PUPILS

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INTRODUCTION

The iris is a structure located anterior to the lens. The centre aperture is the pupil. The sphincter muscles of the iris are innervated by parasympathetic fibers that originate in the Edinger-Westphal nucleus.

The pupils provide information on the ocular motor function and the retina. Pupillary function depends on the integrity of the structures along the path of the pupillomotor pathway (Figure 1.1):

- Retinal receptors
- Ganglion cell axons in the optic nerve
- Optic chiasma
- Optic tract
- Brachium of the superior colliculus
- Pretectal area of the mesencephalon
- Interconnecting neurons to the pupilloconstrictor motor cells in the oculomotor nuclear complex
- The efferent parasympathetic outflow accompanying the third cranial nerve
- The efferent sympathetic pathway from the hypothalamus to the pupil dilator muscle

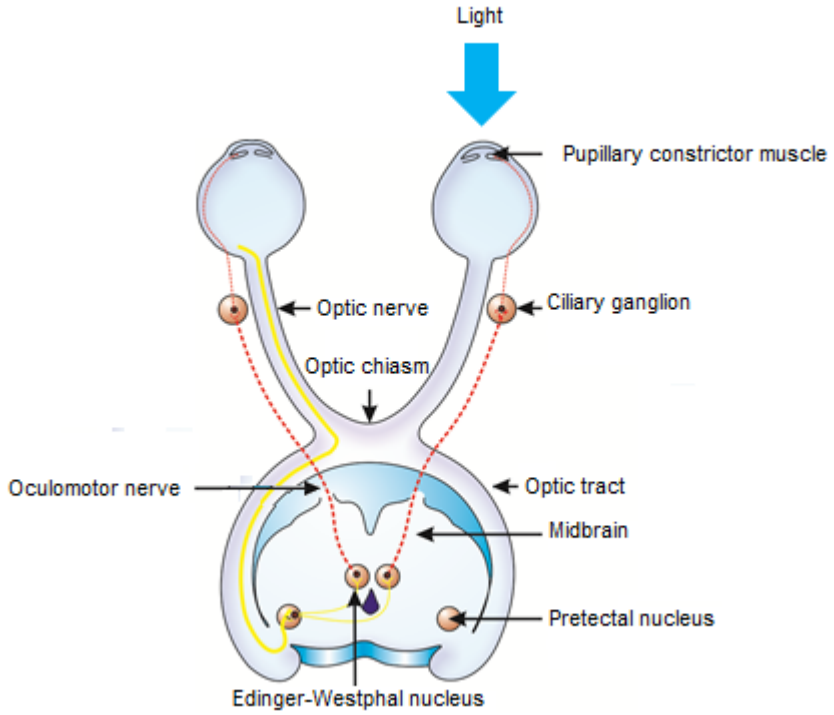

Figure 1.1. *Light reflex pathway*
Inspired by Kanski, 2011

LIGHT REFLEX PATHWAY = 4 NEURON PATHWAY (REFER TO NOTES IN COP 1)

1. Afferent neurons from retinal ganglion cells to pretectal area bypassing the lateral geniculate nucleus where there is no synapse
2. Interneurons from pretectal complex (dorsal aspect of the midbrain) to Edinger-Westphal nuclei which lies ventrally and fibers join the 3rd cranial nerve
3. Parasympathetic outflow with 3rd nerve to ciliary ganglion
4. From ciliary ganglion to iris sphincter (10% of fibers contribute to the pupillary light reflex)

Ipsilateral 3rd nerve palsy: this occurs if the direct response is absent but the consensual response is intact.

Contralateral 3rd nerve palsy: this occurs if the direct response is intact but the consensual response is absent.

NEAR SYNKINESIS

Correct technique for testing accommodation

Figure 1.2: *Testing for accommodative response*

A blurred retinal image or the conscious visual fixation of a near object results in an accommodative effort. A near synkinesis (Figure 1.2) is evoked and includes:

- Increased accommodation of the lens
- Convergence of the visual axes of the eyes
- Pupillary constriction

The accommodative drive comes from the frontal lobe and blurred images are sensed in the occipital cortex and corrected via occipitotectal tracts.

The Edinger-Westphal nucleus is divided into the:

- Rostral portion: this portion is involved in accommodation
- Caudal portion: this portion elicits pupil constriction
- Middle segment: when this portion is stimulated, it results in accommodation and pupil constriction

The final pathway for pupil constriction consists of the:

- Oculomotor nerve
- Ciliary ganglion
- Short posterior ciliary nerves

The pathway is more ventrally located than the pretectal afferent limb of the light reflex. The anatomical location is the basis for light-near dissociation. For example in Argyll Robertson pupils, the convergence centre is still intact because it does not coincide anatomically with the light reflex location. The final pathway consists in the 3rd cranial nerve, the ciliary ganglion and the short ciliary nerves.

NORMAL PUPILLARY PHENOMENA

Proper evaluation of the pupils should include the following elements:
- Size: the normal size of the pupil ranges between 2-6mm
- Shape: Assess if the pupils are regularly or irregularly shaped and whether they are symmetrical
- Direct and indirect responses to bright light
- Accommodation reaction

The size of the pupil changes with age. At birth the pupils are larger and get smaller with age. The size of the pupils is controlled by the Parasympathetic and Sympathetic Nervous Systems.

The pupil has three main optic functions:

- To regulate the amount of light reaching the retina
- To diminish the chromatic and spherical aberrations produced by the peripheral imperfections of the optical system of the cornea and lens
- To increase the depth of field

Physiologic anisocoria occurs in 20% of the general population. Less than 0.5 mm (can be up to 1 mm) anisocoria is considered as a normal or physiological pupillary phenomenon. The degree of anisocoria can vary from day to day and even switch sides. Pupillary unrest (Hippus phenomenon) occurs during distance fixation with constant, ambient illumination. The pupils should be bilaterally symmetrical, and rhythmical unrest or variation in size change should usually be less than 1mm. Near Synkinesis is another normal pupillary phenomenon. When light is introduced to the pupils, the miosis is greater than when a patient is looking at a near object. The psychosensory reflex occurs during light or near stimuli and when the patient is subjected to a loud noise or pain. During these occurrences the pupils will dilate due to active sympathetic discharges.

If the anisocoria is greater in dim light, then the defect is in the sympathetic innervation of the pupil (Figure 1.3). If the anisocoria is greater in bright light, then the lesion is in the parasympathetic innervation of the pupil. If a large pupil is poorly reactive to light and the visual afferent system is normal, then a defect in the efferent parasympathetic innervation to this pupil is likely (Burde, 1992). If the light reaction is difficult to compare to the fellow eye, then a measurement of the anisocoria in bright and dark conditions may help determine the pupillary abnormality.

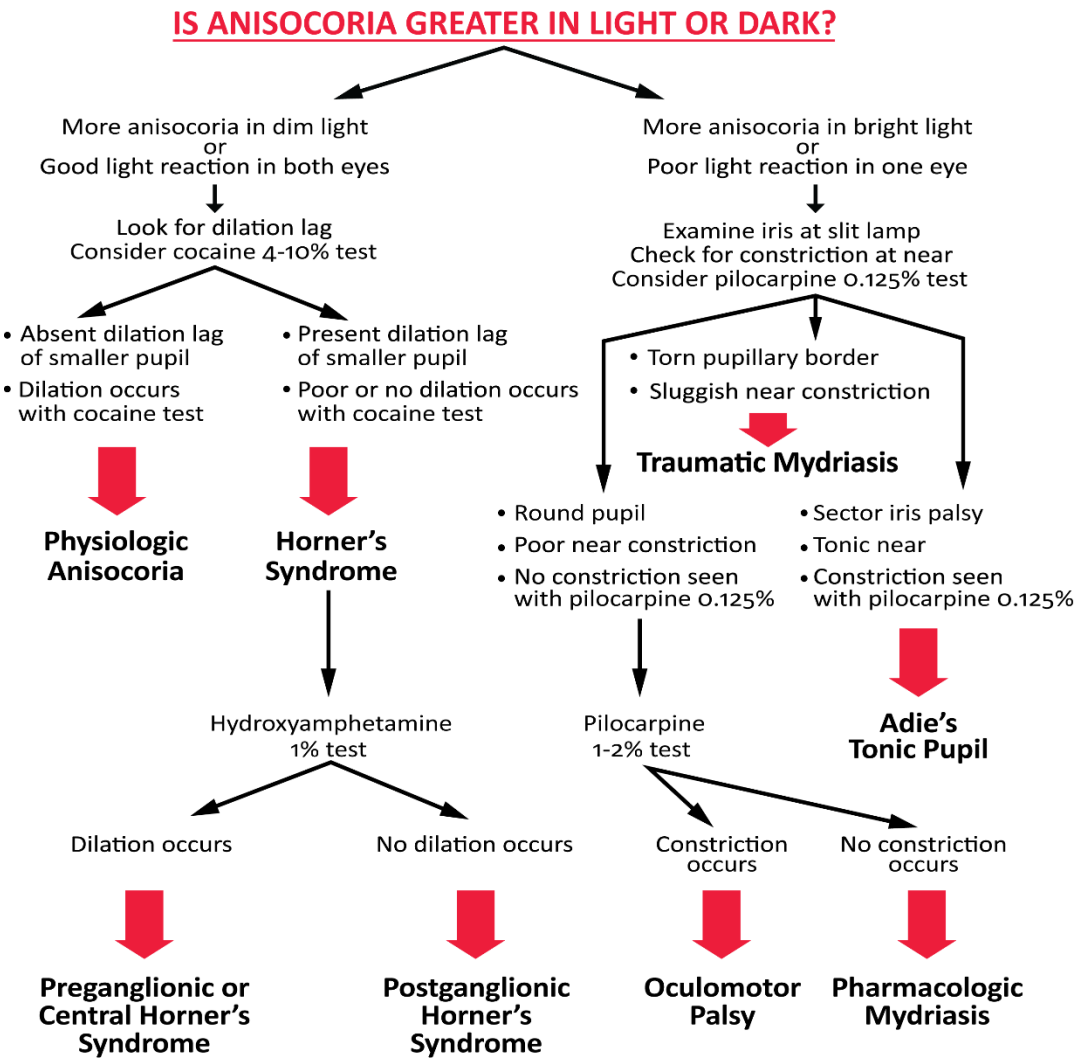

Figure 1.3: *Flow chart of investigation of anisocoria*

PUPILLARY TESTING

While extremely simple to examine, the pupils can provide a wealth of information. When looking at the pupils we should assess the:

- Size
- Shape
- Symmetry
- Responses to light stimuli
- Accommodative reaction of the pupils.

It is advisable to perform pupillary testing in dim illumination. The following reflexes should be assessed:

Direct Light Reflex: shine the light in a pupil and look at the same pupil (Figure 1.4)

Consensual Reflex: shine the light in a pupil and look at constriction in the other pupil

Swinging flashlight test: Bright hand light in a darkened room
Patient should fixate on a distant object
Light should cross from one eye to the other fairly rapidly and remain 3 to 5 seconds on each eye to allow pupillary stabilization.

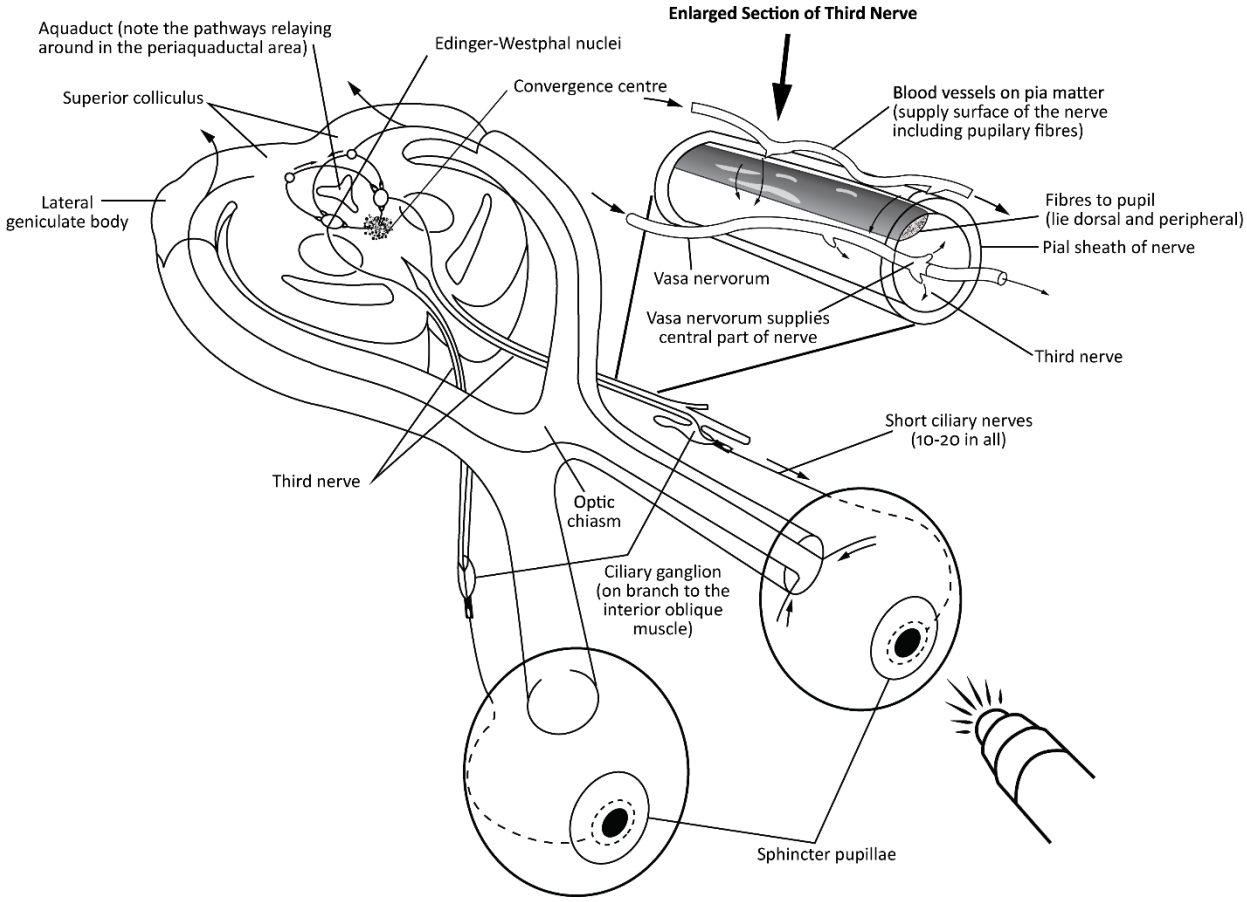

Figure 1.4: *Light reflex pathway: direct response*

ABNORMALITIES OF THE LIGHT REFLEX AND PARASYMPATHETIC PATHWAY

- Marcus Gunn Pupil or Relative Afferent Pupillary defect: The optic nerve is diseased
- Parinaud Syndrome: If pretectal nucleus is diseased
- Argyll Robertson Pupil: If pretectal nucleus is diseased but accommodation is intact
- 3rd Nerve palsy
- Holmes Adie Pupil (Adie's tonic pupil): Dilated pupil on one side and otherwise asymptomatic
- Trauma
- Diphtheria (affects 3rd cranial nerve)

AFFERENT PUPILLARY DEFECT (MARCUS GUNN PUPIL)

The Marcus Gunn pupil is a relative afferent pupil defect (RAPD), where the amount of light transmitted from one eye, the diseased eye is less than the other, the normal eye. During the swinging flashlight test if an afferent pathway problem exists, there will be dilatation instead of constriction of the diseased eye. There will be a sluggish direct response and so the corresponding consensual response of the other eye will also be sluggish. There has to be marked asymmetry or unilateral disease. Bilateral APDs can occur but only unilateral RAPD exist.

Neutral Density Filters (NDF) can be used to grade the afferent pupillary defect. Introduce a neutral density filter before the normal eye and perform the swinging flashlight test. If there is no APD with the neutral density filter of 2 log units this indicates that an APD of NDF 2 log units exists.

Table 1: Grading of Afferent Pupillary Defects:

1+	Initial constriction. Greater escape to larger intermediate size. Pupillary escape indicating that the number of fibers affected is not as many
2+	No change in pupil size initially. Followed by dilatation of pupil. Slight delay and then dilation.
3+	Immediate dilation of pupil, instead of normal initial constriction.
4+	Patient has No Light Perception. Completely amaurotic pupil. Immediate dilatation.

RELATIVE AFFERENT PUPILLARY DEFECT: MARCUS GUNN PUPIL (MG)

Optic Neuropathy must be unilateral or markedly asymmetric to get an RAPD. Ocular media opacities such as corneal scars, cataracts and vitreous hemorrhages **will not** cause a MG pupil. Maculopathy (e.g. ARMD) or amblyopic ('lazy eye') will not cause MG pupil unless the VA < 20/200, in which case only a 1+ APD will occur. Extensive retinal damage will cause a significant Marcus Gunn phenomenon but has to be extensive, almost all of the retina must be affected.

Amaurotic pupil: = 'Blind eye' 4+ APD. There is maximum MG pupil imaginable.

- Bilateral MG pupils cannot occur.
- Isolated, unilateral optic neuropathy does not cause the ipsilateral pupil to be larger due to the consensual light reflex.
- Therefore Amaurotic Mydriasis does not exist → with optic nerve disease on one side, the pupil size should not be affected.
- Detection of APD requires only one 'working' pupil.

ARGYLL ROBERTSON (AR) PUPIL

The characteristics of an Argyll Robertson pupil include:

- Miotic irregular pupils
- Light-near dissociation (the pupils constrict to convergence but not to direct light)
- Poor dilation in darkness
- Poor response to mydriatic agents

It is usually bilateral, and often asymmetric.
The main cause is neurosyphilis while other reported causes include diabetes mellitus, chronic alcoholism, multiple sclerosis and sarcoidosis.
The most likely site of the lesion is the region of the Sylvian Aqueduct in the rostral midbrain. Argyll Robertson pupils occur in secondary and tertiary syphilis. With tropicamide, the normal pupil will dilate and but the abnormal pupil will not dilate. Treatment of the Argyll Robertson pupil from neurosyphilis is with penicillin.

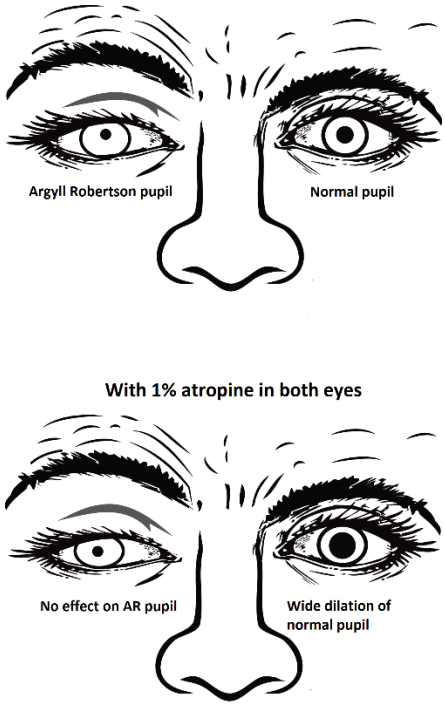

Figure 1.5: *The effect of atropine on Argyll Robertson pupil*

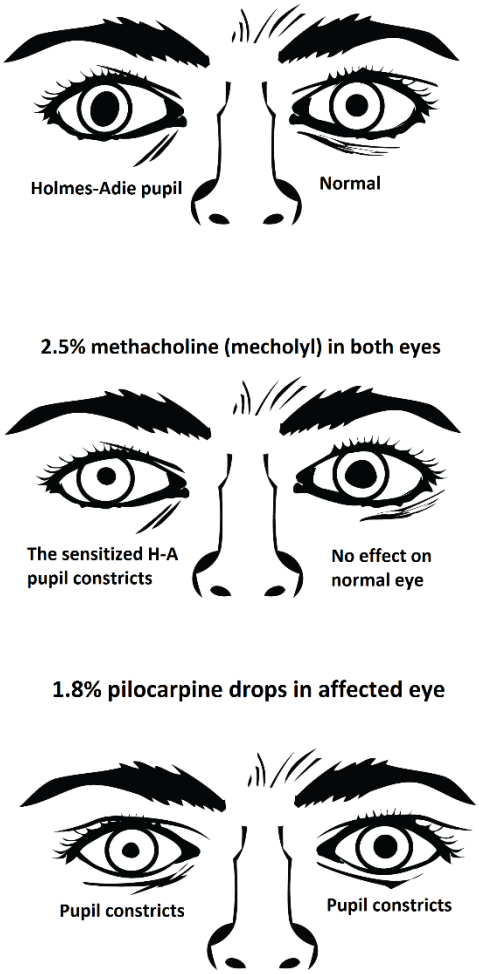

Figure 1.6: *The effect of 2.5% Methacholine and Pilocarpine on Holmes Adie and Argyll Robertson pupils*

ADIE'S TONIC PUPIL

Adie's pupil is an idiopathic, benign cause of internal ophthalmoplegia. It is probably due to a viral infection at the ciliary ganglion with destruction of fibers going to the iris. The remaining fibers compensate by an increase in receptors and therefore there is denervation supersensitivity. Compensation takes a couple of days to occur. A large dilated pupil on one side characterizes it and there is constriction of the fellow pupil.

80% of Adie's tonic pupil cases are initially unilateral. They become bilateral at the rate of 4% per year. There is a female predilection (70% vs 30%) and occurs in young adults, ages 20 – 40 years.

The characteristics of Adie's tonic pupil include:

- A dilated pupil with poor to absent direct light reaction
- Slow constriction to prolonged near effort
- Slow redilation.

The constriction in the abnormal pupil lasts much longer hence the 'Tonic pupil'. There is constriction on convergence. There is initial accommodative paresis which resolves over months. There is also segmental palsy of the iris sphincter muscle.
This condition is diagnosed using cholinergic drugs. Super-sensitivity to weak Pilocarpine solutions (0.125% or 0.1%) occurs (Figure 1.7).
The etiology is unknown but is possibly due to viral infection or is post infectious. The lesion occurs in the ciliary ganglion or short posterior ciliary nerves. There is aberrant regeneration of more numerous fibers innervating the ciliary muscle (97%) than the iris sphincter (3%). This is only in Adie's pupil.

Adie's syndrome: Refers to the Adie's pupil with diminished tendon reflexes, thus suggesting a systemic para-infectious disorder.

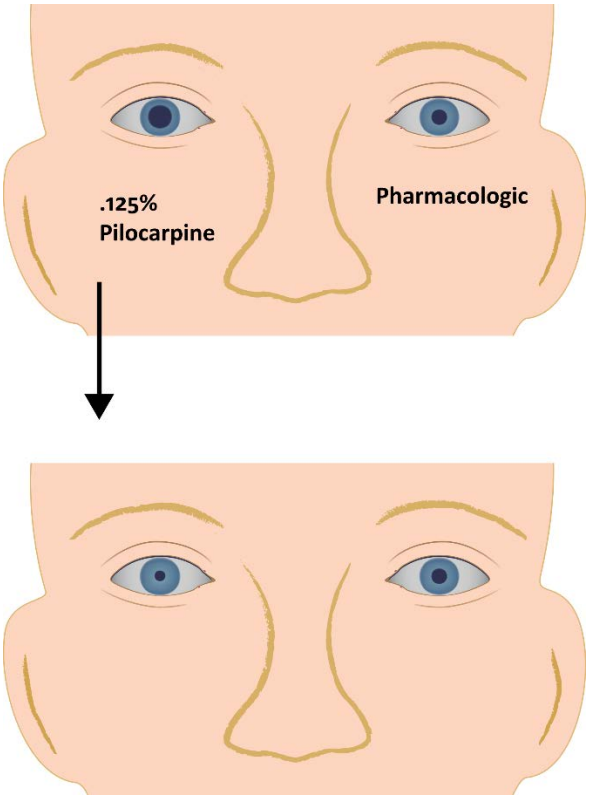

Figure 1.7: *The response of the Tonic pupil to 0.125% Pilocarpine. Constriction of the abnormal pupil occurs due to denervation supersensitivity.*

THE OCULO-SYMPATHETIC PATHWAY

The dilator muscle of the iris is innervated by sympathetic fibers. A three neuron pathway exists which starts in the brain, goes down the brainstem to the lateral part of levels C8 to T2 of the spinal cord, then to the sympathetic plexus over the top of the lung and to the superior cervical ganglion (SCG). It re-enters the head along the carotid artery to the cavernous sinus. Finally, it enters the orbit along the nasociliary branch of the trigeminal nerve to supply the dilator fibers of the iris. It is important to note that this pathway remains ipsilateral throughout its course.

A lesion of the sympathetic supply to the eye results in the Horner Syndrome, which is characterized by:

- Miosis
- Partial ptosis of the upper and lower lids
- Anhidrosis
- Enophthalmos

When there is a Horner Syndrome the lesion is always ipsilateral to the side of the Horner's, regardless if it's a lesion in the brain, brainstem, spinal cord, apex of the lung, SCG, internal carotid, cavernous sinus or orbit.

Depending on the company it keeps, the site of lesion causing the Horner Syndrome can be localized. For example, if the patient has weakness of the upper limb and an ipsilateral Horner Syndrome, one may localize the lesion to the lower trunk of the brachial plexus.

Following the synapse in the SCG, some of the fibers continue along the external carotid artery to the face and are responsible for facial sweating. Therefore a Horner Syndrome plus lack of sweating (anhidrosis) implies a more proximal lesion along the sympathetic pathway.

In the orbit, the sympathetic fibers innervate the dilator muscles of the iris, the inferior tarsal muscle in the lower lid and Müller's muscle in the upper lid. Consequently, the upper lid moves down (partial ptosis) and the lower lid moves up (upside down ptosis), causing an apparent enophthalmos.

3 NEURON PATHWAY (Figure 1.8)

Summary:

1st order neuron: From the hypothalamus to C8-T2 level of the spinal cord

2nd order neuron (preganglionic): From the spinal cord to the paravertebral sympathetic chain. Ends at the superior cervical ganglion (SCG)

3rd order neuron (postganglionic): From the SCG, along the internal carotid artery, joins the ophthalmic nerve and enters the orbit through the superior orbital fissure. It terminates at the iris, Müller's muscle and the inferior tarsal muscle. Sudomotor and Vasomotor fibers to the face travel with the external carotid artery and its branches.

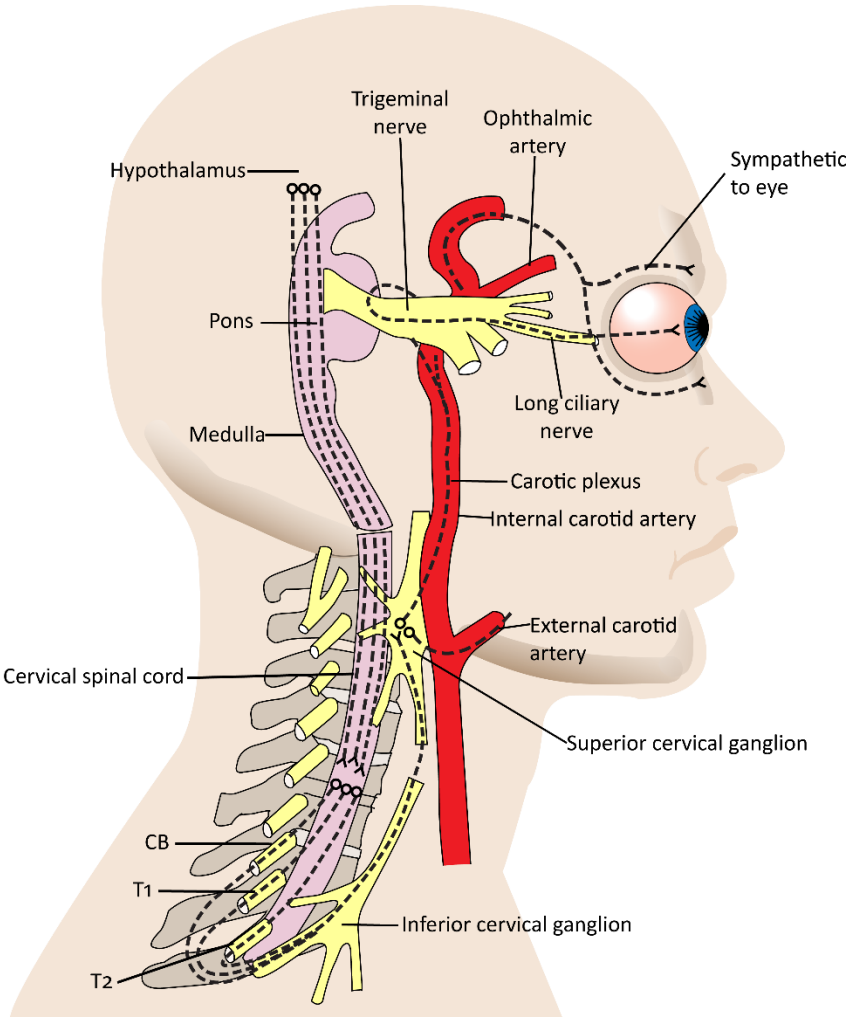

Figure 1.8: *The 3 neurons pathway of the sympathetic supply to the eye.*

HORNER SYNDROME

A lesion of the oculo-sympathetic pathway results in Horner syndrome.

The features of Horner Syndrome include:

- A small pupil (miosis)
- Ptosis
- Conjunctival injection due to vasodilatation
- Anhidrosis
- Enophthalmos – apparent (because of upper and lower lid ptosis).

A congenital Horner's is characterized by iris heterochromia and is due to loss of the sympathetic drive required for iris pigmentation. This is due to the affectation of the sympathetic system during childbirth. The face will appear flushed on one side, with a sharp dividing line that runs precisely along the sagittal midline.

CAUSES OF HORNER SYNDROME

The causes of Horner's syndrome includes:

- Hemispheric lesions involving the hypothalamus (e.g. Stroke)
- Brainstem lesions (e.g. stroke)
- Cervical cord lesions
- Root lesions at T1 (root compression)
- Sympathetic Chain lesions (whiplash can result in internal carotid artery dissection)
- Cavernous sinus lesions
- Orbit lesions
- Migraine and cluster headache.

Assessment:
4% cocaine has no effect on an abnormal pupil whereas the normal pupil dilates (Figure 1.9). Due to denervation supersensitivity, the abnormal pupil dilates to dilute adrenaline and the lid elevates. No response to dilute adrenaline occurs in the normal pupil. Unlike cocaine, that has a negative effect on the abnormal pupil, adrenaline has a positive effect on the abnormal pupil to confirm the presence of Horner Syndrome. Apraclonidine (iopadine) a weak alpha-1 agonist has a similar response to adrenaline.

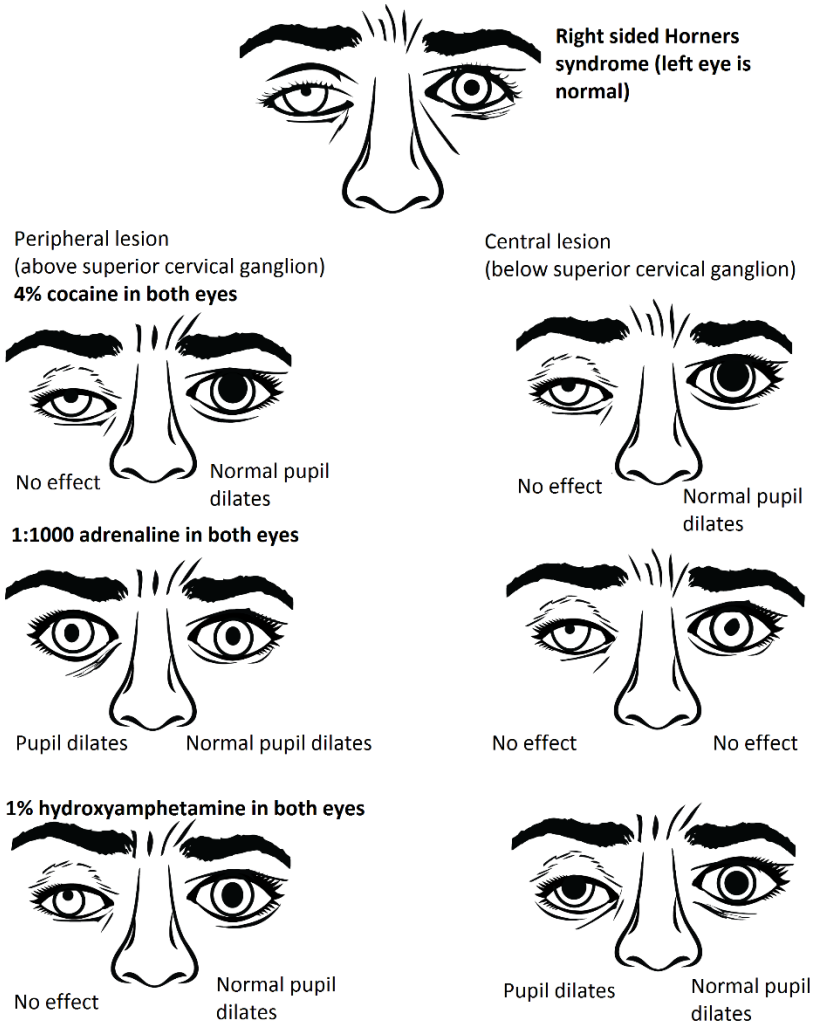

Figure 1.9: *The effect of cocaine, adrenaline and hydroxyamphetamine on the Horner pupil. Hydroxyamphetamine is used to differentiate between a preganglionic and postganglionic cause of Horner.*

With 1% hydroxyamphetamine, a 3rd order neuron lesion does not result in pupil dilatation whereas a 1st and 2nd order neuron lesion does. Hydroxyamphetamine, like cocaine, is not readily available and its routine use in localizing Horner's has become less popular.

The Parker pen test is a test where a pen is run on both sides, and there is less smooth movement on the affected side.

Clinically, it is important to note that anisocoria which is greater in dim light suggests a sympathetic problem and that Horner's pupil constricts to light. Another important feature is that in darkness, a Horner pupil may demonstrate dilation lag. On switching off the lights, at 5 seconds there is marked anisocoria, but by 20 seconds, no anisocoria may be present, especially in mild disorders. There is no response to cocaine in abnormal pupils.

NB: Aniscoria which is greater in bright light is a parasympathetic problem and can occur in an oculomotor nerve palsy. The abnormal pupil does not constrict to bright light.

PUPIL EXAMINATION IN AN UNCONSCIOUS PATIENT

The pupil reflex is an objective clinical sign. A normal pupil reflex in a comatose patient suggests a metabolic cause, such as hypoglycemia, liver failure or kidney failure. Abnormal pupils in a comatose patient suggest a structural cause.

Normal pupils:

- Metabolic encephalopathy (70%) DM
- Hypoglycemia
- Uremia
- Liver failure
- Drug overdose

Unequal pupils:

- May indicate some brain pathology.
- A dilated pupil can indicate a herniated temporal lobe
- Hutchinson's pupil occurs due to raised intra-cranial pressure which causes a 3rd cranial nerve compression at the tentorium cerebellum

Bilateral dilated pupils (unreactive):

- Progressive tentorial herniation
- Implies irreversible brain damage

Bilateral pinpoint pupils:

- Massive pontine hemorrhage (usually due to hypertension)
- Opiate
- Pilocarpine drops