1. Aqueous Humor
   
   A. Composition: Aqueous is a transparent, colorless solution continuously formed from plasma by the epithelial cells of the ciliary processes. Its composition and formation resembles cerebrospinal fluid. Notable features of its composition include:

   1. Very low protein concentration (0.5% of plasma). Proteins found in normal eyes include Albumin, IgG (but not IgA, IgM and IgD as these are larger molecules) and trace quantities of complement, and the fibrinolytic and coagulation system. Plasminogen and plasminogen proactivators are in more substantive concentrations. There is very low concentrations of inhibitors of plasminogen activators) to ensure that the trabecular meshwork remains free of fibrin.

   2. Most species have very high concentrations of ascorbate in the aqueous which is actively secreted into the posterior chamber. Ascorbate is concentrated by the lens epithelium and has been shown to have a protective effect against UV-induced DNA damage to lens epithelium. Ascorbate may function as an antioxidant, regulate the sol–gel balance of mucopolysaccharides in the trabecular meshwork, or partially absorb UV radiation. Diurnal mammals have approximately 35 times the concentration of aqueous ascorbate of nocturnal mammals.

   3. Lactate is produced as a result of the glycolytic degradation of glucose by both the ciliary body and the retina. It diffuses into the posterior chamber but is present at only marginally higher concentration than in the plasma at this site. However, it accumulates in the anterior chamber at considerably higher concentration than in the plasma presumably due to contributions by the lens, iris and posterior cornea.

   4. The concentration of amino acids is frequently higher in the aqueous than in the plasma except in dogs where there is a lower concentration of amino acids in the aqueous than in the plasma.

   5. The distribution of ions varies greatly amongst different species. For example, the monkey has a higher concentration of H⁺ and Cl⁻ and a lower concentration of HCO₃⁻ compared to plasma but rabbit aqueous has a lower concentration of Cl⁻ and H⁺ and a higher concentration of HCO₃⁻ compared to plasma. Active transport of Cl⁻ across the feline isolated ciliary epithelium has been reported. The concentration of Na⁺ in the aqueous is almost the same as in the plasma in many species.

   6. Glucose is thought to diffuse into the aqueous, where its concentration is approximately 80% that of plasma. Glucose also diffuses into the cornea. Its concentration within the corneal endothelium is approximately half that in the aqueous. In diabetes mellitus, the aqueous concentration of glucose is increased.

   7. Oxygen is also present in the aqueous humor, at a tension determined to lie between 13 to 80 mm Hg, depending upon the method of measurement. The tension of oxygen in the aqueous can be decreased by topical epinephrine, possibly as a result of uveal vasoconstriction or by hard contact lenses.

   8. Transforming growth factor (TGF) β2 is a component of normal aqueous humor detected in many mammalian eyes and may play a role in glaucoma pathogenesis. The intrinsic activity of TGFβ2 is considered to be an important factor for the maintenance of the anterior chamber-associated immune deviation (ACAID).
9. The key oxidant in the aqueous humor, hydrogen peroxide, is normally present due to reactions of ascorbic acid and trace metals. Additional hydrogen peroxide and reactive oxygen species are generated by light-catalyzed reactions, metabolic pathways, and phagocytic or inflammatory processes. Human trabecular meshwork cells exposed to 1 mmol of hydrogen peroxide show reduced adhesiveness to the extracellular matrix proteins fibronectin, laminin, and collagen types I and IV. Extensive and repeated oxidative stress \textit{in vivo} may result in reduced TM cell adhesion, leading to cell loss that is identified as one of the major culprits in glaucomatous conditions.

B. Function

1. Delivery of oxygen and nutrients to the posterior cornea, lens and perhaps anterior vitreous. Also removes waste products, blood, macrophages, inflammatory products or other debris

2. Continuous formation and drainage of aqueous maintains IOP which is necessary to keep the shape of the eye and maintain the internal alignment of ocular structures – i.e. optimizes the optical properties of the eye.

3. Maintains a transparent and colorless medium of lower refractive index between the posterior cornea and the lens, and thus constitutes an important component of the eye's optical system.

II. Overview of Aqueous Humor Dynamics: Although Maklakoff was one of the first to introduce quantitative measurement of IOP by tonometry in 1885, aqueous humor was typically thought to be a stagnant fluid up to the early 20\textsuperscript{th} century. Study of aqueous humor dynamics didn’t really get going until 1921 when Seidel cannulated a rabbit eye, connected this to a bottle of carmine dye, raised the bottle to an IOP = 15 mm Hg and found that the dye entered the anterior chamber and exited via the episcleral veins. This was considered proof that at physiologic IOPs aqueous humor must continuously enter and leave the anterior chamber.

A. Aqueous humor in equilibrium. Maintenance of a physiologic IOP relies on a delicate equilibrium between aqueous humor production and outflow. In most mammalian species, the rate of aqueous humor formation and drainage is about 1\% -1.5\% of the anterior chamber volume per minute (i.e. the entire volume of aqueous is replaced approximately 60 to 100 minutes).

1. Math \textsuperscript{©} See appendix. Although regulated by exquisitely complex and incompletely understood mechanisms, aqueous humor dynamics can be broadly defined by a relatively simple equation.

\textbf{Goldmann Equation:}

\[ \text{Flow in} = \text{Flow out} \]

\[ \text{Rate of formation} = \text{Pressure gradient across entire outflow pathway} \times \text{Ease with which fluid can exit} \]

\[ F = (P_i - P_e) \times C \]

\[ F = \text{rate of aqueous formation in } \mu l/\text{min} \]

\[ P_i = \text{IOP in mmHg} \]

\[ P_e = \text{episcleral venous pressure in mmHg} \]

\[ C = \text{facility of aqueous outflow in } \mu l/\text{min/mmHg} \]

III. Aqueous Humor Production:

A: Ciliary body anatomy: The ciliary body is composed of:

1. A double layer of epithelium (inner non-pigmented (NPE), outer pigmented) lining ciliary processes. These cells are highly folded which greatly increases surface area to facilitate secretion. In rabbits the surface area of the ciliary processes may be 5.7 cm\textsuperscript{2} which greatly increases access to the relatively small posterior chamber.

   a. These two layers are arranged apex to apex due to invagination of the optic cup. The basement membrane of the NPE in communication with the posterior chamber and fuses with the zonules whereas and the basement membrane of the pigmented layer in contact with the ciliary body stroma.
b. Numerous gap junctions between NPE and PE cells means that these cells freely communicate with each other and actually function together as a syncytium. This direct inter-cellular communication has clinical implications.

c. Tight junctions between adjacent non-pigmented ciliary epithelial cells contribute to the blood-aqueous barrier

2. Blood vessels that lie at the core of ciliary processes. These feed an extensive network of highly permeable (fenestrated) capillaries just under the pigmented epithelium.

3. Ciliary muscle – varies in degree of development and fiber orientation between species
   a. The contribution of ciliary muscle tone to aqueous humor dynamics in veterinary patients has been somewhat neglected but is being increasingly recognized.[5-6]

4. Autonomic nervous system nerve terminals
   a. Adrenergic and cholinergic mechanisms play a role in regulation of IOP – both via effects on aqueous production and on the outflow pathways and are of both physiologic and pharmacologic importance

B. Aqueous humor Production: Diffusion, ultra-filtration and active secretion

1. Diffusion: A passive process in which solutes flow down a concentration gradient across the ciliary epithelium i.e. it moves from a higher concentration to a lower concentration. Most capillary walls are permeable to water, dissolved gases (O₂, CO₂ etc) to many small molecules (glucose etc) and ions (Na⁺, K⁺, H⁺, HCO₃⁻ etc). It is also a way for lipid soluble substances to enter the posterior chamber as these substances easily penetrate lipid membranes. The rate of this movement follows Fick’s Law [Rate of movement = K(C₁ - C₂)] where C₁ and C₂ represent the difference in concentration of the solute on the two sides of the membrane and K is a constant that depends on the nature and permeability of the membrane, the nature of the solute and solvent (water) and temperature.

2. Ultrafiltration: Once thought to be a major method of aqueous production numerous studies have demonstrated that is likely a minor component in normal eyes. Also a passive process which represents the bulk flow of plasma across fenestrated ciliary capillaries into the ciliary body stroma under the pigmented epithelium. It is also augmented by hydrostatic “driving forces” which means that production via this route is pressure dependent and decreases with increasing IOP. Most biologic solutions are a combination of water, salts, sugars, proteins and other large molecules. Most biological membranes are permeable to water, salt and some small organic molecules but are relatively impermeable to larger molecules such as proteins. If a solution of protein and salt (i.e. blood) is separated by a semi-permeable membrane (capillary walls) from a less concentrated protein/salt solution (ciliary body stroma) water will move towards the protein side (blood) but salt will tend to move towards the stroma. This is called dialysis (in peritoneal dialysis unwanted salts and small molecules such as urea leave the blood via this mechanism). If you apply hydrostatic pressure (due to blood pressure) on the protein side of the system the exchange of salt and water is accelerated and the final respective concentrations are changed slightly. This process is called ultrafiltration and is very closely related to dialysis. Since most proteins carry an overall electrical charge (usually negative) Na⁺ and K⁺ tend to shift slightly more than expected to the protein side of the membrane and CL- and HCO₃⁻ tend to shift to the non-protein side. This is called the Gibbs-Donnan effect. Additionally, with pure ultrafiltration there should be no differences in organic substances on the two sides of the membrane. The fact that there are differences in the concentration of organic substances and that the ratios of cations and anions on the two sides of the membrane are not exactly as expected by the Gibbs-Donnan effect indicates that an active metabolic process must also be occurring.
3. **Active Secretion:** An active, energy dependent (derived from ATP hydrolysis) process that is responsible 80-90% of normal aqueous humor production. This process continues despite an increase in IOP. Substances secreted against a concentration gradient:

   a. **Na\(^+\) = 95% of cations in aqueous humor**
      i. via Na\(^+\)/K\(^+\) ATPase enzyme complexes on the cell membrane of the lateral interdigitations of the NPE. Inhibition of this pathway reduces aqueous humor production by 70% in a variety of species indicating that this is a major route of aqueous humor production. In the dog it has been shown that the rate of Na\(^+\) entry into the posterior chamber approximates the rate of fluid formation.
      ii. Na\(^+\) is accompanied by Cl\(^-\) to maintain electrical neutrality and a net flow of H\(_2\)O into the posterior chamber.

   b. **Active transport of Cl\(^-\)** may also be important in some species due to species differences in aqueous: plasma ratios of Cl\(^-\) (high in humans and low in rabbits) and some studies suggest that in the bovine eyes chloride transport is the major method of production.

   c. **Water transport** across the ciliary epithelium appears to be facilitated by a family of different small membrane proteins called aquaporins. These proteins are expressed in animals, plants and lower organisms. AQP1 and AQP4 are expressed in the ciliary epithelium.

   d. **There is also species dependent active transport of certain amino acids and ascorbate.** Diurnal mammals have 35X the concentration of ascorbate of nocturnal mammals suggesting it may play a role in partially absorbing UV light (as well as play a role in regulating the sol-gel balance of the mucopolysaccharides in the trabecular meshwork.

   e. **Bicarbonate**
      i. Carbonic anhydrase in the NPE and PE catalyzes CO\(_2\) + H\(_2\)O → H\(_2\)CO\(_3\). This is followed by an almost instant ionic dissociation to H\(^+\) + HCO\(_3^-\).  
      ii. HCO\(_3^-\) is then passively transported to the posterior chamber simultaneously with the active transport of Na\(^+\) also accompanied by a net flow of H\(_2\)O into the posterior chamber.
      iii. Inhibition of carbonic anhydrase may reduce aqueous production (and hence IOP) by 1) decreasing HCO\(_3^-\) that is available to move with Na\(^+\) to maintain electroneutrality 2) a reduction in intracellular pH may inhibit Na\(^+\)-K\(^+\) ATPase and reduce Na\(^+\) secretion into the posterior chamber 3) decreased availability of H\(^+\) decreases the amount of H\(^+\) for exchange with Na\(^+\) (to maintain electroneutrality) thereby reducing the amount of intracellular Na\(^+\) that can be transported into the posterior chamber.
      iv. There is a huge excess of carbonic anhydrase in the ciliary body meaning that >99% of CA enzyme activity needs to be suppressed to significantly decrease aqueous secretion.

   f. **Factors that contribute to reduced aqueous humor production include:**
      i. Age, Diurnal cycle, Exercise
      ii. Low blood pressure, hypothermia, acidosis, general anesthesia, diencephalon stimulation
      iii. Uveitis, retinal detachment, IOP elevation
      iv. Pharmacologic
      v. Surgical – cyclodialysis and cyclodestructive procedures

**IV. Aqueous Humor OutFlow**
A. Aqueous is produced by the ciliary processes and enters the posterior chamber. A small amount may enter the vitreous. From the posterior chamber (volume of 60 ul in humans), aqueous flows through the pupil into the anterior chamber (volume of 200 ul in humans). There is very little resistance to flow through the pupil but the posterior chamber must have a pressure that is very slightly higher than that in the anterior chamber in order for flow to occur. Flow of aqueous through the eye occurs by:

1. Minor pressure differences between the posterior chamber, anterior chamber and episcleral veins
2. Gravity pulls aqueous inferiorly
3. Thermal convection currents in the anterior chamber as aqueous cools and flows downward close to the cornea and upward as it warms, close to the lens
4. Movements of the head and eye

B. Conventional Outflow: The majority of the aqueous humor exits the eye through the trabecular meshwork, which consists of the innermost uveal trabecular meshwork, the corneo-scleral trabecular meshwork, and the juxta-canalicular meshwork.

1. From the anterior chamber aqueous humor then enters the ciliary cleft via spaces within the pectinate ligament, which spans the iridocorneal angle (ICA).

2. Within the ciliary cleft, aqueous humor percolates through spaces between collagenous beams of the uveal trabecular meshwork (TM), then corneo-scleral TM and ultimately the juxta-canalicular meshwork. The trabecular meshwork consists of sheets and beams, with each beam comprising a central connective tissue core, covered by endothelial cells. The resulting sponge-like mesh contain relatively large spaces, becoming smaller as they approach the juxtacanalicular region. These spaces contain ground substance consisting of a wide range of ECM macromolecules, including glycosaminoglycans, collagen, fibronectin etc. It is believed that the trabecular meshwork offers 60-80% of the resistance to outflow and that much of this occurs in the juxta-canalicular tissue because the spacing between the beams in the trabecular meshwork is relatively large (and hence offers relatively little resistance).

3. The corneo-scleral TM is closely associated with the collector vessels of the angular aqueous plexus, which is analogous to the annular “Schlemm’s canal” of primates.

4. Fluid is then transported by a pressure dependent mechanism across the juxta-canalicular meshwork and via the vacuolating endothelium of the angular aqueous plexus, to the radially oriented collector channels of the intrascleral venous plexus. From there, aqueous passes into the scleral and choroidal veins. Aquaporin water channels described earlier in the ciliary epithelium, are also found in trabecular meshwork and Schlemm's canal cells and may facilitate outflow.

5. It is believed that much of the flow occurs via the above mechanism but it is also possible that outflow is an active phenomenon driven by means of a mechanical pump. In one theory the aqueous outflow pump receives power from transient increases in IOP such as occur in systole of the cardiac cycle, during blinking and during eye movement. These transient pressure spikes cause microscopic deformation in the elastic structural elements of the trabecular meshwork, and outflow pathways and these actively pump aqueous out of the eye.

6. Primary resistance to aqueous outflow (inversely proportional to outflow facility) is thought to be localized to inner wall of the intrascleral plexus (ISP)/ endothelial lining of the angular aqueous plexus and extracellular matrix proteins and glycosaminoglycans within the outermost, juxta-canalicular trabecular meshwork.
7. Episcleral (or Intrasceral) venous pressure (7-8 mmHg) is a major contributor to the back-pressure resistance that determines IOP.

8. Postulated routes for aqueous humor passage into the angular aqueous plexus (analogous to Schlemm’s canal) include:
   i. Large vacuoles in the vacuolating endothelium
   ii. Transcellular pores
   iii. Pinocytic vesicles,
   iv. Phagocytosis (trabecular meshwork cells and macrophages)

C. Unconventional Outflow: In addition to pressure dependent “conventional” drainage via the trabecular meshwork into intrasceral and episcleral veins, it has been shown, using tracer molecules that there is a second “unconventional route” for aqueous outflow that is relatively pressure insensitive (it appears to be a constant value between 10-40 mm Hg in humans), except at low or very high IOPs. The reasons why flow through this route are relatively insensitive to changes in IOP are unclear. This terms refers to outflow via any pathway other than the trabecular meshwork and includes outflow via the cornea (negligible), iris (negligible), retina (due to the pumping capacity of the RPE but is small as long as the retina is attached) and via the posterior aspect of uveal meshwork, through the ciliary muscle and exiting via the supra-ciliary and supra-choroidal spaces and vortex veins.

1. Because the interstitial spaces of the anterior uvea communicate with the inter-trabecular tissues of the posterior uveal trabecular meshwork aqueous aqueous can percolate through the ciliary body interstitium between the longitudinal muscle fibers of the ciliary body to the supra-ciliary and supra-choroidal space. Where the fluid leaves from here is debated but most is believed to seep through the sclera and episclera (especially on the outside of blood vessels that pierce the sclera) and passes into the orbit where it is absorbed by the orbital vasculature (i.e. the uveoscleral pathway). Another fraction may be absorbed by the choroidal vasculature and pass into the vortex veins (i.e. the uveovortex pathway). Finally, some studies have suggested that a “uveolymphatic” pathway may exist in which the aqueous drains into ciliary body lymphatics and then out the eye. The existence of such lymphatics under normal physiologic conditions, however, is controversial.

2. The main determinant of resistance to aqueous outflow via the uveoscleral route appears to reside in the ciliary body especially the interstitial spaces of the ciliary muscle. Pilocarpine, by contracting the ciliary muscle, reduces Fus, whereas relaxation of the ciliary muscle with atropine enhances it. (By virtue of tendinous insertion into the TM, contraction of the ciliary muscle actually enhances outflow via the conventional route, thus IOP is still reduced)

3. Water and small molecules can readily diffuse through the sclera whereas larger molecules and proteins can pass through perivascular spaces and channels within the sclera.

4. Progressively larger molecules ranging from 10nm to 1µm will pass into the sclera, perivascular loose connective tissue within the sclera, or ciliary muscle respectively.

5. As uveoscleral flow can’t be directly sampled, indirect techniques, e.g. using labeled tracers, such as albumin, are required.

6. Species Differences: Marked differences in uveoscleral outflow may reflect, at least to some extent, the degree of development of the ciliary muscle. Estimates of uveoscleral outflow vary considerably between humans, and initial reports indicated a much lower proportion of aqueous outflow via this route but more recent work suggests that uveoscleral outflow accounts for 50% of the outflow in young humans and that this decreases with age. Age-related variation is considerable and age-related reduction in Fus may relate to the substantial increase in ciliary body connective tissue that is seen with aging in humans and
some mammals. Uveoscleral outflow has been estimated to account for as little as 3% (i.e. 0.36µl/min) to as much as 22-34% (2.3µl/min, more accurate tracer studies) in normal cats depending on the methodology used. In dogs uveoscleral outflow is about 15% of aqueous outflow in normal beagle dogs and this reduced to 3% in beagles with POAG. Unlike in some species in which unconventional outflow is relatively pressure insensitive, unconventional outflow increased as IOP increased from 20 to 50 mm Hg in beagle. However, the diameter of the spaces within these pathways became smaller above 20 mm Hg as 1 micron microspheres passed less easily with increasing IOP.[12-14]

V. Methods of Measuring Various Components of Aqueous Humor Dynamics

A. Another way of stating the Goldman equation is: $F_{in} = F_{out} = C_{trab} (P_i-P_e) + F_u$

- $F_{in}$ = Total Aqueous Humor Inflow,
- $F_{out}$ = Total Aqueous Humor Outflow
- $C_{trab}$ = Facility of outflow via the trabecular pathway
- $P_i$ = IOP
- $P_e$ = Episcleral Venous Pressure
- $F_u$ = Uveoscleral outflow

B. Estimating IOP (Pi).

1. **Tonometers** – they only estimate IOP by measuring the “tone” of the eyewall and from that inferring actual IOP. There are inherent errors in these measurements as most of these instruments are calibrated for the human eye and underestimate true IOP in animals. The TonoVet rebound tonometer probably comes the closest to estimating true IOP in dogs, horses, and cats but it is subject to errors introduced by corneal pathology.

2. **Direct cannulation** of the anterior chamber and connecting this to pressure transducer is more accurate at measuring true IOP but its invasive nature makes it unsuitable for clinical use.

C. Estimating Episcleral Venous Pressure

1. **Episcleral Venomanometry** - A commercially available device (Eye Tech episcleral venomanometer model EV-310, Eye Tech Ltd, Morton Grove, IL) is attached to a table mounted slit-lamp. It uses a thin flexible, transparent silicone membrane which is connected to an air chamber that can be pressurized by adjusting a gauged dial much like that found in a Goldman tonometer. The examiner looks through the slit-lamp and the thin membrane and positions the membrane against the conjunctiva over an episcleral vessel and adjusts the pressure until the episcleral vessel is half-blanched (some studies suggest 90% or 100% blanched is the most accurate but this varies from investigator to investigator). Although non-invasive and repeatable this requires general anesthesia in dogs (which may alter EVP), has a somewhat subjective endpoint and likely is also affected by differences in conjunctival thickness. Estimates of EVP can vary by several mm Hg simply due to differences in subjective interpretation of the endpoint.

2. **Direct cannulation** - EVP can also be measured by direct cannulation but this too requires general anesthesia, is not repeatable over time and the small caliber of the blood vessels poses technical challenges.

D. Estimating Aqueous Humor Production

1. **Fluorophotometry using topically applied fluorescein** – this is the gold standard in measuring production in humans and uses a specialized instrument – a fluorophotometer. Two types of fluorophotometers exist. Some are on a slit-lamp with an illuminator, a pair of filters to transmit and excite the light and a light detector. These can usually measure only a small volume of aqueous. Scanning fluorophotometers are similar but can scan the anterior chamber in a one-dimensional or two-dimensional pattern and are generally regarded to be superior
instruments. The anterior chamber volume is derived from keratotomy and pachymetry measurements (the cornea acts like a fluorescein depot and must be within a certain range for the fluorophotometer to be accurate), and the eye is scanned for background fluorescence before fluorescein is applied topically to the eye. Although most is lost in the tears a small amount subsequently penetrates the corneal epithelium and enters the stroma. Fluorescein is not metabolized by the eye and thus can disappear in only three ways: (i) rediffusion through the corneal epithelium and loss with the tears, (ii) lateral diffusion into the limbal tissue, or (iii) penetration of the endothelium and entrance into the aqueous humor, from where it is washed away by flowing aqueous, or is lost by diffusion into the iris (approximately 10% of fluorescein in the aqueous is lost by this route in the human eye). The third pathway of movement of fluorescein from the corneal stroma offers the least resistance, and thus is the major pathway of loss of fluorescein from the stroma. After a period of 3 hours or more several scans of the anterior chamber are then repeated at various intervals over several hours and the rate of loss of fluorescein (which is assumed to be the same as the rate of aqueous humor production) is calculated (usually with an on-board computer).

2. Alternatively aqueous humor production may also be calculated using the above equation. IOP and EVP are measured as described above and Ctrab and Fu are measured using radiolabeled albumin as described below.

E. Estimating Total Outflow Facility – In both two-level constant pressure perfusion and tonography one potential artifact is “pseudofacility” in which a decrease in production due to changes in IOP is mistakenly assumed to represent an increase in outflow facility. This can occur because the ultrafiltration component of aqueous humor production depends on IOP. Hence, with increased IOP aqueous production drops but these two methods interpret them to be an increase in outflow facility. The extent of “pseudofacility” can be measured and is believed to be small (less than 5%) of total estimated outflow facility.

1. Two level constant pressure perfusion. Developed by Bárány's it is the main method of estimating total outflow facility in experimental animals. Under general anesthesia the anterior chamber is cannulated with one needle that is attached to a pressure transducer (so as to record IOP). A second needle is used to cannulate the eye and this needle is connected to tubing and ultimately a fluid bottle containing mock aqueous humor solution. The bottle is maintained at a particular height above the eye resulting in an artificially elevated IOP. Additionally the bottle is mounted on a sensitive strain gauge that is attached to a pen-recorder thereby recording the weight of the bottle. Solution flows from the bottle to the anterior chamber, and from there flows through the outflow pathways of the eye. The rate at which the bottle empties is calculated from its change in weight with time. The procedure is run for 4 minutes, whereupon the bottle is raised to a new, higher level, creating a higher IOP. The procedure is then run for 4 minutes more, and then the bottle lowered to its original level; the procedure is run for a further 4 minutes, and so on. Then, the mean rate at which the reservoir empties at each pressure is calculated. Total outflow facility is calculated as the difference in the mean rates of emptying of the reservoir at the two different pressures, divided by the pressure difference, and is expressed in microliters per minute per millimeter of mercury ($\mu$L/min/mm Hg).

2. Tonography - is a less accurate but noninvasive method of determining total outflow facility that can be serially repeated in patients. It records the decrease in IOP continuously over a period of 4 minutes while a known weight (such as with a Schiotz tonometer or a pneumatonometer) is applied to the eye. From the rate of change of pressure (the slope of the pressure recording), the outflow facility may be calculated. The assumptions underlying this method are that episcleral venous pressure maintains a constant value, and that little or no change in aqueous formation is induced by the instrument itself. The values of flow, IOP, and an assumed or
measured value for $P_e$ can be substituted into the equation in order to obtain a value for outflow facility. There are many sources of error in tonography, but many of these errors appear to cancel each other out because the figures agree quite well with those obtained by the perfusion method, even in the same eye. Values might be a bit lower than expected but this may be due to the fact that uveoscleral outflow, because of its relative pressure-independence, is not measurable by tonography. Variations of tonography, such as the perilimbal suction cup technique or tonography performed at constant pressure have been devised, but the original form devised by Grant has become the standard for the measurement of outflow facility and is the most convenient (albeit not the most accurate) method of estimating aqueous humor flow in humans.

3. **Fluorophotometry** An indirect technique for measuring outflow facility and also uveoscleral outflow in humans as well as monkeys. It is based on calculations done with fluorophotometry measurements before and after aqueous flow suppression with acetazolamide and timolol. Fluorophotometric outflow facility is calculated from the change in flow and IOP measurements before and after acetazolamide and timolol intervention (which suppress aqueous humor production and drops IOP 3-10 mm Hg). Uveoscleral outflow is then calculated. This technique is currently the method of choice for obtaining uveoscleral outflow estimates in humans and has been used extensively to elucidate changes in aqueous humor dynamics with age and in glaucoma as well as the mechanisms of action and interactions of the newer glaucoma experimental and therapeutic agents.

F. **Differentiating between trabecular and unconventional outflow.** Unconventional outflow can be measured using direct tracer based methods or via indirect calculations in which total aqueous humor production and aqueous humor outflow via the trabecular meshwork are measured and the unconventional outflow is assumed to represent the difference. Although the following techniques for direct measurement are the most accurate for the determination of rate of aqueous humor outflow, their invasive nature makes them unsuitable for clinical use. Furthermore, the techniques for resolution of trabecular and uveoscleral outflow using radiolabeled albumin are very complex, time consuming, costly, and difficult to perform in practice.

Any tracer in the anterior chamber is carried away by aqueous humor drainage but two characteristics of the tracer can be used to differentiate conventional versus unconventional outflow: (i) the time required to leave the eye and (ii) filtration based on size of the tracer. Outflow through the conventional pathway is relatively fast (a minute or less) and fairly insensitive to tracer molecular size, such that the rate of tracer appearance in the blood can be used to determine the flow rate through the conventional outflow pathway. In contrast, tracers draining through the unconventional pathway are relatively slow to move through the unconventional outflow pathway (their transit may take up to two hours depending on tracer size, animal species and dimensions of the eye). Tracer accumulation in the uveal tissues thereby provides a means to estimate the unconventional outflow rate as well as identifying the anatomical route of unconventional outflow.

1. **Estimating outflow via the trabecular meshwork.** One technique involves taking advantage of the fact that relatively large tracers or 40KD or larger pass quickly through the conventional outflow pathway but get caught up and pass slowly through the unconventional pathway. This method infuses $^{131}$I-Albumin into the anterior chamber using a pump which maintains a constant IOP and constant concentration of the tracer in the anterior chamber (by both infusing and withdrawing it at the same rate). Blood samples and then drawn and when the appearance of tracer in the blood becomes relatively constant the conventional outflow rate can be calculated using a mathematical formula.
2. **Estimating unconventional outflow using radiolabeled albumin or high molecular weight fluorescinated dextrans.** It is possible to differentiate trabecular and uveoscleral outflow, and their respective facilities, by perfusion of the anterior chamber with a solution of radiolabeled albumin or fluorescinated dextrans. In the radiolabeled procedure, if both eyes are to be studied, one eye is perfused with $^{125}$I-albumin, and the other with $^{131}$I-albumin. The radiolabeled albumin is continuously circulated through the anterior chamber at a constant concentration by a pump as described above. As secreted aqueous humor drains through the trabecular pathway, it takes some of the radiolabeled albumin with it and passes it directly to the general circulation almost immediately. The proportion of aqueous that flows via the uveoscleral route, however, takes approximately 2 hours to reach the general circulation, and so the radiolabel flowing with this proportion of the aqueous does not appear in the blood for this time, after commencement of the perfusion. The experiment is run for 1 hour and 40 minutes. During this time, blood samples are withdrawn from the experimental animal every 5 minutes, and counted on a $\gamma$-counter. This yields an estimate of the rate of flow of the radiolabel to the general circulation via the trabecular meshwork, equated with trabecular outflow. One can modify the technique so that an estimate of trabecular outflow facility may be calculated by determining the difference between such flow measurements made at two different intraocular pressures. Uveoscleral outflow can be determined directly by subsequent euthanasia of the animal, dissection of the eye, and counting of the tissues involved in the uveoscleral outflow pathway (the amount of radioactivity is measured in each of these tissues and the volume of fluid that would be required to deliver this mass is calculated and this is used to determine outflow via this route). Again, if perfusion at two different pressures is undertaken, uveoscleral outflow facility may also be calculated. High molecular weight fluorescinated dextrans yield values comparable to those with labeled proteins. As an alternative to killing the experimental animal, aqueous flow rate (assumed to be equal to the rate of secretion) can be estimated by monitoring the rate of loss of radioactivity circulating through the anterior chamber using a multichannel analyzer. From this, uveoscleral outflow can be calculated indirectly as the algebraic difference between aqueous flow rate and trabecular outflow.

3. **Estimating uveovortex outflow** – This can be estimated by maintain a constant concentration of fluorescein in the anterior chamber using the pump system described above and cannulating one of the vortex veins. The concentration of fluorescein in the vortex vein and the general circulation are determined and mathematical formulae are used to estimate the uveovortex outflow rate.

4. **Calculating unconventional outflow using the Goldman equation.** Because direct methods are invasive indirect calculations of unconventional outflow are commonly used. However, estimates of unconventional outflow determined by this method have varied greatly and often show poor agreement with direct measurements using tracers and this difference can vary by an order of magnitude even within the same study. This method may be able to show a difference between pre- and post-drug values in unconventional outflow in a given study but values may not be transferable across studies or be particularly valuable for quantifying all of the components of aqueous humor dynamics.
Classification of the Glaucomas

Paul E. Miller, DVM, Diplomate ACVO
Clinical Professor of Comparative Ophthalmology University of Wisconsin-Madison

I. Pathogenesis

A. Stable IOP requires aqueous humor production = aqueous humor outflow. In theory glaucoma can be the result of either overproduction (with a normal outflow system) or impaired outflow with normal (or even subnormal) aqueous humor production. In some patients both production and outflow can be abnormal, resulting in glaucoma

B. “Overproduction”

1. Believed to be very rare to non-existent.

2. Plasma leakage into the anterior chamber as occurs with acute breakdown of the blood aqueous barrier can mimic overproduction. This may be a contributing mechanism to the increased IOP immediately following lens extraction.

3. Ocular Hypertension: A diverse group of disorders characterized by elevated IOP without vision loss

4. Mechanisms of post-lens extraction hypertension

a. Breakdown of BAB mimics overproduction

b. Blood reflux into trabecular meshwork

c. Fibrin/protein in TM

d. Collapse of ciliary cleft that increases with time

e. Normalization of IOP is not due to cleft re-opening but is due to decreased production and perhaps less blood/fibrin

5. Randomized Prospective Masked Clinical Trials of Post-Lens Extraction Ocular Hypertension

a. Carbachol vs. Placebo (JAVMA 1998;212:1885)

0/16 dogs spiked with carbachol

12/16 dogs spiked with placebo

Spikes not related to phaco time or IOL presence

b. Carbachol vs. Latanoprost (IOVS 2001;42:S840)

0/14 dogs spiked with carbachol

6/14 dogs spiked with latanoprost

6. Non-randomized Retrospective Case Series (Vet Ophth 2010;13:14) – No differences between no therapy, carbachol and latanoprost
C. “Impaired Outflow”
1. Most forms of glaucoma result when the egress of aqueous humor from the eye is impaired, but aqueous production continues at a relatively excessive (although usually less than normal) rate.

2. Primary impairments to outflow
   a. No consistent obvious association with another ocular or systemic disorder, are typically bilateral, have a strong breed predisposition and hence are believed to have a genetic basis.
   b. Primary open-angle glaucoma (POAG) in which the drainage angle appears gonioscopically normal (presumably because the impediment to aqueous outflow is deep to the pectinate ligaments)
   c. Primary angle-closure glaucoma (PACG) in which the drainage angle appears gonioscopically narrowed or closed.
      1) PACG is at least 8 times more frequent than POAG in dogs
      2) Acute PACG also is 2.1 times more common in female dogs than in male dogs.

3. Secondary impairment to outflow
   a. Are associated with another ocular or systemic disorder that results in altered aqueous humor dynamics and glaucoma. May be unilateral or bilateral, may or may not be inherited.
      1) “Open angle secondary glaucoma”
      2) “Closed angle secondary glaucoma”
   b. Often the exact mechanism by which outflow is impaired in secondary glaucoma is unclear.
   c. Twice as common as primary glaucomas in dogs (and even more common in cats)

II. Clinical Approach to Patients with Glaucoma - Attempt to identify exactly where the impediment to outflow is, and devise a strategy to circumvent that obstruction. With all patients with glaucoma it is important to remember that in slowly developing glaucomas that large number of retinal ganglion cells (50% or more) may die before any vision loss can be detected even by visual field testing. Therefore “glaucoma” may be present prior to the recognition of a sustained increase in IOP or blindness and classification schemes need to have both an “overt” and “covert or latent” phase.

A. Classification of Glaucoma by Inciting Location of Increased Resistance to Aqueous Humor Outflow (Anterior to Posterior)
1. Post-trabecular Meshwork Forms
   a. Episceral vein obstructions
   b. Scleral outlet channel obstructions
   c. Angular aqueous plexus obstructions

2. Trabecular meshwork obstructions
a. Primary Open-Angle Glaucoma
   1) Adult onset
   2) Primary Juvenile-Onset Open-Angle Glaucoma
b. Secondary Obstructions of a Conformationally “Open-Angle”
   1) Pretrabecular Forms - Pre-iridal fibrovascular membranes
   2) Trabecular Forms – Material within the meshwork
      - Vitreous
      - Plasma proteins
      - Neoplastic cells
      - Red blood cells – intact and ghost
      - Pigment
      - Epithelial down-growth
3. Block at the level of the “Angle”
   a. Primary Angle-Closure Glaucoma
   b. Secondary Angle-Closure Glaucomas
      1) Anterior “pulling” – peripheral anterior synechia
      2) Posterior “pushing” +/- pupillary block
4. Block at the level of the Iris (pupillary block)
   a. Relative pupillary block due to iris-lens apposition
   b. Posterior Synechia/Iris Bombé (absolute block)
   c. Lens within pupil aperture – Luxations, Intumescent lens
   d. Vitreous within pupil aperture
5. Block at the level of the Ciliary Body
   a. Plateau iris – large or anteriorly rotated ciliary processes
   b. Iris-ciliary body cysts
6. Block at the level of the Lens
   a. Phacomorphic glaucoma (swollen lens)
7. Block at the level of the Vitreous (Malignant Glaucoma)
   Components may include:
a. Previous acute or chronic angle-closure
b. Anterior chamber shallowing
c. Forward lens movement (zonules intact)
d. Pupil block by lens or vitreous
e. Zonular laxity
f. Anterior rotation/swelling of ciliary body
g. Expansion of vitreous
h. Posterior aqueous misdirection into or behind vitreous
i. Choroidal effusion

8. **Combined Mechanism** – More than one level is affected. Often posterior lesions also affect a preceding level.

9. **Low-tension Glaucoma** – problem at lamina cribrosa

10. **Idiopathic mechanisms**
Appendix

Complex Inter-relationships and IOP

Unfortunately, although the Goldmann equation is perhaps the easiest hydrodynamic formula to understand, it cannot fully describe the complex inter-relationships involved in aqueous humor fluid mechanics related to drainage. In the 1987 edition of Adler’s Physiology of the Eye Moses warned “…predictions from such a model must be checked by observation and experiment. The actual living organism is so complex that our model must be a reduction of fact, and extrapolations from it may be worthless without further information.” Nevertheless the Goldmann equation and variations on it highlight some key inter-relationships in aqueous humor dynamics.

Let:

- \( F \) = flow (\( \mu l /min \))
- \( F_{in} \) = total aqueous humor inflow
- \( F_s \) = inflow from active secretion
- \( F_f \) = inflow from ultrafiltration
- \( F_{out} \) = total aqueous humor outflow
- \( F_{trab} \) = conventional outflow via the trabecular meshwork pathway
- \( F_u \) = uveoscleral outflow
- \( P \) = Pressure
- \( P_i \) = IOP
- \( P_e \) = episcleral venous pressure
- \( R \) = resistance to flow (mmHg x min/\( \mu l \))
- \( C \) = Facility (conductance) of flow (\( \mu l/min/mmHg \)) = 1/R
- \( C_{tot} \) = total aqueous humor outflow
- \( C_{trab} \) = Facility of outflow via the trabecular pathway
- \( C_u \) = Facility of outflow via the uveoscleral pathway
- \( C_{ps} \) = Facility of inflow – negligible in a non-inflamed eye (pseudo-facility)

Then:

\[
F_{in} = F_s + F_f
\]
\[
F_{out} = F_{trab} + F_u
\]
\[
C_{tot} = C_{trab} + C_u + C_{ps}
\]

At a steady state:

\[ F = F_{in} = F_{out} \]

Thus a modification of the Goldmann equation to take into account uveoscleral outflow (\( F_u \))

……but ignore other factors unlikely to be of clinical significance would be:

\[
F_{in} = F_{out} = C_{trab}(P_i - P_e) + F_u
\]
Suggested Readings


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Primary and Secondary Angle-Closure Glaucoma  
Paul E. Miller, DVM, Diplomate ACVO  
Clinical Professor of Comparative Ophthalmology  
University of Wisconsin-Madison

“The superior physician helps before the early budding of the disease…the inferior physician begins to help when the disease has already developed.”
Huang Ti over 4500 yrs ago

I. Introduction

A. Glaucoma

Glaucoma = a diverse group of diseases united by a common theme in which IOP is too high for the retina/optic nerve to function normally and progressive vision loss occurs

1. Incidence - VMDB over 20 years: 1 in 119 dogs 1 in 367 cats
2. PACG is at least 8 times more common than POAG
3. Screening cats > 7 years old - 1 in 111 cats in private practice
4. Optic Cupping – Human
   a. Optic Cup - Center of disc with no neural disc tissue
   b. Neuroretinal rim - Between outer edge of cup and disc margin
   c. Cupping - Seen as small blood vessels bend as they cross the disc
   d. Cup:disc ratio – the ratio of the cup to disc. In dogs and humans this ratio is about 0.3.
   e. Early Cupping - There is an irreversible decrease in number of nerve fibers, glial cells, and blood vessels
   f. Advanced Cupping - Lamina bows posteriorly as tissue loss continues beyond lamina
   g. Pallor - Maximal area of color contrast or area of the disc that lacks small blood vessels

5. Optic cupping – dogs. Although this condition occurs it appears to have a somewhat different course than in humans and a progressive increase in the "cup to disc" ratio is not typically seen in dogs. This may be due in part to myelination of the disc obscuring the true optic cup in dogs. Optical coherence tomography of dogs with POAG shows little change in the early to moderate stages of glaucoma but dramatic changes in the late stages. Dogs with acute PACG may have a swollen, edematous disc with or without small disc hemorrhages and show cupping only weeks to months later.

B. Human PACG vs Canine PACG

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3. **Mechanisms** - PACG in dogs has been suggested to be associated with a functional block to aqueous outflow at the pupil – a so-called “reverse pupillary block”. This creates a “ball-valve” in which aqueous humor “pumped” into the anterior chamber cannot equilibrate with the posterior chamber. The iris assumes a sigmoidal conformation as the peripheral iris shifts anteriorly and peripherally – leading to appositional closure of the ICA and ciliary cleft. Eventually a type of peripheral anterior synechia forms, preventing the angle/cleft from reopening. The initial impediment to outflow at the level of the pupil may be associated with a relatively anteriorly positioned lens with intact zonules, and/or an increased axial length of the lens or vitreous in proportion to the overall length of the eye. In humans the blocking force to the flow of aqueous humor through the pupil has been calculated to be the greatest when the pupil is midrange, and it is believed that this size pupil allows for sufficient relaxation of the peripheral iris so as to be displaced anteriorly into the ICA. The majority of these dogs also have pectinate ligament dysplasia (PLD) which is clearly associated with increased risk for PACG but is not sufficient in and of itself to produce PACG. PLD may be only a marker for a relatively floppy peripheral iris, or may predispose an eye to PACG simply because it mimics peripheral anterior synechia and primes the eye for closure of the ICA. To circumvent this impediment to outflow, then, one could use a miotic agent that would decrease the pupil blocking forces by making the pupil smaller and would also tighten the peripheral iris and thereby make it less susceptible to “rolling” into the ICA. These drugs also open the ciliary cleft. Demecarium bromide, a potent organophosphate miotic, is just such a drug and has been demonstrated to delay the onset of PACG by almost 4-fold in the fellow normotensive eye in dogs with unilateral PACG.

II. **Primary Angle-Closure Glaucoma – Subclassification** – The block to aqueous outflow is at the angle and perhaps other areas as well

A. **Terminology**
1. **Appositional closure** – the iris and peripheral cornea touch but are not adhered to each other. This appears to be a relatively short lived phased in dogs.

2. **Synechial closure** – a “peripheral anterior synechia-like process has effectively prevented re-opening of the ICA.

3. **Indentation gonioscopy** – with pressure on the cornea the appositionally closed angle may be seen to re-open. The key is to have a “foot-plate” of the goniolens that is smaller than the corneal diameter as uniform pressure on the cornea will not re-open even an appositionally closed angle.

4. **PACG – Overlapping Forms** – Latent, Intermittent (subacute), Acute congestive, Post-congestive, Chronic, Absolute

B. **Latent PACG (Fellow Eye)**

1. **Clinical features**
   a. Normal IOP
   b. Shallow AC
   c. Convex iris-lens diaphragm in humans, sigmoidal iris configuration in dogs
   d. Occludable angle
   e. Close proximity peripheral iris to cornea

2. **Risk Factors**
a. **Predisposing Anatomy:** sigmoidally shaped iris configuration with a lot of iris:lens contact and ability to block at the level of the pupil. May be accompanied by pigment rubbing off the posterior iris and entering the ICA. The anterior chamber may be more shallow than normal (especially in females). The angle is typically abnormal (PLD or narrowed). The cleft is open initially but can close over time. These eyes may remain normal, develop intermittent of acute angle closure, or develop chronic angle closure. The female predisposition may be due to the reported significantly smaller angle opening distance in females versus males (Vet Ophth 2012: Suppl 1:60-3).

b. **Risk factors in a prospective study of Bouvier des Flandres (JAVMA in press)**

i. 92 dogs examined as young dogs and followed for 9 years. Nine dogs (9.8%) developed PACG.

ii. Previous attacks in the fellow eye were a strong predictor of an attack with all 4 dogs with PACG in one eye developing it in the fellow eye (100%) versus only 5.7% (5/88) dogs who did not have PACG in either eye at the initial examination.

iii. 2:1 ratio of females to males but not statistically significant due to small sample size (9).

iv. There was an association between development of PACG and angle index (p<0.001), with a doubling of PACG odds for each 0.20 index decrease. The angle index was calculated by giving a closed angle a value of 0, a very narrow angle a value of 1, a mildly narrowed angle a value of 2, an open angle a value of 3, and a wide open angle a value of 4 per the previously described Ekesten et al. criteria. For scoring PLD the percentage of the iridocorneal angle (for 360 degrees) affected by sheeting was visually estimated. The angle index was then calculated by multiplying the angle width score by (1 – the percentage of sheeting.) For example, if the iridocorneal angle width was scored a “2” and 80% of the iridocorneal angle was sheeted by PLD, the angle index was 2 x (1- 0.80) = 2 x 0.20 = 0.40. With this scheme the maximal angle index value was 4.0 and the minimum value was 0. Therefore, in the preceding example the eye has only 0.4/4 or 10% of the estimated outflow capacity of a normal eye.

v. An association between PACG and a narrow or closed ciliary cleft was found (p<0.001). The rate of development of glaucoma in dogs with at least one eye with a narrow or closed cleft was 24% (8/33) compared to 1.8% (1/57) in dogs with bilaterally open clefts.

vi. Genetics - A single male of unknown disease status was identified as the father/grandfather of each dog which developed PACG.

vii. There was no association with initial refractive error, any relative or absolute A-scan measurement, any qualitative feature of B-Scan, initial IOP or post-dilation IOP.

3. **Latent PACG – Provocative tests**

a. Prone in dark room for 1 hr

b. Mydriatic (when pupil > 5 mm check IOP q 10 min X 1 hr)

   + ve = \( \uparrow IOP \geq 8 \text{ mm Hg} \) and angle gonioscopically closes c. UBM/HRUS imaging in the dark

4. **Clinical Course**

a. Remain normal

b. Develop acute or intermittent angle closure
c. Develop chronic angle closure with or without prior acute/intermittent angle closure

5. Latent PACG –Therapy

a. **Prophylactic Therapy in dogs with acute unilateral primary angle closure glaucoma (PACG) – My Thoughts.** I prefer either 0.125% or 0.25% demecarium bromide (Humorsol, Merck) +/- a topical corticosteroid (both at bedtime q 24 hrs) or 0.5% betaxolol q12 hrs. These are the only 2 drugs that have been demonstrated in a prospective case controlled clinical trial to be effective. Most retrospective studies without controls do not demonstrate a benefit to prophylactic therapy whereas those with controls typically show a benefit. Both demecarium and betaxolol reduce the risk of glaucoma in the fellow eye from a median of 8 months (if no therapy is given) to a median of 31 months. The ability of other drugs to delay an attack, although they are widely used, remains unclear. Given the mechanism by which PACG occurs it seems likely that 0.005% latanoprost will also be effective – at least in the short term. In my experience, however, latanoprost is effective only for a few months but the anterior chamber shallowing it induces may lead to creeping angle closure. Prophylactic therapy is life-long and my protocol is to check IOP once per month for 3 months then every 3-4 months thereafter. IOP is maintained below 20 mm Hg and if it is creeping up over time additional drugs are added prior to an overt attack. It also appears that this therapy makes the eye more responsive to therapy once an overt attack occurs since we have not allowed the drainage angle to become irretrievably collapsed. To date there has not been any benefit shown in treating dogs with abnormal drainage angles (goniodysgenesis) but who never have had an attack of glaucoma in either eye since the vast majority (99%) of these dogs will not develop glaucoma in their lifetime.

b. **Literature Review of Prophylactic Therapy**

i. Slater JAVMA 1986;188:1028-30. A retrospective non-randomized clinical case series with a concurrent control (no treatment or the owner stopped treatment). Included 46 of 70 dogs with data on what happened to the fellow eye. If they received any treatment the median time to an attack of overt PACG was 10 months (n=24). With no treatment, or if the treatment was stopped the median time to an attack was 5 months (n=22). This was statistically significant (p < 0.01) But this only applied to predisposed breeds (Basset Hound, Beagle, Boston Terrier, Cocker Spaniel, Dalmatian, Miniature Poodle, Norwegian Elkhound, and Siberian Husky) and not all breeds. A wide variety of drugs were used and follow up was inconsistent. Females were predisposed 2:1 to males.


- ≈ 4,000 new cases of 1st glaucoma/yr to ACVO Diplomates (VMDB reported 65 cases/yr in the same time frame)
- 89% Rx normotensive eye with abnormal angles in unilateral PACG
- 80% Don’t Rx abnormal angles if no glaucoma in either eye
- ≈ 35 different protocols
  - 20% had no specific protocol
  - 40% used one drug (miotic or beta blocker most often)
  - 40% used multiple drugs
- 70% who Rx not sure if better than placebo
- 49% would participate in randomized placebo controlled trial

But: Only if their drug is used, there was extramural funding to cover costs. The ACVO diplomats who would randomize also tended to see few cases/yr whereas those with a large glaucoma case load believed prevention was effective.
iii. Miller JAAHA 2000;36:431-438 – A prospective, concurrent control open-label non-randomized clinical Trial. Preventative treatment was highly effective (P<0.01) versus no treatment at all.
   1. Control: Presents for second eye (n=20, median = 8 months to attack)
   2. 0.25% demecarium bromide + Gentocin Durafilm q24 hrs (n=55, 31 months to attack)
   3. 0.5% betaxolol q 12 hrs (n=31, median = 30.7 months to attack)
   4. To calculate mean time to an attack data included dogs who did and who did not develop PACG (unlike retrospective studies that evaluated only dogs who had an attack and hence biased the numbers downward).
   5. Rechecks approximately q3-4 months
   6. Two different mechanisms of action of the drugs and both effective
   7. Mild KCS more common with betaxolol than demecarium.

   1. Control: None – all were treated and all developed PACG (i.e. dogs who did not develop PACG in the second eye were excluded).
   2. Rx: Varied - Propine, Trusopt, Azopt, Xalatan, Travatan, Laser CPC.
   3. 49 Dogs (39.8%) became bilaterally affected. Of those they had 23 Dogs (18.7%) that they had dates from first eye to second eye Median = 19.2 mos (1 day to 5.6 yrs). Hence all dogs evaluated failed treatment and most dogs were not evaluated
   4. Small numbers make it difficult to arrive at a definitive conclusion but 19 mos is > 5-8 mos with no therapy in literature. They also evaluated only eyes that developed PACG in the second eye (i.e. they had to fail treatment). This would bias the time to glaucoma to a lower value as dogs who did not develop glaucoma were excluded.

   1. Control: None - all treated
   2. 88 Dogs - 100% got glaucoma (i.e. excluded if retained vision)
   3. Rx: Compared:
      Demecarium - 0.125% - 330 days to an attack or 0.25% for 195 days to an attack
      Latanoprost 284 days to an attack
      Dorzolamide  272 days to an attack
   4. Also may have gotten 1% pred, NeoPolyDex or diclofenac
   5. No difference between treated groups but no control to determine if treatment was better than nothing
   6. Anti-inflammatory plus anti glaucoma drugs went 324 days to an attack vs 195 days to an attack if anti-glaucoma drugs only were used - but not statistically significant.

vi. Stavinohova J Sm Anin Pract 2015;56:662-6. A retrospective non-randomized clinical case series
   1. Control: None - all treated
   2. 40 Dogs - 20 developed glaucoma (median = 9.2 mo)
   3. Rx: Compared:
      1% brinzolamide (n= 10)
      2% dorzolamide hydrochloride (n = 18)
      2% dorzolamide hydrochloride and 0.5% timolol (n = 12)
   4. No statistically significant difference between groups but no control to determine if treatment was better than no treatment
5. Statistical power to detect a difference was low
6. Males median time to glaucoma was 27.4 mo versus 5.9 mo for females (p=0.013)

C. Is there a role for Laser or surgical iridotomy?

1. Pathophysiology
   a. Angle normal in one region but not another
   b. Rapid partial closure and spontaneous re-opening resulting in intermittent IOP increases that spontaneously resolve. Angle closure is only appositional but may eventually lead to synechial
   c. Attacks precipitated by
      – Mydriasis
      – Prone position (shallows AC)
      – Emotional stress
   d. Recurring attacks broken by:
      – Sunlight
      – Sleep

2. Clinical signs
   a. Transient blurred vision (corneal epithelial edema)
   b. “Eye-ache” or frontal “headache”
   c. Usually not “congested” vessels
   d. ± Semi-dilated pupil
   e. ± Corneal epithelial edema
   f. Narrow angle
   g. Eye appears normal between attacks
   h. HRUS may show ciliary cleft is closing/closed

3. Clinical Course
   a. Remain normal - rare
   b. Develop acute angle closure – most common
   c. Develop chronic angle closure with or without prior acute angle closure – occurs

4. Therapy
a. Consider diurnal IOP curves especially at night
b. Latanoprost?
c. Demecarium bromide
d. Betaxolol
e. Carbonic anhydrase inhibitors?
f. Surgery?

D. Acute Congestive PACG

1. Pathophysiology
   a. Presumed “reverse pupillary block”
   b. Sudden total angle closure
c. Appositional closure may rapidly lead to synechial closure
d. Plateau Iris Syndrome
   1). Same signs as acute PACG
   2). Not associated with pupil block
   3). Results from anteriorly positioned ciliary processes that structurally supports the peripheral iris
   4). Uncommon in humans, questionable in dogs

2. Differential diagnosis
   a. Neovascular glaucoma
   b. Chronic POAG with angle closure
c. Secondary ACG by intumescent lens
d. Phacolytic glaucoma
e. Glaucomatocyclitic crisis
   f. Only 50% have Hx of intermittent PACG

3. Clinical signs - acute
   a. Rapidly progressive vision loss
   b. Peri-ocular pain
c. Congested episcleral blood vessels
d. Nausea and vomiting
   f. Severe increases in IOP
g. Corneal edema with vesicles
h. Shallow AC (relative)  
i. Vertically oval pupil which is fixed and semi-dilated

4. **Clinical Signs – once edema clears**  
a. Aqueous flare/cell  
b. Dilated/congested iridal BVs  
c. Complete angle closure on gonioscopy  
d. Optic nerve may be pale, edematous or hyperemic  
e. Choroidal “wedges” of infarction

5. **Treatment – Medically initially**  
a. Latanoprost  
b. Hyperosmotics  
c. Carbonic Anhydrase Inhibitors  
d. Pilocarpine  
e. Corticosteroids

6. **Treatment – Surgery**  
a. If > 50% synechiated (most) -Cyclodestruction and Gonio-implantation  
b. Iridectomy/Iridotomy  
c. Laser gonioplasty (laser iris retraction)

E. **Post-Congestive PACG**

1. **A term to describe eyes that:**  
a. Were successfully treated for acute PACG  
b. Had spontaneous resolution of intermittent PACG (infrequent)  
c. Have a closed angle but normal IOP secondary to ciliary shutdown

2. **Clinical Signs**  
a. IOP normal, decreased, or slight increased  
b. Fixed, semi-dilated pupil (sphincter atrophy/synechia)  
c. Descemet’s folds if IOP dropped fast  
d. Fine pigment on corneal endothelium/iris surface  
e. Angle usually closed but may be partially open
f. Aqueous flare/cell

g. Glaukomflecken anterior caps/subcaps lens opacities

h. Optic disc congested or white/atrophic

i. Wedges of choroidal infarction

F. Chronic PACG

1. Mechanisms
   a. Type 1 – Gradual progressive (creeping) due to synechial closure from iridocorneal contact
   b. Type 2 – Synechial angle closure from intermittent (subacute) attacks

2. Clinical Signs
   a. Similar to POAG
   b. Angle synechiated on gonioscopy

G. Absolute PACG
   1. End stage disease where eye is completely blind and pain relief +/- globe salvage is the goal of therapy

II. Secondary Angle-Closure Glaucoma

A. Mechanisms

1. Anterior “pulling”
   a. peripheral anterior synechia
   b. inflammatory membranes
   c. fibrovascular membranes

2. Posterior “Pushing” forces +/- pupillary block
   a. Iris bombé
   b. Neoplasia
   c. Ciliary cysts
   d. Retinal detachments

B. Neovascular Glaucoma

1. Causes
   a. Widespread posterior segment hypoxia (most) or localized anterior segment hypoxia
   b. Angiogenesis factors released
c. Synechial angle closure by contraction of a fibrovascular membrane

d. Intraocular tumors

e. Chronic intraocular inflammation

f. Retinal detachment

g. Retinal vascular diseases

h. Diabetes mellitus

2. **Stages: Rubeosis iridis (Pre-glaucoma stage)**

a. Normal IOP

b. Tiny, dilated capillary tufts at pupil margin – high magnification essential! Not simply dilated iris BVs

c. Fine, randomly oriented vessels on iris surface

d. Iris fluorescein angiography may help

e. Vessels grow radially towards iris root

f. May or may not progress to glaucoma

3. **Secondary Open-angle Glaucoma Stage**

a. Elevated IOP – may be sudden spikes

b. More florid rubeosis and aqueous flare/cell

c. Vessels arborize in angle and block TM

d. Gonioscopically open “angle”

e. Differentiate from other causes of rapid IOP rise such as acute PACG and uveitic glaucoma

4. **Synechial Angle-closure Glaucoma Stage**

a. Severely elevated IOP

b. Ectropion uvea/iris surface sheen

c. Pupil often dilated and iris pulled away from lens

d. Fibrovascular tissue in angle contracts and “zips” the angle closed

5. **Clinical features**

a. Vision loss

b. Very high IOP

c. Corneal edema

d. Aqueous flare
e. Severe rubeosis iridis
f. Dyscoria
g. Ectropion uvea
h. Angle closure

6. **Medical Treatment**
a. β-blockers and CAI’s are mainstay but may be of limited benefit
b. Atropine and topical corticosteroids for pain relief in advanced cases
c. Anti-angiogenic therapy?
d. Avoid pilocarpine and latanoprost
e. Topical epinephrine derivatives may increase pain

7. **Surgical Treatment**
a. Address cause of hypoxia if possible
b. Pan-retinal argon laser photocoagulation
c. Peripheral retinal cryotherapy (hazy media)
d. Gonioimplantation
e. Cyclodestructive procedures
f. Enucleation/intrascleral prosthesis

C. **Inflammatory Glaucomas**

1. **Classification**
a. Angle-closure with pupillary block
b. Angle-closure without pupillary block
c. Open-angle

2. **Mechanisms**
a. PG-associated apparent increases in aqueous humor production (or blood:aqueous barrier breakdown)
b. Acute outflow obstructions
   1). Inflammatory cells, fibrin, serum proteins
   2). Swelling/dysfunction of the trabecular meshwork
   3). Precipitates on the trabecular meshwork
   4). Corticosteroid-associated changes in outflow
   5). Uveal effusion and angle closure by anterior rotation of CB
6). Angle-closure secondary to massive exudative retinal detachment and anterior displacement of the lens-iris diaphragm

c. **Chronic outflow obstructions**
   1). Scarring and obliteration of outflow channels
   2). Fibrovascular, endothelial or epithelial membranes
   3). Peripheral anterior synechia and angle-closure as membranes contract or induced by inflammatory debris
   4.) Posterior synechia with iris bombé

d. **Angle Closure with pupillary block**
   1). Block initially at pupil (seclusio pupillae)
      a). If ciliary body shutdown IOP is low to normal
      b). If ciliary body is functioning glaucoma may result
   2). Iris bows anteriorly and peripherally (iris bombé)
   3). AC shallows
   4). Apposition of peripheral iris to angle/cornea
   5). Peripheral anterior synechia form
   7). IOP fluctuates widely
   8). Angle closure with pupillary block - Treatment
      a). Aggressively treat uveitis (q 1 h corticosteroids) and systemic CS or NSAIDS
      b). Atropine to prevent synechia
      c). Tropicamide 1% BID to keep pupil moving
      d). Lower IOP:
         - IOP < 30 mm Hg use β-blockers ± sympathomimetics
         - IOP > 30 mm Hg add in CAIs
         - ± hyperosmotics in acute cases
         - Iridectomy – surgical, Argon, Nd:YAG

e. **Angle Closure without pupillary block**
   1). Inflammatory debris deposited in angle/TM
   2). Contraction of peripheral iris (PAS)
   3). Gradual IOP increases which vary with degree of uveitis and ciliary body shutdown
4). Deep AC ± quiet AC
5). Angle gonioscopically closed
6). Medical therapy
   – Address uveitis aggressively
   – Avoid miotics
   – Topical β-blockers or epinephrine
   – Topical or systemic CAI’s
   – +/- hyperosmotics acutely

7). Surgical therapy - Gonioimplantation, Cyclodestruction or Filtration procedures

f. Inflammatory – Secondary open-angle glaucoma

1). Often see as uveitis resolves and ciliary body regains function or endogenous PG levels drop and uveoscleral outflow returns to normal values

2). Results from:
   – Inflammatory debris/cells/protein obstructing TM
   – Trabecular scarring/sclerosis
   – Acute trabeculitis (edema/inflammation of the TM itself)
   – Prostaglandins have a biphasic effect on IOP
   – Corticosteroid associated

3). Usually short-lived