58 | The Pupils

ROBERT H. SPECTOR

Definition

The normal pupil size in adults varies from 2 to 4 mm in diameter in bright light to 4 to 8 mm in the dark. The pupils are generally equal in size. They constrict to direct illumination (direct response) and to illumination of the opposite eye (consensual response). The pupil dilates in the dark. Both pupils constrict when the eye is focused on a near object (accommodative response). The pupil is abnormal if it fails to dilate to the dark or fails to constrict to light or accommodation.

The popular acronym PERRLA—pupils equal, round, and reactive to light and accommodation—is a convenient but incomplete description of pupillomotor function. It specifically omits important clinical data such as the actual size and shape of each pupil, the speed and extent of pupillary constriction, and the results of determining an afferent pupillary defect.

Technique

The examiner first must check the size, shape, equality, and position of the pupils, and their response to a bright light. Because these phenomena are best tested with the pupils in a semidilated state, clinical observations should be made in a dimly lighted room. Patients should be encouraged to fixate visually on a distant object, because if they inadvertently look at your nose or the flashlight, the attempt to converge will reflexly evoke miosis, and certain signs may be overlooked (e.g., anisocoria, light-near dissociation, or a subtle Marcus Gunn sign. For the same reasons, try not to startle or touch patients with your hands or instruments, as psychosensory stimulation induces mydriasis, hippus, and relatively hyperactive pupils.

To assess pupillary size in a darkened room, illuminate the face from below. Slowly move the light up to the patient's eye level and check the pupillary response to the bright light on each side several times. Grade these responses from 1+ to 4+. Next, look at the amount of pupillary constriction that occurs when the patient is forced to focus on a near object, such as a thumb held 15 to 20 cm above the eyes. Record these data so that they are easy to read and recall. Below is an example of one method:

	R	L
Size	5.0 mm	5.9 mm
Shape	Oval	Round
Light	+3	+3
Near	+3	+3

Normally, the convergence reaction is as brisk and as extensive as the light reaction. The extent of constriction depends also on the condition of the iris. A brown iris contracts less than a blue iris. In old people and in patients with iris atrophy, the sphincter becomes rigid, hence the light reaction diminishes in extent.

Basic Science

The size of the pupil is controlled by the activities of two muscles: the circumferential sphincter muscle found in the margin of the iris, innervated by the parasympathetic nervous system; and the iris dilator muscle, running radially from the iris root to the peripheral border of the sphincter. The iris dilator fibers contain α-adrenergic sympathetic receptors that respond to changes in sympathetic tonus and changes in the blood level of circulating catecholamines.

The pupillary light reflex arc begins in the retina (Figure 58.1). Considerable evidence exists that the visual cells of the retina, that is, the rods and cones, also serve as light receptors controlling pupillomotor activity. Fibers originating from the nasal neuroreceptor cells decussate in the optic chiasm to the opposite optic tract, whereas the temporal fibers continue in the homolateral optic tract. "Pupillary fibers" from both eyes within the optic tract pass via the superior quadrigeminal brachium and the superior colliculus to the mesencephalic pretectum and pretectal nuclei. Axons from each pretectal nucleus pass ipsilaterally and contralaterally to the ipsilateral and contralateral Edinger–Westphal (E–W) nucleus, a subnucleus of the oculomotor nuclear complex. The hemidecussation of the pupillary fibers at the optic chiasm and between the pretectal nuclei ensures that each E–W nucleus receives information about the level of incoming light from each eye. Hence, the pupils should be equal in diameter regardless of the level of vision of either eye. For example, in a patient with one blind eye, the pretectal nuclei would register and transmit to each E–W nucleus only one-half the normal level of illumination. The transmission of less pupilloconstrictor tone to each iris sphincter would result in slightly larger pupils but of equal diameter. Accordingly, anisocoria (unequal pupillary diameter) is not attributable to the angle at which light strikes the face, unilateral cataracts, or an asymmetric refractive error, unless there is local disease of the anterior segment.

Parasympathetic axons from the E–W nucleus join the outflow of the other oculomotor subnuclei to form the trunk of the oculomotor nerve. Pupillomotor fibers assume a superficial location in the nerve as it exits the mesencephalon in the interpeduncular space.

In the orbit, the parasympathetic components synapse in the ciliary ganglion. Postganglionic fibers traveling in the short ciliary nerves innervate both the ciliary body, inducing lens accommodation, and the pupilloconstrictor muscles of the iris. The ratio of fibers innervating the ciliary body to those supplying the pupil is approximately 30:1. Acetylcholine serves as the neurotransmitter for both functions.

The pupillary near reflex consists of three separate, synergistic phenomena: accommodation, convergence, and

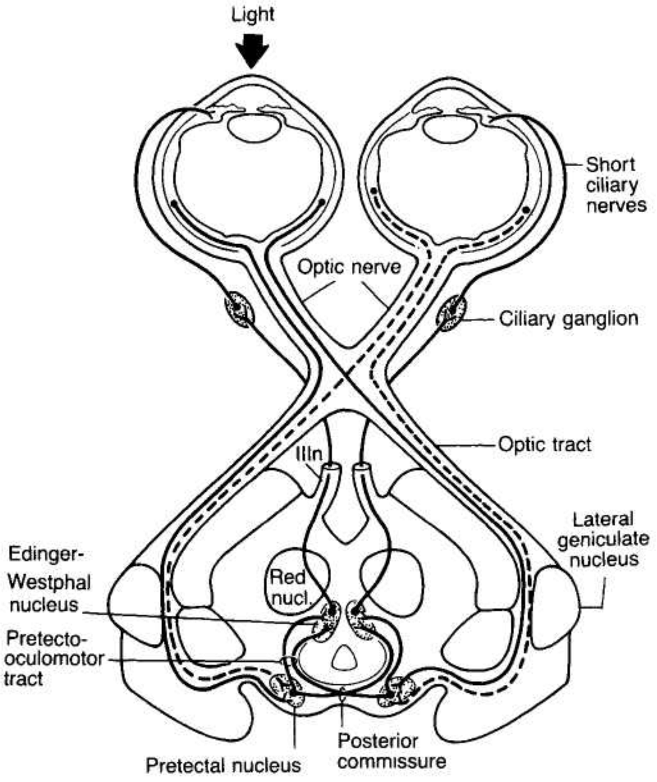

Figure 58.1
Neuroanatomy of the light reflex.

pupillary constriction. The near reflex, in general, is a fundamental component of stereoscopic vision. Using the macaque monkey, Jampel (1967) showed that all three components of the near reflex can be elicited by electrical stimulation of the occipital association cortex. In fact, by slight variations in the position of the stimulating electrode or by changing the stimulus intensity, the various components could be obtained in partial combinations or, on occasion, alone. The exact anatomic pathways connecting cerebral cortex to midbrain are unresolved. There is evidence, however, derived mainly from clinical observations, that the fibers mediating pupillary constriction in the near reflex follow a more ventral course than those subserving the light reflex at the mesencephalic level.

Clinical Significance

The afferent pupillary defect, or Marcus Gunn (MG) sign, is virtually diagnostic of a lesion, at times asymptomatic, in the prechiasmal portion of the ipsilateral optic nerve. It rarely occurs in visual loss resulting from impairment of the cornea, lens, vitreous, or retina. Its absence in a patient with unilateral visual loss should redirect the examiner's attention to nonneurogenic etiologies such as a refractive error, suppression amblyopia, macular disease, or functional visual loss.

When evaluating for an MG sign, be certain to check the patient in a relatively dark room and with a bright handlight. Too dim a light source produces insignificant pupillary movements; too bright a light source causes afterimages that keep the pupil small for several seconds, obscuring pupillary escape in the other eye. The patient must be continually urged to fixate afar to avoid convergence-induced miosis. The examiner then shines a bright light in one of the patient's eyes, observes the speed and extent of the contraction, and then quickly moves the light to the other pupil and makes the same observations. The difference in pupillary reactions to light may be enhanced by swinging a flashlight back and forth from one eye to the other. The light should remain 3 to 5 seconds on each eye until the pupil has stabilized. Do not leave the light on one eye longer than the other, since this will create or exaggerate a relative afferent defect in the eye with the longer light exposure. As the light falls on each eye, look carefully at pupillary movement. Normally, there is an initial constriction, followed several seconds later by slow redilatation. In a patient with a profoundly positive MG sign, the initial pupillary movement is dilatation rather than constriction. With small afferent pupillary defects, there is a relatively brief constriction before the pupil "escapes." Asymmetric pupillary escape differentiates a subtle MG sign.

While a positive MG sign most commonly signals the presence of an ipsilateral optic nerve lesion, it may also occur with homonymous visual loss related to an optic tract lesion. Partial optic tract lesions cause asymmetric or incongruous homonymous hemianopia. The MG sign is seen in the eye with the greater amount of field loss.

Since only one working iris sphincter is required for the MG test, the search for it can be performed in the presence of an ipsilateral corneal opacity, third nerve palsy, or atropinized pupil. The examiner observes the behavior of only the intact pupil as each eye is alternately illuminated. As before, the afferent pupillary defect is on the side that, when stimulated, results in dilatation of the observed pupil.

Oculomotor Paralysis and Recovery

Acute ophthalmoplegia of the third nerve including involvement of the pupil occurs most commonly after severe head trauma or as a result of rupture or sudden expansion of a posterior communicating artery. In diabetic, hypertensive, or other ischemic-type oculomotor lesions, the pupil is rarely involved. There may be severe pain as well as ptosis and ophthalmoplegia, but the pupil in these cases is normal in size and shows normal or near-normal reactivity. Pain, regardless of its severity, does not distinguish a "medical" third nerve palsy from one caused by a cerebral aneurysm. The pupillary response to light remains the most reliable way of differentiating between these two acute conditions.

The term *pupillary sparing* requires careful definition. It should be limited to the clinical situation where there is complete ptosis and paralysis of ocular elevation, depression, and adduction, but normal pupillary size and movement. Pupillary reactivity with partial ptosis and/or partial ophthalmoparesis does not constitute true pupillary sparing. These patients have *partial* involvement of the third nerve, including the pupillomotor fibers, and frequently harbor a space-occupying lesion in the parasellar fossa. Patients with third nerve paralysis and *true* pupillary sparing can be followed clinically. If the pupil retains normal size and reactivity after 1 week of observation, they need not undergo CT or cerebral angiography in search of a cerebral aneurysm. Almost assuredly, they will spontaneously improve within 3 months. If not, further analysis is indicated.

Tumorous or aneurysmal compression of the third nerve variably affects pupil size, depending on the location of the lesion. A large posterior communicating artery aneurysm, for instance, distorts the subarachnoid portion of the third nerve and almost always produces mydriasis. In lesions of the cavernous sinus, however, the pupillary reaction to a light and near stimulus may be fully preserved in the anterior cavernous sinus. The oculomotor nerve separates into a superior and an inferior division. Relative pupillary sparing may in part reflect sparing of the inferior division, which also innervates the medial and inferior rectus and inferior oblique muscles. It may also be explained by the fact that the pupillomotor fibers, in the process of joining the twig to the inferior oblique muscle, may either assume an independent course or descend from the vulnerable superficial position in the subarachnoid portion of the nerve to a presumably more protected position, either within the substance of the nerve or on its lateral or inferior aspects.

Aberrant regeneration of the third nerve occurs after axonal destruction. It is characterized clinically by synkinetic eye muscle activity. For instance, there may be elevation of the involved lid on adduction, lowering of the lid during abduction, or elevation of the lid on depression of the eye. The pupil in these cases is usually larger than its mate and also shows synkinetic activity. It may not react to a bright light, but portions of the iris sphincter will contract during adduction, depression, or elevation of the globe, indicating that the pupillosphincter contracts simultaneous with the medial or with the inferior or superior rectus muscles, respectively.

Adie's Tonic Pupil Syndrome

Adie's tonic pupil (ATP), the most common cause of isolated internal ophthalmoplegia, results from postganglionic parasympathetic denervation of the internal ocular muscles (the ciliary muscle and iris sphincter). The neuropathologic findings comprise nonspecific necrosis and neuronal loss in the short ciliary nerves and/or ciliary ganglion.

The patient with ATP may be totally asymptomatic, and is often brought to a physician's office by a friend or relative who notices that he or she has one large pupil. Of the 122 patients with ATP studied retrospectively by Thompson (1977), 80% had symptoms, which included anisocoria, photophobia, and difficulty with dark adaptation. Ciliary muscle-related symptoms, present in 35% of affected individuals, included blurred vision, pseudomyopia, and brow-ache with near work.

If the ocular examination is performed at the onset of symptoms, the patient manifests a large, immobile pupil. Neurologically, diminished or absent deep tendon reflexes in the lower extremities are found in one-third to half of patients (Holmes–Adie syndrome). With time, aberrant reinnervation of the pupil and ciliary body occurs. Because the overwhelming number of postganglionic parasympathetic fibers from the ciliary ganglion control accommodation, the iris sphincter becomes reinnervated almost exclusively by accommodative elements, and the near reflex consequently becomes extensive—in fact it is prolonged. Such a "tonic" near response is best appreciated when the patient changes fixation from a near to a far stimulus. The normal pupil readily redilates, while the Adie's pupil redilates at a much slower rate.

Aberrant regeneration of the parasympathetic nerve supply to the intraocular muscles also causes sector palsies of the pupillary sphincter and ciliary muscle. Asynchronous contractions of these muscles cause the following signs: induced astigmatism, tonicity of accommodation, and cholinergic supersensitivity of the ciliary muscle. The examiner notes pupillary light-near dissociation, vermiform contractions of the pupil, and pharmacologic evidence of denervation supersensitivity. A dilute parasympathomimetic agent such as 0.125% pilocarpine is used for this purpose. It produces marked constriction of an Adie's pupil, but has no effect on the diameter of a normal pupil. Demonstrating denervation supersensitivity by this method differentiates an acute Adie's pupil from the large, immobile pupil observed in early third nerve lesions and from a pharmacologically dilated pupil.

Although ATP is most commonly a unilateral disorder it can be bilateral, developing in both eyes either simultaneously or consecutively. Symmetric bilateral ATPs have been observed with widespread peripheral neuropathies such as in diabetes or the Charcot–Marie–Tooth syndrome. They are frequently found in association with other signs of autonomic dysfunction—orthostatic hypotension, progressive segmental anhidrosis, and as a constituent of the Shy–Drager and Riley–Day syndromes.

Sylvian Aqueduct Syndrome

With rostral midbrain lesions in the area of the pretectal nuclear complex, interruption of the retinotectal fibers with preservation of the supranuclear accommodative fibers produces bilateral pupillary light-near dissociation. The associated damage to the pretectal pupilloconstrictor nuclei results in pupils that are 4 to 6 mm in diameter; they do not react to light but constrict during the attempt to converge; and these findings occur with other signs, such as supranuclear paralysis of upgaze, lid retraction, and convergence–retraction nystagmus.

Pharmacologically Dilated Pupil

As an isolated finding, an extremely large pupil, obliterating the iris and unresponsive to a light or near stimulus, is almost always due to inadvertent or factitious application of a parasympathomimetic agent (eye drops, scopolamine, Jimson weed, marijuana, LSD). Medical personnel, including nurses, doctors, and pharmacists, are especially liable to accidental instillation of mydriatic agents.

Instillation of 1% pilocarpine helps differentiate pharmacologic mydriasis from other causes of a large, unreactive pupil. With parasympathetic denervation of the pupil from oculomotor palsy or an ATP, the response is prompt miosis. Failure to note any change on the side of the mydriatic pupil is strong clinical evidence of pharmacologic dilatation, provided the pupillosphincter muscle is anatomically intact.

Argyll Robertson Pupil

"Spinal miosis" has been known for some time when Douglas Argyll Robertson (1869) described his five patients, all of whom had very small pupils. It was found later that bilateral pupillary light-near dissociation occurred in patients who did not have central nervous system syphilis. Some had tumors in the midbrain (sylvian aqueduct syndrome), others developed internal ophthalmoplegia from unknown cause (?ATP), and some patients with diabetes mellitus developed abnormal pupils along with their diffuse peripheral neuropathy. It is now generally accepted that true Argyll Robertson pupils related to syphilis are small in diameter, irregular in shape, slightly unequal, and fail to dilate in darkness or with traditional mydriatic agents. The Argyll Robertson sign must include relatively intact visual function to exclude nonsyphilitic causes of pupillary light-near dissociation.

Horner's Syndrome

The iris pupillodilator fibers are innervated by the sympathetic nervous system (Figure 58.2). The first-order neuron of this pathway resides in the posterolateral hypothalamus. Exiting axons descend uncrossed through the brainstem tegmentum to synapse in the intermediolateral cell column of the spinal cord at the C8-T2 level. Second-order preganglionic fibers travel along the C8, T1, and T2 motor nerve roots to join and ascend in the sympathetic chain over the pulmonary apex to the superior cervical ganglion. The third-order neuron supplies sudomotor axons, which are distributed to the face along branches of the external carotid artery and to the orbits by the ophthalmic artery and ophthalmic division of the trigeminal nerve. The distal portions of the third-order neuron release norepinephrine, effecting pupillary dilation. For a more detailed discussion regarding the intracranial sympathetic pathways, the reader should consult Vijayan's article (1978) on pericarotid syndrome.

The classic signs of a Horner's syndrome include ptosis of the upper lid, slight elevation of the lower lid (upside-down ptosis), miosis, and ipsilateral anhidrosis. The illusory enophthalmos resulting from a narrow palpebral aperture is not measurable.

Occasionally, the signs are minimal. The miosis especially need not be marked; usually the pupillary diameter is reduced by only .5 to 1 mm. Lesions of the sympathetic pathway proximal to the external carotid artery make the ipsilateral face dry, warm, and hyperemic due to denervation of the facial sweat glands and vasoconstrictor fibers. If the lesion is located distal to the superior cervical ganglion, the postganglionic sudomotor and vasomotor fibers to the face are likely to be preserved. In this case, facial sweating is normal.

Two pharmacologic tests may be applied to patients with Horner's syndrome. Cocaine 5 to 10% prevents the presynaptic reuptake of norepinephrine at the sympathetic neuromuscular junction in the pupillodilator muscle. It will dilate a pupil when the entire sympathetic pathway is intact, that is, when norepinephrine is being tonically released. Sympathetic damage reduces the availability of norepinephrine at the myoneural junction, so a Horner's pupil may dilate but not to the same extent as a normal pupil.

Paredrine, a 1% solution of hydroxyamphetamine, stimulates norepinephrine release at the myoneural junction, inducing pupillary dilation. The third-order neurons produce, transport, and store norepinephrine. When the third-order neurons (the superior cervical ganglion or postganglionic fibers) are damaged, paredrine produces little or no pupillary dilation in the affected eye. However, with lesions of the sympathetic pathway that are proximal to the superior cervical ganglion, the pupil dilates in response to paredrine because adequate amounts of norepinephrine are available for release. Thus, the *cocaine* test helps differentiate a Horner's syndrome from other causes of anisocoria, and the *paredrine* test can distinguish a third-order neuron Horner's syndrome from first- and second-neuron syndromes.

In addition to the pharmacologic tests, the topical diagnosis of Horner's syndrome depends on accompanying signs and symptoms. Pain in the homolateral supraclavicular fossa and weakness and wasting of the intrinsic hand muscles, for example, suggest an apical lung tumor. Nystagmus, numbness of the ipsilateral face and contralateral extremities and trunk, dysarthria, and dysphagia point to involvement of the posterolateral medulla. Ipsilateral iris

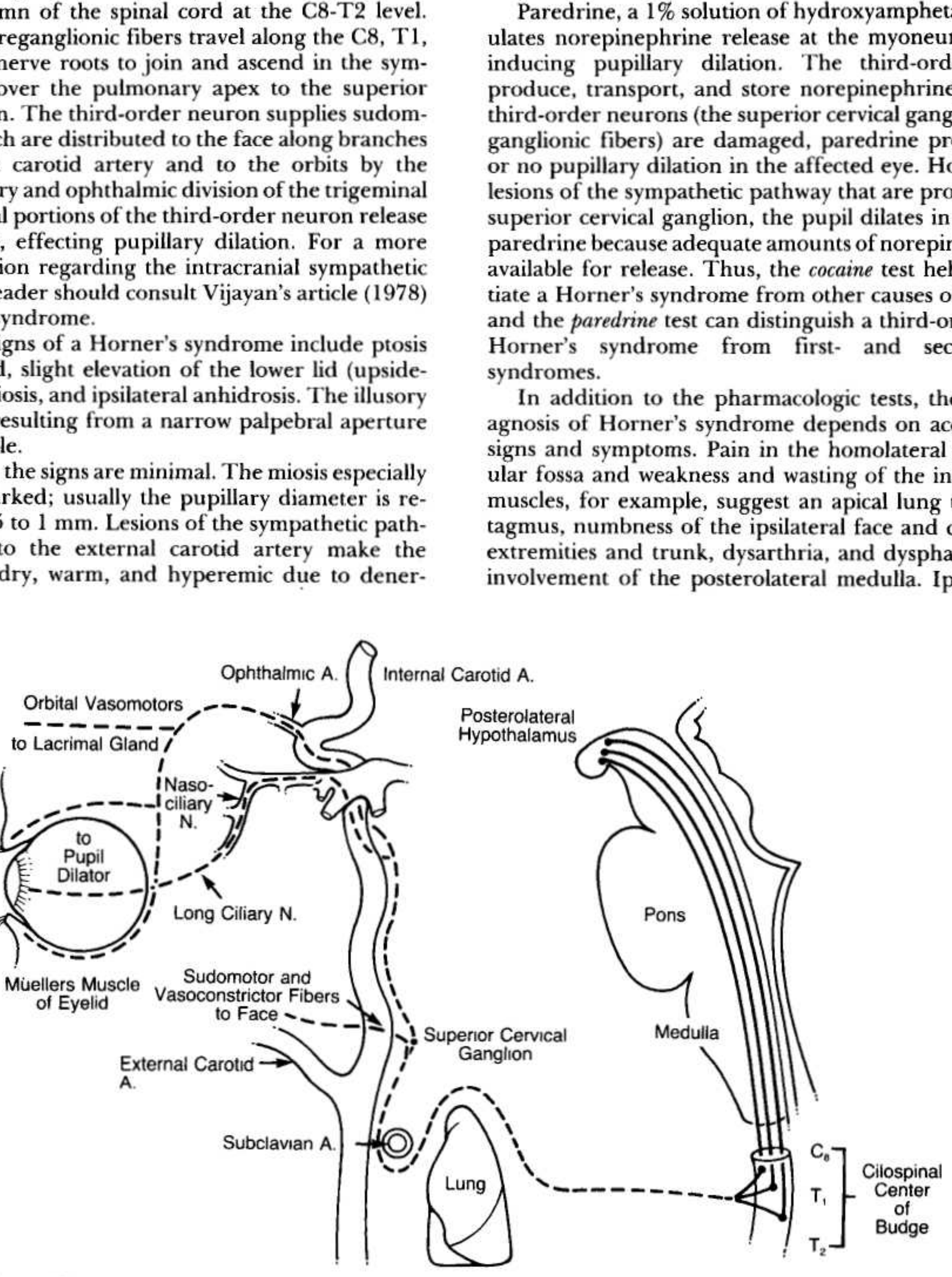

Figure 58.2
Pupillary sympathetic pathway.

heterochromia is a good sign of congenital Horner's syndrome. Horner's pupil plus ipsilateral palsy of cranial nerves IX, X, XI, and XII may be caused by a glomus jugulare tumor arising near the carotid bifurcation. Hemifacial pain, along with pharmacologic evidence of a third-order neuron lesion, may be the salient manifestation of an occlusion or dissection of the ipsilateral internal carotid artery.

Essential Anisocoria

About 20% of the healthy population have essential ("functional," "congenital") anisocoria. Yet it may be "suddenly discovered" by a relative or friend, by an eye doctor, or even by a patient while shaving or applying makeup. In essential anisocoria, the difference between the pupil diameter remains the same regardless of ambient illumination. With sympathetic denervation, as in Horner's syndrome, the pupil will not dilate as quickly or as extensively as a normal pupil in darkness, so the difference in pupillary size observed in ambient light will be accentuated in subdued illumination. In parasympathetic defects, conversely, the anisocoria increases in bright light.

The examiner should assiduously determine the duration of anisocoria. Inspecting a series of old photographs can frequently prove that the anisocoria is not as "newly acquired" as thought. Obviously, acquired anisocoria of recent onset has more ominous implications than anisocoria that dates back many years or even a lifetime.

References

Bender MB, Fulton JF. Functional recovery in ocular muscles of a chimpanzee after section of oculomotor nerve. J Neurophysiol 1938;1:144–51.

Cox TA, Thompson HS, Corbett JJ. Relative afferent pupillary defects in optic neuritis. Am J Ophthalmol 1981;92:685–90.

Czarnecki JSC, Thompson HS. The iris sphincter in aberrant regeneration of the third nerve. Arch Ophthalmol 1978;96:1606–10.

Giles CL, Henderson JW. Horner's syndrome: an analysis of 216 cases. Am J Ophthalmol 1958;46:289–96.

Goldberg MF, Payne JW, Brunt PW. Ophthalmologic studies of familial dysautonomia: the Riley-Day syndrome. Arch Ophthalmol 1968;80:732–43.

Harriman DGF, Garland H. The pathology of Adie's syndrome. Brain 1968;91:401–18.

Hughes JM, Blumenthal JR, Merson MH, et al. Clinical features of types A and B food-born botulism. Ann Intern Med 1981; 95:442–45.

Jampel RS. Representation of the near-response on the cerebral cortex of the Macaque. Am J Ophthalmol 1959;48:573–82.

Jampel RS, Mindel J. The nucleus for accommodation in the midbrain of the Macaque. Invest Ophthalmol 1967;6:40–50.

Kerr FWL, Hollowell OW. Location of pupillomotor and accommodation fibers in the oculomotor nerve: experimental observations on paralytic mydriasis. J Neurol Neurosurg Psych 1964;27:473–81.

Kissel JT, Burde RM, Klingele TG, et al. Pupil-sparing oculomotor palsies with internal carotid-posterior communicating artery aneurysms. Ann Neurol 1983;13:149–54.

Korczyn AD, Rubenstein AE, Yahr MD, Axelrod FB. The pupil in familial dysautonomia. Neurology 1981;31:628–29.

Kori SH, Foley KM, Posner JB. Brachial plexus lesions in patients with cancer: 100 cases. Neurology 1981;31:45–50.

Levatin P. Pupillary escape in disease of the retina or optic nerve. Arch Ophthalmol 1959;62:768–99.

Loewenfeld IE. The Argyll Robertson pupil, 1869–1969, a critical survey of the literature. Surv Ophthalmol 1969;14:199–299.

Loewenfeld IE, Thompson HS. The tonic pupil: a re-evaluation. Am J Ophthalmol 1967;63:46–87.

Loewenfeld IE, Thompson HS. Mechanism of tonic pupil. Ann Neurol 1981;10:275–76.

Lowenstein O, Loewenfeld IE. Pupillotonic pseudotabes. Surv Ophthalmol 1965;10:129–85.

Mikolich JR, Paulson GW, Cross CJ. Acute anticholinergic syndrome due to Jimson seen ingestion. Ann Intern Med 1975;83:321–25.

Miller SD, Thompson HS. Pupil cycle time in optic neuritis. Am J Ophthalmol 1978;85:635–42.

Nadeau SE, Trobe JD. Pupil sparing in oculomotor palsy: a brief review. Ann Neurol 1983;13:143–48.

Riley FC, Moyer NJ. Oculosympathetic paresis associated with cluster headaches. Am J Ophthalmol 1971;72:763–68.

Robertson AD. Four cases of spinal miosis; with remarks on the action of light on the pupil. Edinburg Med J 1869;15:487.

Spector RH, Faria MA. Aberrant regeneration of the inferior division of the oculomotor nerve. Arch Neurol 1981;38:460–61.

Thompson HS. Adie's syndrome: some new observations. Trans Am Ophthal Soc 1977;125:587–626.

Thompson HS, Mensher JH. Adrenergic mydriasis in Horner's syndrome. Am J Ophthalmol 1971;72:472–80.

Thompson HS, Newsome DA, Loewenfeld IE. The fixed dilated pupil. Arch Ophthalmol 1971;86:21–27.

Thompson HS, Zackon DH, Czarnecki, JSC. Tadpole-shaped pupils caused by segmental spasm of the iris dilator muscle. Am J Ophthalmol 1983;96:467–77.

Trobe JD, Glaser JS, Post JD. Meningiomas and aneurysms of the cavernous sinus. Neuro-ophthalmologic features. Arch Ophthalmol 1978;96:457–67.

Vijayan N, Watson C. Pericarotid syndrome. Headache 1978; 18:244–54.

Wirtschafter JD, Volk CR, Sawchuck RJ. Transaqueous diffusion of acetylcholine to denervated iris sphincter muscle: a mechanism for the tonic syndrome (Adie's syndrome). Ann Neurol 1978;4:1–5.