Dear Colleagues:
This course is designed to bring you the latest information regarding diagnosis and management of glaucoma in a case-based format. We have included in this handout some key points regarding these clinical entities to satisfy the course requirements, however we vastly prefer to have an engaging dialogue with the audience – this cannot unfortunately be encapsulated in a handout. Please realize that these “notes” are neither exhaustive nor organized consistent with our presentation. They simply represent some facts about the entities which I may or may not cover.

We hope you understand our philosophy and enjoy the program!

Primary Open Angle Glaucoma:
- A constellation of risk factors in addition to loss of neural tissue with increased cupping of a progressive nature
- Progressive loss of visual field
- Risk factors make this a multifaceted disease.

Ocular Hypertension (HTN) vs. Glaucoma Suspect
- Ocular hypertension is defined as IOP of 21 mm hg or more in the absence of structural and functional changes
- 10%-34% develop glaucoma after 20 yrs.
- Depends upon study cited and IOP level used in definition
- 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
- 4-10% of individuals over 40 years have ocular hypertension (up to 10 million Americans)
- Prevalence increases with age
- 75% of ocular hypertensives are over 60 yrs.
- 24% of people over 70 yrs may be ocular hypertensives

Primary Open Angle Glaucoma (POAG)
- 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 neuropathy- cupping which is usually vertically oriented
- Rim notching
- NFL defects
- Characteristic 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
     Theories: mechanical, vascular, cytotoxic, apoptosis
  5) Deepening and enlargement of optic cup
• Later Changes
  1) Additional compression of laminar sheet
  2) Posterior and lateral displacement of laminar sheet
• Diffuse vs Focal Damage
  Diffuse
  1) Nerve head changes
  2) Later onset of visual field defects
  Focal
  1) Superior and inferior poles- hour glass area of susceptibility
  2) Nerve head changes- focal damage of neuroretinal rim is 87% specific for glaucoma. Earlier onset of visual field defects.

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
• NTG may be a systemic or inherited or non-progressive condition and thus does not factor in to the equation

POAG: Diagnosis
• ONH damage consistent with glaucoma
• Visual field loss consistent with glaucoma
• Progression
• IOP
• Other risk factors

Risk Factors for Developing POAG:
- Elevated IOP: This is the most significant risk factor overall
  - Mean IOP 16 +/- 2.5 mm hg
  - IOP which is statistically abnormal is not necessarily physiologically abnormal for an individual eye. Conversely, IOP that is statistically normal is not necessarily physiologically normal for an individual eye. Thus, 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. IOP measurement is an inadequate screening item.
  - IOP increases with age
  - IOP decreases with exercise (transiently)
  - Increased blood osmolarity decreases IOP (mannitol, glycerin, alcohol)
- Diurnal Variation of IOP
  - < 5 mm is normal
  - Glaucoma patients: 15 mm or more can occur, especially with secondary glaucomas
  - 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 occurs when the patient is sleeping in the supine position.
- Age
  - Older age disease
  - Age is the most significant systemic risk factor for glaucoma development
- Race (1/8 blacks over age 60 develop glaucoma)
  - Earlier onset
  - More aggressive course
    - Especially aggressive in patients of Caribbean descent
  - Older Hispanics have higher incidence of glaucoma than pts of African descent
- Family History
  - Direct relative- parent, sibling, child
  - History of blindness very important
- Central Corneal Thickness (CCT)
  - Thick corneas overestimate true applanation pressure and thin corneas underestimate true applanation pressure. However, beyond errors imparted by applanation, 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
- Thin cornea is a risk factor for glaucoma at all levels of IOP, thus independent of IOP
- There is no scientifically validated conversion factor to adjust for the role of CCT on IOP.
- Diabetes
  - Controversial- likely a minimal impact/ risk factor
- Hypertension (HTN)
  - Causing vascular compromise and arteriolosclerosis
    - Treatment of HTN may actually contribute to ONH damage
- Hypotension, carotid artery disease, cardiac disease
  - Causing poor ONH perfusion
- Ocular Perfusion Pressure (OPP)
  - The difference between systemic blood pressure and intraocular pressure.
    - A measure of retinal and optic nerve perfusion
  - Systolic Perfusion Pressure (SPP)
    - \( SPP = \text{Systolic Blood Pressure} - \text{IOP} \)
  - Diastolic Perfusion Pressure (DPP)
    - \( DPP = \text{Diastolic Blood Pressure} - \text{IOP} \)
  - Mean Perfusion Pressure (MPP)
    - \( MPP = \text{Mean arterial pressure} - \text{IOP} \)
      - Mean Arterial Pressure = \( \frac{2}{3} \text{DBP} + \frac{1}{3} \text{SBP} \)
  - Baltimore Eye Survey
    - Lower OPP strongly associated with prevalence of POAG
    - Six-fold excess risk of having glaucomatosus optic nerve damage in persons with lowest category of OPP
  - The Egna-Neumarkt Study
    - Lower DPP associated with a higher risk of having glaucomatosus optic nerve damage
  - Proyecto Ver Study
    - Persons with Diastolic Perfusion Pressure < 50 mmHg had a four-fold higher risk of having POAG compared to those with Diastolic Perfusion Pressure of 80 mmHg
  - Los Angeles Latino Eye Study
    - Persons with Low Diastolic and Systolic perfusion pressures had a higher risk of having POAG
  - Barbados Incidence Study
    - 4-year risk of developing glaucomatosus optic nerve damage increased dramatically at lower
      - Systolic Perfusion Pressure 2.6 fold
      - Diastolic Perfusion Pressure 3.2 fold
      - Mean Perfusion Pressure 3.1 fold
• 9-year risk of developing glaucomatous optic nerve damage increased at lower
  • Systolic Perfusion Pressure 2.0 fold
  • Diastolic Perfusion Pressure 2.1 fold
  • Mean Perfusion Pressure 2.6 fold
• Glaucoma medications can affect OPP
  • Prostaglandin analogs and carbonic anhydrase inhibitors increase DPP at all time points
  • Beta blockers decrease DPP from 4 am – 4 pm but not at other times
  • Alpha agonists reduce DPP at multiple time points

Sleep Apnea:
• Glaucoma prevalence in pts with obstructive sleep apnea (OSA) 5.7 – 27%
• OSA prevalence in glaucoma 20-55%
• However, 5 recent studies saw no association between glaucoma and OSA
  o Still an unknown entity in glaucoma risk factors

Cerebrospinal Fluid Pressure (CSF)
• Studies have shown that the anatomy of the optic nerve head including the intraocular pressure, the anatomy and biomechanics of the lamina cribrosa and peripapillary sclera, retrobulbar orbital cerebrospinal fluid pressure and the retrobulbar optic nerve tissue pressure may be of importance for the pathogenesis of open angle glaucoma
• An experimental investigation suggested that a low cerebrospinal fluid pressure may play a role in the pathogenesis of normal (intraocular-) pressure glaucoma
• Recent clinical studies reported that patients with normal (intraocular-) pressure glaucoma had significantly lower cerebrospinal fluid pressure and a higher trans lamina cribrosa pressure difference when compared to normal subjects. One may, therefore, postulate that a low cerebrospinal fluid pressure may be associated with normal (intraocular-) pressure glaucoma. A low systemic blood pressure, particularly at night, could physiologically be associated with a low cerebrospinal fluid pressure, which leads to an abnormally high trans lamina cribrosa pressure difference and as such to a similar situation as if the cerebrospinal fluid pressure is normal and the intraocular pressure is elevated.

Glaucomatocyclitic Crisis
• AKA Possner-Schlossman Syndrome
• Ocular hypertensive syndrome associated with mild anterior chamber reaction
• Occurs mostly between ages of 20 and 60 years, and is rare over age 60
• Unilateral
• Most likely of any glaucoma to be recurrent; that is, there are periods where the eye is quiet and normal and periods where the IOP is elevated.
• Intervals of months to years
• Mild symptoms, or may be asymptomatic. Intense pain does not occur
• 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 (30 mm Hg-60 mm Hg is typical, but 90 mm Hg has occurred)
- 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.

**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 (and it is recommended that you do treat), direct treatment toward the inflammation first and the ocular hypertension secondarily. _Avoid miotics and prostaglandin analogs_. Cease treatment between attacks, and 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 such as prednisolone acetate, loteprednol, and dufluprenate are treatment of choice
- Cycloplegics/mydriatics are generally unnecessary
- Beta blockers, alpha adrenergic agonists, CAI’s

**Lens Induced Glaucoma: Phacolytic**
- 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
• IOP typically exceeds 35 mm Hg
• 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
• Outflow blockage
• Trabecular meshwork effects (open angle)
• If inflammation is bad enough, there can be posterior synechiae and pupil block with angle closure or angle closure without pupil block.
• Cured by lensectomy and vitrectomy
  • Some surgeons have had success with ECCE without vitrectomy
  • Possibility of capsular rupture with vitrectomy required
  • ICCE often the procedure of choice
• 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 Xalatan
  • Avoid miotics such as pilocarpine at all costs!

Pigmentary Glaucoma
• 1-1.5% of glaucoma in the Western world
• Heredity
  • Autosomal dominant
  • Chromosome 7 (35Q, 36Q)
• Open angle
• Most common in young, myopic, white males (20-45 years)
• Can occur in women 45-53 years
• May be seen in black patients, but may have very different presentation
  • May be more severe and difficult to manage in these patients
• Bilateral, but may be asymmetric
• Pigment dispersion syndrome (PDS) is the precursor
  • 50% conversion rate to Pigmentary glaucoma over lifetime
• Insidious
Decreases with age due to changing status of lens zonule/posterior iris apposition

**Pigmentary Glaucoma: Pathophysiology**

- Irido-zonular contact
- Posterior bowing of mid-peripheral iris (Q configuration on gonioscopy)
- Aqueous is trapped in anterior chamber
  - Valve-effect is created
- Reverse pupillary block created
  - Constant rub between iris and lens zonules
- Pigment release
- Development of Krukenberg’s spindle (KS)
- The presence of Krukenberg’s spindle or endothelial pigment should lead you to transilluminate the eye.
- Pigment is phagocytized by endothelial cells
- Transillumination defects (the presence of transillumination defects should lead you to perform gonioscopy)
- Transillumination defects not always present- in fact are rather uncommon
  - 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.
- Heavy pigment accumulation in trabecular meshwork
  - Not directly related to IOP
- Pigment release with dilation and exercise- pts may have IOP spike after exercise
- Trabecular meshwork may have pigment deposition w/o IOP increase- depends on the ability of TM to process and phagocytize pigment
- Pigment on lens equator – Scheie line: pathognomonic for PDS/PG
- Need wide dilation to see it
- PDS / PG in Black & African American patients:
  - Minimal to no endothelial pigment
  - Rarely iris transillumination defects
  - Pigment deposition on peripheral lens most common
- IOP rise is truly unknown entity
  - Seems to be TM blockage
  - Mechanical collapse of trabecular beams
  - Not proven

**Pigmentary Glaucoma: Management**

- Actual glaucoma management in PDS is relatively rare. Treat this as a risk factor for glaucoma development. Initial fields are probably indicated to assess what status of damage may have already occurred.
- Dx is difficult
- Tx as POAG
  - Beta blockers, CAI, adrenergic agonist
• Prostaglandin analog? There is an argument that because they increase the size of the pigment cells, it may exacerbate the blockage. This concept is unproven, however.
• 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
• Argon laser trabeculoplasty (ALTP)
  • Heavy pigment makes this treatment effective
  • ALTP success in Pigmentary glaucoma:
    • 80% @ 1 yr.
    • 62% @ 2 yrs.
    • 45% @ 3 yrs.
• Trabeculectomy
  • 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.

**Primary Angle Closure With Pupil Block**
• 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
• Permanent synechial closure if contact remains too long
• Alleviated by 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 will benefit.
• Very few doctors will dilate a patient in angle closure
• IOP rise (40-70 mm Hg or higher)
• Possible central retinal artery closure due to elevated IOP
• Peripheral anterior synechiae (PAS) formation
  • Permanent
• Laser Peripheral Iridotomy (LPI) or trabeculectomy: 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 and is most appropriate treatment.
• Potentially curable
• Prevalence: 0.09%
• Anatomic features:
- Small corneal diameter
- Thick lens
- Small axial length
- Moderate hyperopia
- Shallow anterior chamber

Angle Closure Glaucoma: Chronic
- Most difficult to Dx
- Asymptomatic
- PAS - zippering shut of angle
- Especially superior angle
- Discovered on routine exam
- Cataract and glaukomofleken
- Mistaken for POAG - do gonioscopy
  - value of indentation gonioscopy
  - Iridotomy first, then filtering surgery if not controlled

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

Angle Recession Management
- Observation if IOP, discs normal
- Fair to poor response to medication
- Aqueous suppressants
- Miotics very questionable due to changes in meshwork
- Prostaglandin analogs seem to work well- probably the best option
- Beta blockers, CAI's
- Argon laser trabeculoplasty not useful - poor response if recession > 180°
- Filters work 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.
Normal Tension Glaucoma: Pathophysiology

- Etiology is truly unknown at this time
- Theories:
  - Small vessel disease
  - Vasospasm
  - Hemodynamic crisis (single event theory)
  - Nocturnal hypotension
  - Structurally weak lamina (collagen vasculopathy)
- Carter et al. Ophthalmology 97; 1990:49-55- compared vascular profiles, coagulation tests, and rheologic profiles of 46 NTG, 69 POAG, and 47 controls and found no differences and concluded that if vascular disease is responsible for NTG, then it must be localized or vasospastic.
- New theory: autoimmunity
  - 30% prevalence of systemic autoimmune diseases in NTG vs. POAG and controls
  - Immuno-pathogens may damage optic nerve, vessels, or both
  - Patients with “NTG” have increased prevalence of monoclonal paraproteinemias
  - Paraproteinemias are seen in patients with peripheral neuropathies

Current Update: Results from the Collaborative Normal Tension Glaucoma Study Group (CNTGSG) 1998

- Randomized, controlled clinical trial 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
- 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.

- 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