaglandin analogs
    • There will be high levels of prostaglandins already in the anterior chamber that mitigate the inflammatory reaction. May worsen condition, but more likely to not help rather than hurt

Clinical Pearl: In cases of uveitic glaucoma, beta blockers tend to be less effective and topical CAIs tend to be more effective than in POAG.

Glaucoma Associated with Acute Anterior Uveitis: Surgical Therapy
• For pupil block, reform communication between anterior and posterior chambers
  • Multiple laser PI
    • Surgical iridectomy if laser PI fails
• Effective only if less than 75% of angle compromised by PAS
• Trabeculectomy with antimetabolites and possible implant surgery

Glaucoma Secondary to Chronic Iridocyclitis:
• IOP can easily vary by 10-30 mm Hg week to week
• Likely due to trabeculitis and not angle closure or inflammatory cell accumulation within meshwork
• Patient not in pain but may have discomfort
• Vision may be variable due to increased inflammation and protein in the aqueous
• Biomicroscopic appreciation of changes in inflammation difficult
• Typically occurs when steroids are tapered or disease in not being well controlled
  • Needs increased steroid dosage

Clinical Pearl: The increased prevalence of glaucoma in chronic uveitis reflects the cumulative effects of inflammation and steroid use. In older patients, minimal amounts of inflammation may overcome a trabecular meshwork with declining function. In younger patients, severe inflammation is usually necessary to overcome a healthy, functional trabecular meshwork.
Clinical Pearl: Glaucoma is more likely to occur with chronic uveitis rather than acute uveitis.
Clinical Pearl: Regardless of the mechanism of pressure rise (i.e., angle status) in uveitic glaucoma, the treatment is essentially the same: Aggressive use of steroids, cycloplegics, mydriatic agents, and aqueous suppressants. Avoid prostaglandins and miotics.

Hypertensive Uveitis Syndromes: Glaucomatocyclitic Crisis
- Possner-Schlossman Syndrome
- Idiopathic and idiosyncratic
- Ocular hypertensive syndrome associated with mild AC reaction
- Occurs mostly between ages of 20 and 60 years, and is rare over age 60
- Unilateral
- Recurrent
  - Intervals of months to years
- Mild symptoms, or may be asymptomatic
- Blurred vision secondary to corneal edema common
- Mild anterior chamber reaction
- Keratic precipitates are often the only sign of inflammation, and may not even be present
  - Flat, round, and non-pigmented
  - Concentrated over inferior endothelium
- The conjunctiva may be white and quiet, or mildly injected
- Anterior chamber angle is open and normally pigmented
- Pupil may be mid-dilated
- Iris hypochromia may occur, but is uncommon
- High IOP (30mm hg-60mm hg is typical, but 90 mm hg has been reported)
  - IOP elevation can precede inflammation signs
  - IOP level is disproportional to amount of inflammation
- Self limiting
- Duration: hours to weeks- typically will last for several days, but can persist for months
- Normal fields and discs
  - There is a strong association with POAG in these patients
- All findings normal between attacks

Glaucomatocyclitic Crisis: Pathophysiology
- An obscure etiology.
- Decreased outflow suggests a trabeculitis as the causative mechanism.
- Prostaglandin E (causing a breakdown of the blood-aqueous barrier) found in high concentrations, which may increase the blood-aqueous barrier permeability and lead to increased aqueous production.
  - Also, prostaglandins will lead to an increase in cells and proteins in the AC due to the barrier breakdown.
  - Prostaglandin E has been found in high levels during acute attacks and normal levels have been found in the same patients during normal times.
• Prostaglandin inhibitor indomethacin has been more effective at lowering IOP than Diamox, dexamethasone, and epinephrine
• There has been evidence of the herpes virus in the anterior chambers of patients with glaucomatocyclitic crisis

Clinical Pearl: There is something unique about the Herpes virus that causes trabeculitis.

Glaucomatocyclitic Crisis: Treatment
• This is self-limiting and will spontaneously resolve. If you are sure of the diagnosis, the patient can potentially be monitored without medical treatment. If you decide to treat (especially if IOP is very elevated), direct treatment at the inflammation first and the ocular hypertension secondarily. Avoid miotics and prostaglandin analogs. Cease treatment between attacks, but monitor closely between attacks as there is a high incidence of concomitant POAG in these patients. These patients may develop POAG or they may spend more time in attacks than normal and this will lead to permanent damage.
• Corticosteroids are treatment of choice
• Cycloplegics/mydriatics are generally unnecessary
• Beta blockers, alpha adrenergic agonists, CAI’s

Clinical Pearl: Glaucomatocyclitic crisis is frequently misdiagnosed. Consider this condition in cases of mildly symptomatic red eye with elevated IOP.

Clinical Pearl: When trying to diagnose Glaucomatocyclitic crisis: Look carefully in the anterior chamber for a rare cell or two, and check the endothelium for any keratic precipitates.

Clinical Pearls: The highest pressures that I have ever encountered have been in patients with inflammatory conditions.

Fuch’s Heterochromic Iridocyclitis
• Diagnosis usually made between ages 30 and 60, but ranges from teens to 70’s
• Most missed cause of uveitis
• Triad: heterochromia, iridocyclitis, and cataract
• Heterochromia may be absent or subtle
• Chronic anterior chamber reaction
• Keratic precipitates distributed over entire endothelium (characteristic of this condition)
• Synechiae are atypical and do not contribute to glaucoma due to small size
• Cataract present in most patients, but occur later and do not help in diagnosing early cases
• Chorioretinal lesions reminiscent of toxoplasmosis occur frequently
• 60% of Fuch’s patients with chorioretinal scarring had positive toxo titres
• Glaucoma is the main cause of vision loss in Fuch’s patients
  • Etiology is unknown, but believed to be due to chronic trabecular inflammation leading to sclerosis
  • Unless glaucoma develops, no treatment is necessary
  • Steroids don’t work
  • Treat as POAG

Clinical Pearl: Consider Fuch’s heterochromic iridocyclitis in cases of uveitis that doesn’t respond to steroids, glaucoma, and cataract, especially in younger patients.

Clinical Pearl: The systemic disease that I have found most associated with uveitic glaucoma is herpes zoster. Conversely, the most common ocular manifestation of herpes zoster is uveitic glaucoma. In these cases, the IOP was disproportionate to the severity of the uveitis. As the herpes virus has been isolated in the aqueous of patients with glaucomatocyclitic crisis, there is evidence that there is something unique to the herpes virus in its ability to produce a profound trabeculitis.

Clinical Pearl: Avoid prostaglandins and miotics in cases of uveitic glaucoma.

Pediatric and Congenital Glaucoma

Pediatric glaucoma is a term that includes any form of glaucoma that presents between birth and age 18 years. Pediatric glaucoma can be either primary or secondary and the angle may be open or closed. However, there is confusing and overlapping terminology. Primary congenital and primary infantile glaucoma occur secondary to trabeculodysgenesis, a developmental angle anomaly, and can manifest any time between birth and early childhood. Pediatric developmental glaucomas are also classified by the time that they appear in a patient; primary congenital glaucoma occurring between birth and 2 months of age, primary infantile glaucoma occurring between 2 months and 2 years of age, and late onset primary infantile glaucoma (also known as juvenile glaucoma) occurring after 2 years of age. Primary infantile glaucoma overlaps with juvenile-onset open angle glaucoma (JOAG), a non-developmental glaucoma similar to primary open angle glaucoma in adults, which develops late in childhood in the absence of angle anomalies. It is most commonly accepted that the term primary congenital glaucoma refers to patients in all three age groups in the presence of developmental anterior chamber angle abnormalities.

Primary congenital glaucoma
• Developmental anomaly of the trabecular meshwork – trabeculodysgenesis
  • Aqueous outflow is impaired by an isolated trabeculodysgenesis
  • Maldevelopment of the trabecular meshwork, including the iridotrabecular junction, with no other major ocular abnormalities
  • Characterized by absence of the angle recess with the iris inserted directly into the trabecular meshwork. This insertion can be either flat or concave
Flat iris insertion manifests with the iris inserting flat and flush at or anterior to the scleral spur.  
Concave insertion is one where superficial iris tissue sweeps over the iridotrabecular junction. The scleral spur and ciliary body are obscured by the overlying iris tissue which is either sheet like or consists of a dense arborizing meshwork.  

- 75% bilaterality  
- Surgical  
- 90% cure rate  
- Known as buphthalmos  
- IOP elevated during intrauterine life  
- Birth through 2 mos  

**Primary infantile glaucoma**  
- Trabeculodysgenesis  
- Manifests between 2 mos and 2 yrs  
- Late-onset primary infantile – after 2 years of age  
  - Overlaps with juvenile open angle glaucoma (JOAG)  
    - Difference is trabeculodysgenesis, which is not present in JOAG  
    - Thus, categorizing childhood glaucomas based upon time of onset is not as exact as by mechanism of glaucoma development  

**Juvenile open angle glaucoma**  
- POAG diagnosed during childhood  
- Occurring between age 3 years and early adulthood  
- Pressure rise occurs after 3rd birthday, but before 16th birthday  
- Least common  

**Other Pediatric Glaucomas**  
- In aphakic or pseudophakic children following congenital cataract surgery.  
  - Mechanism in aphakic glaucoma is unclear, but gonioscopy may reveal a blockage of the trabecular meshwork secondary to an acquired repositioning of the iris against the posterior trabecular meshwork. Also, prolapsed vitreous may block meshwork  
  - There is often associated abnormal pigmentation and synechiae formation within the meshwork.  
- Glaucoma can occur in a pediatric patient from a number of other causes including but not limited to trauma, inflammation, episcleral venous pressure elevation as seen in Sturge-Weber syndrome, tumor, pupil block from subluxation, retinopathy of prematurity and infectious disease
Clinical Pearl: Any glaucoma occurring before age 18 years is considered pediatric glaucoma. The terms congenital, developmental, and infantile are overlapping and confusing. Any childhood glaucoma caused by trabeculodysgenesis is considered primary congenital glaucoma. A child with glaucoma but without angle abnormalities has JOAG.

Clinical Pearl: Aphakic and pseudophakic children must be followed lifelong for the development of glaucoma. However, the presence of an intraocular lens seems to reduce the incidence of glaucoma development, though the reasons are unclear.

Signs and Symptoms of Primary Congenital Glaucoma
- The classic triad of congenital glaucoma is epiphora, photophobia, and blepharospasm
- Corneal clouding from edema
- Megalocornea-corneal enlargement (> 12mm)
- Myopia
- Amblyopia
- IOP > 20 mm hg
- Globe enlargement
- Descemet's tears-horizontal or vertical (Haab’s striae)
- Scleral ring enlargement
- Rapid cupping
  - Cupping reversible if caught in time
- In infants, C/D ratio greater than 0.3 or asymmetrical cupping, myopic refractive error, or enlarged axial length lead to suspicion of glaucoma

Management
- Obvious referral to pediatric glaucoma surgeon:
  - Descemet’s tears, megalocornea, classic triad, corneal edema
- Large c/d ratio w/o IOP rise:
  - Photos and imaging
- Elevated IOP with normal angle and disc
  - Photos and imaging

Surgical options for congenital glaucoma
- Goniotomy
  - A knife is passed through the cornea through the anterior chamber, and cuts the trabecular meshwork for 180°.
- Trabeculotomy
  - A probe is introduced into the lumen of Schlemm’s canal and rotated into the anterior chamber, thus rupturing the trabecular meshwork.
- Viscocanalostomy
- Filtering surgery
- Cyclocryotherapy
• YAG cyclophotocoagulation
• Diode laser photoablation

Medical therapy
• Medicines only adjunctively with surgery
• Primary medical therapy for congenital glaucoma inappropriate
• Topical beta blockers are a safe and effective class when used in children.
• Prostaglandin analogs are safe and well tolerated, but unfortunately not very effective in the pediatric glaucoma population. The children where efficacy is best demonstrated are older children with JOAG.
• Topical carbonic anhydrase inhibitors (CAIs) are a safe and effective means by which to lower IOP. Probably the best option.
• Brimonidine, though effective in lowering IOP in children, crosses the blood-brain barrier and can potentially affect the central nervous system (CNS). This medication has demonstrated an unacceptable level of adverse events in children and should not be used

Clinical Pearl: IOP does not have to be dramatically high in a child for glaucoma to develop. IOP above 20 mm Hg in a child is concerning.

Clinical Pearl: Children can have undiagnosed glaucoma. It is important to perform tonometry on every patient regardless of age.