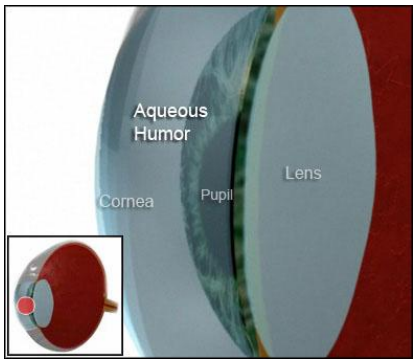
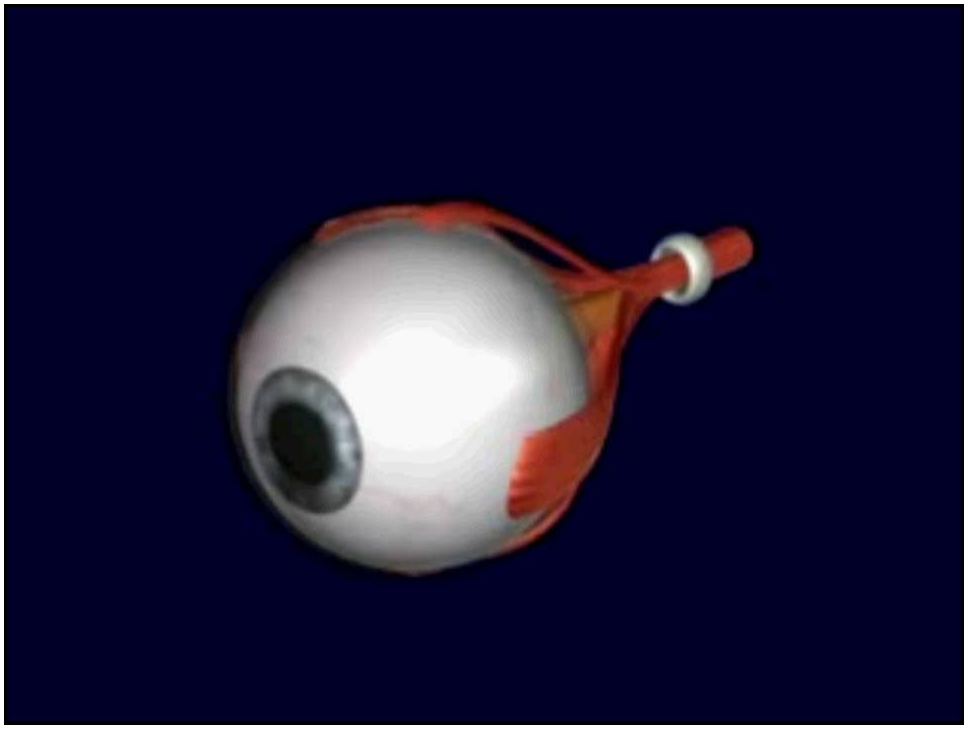
Fluid Dynamics in Glaucoma

Dr Taha Abdel Moneim Labib
Professor of Ophthalmology
Cairo University

- *Aqueous humor* is a clear fluid that fills and helps form the anterior and posterior chambers of the eye.
- The lens and cornea must remain clear to allow light transmission, and therefore cannot be invested within a vasculature...





Functions

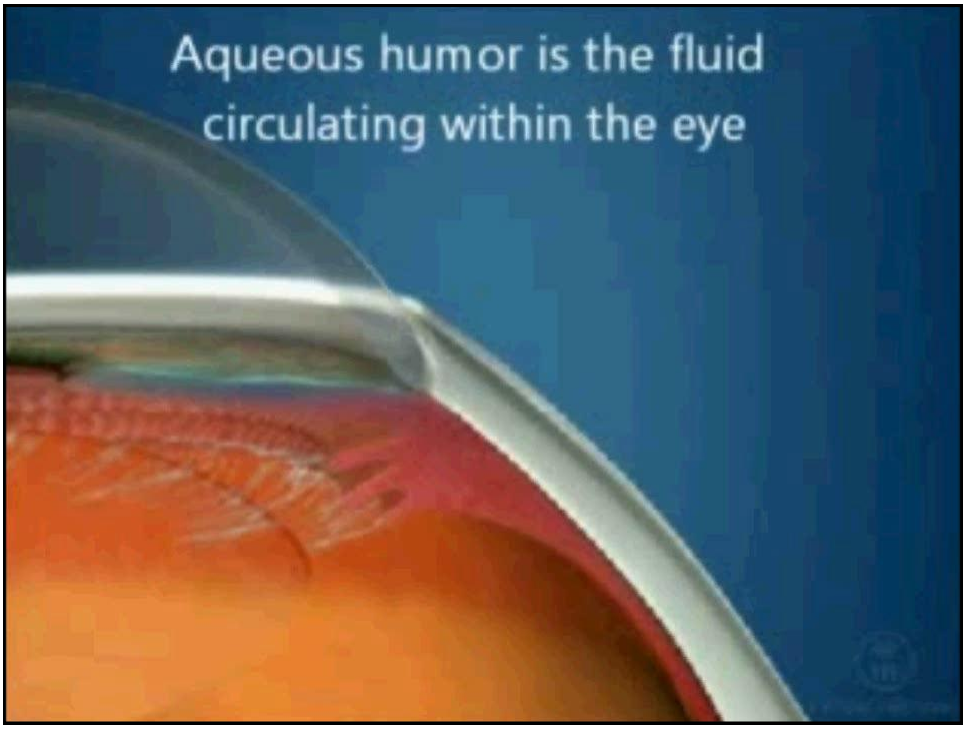
- The aqueous humor:

1. Provides nutrition
2. Removes excretory products from metabolism
3. Transports neurotransmitters
4. Stabilizes the ocular structure
5. Contributes to the regulation of the homeostasis of these ocular tissues.

Functions (continued)

6. Provides a transparent and colorless medium between the cornea and the lens and constitutes an important component of the eye's optical system.

7. Permits inflammatory cells and mediators to circulate in the eye in pathological conditions, as well as drugs to be distributed to different ocular structures



Formation

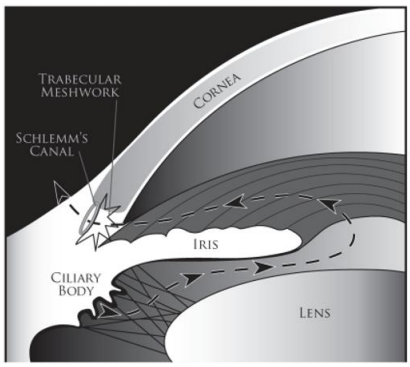
- Three mechanisms are involved in aqueous humor formation:

1. **Diffusion,**
2. **Ultrafiltration**
3. **Active secretion**

The first two processes are **passive** and do not entail active cellular participation.

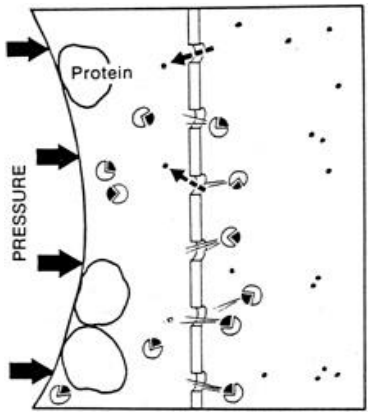
Formation

- **Diffusion** occurs when solutes are transported through the lipid portions of the membrane of the tissues between the capillaries and the posterior chamber, proportional to a concentration gradient across the membrane

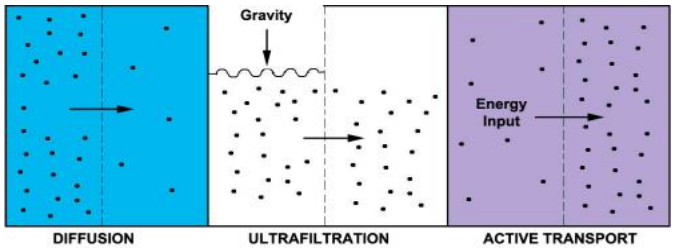


Formation

- **Ultrafiltration** is the flow of water and water-soluble substances across fenestrated ciliary capillary endothelia into the ciliary stroma, in response to an *osmotic gradient* or *hydrostatic pressure*



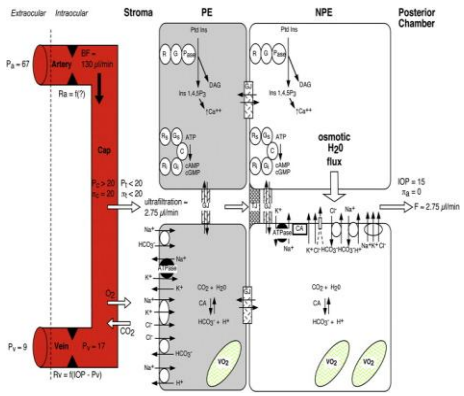
Formation



- Diffusion and ultrafiltration are responsible for the accumulation of plasma ultrafitrate in the stroma, behind tight junctions of the non-pigmented epithelium, from which the posterior chamber aqueous humor is derived

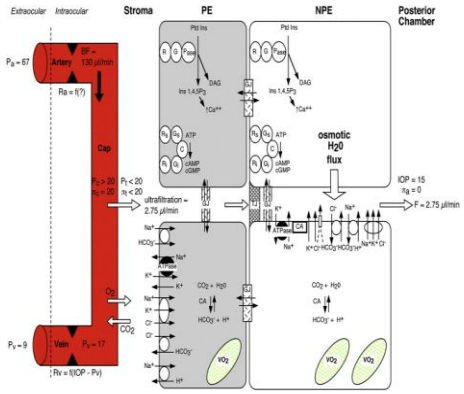
Formation

- **Active secretion** is thought to be the major contributor to aqueous formation, responsible for approximately 80% to 90% of the total aqueous humor formation
- The main site for active transport is the non-pigmented epithelial cells.



Formation

- Active transport takes place through selective trans-cellular movement of *anions*, *cations*, and *other* molecules across a concentration gradient in blood-aqueous barrier.
- This is mediated by **protein transporters** distributed in the cellular membrane.



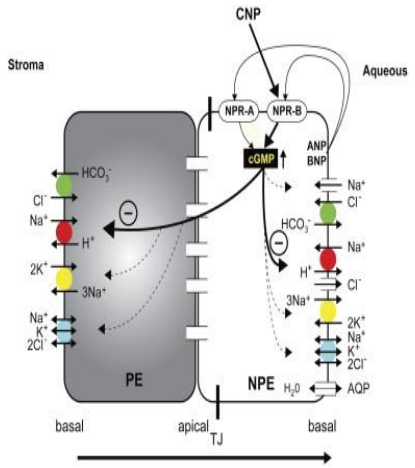
Formation

- Aquaporins (AQPs) are molecular water channels which aid with rapid bulk transport of fluid or transport of fluids against an insufficient osmotic pressure gap.
- Two AQP's, AQP1 and AQP4, have been shown to contribute to aqueous humor secretion*

*Yamaguchi Y, Watanabe T, Hirakata A, Hida T. Localization and ontogeny of aquaporin-1 and -4 expression in iris and ciliary epithelial cells in rats. Cell Tissue Res. 2006;325(1):101–9.

Formation

- The energy required for the transport is generated by hydrolysis of ATP to ADP, which is mediated by Na^+-K^+-ATPase, an enzyme located in both the *non-pigmented* and *pigmented* ciliary epithelia



Formation

- Na^+-K^+-ATPase can be inhibited by many different molecules, including cardiac glycosides, dinitrophenol, vanadate , and possibly acetazolamide through pH changes.
- *Thus, Na^+-K^+-ATPase is of particular interest in pharmacological studies of aqueous humor dynamics.*

Formation

- Another enzyme, carbonic anhydrase, found in the *non-pigmented* and *pigmented* ciliary epithelia , mediates the transport of bicarbonate across the ciliary epithelium by the reversible hydration of CO_2 to form HCO_3^- and protons through the reaction:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$$

Formation

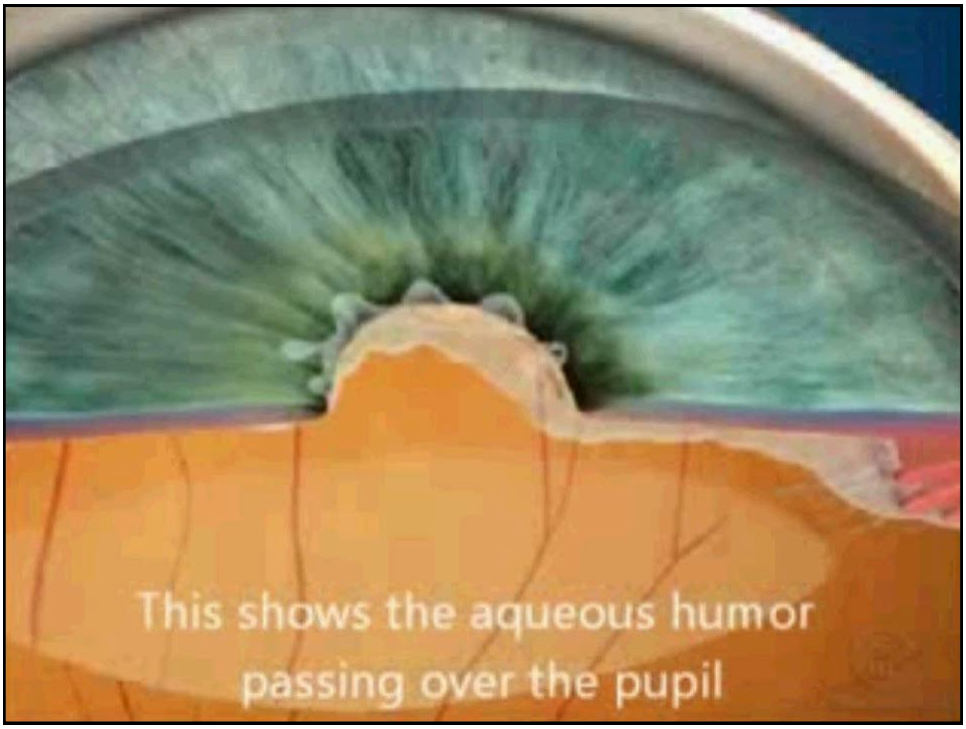
- Bicarbonate formation influences fluid transport by affecting Na^+, possibly by regulating the pH for optimal active ion transport
- The movement of electrolytes across the ciliary epithelium is regulated by electrochemical gradients and, although there is a net direction of secretion across the epithelium, hydrostatic and oncotic forces favor resorption of aqueous humor.

Formation

- **Chloride ion** is the major anion transported across the epithelium through Cl^- channels.
- Other molecules are also actively transported, including **ascorbic acid**, which is secreted against a concentration gradient by sodium-dependent vitamin C transporter 2 (SVCT2) and certain amino acids, which are secreted by at least three different solute carriers.

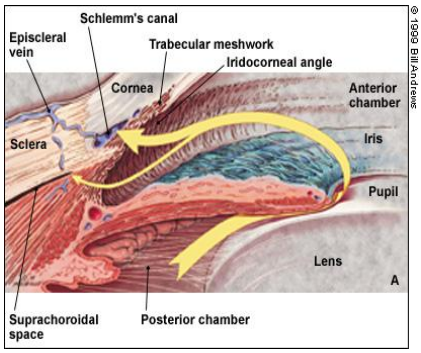
Formation

- Active transport produces an osmotic gradient across the ciliary epithelium, which promotes the movement of other plasma constituents by ultrafiltration and diffusion



Outflow

- The aqueous humor exits the eye through both **conventional** and **unconventional** pathways.
- Regulation of the extracellular matrix (ECM) composition appears to influence aqueous humor outflow resistance in both pathways .

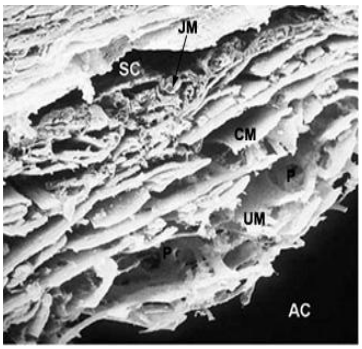


Outflow

- Fluid movement takes place down a *pressure gradient* from the TM into Schlemm's canal and through the inner wall of Schlemm's canal, following the conventional route, and appears to be a passive pressure-dependent transcellular mechanism, frequently associated with *paracellular routes*, such as giant vacuoles and pores acting as one-way valves.

Outflow

- These pores range in size from **0.1 to 3µm** in diameter, and are the main passageway not only for aqueous humor, but also for particulate materials, such as cells, ferritin and microspheres.

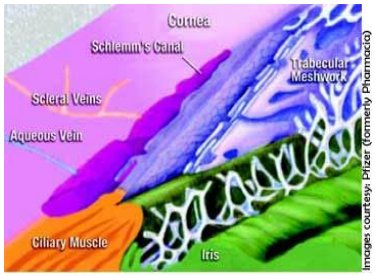


Outflow

- Changes in IOP bring about changes in the structure of the endothelium lining Schlemm's canal. Elevated IOP leads to an increase in the number and size of these vacuoles, and vice versa.
- The inner wall of Schlemm's canal is a complex tissue that is poorly understood - there is still doubt if it influences outflow facility in normal or glaucomatous eyes, even though circumstantial evidence points in that direction

Outflow

- After exiting Schlemm's canal, the aqueous humor enters the aqueous veins and, subsequently, mixes with blood in the episcleral veins, where the pressure is approximately **8–10 mmHg**, and the resistance of the conventional aqueous drainage tissues is approximately **3–4 mmHg/µl/min**.
- This results in an average IOP of 15.5 ± 2.6 mmHg (mean ± SD) for the general population.



- In humans, **75%** of the resistance to the aqueous humor outflow is localized to the **TM**, and **25%** occurs beyond **Schlemm's canal**.
- On this basis, trabeculotomy and trabeculectomy were proposed as surgical therapies for treatment of POAG.
- The major site of resistance within the TM structure has not yet been well characterized, but there is strong evidence that it resides in the juxtacanalicular portion

Outflow

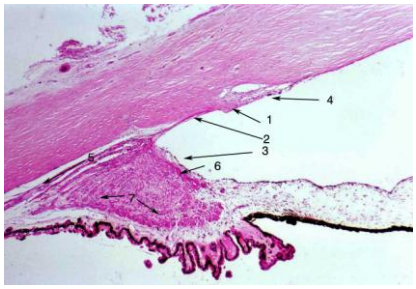
- Some studies suggest that glycosaminoglycans, which constitute the fundamental substance of the ECM of the TM , are partly responsible for increased resistance to outflow.
- The osmotic forces exerted by glycosaminoglycans may induce hydration (edema) of the TM, which can cause obstruction of the trabecular structure.
- **Catabolic enzymes** released from lysosomes depolymerize glycosaminoglycans and prevents this obstruction.
- This effect is also inhibited by *corticosteroids*, which prevent the release of the enzymes by stabilizing the lysosomal membranes and has been associated with a role in outflow obstruction and glaucoma pathogenesis.

Outflow

- In glaucomatous eyes, an increase in the ECM thickness beneath the inner wall of Schlemm's canal and in the juxtacanalicular meshwork compared with age-matched healthy controls has been observed.
- Other studies suggest that the interaction of ECM components with different proteins may induce formation of deposits that obstruct aqueous humor outflow through the TM.
- **Cochlin**, a protein of incompletely understood function, has been identified in the glaucomatous TM but not in healthy controls. Cochlin, along with mucopolysaccharide deposits, have been found exclusively in glaucomatous TM

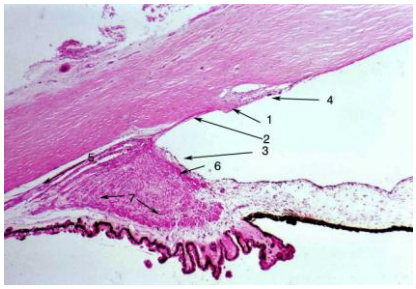
Outflow

- The influence of **the iris and ciliary muscle,** two contractile structures innervated with cholinergic nerves, on the resistance to aqueous outflow has also been contemplated.
- The *anterior* tendons of the ciliary muscle insert into the outer portion of the corneoscleral meshwork and into the juxtacanalicular meshwork.



Outflow

- During contraction, the ciliary muscle moves in an anterior and inward direction, resulting in spreading of the TM and dilation of Schlemm's canal, thus decreasing outflow resistance.
- During relaxation, the opposite occurs, thereby increasing outflow resistance.
- Studies in various animal species demonstrated that voluntary accommodation, electrical stimulation of the trigeminal nerve, and local or systemic administration of cholinergic agents decrease outflow resistance



Outflow

- Direct and indirect acting **muscarinic cholinergic agonists** have been used in the medical management of *primary open angle glaucoma*.
- Recent studies demonstrate the presence of at least two different subtypes of muscarinic receptors in the ciliary muscle and in the trabecular meshwork tissue or cell cultures from human eyes .
- In addition, cholinergic agonists, such as **oxotremorine**, induce the contraction of the ciliary muscle by binding selectively to receptors located in the longitudinal portion of the muscle, indicating that these agents may modulate the outflow facility independently from accommodation and miosis.

Outflow

- **Uveoscleral outflow** was described by observing the exit of radioactive tracers into the anterior chamber of the cynomologous monkey eye.
- Further characterization of this pathway derives mostly from animal experiments and from mathematical calculations of an expanded Goldmann equation

$$F = (P_i - P_e) \times C + U$$

- Where F is the rate of aqueous humor formation, P_i is the intraocular pressure, P_e is the episcleral venous pressure, C is the tonographic facility of outflow and U is the pressure insensitive parameter to symbolize uveoscleral outflow

Outflow

- Ciliary muscle contraction greatly affects uveoscleral outflow, and prostaglandin F2α greatly increases uveoscleral outflow by decreasing the flow resistance of the interstitial spaces in the ciliary muscle

Outflow

- IOP is the loading force to which the outflow system normally responds.
- Evidence of tissue and cellular deformation in response to an IOP-induced load places TM resistance to IOP at the level of the endothelium of Schlemm's canal.
- Schlemm's canal endothelium attaches tightly to the TM by extending cytoplasmic processes into the juxtacanalicular space
- Well-characterized desmosomes, capable of sustaining cellular stress, are present between cell process attachments.
- The trabecular lamellae contain type I and III collagen, which provide structural support in tension, and elastin, and a recoverable response over large excursions.

Outflow

- Current pharmacological therapies for lowering the intraocular pressure in glaucoma include increasing aqueous humor outflow and suppression of aqueous humor production.
- For example, aqueous humor production is reduced by both topical and systemic **carbonic anhydrase inhibitors** which decrease the production of aqueous humor by the epithelial cells of the ciliary body.
- Aqueous humor outflow is increased by **prostaglandin agonists** that increase outflow mainly through the uveoscleral pathway, possibly through the activation of ***matrix metalloproteinases***, and also through the trabecular meshwork.

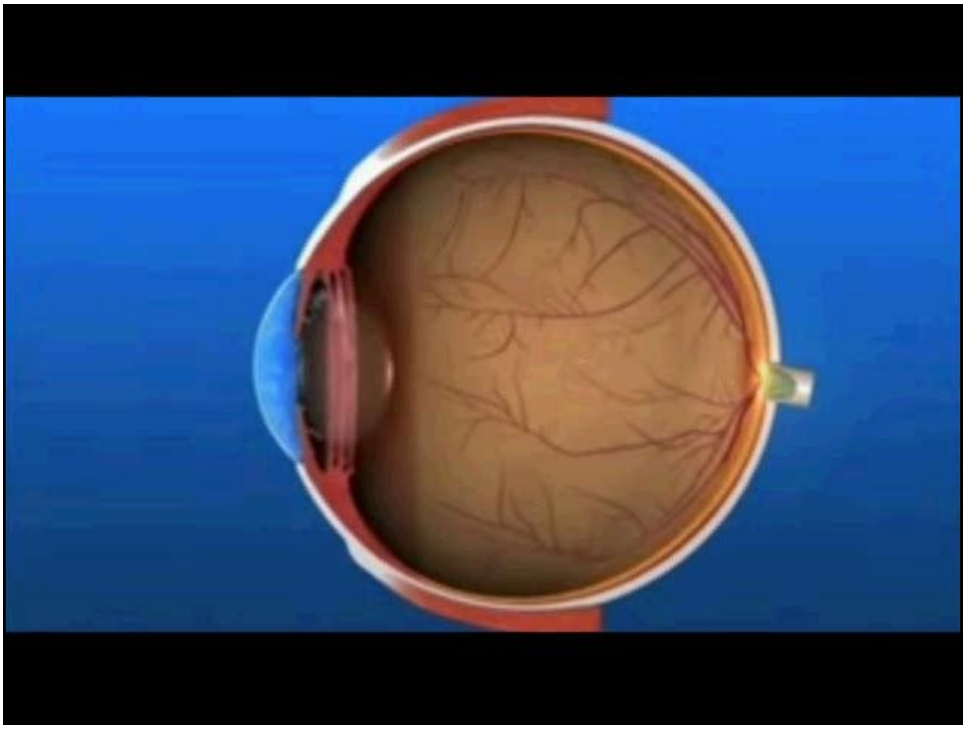
Outflow

- Current surgical therapies also seek to lower the intraocular pressure by increasing aqueous outflow or decreasing aqueous humor production.
- For example, cyclcophotocoagulation seeks to partially destroy the cililary body to decrease aqueous production.
- In contrast, laser trabeculoplasty modifies the trabecular meshwork (in a manner still not known) to decrease outflow resistance.

Outflow

- Other surgeries such as **trabeculectomy, glaucoma drainage implants, and glaucoma shunts** (which penetrate the trabecular meshwork and cannulate Schlemm's canal or create a path through the scleral wall) bypass outflow resistance by shunting aqueous humor through or around the trabecular meshwork.

- Newer procedures such as **canaloplasty** (which dilates Schlemm's canal) and other shunts which seek to open the uveoscleral pathway by creating a mini-cyclodialysis cleft all involve increasing outflow by opening existing aqueous drainage pathways or creating new pathways.



Dynamics

- The rate of aqueous humor turnover is estimated to be 1.0% to 1.5% of the anterior chamber volume per minute, which is 2.4 ± 0.6µl/min
- Using *fluorophotometry*, **diurnal variations** were observed in aqueous humor turnover rates, reflecting a pattern known as the **circadian rhythm** of aqueous humor flow in humans.

Dynamics

- Aqueous humor flow is higher in the morning than at night.
- Aqueous humor flow is normally about 3.0µl/min in the morning, 2.4µl/min in the afternoon, and drops to 1.5µl/min at night. The mechanism that controls this biologic rhythm is poorly understood.
- Circulating **epinephrine** available to the ciliary epithelia may be a major driving force

Dynamics

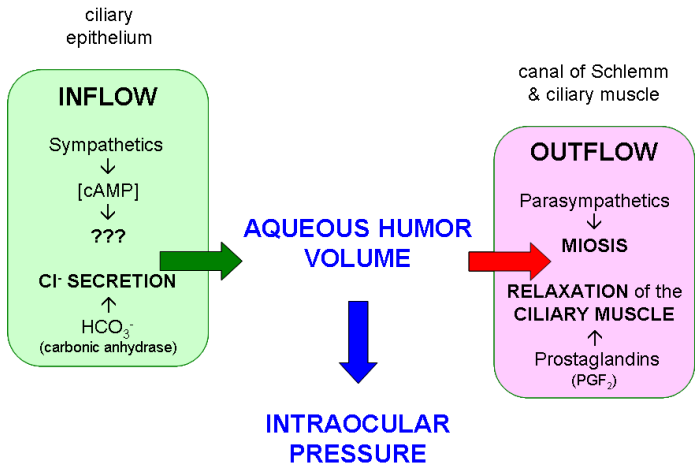
- The effect of **timolol, epinephrine** and **acetazolamide** on the rate of aqueous humor flow through the anterior chamber has been studied:
- **Epinephrine** increased the rate of aqueous flow in sleeping subjects to a greater extent than it did in awake subjects.
- **Timolol** reduced the rate in awake individuals, but not in sleeping ones

Dynamics

- **Acetazolamide** reduced the rate of flow in both awake and epinephrine-stimulated subjects.
- **Norepinephrine** has also been shown to stimulate aqueous flow, but not as effectively as epinephrine.
- Another hypothesis supporting epinephrine influence on circadian rhythm could be a ciliary production of this hormone. However, epinephrine concentration in human aqueous humor appears to be very low, ranging from 0 to 0.1 ng/ml

Dynamics

- Moreover, in patients with surgical adrenalectomy or Horner syndrome (reduced or absent sympathetic innervation on one side), the circadian flow pattern was observed to be normal.
- Other hormones, such as *melatonin*, *hormones related to pregnancy*, and *anti-diuretic hormones*, do not appear to alter the normal circadian rhythm of the aqueous flow.



Thank you

for you kind attention