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# Anisocoria

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The study of the pupils is of unusual importance and interest in ophthalmology, neurology, and clinical medicine not only because they serve as a delicate index of disease, but also because the widespread ramifications of the pupillary pathways, both within the central nervous system and without, link them up with many diverse disorders. Their complex pathways traverse tissues unusually sensitive to pathological changes and the ease and accuracy of pupillary examination afford unusual opportunities for early and subtle differentiation. This paper deals with one of the most obvious discrepancies readily found upon even the most superfluous examination of the eye. Anisocoria, or pupillary inequality, is a frequent finding.

## INCIDENCE

Barriel[1] recorded his observations of 326 men, none of whom showed signs of ocular disease or involvement of the central nervous system, in which he found unequal pupils in 35 or eleven per cent of the total number. He concluded that anisocoria was a frequent physiological condition, and that it may be associated with all refractive errors, especially myopia. A larger study was reported by Snell and Cormack[2] who examined 3,000 prisoners and found anisocoria in 576 on the night of

their reception at the prison. When reexamined the next morning, after a night's rest, however, 281 (48.8 per cent) of the original 576 men no longer showed any pupillary inequality, a finding which the authors suggested might be due to the effect of fatigue. Persistent anisocoria was noted in 295, or 9.8 per cent of the total number. Of these, there were 139, or about five per cent of the total number, in which no other abnormality was revealed during their complete medical workup. Myer[3] reported that in his examination of five hundred neurologically normal persons, seventeen per cent showed slight but perceptible anisocoria while four per cent showed a marked difference in pupillary size. Actually there is a degree of anisocoria present in most people. The figures vary from two to ninety per cent of the population depending on the standard chosen. In a small number of people there is a considerable anisocoria, and in the vast majority there is a minor anisocoria.

## SIGNIFICANCE

Opinion varies somewhat regarding the significance of anisocoria. De Schweinitz[4] stated that the earlier view that inequality of the pupils is always pathologic is subject to revision. He agreed that one should speak of pathological and nonpathological anisocoria

and that slight differences in the width of the pupils may be compatible with perfect ocular and general health. He cited the assertion of Uhthoff that in nonpathological anisocoria the pupils are round and react normally, which is not the case with pathological pupillary inequality. Brooks[5], however, concluded that anisocoria is always pathological unless it is due to diseases of the eyes or to errors of refraction. French[6] declared that "inequality of the size of the pupils is observed frequently and may have no pathological significance."

## CLASSIFICATION

Under normal circumstances, both pupils are equal in size and react equally to the stimulus of light and upon accommodation. If a difference in size of the pupils exists in the resting state, the condition is termed static anisocoria. If the inequality is only brought out in the excursions of reflex activity, it is called dynamic anisocoria. Static anisocoria is usually a physiological type of anisocoria, while dynamic anisocoria is usually a pathological type of anisocoria, although both dynamic physiological and static pathological anisocoria exist.

According to Brain[7], anisocoria may occur when one pupil is either pathologically small or pathologically large, or when one is of moderate size but fails to react

to light; in which case the normal pupil will be the larger when it is dilated and the smaller when it is contracted. Clinical testing for anisocoria demands care and necessitates standard conditions of illumination and measurement. Because of the varying pupillomotor potential of different parts of the retina, the examination must be made not only so that the two pupils are illuminated with the same intensity of light for equal time intervals, but the angle of incidence of the light on each must correspond. Rea[8] described a special instrument, the Braun hemikinesimeter which was specially developed for this purpose. Lowenstein[9] used a method called pupillography utilizing infra-red light cinematography in his experimental work on the pupil. Such methods enabled Duke-Elder[10] to state that; "Slight difference (less than 0.25 mm.) between the two pupillary diameters may be regarded as physiological in the static condition, but if such an inequality is accentuated during contraction or dilation, particularly with cocaine, the difference acquires significance."

## PHYSIOLOGICAL ANISOCORIA

### Static

No prognostic significance apart from recognition of the condition is attributed to physiological anisocoria, which can be either static or dynamic. Fuchs[11] described

a congenital familial type of static anisocoria present in from two to forty per cent of the population which he stated could be easily recognized from the fact that it existed throughout the lifetime of the patient unassociated with any disturbance in innervation or abnormality in pupillary reaction.

Anisometropia is commonly overlooked as a cause of static physiological pupillary inequality, the pupil of the more myopic eye being larger. The Fromagets[12] did not believe that difference of refractive power of the two eyes could of itself produce unequal pupils. Hirsch and Weymouth[13], however, found it to be present in one per cent of a series of 266 Stanford University students. They stated the myopic pupil appears to be larger because the corneal power and anterior chamber depth are both greater than in the normal eye. It is more satisfactorily explained on a reflex basis than by this simple magnification theory. In myopia, parallel rays of light cross in front of the retina reaching it out of focus. This is interpreted as blurring of distant vision by the visual cortex which transmits impulses to the midbrain in an attempt to produce what might be called reverse accommodation. The resulting inhibition of the Edinger-Westphal and oculomotor nuclei on the affected side produces the unilateral mydriasis and exophoria sometimes seen in unequal or unilateral myopia.

Dynamic

Two types of dynamic physiological anisocoria occur. The first of these, Tournay's reaction, is a normal dilation of the pupil of the abducting eye coupled with a constriction of the pupil of the adducting eye when the eyes are turned strongly to one side. The dilatation, which averages 0.5 mm., commences after an interval of three to five seconds, and remains as long as the sidelong glance is maintained (Duke-Elder).

The second type of dynamic physiological anisocoria is noticed on oblique illumination of the normal eye in which the pupil on the side of the illumination is slightly narrower than the pupil of the other eye. Jones[14] is the only writer who failed to accomplish this in his series on 25 normal persons. Behr[15] attributed it to the pupillomotor prevalence of the nasal half of the retina and its closer connection with the homolateral sphincter nucleus. The importance of this lies in the fact that on clinical examination the pupils are usually illuminated from the side and the resulting slight inequality may be misleading.

STATIC PATHOLOGICAL ANISOCORIA

Homologous to those of physiological anisocoria, both static and dynamic types of pathological anisocoria occur. Static pathological inequality of the pupils may be due to ocular, visual, or nervous conditions. Ocular

conditions may determine a considerable degree of anisocoria depending upon mechanical or reflex hindrances to the movements of the iris. Such conditions occur in the local irritation and inflammatory infiltration of iritis, the reflex stimulation of keratitis, the mechanical restraint of synechiae, the limitations to contractions depending on atrophy of the tissues, or the immobility imposed by rupture of the sphincter muscle. The visual embarrassment of one eye, whether due to intraocular or extraocular conditions resulting in total blindness of that eye, determines a condition called amaurotic mydriasis in which the pupil of the blind eye is usually 0.25 mm. larger than that of the other. The physiology of this will be considered later in this paper under nervous conditions producing pathological anisocoria.

Anatomy

Before beginning the discussion of that topic, a review of the neuroanatomy and physiology of the iris is necessary. Normally, the pupil is a circular opening in the iris diaphragm of the eye. The size and to a certain extent the shape of the pupils are determined by two muscular structures; the circular muscle fibers of the iris, the sphincter pupillae, and the radial muscle fibers of the iris, the dilator pupillae. Both muscles are innervated by the autonomic nervous system; the sphincter by the parasympathetic, the dilator by the sympathetic

nervous system. The two muscles are true antagonists. Active innervation (stimulation) of one is coupled with a decrease in tonus (inhibition) of the other. The interplay of these two guarantees the fine regulation of the movements of the iris. Langworthy[16] stated that the sphincter must be regarded as having the greater functional significance of the two. The parasympathetic acts locally on the iris musculature by contraction and relaxation brought about by central discharges of excitation and inhibition. As Langworthy and Ortega[17] pointed out, section of the oculomotor nerve results in paralytic mydriasis, a maximal dilation with no reflex activity, and section of the cervical sympathetic interferes only slightly with pupillary reactions. The sympathetic maintains a constant state of tone in the dilator muscle to supplement the effect of relaxation of the sphincter. The most important role of the sympathetic seems to be its central inhibition of the constrictor center. Emotional stimuli produce mydriasis through this inhibition.

The parasympathetic impulses for the sphincter originate in the Edinger-Westphal nucleus located in the midbrain. This nucleus consists of a paired group of small cells, lying anteriorly between the diverging extremities of the lateral nuclei which subserve the extraocular muscles (oculomotor nucleus). From the Edinger-Westphal nucleus the pupilloconstrictor fibers travel

through the oculomotor fascicle in the brain stem and through the oculomotor nerve. When this nerve divides into its several branches, the pupilloconstrictor fibers join the branch for the inferior oblique muscle. They soon separate from it and constitute the short or motor root of the ciliary ganglion. After a synapsis in this ganglion the short ciliary nerves travel to the eyeball, pierce the sclera around the optic nerve and run in the supra-choroidal space anteriorly to the sphincter muscle. The sphincter muscle is composed of 70-80 segments which are innervated separately. Nathan and Turner[18] suggested that the pupilloconstrictor fibers for convergence may run from the IIIrd nerve nucleus to find a relay station in the accessory episcleral ganglia of Axenfeld, thence relaying to the ciliary body without traversing the ciliary ganglion. Doggart[19] stated; "The Edinger-Westphal nucleus receives excitatory stimuli from the occipital and frontal regions of the cortex, and recent research has shown that the frontal cortex also sends out inhibitory impulses. In other words, mydriasis formerly regarded as mediated by stimuli travelling from the frontal cortex to the sympathetic center in the hypothalamus is really attributed to cortical inhibition exerted on the Edinger-Westphal nucleus. Another important anatomical feature is the existence of an inhibitory sympathetic path from the hypothalamus to the constrictor center, and it is abundantly proved that mydriasis accompanying powerful

emotion is achieved not so much by stimulation of sympathetic fibers as by inhibition of parasympathetic constrictor fibers." Jaffe[20] shared this opinion concerning the mechanism of immediate pupillary dilatation due to psychosensory stimuli.

In considering the sympathetic innervation of the dilator pupillae, the central connection of the sympathetic fibers are in the main still conjectural. Stimulation of cortical areas concerned with ocular movements in the frontal lobe and the calcarine area produces certain effects, among them dilation of the pupil which is characteristic of the stimulation of the cervical sympathetic. This is minor. The pupillary sympathetic center is located in the hypothalamic area of the midbrain lateral to the infundibulum near the sphincter center. As mentioned above, from this center an inhibitory pathway travels to the constrictor center. The first neuron of the main efferent pathway begins in the sympathetic center; in the midbrain it lies ventrally and near the midline; in the pons it travels beneath the grey matter around the central canal; in the restiform body it shifts ventrally and laterally toward the lateral spino-thalamic tract; in the medulla it runs through the intermediate or lateral part of the ventral reticular formation and down the lateral columns of the upper cervical cord suffering a partial decussation to

terminate in the inferior cilio-spinal center of Budge located at the level of the eighth cervical and first and second thoracic segments. The second neuron runs from Budge's center through the white rami communicantes to the cervical sympathetic chain and through the inferior and middle cervical ganglion to the superior cervical ganglion where there is a synapsis. This second neuron represents the pre-ganglionic fibers. The third neuron (post-ganglionic fibers) begins at the superior cervical ganglion. The fibers run as nervus caroticus internus along the carotid artery through the carotid canal into the skull. Here the nervus caroticus breaks into a fine plexus. The fibers concerned with the dilator travel to the Gasserian ganglion and opthalmic branch of the Vth nerve, going along the naso-ciliary branch of the opthalmic nerve to reach the globe by the long ciliary nerves.

Lesions of either of these pathways, whether irritative or paralytic in nature, located unilaterally will produce a static type of pathological anisocoria. The normal range of pupillary size is about 2.5 to 4 mm., with an average of about 3.5mm. A pupil larger than normal is said to be mydriatic, and one smaller is said to be miotic. Static pathological pupillary inequality can be conveniently divided into these two conditions, pathological mydriasis or pathological miosis.

Static Pathological Mydriasis

The first of these, pathological mydriasis, may be

due to pathological conditions within the eyeball, paretic lesions of the parasympathetic, irritative lesions of the sympathetic, or cerebral events leading to inhibition of the constrictor center.

The ocular causes of mydriasis, according to Duke-Elder[21], can be shortly dismissed -- an immobility of the pupil in dilation occurs in atrophic conditions of the iris or in glaucoma, and a paralytic mydriasis results from contusions to the globe (Iridoplegia Traumatica). An absolute paralysis has been described as an early sign of metastatic ophthalmia, and a unilateral pupil should suggest the possibility of an intra-ocular foreign body. Amaurotic mydriasis, which has been mentioned previously, is the dilation of the blind eye which results when total unilateral amaurosis occurs in that eye. Each optic tract is more intimately related functionally with the contralateral constrictor center that the homolateral. The pupillomotor value of the nasal retina is greater than the temporal. Since the fibers from the nasal half of the only effective retina travel up to the contralateral tract and decussate again in the posterior commissure, they influence particularly the homolateral center. The tone of the sphincter is therefore greater on the side of the seeing eye. The less effective temporal half of this eye governs particularly the other constrictor center for the blind eye, the pupil of which is therefore dilated.

Paretic lesions of the parasympathetic causing

pathological mydriasis due to paralytic lesions of the nucleus or efferent pathways between the Edinger-Westphal nucleus and the eye are myriad. The pupil is widely dilated owing to the unantagonized action of the iridodilator muscle. The reaction to both light and accomodation may be lost. Paralysis of the sphincter pupillae occuring without paralysis of the extraocular muscles is usually due to a lesion either of the nucleus of Edinger-Westphal or of the ciliary ganglion. Lesions causing paralytic mydriasis may arise in the midbrain, the meninges, the basal structures, the cavernous sinus, the superior orbital fissure, the nasal sinuses, and the apex of the orbit. Such lesions can occur in encephalitis lethargica, anterior poliomyelitis, vaccinal encephalitis, multiple sclerosis, bacterial encephalitides, herpes zoster, leprosy, meningo-vascular lues, tuberculous and purulent neningitides, vitamin B insufficiency, hereditary ataxias, tetanus, botulism, and acute lead or carbon monoxide poisoning. Any space taking lesion, whether it be neoplasm, aneurysm, or hemorrhage which according to Eareckson and Miller[22], Collier[23], and Gray[24] is occassionally seen in diabetics may have a similar effect. Transient paralytic mydriasis is sometimes seen with infection of the posterior ethmoid cells, as Spiegel and Sommer[25] stated. Trauma may cause a nuclear lesion resulting from damage to the brain stem; a nerve injury from tearing or bruising the nerve trunk or compression

by hemorrhage at the base of the skull in the vicinity of the sphenoid fissure or within the orbit; or an injury to the ciliary ganglion or the ciliary nerves from the effects of concussion.

The lesions causing irritation of the sympathetics and consequent pathological mydriasis are also manifold and may occur in the hypothalamus, midbrain, medulla, or cervical cord. This spastic mydriasis is part of a syndrome characterized by ipsilateral pupillary dilation and widening of the palpebral fissure which causes what appears to be a slight exopthalmus. It may be associated with vasoconstriction, lowering of the temperature, and hyperidrosis on that side of the face. The central lesions causing this include many of the lesions mentioned above which might cause irritation of the sympathetics, such as neoplasm, encephalitis, and syringomyelia. Tumors of the spinal cord may cause irritation of the spinal nerve roots, as may a cervical rib, aneurysm of thoracic vessels, mediastinal tumors, or tuberculous pleurisy. Other conditions in the neck may have similar effects. Among these conditions are retropharyngeal tumors, enlarged thyroid or cervical lymph glands, and trauma with hematoma formation. Visceral disease may be manifest through a spastic mydriasis. This is often seen in pleuro-pulmonary tuberculosis in which sympathetic irritation is caused by thickening or retraction of the pleura or by tracheo-bronchial

adenopathy. A left sided mydriasis is said to occur in aortic dilatation and exudative endocarditis. This is called Roque's sign. Moshowskij's sign, or right sided mydriasis associated with acute abdominal conditions such as appendicities, cholecystitis, or colitis is occasionally seen. Salmon[26] described seven cases of ruptured ectopic pregnancy associated with shoulder pain and pupillary dilatation on the same or opposite side of the ectopic gestation. He attributed the shoulder pain to diaphragmatic irritation with consequent spread of afferent impulses through the phrenic nerve to the adjacent segments of the cervical cord, and he felt the mydriasis could be explained on the same basis. Singultus, alone or with pupillary changes may likewise result. Piperno[27] stated dental conditions frequently produce a similar reflex sympathetic irritation resulting in ipsilateral mydriasis.

Cerebral events leading to inhibition of the constrictor center usually produce contralateral dilatation in tumors or abscesses of the fronto-parietal, parietal, temporal, and temporo-occipital areas of the cerebral cortex; and ipsilateral pupillary dilatation when the hypothalamus is stimulated. Pupillary changes are common after cerebral injury or hemorrhage and probably constitute the most constant sign of a

fractured skull. Unilateral dilatation with loss of all pupillary reflexes is a constant accompaniment of extradural hemorrhage and a frequent accompaniment of intradural bleeding and is an indication for decompression (Duke-Elder). A condition called functional unilateral mydriasis by Ross[28] due to an inhibition of the tone of the constrictor nucleus by the hypothalamic sympathetic center and associated with marked pupillary unrest and increased psychosensory pupillary reflexes is sometimes seen in psychoneurotic states, schizophrenia, and hysteria. Lewis and Schilder[29] discussed a condition due to a similar cause which was first described by Westphal under the title of the catatonic pupil. In this condition, transient states of mydriasis occur with mobile spasm so that reactivity varies from a prompt response to immobility in association with variations in size and equality of the pupils from moment to moment. This phenomenon is seen in catatonia, hysteria, post-encephalitic states, syphilis, alcoholism, traumatic neurosis, schizophrenia, dementia praecox, other psychotic states, and in neurotic and anxious person who are otherwise normal in which case it is termed Bumke's anxiety pupils.

Static Pathological Miosis

The second type of static pathological anisocoria, pathological miosis, may be due to pathological conditions

within the eyeball, irritative lesions of the parasympathetic, paretic lesions of the sympathetic, or cerebral events leading to removal of inhibitory influences from the constrictor center.

Pathological miosis due to conditions within the eyeball is a spastic condition caused by contraction of the sphincter muscle by some irritant, either by direct irritation in iritits or reflexly in keratitis. It may also be produced by sudden decrease in intra-ocular pressure as in intra-ocular injuries, paracentesis, or operations.

Irritative lesions of the parasympathetic leading to spastic miosis occur in central afflictions such as pontine hemorrhage or tumors, and epidemic encephalitis. Nerve trunk irritation at the base of the skull occurs in purulent meningitis, and in suppurative otitis media as Berberich[30] pointed out. Spastic miosis may also occur in irritative or inflammatory lesions of the cavernous sinus, superior orbital fissure, or orbit when the ciliary ganglion is involved.

A paretic lesion of the sympathetic produces a constriction of the pupil by the unopposed action of the iridoconstrictor muscle. The pupil fails to exhibit the normal dilatation when the eye is shaded, in states of pain and emotional excitement, and reflexly when the skin of the same side of the neck is scratched with a pin -- the ciliospinal reflex. The iridodilator fibers

throughout their course are close to the other fibers of the ocular sympathetic. Paralysis of the dilator of the iris is therefore usually manifested in Horner's syndrome which is characterized by miosis, ptosis, and empththalmus. Unilateral vasodilation, increased temperature, decreased sweating, increased accommodative power, and decolorization of the iris on the affected side are also said to occur in this condition. Adler[31] stated that if the affection of the nerve is slight, miosis alone may occur which is usually slight and associated with normal pupillary reflexes. A lesion in any part of the long sympathetic pathway may produce Horner's syndrome. In the brain-stem it may be due to multiple sclerosis, encephalitis, syphilis, pontine tumors, or hemorrhage. It may be produced by lesions of the lateral part of the medulla such as posterior inferior cerebellar artery thrombosis. In the lower brain-stem it may be due to multiple sclerosis, poliomyelitis, tabes, syringomyelia, hematomyelia, progressive muscular atrophy, meningitis, and spondylitis. Traumatic or neuritic affections of the brachial plexus such as Klumpke's paralysis or traction by a cervical rib may destroy the sympathetic white rami to cause this syndrome. The effects of a cervical rib may appear on the opposite side. Intrathoracic conditions such as tuberculosis, aneurysms of the aorta, subclavian or carotid arteries, or mediastinal glands or tumors may be in-

criminated. In the neck retropharyngeal tumors, carcinoma of the esophagus, enlarged thyroid or lymph glands, esophageal diverticula, aneurysms, or neuroma of the sympathetic chain may be the etiological factor. Trauma may also be the cause, as in hematoma of the spinal cord or fracture of the skull, spine, or clavicle. Within the cranium the post-ganglionic fibers may be damaged by the pressure of a tumor or aneurysm behind the orbit.

Horner's syndrome, then, can be caused by lesions affecting the first neuron (corpus subthalamicum to cervical spine), pre-ganglionic fibers, or post-ganglionic fibers. The seat of the lesion can be localized more definitely by pharmacologic differentiation and by the behavior of the psychosensory reaction (painful stimulation). Atropine is always effective in all cases of Horner's syndrome, regardless of its seat. Cocaine is not effective if the lesion is in the pre- or post-ganglionic fibers, but its effectiveness is increased if the first neuron is damaged. Adrenalin instilled into the conjunctival sac will not dilate the miotic pupil if the first or second neuron are affected, but it will cause a marked dilatation if the seat is in the third neuron (post-ganglionic fibers). The psychosensory reflex dilatation to painful stimulation is markedly increased with a lesion in the second or third neuron.

Central lesions causing removal of inhibitory influences from the constrictor nucleus and thereby leading to unilateral miosis may occur in epilepsy, increased intracranial pressure, schizophrenia, and dementia praecox due to cortical disturbances. Lesions in the corpus striatum as seen in Parkinsonism and cerebral arteriosclerosis may likewise produce a miosis.

Periodic Phenomena

In addition to the miotic and mydriatic types of anisocoria originating from nerve imbalance, certain phenomena occur which are characterized by periodic or cyclic movements of the pupil which are also determined by autonomic activity. One of these, cyclic oculomotor spasm, seems to be due to spasm of the parasympathetic; while the other two, cyclic sympathetic spasm and springing pupil seem to be mediated through the sympathetic.

Cyclic oculomotor spasm is a rare condition which is either congenital or acquired in the first years of life and in which are exhibited rhythmically alternating phases of spasms and relaxation that occur even in sleep. The phase of relaxation consists of unilateral, usually total, paralysis of the oculomotor nerve with ptosis and iridoplegia. After approximately one minute the spastic phase sets in during which the lid opens, the eye is

adducted, and the pupil contracts often to maximal miosis. Lowenstein and Givner[32] felt that this condition resulted from partial destruction of the sphincter nucleus combined with supranuclear lesions involving, among others, particularly the connection between the sphincter nucleus and the hypothalamus. "The automatic nature of the movements is explained by the particular combination of (a) partial destruction of the sphincter nucleus which produces increased fatigue, combined with (b) a supranuclear lesion which produces increased irritation of the remaining part of the nucleus. The increased fatigue produces a pathologically prolonged refractive stage; the increased irritation causes small stimuli normally below the threshold to become effective. Such stimuli are those of pupillary unrest. They also explain the persistence of the periodic spastic oculomotor phenomena during sleep."

Lowenstein and Levine[33] reported one case of cyclic sympathetic spasm, which is the only one in the literature. They concluded that the causal lesion lay in the hypothalamus.

They also discussed the phenomena of springing pupils, which is also probably produced through sympathetic activity. This condition is characterized by varying anisocoria. At one time one pupil is larger, at another time the other is larger. It occurs in two forms; either

both pupils take part or only one. In the former case one pupil may be larger today, the other tomorrow; in the second case only one pupil changes its diameter. Springing pupils have been observed in tertiary lues, both tabes and general paralysis; in functional states such as neurasthenia; in veronal poisoning; and in apparently normal individuals. Its clinical significance is unknown. This concludes the consideration of static pathological anisocoria.

## DYNAMIC PATHOLOGICAL ANISOCORIA

Pathological dynamic anisocoria, on the other hand, is brought out in the excursions of reflex activity and may occur either during contraction or dilatation. Anisocoria occuring or increasing during dilatation is usually due to a lesion affecting the sympathetic. Anisocoria occuring or increasing during contraction is generally due to a paretic lesion of the IIIrd nerve, its nucleus or its supranuclear inhibiting pathways. In nuclear or infranuclear lesions the ipsilateral pupil is generally large, in supranuclear lesions it is generally small. Of the various reflexes which bring about changes in the pupillary size the light reflex, the near reflex, and the psychosensory reflex are most important from the clinical standpoint. A short resume of the neuroanatomy of these reflexes should be considered before discussing the anomalies associated with them.

Anatomy

If one eye is exposed to light, a constriction of both pupils normally occurs. The response of the pupil of the eye upon which the light falls is called the direct reflex, that of the opposite pupil the consensual reflex. According to Lowenstein and Lowenfeld[34], the light reflex is primarily a parasympathetic reflex.

The afferent impulses of the light reflex arise in the retina and follow the path of the visual afferent fibers as far as the optic tracts, with a similar decussation of those from the nasal halves of the retina at the optic chiasma. It is not known whether the fibers for the light reflex are the same as those for vision. Clark[35] showed that the retinal impulses to the lateral geniculate body are conveyed by fast conducting fibers, while those to the midbrain are fine and slowly conducting. Magoun and Ranson[36] and Magoun, Atlas, Hare and Ranson[37] stated: "The light reflex fibers traverse the portion of the optic tract which runs medial to the lateral geniculate body, and passes caudally along the lateral and dorsal aspects of the medial geniculate body, to reach the brachium of the colliculus. It is clear that after reaching the brachium of the superior colliculus the light reflex pathway does not enter the superior colliculus itself, but turns rostrally and medially into the pretectal region, or the transition area between the

thalamus and midbrain. From the pretectal region the pathway descends around the rostral end of the gray matter of the aqueduct to the oculomotor nuclei. Central crossings in the path were found to occur both in the posterior commissure and ventral to the cerebral aqueduct in the immediate vicinity of the oculomotor nuclei." It is clear that both optic tracts must be connected with both IIIrd nerve nuclei since light falling on any part of either retina causes bilateral contraction of the pupils. The efferent pathway from the Edinger-Westphal nuclei to the constrictor of the iris has already been described.

The near reflex as it is called by Duke-Elder[38] is made up of two components; the convergence reflex and the accommodation reflex. The convergence reflex is stimulated by the movement of convergence. Its nerve pathway is not associated with the visual pathways. This reflex is activated by proprioceptive impulses initiated by the contraction of the two internal recti muscles. The afferent pathway has not been defined, but probably the fibers ascend the IIIrd nerve itself to reach the mesencephalic root of the trigeminal to be relayed to Perlia's nucleus which has connections with the Edinger-Westphal nucleus. The accommodation reflex is activated in the retina and the impulses are carried up the visual pathway through the external geniculate body to the calcarine cortex (area 17) from which a relay

is made to the prestriate area (area 19). From here the reflex paths travel down the occipito-mesencephalic tract to the midbrain and Perlia's nucleus, from which connection is made with the Edinger-Westphal nucleus. The efferent pathways for these two reflexes from this nucleus travel down the oculomotor nerve leaving it proximal to the ciliary ganglion to synapse in an accessory ganglion from which post-ganglionic fibers reach the constrictor pupillae. According to Cogan[39] the convergence reaction is the more potent of the two. The psychosensory reflex has been mentioned previously.

Failure of the Light Reflex

Failure of the light reflex may be due to a lesion in any part of the afferent or efferent pathways. If the afferent pathways are severed which are concerned with carrying both visual and pupillary fibers, an amaurotic pupillary paralysis will result which has been discussed earlier as a cause of anisocoria. In amblyopic pupillary paresis from a similarly placed incomplete lesion resulting in diminished, but not abolished, vision, the pupillary light reflexes will be affected to produce a dynamic anisocoria in which the ipsilateral direct and contralateral indirect light reflexes are diminished. If such lesions are so placed as to cause blindness in only half the visual field, pupillary hemikinesia will result with loss of light reflex when the blind half of the retina is

stimulated. If this occurs unilaterally, an anisocoria results wherein the pupil on the side opposite the lesion is larger than its fellow and reacts less markedly to light. This is called Behr's pupillary phenomena. The underlying mechanism has been previously described under amaurotic pupillary paralysis.

Failure of the light reflex which may occur alone is called reflex iridoplegia. Loss of the pupillary light reflex depends upon a lesion at some point of the reflex pathway, and the preservation of the reaction on accommodation implies that the lesion does not involve those fibers. The loss of the light reflex alone is termed the atypical Argyll Robertson pupil. Adie[40] stated that it may occur in congenital cerebral defects; cerebral hemorrhage or thrombosis; encephalitis lethargica; tumors of the region of the anterior corpora quadrigemina, the third ventricle, or aqueduct; sclerotic or senile dementias; internal hydrocephalus; meningitis; disseminated sclerosis; trauma, either affecting the Edinger-Westphal nucleus or the orbit; chronic alcoholism; nicotine and carbon disulphide poisoning; poliomyelitis; syringomyelia; diabetes; herpes zoster; and syphilis, both paretic and meningo-vascular. To produce an anisocoria, the causal lesion must be unilaterally placed in the brain stem, within the constrictor center, along the nerve trunk, or within the orbit. Miosis is not necessarily associated with this reflex iridoplegia.

When absolute or relative miosis is associated with light rigidity in connection with prompt and full contraction to accommodation and convergence, normal vision, imperfect dilatation to mydriatics and painful stimuli, and absence of reaction to vestibular stimulation the typical Argyll Robertson pupil occurs as described by Merritt and Moore[41], who felt that it is pathognomonic of central nervous system lues. They found it present in 60.8 per cent of patients with tabes, and 50.2 per cent of patients with dementia paralytica. Herman[42] has observed the typical Argyll Robertson pupils in three cases of chronic alcoholism. The Argyll Robertson pupil is often unilateral or at least not equally well developed in the two eyes. As a result a typical anisocoria develops with the pupil of the affected eye being narrower than that of the other eye. It is typical of the full blown cases that the pupillary diameter is unusually constant. This is very characteristic of the syndrome and is due to the fact that the psychosensory reflexes are markedly diminished. In the early stages of the condition, however, the pupillary unrest is increased, only to disappear later. The Argyll Robertson pupil is not only fixed and miotic, but also often irregular as a result of the unequal alternation in the tonus of the sphincter muscle in its various segments. Paton and Mann[43] felt that the occurrence of Argyll Robertson pupils depends on a break in the

reflex arc in that part of the pathway consisting of the intercalated colliculo-nuclear neuron and the nucleus of origin of the efferent iridoconstrictor fibers. Adler[44] stated that when bilateral Argyll Robertson pupils occur the intercalated fibers of both sides are damaged. Harris[45] shared this opinion that the site of the lesion was in the upper half of the midbrain, near the aqueduct of Sylvius, where it may interrupt the fibers approaching the iridoconstrictor nucleus. Nathan and Turner[46] felt that the lesion might lie in the ciliary ganglion where the fibers affecting the near reflex would not be damaged. Magoun and Ranson[47] stated that they doubted if a single lesion of moderate extent would affect the nervous pathways to both eyes, and for that reason none of the hypothesis put forth so far are actually satisfactory to explain the location of the lesion. Although the actual location is unknown, as Walsh[48] stated, one general statement can be made regarding the typical Argyll Robertson pupil and that is that it is indicative of parenchymatous involvement of the central nervous system of the tabetic or dementia paralytica type.

Failure of the Dark Reflex

In addition to contraction of the normal pupils in response to increased illumination, dilatation occurs when the light is decreased in intensity. On

shading the normal eye in a case of unilateral visual failure while the patient looks at a source of light, a marked anisocoria occurs with dilatation of the affected pupil. This indicates ipsilateral disease of the macula or optic nerve. This phenomena occurs in cases of unilateral abolition of the pupillary reflex activity where the consensual darkness reflex derived from the other eye may dominate the pupillary reaction. This Pseudo-Anisocoric Sign of Kestenbaum (Duke-Elder) is of diagnostic value when the fundus is normal, and may be used to differentiate an organic retrobulbar lesion from a functional disturbance of vision.

Failure of the Near Reflex

An isolated paralysis of the near reflex occurs in the presence of a lesion affecting the connection between Perlia's nucleus and the Edinger-Westphal nucleus, and can occur unilaterally to produce anisocoria. This is called the Inverse Argyll Robertson pupil. With it the near reflex is lost and the light reflex retained. It has been reported in tabes, diphtheria, and tumors near the corpora quadrigemina. A physiological Inverse Argyll Robertson pupil occurs in myopia over three diopters where accommodation is unnecessary because of the refractory error.

Failure of the Psychosensory Reflex

Failure of the psychosensory reflex occurs in absolute

iridoplegia, tabes, and general paralysis in association with loss of the light reflex. It may occur with normal light reflexes in catatonia to produce anisocoria. Mention has been made of the use of this in testing for lesions of the cervical sympathetic in Horner's syndrome.

TONIC PUPILLARY REACTION

In addition to the above cuases of pathological dynamic anisocoria, a condition of unknown etiology exists which is characterized by sluggish pupillary reaction and absent tendon reflexes. This tonic pupillary phenonmena is unilateral in 80 per cent ofcases. Adler[49] cited the work of Ware who first described the features of the tonic pupil in 1813. According to Farrell[50] , the association of a tonic pupil and the absence of tendon reflexes was first described independently by Saegner and Strasburger in 1902. Holmes[51] referred to the condition as partial iridoplegia, and later[52] introduced the term tonic pupils. It was not not until Adie's clear description[53] of the syndrome that it received the serious consideration that it deserves. He described the disorder as (1) the complete form with typical tonic pupil and absence of reflexes and (2) the incomplete forms; (a) tonic pupils alone, (b) atypical phases of the tonic pupil alone, (c) atypical phases of the tonic pupil with absent reflexes, and (d) absent reflexes alone. Kern[54] stated that the pupillotonic phenomena is characteristically unilateral, with

the involved pupil considerably larger than the normal and usually oval or irregular in shape. Sykowski[55] pointed out that although the pupil is usually moderately dilated, it may be smaller than its fellow.

The direct and consensual reactions to light are completely or almost completely absent. After an hour in the dark, however, the pupil dilates and on exposure to bright light a slow contraction may be observed after a brief interval; often this continues until the pupil becomes smaller than it was before it dilated in the dark. After removal of the light, the pupil, again after a short delay, dilates to its original size.

Perhaps the most striking feature of the tonic pupil is its behavior on convergence. Adie[56] in describing the phenomena said: "If the patient fixes on a near object and continues to gaze at it intently the pupil, sometimes after a delay of several seconds, contracts slowly and with increasing slowness through a range often greatly in excess of the normal. Contraction down to pinhead size is not uncommon; the larger pupil then becomes smaller than its fellow." After relaxation of the effort to converge, contraction may continue, the pupil may remain fixed for a few seconds or it may begin to dilate slowly. Dilation once started proceeds even more slowly than did the contraction. The accommodation reaction is occasionally affected, so that on fixation of a distant

object the sluggishness of dilation may produce slight temporary disturbance of vision. The tonic pupil responds normally to mydriatics and miotics. Atypical forms of the tonic pupil manifest various degrees and combinations of the features described.

Lost of tendon reflexes is characteristic of the complete form of Adie's syndrome. Most frequently there is an absence of one or both ankle jerks, and it has been observed that loss of other tendon reflexes does not occur in the presence of both ankle jerks. Kennedy and his co-workers[57] reported two cases in which there was an absence of all deep reflexes. Several authors have expressed skepticism concerning Adie's subdivision of absent reflexes alone. Jelliffee[58] stated that absence of tendon reflexes occurs in one to two per cent of the normal population, therefore making it a diagnostically unreliable sign.

Moore[59] believed the condition might be congenital but this has not been proven. All reports have shown a greater incidence in females. Adie's syndrome is usually seen in young adults, although McKinney and Frocht[60] have reported cases in children. The age of onset is usually about the third decade. The onset is usually sudden; the patient noticing mistiness of vision, of being informed of the pupillary inequality by other observers.

The etiology and pathogenesis of Adie's syndrome are still obscure. Adler and Scheie[61] postulated that

the disturbance was a partial denervation of the parasympathetic supply to the pupil at or peripheral to the ciliary ganglion. They concluded this after demonstrating that instillation of a 2.5 per cent solution of mecholyl into the conjunctival sac of both eyes caused the tonic pupil to constrict to the size of the normal pupil which was uneffected. This constitutes a very satisfactory test for differentiating this condition, and may be used as a form of therapy when the patient complains of visual disturbances. Much the same experiment was carried out later by Lowenstein and Friedman[62] using physostigmine. They concluded that pupillotonic reactions may be caused by peripheral lesions of the IIIrd nerve both pre- and post-ganglionic, and by lesions in the vegatative centers of the diencephalon and their connections with the mesencephalon. They suggested, "Adie's syndrome is due to heredodegenerative disease localized in the great autonomic centers of the diencephalon and the connections with the mesencephalon. It is characterized by pupillotonic reactions with irritative sympathetic symptoms and absence of tendon reflexes. It generally has not syphilitic etiological factor but as a syndrome may be produced by so-called asymptomatic syphilis nervosa." Most writers agree that it is unrelated to lues. Myotonic pupils have been described in patients with diabetes, poliomyelitis, polioencephalitis, influenza, cervical

rib, injuries to the cervical plexus, apical tuberculosis, alcoholism, skull injury, delayed apoplexy, feeblemindedness, catatonia, syringomyelia, multiple sclerosis, aortic aneurysm, cervical pachymeningitis, arthritis, dysthyroid states, asthma, and epilepsy. These have been coincidental findings however, and their relationship to the findings of the tonic pupil are in no way related to its etiology.

Adie's syndrome has been established as a benign condition. Moore[63] cited a case in which the patient had been aware of the pupillary asymmetry for 47 years, with no complications arising. Weber[64] examined the patient reported by Markus[65] 27 years previously, and found the tonic pupil and absent reflexes the same as first reported with no other symptoms. Rudolf[66] observed a patient with Adie's syndrome over a period of 32 years, during which time the condition remained benign. He reported that this patient's daughter developed the condition in the same eye (left) as her mother, and at approximately the same age (29 years). Once developed, this condition remains unchanged. Occasionally the other eye becomes involved.

No treatment is indicated unless the patient complains of difficulty in accommodating in which case mecholyl or physostigmine may be used. The patient should be assured that the condition is not of luetic

etiology. This differential diagnosis is not difficult as the Argyll Robertson pupil is smaller than normal, immobile to light, briskly reactive to convergence, and poorly responsive to mydriatics; which differs in all respects from the myotonic pupil of Adie.

## COMMENT

In attempting to determine the etiology of anisocoria, careful observation of the pupils should be made to determine if the condition exists before a stimulus had induced a movement, in which case it is static in type. Dynamic anisocoria may occur during contraction or during dilation, which should also be noted. The various pupillary reactions should be tested thoroughly; the light reflex, dark reflex, near reflex, and psychosensory reflex should be ascertained to be present or absent. Ample opportunity should be given for the pupillary reactions to occur should the pupil be myotonic. If anisocoria is noted, the conditions under which the observations were made should be investigated to determine any possibility of a physiological anisocoria. Some method of checking gross visual acuity should be employed to discount the presence of an amaurotic condition. The refractory powers of the two eyes should be measured for any great variation between the two. Needless to say, a complete medical history should be taken with special reference to visual changes and trauma,

and a thorough physical and neurological examination should be performed to determine any related findings. The necessary pharmacological tests should be utilized.

When attempting to localize the site of a lesion, certain basic principles should be utilized. Lowenstein[67] remarked that the parasympathetic system discharges in the form of local reflexes, while the sympathetic discharges en masse with such actions as vasoconstriction of the blood vessels in the skin, increased blood pressure and pulse rate, and widened palpebral fissures. The reflex to dark, psychosensory restitution phenomena, and psychosensory dilatation are sympathetic reflexes; whereas, the light reflex and near reflex are parasympathetic reflexes[68]. His "Law of Convergency and Divergence of Pupillary Reactions"[69] stated that static sympathetic conditioned anisocoria diminishes during contraction; static parasympathetic conditioned anisocoria increases during contraction of the pupil. Dynamic anisocoria of the dilation phase is generally due to a lesion within the sympathetic part of the reflex arc; dynamic anisocoria occuring or increasing during the contraction phase is generally due to a lesion in the parasympathetic fibers[70].

When static anisocoria is caused by a lesion either in the third or second sympathetic neuron, contraction will not be hindered on the side of the lesion, It is characteristic of this kind of sympathetic

anisocoria that in contraction it will diminish or at least will maintain its former degree. During the dilation phase this kind of anisocoria will increase. It will also increase in relation to darkness and to psychosensory stimuli, but the psychosensory restitution phenomena will be diminished on the side of the lesion. The psychosensory restitution phenomena is observed in the restoration of the ability of the fatigued pupils to react to light stimuli following psychosensory stimuli after the light reaction had been lost. In association with a lesion of the third neuron, there will also be a dilation in response to adrenalin with no response to cocaine. In a lesion of the second neuron, there will be a response to neither adrenalin nor cocaine. A lesion in the first neuron may have either of two distinct features; it may produce either a miosis or a mydriasis, depending whether the lesion be paralytic or irritative. The former lesion produces Horner's syndrome in which the pupil dilates in response to cocaine and to psychosensory stimuli, but the psychosensory restitution phenomena is absent. In case of irritation, one must distinguish between an irritation of lesser or greater degree. In the case of irritation of a lesser degree, the psychosensory dilation is increased, and the psychosensory restitution phenomena is also increased but is easily

fatigued. In case of irritation of greater degree, the pupil no longer reacts to light but recovers the ability to react to light under the influence of physostigmine. The dilation in response to psychosensory restitution phenomena is absent.

Anisocoria which is due to a lesion of the third nerve may be characterized by either a larger or a smaller pupil on the side of the lesion. A large pupil is due to a lesion between the third nerve nucleus and the periphery. If the lesion is complete, the reaction to physostigmine no longer occurs. If the pupil is small, the condition is due to a supranuclear lesion. Such a lesion may be found by eliciting a reflex to light, since it is characterized by a more or less pronounced dynamic anisocoria.

Anisocoria which is due to a sympathetic lesion is generally not syphilitic in origin. Anisocoria due to a lesion located in the parasympathetic pathways, however, is frequently syphilitic. These statements apply only to acquired syphilis; congenital syphilis may give rise to lesions in the sympathetic, the parasympathetic, or both. Dynamic anisocoria in the contraction phase is a valuable sign in the early diagnosis of lesions which in adults are nearly always due to syphilis.

Following the localization of a lesion producing some type of pupillary inequality to the involved nerve

pathway, the pertinent diagnostic procedures necessary for the identification of the lesion should be carried out. The specific diagnostic tests vary a great deal with the type and location of the suspected lesion. If the cause be intracranial, such things as skull films, electroencephalograms, sinus X-rays, intracranial pneumography or angiography[71], and funduscopic examination for evidence of increased intracranial pressure may be of value in addition to the procedures mentioned above. In some cases, spinal puncture should be done with determination of pressure in addition to chemical and microscopic examination of the spinal fluid. The colloidal gold curve should be determined along with peripheral blood serology. Blood studies may also reveal evidence of such things as acute or chronic infections, neoplasms, diabetes, and dysthyroid states which may in some manner explain the anisocoria. Other laboratory studies including the basal metabolic rate, Mantoux test, and serum agglutination tests for various bacterial or viral agents capable of causing a meningitis or encephalitis may reveal the etiology of the lesion. If the causative factor seems to be a condition localized within the neck, radiographic and fluroscopic examination may be of help. Intrathoracic conditions may also be visualized by these techniques. In some cases, surgical exploration or biopsy might be indicated. In general, all available diagnostic procedures indicated should be utilized.

There is probably no treatment for anisocoria, except in a few instances such as myopia or Adie's syndrome, other than determination of the cause and proper management of it. In most cases the pupillary inequality produces no symptoms demanding treatment; whereas the underlying causative factors may be of serious import demanding vigorous and aggressive therapy. The significance of that fact should be remembered.

## SUMMARY

Anisocoria, or pupillary inequality, is not an uncommon finding, and may be found in physiological and pathological proportions. Before adjudging the condition pathological, the examiner should be assured that the condition is not familial, the eyes are fixed on an object directly in front of the patient, the illumination of the two eyes is equal, and neither eye is greatly more myopic than its fellow. Only in this manner can physiological causes of anisocoria be discounted. The benign non-luetic condition of Adie's syndrome characterized by sluggish pupillary reflexes, absent tendon reflexes, and prompt reaction of the myotonic pupil to mecholyl should be ruled out next.

Any case in which the patient presents anisocoria which cannot be explained by the above mechanisms should be considered as being pathological and demanding thorough investigation by all appropriate means available.

Many diverse conditions may be responsible for this finding, and a complete examination in an attempt to discover the cause of the anisocoria may be rewarded by the revelation of an underlying factor which may be of grave prognostic significance but still amenable to treatment. Syphilis is only one of these conditions and probably greatly exaggerated as a cause of anisocoria at the present time, although the typical Argyll Robertson pupil is pathognomonic of central nervous system lues.

In attempting to place the site of a lesion, it is useful to remember that miosis may be due to paralysis of the sympathetic or stimulation of the parasympathetic, and that mydriasis may be due to paralysis of the parasympathetic or stimulation of the sympathetic. Static sympathetic conditioned anisocoria diminishes during contraction, while static parasympathetic conditioned anisocoria increases during contraction. Dynamic sympathetic conditioned anisocoria occurs or increases during dilation, whereas dynamic parasympathetic conditioned anisocoria occurs or increases during contraction.

Lesions involving the sympathetic pathways may be localized by means of the effects of cocaine, adrenalin, and painful stimulation (psychosensory stimulation). In a lesion involving the first neuron, cocaine and painful stimulation are very effective, while adrenalin is ineffective. In a lesion involving the second neuron,

cocaine and adrenalin are ineffective, while painful stimulation is moderately effective. In a lesion involving the third neuron, cocaine is ineffective, while adrenalin is very effective and painful stimulation moderately effective.

Lesions of the IIIrd nerve may be associated with either a larger or smaller pupil on the side of the lesion. A larger pupil is due to a lesion between the third nerve nucleus and the periphery, and if the lesion is complete no reaction to physostigmine occurs. If the pupil is small, the condition is due to a supranuclear lesion which is usually associated with a pronounced dynamic anisocoria when eliciting the light reflex.

Observations of other ocular phenomena such as ptosis, enophthalmus, and divergent strabismus should immediately draw attention to the location of the lesion. Amaurosis may likewise explain the cause of an anisocoria.

Many cases of pupillary inequality are illusive to any explanation on an organic basis, in which event psychiatric evaluation of the patient may be fruitful. Many cases exist in apparently normal individuals, the cause of which remains unexplainable.

The treatment of anisocoria depends upon the accurate diagnosis of the cause, and is directed primarily at the pathogenic factors. The pupillary inequality usually produces no symptoms per se, except in such instances as Adie's syndrome which may be treated with mecholyl.

## CONCLUSIONS

1. Anisocoria is a frequently found physical sign which should be considered pathological until proven physiological or benign (Adie's syndrome).

2. Pathological anisocoria may be associated with a great number of diverse conditions, of which syphilis is only one. The typical Argyll Robertson pupil, however, is pathognomonic of central nervous system lues.

3. All patients with anisocoria should be thoroughly investigated by all means available in an attempt to arrive at the diagnosis of the primary cause.

4. Certain facts regarding the size and reaction of the pupils set forth in this paper are of assistance in localizing the site of a lesion in the pupillary nerve pathways.

5. The finding of pupillary inequality frequently can not be explained on an organic basis. Anisocoria may be due to psychiatric causes.

6. Anisocoria unassociated with other visual, medical, or neurological findings often occurs in normal persons.

7. Anisocoria per se requires no treatment, except in occasional instances. The treatment is that of the underlying cause.

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