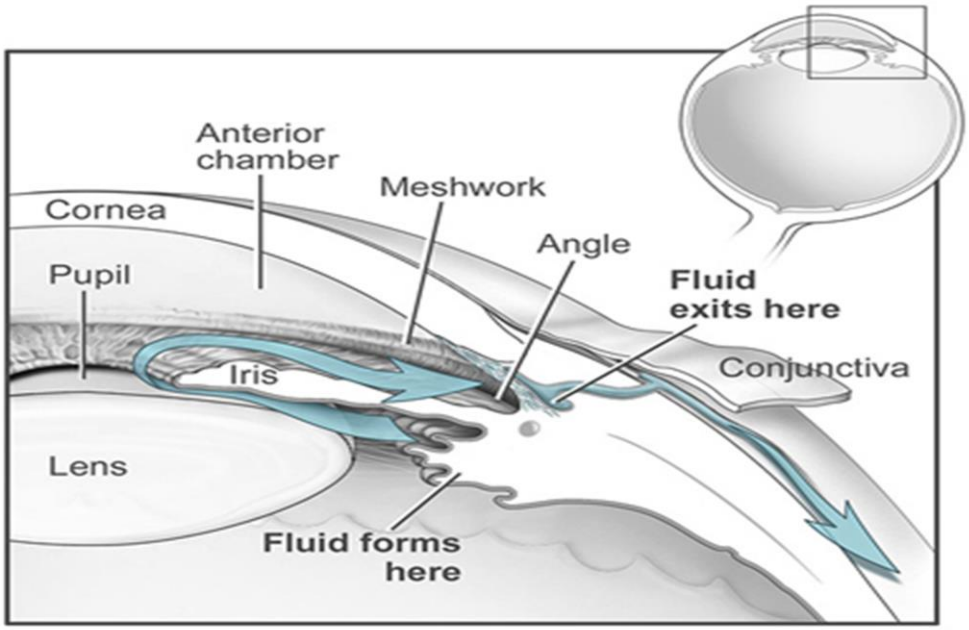
<u>INTRAOCULAR PRESSURE(IOP)</u>: is the fluid pressure inside the eye. IOP is determined by the **production** and **drainage** of aqueous humor. Aqueous humor is secreted by the ciliary processes and flows from the posterior chamber, through the pupil, and into the anterior chamber and leaves the eye primarily by the trabecular meshwork and canal of Schlemm, thence to an episcleral venous plexus and into the systemic circulation. This conventional pathway accounts for 80%–95% of aqueous humor outflow and is the main target for cholinergic drugs used in glaucoma therapy. Another outflow pathway is the uveoscleral route (i.e., fluid flows through the ciliary muscles and into the suprachoroidal space), which is the target of selective prostanoids.

Normal eye pressure is usually considered to be between 10-20 mm Hg. Elevated eye pressure can cause glaucoma and nerve damage.

Current medical therapy of open-angle glaucoma (which is the most common type) is aimed at:

- decreasing aqueous humor production or
- increasing aqueous outflow.



Ciliary Body:

The ciliary body serves two very specialized roles:
• Production and secretion of aqueous humor by the epithelial bilayer
• Accommodation by the ciliary muscle: contraction of the ciliary muscles results in thickening of the lens which focuses on close objects (it changes the shape of the lens not the size of the pupil).
Contraction of the longitudinal fibers, which insert into the trabecular meshwork in the anterior chamber of the eye, cause an increase in the meshwork pore size which will increase aqueous humor flow into the Schlemm canal.

Pilocarpine: The alkaloid pilocarpine produces muscarinic and nicotinic effects by directly interacting with the receptors. It has predominant muscarinic actions especially on secretory activity. It is used primarily in ophthalmology. Pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. Pilocarpine is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity.
*Pilocarpine is used to treat glaucoma and is the drug of choice for emergency lowering of IOP of both open-angle and angle-closure glaucoma. Pilocarpine is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure because of the increased drainage of aqueous humor.
The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine.
The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and ***cevimeline***, a cholinergic drug that also has the drawback of being nonspecific.

- Adverse effects are salivation, sweating, bradycardia, diarrhoea, bronchospasm; pulmonary oedema can occur following systemic therapy.

Indirect-Acting Cholinergic Agonists (Anticholinesterase Agents) or (Cholinesterase Inhibitors):

They inhibit the enzyme cholinesterases, which is responsible for hydrolysis of acetylcholine. Thus, ACh is not metabolized, gets accumulated at muscarinic and nicotinic sites, and produces cholinergic effects. Hence, anticholinesterases are called indirectly acting cholinergic drugs.

A/ Reversible anticholinesterases:

Physostigmine: it is found naturally in plants. Physostigmine has a wide range of effects and stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ. Muscarinic stimulation can cause contraction of GI smooth muscles, miosis, bradycardia, and hypotension. Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses). Its duration of action is about 30 minutes to 2 hours, and it is considered an intermediate-acting agent. Physostigmine can enter and stimulate the cholinergic sites in the CNS.

* Physostigmine is used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, and to reverse the effects of NMBs.

Neostigmine: is a synthetic compound that reversibly inhibits AChE in a manner similar to physostigmine. Unlike physostigmine, neostigmine has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. Its effect on skeletal muscle is greater than physostigmine, and it can stimulate contractility before it paralyzes. Neostigmine has an intermediate duration of action, usually 30 minutes to 2 hours.

*It is used to stimulate the bladder and GI tract and as an antidote for competitive neuromuscular-blocking agents. Neostigmine is also used to manage symptoms of myasthenia gravis.

- Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine.

#Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present.

Pyridostigmine: is another cholinesterase inhibitor.
*It used in the chronic management of myasthenia gravis. Its duration of action is intermediate (3 to 6 hours) but longer than that of neostigmine.

❖ Adverse effects are similar to those of neostigmine.

***Edrophonium*:** it binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It has a short duration of action of 10 to 20 minutes due to rapid renal elimination. Edrophonium is a quaternary amine, and its actions are limited to the periphery.

*It is used in the diagnosis of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes the degradation of the nicotinic receptors, making fewer receptors available for interaction with ACh. Intravenous injection of edrophonium leads to a rapid increase in muscle strength in patients with myasthenia gravis. Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote). Edrophonium may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing neuromuscular blockers (NMBs) after surgery.

Due to the availability of other agents, edrophonium use has become limited.