CHAPTER 16

Disorders of Pupillary Function, Accommodation, and Lacrimation

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In this chapter I describe various disorders that produce dysfunction of the autonomic nervous system as it pertains to the eye and orbit, including congenital and acquired disorders of pupillary function, accommodation, and lacrimation. Although many of these disorders are isolated phenomena that affect only a single structure, others are systemic disorders that involve various other organs in the body.

DISORDERS OF THE PUPIL

The value of observation of pupillary size and motility in the evaluation of patients with neurologic disease cannot be overemphasized. In many patients with visual loss, an abnormal pupillary response is the only objective sign of organic visual dysfunction. In patients with diplopia, an impaired pupil can signal the presence of an acute or enlarging intracranial mass. An adequate clinical examination of the pupils requires little time and can be meaningful when approached with a sound understanding of the principles of pupillary innervation and function. In most cases, one needs only a hand light with a bright, even beam, a device for measuring pupillary size (preferably in half-millimeter steps), a few pharmacologic agents, and an examination room that permits easy control of the background illumination.

This section commences with an overview of congenital and acquired diseases of the iris that affect pupil size, shape, and reactivity because these structural defects may be the cause of ''abnormal pupils'' and often are easy to diagnose at the slit lamp. Furthermore, if a preexisting structural iris defect is present, it may confound interpretation of the neurologic evaluation of pupillary function; at the very least, it should be kept in consideration during such evaluation.

STRUCTURAL DEFECTS OF THE IRIS

Congenital Defects

Aniridia

Aniridia is a rare congenital abnormality in which the iris is partially hypoplastic or completely absent (1,2) (Fig. 16.1*A*). Patients with aniridia initially may be thought to have fixed, dilated pupils until a more careful examination is performed. In almost all cases, histologic or gonioscopic

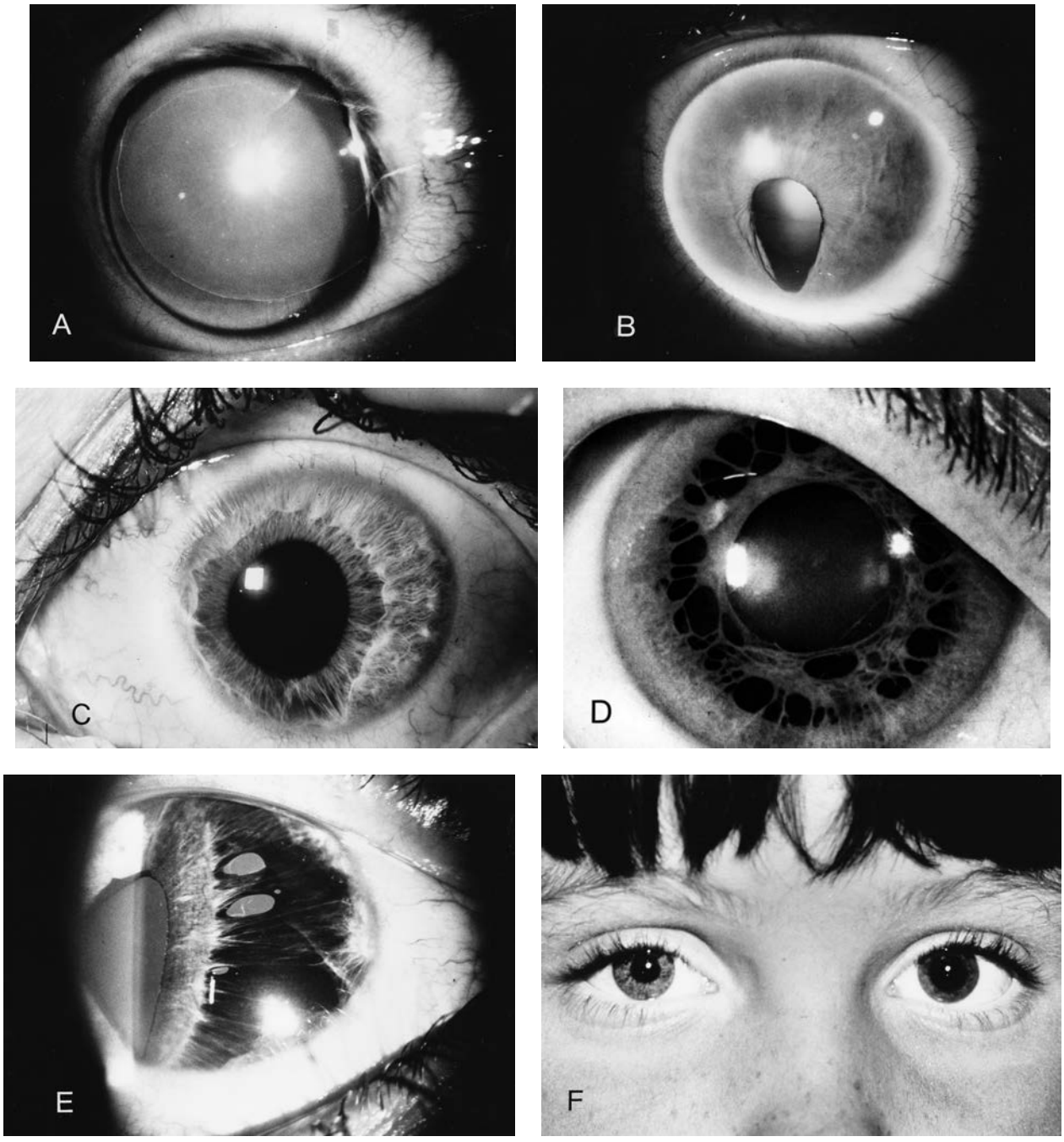

Figure 16.1. Iris anomalies that may simulate neurologic pupillary abnormalities. *A*, Aniridia. Note associated upward lens dislocation. *B*, Typical iris coloboma. *C*, Acquired corectopia in iridocorneal–endothelial adhesion syndrome. *D*, Persistent pupillary membrane. *E*, Pseudopolycoria from iridocorneal–endothelial adhesion syndrome. *F*, Heterochromia iridis in a patient with congenital Horner syndrome. The lighter iris is in the eye with Horner syndrome. (*A* and *B*, Courtesy of Dr. Irene H. Maumenee. *C*, Courtesy of Dr. Harry A. Quigley. *D,* From Gutman ED, Goldberg MF. Persistent pupillary membrane and other ocular abnormalities. Arch Ophthalmol 1976;94:156–157. *E,* Courtesy of Dr. Harry A. Quigley.)

examination reveals small remnants of iris tissue. The iris is only minimally developed, and the iris musculature usually is hypoplastic. Patients with aniridia often have photophobia, poor visual acuity, and other ocular defects, including glaucoma, cataracts, ectopia lentis, corneal opacification, ciliary body hypoplasia, optic nerve hypoplasia, foveal hypoplasia, strabismus, and nystagmus (3). The condition usually is bilateral, and two thirds of cases are inherited in autosomal-dominant fashion (4).

The gene defect resulting in aniridia is a nonsense or frameshift mutation in the large PAX6 gene on chromosome 11p13 (3). The PAX6 gene is a master regulator gene, critical in the development of the eye and central nervous tissues. Mutations of this gene are associated with other ocular abnormalities, such as anterior segment defects and foveal hypoplasia, in addition to aniridia. Mutations can be sporadic or inherited; in most cases, loss of one allele (heterozygous PAX6 mutation) is sufficient to result in ocular structural defects. Detection of a PAX6 mutation necessitates genetic counseling.

Systemic abnormalities found in patients with aniridia are many and varied. They include polydactyly, oligophrenia, cranial dysostosis, malformations of the extremities and external ears, hydrocephalus, and mental retardation (2). The most important association, however, is with the childhood cancer, Wilms' tumor. Aniridia occurs in 1 in 73 patients with Wilms' tumor, compared with a frequency of 1 in 50,000–100,000 in the general population (1). The reason for this high association is the close proximity of the aniridia gene to the gene for Wilms' tumor (WT1) (5). The association of Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation is known as WAGR syndrome and is due to a contiguous defect on chromosome 11p13 that encompasses both the PAX6 and the WT1 genes. Although spontaneous deletions can occur simultaneously in both genes, the detection of an intragenic PAX6 mutation in a patient with sporadic aniridia can eliminate the need for routine kidney ultrasounds (3).

Coloboma of the Iris

A coloboma is a notch, hole, or fissure in any of the ocular structures (cornea, iris, ciliary body, zonules, choroids, retina, and optic disc) due to defective embryogenesis. Affected eyes are frequently microphthalmic. The term ''typical'' coloboma specifically refers to one caused by defective closure of the fetal fissure. Typical colobomata occur in the inferonasal quadrant and are the most common type (Fig. 16.1*B*). According to Pagon, only iris colobomata that are ''typical'' are associated with chorioretinal or optic disc colobomas (6). ''Atypical'' colobomata may result from (*a*) interference with embryonic growth of the neuroepithelial layers; (*b*) mechanical blockage of the advancing neuroectoderm by mesodermal elements present at the edge of the optic cup; and (*c*) occlusion of vessels within the embryonic iris tissue, with subsequent iris atrophy. When an atypical iris coloboma does not extend to the pupillary margin, it produces pseudopolycoria, a defect in the iris that has the clinical appearance of an accessory pupil.

A ''complete'' iris coloboma extends the full thickness of the iris and typically produces an oval-shaped or keyhole-shaped pupil, whereas an ''incomplete'' iris coloboma is a partial-thickness defect best seen as a wedge-shaped transillumination defect of the iris (7). An isolated coloboma in a microphthalmic eye has an established autosomal-dominant inheritance pattern, but penetrance is incomplete. A few pedigrees supporting an autosomal-recessive or X-linked–recessive inheritance pattern have been reported. Nevertheless, regardless of the type, location, and completeness of a colobomatous defect, patients with a coloboma should undergo an evaluation to determine whether it truly is an isolated finding or part of a multisystem disorder.

One well-known congenital multisystem syndrome with heterogeneous etiologies is the CHARGE association (coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital hypoplasia, and ear anomalies or hearing loss) (6). Patients with the phenotypic CHARGE association can be given a more specific diagnosis if an etiologic basis is found, such as a teratogenic agent (retinoic acid) or a gene defect (partial tetrasomy of chromosome 22, the cat-eye syndrome) (8).

Cat-eye syndrome is one clinical phenotype resulting from a genomic disorder of 22q11. Specifically, there is a partial tetrasomy (four copies) of this region of chromosome 22. Patients commonly have ocular colobomata, anal atresia, and preauricular skin tags. Other anomalies include heart defects (particularly total anomalous pulmonary venous return), renal malformations, craniofacial anomalies, genital anomalies, and mental retardation (9).

Square Pupils

Square pupils are thought to represent incomplete aniridia. White and Fulton observed, in homozygous twins whose mother showed the same defect, large, irregular, roughly quadrilateral pupils that responded to constricting stimuli only in certain quadrants (10). Similar pupils were observed in a mother and daughter with incomplete aniridia and cataracts (11).

Elliptic Pupils

Elliptic pupils occasionally occur. In strong illumination, such pupils take on the form of elliptical slits (12,13).

Scalloped Pupils

Irregular, cup-shaped indentations in the pupillary margins have been described as a congenital anomaly in large pupils that otherwise react normally to light and near stimuli (14). Scalloped pupils probably are more commonly an acquired disorder, particularly in familial amyloidosis (15,16). The pupil also may develop a scalloped appearance after trauma to the sphincter muscle, causing multiple tears, segmental sphincter atrophy, or both. A scalloped pupil can occur after uveitis that is complicated by the development of posterior synechiae (adhesions between the iris and lens).

Peninsula Pupils

Bosanquet and Johnson reported 40 patients from Newfoundland and Labrador with an unusual form of partial iris sphincter atrophy that resulted in an oval pupil (17). The condition, called peninsula pupils, was bilateral in most cases. The anomaly was confined to the iris, and there were no associated systemic disorders. Most of the affected individuals were male, and all had blue irides. Three of the patients believed that their pupils had been large and oval since birth. This pupillary anomaly may be an inherited trait peculiar to the Newfoundland-Labrador region.

Ectopic (Misplaced) Pupils

Misplaced or ectopic pupils (corectopia, ectopia pupillae) are observed frequently. Isolated ectopic pupils may be inherited as either a dominant or a recessive trait. The condition usually is usually bilateral and symmetric (18). Although the pupils may be displaced in any direction, they often are up and out from the center of the cornea. Such displacement of the pupils is frequently associated with ectopia lentis, congenital glaucoma, microcornea, ocular coloboma, and high myopia (19). Ectopic pupils also occur in some patients with albinism and some patients with Axenfeld-Rieger anomaly. In addition, three families were reported in which affected members had ectopic pupils, ptosis, and ophthalmoplegia (20–22).

Although acquired corectopia may occur in patients with severe midbrain damage, the clinical setting and the variability of the acquired defect usually allow the physician to distinguish easily between the congenital and acquired forms (23–25). Similarly, the corectopia that occurs during the course of purely ocular disorders such as the iridocorneal–endothelial (ICE) adhesion syndromes and posterior polymorphous corneal dystrophy should be differentiated easily from congenital and neurologic corectopia by the clinical setting and the associated ocular signs (Fig. 16.1*C*).

Persistent Pupillary Membrane Remnants

Persistent pupillary membrane remnants are vestiges of the embryonic pupillary membrane that can appear as threadlike bands running across the pupillary space and attaching to the lesser circle of the iris (26,27) (Fig. 16.1*D*). Occasionally, such remnants are attached to the lens and may be associated with an anterior capsular cataract. Persistence of the entire membrane can block visual input, but most cases are visually insignificant. Excision of the membrane has been performed in young patients who are at risk for amblyopia and in others with visual impairment during pupillary constriction (e.g., in bright sunlight) (28).

Polycoria and Pseudopolycoria

In true polycoria, the extra pupil or pupils are equipped with a sphincter muscle that contracts on exposure to light (29). This is an extremely rare condition. Most additional pupils are actually just holes in the iris without a separate sphincter muscle. This pseudopolycoria may be a congenital disorder, such as an iris coloboma or persistent pupillary membrane, or it may be part of one of several syndromes characterized by mesodermal dysgenesis (30). A distinctive feature of pseudopolycoria is passive constriction, distortion, or even occlusion of the accessory pupil when the true pupil is dilated (31). More commonly, pseudopolycoria occurs as an acquired disorder from direct iris trauma including surgery, photocoagulation, ischemia, or glaucoma or as part of a degenerative process such as the ICE syndrome (Fig. 16.1*E*).

Congenital Miosis

Congenital miosis usually is bilateral and characterized by extremely small pupils that react slightly to light stimuli and dilate poorly after instillation of sympathomimetic agents (32,33). The anomaly appears to result from congenital absence of the iris dilator muscle. Additionally, the iris sphincter muscle may be contracted excessively because of the lack of counterpull normally supplied by the dilator muscle. Congenital miosis may occur sporadically or may be inherited. Most of the inherited cases are transmitted as an autosomal-dominant trait, although pedigrees with autosomal-recessive inheritance have been reported (34,35).

Congenital miosis may be an isolated phenomenon, or it may be associated with other ocular abnormalities, including microcornea, iris atrophy, myopia, and anterior chamber angle deformities (32). In addition, congenital miosis can occur in patients with systemic disorders. Patients with congenital miosis also may have albinism, the congenital rubella syndrome, the oculocerebrorenal syndrome of Lowe, Marfan syndrome, or multiple skeletal anomalies (33,36–39). Congenital miosis was noted in four members of a family with hereditary spastic ataxia, and it is one of the main features in Stormorken syndrome, a dominantly inherited metabolic disorder also characterized by bleeding tendency, thrombocytopathia, muscular weakness, postexertional muscle spasms, ichthyosis, asplenia, dyslexia, and headache (40).

Congenital Mydriasis

Congenital mydriasis may be similar to or identical with the condition described above as square pupils. This condition may be difficult to distinguish from aniridia unless a careful ocular examination is performed. Caccamise and Townes described a 73-year-old woman with bilaterally large, round pupils that were present from birth (41). The condition appeared to have been inherited as an autosomal-dominant trait, although all other affected family members were female. Both pupils constricted to topical 4% pilocarpine solution, suggesting an intact iris sphincter muscle, and both pupils dilated rapidly to topical 10% phenylephrine solution, indicating an intact iris dilator muscle. However, neither pupil reacted to a potent topical cholinesterase inhibitor, suggesting an abnormality of acetylcholine production at the parasympathetic neuromuscular junction.

Magnetic resonance (MR) imaging has shown an enlarged fourth ventricle and atrophy of the cerebellar vermis in one case report of congential mydriasis (42). In another patient with bilateral congenital mydriasis and absent accommodation, the pupils did not react to light, lid closure, or adminis-

tration of topical 1% pilocarpine solution; however, both pupils dilated further after topical administration of 2.5% phenylephrine (43). A patient with the Waardenburg syndrome who had a unilateral, congenitally fixed, dilated pupil has been reported (44). Pharmacologic studies in this patient suggested the possibility of congenital agenesis of the iris sphincter muscle.

Congenital Abnormalities of Iris Color

The color of the iris depends on the pigment in the iris stroma. In albinism, there is failure of mesodermal and ectodermal pigmentation. Consequently, the iris has a transparent, grayish-red color and transilluminates readily.

In a number of congenital and acquired conditions, the iris of one eye differs in color from the iris of the other eye. In other instances, one iris is entirely normal, and a part of the iris in the opposite eye has a different color than the rest of the iris surrounding it (iris bicolor). These abnormalities, collectively called heterochromia iridis, may occur (*a*) as an isolated congenital anomaly; (*b*) in association with other ocular abnormalities, such as iris or optic disc coloboma; (*c*) in association with systemic congenital abnormalities, as in patients with the Waardenburg syndrome, congenital Horner syndrome, or incontinentia pigmenti; or (*d*) from an acquired ocular condition (45) (Fig. 16.1*F*). When iris heterochromia is part of a pathologic condition, it is necessary to determine which iris is abnormal. For example, the darker iris is abnormal in patients with a diffuse iris and ciliary body melanoma and in siderosis from an intraocular foreign body or vitreous hemorrhage. The lighter iris is pathologic in congenital Horner syndrome, in Fuchs heterochromic iridocyclitis, and after iris atrophy following a unilateral iritis or acute glaucoma.

Acquired Defects

Inflammation

Iritis or iridocyclitis in its acute stages produces swelling of the iris, miosis, and slight reddening of the circumcorneal tissues. The miosis of iritis results from the release of a neurohumor, substance P, that produces miosis through interaction with a specific receptor in the iris sphincter muscle (46).

In patients with intraocular inflammation, dilation of the pupil with mydriatics may be difficult because of adhesions between the iris and the lens (posterior synechiae). These adhesions in chronic iritis may distort the shape of the pupil. They also may fix the pupil in a dilated position. Occasionally, the adhesions are not evident until the pupil is further dilated by a mydriatic. Such adhesions and black pigment on the lens suggest iritis, active or inactive. True neurogenic, paralytic mydriasis may occur as part of certain inflammatory disorders that affect the eye and orbit, such as herpes zoster.

Ischemia

Ischemia of the anterior segment of the globe may be acute or chronic. Both types can produce iridoplegia. Transient dilation of the pupil may occur during an episode of monocular amaurosis associated with carotid occlusive disease, migraine, or Raynaud disease. This unilateral pupillary change is not caused by the blindness but by the hypoxic process that affects the entire eye, including the iris sphincter. Emboli that enter the central retinal artery frequently involve other branches of the ophthalmic artery, particularly the posterior ciliary arteries. If venous outflow from the globe is briefly impaired, the retina may shut down temporarily without producing an ipsilateral mydriasis. If the whole globe is ischemic (as in angle-closure glaucoma), iris ischemia will relax the iris sphincter and dilate the pupil (47).

Chronic ischemia of the anterior segment of the globe results in neovascularization of the chamber angle and the surface of the iris (rubeosis iridis), producing iris atrophy, ectropion of the pigment layer at the pupillary margin (ectropion uveae), glaucoma, and immobility of the iris. This type of chronic ischemia of the anterior segment may result from severe occlusive disease in the carotid system or the aortic arch. It also may be produced by microvascular disease or drug toxicity (e.g., quinine).

Severe, generalized atherosclerosis may result in vascular insufficiency of both irides, producing oval pupils from bitemporal palsy of the pupillary sphincters (48). Such patients have no evidence of iris atrophy or synechiae. Conversely, local iris ischemia was postulated to cause focal temporal atrophy of the iris and a nonreactive pupil in a patient with advanced keratoconus (49).

Tumor

Very few tumors affect the iris, but those that do can cause irregularity of the iris border, anisocoria, and an abnormally reactive pupil. Leiomyoma, malignant melanoma, and lymphoma can all present in this fashion.

Trauma

Spastic miosis is a constant and immediate result of trauma to the globe and occurs immediately after blunt trauma to the cornea. A similar spastic miosis follows perforating injury to the eye. The constriction of the pupil is profound but usually transient and often followed by iridoplegia. Transient spasm of accommodation often occurs in this setting and lasts 1–2 hours.

Dilation of the pupil frequently occurs after concussion of the globe and often is followed by paralysis of accommodation after the initial intense miosis has resolved. Because both the iris sphincter and dilator muscles are involved, the term ‘‘traumatic mydriasis’’ is misleading, as it suggests injury to the sphincter alone. The functions of the iris and ciliary muscle usually are affected together, but occasionally one is impaired without the other. The clinical picture is that of a moderately dilated pupil with both the direct and consensual reactions to light and near stimuli being diminished or absent. The deformity may resolve in a few weeks, but it usually is permanent. This abnormality may have several causes. The frequent absence of detectable pathologic change suggests that the effect may occur from injury of the fine nerves of the ciliary plexus. These may be damaged or

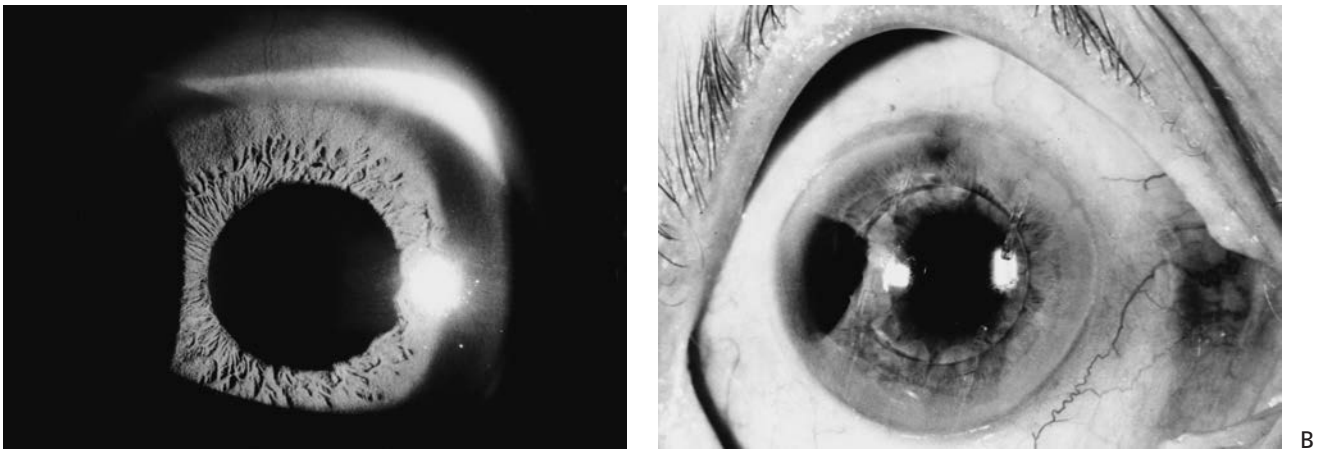

Figure 16.2. Pupillary changes after direct iris trauma. *A*, Tears in the iris sphincter causing pupillary dilation. *B*, Iris dialysis producing pseudopolycoria. (Courtesy of Dr. Walter J. Stark.)

torn by the tissue distortion caused by a pressure wave initiated by the impact. In other cases, contusion necrosis directly produces a lesion in the iris and ciliary body. Finally, as noted above, tears in the iris or rupture of the iris sphincter may be identified using slit-lamp biomicroscopy with transillumination (Fig. 16.2*A*), and a traumatic, peripheral iridodialysis may be present, with resultant distortion of the normally round pupil (Fig. 16.2*B*).

Traumatic iridoplegia in the unconscious patient with multiple head injuries may pose a difficult diagnostic problem. If it cannot be established beyond question that the iridoplegia is the result of direct ocular or orbital damage, it must be assumed that the patient has a tentorial herniation from subdural or epidural hematoma.

Acute Angle-Closure Glaucoma

An acute attack of angle-closure glaucoma usually presents no problem in diagnosis, but occasionally the pain is minimal or nonexistent. Redness of the eye is common. The pupil is usually mid-dilated and fixed (Fig. 16.3), but it may be oval. If the acute rise in intraocular pressure abates in an hour or two, the patient may never complain about the pain but instead may seek medical attention for iridoplegia. If the physician fails to notice the shallow anterior chamber or measure the intraocular pressure, he or she may be unable to explain the iridoplegia or may mistakenly attribute it to an oculomotor nerve lesion (11).

The dilated pupil that is associated with acute glaucoma initially occurs because there is maximum contact between the iris and the lens when the pupil is in a mid-dilated position. Thus, most angle-closure attacks occur when the pupil is mid-dilated (e.g., in darkness), and tonic pupil has been reported as a possible risk for angle closure (50). The iris becomes trapped in this position as intraocular pressure rises. Eventually, the increased pressure results in iris ischemia so that even when the pressure is reduced, the iris no longer functions properly and remains in the mid-dilated position.

Atrophy

Iris atrophy may be caused by inflammation, ischemia, or trauma (Fig. 16.4). It may be circumscribed or diffuse and may involve the anterior border layer, the stroma and sphincter muscle, the anterior epithelium and dilator muscle, the posterior pigmented epithelium, or a combination of these structures. Patients with unilateral iris atrophy that involves the dilator muscle often develop anisocoria, with the smaller pupil on the side of the atrophy. Patients in whom iris atrophy involves the sphincter muscle develop anisocoria with the larger pupil on the side of the atrophy.

Feibel and Perlmutter reported that patients with the pig-

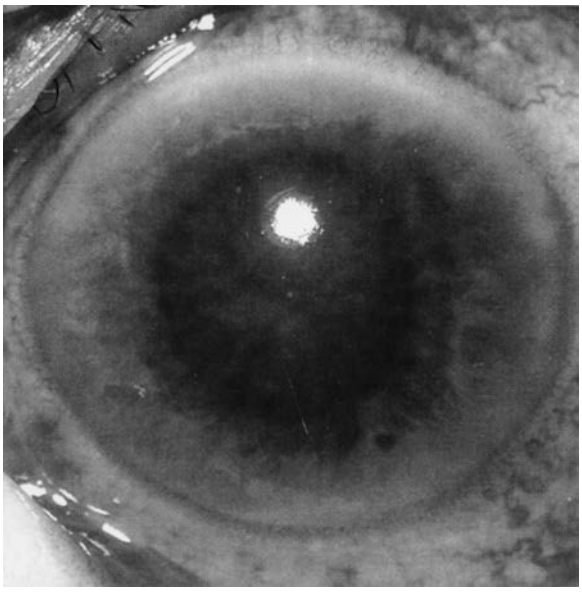

Figure 16.3. Appearance of the eye during an attack of acute angle-closure glaucoma. The pupil is fixed and asymmetrically dilated. Note the opaque, thickened cornea and dilation of the conjunctival vessels.

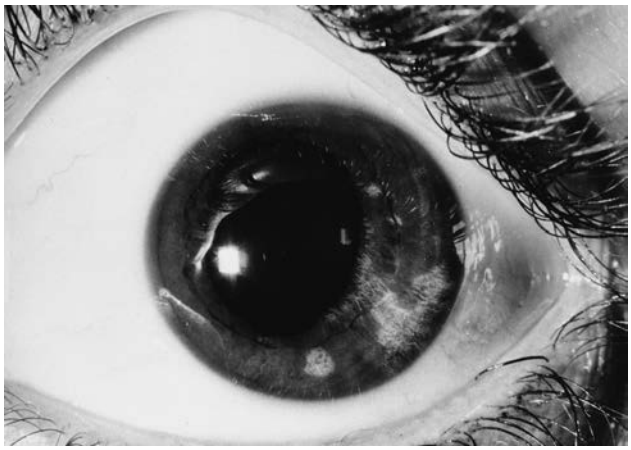

Figure 16.4. Iris atrophy following several attacks of herpes zoster ophthalmicus. (Courtesy of Dr. David L. Knox.)

ment dispersion syndrome and anisocoria had greater transillumination defects of the iris on the side of the larger pupil (51). Histologic studies of affected irides in patients with this syndrome show both atrophic and hypertrophic focal changes in the dilator muscle. The etiology of the anisocoria in these patients remains unclear; in some cases, it stems from an unrelated, coexisting condition such as a tonic pupil, Horner syndrome, or physiologic anisocoria. In others, the anisocoria may be a result of structural change or irritative stimulation of the iris due to pigment dispersion (51–53).

With age, the iris may become gray and of a more uniform color. Its stroma becomes thin, and the sphincter appears as a gray-brown ring. Stromal fibers may be partly torn and may float in the anterior chamber (iridoschisis). Typical of the aged iris are changes on the edge of the pupil, which becomes thin and loses its pigment so that it resembles a fine lacework. Another characteristic finding easily seen by slit-lamp biomicroscopy in elderly persons is the deposition of hyaline about the pupillary margin (54). Histologic examination of excised iris tissue in such cases shows deposition of hyaline in the iris stroma and in the muscles of the iris that also are atrophic.

Postoperative Mydriasis

In 1963, Urrets-Zavalia described several patients who suffered an irreversible mydriasis and pupillary immobility after an otherwise uncomplicated keratoplasty for keratoconus (55). In the typical case, a patient with keratoconus and a normally reacting pupil undergoes an uncomplicated penetrating keratoplasty, following which the pupil dilates and will not react to miotics of any type or strength. The cause of this dilation is unknown, but certain patients may be predisposed to develop this disorder because of preexisting hypoplasia of the iris stroma (56). In patients who develop microperforations in Descemet's membrane during deep lamellar keratoplasty, a fixed and dilated pupil can occur after the air/gas injection into the anterior chamber (57). The mechanism here is speculated to be induced pupil block causing an acute rise of intraocular pressure and secondary iris ischemia.

Postoperative mydriasis occasionally occurs after an otherwise uneventful cataract extraction with placement of an intraocular lens (58,59). It sometimes is called an ''atonic pupil.'' This condition presumably occurs from direct damage to the iris sphincter muscle during surgery.

Surgical or laser-induced damage to the short ciliary nerves or ciliary ganglion can produce a postoperative tonic pupil. Affected patients show a mild mydriasis with anisocoria that is less than 1.0 mm. The most common setting is after excimer laser photorefractive keratectomy. The mechanism may be a medication effect of topical steroids on a susceptible cornea. The mydriasis seems to improve with time in these cases (60).

AFFERENT ABNORMALITIES

Relative Afferent Pupillary Defect

The relative afferent pupillary defect (RAPD) is one of the most important objective signs of dysfunction in the afferent visual pathway. The methods of RAPD detection and quantification were reviewed in Chapter 15. In this section, we discuss the various conditions that should be considered when one finds an RAPD.

Optic Nerve Disorders

Most patients with a unilateral or asymmetric bilateral optic neuropathy, regardless of the cause, have an RAPD (61). In general, the magnitude of an RAPD correlates with the extent of central visual field loss (62–64). The correlation is higher with compressive and ischemic optic neuropathies than with demyelinating optic neuritis (62,65). Patients with acute optic neuritis have a substantial RAPD (1.0–3.0 log units) (66). After recovery, even when there are no remaining visual complaints, there often is a small RAPD (0.3–0.6 log units) still present in the affected eye. In optic nerve compression, the RAPD can be used as an additional test to monitor progression or recovery of optic nerve damage. Patients with glaucoma have an RAPD when the cupping and field loss is unilateral or asymmetric (67,68). Likewise, patients with optic disc drusen have an RAPD when there is functional asymmetry of vision between the two eyes (68).

Initial studies of patients with visual loss from Leber hereditary optic neuropathy (LHON) found that their pupil responses were not significantly different from those of normal persons and suggested that this visual–pupil dissociation was a characteristic finding of this optic neuropathy (69). Subsequent studies of patients with LHON, including those with clinical or electrophysiologic evidence of uniocular involvement, have demonstrated a pupil response deficit consistent with the visual deficit (70,71). Bremner et al. quantified the focal pupil and visual sensitivity at various points within the visual scotoma of patients with LHON (72). A pupil deficit was detected at all test locations, but it was smaller than the corresponding visual deficit (about 7.5 dB difference; i.e., a relative pupil sparing). The authors hypoth-

esized that there may be a lower susceptibility of pupil fibers to damage in LHON.

The RAPD appears to have some prognostic value in traumatic optic neuropathy. In 19 patients with indirect traumatic optic neuropathy treated acutely with similar megadoses of methylprednisolone, patients who had an initial RAPD less than 2.1 log units improved to visual acuity of 20/30 or better. Patients with an initial RAPD larger than 2.1 log units showed little improvement of vision (73).

Retinal Disease

Diseases of the retina are uncommon causes of an RAPD. Most of the pupillomotor input derives from the central retina, so in a suspected retinopathy, the presence of a RAPD usually indicates macular involvement (see Table 15.1). In macular visual loss with visual acuity of 20/200 or better, the RAPD usually is 0.5 log units or less. A RAPD greater than 1.0 log units with a lesion confined to the macula is unusual (74,75). Kerrison et al. demonstrated that in monkeys with controlled laser destruction of the macula, approximately 25–50% loss of ganglion cells was needed to produce a 0.6 log-unit RAPD (76). Central serous maculopathy produces very little RAPD, usually 0.3 log units or less. When the subretinal fluid disappears, so does the RAPD (77). An RAPD can occur in a patient with a retinal detachment (78). In this setting, each quadrant of a fresh, bullous detachment produces about 0.3 log of RAPD, and when the macula detaches, the RAPD increases by about another 0.7 log units (79).

An RAPD can be used to help separate nonischemic from ischemic central retinal vein occlusion (CRVO). Servais et al. studied 120 patients with a unilateral CRVO and found that 90% of nonischemic CRVOs had an RAPD of 0.3 log units or less, and none had an RAPD larger than 0.9 log units (80). In contrast, in 33 patients with ischemic CRVO, 91% had an RAPD of 1.2 log units or more, and none had an RAPD smaller than 0.6 log units. In eyes that initially were nonischemic, a significant increase in the RAPD was an early indicator of ischemic conversion, even when the fundus appeared relatively unchanged.

Induced RAPD from Asymmetric Retinal Adaptation

An eye that is occluded by a ptotic lid or eye patch becomes increasingly dark-adapted during the first 30 minutes of occlusion. This can produce up to 1.5 log units of a false RAPD in the unpatched eye (81,82). Therefore, assessment of an RAPD in a patient wearing an eye patch should not be performed immediately after patch removal because of underlying asymmetry of retinal light sensitivity between the two eyes. This is particularly important to remember in patients with traumatic optic neuropathy (a real RAPD in the patched eye may be overlooked) and in patients with nonorganic visual loss (an RAPD may mistakenly be attributed to the opposite eye). After 10–15 minutes in room light with both eyes open, retinal sensitivity equalizes, and any RAPD detected should be considered valid.

An anisocoria of 2 mm or more, especially if one pupil is very small, can produce a clinically significant difference in the amount of light entering the retina. A general rule put forth is 0.1 log unit RAPD on the side of the smaller pupil for every 1 mm of anisocoria (83).

Amblyopia

A small RAPD, generally less than 0.5 log units, often can be seen in an amblyopic eye. The magnitude of the RAPD does not correlate well with the visual acuity (84,85), nor does it predict the effect of occlusion therapy (86). That such pupillomotor asymmetry is not always observed suggests that it may be seen only in patients who do not take up fixation in the amblyopic eye, even though a bright light is effectively blocking the good eye.

Local Anesthesia and RAPD

A transient RAPD typically is seen following local anesthesia in the orbit. In one study, the method of anesthetic delivery (peribulbar versus retrobulbar versus sub-Tenon) did not affect the degree of induced RAPD or its recovery time (87).

Media Opacities

Dense intraocular hemorrhage that mechanically blocks light from reaching the retina can produce an RAPD that resolves as the hemorrhage clears (88). In contrast, a dense unilateral cataract does not produce an RAPD in the affected eye. Instead, a very small RAPD occasionally is found in the opposite eye. This may be partly because of the dark-adapted retina behind the cataract and partly because the incoming light is scattered by the opaque lens, allowing more light to hit the macular area directly (89–92). DuBois and Sadun also suggested that retinal sensitivity may be upregulated slowly behind a cataract by a neurogenic mechanism that is unrelated to routine receptor photochemistry (81).

Optic Tract Disorders

A complete or nearly complete lesion of the optic tract produces a contralateral homonymous hemianopia and a small to moderate RAPD (0.3–1.6 log units) in the contralateral eye (i.e., the eye with the temporal field loss) (93–95). Assuming an asymmetric distribution of crossed and uncrossed pupillomotor fibers in each optic tract similar to that of visual fibers, the contralateral side of the RAPD found in optic tract (and midbrain tectal) lesions can be understood. However, the large range and magnitude of tract RAPDs is not explained by the percentage of decussating pupillomotor input and may be related instead to individual differences in the pupillomotor sensitivity of the temporal and nasal retina. Additionally, an asymmetric distribution of efferent impulses from each pretectal nucleus to the Edinger-Westphal nuclei would produce an efferent deficit in the eye contralateral to the lesion (i.e., the eye with the afferent deficit). This relative efferent deficit, which is most evident when comparing only the direct pupil response between the two eyes in a patient with an optic tract (or tectal) lesion, can lead to overestimation of the RAPD. Cox and Drewes suggested that this efferent part of the asymmetry can be avoided

by watching one eye only and comparing its direct and consensual responses (96). This makes the examination more difficult, but it is necessary in some clinical settings.

Pretectal Nucleus

A unilateral lesion in the pretectal nucleus or in the brachium of the superior colliculus from an arteriovenous malformation, infarct, tumor, or other lesion will damage the afferent pupillomotor fibers that derive from the ipsilateral optic tract. This can produce a contralateral RAPD without any visual field defect (97,98). The tectal RAPD occasionally is associated with an ipsilateral or contralateral trochlear nerve paresis if the lesion affects the ipsilateral trochlear nerve nucleus, the predecussation portion of the ipsilateral trochlear nerve fascicle, or the postdecussation portion of the contralateral trochlear nerve fascicle (99,100).

Geniculate and Retrogeniculate Lesions

Lesions that involve the lateral geniculate nucleus or the proximal portion of the retrogeniculate pathway may be associated with a contralateral RAPD if there is also involvement of the adjacent intercalated (pretectal) neurons in the dorsal midbrain that serve as the link between the afferent visual pathway (optic tract) and the efferent pupillomotor centers (Edinger-Westphal nuclei). These are, then, essentially the same as tectal RAPDs (101). Congenital postgeniculate lesions causing homonymous hemianopia also have a contralateral RAPD, presumably from transsynaptic degeneration of the optic tract ipsilateral to the lesion (102).

Nonorganic Visual Loss

Neither nonorganic loss of visual acuity nor nonorganic constriction of the visual field in one eye ever produces an RAPD (103). This obviously is of great clinical importance. Although Kosmorsky et al. (104) reported five patients with neurogenic monocular temporal visual field defects who did not have an RAPD, the vast majority of patients with monocular neurogenic loss of the visual field do have one in the eye with visual loss. We have no explanation for the findings of Kosmorsky et al.

RAPD in Normal Eyes

Some normal subjects show a small RAPD, clinically and pupillographically, in the absence of any detectable pathologic disease (105,106). The RAPD in such cases usually is 0.3 log units or less and variable in degree. It also may vary from side to side. The RAPD in normal subjects was hypothesized as representing, in part, a real but ''normal'' degree of asymmetry in interocular retinal sensitivity as well as the degree of uncertainty inherent in quantifying a fluctuating, biologic process (i.e., the pupil light reflex). Thus, the presence of a very small RAPD in a healthy subject with no visual or neurologic complaints or deficits probably is of no significance. It also is possible that some normal patients, especially those with a small but persistent RAPD on the same side, harbor underlying pathology (i.e., an early compressive lesion of the optic nerve, subclinical optic neuritis) (11). Whether further investigation is warranted for such patients should be individualized based on the clinical setting.

Wernicke Pupil

When the optic chiasm is bisected sagittally, the nasal halves of each retina become insensitive to light so that there is not only a bitemporal hemianopia but also a bitemporal pupillary hemiakinesia; that is, light falling on the nasal retina of either eye will fail to produce a pupillary constriction. Clinical demonstration of this sign with a flashlight is difficult because of intraocular scatter: when light strikes the retina in one quadrant, it tends to be spread evenly, and the beam from a flashlight directed upon the blind hemiretina thus spills onto the seeing half, causing pupillary constriction. Thus, if a very bright but small beam of light such as that produced by a slit lamp is shined on the nonseeing hemiretina of a patient with damage to the optic chiasm or optic tract and then is shined on the seeing hemiretina, it is possible to see that the pupil reacts better when the light shines on the seeing hemiretina than when it shines on the nonseeing retina. However, for practical purposes, the results of this test when performed at the bedside are often inconclusive and unreliable, and this has disappointed several generations of ophthalmologists and neurologists since Wernicke popularized the test in 1883.

Poorly Reacting Pupils from Midbrain Disease

Fixed dilated pupils and pupils that react poorly to both light and near stimuli may be produced by damage to the visceral oculomotor nuclei and their efferent fiber tracts. The precise location of such lesions is almost impossible to determine unless there is associated evidence of ocular motor nerve dysfunction. Other midbrain lesions damage the afferent input to the Edinger-Westphal nuclei or cause combined afferent and efferent damage. Seybold et al. described a variety of pupillary abnormalities in patients with tumors in the pineal region (107). With a bright light stimulus, four patients had impairment of both light and near reactions, two patients had markedly impaired light reactions and relatively intact responses to near stimuli (classic light–near dissociation), and two patients had relatively intact light reactions but impaired responses to near stimuli (inverse Argyll Robertson pupils). With a dim light stimulus, five patients had impairment of reactions to both light and near stimuli and three patients had impaired light reactions but relatively intact reactions to near stimuli. In addition, four of the patients had an asymmetric sympathetic reflex dilation. It seems that various combinations of defects involving the pupil light reflex, the pupil near response, and accommodation can occur with lesions of the rostral midbrain.

Bilateral complete internal ophthalmoplegia, when caused by damage to the rostral oculomotor nuclear complex, rarely occurs in isolation. Lesions that produce these changes must be located in the periaqueductal gray matter near the rostral end of the aqueduct. Vascular, inflammatory, neoplastic, and demyelinating diseases that affect this area almost always produce associated signs, including nuclear ophthalmople-

gia, paralysis of vertical gaze, loss of convergence, exotropia, ptosis, and other defects of ocular movement.

Paradoxical Reaction of the Pupils to Light and Darkness

Barricks et al. described three unrelated boys, 2, 6, and 10 years of age, with congenital stationary night blindness, myopia, and abnormal electroretinograms, who showed a ''paradoxical'' pupillary constriction in darkness (108). In a lighted room, all three patients had moderately dilated pupils; however, when the room lights were extinguished, the patients' pupils briskly constricted and then slowly redilated. Subsequent investigators confirmed this observation and reported similar paradoxical pupillary responses in children and adults with congenital achromatopsia, blue-cone monochromatism, and Leber congenital amaurosis (109,110). In addition, such responses occasionally occur in patients with optic disc hypoplasia, dominant optic atrophy, and bilateral optic neuritis. Flynn et al. suggested that the pupillary responses seen in these patients occur not from abnormalities in the central nervous system (CNS) but from selective delays in afferent signals from the retinal photoreceptors to the pupillomotor center (111).

EFFERENT ABNORMALITIES: ANISOCORIA

The presence of anisocoria usually indicates a structural defect of one or both irides or a neural defect of the efferent pupillomotor pathways innervating the iris muscles in one or both eyes. A careful slit-lamp examination to assess the health and integrity of the iris stroma and muscles is an important step in the evaluation of anisocoria. If the irides are intact, then an innervation problem is suspected. As most efferent disturbances causing anisocoria are unilateral, two simple maneuvers are helpful in determining whether it is the sympathetic or parasympathetic innervation to the eye that is dysfunctional: *(1)* checking the pupillary light reflex and *(2)* measuring the anisocoria in darkness and in bright light.

When the larger pupil has an obviously impaired reaction to light stimulation, it is likely the cause of the anisocoria. One can presume the problem lies somewhere along the parasympathetic pathway to the sphincter muscle. Common etiologies include an acute tonic pupil, oculomotor nerve palsy, or pharmacologic blockade. If both pupils have a good light reflex and the degree of anisocoria decreases in bright light (i.e., anisocoria is greater in darkness), then there is either a deficit of sympathetic innervation to the dilator muscle in the eye with the smaller pupil (as in Horner syndrome)

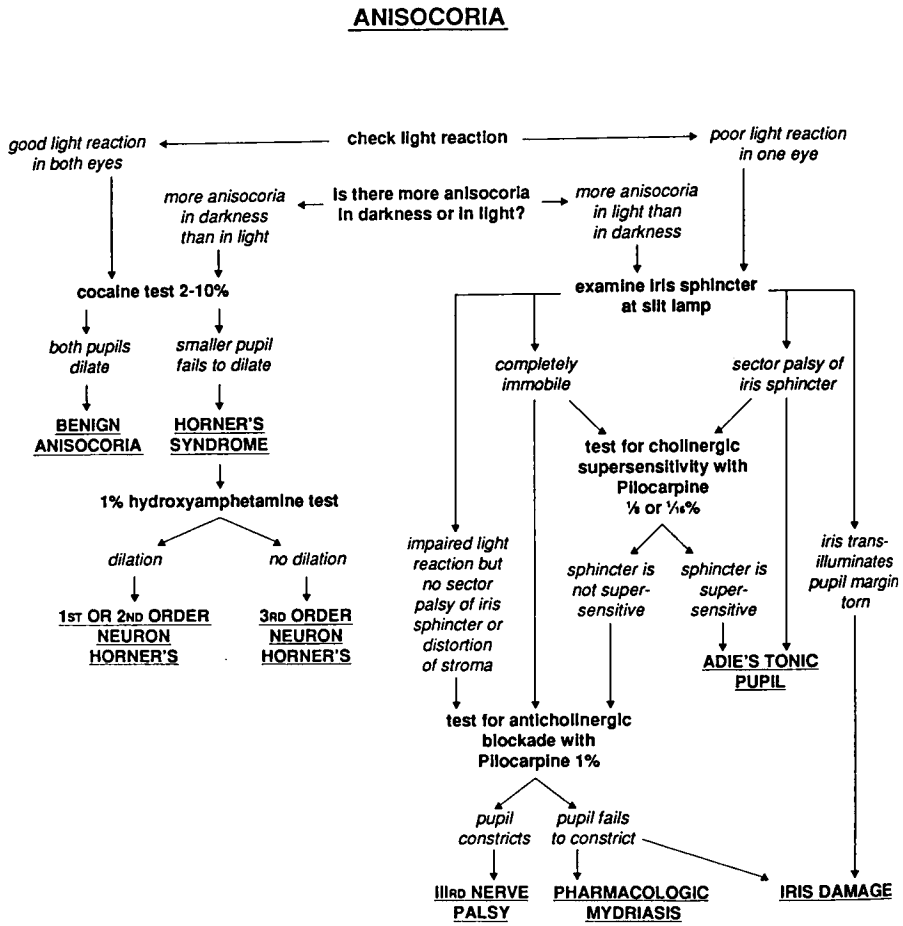

Figure 16.5. Steps that assist the evaluation of anisocoria.

or a physiologic anisocoria. The evaluation of anisocoria is described in the following sections and outlined in Figure 16.5

Anisocoria Greater in Darkness

Physiologic (Benign) Anisocoria

Inequality of pupil size becomes clinically observable when the difference between pupils is about 3 mm. In dim light or darkness, almost 20% of the normal population has an anisocoria of 0.4 mm or more at the moment of examination. In room light, this number drops to about 10% (112–114). This form of anisocoria is known by several names, including physiologic anisocoria, simple central anisocoria, essential anisocoria, and benign anisocoria. It is typically 0.6 mm or less; a difference in size of 1.0 or more is rare (114–116) (Fig. 16.6). The degree of pupillary inequality in physiologic anisocoria may change from day to day or even from hour to hour, however. The anisocoria usually diminishes slightly in bright light, perhaps because the smaller pupil reaches the zone of mechanical resistance first, giving the larger pupil a chance to make up the size difference (117).

Physiologic anisocoria is not caused by damage to the peripheral nerves that innervate the sphincter and dilator muscles of the iris. The pupillary reactions to light and darkness are normal. Instead, it is presumed to occur because the supranuclear inhibition of the parasympathetic pupilloconstrictor nuclei in the midbrain is not balanced with any more precision than is necessary for clear, binocular vision. It is unrelated to refractive error. Occasionally, a reversal of physiologic anisocoria is seen, a phenomenon termed ''see-saw anisocoria'' (112,116).

When physiologic anisocoria is suspected, reviewing old photographs, such as a driver's license or especially a family album, can be a valuable diagnostic tool (Fig. 16.7). In the latter case, the anisocoria usually can be traced back to infancy or early childhood.

Horner Syndrome

When the sympathetic innervation to the eye is interrupted, the retractor muscles in the eyelids are weakened, allowing the upper lid to droop and the lower lid to rise. The dilator muscle of the iris also is weakened, allowing the pupil to become smaller, and vasomotor and sudomotor control of parts of the face may be lost. This combination of ptosis, miosis, and anhidrosis is called **Horner syndrome** (Fig 16.8)

HISTORICAL BACKGROUND

In 1869, Johann Friedrich Horner, a Swiss ophthalmologist, published a short case report in which he emphasized that eyelid ptosis could be caused by a lesion as far away from the eye as the neck by denervating the sympathetically innervated muscle in the upper lid that had recently been described by H. Müller. Although he was not the first to report the clinical condition, his meticulous and scientifically substantiated account of the clinical effects of cervical sympathetic paralysis has firmly attached his name to this syndrome (118). In the French literature, this condition is called the Claude Bernard-Horner syndrome to honor the work of Claude Bernard in 1852 on the physiology of the sympathetic nerves.

Although Horner and Bernard generally are credited with identifying the clinical signs of oculosympathetic paresis, these signs were first produced experimentally in the dog by François Pourfour du Petit in 1727. Pourfour du Petit was never recognized for these contributions; however, Pourfour du Petit syndrome is the term used for the combination of

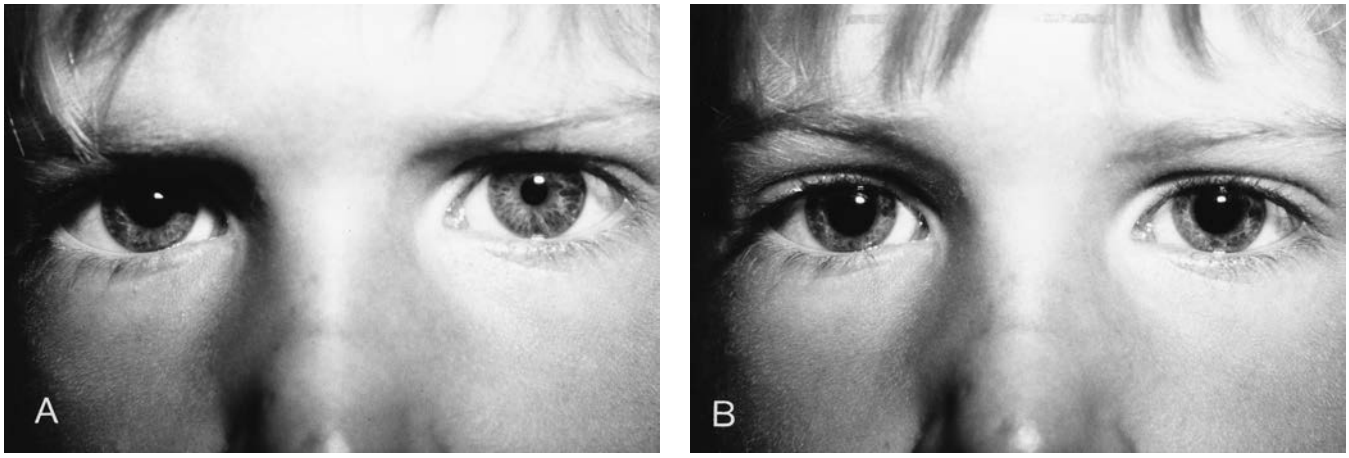

Figure 16.6. Physiologic (benign) anisocoria. The patient was a 5-year-old boy whose parents noted that the right pupil was larger than the other. The anisocoria was more obvious in dark than in light, and both pupils reacted normally to light stimulation. *A*, Appearance of the patient. Note anisocoria with right pupil larger than left. *B*, 45 minutes after instillation of a 10% solution of cocaine into both inferior conjunctival sacs, both pupils are dilated, indicating that anisocoria is not caused by sympathetic denervation.

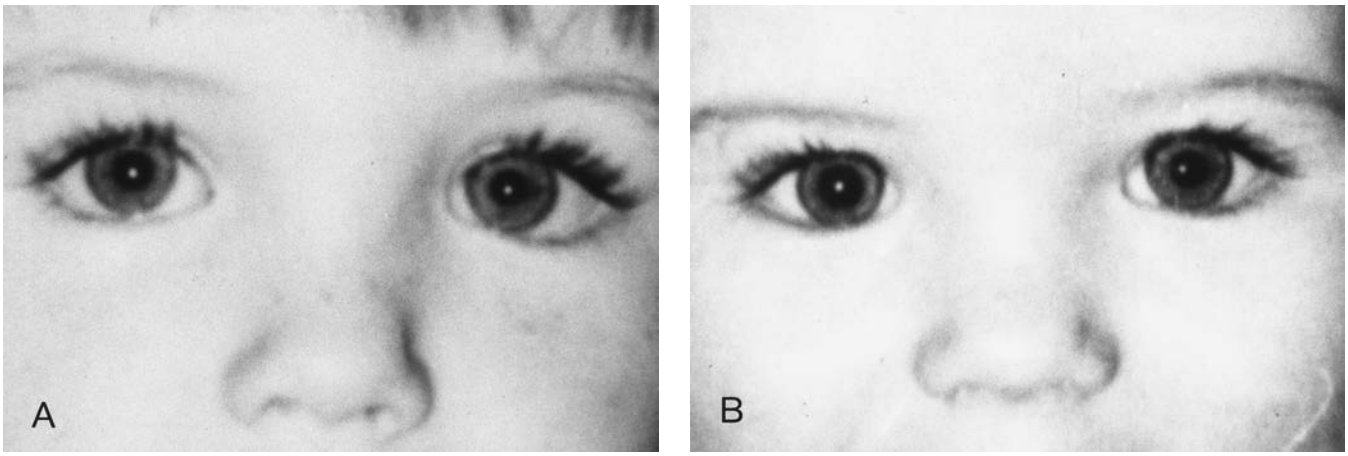

Figure 16.7. Value of old photographs in the assessment of anisocoria. *A*, This 3-year-old boy was noted by his parents to have intermittent anisocoria, with the right pupil larger than the left. The anisocoria was greater in darkness than in light, and both pupils reacted normally to light stimulation. *B*, Photograph of patient at age 7 months shows obvious anisocoria.

signs caused by sympathetic stimulation (i.e., lid retraction, mydriasis, and conjunctival blanching). This eponym is remarkable because Pourfour du Petit never actually stimulated the sympathetic nerve in his experimental animals (119).

CLINICAL CHARACTERISTICS

Ptosis. The affected eye often looks small or sunken in patients with Horner syndrome. The upper eyelid is slightly drooped because of paralysis of the sympathetically innervated smooth muscle (Müller muscle) that contributes to the position of the opened upper eyelid. This ptosis sometimes is so slight and variable that it escapes attention. In one study, ptosis was frankly absent in 12% of patients (120). Similar smooth muscle fibers in the lower eyelid also lose their nerve supply in Horner syndrome; thus, the lower lid usually is slightly elevated, producing an ''upside-down ptosis,'' further narrowing of the palpebral fissure, and an apparent enophthalmos. That the enophthalmos is apparent rather than real has been confirmed by several studies (119,121,122).

Pupillary Signs. *Miosis.* The palsy of the iris dilator muscle in Horner syndrome allows unantagonized action of the iris sphincter, producing a smaller pupil. However, in some patients in the setting of intense emotional excitement, the pupil on the side of the sympathetic lesion becomes larger than the normal pupil. Likewise, if the dilator muscle is stimulated directly (e.g., after an adrenergic eye drop is used), the pupil will dilate widely. This ''paradoxical pupillary dilation'' is caused by denervation supersensitivity of the dilator muscle to circulating and topical adrenergic substances.

Topical apraclonidine is an alpha-adrenergic receptor ago-

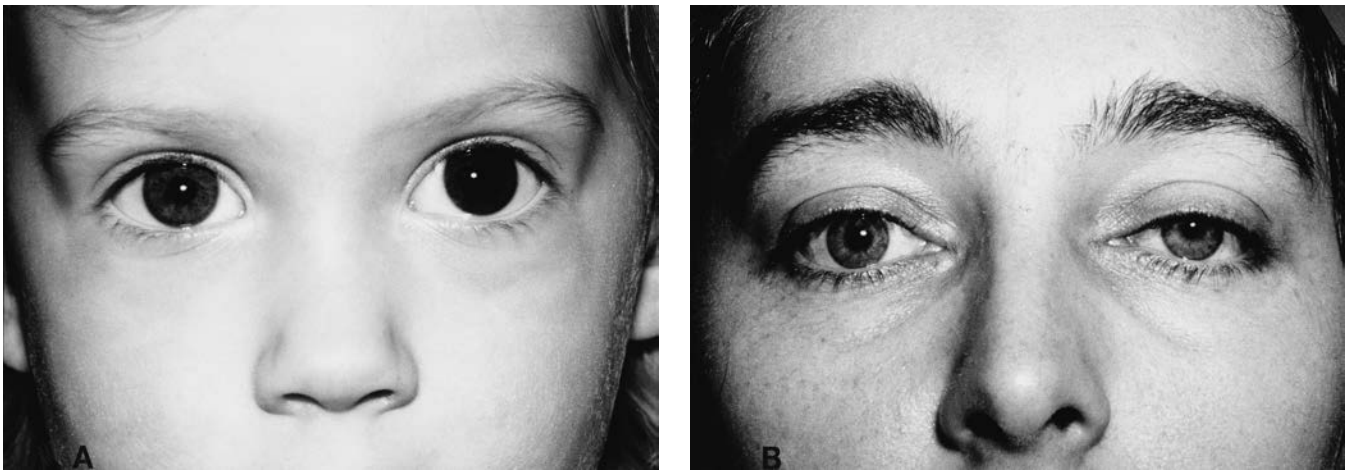

Figure 16.8. Horner syndrome in two patients. *A*, Congenital right Horner syndrome. Note associated heterochromia iridis and minimal ptosis. *B*, Left Horner syndrome after neck trauma.

nist that has little or no effect on a normal pupil but can dilate a Horner pupil due to denervation supersensitivity of the alpha-1 receptors on the iris dilator muscle. Thus, reversal of anisocoria following topical instillation of apraclonidine has been seen in patients with unilateral Horner syndrome (123,124).

Anisocoria. Any anisocoria, when caused by weakness of a single iris muscle, increases in the direction of action of that muscle. With a unilateral oculosympathetic defect, the weakness of the dilator muscle in the affected eye (and resultant anisocoria) is most apparent in darkness. Conversely, the anisocoria almost disappears in light because the normal action of both sphincters (oculoparasympathetic activity) constricts the pupils to almost equal sizes. In regular room light, the degree of anisocoria in Horner syndrome is rather small, on the order of 1.0 mm or less, and can be overlooked or mistakenly attributed to simple anisocoria (125). Furthermore, when a patient is fatigued or drowsy, the size of the pupils and the degree of anisocoria diminish as the hypothalamic sympathetic outflow to both eyes subsides and uninhibited parasympathetic outflow augments. Some patients with Horner syndrome have anisocoria measuring up to 2.5 mm; such a large anisocoria is not seen with benign anisocoria. The actual amount of anisocoria in Horner syndrome thus varies with (*a*) the resting size of the pupils; (*b*) the completeness of the injury; (*c*) the alertness of the patient; (*d*) the extent of reinnervation of the dilator muscle; (*e*) the brightness of the examiner's light or the ambient light in the room; (*f*) the degree of denervation supersensitivity; (*g*) the fixation of the patient at distance or near; and (*h*) the concentration of circulating adrenergic substances in the blood.

Dilation Lag. Paresis of the iris dilator muscle results in a smaller resting pupil size (miosis) and also in impaired pupillary movement during dilation, called dilation lag. Dilation lag can be seen clinically by illuminating the patient's eyes tangentially from below with a hand-held flashlight, and then abruptly turning the room lights out. The normal pupil will immediately dilate, but several seconds will elapse before the Horner pupil begins to dilate. The dilation dynamics of a normal pupil compared with a Horner pupil have been well documented using continuous recording pupillography (119). Immediately following a bright light flash, both pupils are strongly constricted. In the first second of darkness, both pupils synchronously enlarge a small degree, presumably from acute inhibition of parasympathetic impulses. In the next few seconds, the normal pupil, stimulated by an active burst of sympathetic discharges, rapidly dilates, whereas the Horner pupil, denervated of sympathetic impulses, hardly moves. This results in an increasing anisocoria during in the first 5 seconds or so of darkness. Thereafter, the Horner pupil slowly dilates from decreasing parasympathetic tone and catches up in size to the normal pupil. Thus, if both pupils are observed simultaneously for 15–20 seconds after turning off the room light, one sees an initial increase in the degree of anisocoria, followed by decreasing anisocoria (Fig. 16.9).

A psychosensory stimulus such as a sudden noise will cause a normal pupil to dilate. When looking for dilation lag in darkness, interjection of a sudden loud noise just as the lights go out tends to augment the initial increase in anisocoria when a unilateral oculosympathetic defect is present. One can also pinch the patient's neck (the ciliospinal reflex), press over McBurney's point (Meyer's iliac sign), or flex the patient's neck (Flatau's neck mydriasis) to bring this out (126).

There remains controversy about which aspect of pupillary reflex dilation in darkness best identifies the impaired dilation dynamics of a Horner syndrome. Several methods of detecting dilation lag have been proposed. Taking Polaroid photographs 5 seconds after the lights go out and again after 15 seconds of darkness is a simple and readily available

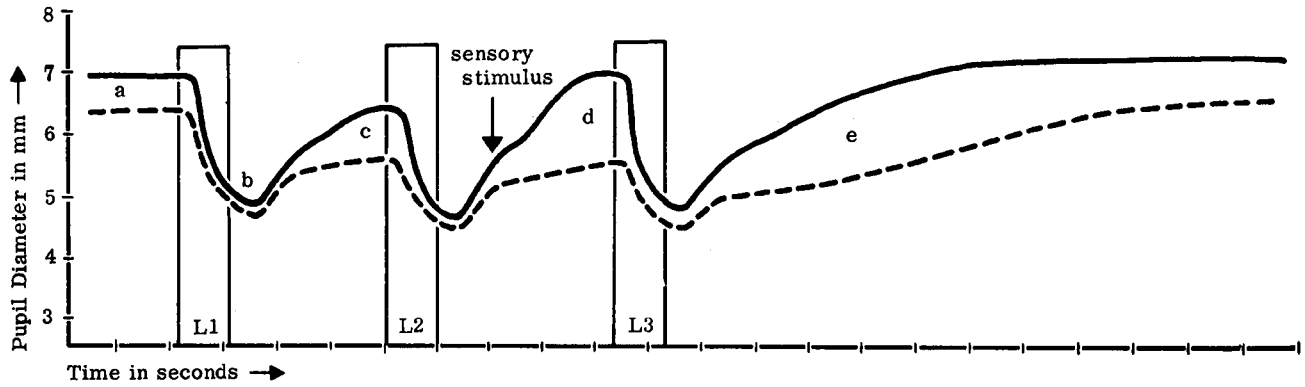

Figure 16.9. Pupillogram of a patient with a left Horner syndrome (*solid line* is a normal pupil; *broken line* is a Horner pupil). Point a is the resting size of both pupils (and anisocoria) in darkness. Following a 1-second pulse of light, the pupils are maximally constricted at b. As the pupils redilate in the darkness, increasing anisocoria seen in c is due to the relative inactivity of the Horner pupil. Addition of a sensory stimulus after the pulse of light further enhances the asymmetric dilation dynamics (d) between the normal pupil and the Horner pupil. In e, the dilation of both pupils is observed over a longer period of time. After the initial increase in anisocoria, there is a gradual decreasing of the anisocoria as the slowly dilating Horner pupil eventually recovers its baseline size in darkness.

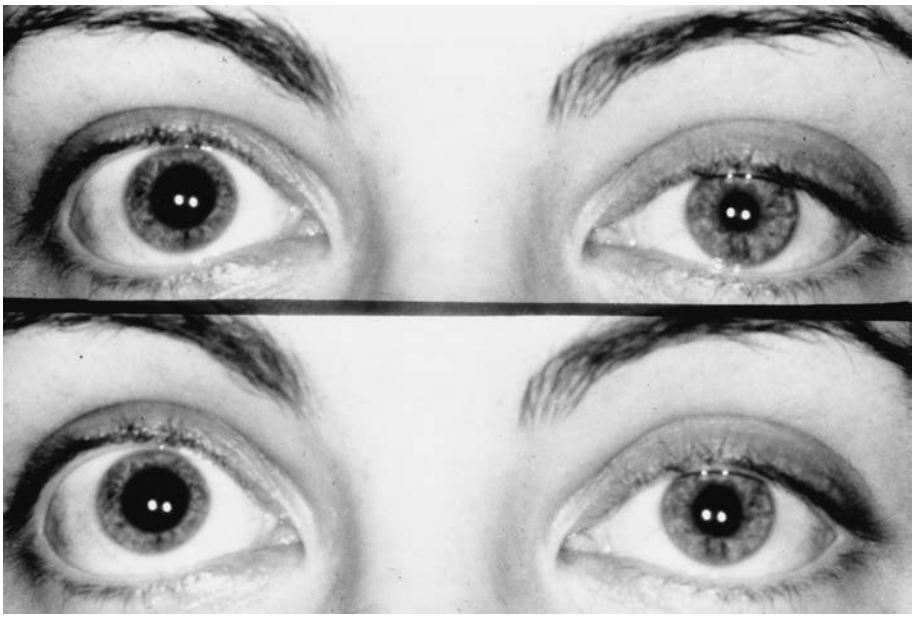

Figure 16.10. Dilation lag in a patient with a left Horner syndrome, observed using regular flash color photos. *Top,* Photo taken 5 seconds after the room lights were turned off. *Bottom,* Photo taken after 15 seconds of darkness. The right pupil is already maximally dilated within 5 seconds of turning the room lights off, but the left pupil still has not dilated maximally after 15 seconds of darkness.

means to assess for dilation lag. Patients with Horner syndrome show more anisocoria in the 5-second photograph than in the 15-second photograph, emphasizing that the absence of continued dilation after 5 seconds in darkness (i.e., demonstration of decreasing anisocoria in the later phase of dilation) is a defining characteristic of an oculosympathetic defect (127,128) (Fig. 16.10). Videography with infrared illumination is one of the best ways to show this phenomenon (129). Others have reported that a single measurement of anisocoria taken within the first 5 seconds of darkness (i.e., assessment of the increase in anisocoria in the early phase of dilation) is adequate for identifying dilation lag. One study reported that 0.6 mm or more at 4 seconds was 82% sensitive for diagnosing a unilateral Horner syndrome (130) Using a binocular infrared video pupillometer with continuous recording of pupil diameters, Smith and Smith found that after a light flash, a delay in the time needed to recover three quarters of the baseline pupil size had a 70% sensitivity and 95% specificity of detecting unilateral Horner syndrome (131). This definition of dilation lag based on a measure of time, instead of the degree of anisocoria, is particularly useful for detecting bilateral Horner syndrome.

Hypochromia Iridis. Depigmentation of the ipsilateral iris is a typical feature of congenital Horner syndrome and occasionally is seen in patients with a long-standing, acquired Horner syndrome (132). It is never seen in patients with an acute or recently acquired Horner syndrome.

Anhidrosis. Characteristic vasomotor and sudomotor changes of the facial skin can occur on the affected side in some patients with Horner syndrome. Immediately following sympathetic denervation, the temperature of the skin rises on the side of the lesion because of loss of vasomotor control and consequent dilation of blood vessels. Additionally, there may be facial flushing, conjunctival hyperemia, epiphora, and nasal stuffiness in the acute stage.

Some time after the injury, the skin of the ipsilateral face and neck may have a lower temperature and may be paler than that of the normal side. This occurs from supersensitivity of the denervated blood vessels to circulating adrenergic substances, with resultant vasoconstriction.

The distribution of the loss of sweating (anhidrosis) and flushing depends on the location of sympathetic lesion. For example, in lesions of the preganglionic neuron, the entire side of the head, the face, and the neck down to the clavicle usually are involved, whereas in postganglionic lesions, anhidrosis is limited to a patch on the forehead and the medial side of the nose. In a warm environment, the skin on the affected side will feel dry, whereas the skin on the normal side will be so damp that a smooth object, such as a plastic bar, will not slide easily on the skin but will stick. Because most persons live and work in temperature-controlled spaces, patients with Horner syndrome rarely complain of disturbances of sweating or asymmetric facial flushing.

Paradoxic unilateral sweating with flushing of the face, neck, and sometimes the shoulder and arm can be a late development in patients with a surgically induced Horner syndrome following cervical sympathectomy (133) or a cervical injury. Apparently, some axons in the vagus nerve normally pass into the superior cervical ganglion. These parasympathetic axons can establish, by collateral sprouting, anomalous vagal connections with postganglionic sympathetic neurons to the head and neck. Affected patients may experience bizarre sudomotor and pilomotor (gooseflesh) activity and vasomotor flushing geared reflexively to certain functions of the vagus nerve. The patterns of anomalous sweating vary but often involve the central portions of the face and forehead (119).

Accommodation. Most reports describe an increase in accommodative amplitude on the side of a Horner syndrome (119). It would appear that an intact sympathetic innervation of the ciliary muscle helps that muscle loosen and tighten the

zonules with alacrity. This is a minor effect and is clinically insignificant.

DIAGNOSIS

Not all patients with unilateral ptosis and ipsilateral miosis have Horner syndrome (134). The prevalence of simple anisocoria in the normal population is about 20%. A ptosis from any cause, such as dehiscence of the levator insertion, eyelid inflammation, or myasthenia gravis, may occur coincidentally on the side of the smaller pupil in a patient who also happens to have simple anisocoria, resulting in a ''pseudo-Horner syndrome.''

The most widely used confirmatory test for the diagnosis of Horner syndrome is the cocaine eyedrop test (135). In 1884, Koller first described using a 2% cocaine solution as a topical ocular anesthetic, at which time it was noted that this substance also dilated the pupil. It was subsequently noted that cocaine also widened the palpebral fissure and blanched the conjunctiva of a normal eye—the same combination of signs that was known to occur when the cervical sympathetic nerve was stimulated. Shortly thereafter, Uhthoff suggested that cocaine be used as a clinical test of the sympathetic integrity to the eye (119).

Cocaine blocks the reuptake of the norepinephrine that is released continuously from sympathetic nerve endings at the neuromuscular synapse, allowing norepinephrine to accumulate at the receptors of the effector cells. In a normal eye, a 2–10% solution of cocaine causes dilation of the pupil. One study noted a mean pupil dilation of 2.14 mm (range, 0.6–4.0 mm) in normal eyes in response to a 5% cocaine solution (125). A lesion anywhere along the three-neuron sympathetic pathway that impairs neural impulses will interrupt the normal spontaneous release of norepinephrine from presynaptic nerve endings. Thus, cocaine has no significant mydriatic effect on a sympathetically denervated iris.

Rarely, a normal pupil will fail to dilate after topical application of 2% cocaine, perhaps because the oculosympathetic nerves of a few lethargic individuals do not release enough norepinephrine for 2% cocaine to have an effect, or because some heavily pigmented irides bind the drug so that it does not reach the dilator muscle (11). Whatever the reason, a 10% solution most often is used to test for a Horner pupil (Fig. 16.11). The first drop stings briefly, then the anesthetic effect takes effect and a second drop can be placed about 1 minute later. Peak effect is attained in 40–60 minutes. There are no apparent psychoactive effects from a 10% solution of cocaine, but metabolites of the drug can be found in the urine in 100% of patients after 24 hours, in 50% at 36 hours, and in 2% after 48 hours (136,137). The odds of an anisocoria being caused by an oculosympathetic palsy increase with the amount of post-cocaine anisocoria, regardless of the amount of baseline anisocoria. For clinical purposes, a post-cocaine anisocoria of 0.8 mm measured in standard room light is sufficient to diagnose a Horner syndrome (138). However, if the smaller (suspected Horner) pupil dilates more than 2 mm, even if the post-cocaine anisocoria is greater than 0.8 mm, a Horner syndrome is unlikely (125).

Some patients with very dark irides simply do not dilate well to cocaine. If the normal pupil has not dilated by 2 mm or more at 40–60 minutes after cocaine instillation, the differential effect of cocaine on a sympathetically denervated iris may not be evident. Apparent inaction of cocaine also can result from an overly bright room and patient drowsiness, both of which promote pupillary constriction.

LOCALIZATION

Localization of the site of injury of a Horner syndrome often can be determined from associated signs and symptoms and can be helpful in the appropriate evaluation of these patients.

Central Horner Syndrome. The central sympathetic pathway has components in the brain, brain stem, and spinal cord. Experimental data suggest that this central sympathetic pathway has cerebral cortical representation and is polysyn-

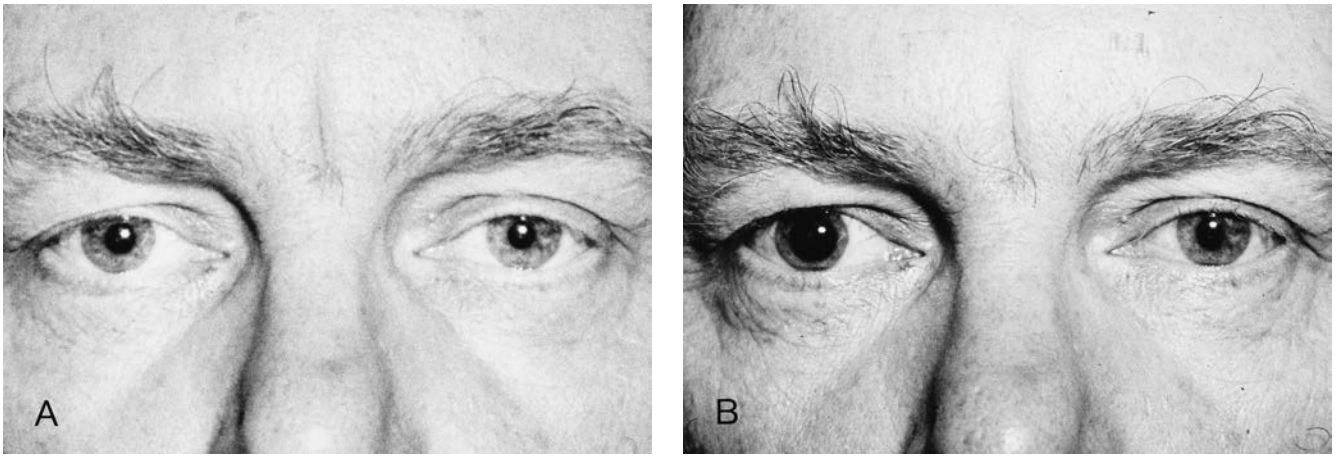

Figure 16.11. Response of normal pupil and a Horner pupil to cocaine. *A*, A 55-year-old man with left Horner syndrome associated with Raeder paratrigeminal neuralgia. *B*, 45 minutes after conjunctival instillation of two drops of a 10% cocaine solution in each eye, the right pupil is dilated, whereas the left pupil remains unchanged (small).

aptic (139). A patient with Horner syndrome after a transient ischemic episode showed only a lesion in the ipsilateral insular cortex (140). From the posterolateral hypothalamus, sympathetic fibers pass through the lateral brain stem and extend to the ciliospinal center of Budge in the intermediolateral gray column of the spinal cord at C8–T1. A central Horner syndrome caused by damage to any of these structures is ipsilateral to the lesion and almost always unilateral. A lesion in this neuron often produces a hemihypohidrosis of the entire body. Lesions of the hypothalamus such as tumor or hemorrhage can cause an ipsilateral Horner syndrome (141,142) with contralateral hemiparesis, contralateral hypesthesia, or both. Patients with a central Horner syndrome caused by a lesion of the thalamus also show a contralateral hemiparesis that often is ataxic (143). Contralateral hypesthesia, vertical gaze paresis, and dysphasia are other associated findings.

The occurrence of a unilateral Horner syndrome and a contralateral trochlear nerve paresis indicates a lesion of the dorsal mesencephalon. The lesion injures either the trochlear nucleus on the side of the Horner syndrome or the ipsilateral fascicle (140,144–146).

Although a Horner syndrome associated with an ipsilateral abducens nerve paresis is most often caused by a lesion in the cavernous sinus (see below), this combination of signs also may occur in patients with pontine lesions (147). In such cases, the Horner syndrome is central rather than postganglionic.

The classical brain stem syndrome characterized in part by a central Horner syndrome is Wallenberg syndrome, also called the lateral medullary syndrome. The typical findings of Wallenberg syndrome are ipsilateral impairment of pain and temperature sensation over the face, Horner syndrome, limb ataxia, and a bulbar disturbance causing dysarthria and dysphagia. Contralaterally, pain and temperature sensation is impaired over the trunk and limbs. The symptoms of Wallenberg syndrome include vertigo and a variety of unusual sensations of body and environmental tilt, often so bizarre as to suggest a psychogenic origin (148,149). Patients may report the whole room tilted on its side or even upside down; with their eyes closed, they may feel themselves to be tilted. Lateropulsion, a compelling sensation of being pulled toward the side of the lesion, is often a prominent complaint and also is evident in the ocular motor findings (150,151). If the patient is asked to fixate straight ahead and then gently close the lids, the eyes deviate conjugately toward the side of the lesion. This is reflected by the corrective saccades that the patient must make on eye opening to reacquire the target. Lateropulsion may even appear with a blink. Wallenberg syndrome is most commonly caused by thrombotic occlusion of the ipsilateral vertebral artery, although isolated posterior inferior cerebellar artery disease is occasionally seen (152). In a series of 130 patients with lateral medullary infarction, the pathogenesis was large vessel infarction in 50%, arterial dissection in 15%, small vessel infarction in 13%, and cardiac embolism in 5% (153). Demyelinating disease of the medulla has also been reported in a case of Wallenberg syndrome (154).

Although most patients with a central neuron Horner syndrome have other neurologic deficits, occasional patients with cervical spondylosis present only with a Horner syndrome and perhaps some neck pain. An isolated central Horner syndrome also can occur from a brain stem syrinx (155).

Lesions of the spinal cord (lower cervical or upper thoracic area) can cause a central Horner syndrome. In most cases there are other neurologic deficits, although in some patients the Horner syndrome is the only neurologic abnormality. Spinal cord lesions that may cause a central Horner syndrome include trauma (most common), inflammatory or infectious myelitis, vascular malformation, demyelination, syrinx, syringomyelia, neoplasms, and infarction. What appears to be an alternating Horner syndrome (i.e., alternating oculosympathetic deficit) can be seen in patients with cervical cord lesions and in some patients with systemic dysautonomias (156–159). Other patients have attacks of autonomic hyperreflexia that excite the ciliospinal center of Budge on the affected side (the C8–T1 intermediolateral gray column may, in fact, be supersensitive as a result of its disconnection). This excess firing of sympathetic impulses (oculosympathetic spasm) dilates the pupils, lifts the eyelid, blanches the conjunctiva, and increases sweating of the face (160). When the oculosympathetic spasm occurs unilaterally and intermittently on the side of an underlying Horner syndrome, the anisocoria appears to reverse; this mechanism may account for some cases of alternating Horner syndrome (161).

Preganglionic (Second-Order Neuron) Horner Syndrome. The preganglionic (second-order) neuron exits from the ciliospinal center of Budge and passes across the pulmonary apex. It then turns upward, passes through the stellate ganglion, and goes up the carotid sheath to the superior cervical ganglion, near the bifurcation of the common carotid artery.

In one large series, malignancy was the cause of about 25% of cases of preganglionic Horner syndrome (162). The most common tumors, not surprisingly, were lung and breast cancer, but Horner syndrome was not an early sign of either of these tumors. Indeed, by the time the Horner syndrome had appeared, the tumor already was known to be present.

Apical lung lesions that spread locally at the superior thoracic outlet cause symptoms of ipsilateral shoulder pain (the most common initial symptom) and pain and paresthesia along the medial arm, forearm, and fourth and fifth digits (the distribution of the C8 and T1 nerve roots) as well as a preganglionic Horner syndrome and weakness/atrophy of the hand muscles. This combination of signs is called the Pancoast syndrome. The majority of lesions causing Pancoast syndrome are carcinomas of the lung (163). Other tumors and infectious processes, including tuberculosis, bacterial pneumonias, and fungal infection, have been reported. A patient with a preganglionic Horner syndrome and ipsilateral shoulder pain should be investigated thoroughly for neoplastic involvement of the pulmonary apex, the pleural lining, and the brachial plexus.

Tumors that spread behind the carotid sheath at the C6 level may produce a preganglionic Horner syndrome associated with paralysis of the phrenic, vagus, and recurrent laryngeal nerves: the Rowland Payne syndrome (164). Just 3 inches lower, at the thoracic outlet, these nerves are more

widely separated and less likely to be involved together. Thus, if a patient is newly hoarse and has a preganglionic Horner syndrome, a chest radiograph may be warranted to see whether the hemidiaphragm ipsilateral to the Horner syndrome is elevated.

Nonpulmonary tumors that produce a preganglionic Horner syndrome include sympathetic chain or intercostal nerve schwannoma, paravertebral primitive neuroectodermal tumor, vagal paraganglioma, mediastinal tumors or cysts, and thyroid carcinoma. Injury to the brachial plexus or spinal roots, pneumothorax, fracture of the first rib, or neck hematoma should be considered in patients whose preganglionic Horner syndrome follows neck or shoulder trauma.

The preganglionic neuron is the most common site of injury for an iatrogenic Horner syndrome. The varied anesthetic, radiologic, and surgical procedures that can produce the condition include coronary artery bypass surgery, lung or mediastinal surgery, carotid endarterectomy, insertion of a pacemaker, epidural anesthesia, interpleural placement of chest tubes, internal jugular catheterization, and stenting of the internal carotid artery (165–170).

Despite advances in neuroimaging and other diagnostic tests, many cases of preganglionic Horner syndrome have no explanation. In one series, about 28% of cases of preganglionic Horner syndrome were of unknown etiology (125).

Postganglionic (Third-Order Neuron) Horner Syndrome. The postganglionic (third-order) sympathetic neuron to the iris dilator muscle begins in the superior cervical ganglion and travels in the wall of the internal carotid artery, where it is called the carotid sympathetic plexus or sometimes the carotid sympathetic nerve. The latter may be a more appropriate term, as the majority of sympathetic fibers ascend as a single bundle. Within the cavernous sinus, the sympathetic fibers leave the internal carotid artery, join briefly with the abducens nerve, and then leave it to join the ophthalmic division of the trigeminal nerve, entering the orbit with its nasociliary branch (171,172). The sympathetic fibers in the nasociliary nerve divide into the two long ciliary nerves that travel with the lateral and medial suprachoroidal vascular bundles to reach the anterior segment of the eye and innervate the iris dilator muscle.

Most lesions that damage the postganglionic sympathetic neuron are vascular lesions that produce headache or ipsilateral facial pain as well and often are lumped under the clinical description of a ''painful postganglionic Horner syndrome.'' Responsible lesions may be extracranial, affecting postganglionic sympathetics in the neck, or intracranial, affecting the sympathetics at the base of the skull, in the carotid canal and middle ear, or in the region of the cavernous sinus. It is unusual for an orbital lesion to produce an isolated Horner syndrome.

Lesions of or along the internal carotid artery are a common cause of a painful postganglionic Horner syndrome, the most common being a traumatic or spontaneous dissection of the cervical internal carotid artery. In 146 such patients, a Horner syndrome was the most common ocular finding (44%) (173). In half of these cases, the Horner syndrome was the initial and sole manifestation of the carotid artery dissection. In the other half, an associated ocular or cerebral ischemic event occurred within a mean of 7 days of the Horner syndrome, emphasizing the need for early recognition and diagnosis of this cause of Horner syndrome. Carotid dissections are discussed in Chapter 40.

Pathologic conditions of the internal carotid artery other than dissection that are associated with a Horner syndrome include aneurysms, severe atherosclerosis, acute thrombosis, fibromuscular dysplasia, and arteritis (174). Mass lesions in the neck that can compress the carotid sympathetic neuron include tumors, inflammatory masses, enlarged lymph nodes, and even an ectatic jugular vein (175,176).

In the deep retroparotid space and around the jugular foramen, oculosympathetic fibers are in close proximity with several lower cranial nerves. Lesions in this area of the neck, usually trauma, tumors, and masses, can result in a Horner syndrome associated with ipsilateral paralysis of the tongue, soft palate, pharynx, and larynx. Such lesions may cause dysphagia, dysphonia, and hoarseness. The ipsilateral posterior pharynx may be hypesthetic. This combination of paralysis of the cervical sympathetics and the last four cranial nerves (the glossopharyngeal, vagus, accessory, and hypoglossal nerves) is called Villaret syndrome (177).

The superior cervical ganglion lies about 1.5 cm behind the palatine tonsil and thus can be damaged by iatrogenic or traumatic penetrating intraoral injury. Tonsillectomy, intraoral surgery, peritonsillar injections, and accidental punctures through the soft palate are some of the etiologies that have been reported to cause a postganglionic Horner syndrome from damage to the superior cervical ganglion (178,179).

Lesions at the skull base can cause a postganglionic Horner syndrome. A middle fossa mass encroaching on Meckel's cave and on the internal carotid artery at the foramen lacerum can produce a postganglionic Horner syndrome associated with trigeminal pain or sensory loss. A basal skull fracture involving the petrous bone can damage the postganglionic sympathetic fibers within the carotid canal, producing a postganglionic Horner syndrome associated with an ipsilateral abduction deficit, facial palsy, and/or sensorineural hearing loss (abducens, facial, and vestibulocochlear cranial nerves) (180).

Any lesion in the cavernous sinus may produce a postganglionic Horner syndrome. In many cases, there is associated ipsilateral ophthalmoparesis caused by involvement of one or more ocular motor nerves as well as pain or dysesthesia of the ipsilateral face caused by trigeminal nerve dysfunction. The occurrence of an abducens palsy and a postganglionic Horner syndrome (Parkinson sign) without other neurologic signs should raise suspicion of a cavernous sinus lesion (181–183). When a Horner syndrome and oculomotor nerve palsy occur together, there is combined sympathetic and parasympathetic dysfunction of the iris muscles. In such cases, the anisocoria is minimal or absent despite the impaired light reaction of the affected pupil, and pharmacologic testing may be the only means to detect an underlying sympathetic paresis (184).

Cluster headaches are severe lancinating unilateral headaches that usually occur in middle-aged men. The headaches often are nocturnal, last 30–120 minutes, and are accompa-

nied by ipsilateral tearing, nasal stuffiness, conjunctival injection, and ptosis (signs of acute oculosympathetic palsy). A postganglionic Horner syndrome occurs in 5–22% of patients with cluster headache (185,186). Otherwise, no other neurologic deficits are present. Cluster headache is thought to be a vasospastic process affecting the carotid arterial system. Raeder paratrigeminal neuralgia is an eponym used for a painful postganglionic Horner syndrome characterized by a persistent ipsilateral trigeminal neuralgia and/or trigeminal nerve dysfunction. It is the trigeminal nerve involvement (pain or sensory change) that is distinctive and warrants investigation for a lesion in the middle cranial fossa medial to the trigeminal ganglion (185–187).

The hydroxyamphetamine test can be used to assist the differentiation between a postganglionic and a preganglionic or central Horner syndrome (188–190) (Fig. 16.12). Hydroxyamphetamine releases stored norepinephrine from the postganglionic adrenergic nerve endings, producing variable mydriasis in normal subjects (191). A lesion of the postganglionic neuron results in loss of terminal nerve endings and their stores of norepinephrine; thus, hydroxyamphetamine has no mydriatic effect. With lesions of the preganglionic or central neuron, the postganglionic nerve endings, though nonfunctioning, remain structurally intact. Thus, the pupil dilates fully and may even become larger than the opposite pupil from upregulation of the postsynaptic receptors on the dilator muscle. A postganglionic Horner pupil occasionally dilates in response to topical hydroxyamphetamine (false-negative result) when patients are tested within the first week of sympathetic injury before the stores of norepinephrine at the presynaptic nerve endings have been depleted (192). Hydroxyamphetamine hydrobromide 1% (Paredrine) is commonly used in the United States but is difficult to obtain or unavailable in other countries. Both tyramine hydrochloride 5% and hydroxymethylamphetamine (Pholedrine) have a mode of action similar to that of hydroxyamphetamine and serve equally well as agents for a localizing pharmacologic test (193,194).

A smaller pupil that fails to dilate to both cocaine and hydroxyamphetamine most likely has a lesion of the post-

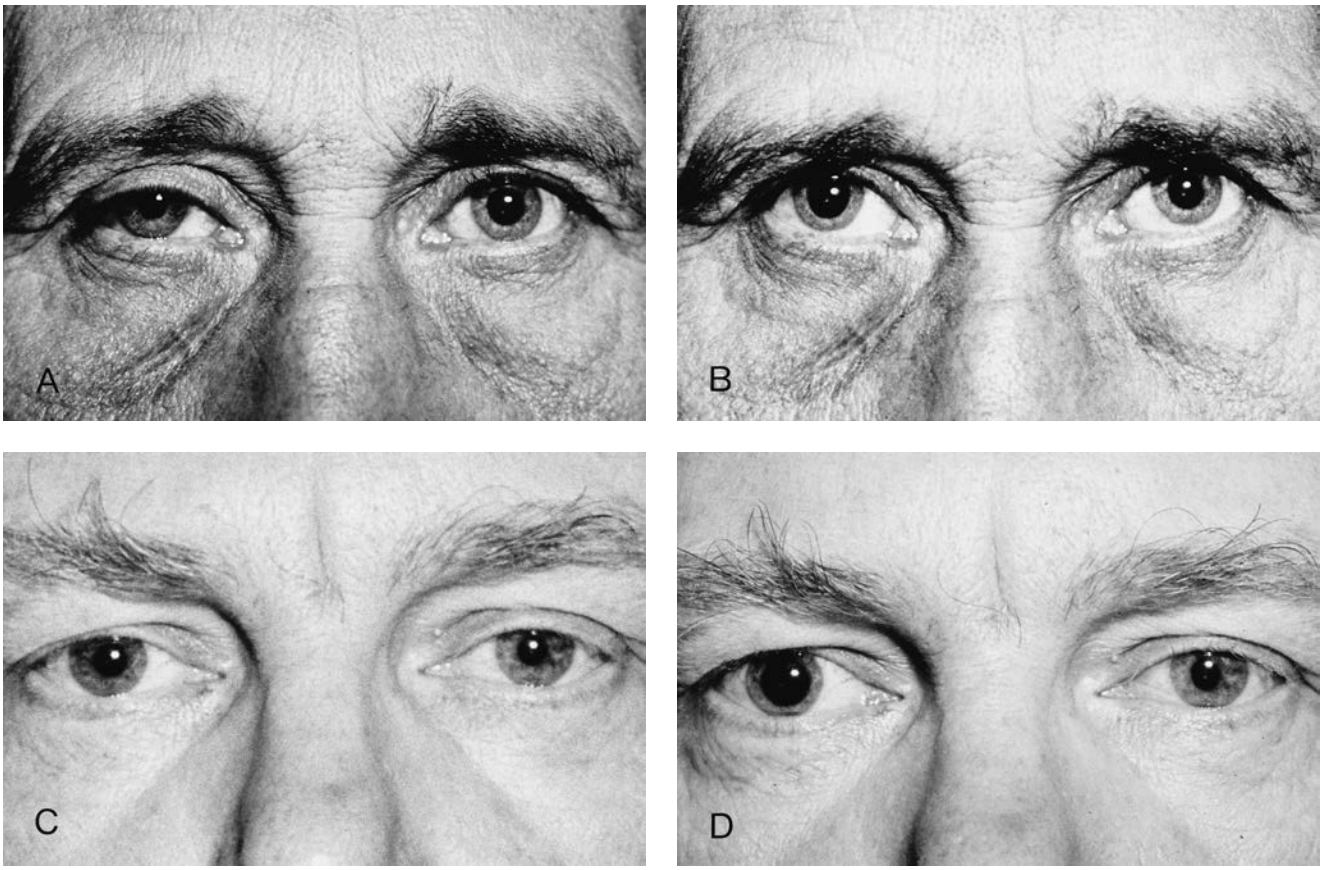

Figure 16.12. Response of Horner pupils to hydroxyamphetamine. *A*, Right Horner syndrome in a 45-year-old man with an apical lung tumor. *B*, 45 minutes after conjunctival instillation of 2 drops of 1% hydroxyamphetamine solution (Paredrine) in each eye, both pupils are dilated, indicating an intact postganglionic neuron (i.e., a preganglionic Horner syndrome). *C*, Left Horner syndrome associated with cluster headaches in a 55-year-old man. *D*, 45 minutes after conjunctival instillation of two drops of 1% hydroxyamphetamine solution in each eye, only the right (normal) pupil is dilated. The left pupil is unchanged, indicating damage to the postganglionic neuron (i.e., a postganglionic Horner syndrome).

ganglionic sympathetic neuron. Such a pupil should dilate to a weak, direct-acting topical adrenergic drug, such as a 1% solution of phenylephrine hydrochloride or a 2% solution of epinephrine due to adrenergic denervation supersensitivity of the iris dilator muscle. Indeed, such a pupil not only will dilate but also will become larger than the opposite normal pupil. Denervation supersensitivity of the iris to adrenergic drugs apparently does not occur immediately after damage to the postganglionic sympathetic nerve but may take as long as 17 days to develop (195). Occasionally, this test is used to differentiate a mechanically restricted pupil (e.g., iris damage) from a postganglionic Horner pupil because the restricted pupil fails to dilate to direct-acting adrenergic agents.

ACQUIRED HORNER SYNDROME IN CHILDREN

Horner syndrome in childhood (under age 18 years) may be congenital (42%), postoperative (42%), or truly acquired (15%) (196). It is this last group that often results from an underlying neoplasm or serious neurologic disease. For example, neuroblastoma is responsible for up to 20% of such cases (197). Other reported etiologies include spinal cord tumors, brachial plexus trauma, intrathoracic aneurysm, embryonal cell carcinoma, rhabdomyosarcoma, thrombosis of the internal carotid artery, and brain stem vascular malformations (196,198). Thus, an acquired Horner syndrome in a child with no prior surgical history, even if the finding is isolated, warrants immediate further investigation. This is particularly important for neuroblastoma because younger age (less than 1 year) is strongly correlated with better outcome.

CONGENITAL HORNER SYNDROME

Patients with a congenital Horner syndrome have ptosis, miosis, facial anhidrosis, and hypochromia of the affected iris (119,199). Even a child with very blue eyes usually has a paler iris on the affected side from impaired development of iris melanophores, causing hypochromia of the iris stroma. This occurs whether the lesion is preganglionic or postganglionic because of anterograde transsynaptic dysgenesis (200). Children with naturally curly hair and a congenital Horner syndrome have straight hair on the side of the Horner syndrome (201). The reason for this abnormality is unclear, but it probably relates to lack of sympathetic innervation to the hair shafts on the affected side of the head.

Parents of an infant with congenital Horner syndrome sometimes report that the baby develops a hemifacial flush when nursing or crying. The flushed side probably is the normally innervated side that appears dramatically reddish when seen against the opposite side with pallor from impaired facial vasodilation and perhaps overactive vasoconstriction as well. In other words, hemifacial flushing in infants is likely to be opposite the side of a congenital Horner syndrome (202,203). Sometimes, a cycloplegic refraction unexpectedly answers the question by producing an atropinic flush. This reaction occurs only when there is an intact sympathetic innervation to the skin (Fig. 16.13).

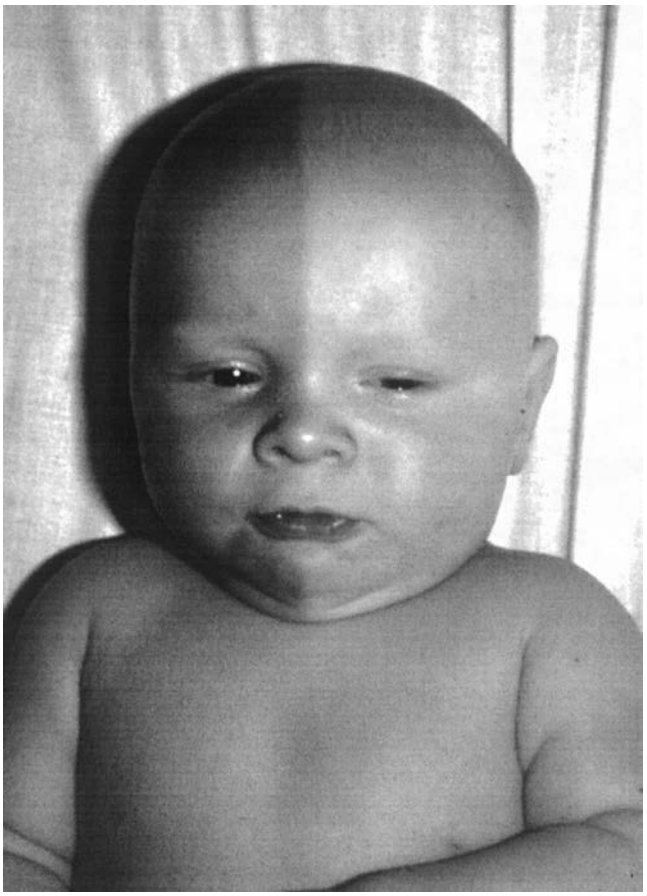

Figure 16.13. Lack of atropinic flushing in a child with a congenital left Horner syndrome. The atropinic flush is present only on the side of the face opposite the Horner syndrome.

Some patients with congenital Horner syndrome have clinical evidence that indicates a preganglionic lesion (e.g., facial anhydrosis, evidence of a brachial plexus injury, history of thoracic surgery), but pharmacologic localization with hydroxyamphetamine indicates a postganglionic lesion. Possible explanations include an embryopathy directly involving the superior cervical ganglion, damage to the vascular supply of the superior cervical ganglion, and transsynaptic dysgenesis of the superior cervical ganglion following a defect located more proximally in the sympathetic pathway (200,204).

Birth trauma probably is the most common etiology of congenital Horner syndrome (196). Use of forceps, history of shoulder dystocia, and fetal rotation can lead to injury of the sympathetic plexus along its course in the neck or near the thoracic outlet. Associated upper extremity weakness is indicative of concomitant damage to the ipsilateral brachial plexus (200) (Fig. 16.14). Neuroblastoma was found in one of 31 congenital cases (''congenital'' being defined as a Horner syndrome detected before 4 weeks of age) (196). Even if the definition of ''congenital'' is extended to include

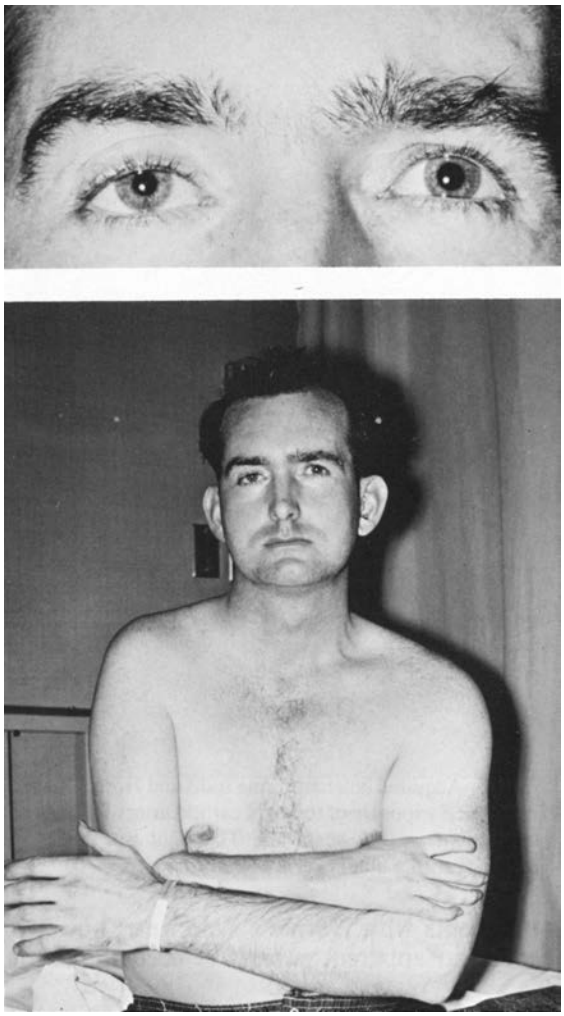

Figure 16.14. Horner syndrome (*top*) associated with injury of the right brachial plexus at birth. Note the underdeveloped right arm and forearm (*bottom*).

cases of Horner syndrome detected within the first year of life, the incidence of neuroblastoma is low, less than 10% (200,205). Other etiologies include congenital tumors, postviral complication, iatrogenic Horner syndrome, and abnormalities of the internal carotid artery such as fibromuscular dysplasia and congenital agenesis (206–209).

Many cases of congenital Horner syndrome are idiopathic, even after initial work-up and long-term follow-up. George et al. reported that no etiology was found in 16 of 23 (70%) infants who were found to have a Horner syndrome in the first year of life. In young infants with an isolated Horner syndrome and no history of birth trauma, a congenital basis may be suspected. Careful general examination and a urine test for catecholamines, with regular follow-up thereafter, constitutes the minimum evaluation (205). For infants in whom the onset of Horner syndrome is firmly established after the first 4 weeks of life (i.e., an acquired process), immediate and thorough imaging is recommended.

Pharmacologic Stimulation of the Iris Sphincter

Almost all cases of acute pharmacologically induced anisocoria are caused by parasympathetic blockade of the iris sphincter muscle, resulting in a fixed and dilated pupil. In such cases, the anisocoria is greater in light than darkness. However, in rare instances, a pharmacologic agent produces anisocoria by stimulating the parasympathetic system, thus producing a fixed miotic pupil in which the anisocoria is greater in darkness. In such cases, a 1% solution of tropicamide typically fails to dilate the pharmacologically constricted pupil. Anisocoria caused by parasympathetic stimulation can occur after handling of a pet's flea collar (210,211) that contains an anticholinesterase pesticide or a garden insecticide that contains parathion, a synthetic organophosphate ester.

Pharmacologic Inhibition of the Iris Dilator

Brimonidine tartrate is an alpha-2-adrenergic agonist that presumably decreases iris dilator action by its effect at the presynaptic alpha-2 inhibitory receptors of postganglionic sympathetic neurons. The resultant pupillary miosis is more apparent in darkness than in light (212).

Anisocoria Greater in Light

Damage to the Preganglionic Parasympathetic Outflow to the Iris Sphincter

The efferent pupillomotor pathway for pupillary constriction to light and near stimulation begins in the mesencephalon with the visceral oculomotor (Edinger-Westphal) nuclei and continues via the oculomotor nerve to the ciliary ganglion. The postganglionic impulses are carried through the short ciliary nerves to reach the iris sphincter (see Chapter 14). Because accommodative impulses begin in the same midbrain nuclei as pupilloconstrictor impulses and follow the same peripheral course to the eye, accommodative paralysis frequently accompanies pupillary paralysis in lesions of the efferent parasympathetic pathway to the iris sphincter. This combination of iridoplegia and cycloplegia was called internal ophthalmoplegia by Hutchinson to distinguish it from the external ophthalmoplegia that occurs when the extraocular muscles are paralyzed in the setting of normal pupillary responses.

Lesions anywhere along the two-neuron parasympathetic pathway to the intraocular muscles cause mydriasis at rest and impaired reflex constriction that ranges from mildly sluggish light reactions to complete pupillary unreactivity. Damage to the preganglionic portion of this pathway to the iris sphincter is caused by lesions involving the parasympathetic midbrain nuclei and the oculomotor nerve.

The Edinger-Westphal Nuclei

When there is isolated damage to the Edinger-Westphal nuclei, bilateral pupillary abnormalities are the rule. Most lesions in this region that produce pupillary abnormalities also affect other parts of the oculomotor nucleus, causing ptosis, ophthalmoparesis, or both.

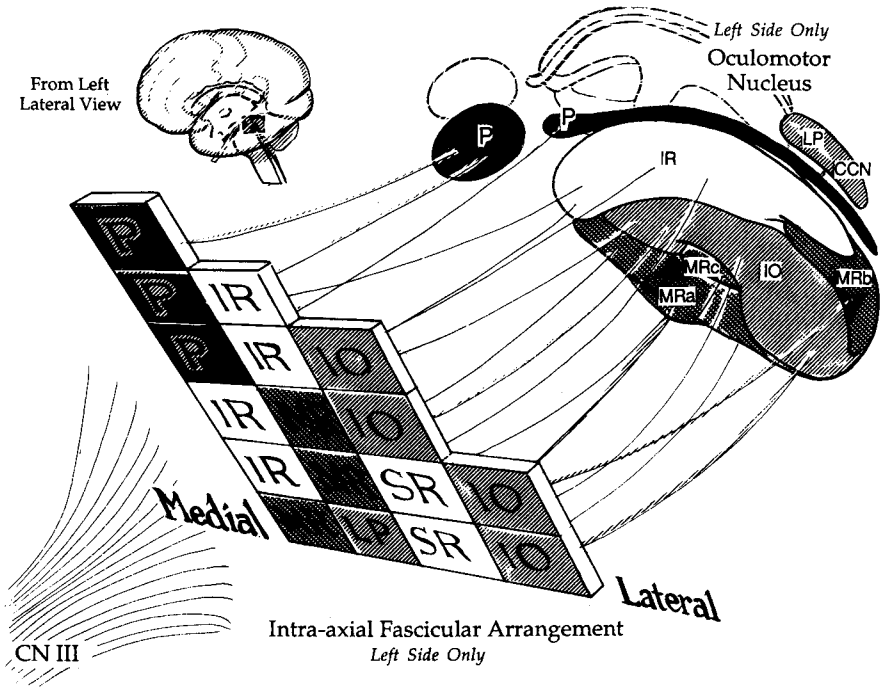

Figure 16.15. Position of the pupillomotor fibers in the fascicle of the human oculomotor nerve. The fibers destined to innervate the iris sphincter muscle (P) are located rostral and medial to the fibers that innervate the extraocular muscles and the levator palpebrae superioris (LP). IO, inferior oblique; IR, inferior rectus; MR, medial rectus; SR, superior rectus; MRa, MRb, and MRc, subnuclei serving medial rectus function in the oculomotor nuclear complex; CCN, central caudal nucleus. (From Ksiazek SM, Slamovits TL, Rosen CE, et al. Fascicular arrangement in partial oculomotor paresis. Am J Ophthalmol 1994;118:97–103.)

Pupillomotor Fascicle of the Oculomotor Nerve

Because the fibers emerging from the Edinger-Westphal nucleus are among the most rostral of the oculomotor fascicles in the midbrain tegmentum, it is possible for a lesion to selectively damage the parasympathetic fibers (213) (Fig. 16.15). Indeed, a unilateral fixed and dilated pupil or bilateral internal ophthalmoplegia may be the sole clinical manifestation of a fascicular oculomotor nerve palsy due to a rostral midbrain lesion (214,215). The fascicular oculomotor nerve can be damaged by a variety of processes, including ischemia, hemorrhage, inflammation, and infiltration. Such processes often involve other structures in the rostral mesencephalon, leading to an oculomotor palsy associated with other neurologic signs such as contralateral hemiparesis or tremor. These well-recognized syndromes are considered in Chapter 20.

Pupillomotor Fibers in the Subarachnoid Portion of the Oculomotor Nerve

As the separate fascicles of the oculomotor nerve exit the mesencephalon, they merge to form one oculomotor nerve trunk in the interpeduncular fossa. The oculomotor nerve passes between the posterior cerebral and superior cerebellar arteries and courses anteriorly to the cavernous sinus. In this part of the oculomotor nerve pathway, the pupillary fibers are superficially located and migrate from a superior medial position to the inferior part of the nerve (216). The location of the pupil fibers makes them particularly susceptible to infectious injury from basal meningitis and direct compression from aneurysms, tumors, and uncal herniation. Basal meningitis (bacterial, fungal, tuberculosis) can produce unilateral or bilateral poorly reactive pupils with complete or relative sparing of the extraocular muscles (217,218). In addition, hemosiderin deposits along the superficial surfaces of the cranial nerves from recurrent blood in the cerebrospinal fluid (CSF) can cause pupillary dysfunction and hearing loss in patients with superficial siderosis (219).

An expanding aneurysm is always a feared potential cause of a large and poorly reactive pupil. However, aneurysms at the junction of the internal carotid artery and the posterior communicating artery that compress the oculomotor nerve nearly always produce some extraocular muscle or eyelid dysfunction, even if such involvement is subtly or variably present, in addition to the pupil impairment. In the oft-quoted case of Payne and Adamkiewicz, a 35-year-old woman developed an acute unilateral internal ophthalmoplegia as the ''principal feature'' of a posterior communicating artery aneurysm (220). It was, however, not the sole manifestation of her aneurysm: she had noticed slight drooping of her eyelid 6 months previously. At the time her pupil became dilated, a ''slight'' and inconstant ptosis was noted. A preexisting strabismus made difficult the possible detection of any subtle extraocular muscle dysfunction. It appears that a dilated and poorly reactive pupil in isolation is rarely due to an aneurysm, and in the case where it is, it is more likely due to an aneurysm of the tip of the basilar artery than an aneurysm of the internal carotid artery (221,222).

Occasionally, intrinsic lesions of the oculomotor nerve in the subarachnoid space produce only an internal ophthalmoplegia. In two cases of an oculomotor nerve schwannoma in the interpeduncular fossa, an isolated dilated pupil and reduced accommodation were the sole manifestations of the tumor for 1 year or longer, before ptosis and external ophthalmoplegia appeared (223,224).

Cavernous Portion of the Oculomotor Nerve

The pupillomotor fibers are located inferiorly and superficially in the portion of the oculomotor nerve located within the cavernous sinus. Any lesion of the cavernous sinus can potentially compress and damage the oculomotor nerve and the pupil fibers. When oculosympathetic fibers in the cavernous sinus are damaged as well, the pupil light reflex may be sluggish, but there may not be an apparent change in the resting pupil size (i.e., there may be no anisocoria) (184).

Damage to the Ciliary Ganglion and Short Ciliary Nerves: The Tonic Pupil

Any injury to the ciliary ganglion or the short ciliary nerves in the retrobulbar space or in the intraocular, suprachoroidal space will cause internal ophthalmoplegia. Within a few days, cholinergic supersensitivity may develop. These findings are due to denervation of the iris sphincter and ciliary muscle. In some cases, denervation is the only pathologic process; when permanent, it results in unilateral paralysis of accommodation and a dilated pupil that reacts poorly to light and near stimulation but constricts well to weak topical pilocarpine. In others, denervation is followed by subsequent reinnervation (both appropriate and aberrant) of the iris muscles that results in recovery of accommodation, a pupillary response to near stimuli that is unusually strong and tonic, and redilation after constriction to near stimuli that is delayed and slow. These are the characteristic features of a tonic pupil (Fig. 16.16). Tonic pupils are generally divided into three categories: local, neuropathic, and Adie syndrome (225,226).

LOCAL TONIC PUPILS

This type of tonic pupil, typically unilateral, is due to orbital or systemic lesions that affect the ciliary ganglion or short ciliary nerves in isolation. Disorders that have been reported to cause this type of ''local'' tonic pupil include herpes zoster, chickenpox, measles, diphtheria, syphilis (both congenital and acquired), Lyme disease, sarcoidosis, scarlet fever, pertussis, smallpox, influenza, sinusitis, Vogt-Koyanagi-Harada syndrome, rheumatoid arthritis, polyarteritis nodosa, giant cell arteritis, migraine, lymphomatoid granulomatosis, viral hepatitis, choroiditis, primary and metastatic choroidal and orbital tumors, blunt injury to the globe, intraocular siderosis from foreign body, and penetrating orbital injury (227–237). In some of these cases, the tonic pupil may have occurred as happenstance. In others, ancillary testing such as MR imaging or orbital color Doppler imaging have demonstrated clear abnormalities at the ciliary ganglion, suggesting local injury related to the primary systemic disease process (238,239).

Various ocular or orbital surgical procedures, including retinal reattachment surgery, inferior oblique muscle surgery, orbital surgery, optic nerve sheath fenestration, retinal photocoagulation, argon laser trabeculoplasty, transconjunctival cryotherapy, transscleral diathermy, retrobulbar injections of alcohol, and even inferior dental blocks, can cause denervation injury (iridoplegia and cycloplegia) and a ''local'' tonic pupil (240–247).

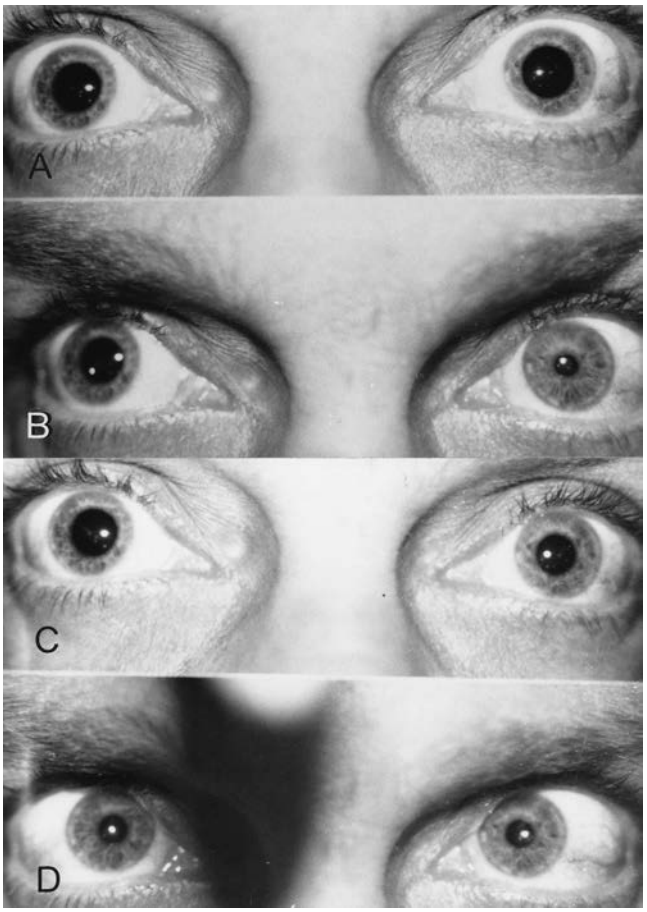

Figure 16.16. Tonic pupil syndrome. About 4 months earlier, this 38-year-old man noted that his right pupil was larger than his left pupil. *A*, In the dark looking in the distance, both pupils are dilated and relatively equal in size. *B*, In bright light, the right pupil does not constrict, whereas the left pupil constricts normally, producing a marked anisocoria. *C*, In room light looking in the distance, there is a moderate anisocoria. *D*, During near viewing, however, both pupils constrict. The right pupil constricted much more slowly than the left and redilated slowly.

NEUROPATHIC TONIC PUPILS

This type of tonic pupil, usually with bilateral involvement, represents one manifestation of a widespread, peripheral, and autonomic neuropathy that also involves the ciliary ganglion, the short ciliary nerves, or both (248). In some cases, there is evidence of both a sympathetic and a parasympathetic disturbance. These include syphilis, chronic alcoholism, diabetes mellitus, amyloidosis, systemic lupus erythematosus, Sjögren syndrome, some of the spinocerebellar degenerations, hereditary motor-sensory neuropathy (Charcot-Marie-Tooth disease), Landry-Guillain-Barré syndrome, and the Miller Fisher syndrome (249–254). Dysautonomias associated with tonic pupils are subacute autonomic neuropathy, Shy-Drager syndrome, and Ross syndrome. Tonic pupils can occur from the distant effects of cancer, occurring either as an isolated phenomenon or as part of a more extensive paraneoplastic autonomic polyneuropathy (255,256).

They also may develop in patients with trichloroethylene intoxication (257).

ADIE (HOLMES-ADIE) TONIC PUPIL SYNDROME

Adie syndrome is an uncommon, idiopathic condition that may develop in otherwise healthy persons and in patients with unrelated conditions. It nearly always occurs as a sporadic entity, although it has been described in three sisters and in twins (258,259). Such reports are simply too rare to suggest any hereditary origin. Adie syndrome is rare before age 15 years (260,261). In a child, secondary causes of a tonic pupil should be ruled out first, and then attention should be directed to management of the anisometropia to avoid amblyopia (262).

Most patients with Adie syndrome are 20–50 years of age. Although the syndrome occurs in both sexes, there is a clear predilection for women (about 70% of cases). Adie syndrome is unilateral in about 80% of cases. When the condition is bilateral, the onset occasionally is simultaneous but usually occurs in separate episodes months or even years apart (263).

Historical Background. William Adie's name most often is associated with the syndrome of tonic pupil and benign areflexia, but he was not the first to describe the syndrome or its features. The earliest description of a tonically reacting pupil was by Piltz, who mentioned the occurrence of a bilateral, tonic light reflex in patients with general paresis (264). Gordon Holmes published a series of 19 cases and reviewed the previous literature on the subject just before the publications of his student William Adie (265). In the United Kingdom, therefore, this condition is called the Holmes-Adie syndrome.

Clinical Characteristics. *Symptoms.* Around 80% of patients with Adie syndrome have visual complaints, usually related to the iridoplegia. These include photophobia and difficulty with dark adaptation (266). Symptoms related to ciliary muscle dysfunction are blurred near vision and brow ache or headache with near work. Over time, the dilated pupil becomes smaller and accommodation improves; however, some patients continue to have difficulty focusing. Such patients can see clearly at rest for both distance and near; however, they experience visual blur when shifting fixation from near to distance (tonicity of accommodation). This is particularly troublesome if the unaffected eye has poor vision from other causes.

If, some years later, the other eye also develops a tonic pupil, the condition seems to produce far fewer symptoms and may even pass unnoticed. This is in part because both eyes are now affected and because the patient has become presbyopic in the interim; therefore, less accommodative difference is induced between the two eyes.

Although patients with Adie syndrome not uncommonly have abnormal tests of autonomic function, they are relatively asymptomatic. Symptoms may include chronic cough, abnormal sweating, or postural dizziness (267,268).

Sectoral Palsy of the Iris Sphincter. As mentioned above, the pathophysiology of an Adie pupil is acute denervation followed by appropriate and inappropriate reinnervation of the ciliary body and iris sphincter. The clinical findings depend in part on the stage of evolution in which the pupil is examined. Acutely following a denervation injury, there is an internal ophthalmoplegia. The pupil is markedly dilated and appears unresponsive to light or near stimulation. At this stage, it often is confused with a pharmacologically induced mydriasis and cycloplegia. However, a careful slit-lamp examination using a bright light usually reveals segmental contractions of the iris sphincter (Fig. 16.16). These segmental contractions to bright light represent remaining areas of normally innervated iris sphincter. Under the slit lamp, the iris segments that contract are seen to tighten and bunch up like a purse-string bag being closed. Conversely, in denervated segments, the iris stroma appears thin and flat. The adjacent pupillary ruff is meager, and the radius of curvature of the pupil margin is flatter. These denervated segments do not contract to a bright light, but the radial markings of the stroma in these denervated segments show a ''streaming'' movement that is caused by mechanical pull from normally contracting segments. These findings are characteristic of sectoral palsy of the iris sphincter (Fig. 16.17). Sectoral palsy of the iris sphincter is a critical diagnostic observation, present in about 90% of Adie pupils. In these cases, the amount of sphincter palsy (estimated in clock-hour segments around the pupil margin) is 70% or more, so detection requires attentive observation of each clock-hour segment (269). Sectoral palsy is not seen with pharmacologic anticholinergic blockade, which paralyzes 100% of the sphincter. About 10% of Adie pupils also have no segmental contraction to bright light (100% sphincter palsy), at least not acutely.

The ''vermiform movements'' of the iris in Adie syndrome probably represent spontaneous pupillary unrest, or hippus, in normally innervated segments of the sphincter and are essentially the same as segmental contractions of the iris. In a rare patient with Adie tonic pupil in one eye, the ciliary muscle in the other eye suddenly shows evidence of dysfunction, even though the pupillary light and near reactions appear normal (272). This probably is a limited form of Adie syndrome.

Accommodative Paresis. In most patients with Adie syndrome, the acute accommodative paresis is moderate to severe because of ciliary muscle denervation and paralysis. Accommodation gradually improves over several months as injured axons begin to regenerate and reinnervate the ciliary muscle. Most of the recovery occurs in the first 2 years after the acute injury.

Aberrant Reinnervation of the Iris Sphincter. In the acute stage, both the pupil light reflex and pupillary constriction to near effort are equally and severely impaired. After several weeks or months, the near response of the pupil begins to increase in amplitude while the light response remains severely impaired (light–near dissociation). However, the pupil movement now is distinctly different than normal. The pupil constriction to a near effort is strong, slow, and sustained (tonic near response). In addition, the redilation movement after cessation of near effort is equally slow and sustained, delaying visual refocus by several seconds (tonicity of accommodation). These findings are caused by aber-

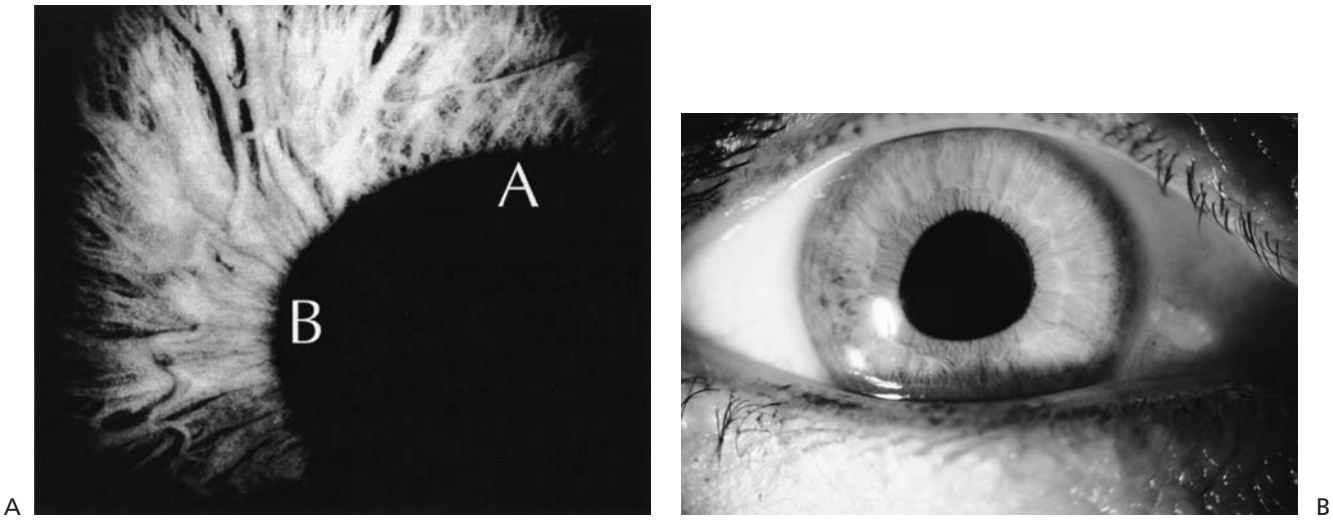

Figure 16.17. Segmental palsy of the iris sphincter in Adie tonic pupil syndrome. *A,* One part of the iris sphincter is denervated and does not react to light. Another segment (*B*) of the iris sphincter constricts to light in this irregularly shaped Adie tonic pupil. *B,* In another case, the area of iris sphincter between 12 and 4 o'clock demonstrates intact pupillary ruff and puckering of the iris stroma consistent with active contraction in this segment, but most of the remainder of the iris sphincter is denervated. The pupillary ruff is mostly absent, the iris stroma is less dense, and the radius of pupil curvature is flatter in this area, particularly between 5 and 7 o'clock and between 8 and 12 o'clock (sectoral palsy). (Courtesy of Dr. F-X Borruat.)

rant reinnervation of the iris sphincter by regenerating accommodative fibers.

Warwick and others showed that the pupillomotor fibers to the iris sphincter constitute about 3% of the total number of postganglionic neurons that leave the ciliary ganglion, whereas the remaining 97% of neurons innervate the ciliary muscle (271). Thus, when the ciliary ganglion is injured, there is a numerically greater chance of survival of cells serving accommodation compared with those serving pupil constriction. In 1967, Loewenfeld and Thompson suggested that the fibers of these surviving cells, originally destined for the ciliary muscle, resprouted randomly, with some of the fibers reaching and reinnervating their appropriate target, the ciliary muscle (272). This explained the recovery of accommodation over time. Other resprouting fibers, however, mistakenly reinnervated the iris sphincter. Thus, pupil constriction also recovered, but only as a misdirection synkinesis. When the patient made a near effort, the accommodative impulses stimulated both ciliary muscle and iris sphincter activity (Fig. 16.18). The long latency and slow, prolonged contraction of the iris sphincter were thought to be related to its inappropriate reinnervation and its cholinergic supersensitivity (272,273).

The light reflex of a tonic pupil remains impaired. Furthermore, in about one third of patients, more segments of sphincter become increasingly impaired over time, suggesting that the degenerative changes in the ciliary ganglion are progressive. Besides being less numerous in quantity, perhaps pupillary fibers have an inherently greater susceptibility to the primary insult that causes these degenerative changes. In any event, it is clear that the pupillary light–near dissociation of a tonic pupil results from impairment of the light reflex with restoration of the near reflex and not from sparing of near reflex fibers, as occurs in some dorsal midbrain lesions.

Decreased Corneal Sensation. Purcell et al. used the Cochet-Bonnet aesthesiometer to demonstrate a regional decrease in corneal sensation in 10 of 11 patients with unilateral Adie syndrome (acute and chronic), consistent with the theory that the lesion in Adie syndrome is located in the ciliary ganglion or short ciliary nerves (275). Interestingly, the areas with reduced sensation did not correlate to the extent or distribution of the iris sphincter denervation.

Absent Muscle Stretch Reflexes. Deep-tendon hyporeflexia or areflexia can be demonstrated in almost 90% of patients with Adie syndrome. As is the case with the pupil light reflex, there can be progressive loss of reflex activity over time. The reflexes of the upper extremities are abnormal almost as often as the reflexes of the lower extremities (226).

Electrophysiologic studies suggest that the cause of areflexia is loss of large-diameter afferent fibers or impairment in their synaptic connections to motor neurons (275–277). Histopathologic studies in patients with Adie syndrome have demonstrated moderate degeneration of both axons and myelin sheaths in the fasciculus gracilis and fasciculus cuneatus (278,279). The dorsal and ventral roots appeared normal, as did the remaining spinal cord. There appears to be a degeneration of cell bodies in the dorsal root ganglia similar to that which occurs in the ciliary ganglion (280).

Cholinergic Denervation Supersensitivity. In 1940, Adler and Scheie reported that the tonic pupil of patients with Adie syndrome constricted intensely to 2.5% methacholine chloride (due to cholinergic supersensitivity), whereas normal pupils did not (281) (Fig. 16.19). Later studies demonstrated large interindividual variability of pupil responses such that it was subsequently dropped as a test for tonic

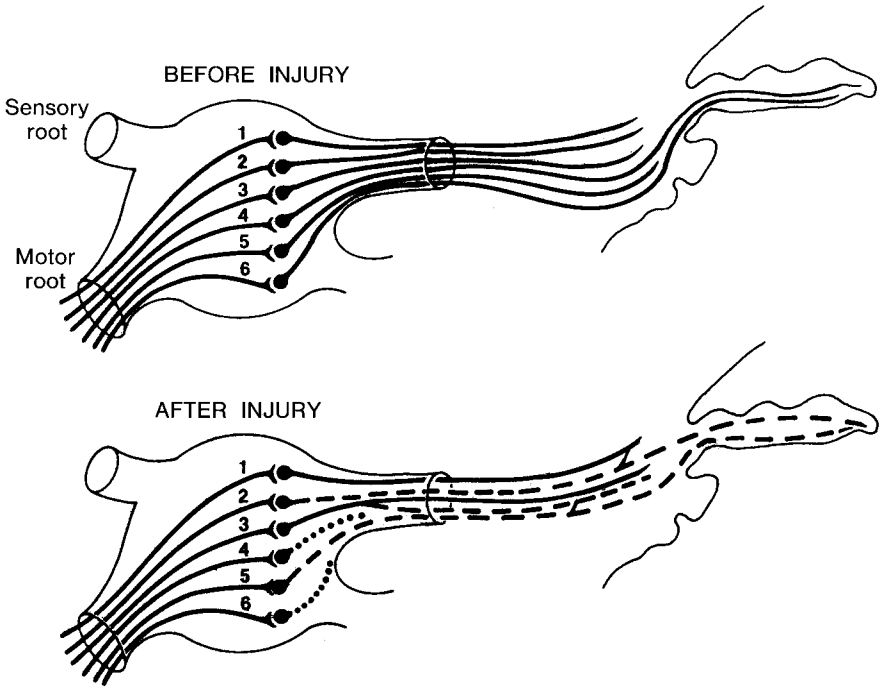

Figure 16.18. Misregeneration theory as it pertains to the findings in the tonic pupil syndrome. *Top,* Before injury, most of the fibers in the ciliary ganglion are destined for the ciliary muscle to produce accommodation. *Bottom,* Following injury, it is more likely that a regenerating postganglionic fiber will be one for accommodation; however, many of these fibers send branches or collaterals to the iris, producing pupillary constriction during attempted accommodation-convergence. In this drawing, postganglionic fiber 1, for accommodation, has not been injured; fibers 2 and 5, also accommodative, have regenerated, sending sprouts to both the ciliary muscle and the iris sphincter; fiber 3, for pupillary constriction, has sent a sprout to the ciliary muscle via the remaining nerve sheath of fiber 4, which has been damaged; fiber 6, for pupillary constriction, has been destroyed and has not regenerated. Thus, accommodation and pupillary constriction will occur primarily on attempted accommodation-convergence.

pupils (282). Instead, dilute pilocarpine (0.1% or less) has become the most popular pharmacologic agent for demonstrating cholinergic denervation supersensitivity of the iris sphincter (283,284). A 0.1% pilocarpine solution can be prepared in a syringe from 1 part commercially available 1% pilocarpine and 9 parts normal saline, although bacteriostatic water also can be used and may have less constricting effect on a normal iris sphincter (285). The criterion for diagnosing cholinergic supersensitivity has been proposed as either (*a*) the affected pupil constricts 0.5 mm more than the unaffected pupil under dim ambient lighting or (*b*) the suspected pupil that is larger than the normal pupil before instillation of pilocarpine becomes the smaller pupil after instillation of pilocarpine (286). Cholinergic supersensitivity develops quickly, usually within days after injury. About 80% of tonic pupils demonstrate cholinergic supersensitivity; the test result is influenced by intersubject variability, differential corneal penetration, mechanical influence of the iris stroma (how small the pupil is at baseline), and the state of reinnervation.

As preganglionic injury can also produce end-organ supersensitivity, oculomotor nerve palsy can also cause a ''positive'' pilocarpine test. Furthermore, the degree of cholinergic supersensitivity is about the same in patients with

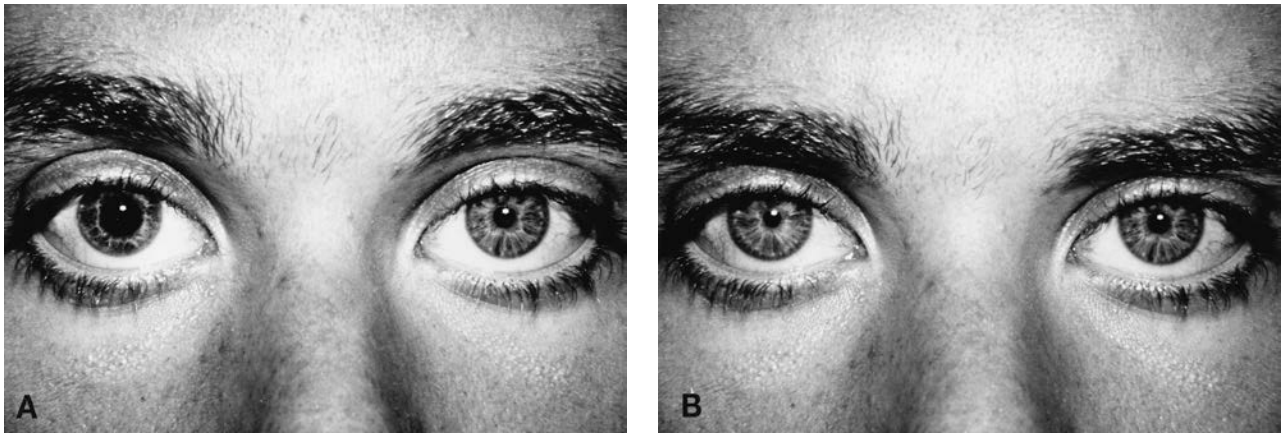

Figure 16.19. *A,* A right tonic pupil in a 36-year-old woman. *B,* 45 minutes after conjunctival instillation of two drops of 0.1% pilocarpine solution in each eye, the right pupil is constricted and nonreactive. The left pupil remains unchanged and normally reactive.

oculomotor nerve palsies and patients with Adie pupils (287).

Ciliary muscle supersensitivity also can be established by measuring the near point of accommodation before and after instillation of dilute pilocarpine, but only if the patient is under age 45 years and has normal accommodation in the normal eye.

Long-Term Features and Prognosis. Several features of Adie syndrome change over time. Accommodation recovers significantly over a year or two. The size of the tonic pupil decreases by 2–3 mm or more over several years (Fig. 16.20). In some patients, it can become the smaller pupil, even in room light, and bilateral cases of chronic Adie pupils can be mistaken for Argyll Robertson pupils (288). The explanation for the progressive miosis in Adie syndrome was proposed by Kardon et al., who used infrared transillumination to evaluate the distribution of segmental iris sphincter reactivity under various stimulus conditions (289). In darkness, reinnervated segments of the sphincter appeared ''denser'' under transillumination compared with normal pupils and became even denser with near effort (i.e., during active contraction). This finding suggested that in darkness, a tonic pupil has a constant volley of low-level impulses from accommodative neurons that keeps reinnervated segments of iris sphincter in a greater state of contraction compared with a normally innervated sphincter that receives no parasympathetic impulses in darkness. In addition, the number and extent of reinnervated segments appear to increase with time. Both of these phenomena probably contribute to the decreasing size of a tonic pupil (Fig. 16.21). Additionally, the active reinnervation process apparently prevents development of iris atrophy, a feature not typically found in chronic Adie syndrome.

Kardon et al. also demonstrated that the degree of cholinergic sensitivity decreases as reinnervation increases (289). Denervated segments that are unreactive to light and near stimulation show an intense increase in density following dilute pilocarpine. However, as these segments are reinnervated and become reactive to near effort, they become less reactive to the pilocarpine.

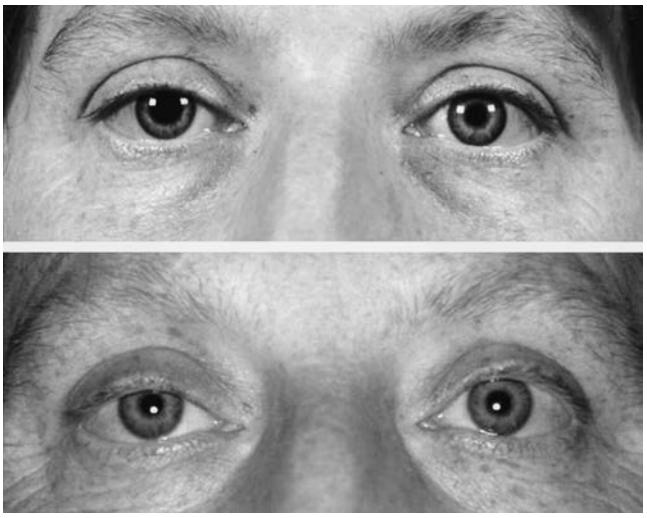

Figure 16.20. Changes in size of an Adie tonic pupil over time. *Top,* Appearance of an acute right-sided Adie pupil in a 33-year-old woman. *Bottom,* Appearance of the same patient 10 years later. The right pupil has become smaller in resting size so that in ambient lighting, there is no apparent anisocoria. (Courtesy of Dr. F-X Borruat.)

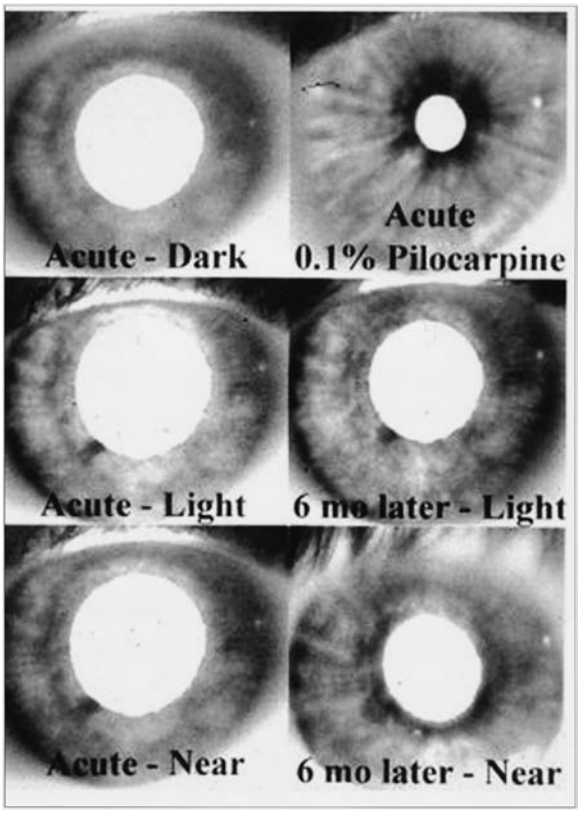

Figure 16.21. Six infrared transillumination views of the same iris in a patient with an acute Adie pupil affecting all but one of the segments. The middle and lower photographs on the right are from the same eye 6 months later. The photographs of the left side show that there is only one small segment (the dense area at the pupil border at the 7 o'clock position) that still contracts appropriately to light and near. This example was chosen because all the rest of the iris sphincter has been denervated so that the changes in density of the remaining, normally reacting segment can be discerned in darkness, in light and at near. In the ''acute-dark'' photograph (*top left*), the area of the 7 o'clock position cannot be seen but becomes dense in response to light stimulation (*middle left*, ''acute-light'') and in response to near stimulation (*bottom left*, ''acute-near''). The change in the sphincter also is shown in response to low-concentration pilocarpine (*top right*). All of the denervated segments show an increase in density after 0.1% pilocarpine, except for the one segment that normally is innervated and, therefore, presumably not supersensitive, which appears translucent at the 7:30 position (*top right,* ''acute 0.1% pilocarpine''). This same patient was examined 6 months later (*right side, middle and bottom photographs*), and the results show a light–near dissociation with an increase in density on near response. The pupil is slightly smaller in light than in the acute state because of some sustained firing of accommodative fibers that have started to reinnervate the sphincter areas. (From Kardon RH, Corbett JJ, Thompson HS. Segmental denervation and reinnervation of the iris sphincter as shown by infrared videographic transillumination. Ophthalmology 1998;105:313–321.)

The light reaction of the Adie pupil generally does not recover. Like the muscle-stretch reflexes, it deteriorates further with passing years in most patients.

Patients with unilateral Adie syndrome tend to develop a tonic pupil in the opposite eye with time. This occurs in about 4% of cases per year (263). Overall, this is a benign condition; however, in some patients with shallow anterior chamber angles, an acute tonic pupil can precipitate an attack of angle-closure glaucoma (50,290).

TREATMENT

Weak solutions of eserine or pilocarpine can be used to constrict a tonic pupil for relief of photophobia and for cosmetic purposes (reduction of anisocoria, especially in patients with light-colored irides) (291,292). Most patients do not need this treatment for very long because within a year or two, the tonic pupil becomes smaller in size and in dim light, and it soon is the smaller of the two pupils (293). For symptoms related to abnormal accommodation, a bifocal add usually suffices, even if it is not yet needed by the unaffected eye.

Damage to the Iris Sphincter

Tears in the iris sphincter or the iris base may occur from blunt trauma to the eye. Such damage may produce a nonreactive or poorly reactive irregularly dilated pupil that may be mistaken for the dilated pupil of an oculomotor nerve palsy, particularly if the patient is lethargic or comatose from the injury. In most cases, careful examination of the dilated pupil with a hand light reveals subtle irregularities in its normally smooth contour, and the iris tears or dialysis are easily observed using a standard or portable slit lamp (Fig. 16.2).

Pharmacologic Blockade with Parasympatholytic Agents

A fixed dilated pupil can be caused by topical administration of one of several parasympatholytic agents, many of which are described in the section on drug effects. It suffices here to emphasize that such agents block the action of acetylcholine on the iris sphincter and ciliary muscles, that they produce both mydriasis and cycloplegia, and that the mydriasis produced by such drugs is extreme, usually more than 8 mm. It is necessary to differentiate a pupil that is pharmacologically dilated from one that is neurologically dilated. Thompson et al. suggested using a 0.5–1% solution of pilocarpine for this task (294). A pupil that is dilated from pharmacologic blockade of the sphincter will be unchanged or poorly constricted by a topical solution of pilocarpine strong enough to constrict the opposite pupil (Fig. 16.22), whereas a tonic pupil that constricts to weak solutions of pilocarpine because of denervation supersensitivity should certainly constrict to 0.5–1% pilocarpine. A pupil that is dilated from oculomotor nerve dysfunction also will constrict well after instillation of pilocarpine.

Pharmacologic Stimulation of the Iris Dilator

Topical cocaine placed in the nose for medical or other reasons can back up the lacrimal duct into the conjunctival sac. Most eye-whitening drops that contain sympathomimetic components are too weak to dilate the pupil, but if the cornea is abraded (e.g., by a contact lens) enough of the oxymetazoline or the phenylephrine in the solution may get into the aqueous humor to dilate the pupil. In addition, mists containing adrenergic or anticholinergic drugs for bronchodilation may escape around the edge of the facemask and condense in the conjunctival sac, inadvertently causing unilateral pupillary dilation.

Anisocoria Due to Sympathetic Hyperactivity

Sympathetic hyperactivity occurs in a number of settings, usually as an episodic phenomenon. In several of these settings, the pupils are affected, and in cases of unilateral or asymmetric oculosympathetic hyperactivity, there may be an anisocoria.

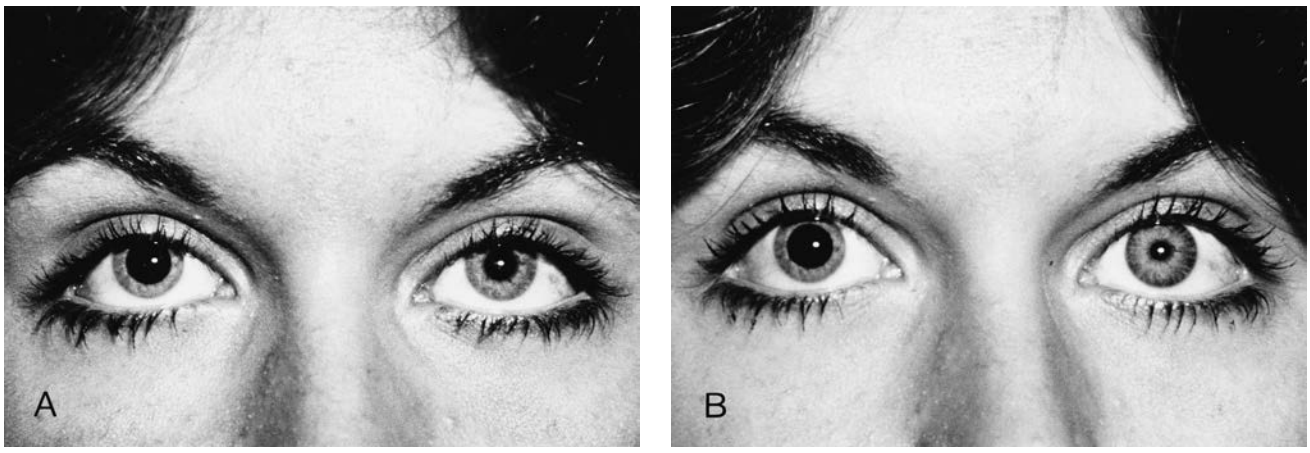

Figure 16.22. Pharmacologically dilated pupil. *A*, Fixed, dilated right pupil in an 18-year-old woman complaining of headache and blurred vision. *B*, 45 minutes after conjunctival instillation of two drops of 1% pilocarpine in each eye, the right pupil is unchanged, whereas the left pupil is markedly constricted. The patient subsequently admitted having placed topical scopolamine in the right eye.

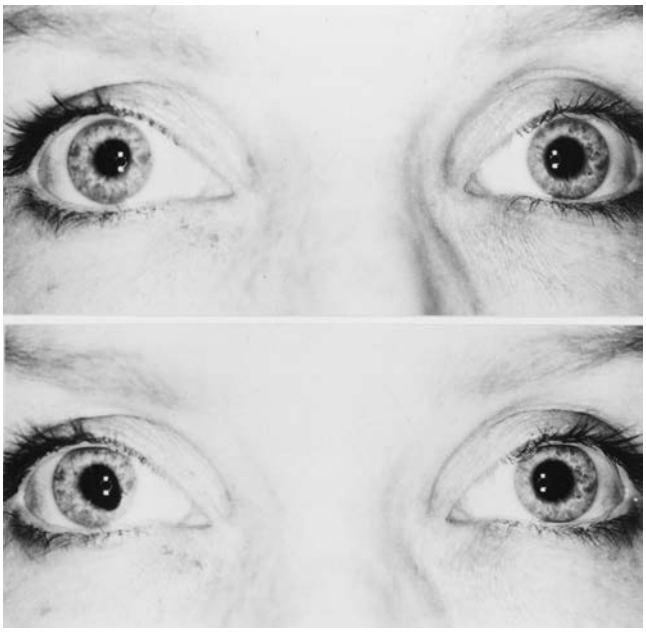

Figure 16.23. Tadpole pupil. *Top*, Before the episode, the pupils are normal in size and shape. *Bottom*, During the episode, the right pupil develops an eccentric shape, with the 5 o'clock portion of the pupil being displaced outward. (From Thompson HS, Zackon DH, Czarnecki JSC. Tadpole-shaped pupils caused by segmental spasm of the iris dilator muscle. Am J Ophthalmol 1983;96:467–477.)

Tadpole-Shaped Pupils

An occasional patient reports that the pupil of one eye becomes distorted for a minute or two. In most cases, the eye feels ''funny'' and the vision in the eye becomes slightly blurred. Looking in the mirror reveals that the pupil is pulled in one direction like the tail of a tadpole, hence the term ''tadpole pupil'' (Fig. 16.23). Often patients describe the direction of the tadpole tail to be different on different occasions. This phenomenon usually occurs many times a day for several weeks, spontaneously remits, and then recurs several months later. Eventually, the condition abates and does not recur (295).

The etiology of tadpole pupils is unclear. Presence of an intact pupil light reflex suggests dilator spasms rather than sphincter paresis. In a review of 26 cases, Thompson et al. noted that 11 patients (42%) also had a partial postganglionic Horner syndrome on the affected side (295). The authors postulated that repeated bursts of sympathetic impulses asymmetrically pulled one segment of the iris toward the limbus and that this repeated irritation eventually could have caused loss of fibers and the Horner syndrome. Thus, testing for Horner syndrome is recommended for patients who give a history of episodic tadpole-shaped pupils (296), even if there is no anisocoria at the time of the examination.

Another mechanism may be responsible for tadpole pupils in the setting of a congenital Horner syndrome. Tang reported the case of a young man with a hypoplastic right internal carotid artery and ipsilateral congenital Horner syndrome who experienced exercise-induced pupillary distortion of the right pupil (297). The same segment of the iris always dilated after strenuous exercise, and it was the same area that failed to dilate with hydroxyamphetamine. In this case, the tadpole pupil presumably resulted from local supersensitivity of a denervated segment of the iris dilator muscle, occurring at moments when the level of circulating catecholamines was increased.

Aberrant regeneration causing segmental spasm of the iris dilator

An iris dilator–deglutition synkinesis resulting in episodic segmental dilator contraction was described in a young boy with Horner syndrome and paresis of the glossopharyngeal, vagus, and hypoglossal nerves (Villaret-like syndrome) following resection of a neuroblastoma in his right upper neck during infancy (298). Later, he had focal dilator spasms of his right pupil that resulted in an elliptical pupil (Fig. 16.24) and were associated with swallowing. Presumably, this dilator–deglutition synkinesis was caused by aberrant vagal nerve sprouts that made an inappropriate synaptic connection at the superior cervical ganglion.

Pourfour du Petit Syndrome

This syndrome is the clinical opposite of Horner syndrome. It represents oculosympathetic overactivity instead of underactivity and usually is caused by lesions along the

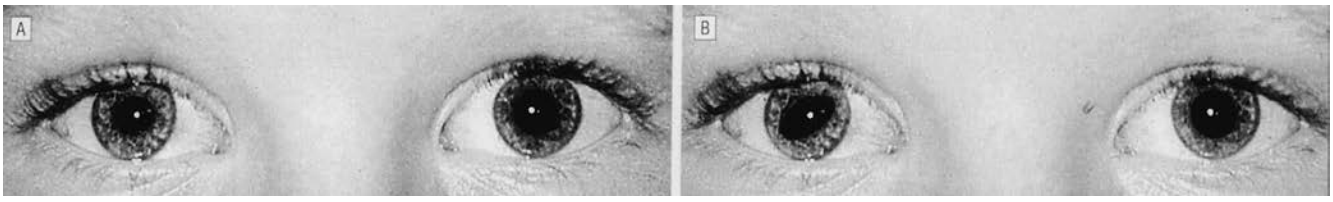

Figure 16.24. Iris dilator–deglutition synkinesis causing segmental iris dilator muscle contraction in 10-year-old boy with a long-standing right Horner syndrome. *A*, The child has a right Horner syndrome that had been present since removal of a cervical neuroblastoma when he was 6 days old. At age 2 years, his parents first noted that while he was drinking, his right pupil would become transiently distorted in shape. *B*, Appearance of the pupils during the act of swallowing. There is segmental dilation of the right pupil at the 1 o'clock and 7 o'clock positions, causing a distorted pupil. The dilation occurs only when the child is swallowing. (From Boehme BI, Graef MH. Acquired segmental iris dilator muscle synkinesis due to deglutition. Arch Ophthalmol 1998;116:248–249.)

cervical sympathetic chain. The clinical signs are unilateral mydriasis, lid retraction, apparent exophthalmos, and conjunctival blanching, all of which may be episodic or constant. The phenomenon is rare and has been described after trauma, brachial plexus anesthetic block or other injury, and parotidectomy and in patients with tumors of the pleural lining or mediastinum (299,300). The oculosympathetic hyperactivity sometimes precedes the development of a Horner syndrome. Presumably, the lesion first irritates the sympathetic fibers and later damages them.

Sympathetic Hyperactivity and Spinal Cord Lesions

Autonomic hyperreflexia is a phenomenon seen in quadriplegic patients who have experienced severe spinal cord injury. It usually appears weeks to months after the acute injury and results from absent cerebral control of the spinal sympathetic neurons that leads to paroxysms of sympathetic hyperactivity that either occur spontaneously or are triggered by nonspecific stimuli below the level of cord injury (301). Occasionally, the oculosympathetic pathway is affected unilaterally or a patient undergoes a local anesthetic procedure that blocks sympathetic activity on one side, making evident the eye findings of autonomic hyperreflexia as episodes of unilateral mydriasis, blurry vision, and lid retraction on the unanesthetized side (302,303). In other patients, passive arm or leg stretching or limb movement can induce a transient asymmetric mydriasis. This may represent a localized form of autonomic hyperreflexia (oculosympathetic spasm) that occurs in response to proprioceptive impulses that ascend to reach the damaged area of the spinal cord (160).

Oculosympathetic hyperactivity has been reported after a relatively minor cord injury. Saito and Nakazawa described a young man who sustained a whiplash injury in a car accident and shortly thereafter developed episodes of unilateral mydriasis (304). The episodes lasted several hours to a few days and occurred once or twice a week. The patient had no other neurologic deficits. Radiographic studies revealed slight narrowing of the disc space at the C5–C6 level. Pharmacologic testing suggested that the mydriasis was caused by episodic sympathetic irritation.

An ''alternating Horner syndrome'' has been reported in patients with lower cervical and upper thoracic cord lesions and in some patients with primary dysautonomia, such as the Shy-Drager syndrome (see below). Some authors believe that it results from a transient oculosympathetic deficit that changes sides at intervals of 2 hours or 2 weeks (157,158,305); however, Moniz and Czarnecki studied pharmacologically two patients with this phenomenon and concluded that the clinical findings also could be explained by a unilateral lesion that causes alternating oculosympathetic hypofunction and hyperfunction (161).

Other Anisocorias

Anisocoria in Lateral Gaze: The Tournay Phenomenon

In 1907, Gianelli noted that when some normal persons look in extreme lateral gaze, the pupil on that side becomes larger and the pupil on the opposite side becomes smaller (306). Gianelli hypothesized that this phenomenon resulted from mechanical traction caused by movement of the globe that stimulated the long ciliary nerves in abduction and the short ciliary nerves in adduction. Tournay independently made similar observations, emphasizing the dilation of the pupil ipsilateral to the direction of gaze, and later recognized Gianelli as the first to observe this phenomenon (307,308). Nonetheless, an anisocoria that develops on extreme lateral gaze is called the Tournay's phenomenon. Sharpe and Glaser studied 25 normal subjects and 5 patients with Duane retraction syndrome by direct observation, photography, and infrared electronic pupillography (309) and could not demonstrate anisocoria in lateral gaze in any of the subjects (309). Loewenfeld et al. examined 150 normal subjects using infrared flash photography and concluded that the Tournay phenomenon does exist but that its prevalence is low and its extent small (e.g., less than 10% of subjects showed a change in anisocoria greater than 0.3 mm) (310). Loewenfeld postulated that the Tournay phenomenon results from ''straying'' of impulses that were meant for the medial rectus subnucleus to the nearby Edinger-Westphal nucleus (119). This would cause slight constriction of the pupil when the eye adducts and relative dilation of the pupil when the medial rectus subnucleus is inhibited during abduction. Whatever the explanation, it is reasonable to conclude that the Tournay phenomenon is relatively uncommon and has little or no clinical significance.

Anisocoria During Migraine Headache

The best-known association of an anisocoria and vascular headache is the cluster headache syndrome mentioned previously. This section deals with those occasional patients who report having one dilated pupil or unequal-sized pupils only during a classic or common migraine headache attack. The induced anisocoria generally is rather small but ranges from 0.3 mm to 2.5 mm (Fig. 16.25) (311–313).

The mechanism of anisocoria during migraine is not fully established. A study that found diminished velocity and amplitude of the pupil light reflex in 10 migraineurs (312) implicates parasympathetic dysfunction as one possibility. In such cases, the abnormal pupil is the larger one, and other evidence for oculoparasympathetic hypofunction should exist. The series by Woods et al. supports this hypothesis in that it showed reduced light responses in five of seven patients examined during their migraine and reduced accommodation in two others (311). One patient had a history of ophthalmoplegic migraines since childhood that evolved into an isolated unilateral mydriasis accompanying her migraine headaches as an adult. Such a limited form of ophthalmoplegic migraine must be rare (314,315). Another etiologic site of oculoparasympathetic dysfunction that has been described with migraine is the ciliary ganglion (316,317). Presumably, migrainous vasospasm can cause local and reversible ischemia of the ciliary ganglion and could also account for the findings described by Woods et al. (311).

Although parasympathetic hypofunction may be the most common cause of unilateral dilation during a migraine attack, it is not the only possible mechanism. An episodic unilateral sympathetic hyperactivity or spasm accompanying

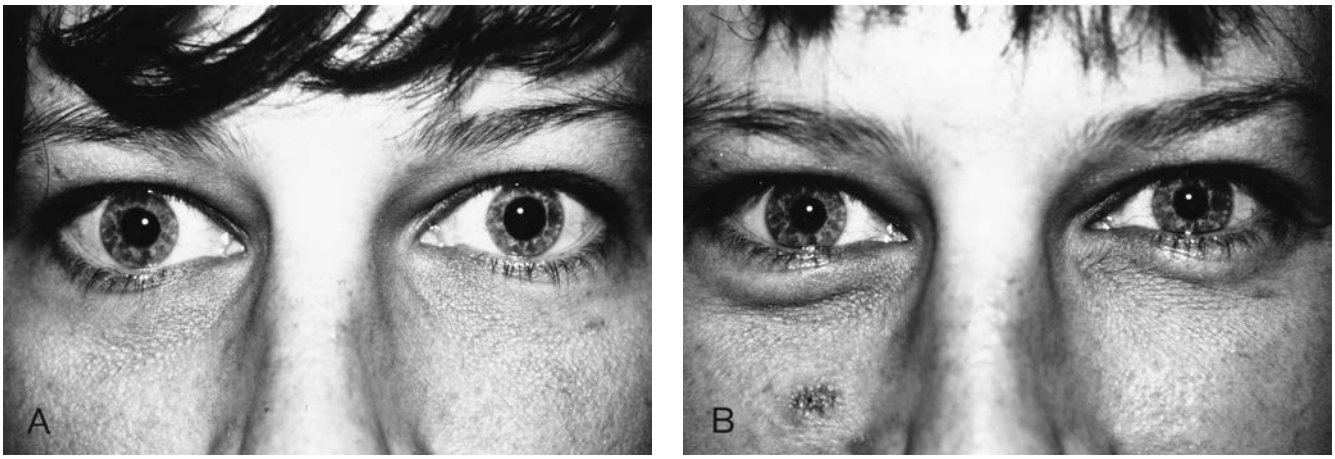

Figure 16.25. Intermittent unilateral pupillary dilation in a young woman during severe migraine headache. *A*, During the migraine attack, the left pupil is dilated and poorly reactive. Accommodation is normal, however, suggesting that the dilation is caused by sympathetic hyperactivity rather than parasympathetic hypoactivity. *B*, Between attacks, the pupils are isocoric.

the attack might cause a similar process. In such a case, the patient would experience no loss of accommodation in the affected eye. We have seen such patients and believe that this mechanism is not uncommon.

Yet another hypothesis for anisocoria during migraine is sympathetic hypofunction. In some migraineurs, pharmacologic pupillary testing has suggested that a bilateral postganglionic oculosympathetic deficit occurs during the headache attack, and in those migraineurs who develop a clinically apparent but transient anisocoria, there is asymmetry of their sympathetic dysfunction (313).

Finally, it is possible that some cases of anisocoria during migraine represent an exaggeration of an underlying benign physiologic anisocoria. At any rate, a transient and isolated anisocoria that is associated temporally with migraine headache attacks and recurs periodically in stereotypic fashion in an otherwise healthy person appears to be a fairly benign syndrome. This clinical picture has not been reported with intracranial aneurysm, midbrain tumor, seizures, or arterial dissection (316).

Sarkies reported that intermittent angle-closure glaucoma can produce a clinical picture similar to the episodic mydriasis that occurs in association with a migraine attack (47). Thus, it is important to consider that entity in patients who experience intermittent episodes of unilateral mydriasis with periocular or retrobulbar pain, especially if there is an associated redness of the eye and blurred vision.

Benign Episodic Mydriasis

Benign episodic mydriasis is the term used to describe recurrent episodes of unilateral mydriasis that are not associated with a concurrent headache or migraine (Fig. 16.26). This condition probably is a variant of the transient mydriasis that occurs during migraine headaches and that is described above. Indeed, about half the patients with benign episodic mydriasis have a history of migraines (318,319).

Benign episodic mydriasis typically occurs and recurs in the same eye. There are no associated neurologic deficits. The duration of mydriasis averages 12 hours, but the range is wide (10 minutes to 7 days). In Jacobson's series, 11 of 24 patients were examined during an episode (319). In these patients, the anisocoria ranged from 1 to 3 mm. Associated symptoms included blur (62%), orbital pain (21%), and red eye (17%). Five patients had a normal pupil light reflex with normal vision, four patients had decreased accommodative function, and one patient demonstrated cholinergic supersensitivity.

Because a small but significant percentage of patients with benign episodic mydriasis experience simultaneous ipsilateral blurred vision, orbital pain, red eye, or a combination of these manifestations, intermittent angle-closure glaucoma must be eliminated as a possibility in patients in whom such a diagnosis is considered (47).

Differentiation Between Causes of Anisocoria

From a practical standpoint, anisocoria that is more evident in darkness than in light indicates that the parasympathetic pathway that constricts the pupils and the iris sphincter muscles are intact (i.e., both eyes have a normal pupil light reflex). The problem thus lies with asymmetric sympathetic activity and dilation in darkness. Most cases represent either simple anisocoria or a Horner syndrome. These two entities are differentiated using 10% cocaine. If the cocaine test indicates that the patient has a Horner syndrome, a hydroxyamphetamine test is performed on another occasion at least 24 hours later to differentiate a central or preganglionic Horner syndrome from a postganglionic Horner syndrome. Once the Horner syndrome is diagnosed and localized, appropriate evaluation for the etiology is required (320).

Anisocoria that is more evident in light than in darkness indicates a defect of the parasympathetic system or the iris sphincter muscle. Thus, the faulty pupil has a poor light reflex. The iris should be examined using a slit-lamp biomicroscope to determine whether there is a sphincter tear or

Figure 16.26. Intermittent unilateral pupillary dilation unassociated with migraine. This operating room nurse was noted to have a dilated left pupil while she was assisting at surgery. She had no headache at the time, nor did she have any visual symptoms other than a vague sense of blurred vision. *A*, During the episode, the left pupil is markedly dilated. Visual acuity at this time was 20/20 OU at both distance and near. The right pupil constricted normally to light stimulation; the left pupil constricted minimally under the same conditions. *B*, 2 hours later, the pupils are isocoric. Both pupils now reacted normally to light stimulation.

other iris damage. If there is no evidence of iris damage, clinical examination usually bears out a diagnosis of oculomotor nerve palsy or tonic pupil. In uncertain cases, a 0.1% solution of pilocarpine can be used to test for denervation supersensitivity. If neither pupil constricts, a 1% solution of pilocarpine can then be used to distinguish between a pharmacologically blocked pupil and a neurologically denervated pupil (321) (Fig. 16.5).

DISTURBANCES IN DISORDERS OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder characterized by pathogenic antibodies against acetylcholine receptors at motor terminals. Clinically apparent weakness of the intraocular muscles is rare. Nonetheless, abnormalities of pupillary function and accommodation are occasionally reported in patients with MG. Two patients with anisocoria and sluggish pupil light reflexes that resolved following treatment with cholinesterase inhibitor have been described (322,323). Pupillary fatigue during prolonged light stimulation has also been noted in other patients (323,324). Yamazaki and Ishikawa used an open-loop stimulus and infrared video pupillography to record direct pupillary responses to light as well as their velocities and acceleration in seven patients with MG and in three healthy persons (325). Their results suggest that involvement of the iris sphincter is common in patients with MG. Lepore et al. reported abnormalities of pupil cycle time, but most of these patients were taking anticholinesterase agents, systemic corticosteroids, or both, which may have affected their pupillary movements (326). In addition, it is not clear whether the pupillary abnormalities observed were caused by direct involvement of the iris musculature, the neuromuscular junction, or central pathways of the pupillary light reflex. Bryant concluded that patients with severe MG tend to show significant interocular differences in pupil cycle times, with the degree of difference correlating with the severity of the illness (327).

It thus appears that some degree of pupillary dysfunction can occur from MG but that in the vast majority of patients, such pupillary dysfunction is not clinically significant and should not confuse the diagnosis; that is, MG should be considered in patients with an ocular motility disturbance and clinically normal pupil responses. On the other hand, patients with ocular motility disturbances and abnormally reactive pupils or anisocoria should first be considered to have a neurologic disorder, not myasthenia. MG is described in detail in Chapter 21.

Botulism

Botulinum toxin is produced by one of several strains of the organism *Clostridium botulinum.* The toxin blocks cholinergic neurotransmission at the neuromuscular junction and cholinergic autonomic synapses. Dilated, poorly reactive pupils and paralysis of accommodation are nearly universally present in patients with clinical botulism (328–331). Interestingly, the accommodation dysfunction often is more severely affected than the pupillary dysfunction. The reason is not clear. There are seven different strains of *C. botulinum,* A–F (including Cα and Cβ), with A, B, and E being of most clinical importance. In type E botulism, internal ophthalmoplegia and ptosis often are the initial neurologic manifestations of the disease, whereas in types A and B, systemic autonomic symptoms tend to occur simultaneously with the onset of ocular symptoms.

Common routes of infection are ingestion of contaminated canned goods or meats, wound infection (particularly in heroin addicts who use subcutaneous injections known as ''skin popping''), and gastrointestinal colonization in infants. Bot-

ulism should be considered in any patient with symmetric, descending muscular weakness; blurred near vision; and poorly reactive pupils. The differential diagnosis and details of this disease are in Chapters 21 and 49.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton syndrome is an immune-mediated disorder (primary or paraneoplastic) in which antibodies are directed against PQ-type voltage-gated calcium channels, resulting in inhibition of neurotransmitter release at cholinergic synapses. The pupil dysfunction is one feature of the cholinergic dysautonomia. One study reported that six of 50 (8%) patients with Lambert-Eaton myasthenic syndrome (LEMS) had sluggish pupil responses to light on clinical examination (332); however, another study using a more quantitative technique found abnormal pupil cycle times in 69% of eyes in seven patients with LEMS (333). Tonic pupils also have been reported in patients with LEMS. One of these patients showed some recovery of the light reaction following administration of 3,4-diaminopyridine and pyridostigmine (334,335).

DRUG EFFECTS

The iris is easy to see because it is suspended in a clear fluid behind a clear cornea. Thus, the actions of the sphincter and dilator muscles on the size of the pupil can be monitored easily. Parasympathetic and sympathetic neural impulses to the iris muscles can be modified by drugs at the synapses and at the effector sites, because it is at these locations that the transmission of the impulses depends on chemical mediators. Thus, the pupil can be and frequently is used as an indicator of drug action.

A few cautionary words should first be said about the interpretation of pupillary responses to topically instilled drugs. There are large interindividual differences in the responsiveness of the iris to drugs placed in the conjunctival sac, and this becomes most evident when weak concentrations are used. For example, a 0.25% solution of pilocarpine will produce a minimal constriction in some patients and a marked miosis in others. The general status of the patient can also influence the size of the pupils (336). If the patient becomes uncomfortable or anxious while waiting for the drug to act, both pupils may dilate. If the patient becomes drowsy, both pupils will constrict. Thus, if a judgment is to be made about the dilation or constriction of the pupil in response to a topical drug, one pupil should be used as a control whenever possible (119).

If only one eye is involved, the drug should be put in both eyes so that the response of the normal and abnormal eye can be compared. When the condition is bilateral, no such comparisons are possible, but an attempt should be made to make sure that the observed response is indeed caused by the instilled drug. Thus, if both eyes are involved, the drop should be put in one eye only so that the responses of the medicated and unmedicated eyes can be compared.

Drugs that Dilate the Pupils

Parasympatholytic (Anticholinergic) Drugs (Fig. 16.27)

Plants from the family Solanaceae occur naturally and contain belladonna alkaloids in various proportions. These plants include deadly nightshade (*Atropa belladonna*), black henbane (*Hyoscyamus niger*), jimson weed (*Datura stramonium*), ''angel's trumpet'' (*Datura suaveolens*), and morning glory. The word belladonna (''beautiful lady'') was derived from the cosmetic use of these substances as mydriatics in 16th-century Venice. The mischief caused by the ubiquitous jimson weed is typical of this group of plants. Jimson weed has been used as a poison, has been taken as a hallucinogen, and has caused accidental illness and death. It also can cause a marked accidental mydriasis if it is inadvertently or purposefully applied to the conjunctiva of one or both eyes (337).

Other solanaceous plants like blue nightshade (*Solanum dulcamara*) and Jerusalem cherry are found in home gardens. They contain solanine, which has effects similar to the belladonna alkaloids. Inadvertent topical ocular application with the juice from the plant can produce a dilated nonreactive pupil that gradually returns to normal in 1–6 days (338–340).

Atropine and scopolamine block parasympathetic activity by competing with acetylcholine at the effector cells of the iris sphincter and ciliary muscle, thus preventing depolarization. Accidental mydriasis and anisocoria can be caused by topical absorption after ocular contact with these drugs in their natural form, but the most frequent ways the drug reaches the eye is by a finger from a scopolamine patch (used for vertigo, seasickness, or postoperative pain) to the conjunctival sac (341), by accidental topical adsorption of the inhalant used to treat asthma (341a) or by the deliberate instillation of the drug into one or both eyes by a person attempting to feign a neurologic disorder. After conjunctival instillation of 1% atropine, mydriasis begins within about 10 minutes and is complete in 35–45 minutes; cycloplegia is complete in about an hour. When concentrations of 2–4% atropine are used, the pupil may stay dilated for several days, but accommodation usually returns in 48 hours. Scopolamine (0.2%) causes mydriasis that lasts, in an uninflamed eye, for 2–5 days. This drug is a less effective cycloplegic than atropine.

A dilated, fixed pupil caused by pharmacologic blockade of the iris sphincter by atropine may be difficult to distinguish from a denervated iris sphincter. One clinically helpful feature is the presence of segmental contractions of the iris sphincter. Atropine weakens the sphincter equally at all segments because convective circulation of the aqueous humor distributes the drug to all parts of the sphincter (342). Thus, at the slit lamp, if there is still any segment of the sphincter that constricts to light, the pupil is not pharmacologically dilated, it is denervated. If the sphincter is diffusely paralyzed (i.e., no segmental contractions seen), then no distinction between a pharmacologically dilated pupil and a parasympathetically denervated one can be made. Preganglionic denervation of the iris sphincter (i.e., oculomotor nerve palsy) may not always be associated with ophthalmoplegia

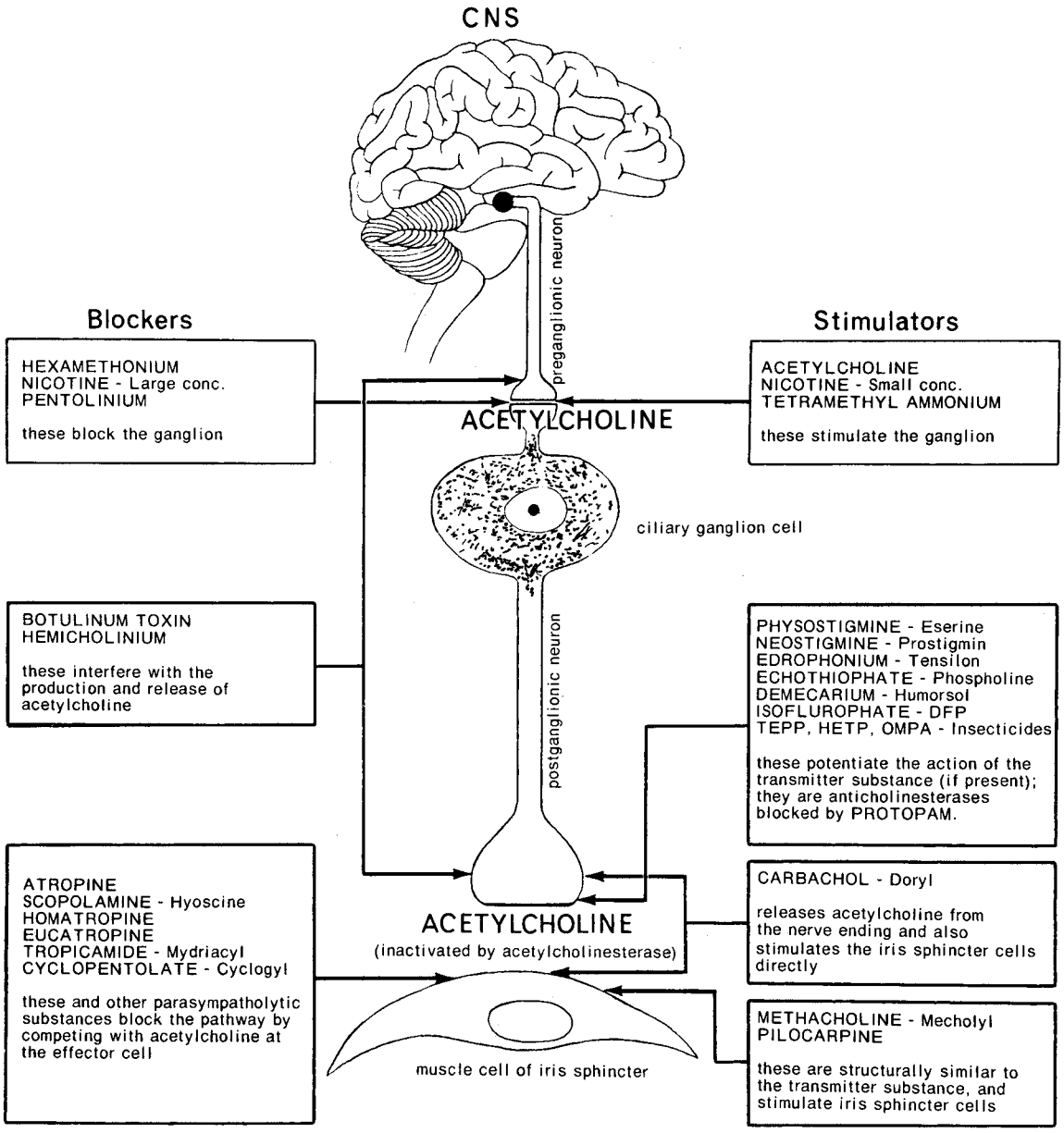

Figure 16.27. The pharmacology of the parasympathetic innervation of the iris.

or ptosis. A minority (about 10%) of postganglionic iris sphincter denervations (i.e., tonic pupils) involve 100% of the muscle (255). As noted above, one can use pharmacologic testing to differentiate between a pharmacologically dilated pupil and a pupil that is parasympathetically denervated (one or two drops of a 0.5–1% solution of pilocarpine in both conjunctival sacs). This concentration of pilocarpine will not displace an anticholinergic drug from the receptors of the iris sphincter muscle, but it will produce a definite constriction of the other normal pupil, and it also will constrict a denervated pupil (from oculomotor nerve palsy or tonic pupil) (226). Even a partial response to 0.5–1% pilocarpine indicates pharmacologic blockade, because a denervated pupil should constrict at least as well as the normal pupil and perhaps even more, if denervation supersensitivity is present.

Results of the pilocarpine test may be misleading in cases of trauma. A pupil that is dilated because of blunt ocular trauma tends to constrict poorly to pilocarpine, not because of pharmacologic manipulation but because the sphincter muscle itself has been damaged. Other observations suggesting related damage to the eye (e.g., tears of the pupillary margin, Vossius' ring, lenticular changes, choroidal rupture, scattered pigment on the anterior iris stroma) generally make it clear that the globe has been severely injured. Iron mydriasis, however, from an unsuspected intraocular iron foreign

body, is mostly caused by toxic damage to the iris nerves rather than to the iris muscle, and these pupils constrict vigorously to pilocarpine like a denervated pupil (236,343).

Tropicamide (Mydriacyl) and cyclopentolate (Cyclogyl) are synthetic parasympatholytics with a relatively short duration of action (344). Tropicamide (1%) is an effective, short-acting mydriatic; its action peaks at 25 minutes and lasts 3–6 hours. The 1% drops produce little loss of accommodation, although mild cycloplegia may be detected between the 25th and 35th minutes after instillation. Compared with tropicamide, a 1% solution of cyclopentolate is a much more effective cycloplegic and perhaps a slightly less effective mydriatic, especially in dark eyes. Mydriasis and cycloplegia approach a maximum in about 30 minutes; accommodation takes about half a day to return, and the pupil still may not be working normally after more than 24 hours. To be completely confident of cycloplegia, second and third drops sometimes are used. In a child, especially a small blond child, enough cyclopentolate may be absorbed through the nasal mucosa after three drops in each eye to produce mild transient symptoms of toxicity, such as flushing of the skin and restlessness (345).

Because patients with Alzheimer dementia have abnormalities in the cholinergic pathways of the brain, it has been hypothesized that the cholinergic pathway to the eye may be defective as well. In 1994, Scinto et al. reported that patients with Alzheimer disease showed greater mydriasis to weak (0.01%) tropicamide (i.e., cholinergic supersensitivity) compared with normal controls (346). Some subsequent studies have confirmed these findings, whereas others have refuted them. As the debate continues, recent investigators have suggested that reducing the peak constriction amplitude is a more sensitive indicator of central cholinergic dysfunction compared with tropicamide-induced pupil dilation, and others have proposed that an even more dilute solution (0.005%) might lower false-positive rates (347,348). At present, there are no standardized guidelines for clinical use of weak tropicamide eyedrops as a diagnostic or differentiating test of Alzheimer dementia.

Botulinum toxin blocks the release of acetylcholine, and hemicholinium interferes with the synthesis of acetylcholine both at the preganglionic and at the postganglionic nerve endings, thus interrupting the parasympathetic pathway in two places. Topical gentamicin may produce a similar effect (349). The outflow of sympathetic impulses also is interrupted by systemic doses of these drugs, because the chemical mediator in sympathetic ganglia also is acetylcholine.

Lidocaine and similar anesthetic agents produce a dilated pupil following intraocular or intraorbital injection (350). In most cases, the anesthetic agent is injected to produce both anesthesia and akinesia for intraocular or strabismus surgery, and the dilation is expected. In other cases, however, the anesthetic is injected anteriorly but diffuses posteriorly. For example, Perlman and Conn described three patients who developed transient fixed dilated pupils after undergoing blepharoplasties using a local anesthetic consisting of a 50/50 mixture of 2% lidocaine with epinephrine 1:200,000 and 0.75% bupivacaine with epinephrine 1:200,000 (351). In most of these cases, the pupil returns to normal within 24 hours. Local anesthesia occasionally enters the orbit by other means. Unilateral mydriasis following dental surgery has been reported after inadvertent injection of lidocaine through the pterygopalatine fossa and inferior orbital fissure into the orbit (11).

Nebulized treatments for asthma containing anticholinergic drugs such as ipratropium bromide sometimes cause a unilateral or bilateral mydriasis when the eye is accidentally exposed to the aerosol from an incorrectly placed mask (352).

Sympathomimetic (Adrenergic) Drugs (Fig. 16.28)

Epinephrine (Adrenalin) stimulates the receptor sites of the dilator muscle cells directly. When applied to the conjunctiva, a 1:1,000 solution does not usually penetrate into the normal eye in sufficient quantity to have an obvious mydriatic effect. Indeed, even a solution of 1.25% epinephrine is insufficient to dilate most pupils of normal subjects (353). If, however, the receptors are supersensitive from previous denervation, or if the corneal epithelium is damaged, allowing more of the drug to get into the eye, these concentrations of epinephrine will dilate the pupil.

Phenylephrine (Neo-Synephrine) in a 10% solution has a powerful mydriatic effect. Its action is almost exclusively a direct α-stimulation of the effector cell. The pupil recovers in 8 hours and shows a ''rebound miosis'' that lasts several days. A 2.5% solution most often is used for mydriasis, in part because this rarely produces systemic hypertension, as does a 10% solution (354). Even weak solutions of phenylephrine may be sufficient to dilate a pupil, but pupils dilated with this drug should still react to light stimulation. Roberts described a patient thought to be comatose from alcohol and benzodiazepine (diazepam, lorazepam) overdose who developed a fixed dilated left pupil after nasotracheal intubation and gastric lavage (355). A diagnosis of possible cerebral herniation was made, and the patient was treated with intravenous mannitol, furosemide, and hyperventilation. A computed tomographic (CT) scan showed no abnormalities. The fixed dilated pupil returned to normal over 3–4 hours, and the patient's condition subsequently improved. It was suspected that the fixed dilated pupil was caused by inadvertent topical ocular contamination with phenylephrine nose spray (0.5%) that had been used in the left nostril in preparation for the endotracheal intubation; however, we would not expect a pupil dilated in this manner to be nonreactive to light stimulation.

Ephedrine acts chiefly by releasing endogenous norepinephrine from the nerve ending. It also has a definite direct stimulating effect on iris dilator muscle cells and can produce significant mydriasis, depending on the concentration used.

Tyramine hydrochloride (5%) and hydroxyamphetamine hydrobromide (1%) have an indirect adrenergic action on the pupillary dilator muscle, releasing norepinephrine from the stores in the postganglionic nerve endings. As far as is known, this is their only effective mechanism of action.

Cocaine (5–10%) is applied to the conjunctiva as a topical anesthetic, a mydriatic, and a test for Horner syndrome (see above). Its mydriatic effect is the result of an accumulation

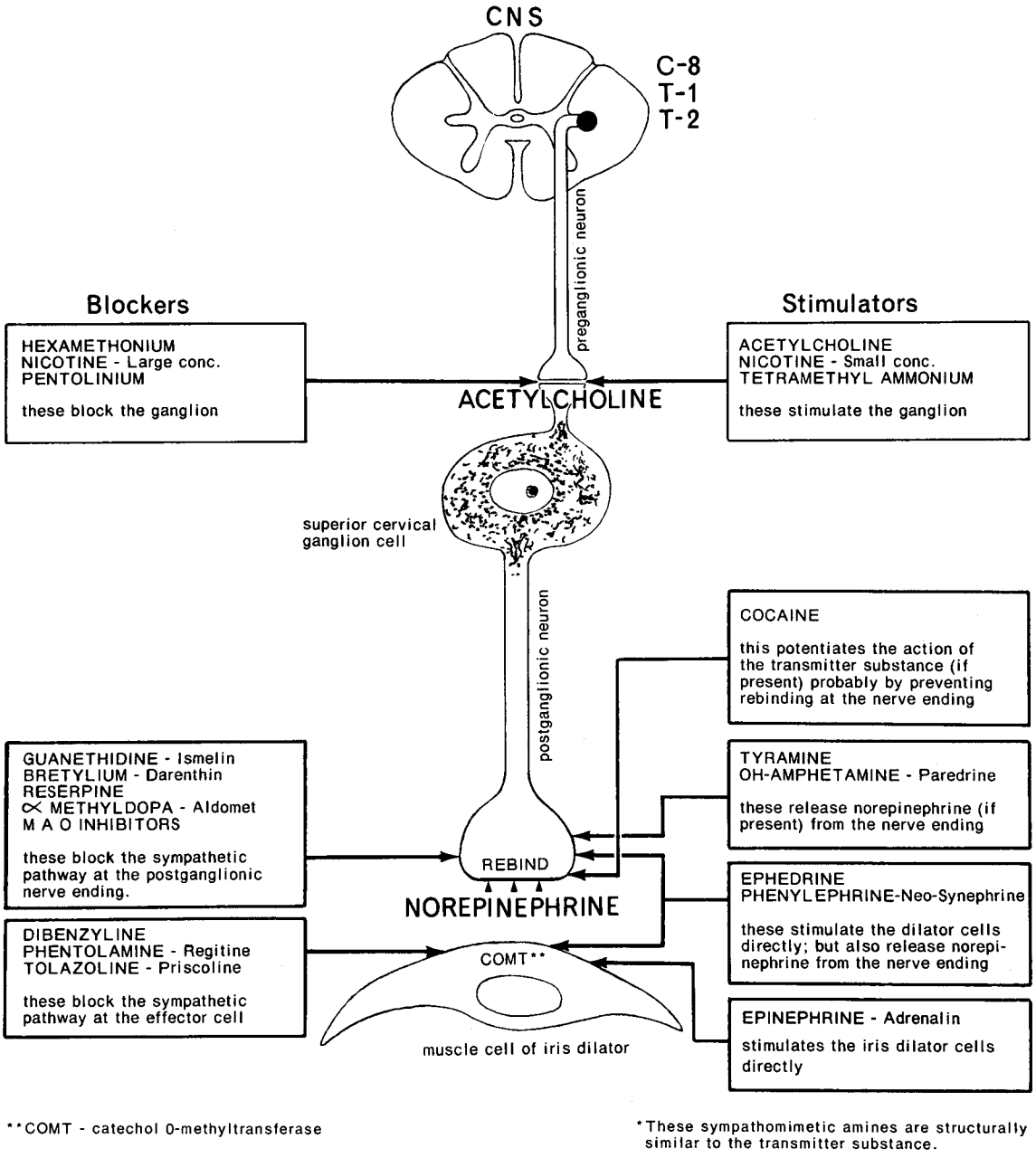

Figure 16.28. The pharmacology of the sympathetic innervation of the iris.

of norepinephrine at the receptor sites of the dilator cells. The transmitter substance builds up at the neuroeffector junction because cocaine prevents the reuptake of the norepinephrine back into the cytoplasm of the nerve ending. Cocaine itself has no direct action on the effector cell, nor does it release norepinephrine from the nerve ending, and it does not retard the physiologic release of norepinephrine from the stores in the nerve ending. Its action is indirect in that it interferes with the mechanism for prompt disposition of the chemical mediator. In this respect, its action is analogous to that of the anticholinesterases at the cholinergic junction. The duration of cocaine mydriasis is quite variable. It may last more than 24 hours. Pupils that dilate from cocaine do not show rebound miosis as the effect of the drug dissipates.

Tetrahydrozoline hydrochloride, pheniramine maleate, and chlorpheniramine maleate are sympathomimetic agents often used in topical ocular decongestants. Instillation of eye drops containing these substances may produce mydriasis, particularly when the drops contain more than one of the drugs (356).

Ibopamine is an ester of N-methyl-dopamine that is nonselectively active on DA1 and DA2 dopaminergic receptors

as well as β-adrenergic and α-adrenergic receptors. Its mydriatic action results from α-receptor stimulation. Both 1% and 2% concentrations of ibopamine produce a maximal mydriasis to slightly more than 9.0 mm in 50–60 minutes. The mydriatic effect of both agents begins to wear off in less than 2 hours, and baseline pupil size is reached by 8 hours. The mydriasis can be rapidly reversed with 0.5% dapiprazole. Ibopamine has no effect on accommodation; that is, it produces mydriasis without cycloplegia (357). These characteristics and a good safety profile make ibopamine an alternative choice for in-office mydriasis for diagnostic funduscopy. Unlike other selective dopaminergic drugs that reduce intraocular pressure, ibopamine increases aqueous humour production and can increase intraocular pressure in patients with outflow impairment. It is being investigated as a ''provocation test'' for glaucoma.

Muscle Relaxants

Papaverine hydrochloride belongs to the benzylisoquinoline group of alkaloids. The most characteristic effect of this drug is the relaxation of the tonus of smooth muscle, especially muscle that is spasmodically contracted. The action on the smooth musculature of cerebral arteries, especially when the vessels are in spasm, provides the basis for the clinical use of papaverine in patients with cerebral arterial vasospasm. The relaxation effect of systemically administered papaverine extends to the bronchial, gastrointestinal, biliary, and urinary musculature. Hendrix et al. reported transient unilateral mydriasis in five patients treated with intraarterial papaverine administered through a catheter positioned in the ipsilateral internal carotid artery a few millimeters proximal to the origin of the ophthalmic artery (358). It was postulated that the drug produced relaxation of both the sphincter and dilator muscles, producing a relative mydriasis, or had a selective effect on the sphincter muscle alone (359).

Drugs that Constrict the Pupils

Parasympathomimetic (Cholinergic) Drugs (Fig. 16.27)

Pilocarpine and methacholine (Mecholyl) are structurally similar to acetylcholine and are capable of depolarizing the effector cell, thus causing miosis and spasm of accommodation (360). Pilocarpine solutions of 0.5–2% usually are required to produce miosis of a normal pupil. Methacholine can be used in a weak (2.5%) solution to test for cholinergic supersensitivity of the sphincter muscle in patients with presumed tonic pupils, but most physicians prefer to use a weak solution of pilocarpine (0.1%) (see above).

Arecoline is a naturally occurring substance with an action similar to that of pilocarpine and methacholine. Its chief clinical advantage is that it acts quickly (361). A 1% solution produces a full miosis in 10–15 minutes (compared with 20–30 minutes for 1% pilocarpine).

Carbachol (carbamylcholine, Doryl) acts chiefly at the postganglionic cholinergic nerve ending to release the stores of acetylcholine. There also is some direct action of carbachol on the effector cell. A 1.5% solution causes intense miosis, but the drug does not penetrate the cornea easily and therefore usually is mixed with a wetting agent (1:3,500 benzalkonium chloride).

Acetylcholine is liberated at the cholinergic nerve endings by the neural action potential and is promptly hydrolyzed and inactivated by cholinesterase. Cholinesterase, in turn, can be inactivated by any one of many anticholinesterase drugs, which either block the action of cholinesterase or deplete the stores of the enzyme in the tissue. These drugs do not act on the effector cell directly; they just potentiate the action of the chemical mediator by preventing its destruction by cholinesterase. It follows from their mode of action that these drugs lose their cholinergic activity once the innervation is completely destroyed.

Physostigmine (eserine) is an anticholinesterase agent that causes marked pupillary constriction (360). Along the Calabar coast of West Africa, the native tribes once conducted ''trials by ordeal'' using a poison prepared from the bean of the plant *Physostigma venenosum.* The local name for this big bean was the esere nut. The synthetic organic phosphate esters (echothiophate [phospholine], isoflurophate [diisopropyl fluorophosphate, DFP], tetraethyl pyrophosphate, hexaethyltetraphosphate, parathion), many of which are in widespread use as insecticides (see above), cause a much longer-lasting miosis than the other anticholinesterases, but even this potent effect, thought to be caused by interference with cholinesterase synthesis, can be reversed by pralidoxime chloride (2-PAM).

Sympatholytic (Antiadrenergic) Drugs (Fig. 16.28)

Thymoxamine hydrochloride (0.5%) and dapiprazole hydrochloride 0.5% (RevEyes) are α-adrenergic blocking agents that can reverse phenylephrine mydriasis by binding the α-receptor sites on the iris dilator muscle. Other drugs that block α receptors are less precise in their modes of action and are rarely used in clinical ophthalmology. These include Dibenzyline (phenoxybenzamine), phentolamine (Regitine), and tolazoline (Priscoline).

Brimonidine tartrate is an α2-adrenergic agonist used in the treatment of glaucoma. It can produce pupillary miosis that is observed best in scotopic conditions (362). The presumed mechanism of action is increased presynaptic inhibition of the terminal sympathetic neuron at the neuromuscular junction of the iris dilator.

Guanethidine (Ismelin) and reserpine interfere with the normal release of norepinephrine from the nerve ending and deplete the norepinephrine stores. When applied to the eye, they produce a Horner syndrome, complete with ptosis, miosis, and supersensitivity to adrenergic drugs.

Other Drugs that Affect the Pupil

Substance P affects the sphincter fibers directly. It will constrict the pupil of a completely atropinized eye. When given parenterally, the opiate alkaloid morphine interrupts cortical inhibition of the iris sphincter nucleus in the midbrain, causing significant miosis. Conversely, topical morphine, even when given in a strong solution (e.g., 5%), has only a minimal miotic effect on the pupil.

Nalorphine and levallorphan are antinarcotic drugs. Given parenterally, they reverse the miotic action of morphine. Naloxone hydrochloride, a similar drug, dilates the pupils of opiate addicts but not the pupils of healthy, unmedicated subjects.

Intravenous heroin seems to produce miosis in proportion to its euphoric effect (363). Habituated heroin users require larger doses than nonhabituated users to produce the same amount of pupillary constriction. Thus, if one knows the concentration of heroin in the plasma and the size of the pupil in darkness, it should be possible to determine a measure of the degree of physical dependence in a given individual.

During the induction of anesthesia, the patient may be in an excited state, and the pupils often are dilated. As the anesthesia deepens, supranuclear inhibition of the sphincter nuclei is interrupted, and the pupils become small. If the anesthesia becomes dangerously deep and begins to shut down the midbrain, the pupils become dilated and fail to react to light.

The concentration of calcium and magnesium ions in the blood may affect the pupil. Calcium facilitates the release of acetylcholine, and when calcium levels are abnormally low, the amount of acetylcholine liberated by each nerve impulse drops below the level needed to produce a postsynaptic potential, thus blocking synaptic transmission. Magnesium has an opposite effect: a high concentration of magnesium can block transmission, and this may weaken the sphincter, resulting in large pupils that react poorly to light (11).

Iris Pigment and Pupillary Responses to Drugs

In general, the more pigment in the iris, the more slowly the drug takes effect and the longer its action lingers. This probably is because the drug is bound to iris melanin and then slowly released. There are wide individual differences in pupillary responses to topical drugs. There probably is a greater range of responses among eyes with blue or light-green irides than between the average response of eyes with light-colored irides and the average response of eyes with irides that are dark brown. Some of these individual differences are related to corneal penetration of the drug.

LIGHT–NEAR DISSOCIATION

Normal pupils constrict not only from light stimulation but also during near viewing as part of the near response of convergence, accommodation, and miosis. Whenever the pupil light response appears sluggish, inextensive, or weak, the near response should be checked. Constriction of the pupils during near viewing that is stronger than the light response (light–near dissociation) is an important clinical observation.

Light–near dissociation may be caused by a defect in the afferent or the efferent system subserving pupillary function. It is the primary feature of the Argyll Robertson pupils that occur from efferent dysfunction, mainly in patients with neurosyphilis. Light–near dissociation also can be seen in patients with pregeniculate blindness, compressive and infiltrative mesencephalic lesions, and damage to the parasympathetic innervation of the iris sphincter.

Argyll Robertson Pupils

Clinical Characteristics

In 1869, Douglas Argyll Robertson published two papers entitled ''On an Interesting Series of Eye Symptoms in a Case of Spinal Disease with Remarks on the Action of Belladonna on the Iris, etc.'' and ''Four Cases of Spinal Miosis: With Remarks on the Action of Light on the Pupil.'' According to his description, the characteristic features of the syndrome shown by his patients, all of whom had ''spinal disease'' (tabes dorsalis), were (*a*) the retina was sensitive to light; (*b*) the pupil did not respond on exposure to light; (*c*) there was normal pupillary constriction during accommodation and convergence for near objects; (*d*) the pupils constricted further with extracts of the Calabar bean (physostigmine), but they dilated poorly with atropine; and (*e*) the pupils were very small (364,365) (Fig. 16.29). These findings are considered in further detail here. The basis for all

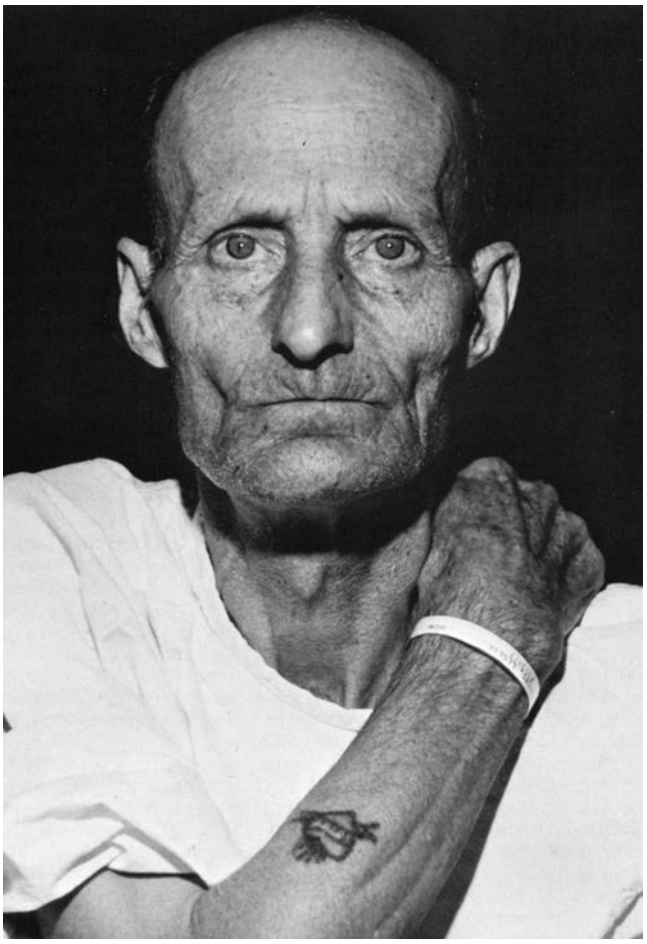

Figure 16.29. Argyll Robertson pupils in a tabetic merchant seaman. Even in the semidarkness that preceded the photographer's flash, the pupils are so small as to be hidden behind the corneal reflection.

the information in this section is the exhaustive review of the literature and personal research presented in Irene Loewenfeld's classic paper on the subject and her superb textbook (119,366).

RETINA IS SENSITIVE TO LIGHT

This statement does not mean that patients with visual dysfunction do not have Argyll Robertson pupils. The implication here is that the degree of retinal or optic nerve disease, if present, does not explain the poor light reflex.

PUPILS DO NOT RESPOND TO LIGHT

In the fully developed Argyll Robertson pupil, there is complete absence of pupillary constriction to light stimulation. However, pupillographic recordings have shown that weak, inextensive reactions remain in most Argyll Robertson pupils. Furthermore, the damaging lesion usually does not develop acutely; there is usually a period of progression, sometimes gradually, sometimes asymmetrically, and sometimes at an uneven rate. During this period, the pupillary light reactions progress from sluggish, incomplete constrictions to complete loss of the light reflex.

An exceptional patient can have improvement and even recovery of the light reaction. Lanigan-O'Keeffe described a 46-year-old man with neurosyphilis who had anisocoria. The larger pupil was unreactive to light but reacted to near stimuli (367). The smaller pupil apparently reacted normally to both light and near stimuli. Two months after a course of parenteral penicillin, the patient's pupils were noted to be equal and normally reactive to both light and near stimuli.

PUPILS CONSTRICT NORMALLY TO ACCOMODATION-CONVERGENCE (NEAR RESPONSE)

Accommodation is typically normal and the extent of pupil constriction in response to accommodative (near) effort often is surprisingly good, particularly when considering that the baseline size of the pupils is already small. However, the near response is never ''better'' than normal and never tonic in movement. The brisk near constriction and the brisk redilation after near effort are the distinguishing features between small, chronic tonic pupils and Argyll Robertson pupils.

In fact, most Argyll Robertson pupils actually have a mildly impaired near reaction when objectively tested, but it is far less impaired than the light reflex. Thus, it is not a normal near response that counts but rather a light–near dissociation that is essential to the syndrome of an ''Argyll Robertson pupil.'' According to Loewenfeld, a significant number of Argyll Robertson pupils eventually lose the near constriction as well and become miotic, immobile pupils. In other patients who also develop syphilitic oculomotor nerve damage, the pupil becomes mydriatic and unreactive to light and near stimulation, and accommodation is lost.

Patients with Argyll Robertson pupils have a normal ''orbicularis oculi-pupillary reflex.'' Their pupils constrict normally on forced closure of the eyelids (the Westphal-Piltz phenomenon or the Galassi-Gifford reaction), supporting the theory that this reflex is the result of inadvertent convergence-accommodation impulses.

PUPILS DILATE POORLY TO ATROPINE

In his original papers, Argyll Robertson actually stated that strong atropine ''induced only a medium dilation.'' Over the years, this statement often translated to become failure to dilate to atropine. This finding is not supported by careful testing of Argyll Robertson pupils to various mydriatic agents. In general, Argyll Robertson pupils dilate well to atropine, as long as there is no associated iris atrophy. Such pupils also constrict well to miotics. Occasional reports of sensitivity of Argyll Robertson pupils to 2.5% Mecholyl may be explained by the assumption of additional peripheral damage to the ciliary nerve endings within the eye or iris.

PUPILS ARE VERY SMALL

Whether miosis is an essential part of the syndrome has been argued back and forth for many years. The controversy was settled by qualifying the definition of miosis in this syndrome: it is a pupil size that, in darkness, is smaller than those of normal persons in the same age group (Fig. 16.29). Using this definition, the presence of this miosis is considered an essential feature of the Argyll Robertson syndrome, as there must be a unique and separate mechanism that keeps the pupil so small in the presence of impaired light reflexes. Such a mechanism obviously is not present in other light–near dissociation syndromes, such as the dorsal midbrain syndrome, in which the pupils typically are moderate to large. Because most patients with Argyll Robertson pupils have normal reflex dilation in darkness and to psychosensory stimulation, the miosis is not related to impaired sympathetic innervation of the iris dilator muscle.

OTHER FEATURES

One important feature not emphasized by Argyll Robertson is irregularity of the pupil shape. This finding is quite common. Other descriptions for the pupil shape include horizontally or vertically directed oval, egg-shaped, teardrop-shaped, irregularly polygonal, serrated, or eccentric. The irregularity of the shape of Argyll Robertson pupil most likely is due to severe syphilitic iritis or uveitis with subsequent structural iris damage. Although frequently observed with the other aforementioned pupil findings, this feature has a peripheral etiology (i.e., it is due to a structural abnormality of the iris, not to its innervation). Thus, it is not considered an essential feature of the classic Argyll Robertson syndrome in which the site of pathology is centrally located (see below). Nevertheless, the presence of iris damage renders the pupil rather immobile and may obscure the usual findings of light–near dissociation, dilation in darkness, and responsiveness to pharmacologic agents.

Argyll Robertson pupils usually are bilateral (80–90%), but there can be asymmetry in both pupillary size and the degree of light–near dissociation. Rarely, the condition is strictly unilateral. Most Argyll Robertson pupils remain unchanged for years, indicating no ongoing lesion activity.

Others become even more miotic and immobile or dilated and nonreactive to both light and near stimulation.

Site of Lesion and Mechanism

The rostral midbrain is the probable location for the lesion responsible for Argyll Robertson pupils. It is speculated that a lesion along the dorsal aspect of the Edinger-Westphal nucleus damages the pretectal fibers of the pupil light reflex yet spares the near vision fibers that have a more ventral location. This would easily explain the light–near dissociation.

In the rat brain, there is a richly developed group of supranuclear adrenergic fibers that contact cells of the Edinger-Westphal nuclei but not other cells within the oculomotor complex (368,369). Damage to this central ''sympathetic'' inhibitory pathway could be responsible for the miosis of the Argyll Robertson pupil. Although this pathway has not been confirmed in humans, the miosis produced by reserpine and α-methyldopa, drugs that deplete central (as well as peripheral) nervous system norepinephrine, suggests that such an inhibitory supranuclear pathway exists. In addition, experimental deafferentation of the oculomotor nuclear complex in a cat demonstrated that the visceral nuclei alone can generate a marked and persistent miosis (370). Lowenstein suggested that the phenomenon of denervation supersensitivity known to apply to central nervous structures, as well as to denervated peripheral organs, might further increase spontaneous firing of the visceral oculomotor neurons that are deprived of their major afferent supply when the light reflex pathway is interrupted (371). It therefore is reasonable to postulate that a lesion in the rostral midbrain could interrupt the descending supranuclear inhibitory fibers to the Edinger-Westphal nucleus. Devoid of its central inhibition, this nucleus would continuously release parasympathetic impulses to the iris sphincter, resulting in a tight miosis.

Anatomic evidence also supports the assumption that a rostral mesencephalic lesion is responsible for Argyll Robertson pupils. Although circumscript focal lesions have not been identified, diffuse damage around the sylvian aqueduct and the posterior portion of the third ventricle is a prominent finding in patients with Argyll Robertson pupils who have died from tabes or general paresis. The ependymitis and subependymal gliosis seen in the area of the light reflex pathways are widespread in neurosyphilis. Such damage may be sufficient to produce Argyll Robertson pupils.

Thus, to summarize, the classic Argyll Robertson pupil results from neuronal damage in the region around the sylvian aqueduct in the rostral midbrain. In this location, the damage interferes with the light reflex fibers and the supranuclear inhibitory fibers as they approach the visceral oculomotor nuclei.

Etiology

Around 1900, when the syphilitic nature of tabes dorsalis and general paresis was firmly established, the Argyll Robertson syndrome was considered pathognomonic for syphilis. The earlier reports of Argyll Robertson pupils in patients suffering from a variety of other diseases, especially severe alcoholism, multiple sclerosis, and age-related dementia, were discounted because they predated the development of serologic tests for syphilis. Only a few years later, however, the severe epidemics of lethargic encephalitis struck (especially the epidemic of 1918–1921), and observations of authentic cases of Argyll Robertson pupils in these patients began to increase. In addition, the effectiveness of penicillin treatment for syphilis has decreased the incidence of tertiary syphilis, and the percentage of nonsyphilitic patients reported with Argyll Robertson pupils has grown precipitously. The syndrome is observed in patients with diabetes mellitus, chronic alcoholism, encephalitis, multiple sclerosis, age-related and degenerative diseases of the CNS, some rare midbrain tumors, and, rarely, systemic inflammatory diseases, including sarcoidosis and neuroborreliosis (119,366,372–374). Nonetheless, a patient with Argyll Robertson pupils should be assumed to have neurosyphilis until proven otherwise. Such a patient should undergo appropriate testing of both serum and CSF in an attempt to diagnose this treatable disease.

Inverse Argyll Robertson Pupils

This rather awkward term is used to describe pupils that react to light but do not constrict during convergence-accommodation efforts. This diagnosis must be viewed with extreme caution, because it often is impossible to be certain that a patient has made an adequate near-vision effort. In unilateral cases, pupillary constriction in the opposite eye during efforts to view near objects demonstrates that ''near'' impulses are being generated. Authentic cases of inverse Argyll Robertson pupils are rare, but they apparently do exist and may be caused by neurosyphilis or other diseases that selectively damage the more ventral portion of the mesencephalic pretectal region (375).

Mesencephalic Lesions

Damage to the dorsal mesencephalon typically produce midposition (3–6 mm) or slightly dilated pupils that fail to constrict to light, or do so very poorly, and yet react well to near stimuli (Fig. 16.30). Dilated pupils from loss of the light reaction may be the first sign of a tumor that compresses or infiltrates the dorsal midbrain or a sign of obstructive hydrocephalus, particularly from aqueductal stenosis or a blocked shunt. Freeman et al. reported a 15-year-old girl with headaches, nausea, and vomiting who was found to have bilaterally dilated pupils with normal ocular motility (376). The right pupil was 7 mm in diameter and had ''sluggish'' reactions to light and near stimuli; the left pupil measured 10 mm in diameter and showed only ''slight'' constriction to light and near stimuli. Subsequent evaluation revealed a large craniopharyngioma that was thought to involve the dorsal mesencephalon. Following subtotal resection of the lesion, the pupils reacted normally to near stimuli but remained large and poorly reactive to light. In most dorsal midbrain lesions, the disturbances of pupillary function are bilateral and accompanied by other deficits such as supranuclear vertical gaze palsy, eyelid retraction, accommodation

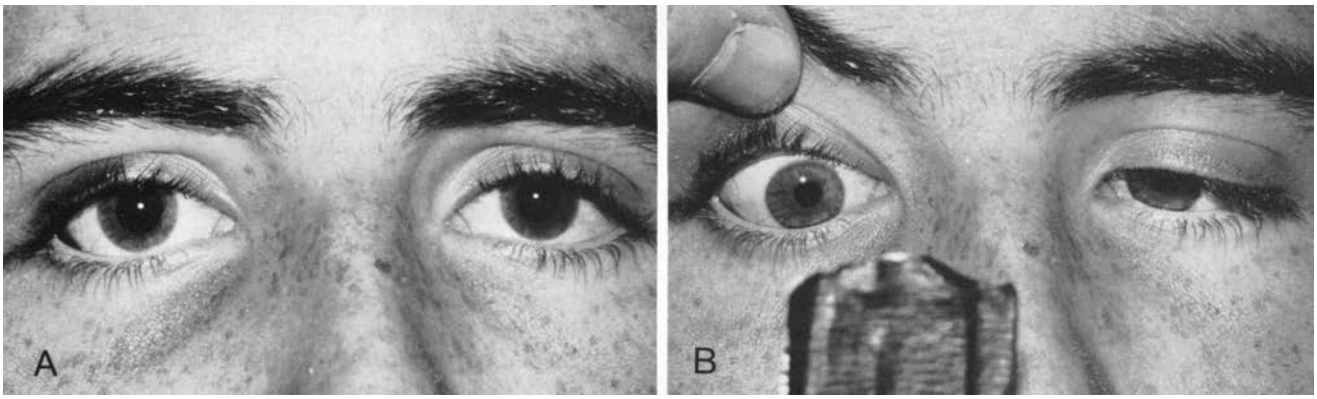

Figure 16.30. Pupillary light–near dissociation in a patient with a germinoma producing a dorsal midbrain syndrome. In a dimly lighted room, both pupils were large and slightly anisocoric. *A*, When a bright light is shined in either eye, both pupils constrict sluggishly and incompletely. *B*, When the patient is asked to look at an accommodative target, both pupils constrict briskly and extensively. The patient also had difficulty with upward gaze.

paresis or spasm, and convergence-retraction nystagmus on attempted upward gaze.

Lesions of the Afferent Pathway

Lesions of the visual sensory pathway from the retina to the point at which the pupillomotor fibers exit impair the light reaction but spare the near response. If a patient is blind from optic nerve disease, for example, there will be no reaction of the pupils to direct light stimulation in the blind eye, but the near reaction may be well preserved. Blindness from retinal, optic nerve, or optic chiasmal disease is the most common setting in which pupillary light–near dissociation occurs in standard clinical ophthalmologic, neurologic, and neurosurgical practice.

Aberrant Regeneration After Damage to the Innervation of the Iris Sphincter

Light–near dissociation following injury to the short ciliary nerves is due to restoration of the pupillary near response by aberrant regeneration. When nerve fibers originally destined for the ciliary muscle mistakenly reinnervate the iris sphincter muscle instead, then every time a near effort is made to focus the lens, a strong pupil constriction ensues. This pathophysiologic process is discussed in the section on the Adie tonic pupil syndrome (see above).

A similar phenomenon occurs in the setting of aberrant regeneration after structural damage to the preganglionic oculomotor nerve. Nerve fibers originally headed for extraocular muscles or the ciliary muscle may be diverted into the iris sphincter, which is such a small muscle that only a few of these fibers are sufficient to make the iris sphincter contract (377–379). The pupil constricts whenever the patient attempts an eye movement or near effort. The constriction is usually segmental, a feature regularly seen with tonic pupils; however, the two cardinal features of a tonic pupil—a slow, sustained contraction to near effort and a slow redilation after constriction—are absent. In general, pupils that show light–near dissociation in the setting of aberrant regeneration of the oculomotor nerve constrict briskly to near stimulation and redilate briskly when near effort ceases.

DISTURBANCES DURING SEIZURES

In 1881, Gowers noted that during the course of a generalized tonic-clonic seizure (grand mal seizure), there was brief bilateral pupillary miosis in the tonic phase of the seizure followed by bilateral pupillary dilation in the clonic phase. Other authors reported loss of the pupil light reflex as well during grand mal seizures. These pupil findings also occur regularly during generalized seizures without motor activity (i.e., petit mal or absence seizures). Jammes examined and photographed the pupillary size and reactivity in six patients during attacks of petit mal seizures (380). He found that bilateral pupillary dilation with loss of reactivity to light occurred consistently in all six patients during their absence attacks. Afterwards, when consciousness was regained, there was often mild pupillary miosis and facial flushing. The mechanism of the pupillary dilation that occurs during generalized seizure activity appears to be a combination of interruption of parasympathetic impulses and irritation of the sympathetic system (119). The postictal miosis probably represents decreased supranuclear inhibition to the parasympathetic midbrain nuclei.

''Diencephalic seizures'' is a term coined to describe clinical episodes of diffuse sympathetic hyperactivity. Patients experience paroxysms of rise in body temperature, blood pressure, heart rate, respiratory rate, and pupil size as well as hyperhidrosis. An underlying central lesion such as tumor, trauma, subarachnoid hemorrhage, and acute hydrocephalus often is found, but during the acute burst of sympathetic discharges, no corresponding electroencephalographic changes have ever been recorded. The episodes are unresponsive to standard antiepileptic medications, although clonidine and morphine appear to control symptoms. A newer term proposed for these episodes is ''paroxysmal sympathetic storms'' as they do not appear to represent a true seizure disorder (381,382).

Rarely, patients experience unilateral pupillary mydriasis during seizures, a phenomenon termed ictal mydriasis (383–385). In all these cases, the seizures are focal. In cases with a lesion or epileptogenic focus in the frontal lobe or amygdala, the mydriasis occurs in the contralateral eye (386–388). If there is contraversive head and conjugate eye deviation during the seizure, the pupillary dilation occurs in the abducting eye, whereas if the seizures are caused by a lesion in the temporo-occipital region, the mydriasis occurs in the adducting eye. Thus, patients who experience contraversive conjugate eye deviation from frontal or amygdaloid lesions develop mydriasis of the eye on the side opposite the lesion, whereas patients whose contraversive eye deviation is caused by a temporo-occipital lesion develop mydriasis in the eye on the side of the lesion (385). These clinical examples of ictal mydriasis are consistent with animal studies in which unilateral mydriasis or anisocoria has been induced by electrical stimulation of focal areas of cortex (frontal gyrus, temporal gyrus, occipital lobe) or by chemical lesioning of areas in the temporal lobe (389,390)

Berreen et al. described a 33-year-old woman who developed episodic dilation of her left pupil that lasted about 1 minute (391). MR imaging revealed a left frontal lobe mass with minimal compression of the frontal horn of the left lateral ventricle. A left frontal craniotomy was performed, at which time a low-grade astrocytoma was found and completely removed. Postoperatively, the patient had no further episodes of left pupillary dilation. This patient did not undergo an electroencephalogram (EEG) to correlate electrical seizure activity with her pupil episodes; however, it is possible that these episodes were caused by irritative effects of the tumor on sympathetic pathways in the frontal lobe.

Ictal miosis appears to be even more rare than ictal mydriasis. Lance and Smee described episodes of left pupillary constriction, visual hallucinations, and left homonymous hemianopia in a patient with a cavernous angioma of the right occipital lobe (392). Afifi et al. described seizure-induced unilateral ptosis and miosis in two patients with contralateral temporal lobe lesions (393). Rosenberg and Jabbari described a 21-year-old man with postencephalitic complex partial and tonic-clonic seizures since childhood who began to complain of episodes of blurred vision (394). During these episodes, which were usually less than a minute, his pupils constricted to 3 mm and became nonreactive to light stimulation. Simultaneously, an EEG showed runs of rhythmic 3- to 5-Hz sharp and slow activity over the left temporo-occipital region. The internal ophthalmoplegia was the only clinical manifestation of these seizures, which subsequently were controlled with carbamazepine.

DISTURBANCES DURING COMA

According to Plum and Posner, consciousness is the state of awareness of the self and environment, whereas coma is a state of unarousable psychological unresponsiveness in which the patient lies with eyes closed (395). Patients in coma show no psychologically understandable response to external stimuli or inner needs. Causes of coma include supratentorial lesions, infratentorial lesions, and diffuse brain dysfunction from a variety of inflammatory, infectious, degenerative, and metabolic processes. The prevalence of pupillary abnormalities in comatose patients is high and may, in some instances, help in the initial understanding and localization of the process. Accordingly, one should carefully examine the pupil size, shape, and reactivity in any patient who appears to be in a comatose state.

Site of Lesion in Coma and Pupil Abnormality

Cerebral lesions may produce primary abnormalities of pupil size and reactivity (386,389). Damage to the hypothalamus, especially in the posterior and ventrolateral regions, may produce an ipsilateral Horner syndrome characterized by miosis, ptosis, and anhidrosis (142). The anhidrosis affects the ipsilateral half of the body. The recognition of hypothalamic dysfunction in patients with coma may be extremely important with respect to ultimate prognosis, because downward displacement of the hypothalamus with unilateral Horner syndrome is often the first clear sign of incipient transtentorial herniation. Crill reported five cases of supratentorial hemorrhage associated with ipsilateral Horner syndrome (396). Of four patients who died and underwent autopsy, two had hemorrhages in the thalamus and hypothalamus and one had a subdural hematoma with transtentorial herniation. The fourth patient had hemorrhage into a cortical metastatic tumor with no direct hypothalamic destruction. That unilateral diencephalic lesions can produce a Horner syndrome is supported by the observation of 15 patients in whom stereotactic thalamic surgery produced ipsilateral sympathetic defects, including ptosis, miosis, and hemianhidrosis (397).

Damage to the diencephalon, particularly during rostral-caudal brain stem deterioration caused by supratentorial lesions (see below), produces symmetrically small but briskly reactive pupils. The pupils dilate to psychosensory stimuli.

Lesions of the dorsal tectal or pretectal regions of the mesencephalon interrupt the pupil light reflex but may spare the response to near stimuli (light–near dissociation). The pupils are either in midposition or slightly dilated and are round. They do not react to light, but their size may fluctuate spontaneously. As with diencephalic pupils, these pupils may dilate to psychosensory stimuli. Recognition of tectal or pretectal effects on the pupil may be important because small lesions in this region often affect the periaqueductal gray matter and interrupt consciousness.

Mesencephalic lesions in the region of the oculomotor nerve nucleus nearly always damage both sympathetic and parasympathetic pathways to the eye. The resulting pupils usually are slightly irregular and unequal. They are midposition (3–6 mm in diameter) and nonreactive to light stimuli. Midposition fixed pupils most commonly are caused by mesencephalic damage from transtentorial herniation, but they also occur when neoplasms, hemorrhages, infarcts, or granulomas damage the midbrain. Lesions that affect the pupillary fibers in the fascicle of the oculomotor nerve can produce a complete or incomplete oculomotor nerve palsy with a dilated, nonreactive pupil. Such parenchymal lesions frequently are bilateral. Selhorst et al. described midbrain cor-

ectopia, an upward, inward movement of the pupils in a comatose patient with mesencephalic disease (23). Such pupillary abnormalities presumably are caused by incomplete damage to the parasympathetic pupillary fibers in the mesencephalon. Midbrain corectopia is not limited to patients in coma, however (24).

Lesions of the tegmental portion of the pons may interrupt descending sympathetic pathways and produce bilaterally small pupils. In many cases, especially those with pontine hemorrhage, the pupils are pinpoint, presumably from a combination of sympathetic interruption and parasympathetic disinhibition. Despite the size of such pupils, a pupil light reflex usually is present and can be observed with the aid of magnification within several hours after the onset of the primary intracranial event (398).

The pupillary fibers within the peripheral oculomotor nerve are particularly susceptible when uncal herniation compresses the nerve against the posterior cerebral artery or the edge of the cerebellar tentorium (399). In these instances, pupil dilation may precede other signs of ocular motor nerve paralysis, and such patients may present with fixed, dilated or fixed, oval pupils (25,400).

The nature of pupillary dysfunction in a comatose patient often reflects the level and degree of brain stem dysfunction. This is particularly true when brain stem dysfunction is produced by an expanding supratentorial lesion. Such lesions accounted for 20% of patients initially diagnosed as ''coma'' in the series reported by Plum and Posner (395). Supratentorial lesions produce neurologic dysfunction by two mechanisms: primary cerebral damage and secondary brain stem dysfunction from displacement, tissue compression, swelling, and vascular stasis. Of the two processes, secondary brain stem dysfunction is the more threatening to life. It usually presents as one of two main patterns. Most patients develop signs of bilateral diencephalic impairment: the central syndrome or rostral-caudal deterioration. In this syndrome, pupillary, ocular motor, and respiratory signs develop that indicate that diencephalic, mesencephalic, pontine, and, finally, medullary function are being lost in an orderly rostral to caudal fashion. Other patients develop signs of uncal herniation with oculomotor nerve and lateral mesencephalic compression (uncal herniation syndrome). The following discussion is obtained from the excellent monograph ''The Diagnosis of Stupor and Coma'' by Plum and Posner (395).

Central Syndrome of Rostral-Caudal Deterioration

The first evidence that a supratentorial mass is beginning to impair the diencephalon usually is a change in alertness or behavior. Initially, patients with such lesions find it difficult to concentrate and tend to lose the orderly details of recent events. Some patients become agitated, whereas others become increasingly drowsy. Respiration in the early diencephalic stage of the central syndrome is commonly interrupted by deep sighs, yawns, and occasional pauses. Many patients have periodic breathing of the Cheyne-Stokes type, particularly as they become increasingly somnolent. The pupils are small (1–3 mm) but maintain a small and brisk reaction to light stimulation unless there is concomitant compression of one or both oculomotor nerves. Some patients show conjugate or slightly divergent roving eye movements and have an inconsistent response to oculocephalic testing (doll's head maneuver). More frequently, the eyes are conjugate and stable at rest, responding briskly to oculocephalic testing. In such patients, caloric testing using cold water evokes a full, conjugate, slow tonic movement toward the irrigated side with impairment or absence of the fast component of the response. Early diencephalic dysfunction in such patients is suggested by the development of bilateral signs of corticospinal or extrapyramidal dysfunction. A few patients develop diabetes insipidus, reflecting severe downward traction on the pituitary stalk and the median eminence of the hypothalamus.

The clinical importance of the diencephalic stage of the central stage of rostral-caudal deterioration caused by a supratentorial mass lesion is that it warns that a potentially reversible lesion is about to become irreversible by progressively encroaching on the brain at or below the level of the tentorium. Once signs of mesencephalic dysfunction appear, however, it becomes increasingly likely that the patient has suffered a brain stem infarction, rather than reversible compression and hypoxia, and the outlook for neurologic recovery is poor.

As mesencephalic and upper pontine damage ensues, abnormally wide fluctuations of body temperature are common. Respirations gradually change from the Cheyne-Stokes type to a sustained tachypnea. The initially small pupils dilate and become fixed in midposition. It is unclear whether this dilation is caused by interruption of the afferent light reflex pathway, damage to the dorsal visceral nuclei of the oculomotor nerve complex, or both. In this stage, the pupils no longer dilate to psychosensory stimuli. Oculocephalic testing often fails to elicit appropriate eye movements, and even caloric testing may fail to produce normal tonic movements toward the irrigated side. Motor dysfunction progresses from decorticate to bilateral extensor rigidity in response to noxious stimuli. Of the adult patients examined by Plum and Posner (1980), none with a supratentorial lesion recovered full neurologic function once mesencephalic signs were fully developed. The prognosis for recovery is often better in children.

After the mesencephalic/upper pons stage, ischemia continues to progress caudally down the brain stem. Hyperventilation resolves, giving rise to a fairly regular breathing pattern with a shallow depth and rapid rate (20–40 per minute). The pupils remain in midposition and do not respond to light stimulation. Oculocephalic testing elicits no ocular movements, and the extremities become increasingly flaccid.

The medullary stage is terminal. Respiration slows and often becomes irregular in rate and depth; it is interrupted by deep sighs or gasps. The pulse is variable, and the blood pressure drops. The eyes are immobile and no longer respond to caloric or oculocephalic stimulation. The pupils may dilate widely during this stage (terminal mydriasis). In the absence of an intact sympathetic outflow pathway, the mydriasis may be caused by hypoxia of the neurons of the Edinger-Westphal nucleus that had previously been deaffer-

ented. Alternatively, it may be caused by an agonal release of adrenergic substances into the blood in response to hypoxia, thus causing the pupil to dilate. Both mechanisms may occur simultaneously.

The size and reactivity of the pupils should never, by themselves, be used as an indication of irreversible coma and brain death. In the first place, some comatose patients whose mid-dilated pupils are thought to be unreactive to light when examined with a hand-held penlight can be shown to react when assessed with infrared pupillometry (401). In addition, even widely dilated, fixed pupils can be observed in comatose patients who eventually recover neurologic function. For example, Cleveland reported the complete neurologic recovery of a 14-year-old boy who suffered a cardiac arrest lasting 3 hours (402). During the entire resuscitation episode, the patient's pupils were widely dilated and fixed. Gauger also emphasized that the observation of widely dilated, nonreactive pupils during the period of resuscitation after a cardiac or respiratory arrest does not, in itself, signify irreversible brain injury (403). Conversely, some patients with irreversible coma develop nonreactive small or pinpoint pupils (404,405). The reason for the small size of the pupils in some of these patients is previous use of miotic agents to treat glaucoma.

Uncal Herniation Syndrome

Patients with the syndrome of uncal herniation have asymmetric pupillary changes in the early phases of coma. During the early third nerve stage, signs of oculomotor nerve dysfunction may occur with almost any level of altered consciousness, from slight drowsiness to complete unconsciousness. The earliest consistent sign is unilateral dilation of one pupil that initially is sluggishly reactive to light but soon becomes widely dilated (6–9 mm) and nonreactive to light stimulation. This pupillary disturbance may last for several hours before neurologic signs other than an altered state of consciousness appear (406).

Traditional teaching held that if a supratentorial mass lesion such as acute hemorrhage causes altered consciousness and an acutely dilated pupil, the dilated pupil indicates the side of the lesion. The iridoplegia occurs from uncal descent and compression of the superolateral aspect of the ipsilateral oculomotor nerve. Occasionally, however, the dilated pupil is contralateral to the lesion, a finding called a ''false-localizing'' pupil (407,408). This phenomenon occurs from shift of the midline away from the lesion, with compression either of the contralateral oculomotor nerve or the contralateral side of the mesencephalon against the lateral tentorial edge. The localizing value of this pupil sign is far less important in this era of modern neuroimaging, but it remains useful in understanding the sequence of events during uncal herniation. In any event, during this early phase, respiration may be normal, extraocular movements and oculocephalic responses may be unimpaired, and motor abnormalities may reflect only a supratentorial process. Nevertheless, once other signs of herniation or brain stem compression appear, deterioration may proceed rapidly, with the patient becoming comatose within a few hours.

Once the pupil is fully dilated, ophthalmoplegia related to oculomotor nerve dysfunction soon follows. In this late third nerve stage, the patient usually becomes deeply stuporous, then comatose. Oculocephalic testing initially shows evidence of ocular motor impairment, with eventual disappearance of all responses. As the opposite cerebral peduncle becomes compressed against the contralateral tentorial edge, hemiplegia develops ipsilateral to the expanding supratentorial lesion (409). The signs of mesencephalic damage continue to develop. The pupil opposite the one that originally dilated may become fixed and widely dilated or assume a midposition (410,411). Eventually, both pupils become dilated and nonreactive to light stimulation. Most patients at this stage show sustained hyperpnea, impaired or absent oculocephalic and caloric responses, and bilateral decerebrate rigidity. From this stage, progression of the uncal syndrome is clinically indistinguishable from that of the central syndrome.

Coma from Metabolic Disease

In patients in deep coma, the state of the pupils may become the single most important criterion that clinically distinguishes between metabolic and structural disease. Pupillary pathways are relatively resistant to metabolic insults. Thus, the presence of preserved pupil light reflexes despite concomitant respiratory depression, caloric unresponsiveness, decerebrate rigidity, or motor flaccidity suggests metabolic coma. Conversely, if asphyxia, drug ingestion, or preexisting pupillary disease can be eliminated as a cause of coma, the absence of pupillary light reflexes in a comatose patient strongly implicates a structural lesion rather than a metabolic process.

In a study of 115 patients presenting to the emergency department with coma (mean Glasgow Coma Scale score of 4) from a variety of structural and metabolic etiologies (cardiopulmonary arrest excluded), both loss of the pupil light reflex and anisocoria were found to be independent predictors of underlying structural pathology (412). Loss of the light reflex had greater sensitivity (83%) for predicting a structural lesion, whereas the presence of anisocoria was less sensitive (39%) but very specific (96%) for a structural lesion. Structural causes of coma included intracerebral hemorrhage, subarachnoid hemorrhage, acute infarction, subdural and epidural hematoma, brain contusion, and tumor. In the same series, 16 of 69 patients (23%) with coma of metabolic origin demonstrated loss of the pupil light reflex; half of these patients were comatose from drug overdose (412).

Normal pupil shape, size, and reactivity are highly indicative of intact midbrain function. In one series of 162 patients with severe head injury, pupillary dysfunction was the feature that correlated best with brain stem ischemia from damage to perforating vessels from the basilar artery (413).

Cheyne-Stokes Respiration

Cheyne-Stokes respiration (CSR) is a pattern of periodic breathing in which phases of hyperpnea regularly alternate

with apnea. The breathing waxes from breath to breath in a smooth crescendo and then, once a peak is reached, wanes in an equally smooth decrescendo. CSR implies bilateral dysfunction of neurologic structures usually lying deep in the cerebral hemispheres or diencephalon, but rarely as low as the upper pons (414).

During CSR, the size of the pupils fluctuates. The pupils dilate in the hyperpneic phase unless there is a concomitant sympathetic nerve paralysis, and they constrict during the apneic phase unless there is a concomitant oculomotor nerve paralysis (415). The cyclic breathing and pupillary movement also are associated with cyclic changes in the level of consciousness. During the apneic phase, the patient slips into a deeper coma; in the hyperpneic phase, the patient may become agitated. In humans, the mydriasis of the hyperpneic phase is almost, but not entirely, blocked by topical sympatholytic drugs (e.g., 5% guanethidine) and does not occur when there is an associated or unrelated Horner syndrome. This suggests that neural activity, mediated by the peripheral sympathetic pathway to the eye, plays an important role in the dilation. This suggests, in turn, that the mechanism of the mydriasis of the agitated phase of CSR may be similar to that of reflex pupillary dilation and related to the intermittent partial arousal of a semicomatose patient.

DISORDERS OF ACCOMMODATION

Abnormalities of accommodation usually are acquired and occur most frequently as part of the normal aging process (presbyopia). However, disturbances of accommodation also may occur in otherwise healthy persons, in persons with generalized systemic and neurologic disorders, and in persons with lesions that produce a focal interruption of the parasympathetic (and rarely the sympathetic) innervation of the ciliary body. Also, accommodative function can be voluntarily disrupted.

ACCOMMODATION INSUFFICIENCY AND PARALYSIS

Congenital and Hereditary Accommodation Insufficiency and Paralysis

Congenital defects are a rare cause of isolated accommodation insufficiency. The ciliary body is defective in a number of congenital ocular anomalies, but in most cases vision is so defective that an inability to accommodate is never noted by either the patient or the physician. Aniridia and choroidal coloboma cause obvious defects of the ciliary body. Ciliary aplasia can occur in well-formed eyes in which the iris is intact and reacts normally to light.

Sédan and Roux described three brothers who could see normally for distance without glasses but required +4.00 spherical lenses for reading (416). None of the children had pupillary constriction during near viewing, although their other ocular functions were normal. The children's retinoscopic findings were not reported, but neither atropine nor physostigmine influenced the state of their accommodation. Aplasia of the ciliary body was the presumed congenital defect. In another family of 10 affected members, an accommodative defect was present in infancy and thereafter nonprogressive by history (417). Pharmacologic assessment with various topical agents suggested a difficulty with either the ciliary musculature or the lens of the affected eyes.

Congenital absence of accommodation has been noted in combination with congenital mydriasis. In three such cases, patent ductus arteriosus was an associated anomaly (43). Defective accommodation was noted in 21 of 78 (27%) dyslexic children, suggesting an association between the two disorders (418).

Acquired Accommodation Paresis

Isolated Accommodation Insufficiency

Accommodation insufficiency refers to an accommodative ability that measures below the minimum for the age of the patient. Most clinicians use the near point of accommodation as their diagnostic criterion for accommodation insufficiency (accommodative amplitude that is 2 diopters or more below the age-appropriate minimum). Isolated accommodation insufficiency occurring in otherwise healthy eyes can be divided into two groups: (*a*) static insufficiency and (*b*) dynamic insufficiency (419).

Static accommodation insufficiency is an inadequate response of either the lens or the ciliary muscle, despite normal ciliary body innervation and neural function. It usually occurs gradually from changes occurring in either the lens or the ciliary body. The most common cause of isolated static insufficiency is presbyopia. In some patients, however, there is sudden loss of accommodation that does not recover. Treatment consists of appropriate spectacle correction.

Dynamic accommodation insufficiency occurs in patients who have inadequate parasympathetic impulses required to stimulate the ciliary musculature but have normal pupil size and reactivity. Such patients usually are asthenopic persons who become ill, often hospitalized, with some unrelated condition. Dynamic accommodation insufficiency also may occur in otherwise healthy young individuals, particularly in children with nonspecific viral illnesses (420,421). The transient loss of accommodation that can occur just before or after childbirth may be another example of this phenomenon (422). Raskind listed various systemic disorders associated with an acquired accommodation insufficiency (423). In all these cases, it is likely that the accommodation insufficiency represents a nonspecific manifestation of the systemic disorder.

The symptoms of dynamic accommodation insufficiency are asthenopia, tiring of the eyes sometimes associated with brow ache, irritation and burning of the eyes, blurred vision particularly for near work, inability to concentrate, and photophobia. As a general rule, symptoms resolve and accommodation recovers following treatment of the underlying illness and restitution of the patient's former state of health. If accommodation insufficiency remains, the prescription of convex (plus) lenses is indicated, regardless of the patient's

age. In patients with an associated convergence insufficiency, convergence exercises or base-out prisms added to the near correction may be of benefit.

Accommodation Insufficiency Associated with Primary Ocular Disease

Iridocyclitis may cause profound dysfunction of the ciliary body. In the acute stage, there may be ciliary spasm and loss of accommodation. In the chronic stage, atrophy of the ciliary body results in accommodation insufficiency. The more severe the uveitis, the more commonly mydriasis and cycloplegia (internal ophthalmoplegia) are associated with it. In addition, viruses such as herpes zoster may produce a uveitis associated with a ciliary ganglionitis, resulting in a tonic pupil syndrome.

Glaucoma in children or young adults causes accommodation insufficiency from secondary atrophy of the ciliary body. The drugs used in the management of glaucoma affect the ciliary body as well as the iris. In patients who still are able to accommodate, miotic drugs frequently produce ciliary spasm with symptoms of blurred vision.

Metastases to the suprachoroidal space may produce cycloplegia and pupillary dilation from damage to the ciliary neural plexus. Lymphoma and carcinoma of the breast, lung, or colon are the most common tumors that produce this condition.

Internal ophthalmoplegia associated with contusion of the globe was discussed in the section above on the pupil. In most cases, when accommodation is paralyzed, the pupil is dilated and fixed. Recovery of accommodation is common, but full recovery of pupillary function is less likely. On rare occasions, the pupil is spared or recovers fully but the ciliary muscle remains paralyzed. Patients who ''accidentally'' notice the inability to accommodate in one eye should be questioned specifically for previous trauma to that eye (11).

Immediately following a concussion injury to the globe, the pupil is small and accommodation is spastic. Subsequently, the pupil dilates and the ciliary muscle becomes paretic. Accommodation usually returns in 1–2 months. The traumatic etiology of the accommodation paresis may be suspected by slit-lamp biomicroscopic observation of tears in the iris sphincter, tears at the root of the iris, or recession of the angle of the anterior chamber with posterior displacement of the ciliary attachment. There also may be associated ocular hypotension or glaucoma. Following trauma to the globe, rupture of zonular fibers with partial subluxation of the lens also may produce loss of accommodation.

Iatrogenic trauma to the eye, such as that which occurs during retinal reattachment surgery, cryotherapy, or panretinal photocoagulation, may injure the ciliary nerves, producing accommodation paresis and mydriasis (424–426). Laser applications at or anterior to the equator and long exposure times are important factors in the development of accommodation paresis following photocoagulation (427). Optic nerve sheath fenestration performed from the lateral approach can damage the short ciliary nerves that penetrate the temporal sclera, causing a postoperative tonic pupil (245). Sector palsy of the iris sphincter has been reported after argon laser trabeculoplasty (244). Transient internal ophthalmoplegia also can result from local anesthesia injected into the lids or gums that inadvertently enters into the orbit (see also the section above on Local Tonic Pupils).

Accommodation Insufficiency Associated with Neuromuscular Disorders

Some diseases produce myopathic changes in the smooth muscle fibers of the ciliary body, but isolated ocular involvement of this type is rare.

Myasthenia gravis may cause defective accommodation (428,429). Manson and Stern studied patients with MG and patients with unexplained accommodation disturbances (430). All patients were questioned about diplopia, ptosis, and the effects of sustained reading or close work upon their vision. Binocular and uniocular accommodation amplitudes were measured. Of nine patients with MG (six with generalized and three with ocular disease), eight had abnormal fatigue of visual accommodation. The accommodation defect improved rapidly after an intravenous injection of edrophonium hydrochloride (Tensilon).

Botulism nearly always causes an acute accommodation paralysis. The toxins produced by *C. botulinum* interfere with the release of acetylcholine at the neuromuscular junction and in the cholinergic autonomic nervous system. Although several different subtypes of toxin exist and routes of human infection can vary (food-borne, wound, gastrointestinal tract colonization in infants), clinical manifestations are similar. These include progressive descending skeletal muscle weakness, ocular motor palsies, bulbar paralysis, and cardiovascular lability (431). Food-borne botulism produces prominent gastrointestinal symptoms as well.

Almost 90% of patients with botulism of any type complain of blurred vision. Paralysis of accommodation and impairment of the pupillary light reflex are common and early signs of botulism, often appearing suddenly about the 4th or 5th day of the illness. Accommodation is usually more severely affected than pupil function, for unclear reasons (Fig. 16.31). In some cases, accommodative failure is the initial and sole sign of nervous system involvement. In a series of nine patients with food-borne botulism, all patients examined acutely had marked or complete accommodative loss but full mydriasis was present in only one patient, and another patient had sluggish pupillary reactions (328). Recognition of the clinical syndrome of botulism is critical, as respiratory failure can result in mortality rates up to 20% (431).

Tetanus can produce accommodation paralysis. In most cases, the accommodation paralysis occurs in the setting of generalized ophthalmoparesis; however, one patient described had normal eye movements and normally reactive pupils to light stimulation (432).

Myotonic dystrophy frequently produces degenerative changes in the lens, the region of the ora serrata, and the anterior chamber angle. It also may be associated with ocular hypotension. It is reasonable to assume that the ciliary muscle also is affected, because other smooth muscle dysfunction occurs in such patients (433).

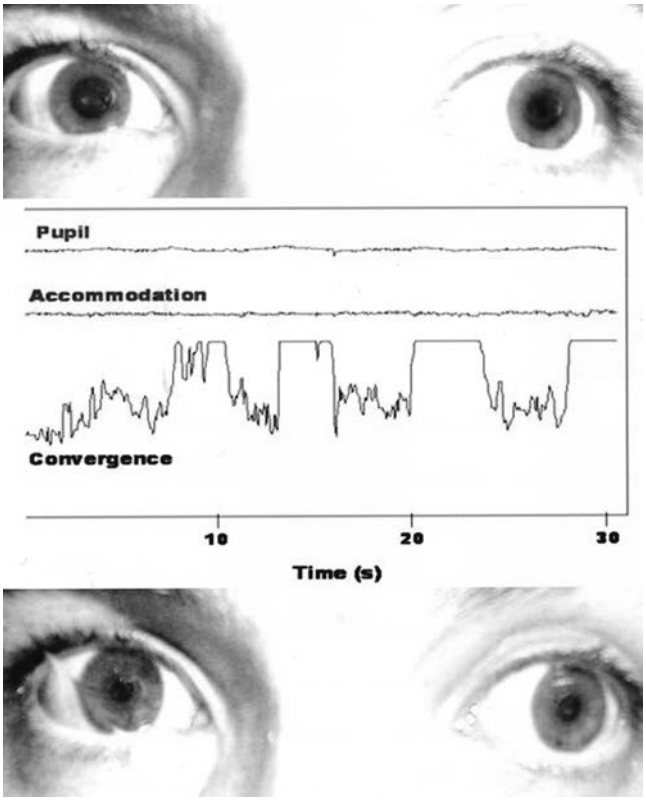

Figure 16.31. The effect of botulism on the elements of the near reflex. The patient was a 33-year-old man with acute food-borne botulism. His symptoms were 4 days of blurred vision, abdominal pain, nausea, and sweating. *Top*, The patient's pupils are large and unreactive to light. *Middle*, Simultaneous recordings of pupil size, accommodation, and convergence to near effort confirm complete paralysis of pupil responsiveness and accommodation, whereas convergence is intact. *Bottom*, Both pupils constrict following instillation of 0.1% pilocarpine. (Courtesy of Dr. Helmut Wilhelm.)

Accommodation Insufficiency Associated with Focal or Generalized Neurologic Disease

Accommodation paresis may be caused by both focal and generalized neurologic disorders that interrupt the innervation of the ciliary body. Supranuclear lesions can influence the signal inputs to the parasympathetic midbrain nuclei for accommodation, resulting in paresis or even paralysis of accommodation. Such lesions include damage to the cerebral cortex, rostral midbrain, superior colliculus, and possibly the cerebellum (434,435). In these cases, convergence insufficiency usually accompanies the accommodation insufficiency because of cross-coupling between these two systems.

Acute infectious or epidemic encephalitis as well as postinfectious acute disseminated encephalomyelitis (ADEM) such as that which is associated with or follows measles, chickenpox, or other viral infections can cause accommodative paralysis (436). Typically, patients have loss of the near triad (convergence palsy, absence of pupillary near response, failure of accommodation) and normal pupil responses to light. Histopathologic examination in fatal cases shows diffuse perivenous white-matter lesions throughout the cerebral hemispheres and brain stem.

An acute focal lesion of the hemispheres may cause acute bilateral accommodation insufficiency. Specifically, this has been reported with an acute ischemic stroke in the territory of the left middle cerebral artery and an acute hematoma in the left pariteo-occipital region (437,438). The issue is whether the accommodation insufficiency is related to a direct effect of these lesions on supranuclear pathways for accommodation or is a nonspecific sequela of a significant focal cerebral lesion. If the former, it remains to be determined whether a lesion in either hemisphere can cause accommodation insufficiency or just a lesion in the left hemisphere.

Acute problems with near vision resulting from an abnormality of accommodation can be one of the earliest symptoms of pressure on the dorsal mesencephalon such as from obstructive hydrocephalus or a pineal tumor. These complaints may appear weeks before the pupil light reaction or ocular motility becomes clinically abnormal. Particularly in previously healthy children and young adults who suddenly lose accommodation, a careful evaluation should be undertaken to exclude lesions in the area of the rostral dorsal midbrain, including the superior colliculus (439,440). Some of these patients also demonstrate a sudden increase of myopia (pseudomyopia) related to accommodation spasm with blurring of distant vision.

Wilson disease is an hereditary disorder of copper metabolism characterized by progressive degeneration of the CNS associated with hepatic cirrhosis. The neurologic syndrome frequently includes rigidity, difficulty speaking and swallowing, and a characteristic tremor of the wrists and shoulders. Ocular findings include a peripheral corneal ring of copper deposition involving Descemet's membrane (Kayser-Fleischer ring), copper pigment under the lens capsule, and various ocular motor disturbances, including jerky oscillations of the eyes, involuntary upgaze, paresis of upgaze, and slowed saccadic movements. Paresis of accommodation is common (441,442), but the location of the lesion responsible for the accommodation paresis is controversial. Some investigators favor a supranuclear lesion (441,443), whereas others postulate a lesion in the region of the oculomotor nucleus that serves the near response (442).

In contrast to the aforementioned supranuclear lesions that result in bilateral paralysis of accommodation with sparing of the pupil light reflex, lesions of the peripheral oculoparasympathetic pathway typically result in unilateral paralysis of accommodation and paralysis of the pupillary light reflex in the same eye. This is because the peripheral impulses for pupil constriction and accommodation originate in the same visceral (Edinger-Westphal) nuclei and follow the same peripheral pathway to the eye. Thus, the patient with an acute lesion in the peripheral pathway subserving accommodation will more likely seek medical consultation for the associated mydriasis than the blurred near vision. The evaluation of such an anisocoria was outlined in an earlier section of this chapter. Common types of injury along this oculoparasympathetic pathway are infection, ischemia, and compression,

resulting in an oculomotor nerve palsy or a tonic pupil syndrome.

Primary and secondary aberrant reinnervation of the oculomotor nerve also can involve the ciliary muscle. Herzau and Foerster described three young patients who had increased myopia during attempted adduction of the affected eye, presumably from aberrant reinnervation (444).

An isolated accommodation paralysis—accommodation paralysis without mydriasis—theoretically can be caused by a lesion of the ciliary ganglion or short ciliary nerves. We are unaware of any well-documented cases of this phenomenon.

Accommodation Insufficiency Associated with Systemic Disease

Children and adults may develop transient accommodation paresis following various systemic illnesses. In such cases, the accommodation paresis often appears to occur as an indirect complication of the systemic disorder rather than from direct damage to the ciliary body or its innervation. There are, however, certain systemic diseases that produce accommodation insufficiency through direct effects on the ciliary body and lens or on their innervation.

In patients with diphtheria, accommodative paralysis usually is bilateral and occurs during or after the 3rd week following the onset of infection. Recovery is the rule but may take several years (445). Because of regular vaccination, the infection from *Corynebacteria diphtheriae* is now rare in most developed countries. Accommodation paralysis has been reported following injection of diphtheria antitoxin. The mechanism of diphtheritic accommodation palsy appears to be related to toxin-induced segmental demyelination of peripheral nerves with preservation of axons (446).

Loss of accommodation may occur in patients with diabetes mellitus from several mechanisms (447). For example, accommodation paresis may develop in young patients with previously uncontrolled diabetes who have just begun treatment. Hyperopia and accommodation weakness develop concurrently within a few days after the patient's blood glucose has been lowered and then gradually return to normal over 2–6 weeks. The mechanisms for the refractive and accommodative changes in diabetes are poorly understood. Sorbitol accumulates in the lens during periods of hyperglycemia, causing it to swell, and the lens appears responsible for the shifts in refraction because these shifts do not occur in aphakic or pseudophakic eyes. The same mechanism may account for accommodation paresis, because lens resiliency probably is decreased from the swelling. Persistent loss of accommodation can occur in patients with both controlled and uncontrolled diabetes mellitus from damage to the parasympathetic innervation to the eye. In this setting, accommodation paresis and mydriasis are due to denervation injury rather than to effects on the lens. Thus, either metabolic or neurologic mechanisms can be responsible for reduced accommodation in patients with this disease.

Lieppman described 12 professional divers who had visual complaints after decompression sickness (448). All of the divers had evidence of severe accommodation and convergence insufficiency that was thought to be caused by a ''central'' lesion. These findings were reproduced in two rhesus monkeys experimentally subjected to similar hyperbaric conditions.

Accommodation Insufficiency Associated with Trauma to the Head and Neck

Theoretically, any cerebral injury could impair the highly complex neurophysiologic system involved in the coordination of the near response. Similarly, abnormal input from the upper posterior cervical roots or contusion to the side of the cervical cord could disturb transmission in the ascending spinotegmental and spinomesencephalic pathways that influence parasympathetic outflow from the Edinger-Westphal median nuclei. Symptoms of difficulty with focusing at near and at far, commonly associated with headache and pains about the eyes, are common complaints in patients who have suffered cerebral concussion or craniocervical extension injuries (449). These vague and ill-defined complaints are most prominent during the first weeks or months after injury. The prevalence of accommodation dysfunction in patients with head or neck trauma is not exactly defined and may be influenced in part by the average age of patients studied, as older patients likely have presbyopia prior to trauma.

In a series of 161 patients with head injury (average age 29 years), Kowal found that 16% had poor accommodation, 19% had over-accommodation (pseudomyopia), and 14% had convergence insufficiency (450). In about half of these patients, near vision complaints improved or resolved within the first year after their injury. Similarly, among 39 patients with whiplash or indirect injury to the neck, Burke et al. found decreased accommodation and convergence in nine (23%), six of whom were symptomatic (451). Five of these six patients recovered accommodation after 9 months.

Tests of accommodation depend upon an earnest, volitional effort by a motivated patient. Thus, patients who have cortical deficits, loss of concentration, poor comprehension, excessive somnolence, or pain often perform poorly on accommodative tests. Other patients attempting to gain material or psychological compensation may intentionally perform poorly on these tests (452). The persistence of symptoms for many months or even years is most common in patients who are seeking compensation for their injury through litigation.

Accommodation Insufficiency and Paralysis from Pharmacologic Agents

Most topical pharmacologic agents that produce pupillary mydriasis also produce cycloplegia, including atropine, scopolamine, homatropine, eucatropine, tropicamide, cyclopentolate, and oxyphenonium. Various investigators have compared the duration and effectiveness of cycloplegia produced by these agents when used as ocular solutions (453,454). None of these agents causes persistent paralysis of accommodation after discontinuation, although there may be some confusion when loss of accommodation occurs after treatment of a severe viral uveitis (e.g., herpes zoster, varicella) with a cycloplegic agent. In such cases, the accommodation

paralysis occurs from the effects of the virus on the ciliary ganglion and not from the cycloplegic drug.

When cycloplegic agents or related substances are incorporated in medications that are taken internally or applied to the skin as ointments or plasters, there may be sufficient absorption to produce paresis of accommodation. In such cases, the accommodation deficit is partial and recovery begins shortly after the medication is discontinued.

Accommodation Paralysis for Distance: Sympathetic Paralysis

Lesions of the cervical sympathetic outflow may produce a defect that prevents the patient from accommodating fully from near to far, but most reports describe an increase in accommodative amplitude on the side of the Horner syndrome (455). Cogan described an ipsilateral increase in near accommodation in five patients with Horner syndrome and noted an apparent paresis of accommodation in one patient (456).

ACCOMMODATION SPASM AND SPASM OF THE NEAR REFLEX

General Considerations

Accommodation spasm is due to excessive activity of the ciliary muscle that results in an abnormally close point of focus. Clinically, there is an apparent or increased myopia that disappears following cycloplegia (pseudomyopia). Accommodation spasm typically affects both eyes, but unilateral cases have been reported (457). It can occur in isolation as pseudomyopia or in association with convergence spasm and excessive pupillary miosis in varying combinations and degrees, all of which probably represent the spectrum of clinical presentations of spasm of the near reflex (458).

Symptoms of isolated accommodation spasm are blurry vision, especially at distance, fluctuating vision, asthenopia, eyestrain, poor concentration, brow ache, and headaches. The diagnostic finding is a greater myopia on manifest refraction compared with cycloplegic refraction, the difference ranging from 1 to 10 diopters. Additionally, the patient will not accept the majority of the cycloplegic refraction, preferring instead the greater myopic correction for visual improvement.

In addition to the symptoms of accommodation spasm, patients with spasm of the near reflex who have convergence spasm also complain of a horizontal diplopia that often is variable in nature. Because of the diplopia and apparent esotropia, such patients initially may be mistaken as having a unilateral or bilateral abducens nerve palsy or ocular myasthenia and undergo extensive neurologic and neuroimaging investigations (428,459). Spasm of the near reflex should be suspected in a patient with an apparent unilateral or bilateral limitation of abduction that is associated with severe bilateral miosis (459,460). The diagnosis is confirmed by demonstrating that the miosis resolves as soon as either eye is occluded with a hand-held occluder or patch (461). Additionally, the apparent abduction weakness present on horizontal gaze testing with both eyes open will disappear when the opposite eye is patched (monocular ductions testing) or when the oculocephalic maneuver is performed. Refraction with and without cycloplegia will establish the presence of pseudomyopia as well.

Accommodation Spasm Unassociated with Organic Disease

Most cases of accommodation spasm (usually as part of spasm of the near reflex) appear to be nonorganic, being triggered by an underlying emotional disturbance or occurring as part of malingering. In such cases, spasm of the near reflex typically occurs as intermittent attacks lasting several minutes (462,463). The degree of accommodation spasm and convergence spasm in such patients is variable; however, miosis is always present and impressive (Fig. 16.32). However, many young persons, when undergoing a noncycloplegic refraction, can accept increasing degrees of overcorrecting concave (minus) lenses. When these same patients undergo a cycloplegic refraction, they are found to be emmetropic or at least significantly less myopic than they appeared to be when not cyclopleged. However, unlike patients with accommodation spasm who prefer the greater myopic correction, these otherwise healthy young persons prefer their cycloplegic refraction for best-corrected visual acuity.

The management of most patients with nonorganic spasm of the near reflex begins with simple reassurance that they have no irreversible visual or neurologic disorder. In other instances, referral for psychiatric counseling is appropriate. Symptomatic relief may be necessary with a cycloplegic agent and bifocal spectacles or reading glasses. Glasses with an opaque inner third of the lens to occlude vision when the eyes are esotropic have been proposed for the convergence spasm (464). Nonorganic spasm of the near reflex also is discussed in Chapter 27.

Accommodation Spasm Associated with Organic Disease

Accommodative spasm has been reported, mostly as single case occurrences, in association with various organic diseases and CNS lesions. These include neurosyphilis, ocular inflammation, Raeder paratrigeminal neuralgia syndrome, cyclic oculomotor palsy, congenital ocular motor apraxia, congenital horizontal gaze palsy, pineal tumor, Chiari malformation, pituitary tumor, metabolic encephalopathy, vestibulopathy, Wernicke-Korsakoff syndrome, epilepsy, cerebellar lesions, and acute stroke (465–471).

Several investigators have reported spasm of the near reflex in patients with MG (472,473). Romano and Stark described a 26-year-old man who developed isolated pseudomyopia as a presenting sign of ocular MG (428). The pseudomyopia was thought to have occurred from ''substitute convergence'' that the patient used to compensate for bilateral medial rectus weakness rather than from true accommodation spasm.

Isolated accommodation spasm and spasm of the near reflex appear to be increasingly recognized as a consequence of head injury (450,474–477). In one series, accommodation

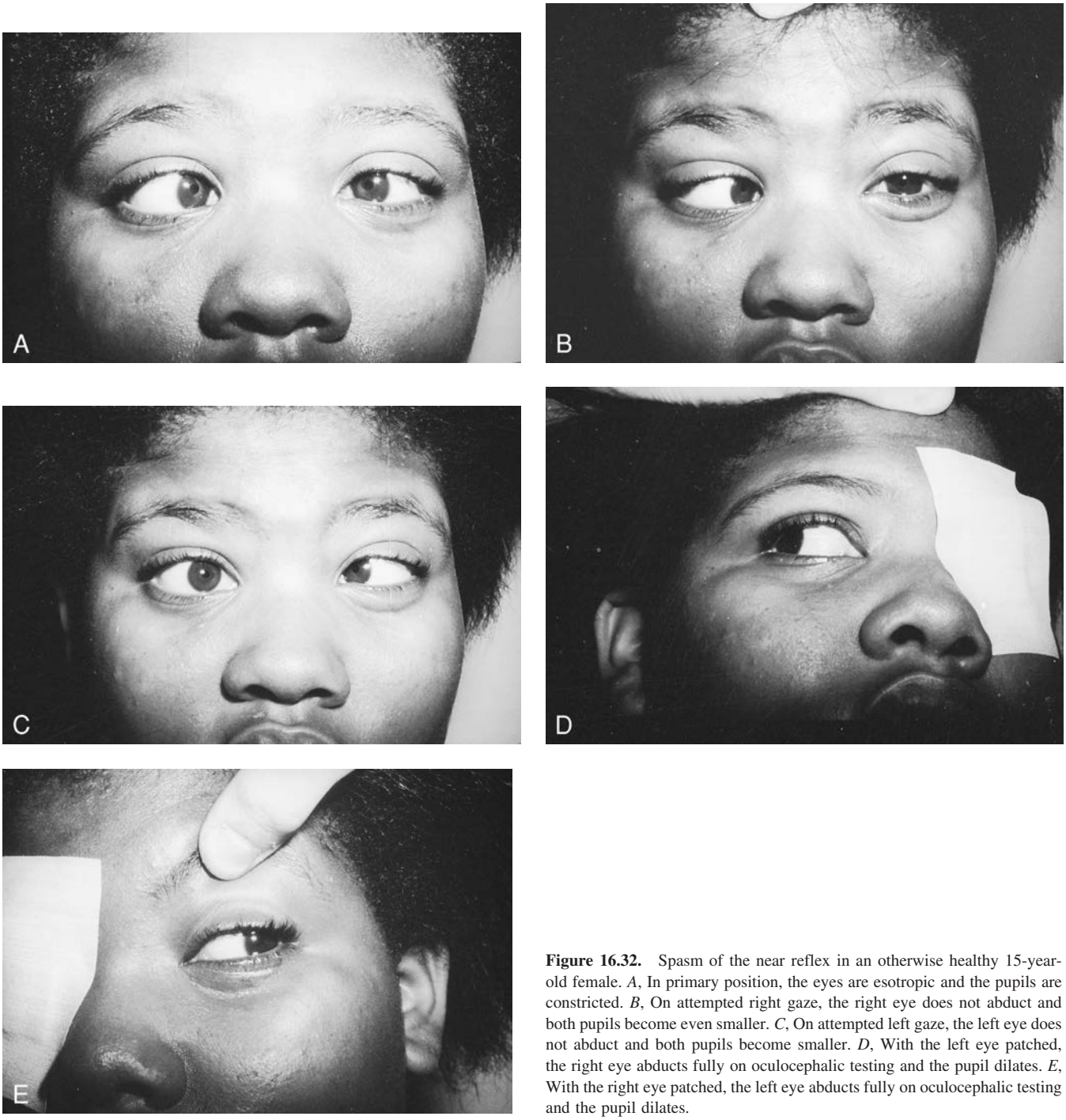

Figure 16.32. Spasm of the near reflex in an otherwise healthy 15-year-old female. *A*, In primary position, the eyes are esotropic and the pupils are constricted. *B*, On attempted right gaze, the right eye does not abduct and both pupils become even smaller. *C*, On attempted left gaze, the left eye does not abduct and both pupils become smaller. *D*, With the left eye patched, the right eye abducts fully on oculocephalic testing and the pupil dilates. *E*, With the right eye patched, the left eye abducts fully on oculocephalic testing and the pupil dilates.

spasm was found in 19% of patients following closed head injury (450). Chan and Trobe reported six patients who recovered from severe brain injury (i.e., comatose more than 1 week, increased intracranial pressure, brain stem deficits) and complained of reduced distance vision (474). Isolated pseudomyopia was found in all six patients, and full manifest correction alleviated the visual blur. Posttraumatic accommodation spasm may be a persistent condition, lasting up to 9 years after head trauma (474,476,478).

DRUG EFFECTS ON ACCOMMODATION

Most of the cholinergic agents mentioned in the earlier section of this chapter concerning pharmacologically induced miosis also produce an increase in accommodation

and, occasionally, accommodation spasm. Pilocarpine, physostigmine, and the organophosphate esters produce the most accommodation, whereas the effect of aceclidine on accommodation is minimal (478).

DISORDERS OF LACRIMATION

Disorders that disrupt the neural control of lacrimation include cerebral diseases and trigeminal nerve lesions as well as lesions along the parasympathetic secretomotor pathway from pons to lacrimal gland. The disorders of lacrimation produced by these lesions generally can be divided into three types: reduced tearing (hypolacrimation), excessive tearing (hyperlacrimation), and inappropriate tearing.

HYPOLACRIMATION

Lesions of the Trigeminal Nerve

The majority of afferent inputs for reflex lacrimation are carried via the ophthalmic division of the trigeminal nerve. Significant hypolacrimation can result from deafferentation of the tear reflex on one side, such as occurs in severe trigeminal neuropathy. However, lesions that damage the trigeminal nerve at the pontine angle, petrous tip, or Meckel's cave often simultaneously damage the nearby parasympathetic lacrimal fibers (either the nervus intermedius or the greater superficial petrosal nerve). In these cases, trigeminal nerve-related reduction of tears represents combined dysfunction in the afferent and efferent limbs of the tear reflex.

Brain Stem Lesions

It might be assumed that any lesion of the brain stem that involves the facial nucleus automatically produces decreased tearing and loss of taste because of the proximity of the structures conveying these modalities. In fact, abnormalities of tear secretion seldom are recognized in patients with lesions of the brain stem. Two patients with Moebius syndrome had bilateral congenital sensorineural deafness and facial motor palsy with intact lacrimation and taste sensation, demonstrating that lesions in this area of the pons can spare both taste and tearing as these functions are anatomically separate from the motor function (479).

Crosby and DeJonge called attention to an acquired brain stem syndrome with unilateral involvement of the superior salivary nucleus (480). One of the small vessels supplying the area near the fourth ventricle at the level of the superior salivary nucleus is prone to develop thrombosis. The vascular accident that develops when this vessel becomes occluded is characterized by a peripheral facial motor palsy, ipsilateral dry eye, and reduced salivary flow from the submaxillary gland. The rostral end of the vestibular nucleus lies in the immediate vicinity, and these patients usually have vertical or torsional nystagmus. The pathways and neurons concerned with lateral gaze also may be affected, causing an ipsilateral palsy of horizontal gaze.

Lesions Affecting the Nervus Intermedius

A peripheral facial palsy associated with ipsilateral loss of reflex tearing suggests a more proximal site of damage along the facial nerve pathway, either at the cerebellopontine angle or in the petrous bone. The secretomotor fibers for lacrimation and salivation exit the brain stem in the nervus intermedius. This nerve is sandwiched between the motor trunk of the facial nerve and the vestibulocochlear nerve as they traverse the cerebellopontine angle and the internal auditory meatus. Lesions in this area, usually tumors, can produce loss of hearing, vestibular dysfunction, facial palsy, decreased salivation, altered taste sensation, and a dry eye on the affected side.

Pulec and House found that 10 of 15 patients with vestibular schwannomas had demonstrable but asymptomatic deficiency of tearing on the side of the lesion (481). Because this sign often is present before any overt clinical evidence of the lesion, such as facial palsy or corneal hypesthesia, careful testing of reflex tearing in such patients may aid in initial diagnosis. Dysfunction of the nervus intermedius also occurs after surgical resection of vestibular schwannomas. In a series of 257 patients who had surgical removal of these tumors, 72% reported significant ipsilateral dry eye (loss or significant reduction of tears) postoperatively compared with 4% preoperatively (482). In addition, crocodile tears (see below) and abnormal taste were reported postoperatively in 44% and 48% of patients, respectively, compared with 2% and 6% preoperatively.

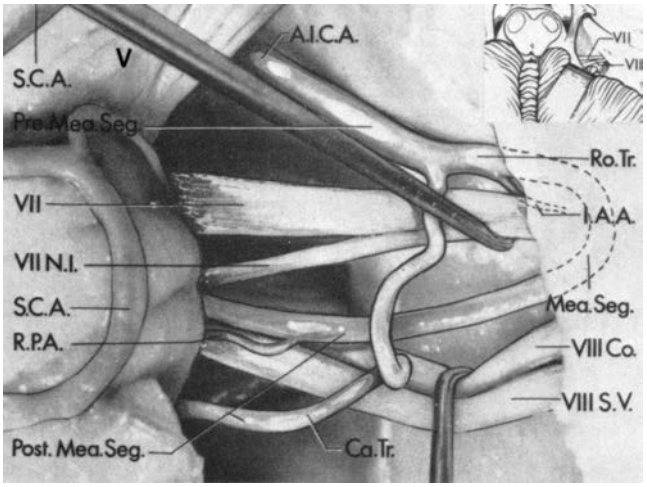

Figure 16.33. Relationships between nervus intermedius, facial nerve trunk, vestibulocochlear nerve trunk, and the superior cerebellar and anterior inferior cerebellar arteries. Nervus intermedius (VII N.I.) exits from the brain stem between the facial nerve trunk (VII) and the cochlear (VIII Co.) and superior vestibular (VIII S.V.) nerve trunks. Note the relationships of the rostral (Ro. Tr.) and caudal (Ca. Tr.) trunks of the anterior inferior cerebellar artery (A.I.C.A) to the facial-vestibulocochlear nerve complex. V, trigeminal nerve; S.C.A., superior cerebellar artery; R.P.A., recurrent perforating artery; I.A.A., internal auditory artery; Mea, Seg., meatal segment. (From Martin RG, Grant JL, Peace D, et al. Microsurgical relationships of the anterior inferior cerebellar artery and the facial-vestibulocochlear nerve complex. Neurosurgery 1980;6:483–507.)

At the end of the internal acoustic meatus, the motor trunk of the facial nerve and the nervus intermedius enter the facial canal that houses the geniculate ganglion (Fig. 16.33). Patients with injury to the facial nerve in the facial canal proximal to or at the geniculate ganglion do not have hearing loss; in fact, they may complain of hyperacusis from loss of the normal damping action of the stapedius muscle. Idiopathic and viral inflammation within the facial canal, skull base fractures, infection of the geniculate ganglion (e.g., herpes zoster, syphilis), and otitis media are common causes of facial nerve injury at this site.

Lesions Affecting the Greater Superficial Petrosal Nerve

Any lesion that involves the floor of the middle cranial fossa in the neighborhood of the gasserian ganglion may injure the lacrimal fibers in the greater superficial petrosal nerve (Figs. 16.34 and 16.35). The resulting deficiency of

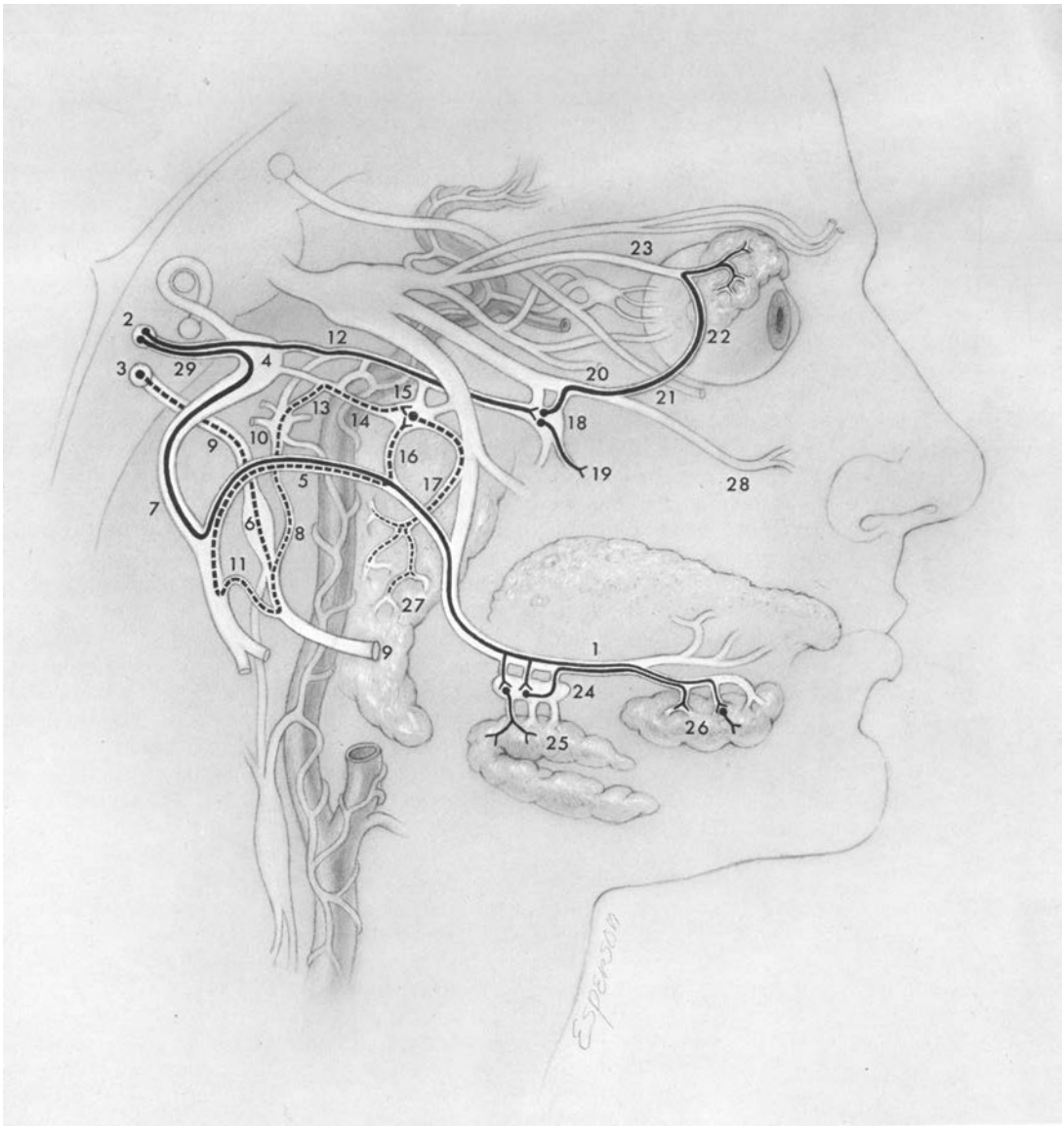

Figure 16.34. Secretomotor pathways for lacrimation and salivation: The efferent visceromotor (parasympathetic) outflow. 1, lingual nerve; 2, superior salivatory and lacrimal nucleus; 3, inferior salivatory nucleus; 4, geniculate ganglion of the seventh nerve; 5, chorda tympani; 6, petrosal ganglion; 7, facial nerve; 8, tympanic nerve; 9, glossopharyngeal nerve; 10, tympanic plexus; 11, anastomotic branch (cranial nerves 9 to 7); 12, greater superficial petrosal nerve; 13, deep petrosal nerve; 14, lesser superficial petrosal nerve; 15, otic ganglion; 16, anastomotic branch; 17, auriculotemporal nerve; 18, sphenopalatine ganglion; 19, branches to nasal mucosa and palatine glands; 20, maxillary division of trigeminal nerve; 21, zygomatic nerve; 22, zygomaticolacrimal anastomosis; 23, lacrimal nerve; 24, submaxillary ganglion; 25, submaxillary gland; 26, sublingual gland; 27, parotid gland; 28, infraorbital nerve; 29, nervus intermedius.

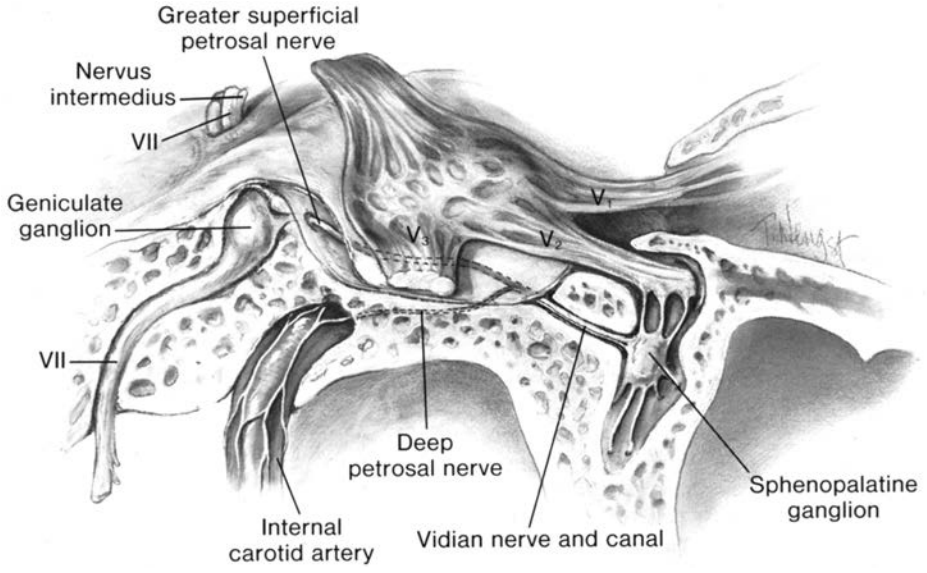

Figure 16.35. Vertical section through the axis of the petrous pyramid of the temporal bone showing the location of the geniculate ganglion and the course of the greater superficial petrosal nerve from the geniculate ganglion to the sphenopalatine ganglion. Some sympathetic fibers leave the internal carotid artery at the foramen lacerum to form the deep petrosal nerve. This nerve joins with the greater superficial petrosal nerve to form the vidian nerve. Note the connections between the sphenopalatine ganglion and the maxillary nerve trunk (V_2). V_1, ophthalmic nerve; V_3, mandibular nerve.

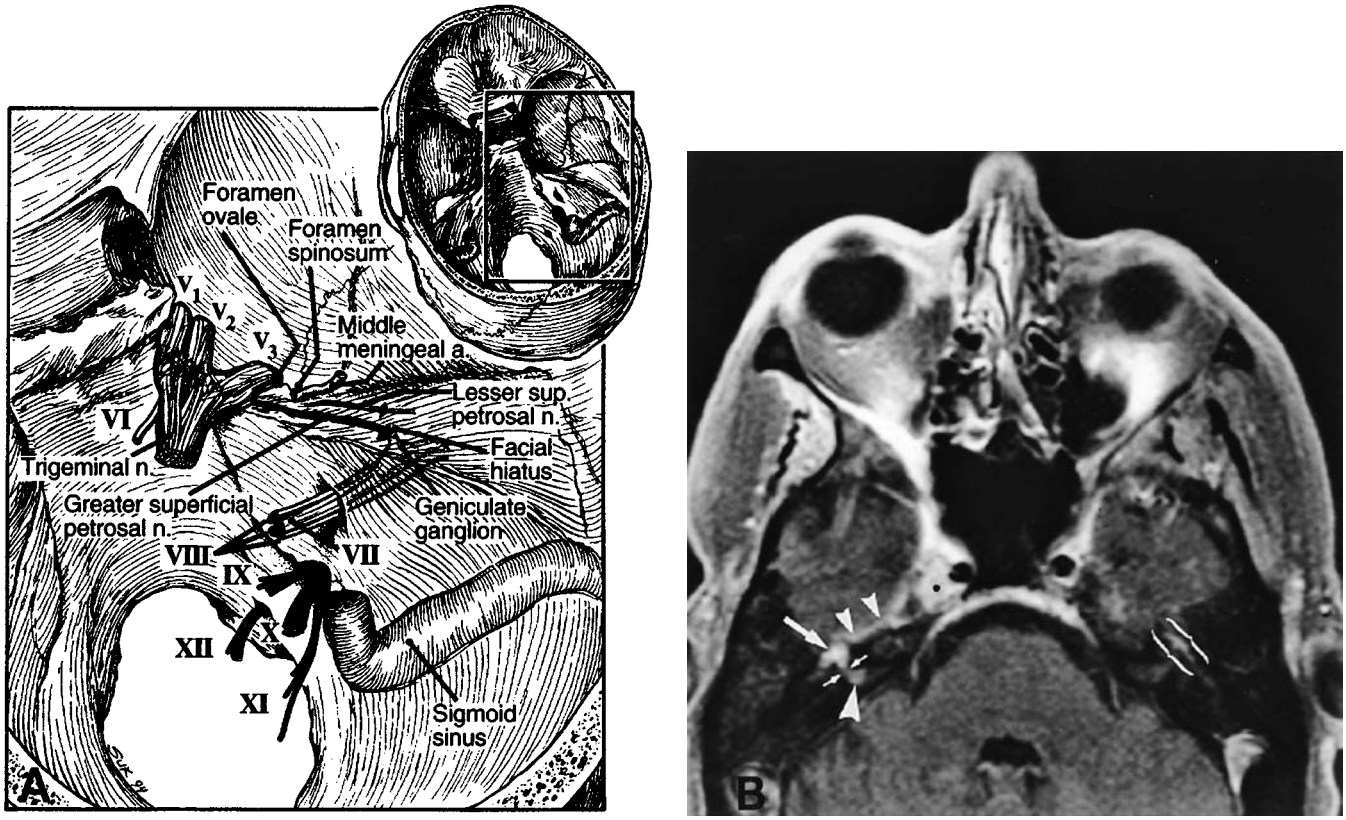

Figure 16.36. The greater superficial petrosal nerve. *A*, Diagram of the proximal facial nerve, including the takeoff of the greater superficial petrosal nerve (GSPN). *B*, Axial contrast-enhanced T1-weighted magnetic resonance image with fat suppression at the level of Meckel's cave and the temporal bone in a patient with perineural spread of adenoid cystic carcinoma along the right GSPN. Note tumor in the right cavernous sinus and anterior aspect of Meckel's cave (*black dot*). The GSPN courses directly beneath this area. Note the enhancement of the GSPN (*small arrowheads*). The geniculate region enhances brightly and is grossly enlarged (*large arrow*). The labyrinthine and distal intracanalicular segments of the facial nerve also show enhancement (*small arrows and large arrowhead*, respectively); these two segments of the facial nerve normally do not enhance. On the left side, the geniculate ganglion is of normal size (and enhances normally), and only the proximal GSPN and the proximal tympanic segment of the facial nerve enhance (*brackets*). (From Ginsberg LE, De Monte F, Gillenwater AM. Greater superficial petrosal nerve: Anatomy and MR findings in perineural tumor spread. AJNR Am J Neuroradiol 1996;17:389–393.)

tears on the affected side rarely is noted unless the patient has an associated palsy of the trigeminal or facial nerve and develops signs of keratitis from drying and exposure of the cornea. Acquired lesions that may damage the greater superficial petrosal nerve include nasopharyngeal tumors, meningeal sarcomas, facial nerve schwannomas, perineural tumor infiltration, inflammations of the gasserian ganglion (e.g., herpes zoster), petrositis, sphenoid sinus disease, aneurysms of the petrous portion of the internal carotid artery, fractures through the middle fossa, alcohol injections, and extradural operations for trigeminal neuralgia (483) (Fig. 16.36).

The finding of impaired tear secretion on the side of an acquired palsy of the abducens nerve is of great localizing value because it indicates a lesion (usually extradural) in the middle cranial fossa. Thus, patients with ''isolated'' abducens nerve palsies should undergo careful testing of reflex tear function in addition to other tests of facial and trigeminal nerve function. Most patients with a combination of an abducens nerve palsy and ipsilateral decreased reflex tearing have nasopharyngeal tumors.

Lesions Affecting the Sphenopalatine Ganglion

Lesions of the sphenopalatine ganglion (also called the pterygopalatine ganglion) frequently cause pain and hypesthesia in the cheek (the area supplied by the maxillary division of the trigeminal nerve) in addition to decreased tearing and dryness of the nasal mucosa on the same side. Thus, the combination of dry eye and cheek pain or numbness on the same side should prompt investigation for a lesion, usually a malignant tumor, in the pterygopalatine fossa (Fig. 16.37). Similarly, a patient with a known tumor or infection of the maxillary (or sphenoid) sinus who develops unilateral reduction of tear secretion should be suspected to have extension of the process beyond the confines of the sinus.

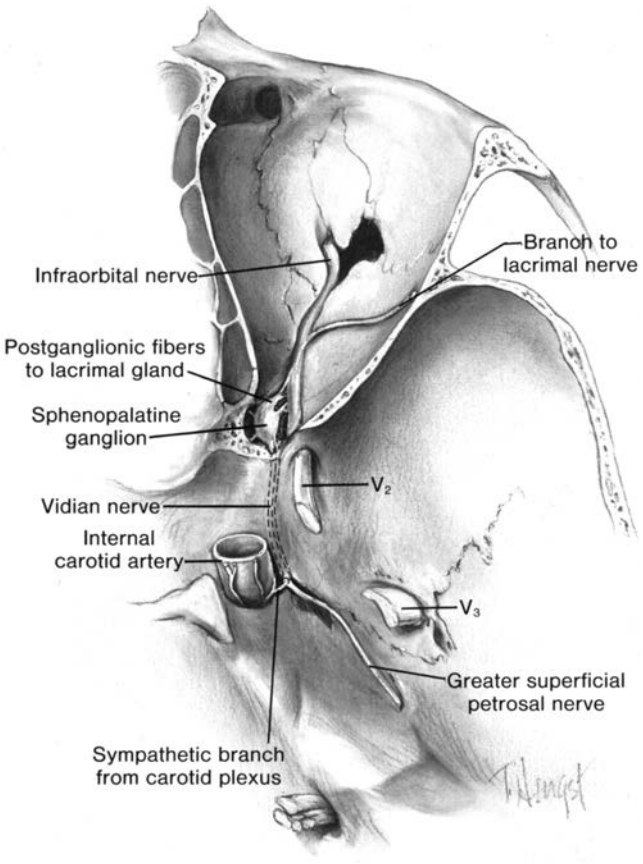

Figure 16.37. Anatomic relations of the sphenopalatine ganglion, the vidian nerve, and the maxillary nerve behind the posterior wall of the orbit and maxillary antrum, viewed from above.

Lesions of the Zygomaticotemporal Nerve

Damage to the zygomaticotemporal nerve produces postganglionic denervation of the lacrimal gland. Such damage usually occurs from facial trauma involving the posterior lateral orbital wall. Occasionally, tumors in this area, particularly metastatic carcinoma, will damage these fibers, resulting in a reduction of reflex tearing.

HYPERLACRIMATION

Reflex hypersecretion can result from excessive afferent triggers of the tear reflex arc or from overstimulation of the efferent parasympathetic fibers.

Supranuclear Lesions

The tear reflex normally can be elicited by a strong emotion such as sadness. This is called psychogenic tearing or crying. In cerebral diseases that significantly damage the frontal lobes, basal forebrain, thalami, or especially the posterior ventral hypothalamus, unexpected and excessive spells of crying (pathologic crying) can occur (484). Pharmacologic studies suggest dysfunction of the serotoninergic system as the cause of this syndrome, which may be treated with serotonin reuptake inhibitors (485). The main characteristics of pathologic crying are an absence of voluntary control and a lack of corresponding mood, such as intense sadness or grief. Pathologic crying and pathologic laughing, often termed emotional incontinence, frequently are associated with diverse neurologic and psychiatric findings. Emotional incontinence associated with dysphagia and dysarthria make up the syndrome of pseudobulbar palsy that may be seen in patients with parkinsonism, various age-related dementias, amyotrophic lateral sclerosis, giant-cell arteritis, hypothalamic tumors, and encephalitis.

Excessive lacrimation also can be associated with the photophobia caused by meningitis or encephalitis. Intermittent spells of excessive tearing were the first indication of recurrence of a craniopharyngioma in a 14-year-old boy (222). The lesion was suprasellar in location and compressed hypothalamic structures in the floor of the third ventricle.

SUNCT Syndrome

SUNCT syndrome (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) is characterized by moderately severe, strictly unilateral attacks of burning or stabbing pain confined to the orbital and

periorbital area associated with excessive lacrimation. The attacks are typically 10–120 seconds in duration, with symptomatic periods lasting days to months. Ipsilateral hyperlacrimation and conjunctival injection are considered essential to the diagnosis, and rhinorrhea and vasomotor signs such as forehead sweating also can occur in patients with this condition. Although certain clinical features suggest a similarity to trigeminal neuralgia or cluster headaches, the pathophysiology of SUNCT remains unknown. Hyperactivity in the thalamus and hypothalamus has been noted using functional MR imaging.

Sphenopalatine Neuralgia

Sphenopalatine neuralgia, also called Sluder neuralgia, is a syndrome of nasal pain accompanied by ipsilateral hyperlacrimation, rhinorrhea, salivation, photophobia, and hemifacial redness. Anesthesia or ablation of the sphenopalatine ganglion abolishes the symptoms (487). Initially thought to be an idiopathic inflammation of the sphenopalatine ganglion, this condition more likely is a neurovascular headache syndrome (488).

INAPPROPRIATE LACRIMATION

Commonly known as crocodile tears (Bogorad syndrome), the gustolacrimal reflex results from an anomalous lacrimal gland innervation that causes profuse and inappropriate tearing in response to stimulation of the taste buds. Most commonly, crocodile tears develop unilaterally in the eye on the side of a facial palsy. However, crocodile tears should not be confused with the watery eye of an acute facial palsy that is due to excess pooling and impaired drainage of tears from loss of normal orbicularis oculis action (blinking). Before discussing the congenital and acquired gustolacrimal reflexes, we will review some of the afferent pathways responsible for transmission of gustatory stimuli and the adjacent efferent pathways to the salivary glands.

Anatomy of the Afferent and Efferent Pathways Involved in the Gustolacrimal Reflex

Anatomy of the Afferent Gustatory Pathways

The taste buds of the tongue are the receptors for gustatory sensation. These afferent impulses are carried by the facial nerve (mediating taste from the anterior two thirds of the tongue) and the glossopharyngeal nerve (mediating taste from the posterior third of the tongue). The gustatory afferent fibers for the anterior two thirds of the tongue pass centripetally with the lingual branch of the mandibular nerve, split off under the base of the skull in the chorda tympani, and in this nerve pass through the petrotympanic fissure, the middle ear, and a special canal in the posterior wall of the tympanic cavity to the facial canal, then upward with the trunk of the facial nerve to the geniculate ganglion, where the cell bodies of these bipolar sensory neurons are located (Fig. 16.38). In the geniculate ganglion, the gustatory fibers continue centrally in the nervus intermedius. Upon entering the pons, they turn caudally as the tractus solitarius and finally synapse in the rostral end of the nucleus solitarius. Gustatory afferents from the posterior third of the tongue travel via the glossopharyngeal nerve to the brain stem and also synapse in the nucleus solitarius.

Anatomy of the Secretomotor (Parasympathetic) Nerves to the Salivary Glands

Preganglionic salivary neurons arise in two different nuclei in the brain stem and follow two separate pathways to their respective parasympathetic ganglia and end organs. Salivary neurons of the superior salivary nucleus leave the lower pons with the lacrimal fibers as the nervus intermedius, pass through the geniculate ganglion without synapsing, proceed down the facial nerve, and leave the facial canal with the chorda tympani. With this nerve, they join the lingual nerve and pass to the submandibular ganglion and the diffuse sublingual ganglia, where they synapse with the postganglionic neurons that innervate the submandibular and sublingual salivary glands.

Salivary neurons of the inferior salivary nucleus leave the medulla with the fibers of the glossopharyngeal nerve and pass through the jugular foramen with the vagus and spinal accessory nerves. These salivary fibers pass through the petrous ganglion of the glossopharyngeal nerve without synapsing, branch off at the base of the skull, and ascend as the tympanic nerve (of Jacobson) to the tympanic cavity through a small canal in the undersurface of the petrous portion of the temporal bone on the jugular fossa. Within the tympanic cavity, the tympanic nerve divides into branches that form the tympanic plexus and are contained in grooves on the surface of the promontory. It is in this location that an anastomosing branch from the tympanic plexus joins the greater superficial petrosal nerve through a foramen in the roof of the tympanic cavity. The secretory fibers leave the tympanic cavity, course through the anterior surface of the petrous bone, enter the middle fossa as the lesser superficial petrosal nerve, and leave through a foramen in the base of the middle fossa (or through the foramen ovale) to end in the otic ganglion, where they synapse with neurons that supply the parotid gland as the auriculotemporal nerve.

The otic ganglion lies at the base of the skull medial to the mandibular nerve and inferior to the foramen ovale. It has a sensory root from the fibers of the glossopharyngeal and facial nerves via the lesser superficial petrosal nerve, a motor root from the nerve to the internal pterygoid muscle, and a sympathetic root from the carotid sympathetic plexus. The otic ganglion gives origin to three communicating nerves: (*a*) the nerve to the pterygoid canal; (*b*) a twig to the chorda tympani; and (*c*) the auriculotemporal nerve. In addition, two motor branches supply the tensor tympani and the tensor veli palatini.

General Considerations Concerning the Gustolacrimal Reflex

The syndrome of unilateral lacrimation associated with eating and drinking was described initially by Oppenheim

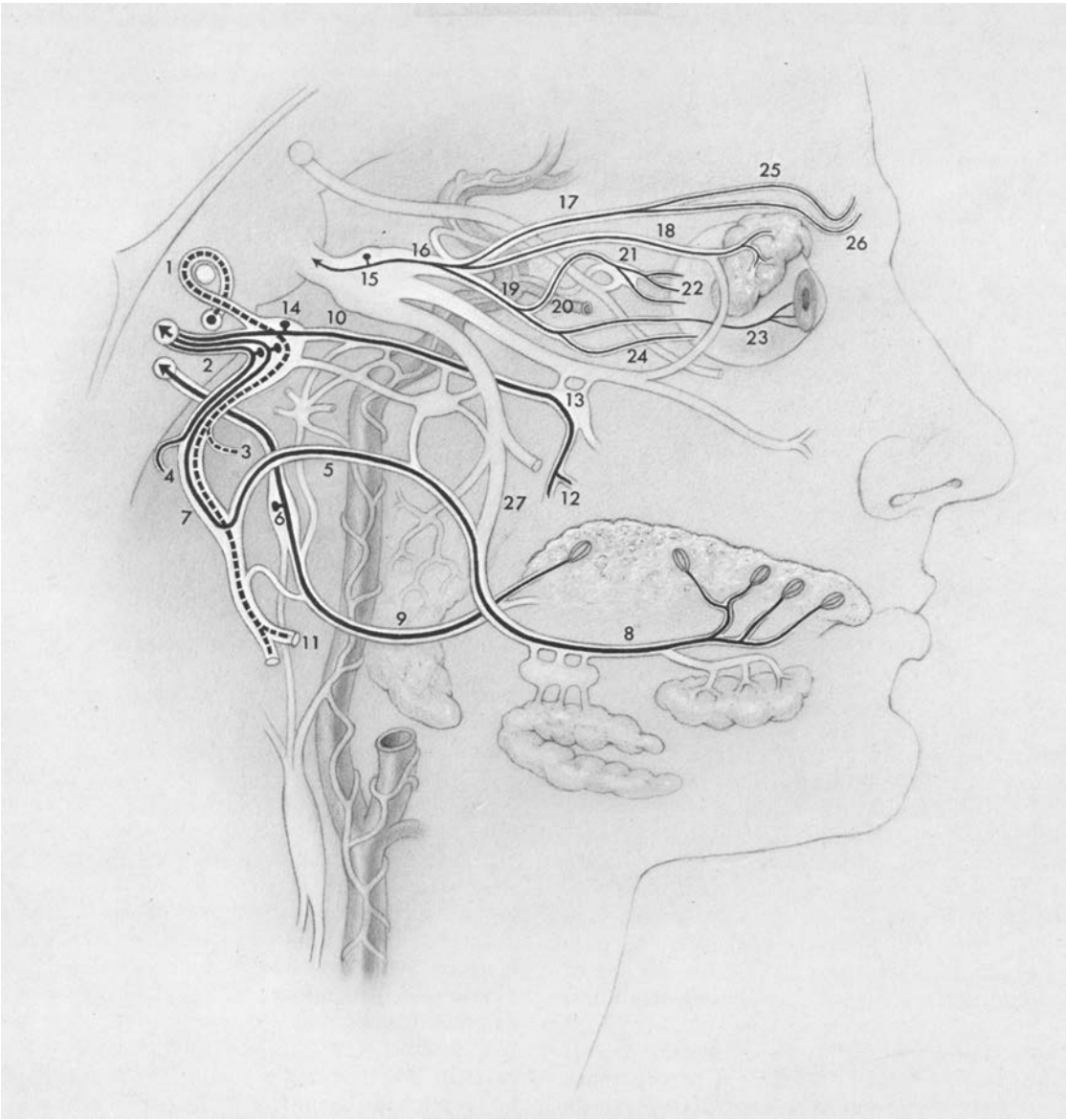

Figure 16.38. Sensory pathways for lacrimal and salivary reflexes. Afferent components of the trigeminal, facial, and glossopharyngeal nerves (*solid lines*). The motor outflow to the facial muscles is indicated as a *dashed line.* 1, motor root of facial nerve; 2, nervus intermedius; 3, motor nerve to stapedius muscle; 4, sensory fibers from eardrum and external auditory canal; 5, chorda tympani; 6, petrosal ganglion; 7, facial nerve; 8, lingual nerve; 9, glossopharyngeal nerve; 10, greater superficial petrosal nerve; 11, motor branches to face; 12, sensory fibers from soft palate and tonsillar region; 13, sphenopalatine ganglion; 14, geniculate ganglion; 15, gasserian ganglion; 16, ophthalmic division of the trigeminal nerve; 17, frontal nerve; 18, lacrimal nerve; 19, nasociliary nerve; 20, sensory root of ciliary ganglion; 21, ciliary ganglion; 22, short ciliary nerves; 23, long ciliary nerve; 24, infratrochlear nerve; 25, supraorbital nerve; 26, supratrochlear nerve; 27, mandibular nerve.

and later in more detail by Bogorad, who called it the syndrome of crocodile tears (489,490). The term appears to have derived from the notion that the crocodile ''will weep over a man's head after he has devoured the body and then eat up the head too'' (491). Bing applied the term ''gustolachrymal reflex,'' a more appropriate designation (492). This reflex may not be as rare as believed (493). In most patients, the symptom of tearing during eating or drinking is little more than an inconvenience and medical advice is not sought. In some, however, the tearing is so profuse that they must hold a handkerchief to their cheek to absorb the flow of tears.

Types of Gustolacrimal Reflexes

It is possible to differentiate at least three separate types of gustolacrimal reflexes. A congenital variety often is associated with congenital paralysis of abduction. One acquired

variety has its onset either in the initial stage of a facial palsy or without clinical evidence of facial palsy. The second acquired—and most common—variety develops after a peripheral facial palsy.

Congenital Gustolacrimal Reflex

Lutman described three patients with a congenital gustolacrimal reflex, two of whom also had congenital paralysis of abduction (494). One of these two patients had a unilateral gustolacrimal reflex and an ipsilateral abduction weakness; the other patient had bilateral gustolacrimal reflexes and bilateral paralysis of abduction. Other authors have described congenital cases in which mastication (chewing and sucking motions) seemed to provide more powerful stimuli for lacrimation than did gustatory stimuli alone (495). It has been speculated that the etiology of the congenital gustolacrimal reflex is related to abnormal differentiation of the lacrimal and the salivary nuclei in the pons associated with a supranuclear or nuclear abnormality of the abducens nerve (495,496).

In support of a central developmental origin of the congenital gustolacrimal reflex is the occurrence of the reflex in some patients with the Duane retraction syndrome, a syndrome known to result from defective development of the abducens nucleus and anomalous reinnervation of the lateral rectus muscle (497–499; also see Chapter 20). An alternative mechanism may be peripheral facial nerve and abducens nerve palsy due to birth trauma with subsequent anomalous reinnervation of the former (11).

Acquired Gustolacrimal Reflex with Onset in the Early Stage of Facial Palsy

Kaminsky reported a patient with onset of the gustolacrimal reflex 3 weeks after the appearance of a facial palsy (500), whereas Christoffel reported another with onset at the time the facial palsy began (501). Bauer reported a 15-year-old girl in whom an acquired gustolacrimal reflex was the presenting symptom of an ipsilateral vestibular schwannoma (502). On examination, the patient also had slight facial weakness, moderate corneal hypalgesia, and subtotal hearing loss. Following surgery to remove the tumor, her facial palsy was complete, but the gustolacrimal symptoms had disappeared.

Chorobski argued that crocodile tears occurring simultaneously with or shortly after the appearance of a facial palsy cannot be explained by misdirection of regenerating fibers (491). He proposed that such cases are best explained by compression, demyelination, and cross-stimulation of neural impulses between the afferent fibers for taste and the secretomotor fibers for lacrimation within the nervus intermedius (i.e., ephaptic transmission between the autonomic fibers of the proximal seventh cranial nerve). This theory of ephaptic transmission also may be particularly attractive for patients in whom the gustolacrimal reflex resolves either spontaneously or after decompression of the proximal portion of the facial nerve (491).

Acquired Gustolacrimal Reflex Following Facial Palsy or Sectioning of the Greater Superficial Petrosal Nerve

The most common type of gustolacrimal reflex develops weeks or months after a total facial palsy from a lesion in the proximal portion of the nerve. The syndrome may follow skull fracture, herpes zoster oticus, or idiopathic facial palsy (Bell's palsy) with reduction in reflex tearing and unilateral loss of taste in the anterior two thirds of the tongue (503). The accepted mechanism in these cases is misdirection of secretomotor salivary fibers into the pathway of the secretomotor lacrimal fibers at the level of the greater superficial petrosal nerve.

Initially, it was thought that this condition developed when preganglionic salivary fibers in the nervus intermedius mistakenly passed into the greater superficial petrosal nerve with the lacrimal fibers. However, in 1949, Boyer and Gardner reported the syndrome of crocodile tears following surgical section of the greater superficial petrosal nerve where it exits from the petrous bone (504). Their findings indicated that salivary fibers could not have established lacrimal innervation via the greater superficial petrosal nerve. On the other hand, they found that sectioning of the glossopharyngeal nerve relieved crocodile tears in two of their patients, suggesting that this nerve was crucial to the development of the condition.

In 1963, Golding-Wood reported additional cases of the gustolacrimal reflex following proximal sectioning of the greater superficial petrosal nerve (505). He proposed that collateral axonal sprouting occurs from the glossopharyngeal preganglionic salivary nerves, where the tympanic branch joins the greater superficial petrosal nerve (493), and that these misdirected salivary branches aberrantly reinnervate the sphenopalatine ganglion and thus stimulate the lacrimal gland. These collateral axons are the aberrant sprouts of intact salivary fibers that have their normal pathway destined to the otic ganglion and the parotid gland. This theory would explain how salivary axons could circumvent a proximally sectioned greater superficial petrosal nerve and still connect into the pathway of the lacrimal gland.

In support of his theory, Golding-Wood demonstrated in his patients that electrical stimulation of the glossopharyngeal nerve exposed surgically within the tympanic cavity reproduced the patients' tearing phenomenon (505). Subsequent anesthetic block of the glossopharyngeal nerve at the jugular foramen stopped the reflex lacrimation. In three other patients, surgical section of the glossopharyngeal nerve within the inner ear was performed with immediate and lasting cure of the abnormal lacrimation.

Transtympanic resection of the tympanic branch of the glossopharyngeal nerve has remained a highly successful surgical treatment of crocodile tears. Other treatment options, including anticholinergic drugs, intraorbital injections to destroy the sphenopalatine ganglion, and subtotal resection of the lacrimal gland, have had variable success rates. Botulinum toxin type A was introduced as an alternative treatment for crocodile tears in 1998 (506,507). Due to its high efficacy in relieving symptoms with minimal complications, especially when the transconjunctival approach to the

lacrimal gland is used (508), this may be the optimal treatment.

DRUG EFFECTS ON LACRIMATION

Lacrimation may be altered by the effects of topical and systemic agents on the main lacrimal gland, its nerve supply, or the accessory lacrimal glands. Some drugs, including methacholine and pilocarpine, induce tearing by direct parasympathomimetic action on the secretory cells of the lacrimal gland (see Chapter 14). Topical drug effects must be differentiated from tearing produced through corneal irritation, local allergic reaction, and so forth. The number of agents that reduce tear secretion is small; they include psychotropic drugs and practolol (509,510).

GENERALIZED DISTURBANCES OF AUTONOMIC FUNCTION

''Dysautonomia'' is a term used to describe any congenital or acquired anomaly in the autonomic nervous system that adversely affects health. This can result in a variety of clinical symptoms, ranging from transient episodes of hypotension to tonic pupil syndrome to progressive neurodegenerative disease. It is not the intention of this chapter to provide a detailed description on the numerous dysautonomic syndromes; however, a few comments will be made on the disorders in which ocular findings are early or prominent signs.

ROSS SYNDROME

In 1958, Ross described a 32-year-old man with Adie syndrome who had become progressively anhidrotic over 12 years (511). Ross syndrome is the eponym now given to the triad of tonic pupils, absent muscle-stretch reflexes, and progressive segmental impairment of sweating. Some patients have a compensatory hyperhidrosis in the early stages of the disease. In the late stage, most patients have generalized anhidrosis.

Histopathologic studies in patients with this condition demonstrate that severe degeneration and loss of cholinergic sudomotor neurons and fibers account for the clinical anhidrosis (512–514). The tonic pupils observed in the Ross syndrome can be unilateral or bilateral and show the same clinical characteristics as an idiopathic tonic pupil.

The combination of idiopathic tonic pupils and areflexia without anhidrosis is known as the Adie (or Holmes-Adie) syndrome (see above). In fact, many patients with Adie syndrome show abnormal sweating patterns when they are formally tested, thus creating confusion in the clinical distinction between Adie syndrome and Ross syndrome (267, 268,515,516). Furthermore, findings of other autonomic deficits such as orthostatic hypotension, abnormalities of cardiovascular reflexes, and chronic cough suggest more widespread autonomic involvement than previously thought in both Adie syndrome and Ross syndrome (267,268,516,517). Shin et al. speculated that Adie syndrome and Ross syndrome (as well as another condition called the harlequin syndrome) may represent a spectrum of clinical manifestations of disorders of neural crest derivatives that include the parasympathetic ganglia, sympathetic ganglia, and dorsal root ganglia (518).

Other studies provide clinical evidence of sympathetic nervous system dysfunction in Ross syndrome. An oculosympathetic defect (Horner syndrome), usually postganglionic, on the side of the facial anhidrosis occurs in some patients with Ross syndrome (518–520). Mild postganglionic sympathetic denervation of the heart also has been demonstrated in some patients (517). Another study showed electrophysiologic evidence of impairment of tactile, temperature, and pain sensation as well as the histopathologic finding of moderately decreased vasomotor and sensory nerve fibers in the epidermis of three patients with Ross syndrome, suggesting progressive degeneration in sensory myelinated and unmyelinated fiber populations in addition to the progressive loss of cholinergic sudomotor fibers (514).

Despite reports of more widespread autonomic and sensory degenerative changes in Ross syndrome, it is the benign and slowly progressive course that distinguishes it from other dysautonomic syndromes (see below).

FAMILIAL DYSAUTONOMIA

Riley-Day syndrome, also called familial dysautonomia, is a rare disorder found almost exclusively in persons of Ashkenazi Jewish descent. The responsible gene maps to chromosome 9q31–33 and is inherited in autosomal-recessive fashion (521). The diagnosis is suspected from clinical signs of generalized autonomic instability such as abnormal sweating, loss of vasomotor control, labile hypertension, episodic fever, and attacks of vomiting. Relative pain insensitivity and a peripheral sensory neuropathy are other features. Two ocular findings are present in all patients: absence or marked insufficiency of tears and corneal anesthesia. Diagnosis is based on five clinical signs: (*a*) lack of flare following intradermal histamine injection; (*b*) absence of fungiform papillae on the tongue; (*c*) pupillary miosis to dilute muscarinic agents such as pilocarpine (cholinergic denervation supersensitivity); (*d*) severe hypolacrimation; and (*e*) absent muscle-stretch reflexes (522,523).

Patients with familial dysautonomia produce an insufficient quantity of tears when crying, an important diagnostic feature of the disease at all ages other than in infancy (because the normal infant does not produce tears in any significant quantity before the 6th–8th week after birth). Reflex lacrimation in response to irritants such as the odor of onions, scratching of the middle turbinate, or filter paper in the conjunctival sac also is deficient (524). Yet these same patients produce a copious flow of tears after a parenteral dose of methacholine, suggesting parasympathetic denervation supersensitivity of the lacrimal gland. Histologically, the lacrimal glands appear to be normal (525).

Topical parasympathomimetic agents administered in low concentration produce miosis in patients with familial dysautonomia. The cholinergic supersensitivity of the pupils most often results from parasympathetic denervation, as occurs in

other tonic pupil syndromes (526,527); however, the authors of one study proposed increased drug penetration across damaged corneal epithelium as another explanation for the strong miotic effect of dilute pilocarpine in their 10 patients with familial dysautonomia who had normal pupil responses to light and near with infrared pupillography (528).

Ocular findings other than markedly diminished tear secretion, corneal anesthesia, and pupillary dysfunction include corneal ulceration and/or keratopathy, exodeviation, anisometropia, myopia, optic atrophy, anisocoria, ptosis, and tortuosity of retinal vasculature (527,529,530).

Consistent histopathologic lesions have not been identified in familial dysautonomia. Pearson et al. (531,532) described several similar pathologic features in two patients with familial dysautonomia: (*a*) marked reduction in sympathetic postganglionic neurons and their peripheral axons; (*b*) marked reduction in sensory dorsal root ganglia and small myelinated and nonmyelinated axons in peripheral nerves; (*c*) variable reduction in sensory axons and neurons thought to be parasympathetic in nature in the submucosa of the tongue; and (*d*) variable reduction of mucosal papillae and taste buds. These pathologic findings, although not substantiated completely by others, fit well with biochemical findings in patients with familial dysautonomia that implicate a disturbed catecholamine metabolism (533). On the other hand, Mittag et al. (534) found evidence of a deficiency or absence of choline acetyltransferase enzyme in the cholinergic nerve terminals of a patient with familial dysautonomia. Although a cholinergic defect could affect both the sympathetic and parasympathetic nervous systems through its effect at the ganglion level, it cannot explain the sensory defects in patients with familial dysautonomia.

SHY-DRAGER SYNDROME

Shy-Drager syndrome is a subtype of multiple system atrophy (MSA), one of the three idiopathic neurodegenerative syndromes (onset usually after age 50 years) that primarily affect the autonomic nervous system. The other two are pure autonomic failure, in which impairment of the autonomic nervous system (orthostasis, bladder dysfunction, sexual impotence) occurs without other neurologic features, and Parkinson disease, in which autonomic impairment occurs with an extrapyramidal movement disorder. In MSA, autonomic impairment occurs with an extrapyramidal movement disorder, a cerebellar movement disorder, or both (535). Patients with MSA are said to have ''Shy-Drager syndrome'' when their symptoms and signs are primarily those related to autonomic failure.

Despite the criteria described above, making the clinical distinction among MSA, Parkinson disease, and pure autonomic failure can be difficult. For example, some patients in the early stages of MSA show only autonomic deficits, and others develop only motor deficits that are strikingly similar to those that occur in patients with Parkinson disease. Certain diagnostic tests may aid in the early differentiation of these disorders, particularly functional tests of myocardial sympathetic function, such as myocardial scintigraphy using ^{123}I (536,537). Patients with Parkinson disease show significantly decreased isotope uptake compared with patients with MSA, consistent with other studies indicating that postganglionic sympathetic cardiac denervation occurs in patients with Parkinson disease and pure autonomic failure but not in patients with MSA.

Histopathologic findings described in patients with MSA are inclusion bodies in the oligodendrocytes and neurons in the CNS and intact normal postganglionic sympathetic neurons, further supporting the theory that the degenerative process of MSA is limited to the autonomic neurons in the CNS (538,539).

MR imaging in 29 patients with MSA (subclassified into the syndromes of Shy-Drager, olivopontocerebellar atrophy, and striatonigral degeneration) included high signal in the basis pontis and middle cerebellar peduncles on T2-weighted images consistent with atrophy, signal abnormalities in the putamen, and cerebral atrophy predominantly involving the frontal and parietal lobes (540). These features were commonly present in all patients, regardless of their clinical presentation.

Common ocular signs in patients with Shy-Drager syndrome include anisocoria, iris atrophy, convergence insufficiency, and nystagmus. Other patients have evidence of significant ocular sympathetic and parasympathetic insufficiency, including alternating Horner syndrome, cholinergic sensitivity, decreased lacrimation, and corneal hypesthesia (541,542).

AUTOIMMUNE AUTONOMIC NEUROPATHY

Idiopathic (Primary) Autonomic Neuropathy

Two forms of primary or idiopathic autonomic neuropathy once were classified by the temporal profile of symptomatic autonomic nervous system dysfunction they produced: (*a*) subacute autonomic neuropathy (also called acute pandysautonomia), having an acute or subacute onset; and (*b*) pure autonomic failure, having a gradual onset and slow progression of symptoms (see the section above on Multiple System Atrophy). Subsequent studies indicate that these two forms of idiopathic autonomic neuropathy are, in fact, two pathogenetically different diseases. Idiopathic subacute autonomic neuropathy is an immune-mediated disorder that often follows a viral or systemic illness, progresses over several days to weeks, and then tends to improve spontaneously or after treatment with immunomodulatory drugs, whereas pure autonomic failure is an idiopathic, progressive, degenerative disorder (543).

Idiopathic subacute autonomic neuropathy is characterized by findings of autonomic dysfunction, including orthostatic hypotension with a fixed cardiac rate, decreased salivation and lacrimation, impaired pupil reactions, anhidrosis, atony of the bladder, gastroparesis, severe constipation, impotence, and abnormal flushing of the skin (544,545).

The pupillary disturbances that occur in idiopathic subacute autonomic neuropathy are seen early in the course of the disease. They include mydriasis, poor or absent constriction to light and near stimuli, and irregularity of the pupillary margin (546,547). Pharmacologic testing of the pupils in such patients is consistent with both parasympathetic and

sympathetic postganglionic denervation, with denervation supersensitivity of both the iris sphincter and iris dilator muscles (548,549).

Patients with pure autonomic failure generally have less prominent pupillary dysfunction, sicca symptoms, and gastrointestinal dysmotility compared with patients with subacute autonomic neuropathy.

Paraneoplastic Autonomic Neuropathy

Paraneoplastic autonomic neuropathy is clinically indistinguishable from idiopathic subacute autonomic neuropathy (543,550). It occurs in about 30% of patients with cancer who have anti-Hu antibodies, and of these, more than half have a clinical and temporal profile similar to subacute autonomic neuropathy (551).

Autoimmune Autonomic Neuropathy

Not only do idiopathic subacute autonomic neuropathy and paraneoplastic autonomic neuropathy have identical clinical findings, they appear to have a similar autoimmune basis. Patients with both disorders test positive for ganglionic nicotinic acetylcholine receptor autoantibodies, as opposed to patients with pure autonomic failure and MSA, who have no evidence of these antibodies (543). Thus, idiopathic subacute optic neuropathy and paraneoplastic autonomic neuropathy are now considered to be forms of a new category of autonomic optic neuropathy called autoimmune autonomic optic neuropathy (AAN). The diagnosis of AAN thus is given to any patient with symptoms of autonomic dysfunction who has positive serum titers of ganglionic acetylcholine receptor antibodies (552). In a study of 18 patients with autoimmune autonomic neuropathy, the mean age was 61.4 years, with a female predominance (544). High titers of ganglionic acetylcholine receptor antibody were associated with symptoms of severe cholinergic dysautonomia such as sicca, upper gastrointestinal dysfunction, large pupils with impaired light and near reactions, and neurogenic bladder. Impaired pupillary function was the clinical feature that most reliably predicted seropositivity; conversely, low antibody titers correlated with mild cholinergic neuropathy. It appears that these receptor antibodies have a pathophysiologic role in the development and severity of clinical symptoms, but the full clinical spectrum of AAN remains to be determined. Thus, if a previously healthy person develops acute or subacute symptoms of autonomic dysfunction, and especially if there is involvement of the pupils, serologic testing for ganglionic acetylcholine receptor antibodies as well as cancer-related antibodies is crucial for both diagnosis and therapy (544).

MILLER FISHER SYNDROME

Miller Fisher syndrome (MFS) is considered a variant of Guillain-Barré syndrome (acute idiopathic polyneuritis). The majority (80–100%) of patients with MFS are positive for anti-GQ1b IgG antibodies. Some patients also show clinical and/or imaging evidence of CNS involvement. Pupillary abnormalities are rather common, being present in 21 of 50 (42%) patients in one study (553). Bilateral mydriasis, poor or no light reaction, anisocoria, and reduced accommodation are typical findings (439,554–556) and indicate primary oculoparasympathetic dysfunction. The results from one patient whose pupils were studied pharmacologically in the acute and recovery stages of MFS suggested that the pupillary involvement was caused by involvement of both the sympathetic and parasympathetic nervous systems (557). MFS is discussed in more detail in Chapter 61.

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