CHAPTER 15

Principles and Techniques of Examination of the Pupils, Accommodation, and Lacrimation

Kathleen B. Digre

ASSESSMENT OF PUPILLARY SIZE, SHAPE, AND FUNCTION

As is the case with any assessment in neuro-ophthalmology, assessment of the pupils requires a meticulous history and a rigorous examination. This is followed in some instances by pharmacologic testing of the pupil using a variety of topical agents. The reader interested in a more extensive discussion of this topic should read the excellent book by Loewenfeld (1).

HISTORY

Patients with disturbances of pupillary size or shape often are unaware that any abnormality is present. More often, their spouse, a friend, or a physician brings the abnormality to their attention. The disturbance may appear suddenly, or it may develop gradually over time. It may be present at all times, or it may be episodic. Some pupillary abnormalities may be present for years and are only detected when someone looks at the iris.

In obtaining a history from a patient with a disturbance in pupillary size or shape, particularly anisocoria, dating the onset of the abnormality may be important. The easiest and most reliable method is to view a driver's license, credit card, or a similar identification card with the patient's photograph on it which the patient is likely to have available at the time of the evaluation. The examination of family album photographs that have been taken over time (sometimes jokingly called ''family album tomography'' or ''FAT scanning'') can be performed with the naked eye or with a magnifying lens and may save both time and money in attempting to determine the date of onset of a pupillary disturbance.

Symptoms that may be elicited in any patient with disturbances of pupillary size and shape include light sensitivity or photophobia, difficulty focusing when going from dark to light or light to dark, and blurring of vision. The blurred vision is typically a nonspecific and poorly defined complaint. If one pupil is large, the blurring may be present when the patient enters brightly lighted environments, and if one pupil is abnormally small, images of objects observed with that eye may appear slightly dimmer than those observed with the opposite eye.

The past medical history also may be helpful in assessing the significance of a disturbance in pupillary size or shape. A history of previous infections (e.g., herpes zoster), trauma, surgery (e.g., in the neck or upper chest; cataract extraction), or chronic illnesses such as diabetes or migraine may suggest the etiology of the pupillary disturbance (2). The patient's occupation also may be important. A farmer or gardener may be exposed to plants or pesticides that can produce pupillary dilation or constriction by topical contamination.

A physician, nurse, or other health professional may work with or have access to topical dilating or constricting substances that may produce changes in pupillary size by design or chance. Medication history also is important because opiates cause constricted pupils (3) and anticholinergic medications, including atropinic substances used in inhalants for asthmatics, may cause pupillary dilation (4).

EXAMINATION

Simple inspection of the anterior segment at the slit-lamp biomicroscope is helpful in determining whether or not there is a pupillary abnormality. For example, examination of the cornea may reveal an abrasion or injury that could affect the pupillary size, whereas examination of the anterior chamber may reveal inflammation that explains a small pupil in the setting of ciliary spasm. It may also be important to perform gonioscopy to assess the anterior chamber angle in a patient with a dilated pupil, particularly when there is a history of pain or redness in the eye (5). Assessment of the iris should include not only inspection of the integrity of the sphincter muscle but also transillumination to determine if there is evidence of iris damage from previous ocular trauma. To retroilluminate the iris, the slit-lamp beam is directed obliquely through the pupil. A normal iris will not show defects, but an abnormality such as atrophy will show reflected light back to the observer. In addition, by placing a wide beam at an angle to the iris and turning the light off and on, the light reflex can be assessed for segmental defects, such as those that occur in eyes with tonic pupils or aberrant regeneration of the oculomotor nerve. One can even draw a diagram showing clock hours of denervation; the diagram can then be used to follow the patient's status. Transillumination of the iris and ciliary body under infrared lighting conditions has been shown to be helpful to find other defects (6).

Pupil measurements can be performed in several ways. A simple handheld pupil gauge can be used to determine pupil size in both light and darkness. Pupil gauges may be circular or linear. They consist of a series of solid or open circles or half-circles with diameters that increase by 0.2 mm in steps (Fig. 15.1). They can be held next to the eye to estimate the size of the pupil. Other calipers and scales to measure pupillary size are also available (7).

An accurate method of measuring pupillary size and comparing pupils before and after pharmacologic testing is with a handheld pupil camera. With this device, the pupils can be photographed in various illuminations, although not in darkness (8).

Infrared video pupillometry is perhaps the most accurate method of assessing the size of the pupil (9). An infrared video pupillometer permits observation of the pupils not only in lighted conditions but also in total darkness. Furthermore, the iris sphincter can even be transilluminated to show the denervated and reinnervated portions (10). Some computer programs associated with these pupillometers allow the examiner to measure not only the diameter and area of the pupil but also the latency and velocity of the pupillary response to both light and near stimulation (11).

During the clinical evaluation of the pupils, it is helpful to determine the answers to several certain questions. For example, because the diameter of the pupil typically decreases with age (12) (Fig. 15.2), the examiner should determine if the pupillary size is appropriate for the patient's age. Other important questions to answer include the following:

Are the pupils equal in size? If not, is the difference greater in darkness or in the light?

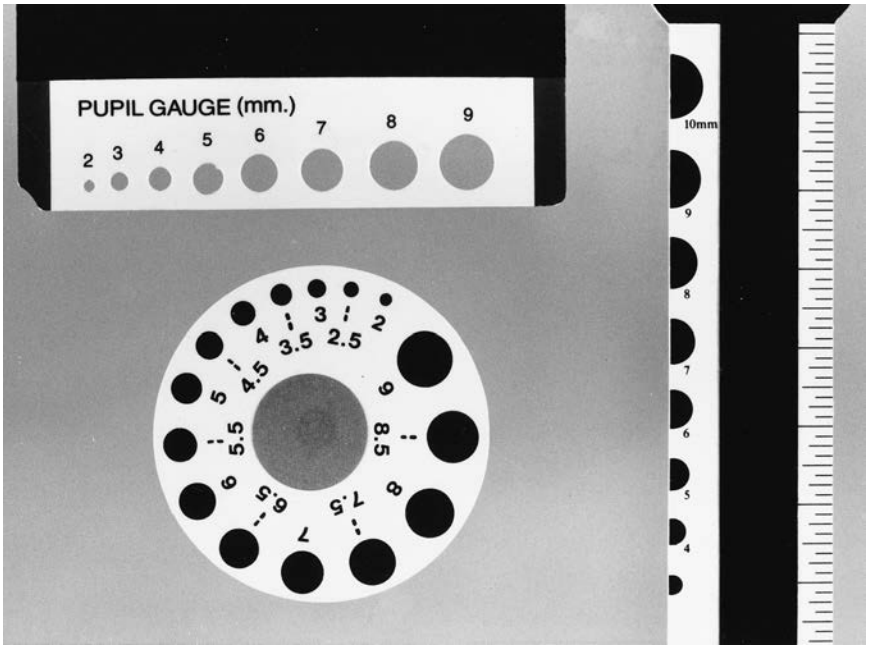


Figure 15.1. Pupil gauges. The best gauges measure in 0.1-mm steps.

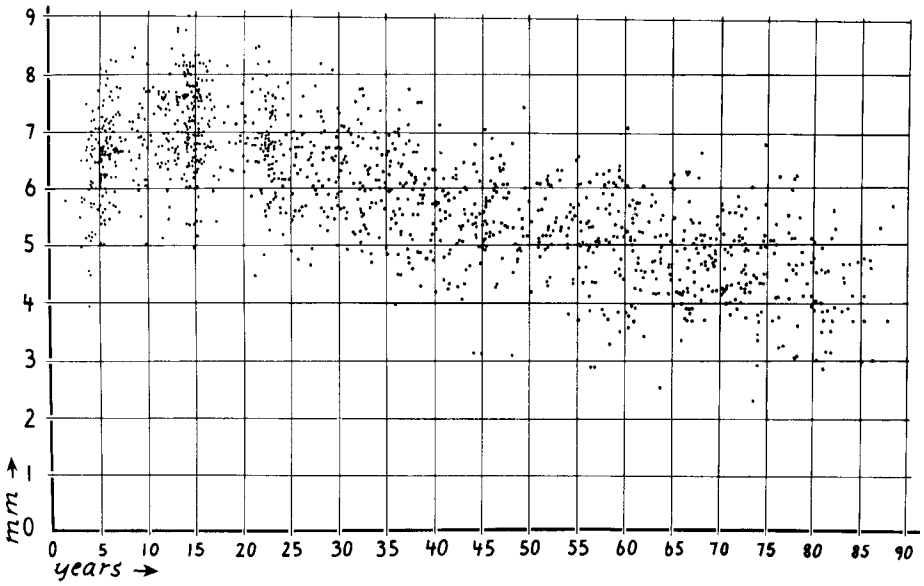


Figure 15.2. Graph showing relationship of age to pupil size in normal individuals. Note that, in general, pupillary size decreases with age. (From Loewenfeld IE. Pupillary changes related to age. In: Thompson HS, ed. Topics in Neuro-ophthalmology. Baltimore: Williams & Wilkins, 1979:124–150).

Do the pupils constrict to light equally and with the same velocity?
Do they redilate equally and with the same velocity?
Is the pupillary reaction to light stimulation equal to the pupillary reaction to near stimulation?
Is there reflex dilation to psychosensory stimulation?
Is there a relative afferent pupillary defect?

Assessing Pupillary Size

The diameter of both pupils should be estimated or measured in light, using either normal room light or a handheld transilluminator or other light source. The diameter of the pupils then should be assessed in darkness, using the dimmest room light in which the examiner can still see the edge of the pupil (13). Finally, the pupillary size should be assessed during near stimulation using an accommodative target to achieve maximum constriction of the pupils. The measurements of the two pupils in light and darkness also should be compared to determine if there is **anisocoria**: a difference of at least 0.4 mm between the two pupils. A substantial percentage of the normal population has clinically detectable anisocoria of 0.4 mm or more, with the percentage increasing with increasing age (14). Whereas 20% of the general population aged 17 years and under have so-called physiologic anisocoria, the prevalence rises to 33% in otherwise normal persons over 60 years of age (15). In addition, anisocoria may be produced by damage to the iris sphincter or dilator muscles or to their nerve supply. The amount of anisocoria may be affected by illumination. For instance, a greater degree of anisocoria is present in darkness than in light in patients with physiologic anisocoria or Horner syndrome (13,16). Anisocoria also can also be affected by the degree of accommodation, by patient fatigue, and by sympathetic drive (e.g., anxiety) (13,16,17).

Recent advances in refractive surgery have made measurement of pupillary diameters in darkness clinically important to reduce the risk of nocturnal halos due to the improper calculation of pupillary size in darkness. Numerous pupillographic devices are available commercially to measure pupillary sizes in darkness (18).

Testing the Direct Pupillary Reaction to Light

When testing the reaction of a pupil to light shined in the eye—**the direct pupillary light reaction**—it is important to have a dimly lit room that is quiet so as to reduce or eliminate emotional effects on the pupil (19). Furthermore, one must be certain that the patient is fixating on a distance target to eliminate any effect of accommodation on pupillary size. The examiner must be certain that the patient is not attempting to close the eyelids during the test, because this produces a variable degree of pupillary constriction.

A relatively bright light source should always be used to illuminate the pupil and produce pupillary constriction, because increased stimulus intensity is associated with an increased light reflex amplitude and a maximum rate of constriction and redilation (20,21). If the light source is too bright, however, a prolonged contraction lasting several seconds (''spastic miosis'') will occur and make determination of the normal light reflex difficult or impossible (22). In general, a fully charged transilluminator or an indirect ophthalmoscope with maximum brightness is the optimum light source. In addition, it is helpful to use a dim secondary light source to provide oblique illumination of the pupil in some cases, because this technique increases visualization of darkly pigmented irides (Fig. 15.3).

The light source should be shined straight into the eye for a few seconds and then moved downward away from the eye to eliminate the stimulation. The pupil response should be assessed during this maneuver, which should be repeated several times. The normal response to a bright light is a contraction called **pupillary capture** (23) (also called the

Figure 15.3. Indirect lighting to view pupils in darkness is helpful in viewing dilation.

phasic response). An abnormal response is **pupillary escape**, in which the pupil initially constricts and then slowly redilates and returns to its original size. Pupillary escape most often occurs on the side of a diseased optic nerve or retina, particularly in patients with a central field defect, although it also occurs in patients with lesions of the contralateral optic tract, in patients with lesions of the brachium conjunctivum, and in normal persons tested with a low-intensity light source (24,25) (see also Chapter 16).

The initial size of the pupil is important in assessing both pupillary capture and pupillary escape; a larger pupil is more likely to show pupillary escape, whereas a smaller pupil is more likely to show pupillary capture (26–28).

The latency and speed with which a pupil constricts to light and redilates after light stimulation can be assessed using pupillography. This technique reveals that normal persons have pupillary wave forms with latency of 0.20–0.28 seconds and duration of contraction of 0.45 seconds (29). There is a modest interindividual difference in latency in normal subjects (between 8.3–35 milliseconds) (30). The use of pupillography to record wave forms of pupillary constriction and dilation is generally limited to pupillary research laboratories.

Testing the Consensual Response to Light

When light is shined in one eye, the contralateral pupil should constrict. This is the **consensual light response**. The consensual response to light is best assessed using a light source for illumination of the pupil of one eye and a dimmer light source that can be held obliquely to the side of the contralateral eye to be observed. The consensual pupillary response should be approximately equal in both velocity and extent to the direct response, because the pupillary decussation in the midbrain is about 50% to each eye. In fact, the consensual reaction to light in normal humans is slightly less than the direct reaction, producing about 0.1 mm or less of what has been called **alternating contraction anisocoria** (22,31). Contraction anisocoria is difficult to see without using pupillography.

Testing the Near Response

The near response, a co-movement of the near triad that also includes accommodation and convergence (discussed later), should be tested in a room with light that is adequate for the patient to fixate an accommodative target. A nonaccommodative target, such as a pencil, pen, or the patient's own thumb may not be a sufficient stimulus to produce a normal near response, even in a normal person, and these targets should be avoided (except in a patient who is blind, in which case one must stimulate the pupillary near response using proprioception from one of the patient's own fingers or thumb). Similarly, the near response should not be induced by having the patient look at a bright light stimulus, because the light itself may produce pupillary constriction. The examiner should attempt to test the pupillary near response several times to give the patient practice. One can document the light and near response with photographs or pupillometry (Fig. 15.4).

If a patient is unable to cooperate for a near effort, some authors advocate using the **lid closure reflex**, in which the patient attempts to squeeze the eyes shut while the physician tries to open them (22). This maneuver typically causes the pupils to constrict.

Assessment of Pupillary Dilation

Dilation of the pupils occurs in a variety of settings. Most often, the pupils dilate after they have constricted to light or near stimulation. In patients with certain retinal and, less often, optic nerve disease, they may actually dilate when light is shined in one eye, or the pupils may constrict to darkness (paradoxical pupillary responses) (32,33). Reflex pupillary dilation can be elicited by sudden noise or by pinching the back of the neck (the ciliospinal reflex).

When assessing pupillary dilation, the examiner should look specifically for **dilation lag** (34). This phenomenon is present when there is more anisocoria 5 seconds after pupillary constriction to light than there is 15 seconds after pupillary constriction (35). Dilation lag typically occurs in patients with a defect in the sympathetic innervation of the pupil (i.e., a Horner pupil).

Dilation lag usually is easy to detect. One method is simply to observe both pupils simultaneously in very dim light after a bright room light has been turned off. Normal pupils return to their widest size within 12–15 seconds, with most of the dilation occurring in the first 5 seconds. Pupils that show dilation lag may take up to 25 seconds to return to maximal size in darkness, with most of the dilation occurring about 10–12 seconds after the light goes out. A second way to determine if dilation lag is present is to take flash photo-

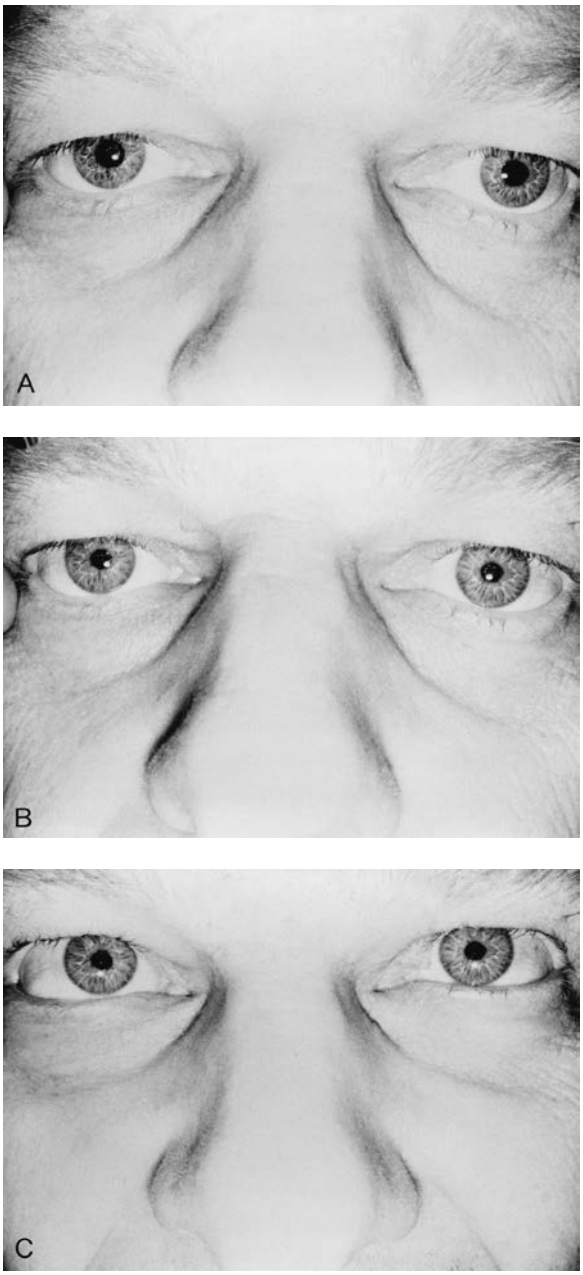


Figure 15.4. A handheld camera documents size of the pupils in light and darkness in a normal subject. *A*, In room light without any other stimulation. *B*, In room light during stimulation with a bright light. *C*, In room light during stimulation with an accommodative target. Note associated convergence.

graphs at 5 and 15 seconds after the lights are turned off. If there is a difference in anisocoria of greater than 0.4 mm at 5 seconds minus the anisocoria at 15 seconds, a Horner syndrome is present (35).

Infrared videography beautifully demonstrates dilation lag because even the most darkly pigmented iris will appear bright with this technique (36). Using infrared videography, some investigators have found that re-dilation lag is the most sensitive diagnostic test to detect either unilateral or bilateral Horner syndrome (37).

Testing for Light-Near Dissociation

Dissociation between the pupillary response to light stimulation and the pupillary response to near stimulation—**light-near dissociation**—occurs in patients with a variety of disorders, including blindness (from optic nerve or retinal damage), neurosyphilis, oculomotor nerve paresis with aberrant regeneration, tonic pupil (e.g., Adie pupil), hydrocephalus, pineal region tumors, and intrinsic mesencephalic disease (see Chapter 16). In almost all cases, **the pupillary reaction to light is impaired, whereas the pupillary response to near is normal or near normal**. Thus, the potential for light-near dissociation should be considered in any patient with an impaired pupillary light reaction.

Although there are rare intracranial lesions that can produce a light-near pupillary dissociation in which the reaction to light is normal and the reaction to near is abnormal, the vast majority of cases of this type of light-near dissociation are caused by lack of effort on the part of the patient during attempted near stimulation.

Testing for a Relative Afferent Pupillary Defect

When a patient has an optic neuropathy in one eye or an asymmetric bilateral optic neuropathy, covering one eye and then the other reveals that the pupil of the normal eye constricts when it is uncovered and the abnormal eye is covered, whereas the pupil of the abnormal eye dilates when it is uncovered and the pupil of the normal eye is covered. (Fig. 15.5). This is known as the ''Marcus Gunn'' or ''Gunn'' phenomenon, and the abnormal pupil is often called a **Marcus Gunn pupil**. In fact, a better term for this phenomenon is ''relative afferent pupillary defect,'' because this term, usually abbreviated as **RAPD**, describes the nature of the pupillary abnormality rather than being an eponym.

The concept of an RAPD is not new. In 1884, Hirschberg described a young woman with retrobulbar neuritis in whom he diagnosed an organic visual loss because of reduced pupillary light reactions when the affected eye was stimulated (38). In addition, he noted that the consensual pupillary reaction in the affected eye was better than the direct reaction. Gunn stated that he was able to differentiate retrobulbar optic neuritis from non-organic loss of vision by the difference in pupillary reactions to prolonged exposure to light and recommended comparing the behavior of the two pupils when one was stimulated directly or consensually for a continued period. He emphasized that the pupil on the side of an eye with optic nerve dysfunction dilated spontaneously after initial constriction if the pupil continued to be exposed to light, whereas the pupil in an eye with non-organic visual loss tended to remain fairly constricted as long as the light was on (39,40). Kestenbaum subsequently popularized the concept of the RAPD and credited Gunn with its discovery (41). The phenomenon described by Kestenbaum and attributed to Gunn thus became known as ''Gunn'' pupil. Kestenbaum also modified the test by covering each eye individ-

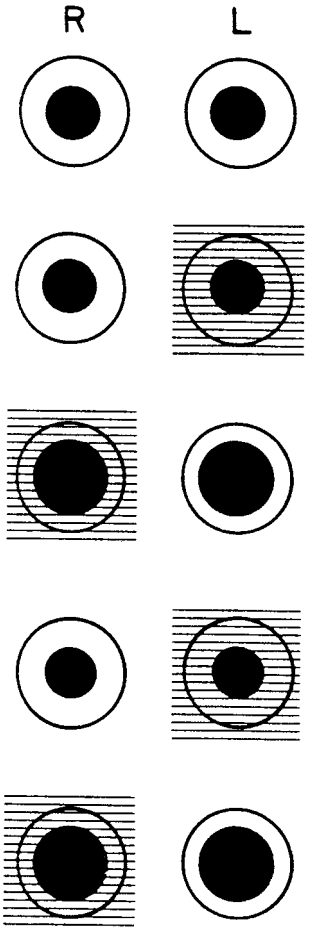


Figure 15.5. Relative afferent pupillary defect in the left eye demonstrated by the alternate cover test as described by Kestenbaum. The left pupil dilates (as does the right) when the left eye is uncovered and the right eye is covered. (From Thompson HS. Pupillary signs in the ophthalmologic diagnosis of optic nerve disease. Trans Ophthalmol Soc UK 1976; 96:377–381.)

ually and measuring the size of each pupil. Indeed, he was one of the first investigators to quantify the RAPD (41).

Levatin substituted an alternating flashlight for the alternating cover test (42) (Fig. 15.6). His theory was that the differences in pupillary response to light would be accentuated if, instead of simply covering one eye and then the other in a lighted room, the patient focused on a distant target in a darkened room, and a pocket flashlight was swung back and forth multiple times to bring out the best response. Levatin et al. subsequently reported on the use of this **swinging flashlight test** to screen patients with possible optic neuropathies and emphasized that the sign was not always obvious (43). In fact, in 1998, Enyedi et al. compared the efficacy of the swinging flashlight test with that of the Gunn test for detecting an RAPD and found the former to be more sensitive (44).

Indeed, the swinging flashlight test is probably the most valuable clinical test of optic nerve dysfunction available to the general physician because it can detect dysfunction of the prechiasmal (and, in fact, pregeniculate) afferent visual sensory system in the absence of any ophthalmoscopic evidence of such a dysfunction.

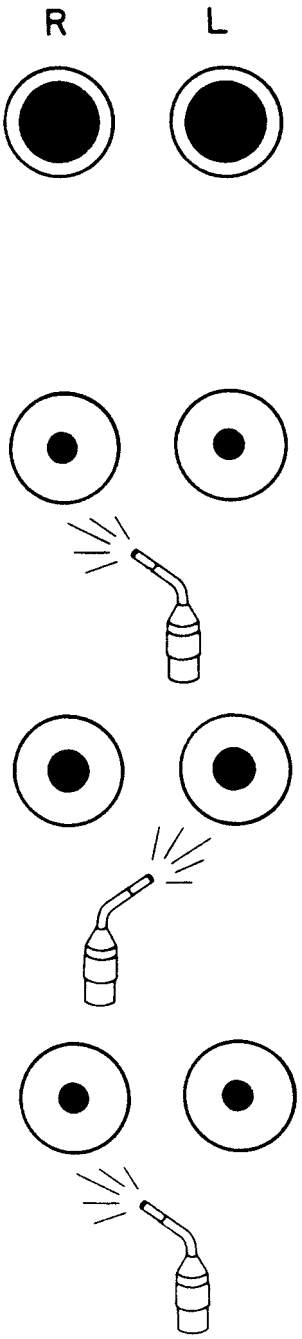


Figure 15.6. Relative afferent pupillary defect in the left eye demonstrated using the swinging flashlight test. The pupils constrict when the light is shined directly into the right eye; however, when the flashlight is swung back to the left eye, both pupils dilate. (From Thompson HS. Pupillary signs in the ophthalmologic diagnosis of optic nerve disease. Trans Ophthalmol Soc UK 1976;96:377–381.)

Thompson and colleagues (45–47) described the method

for performing the swinging flashlight test and emphasized several important points, a few of which are repeated here:

First, a bright handlight and a darkened room are essential. The more contrast there is between the light beam and the darkened room, the greater will be the amplitude of the pupillary movement, and the easier it will be to see a small RAPD. It is possible, however, to use too much light. In such cases, a bright afterimage is produced that may keep the pupils small for several seconds, thus obscuring the pupillary dilation in the abnormal eye (48).

Second, the patient must fixate on a distant target during the test. This prevents the miosis that occurs during the near response, making the assessment of pupillary constriction difficulty if not impossible.

Third, in patients with ocular misalignment (i.e., strabismus or displacement of the globe by an orbital or intracranial process), care must be taken to shine the light along the visual axis. Shining the light directly into one eye and obliquely into the other may produce an RAPD.

Fourth, the light should cross from one eye to the other fairly rapidly but should remain on each eye for 3–5 seconds to allow pupillary stabilization.

Thus, there really are two parts of the pupillary response that must be observed during the swinging flashlight test: the initial pupillary constriction response, and the pupillary escape that is observed for 2–5 seconds after the light is shined into the eye. Most examiners vary the rate at which they move the light from eye to eye, and there is often an optimum ''swing rate'' that brings out an RAPD that varies among patients. Some authors recommend moving the light from one pupil to the other before the latter can escape from the consensual response to bring out an RAPD (49); however, **the light should never be left longer on one eye than on the other** as this might tend to create an RAPD in the eye with the longer light exposure, because the longer the light is kept on the eye, the more pupillary dilation occurs as the eye adapts to the light. In addition, if the retina becomes bleached in one eye and not in the other, a small RAPD will be produced. Special care must be taken to keep retina bleach equal, especially when measuring with neutral density filters greater than 1.2 log units in density (50) (see later).

Finally, the swinging flashlight test can be performed as long as there are two pupils, even when one pupil is nonreactive and dilated or constricted from neurologic disease, iris trauma, or topical drugs. Recall that as the light is shifted from the normal to the abnormal eye, the total pupillomotor input is reduced. Thus, the efferent stimulus for pupillary constriction is reduced in **both eyes** so that both pupils dilate. In performing the swinging flashlight test, one tends to observe only the pupil that is being illuminated; however, **the opposite pupil is responding in an identical fashion**. Thus, if one pupil is mechanically or pharmacologically nonreactive, the examiner can simply perform a swinging flashlight test observing only the reactive pupil. If the abnormal eye is the eye with a fixed pupil, then the pupil of the normal eye will constrict briskly when light is shined directly in it and will dilate when the light is shined in the opposite eye. If the abnormal eye is the eye with the reactive pupil, the pupil will constrict when light is shined in the opposite eye and dilate when the light is shined directly in it. This is extremely helpful in attempting to determine if a patient with an oculomotor nerve paresis or traumatic iridoplegia also has an optic neuropathy or retinal dysfunction (22).

The swinging flashlight test can be refined further in patients in whom a unilateral optic neuropathy is suspected but who do not seem to have an RAPD when a standard swinging flashlight test is performed. In such patients, the use of a neutral density filter with a transmission of 0.3

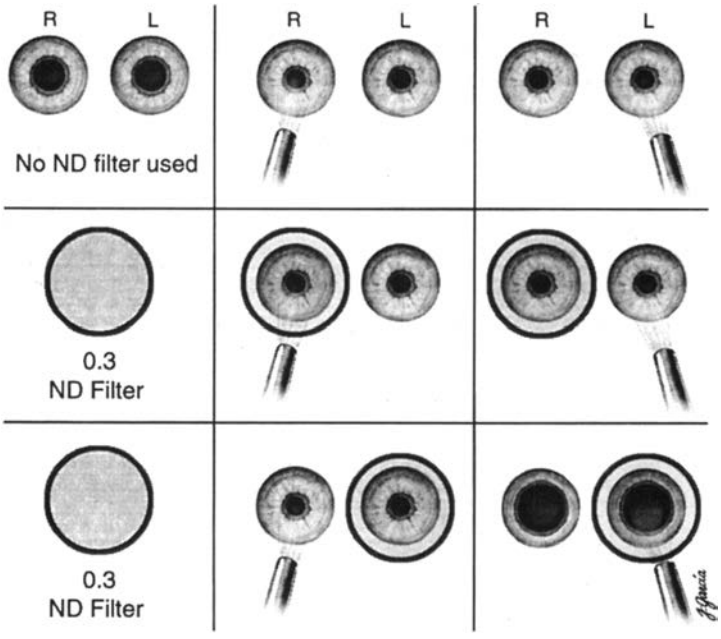


Figure 15.7. The use of neutral density filters to bring out a relative afferent pupillary defect (RAPD). *Above,* The patient has decreased vision in the left eye, but a swinging flashlight test fails to demonstrate a convincing RAPD in the left eye. *Middle,* A 0.3 log unit neutral density filter is placed over the right eye, and a swinging flashlight test is performed. No relative afferent pupillary defect is induced. *Bottom,* The filter is then place over the left eye, and the test is repeated. There is now a left relative afferent in the left eye, when the filter is placed in front of the right eye and the swinging flashlight test is performed, the reduced brightness in the right eye will tend to balance the reduced brightness in the left eye (from the optic neuropathy), and no RAPD will be seen. However, placing the filter in front of the left eye while performing the swinging flashlight test further reduces the light input in the left eye and further increases the difference in light input between the two eyes. Thus, there is now an obvious RAPD during the test.

logarithmic units often permits the detection of the defect (51) (Fig. 15.7). The test is performed as follows. The filter is first placed over one eye, and the swinging flashlight test is performed. The filter is then placed over the opposite eye, and the swinging flashlight is repeated. If there is truly no defect in the afferent system in either eye, placing the filter over either eye will simply induce a slight but symmetric RAPD in the eye covered by the filter from reduction in the amount of light entering the system through that eye. On the other hand, if one eye already has a mild RAPD, placement of the filter over that eye will further reduce the amount of light entering the system through that eye, thus increasing the previously inapparent or subtle defect and causing it to become obvious, whereas placement of the filter over the opposite (normal) eye will simply balance the RAPD in the opposite eye, and there will be no significant asymmetry in pupillary responses to light.

One can also quantify the RAPD using graded neutral density filters that are calibrated in percent transmittance (52). After determining that an RAPD is present, the examiner balances the defect by adding successive neutral density filters in 0.3 logarithmic steps over the **normal eye** while performing the swinging flashlight test, until the defect disappears (Fig. 15.8). The most useful neutral density filters are those ranging in transmission from 80% (0.1 log unit) to 1% (2.0 log units). Separate filters can be used individually or in combination in front of the eye (Fig. 15.9).

When using neutral density filters to quantify an RAPD, the examiner should make a decision about the presence of absence of the RAPD within 2–3 swings after the filter is placed in front of the normal eye. If more swings are needed, he or she must rebleach the retina of the covered eye and resume measuring. The neutral density filters should be held near the nose, so that stray light does not affect the measurement. Filters more than 1.2 log units in density are so dark that it is hard to see the pupil through them, even when light is shined on the eye. The examiner thus may need to peek around the filter to make a judgment. To reach the endpoint of the test, the examiner should overshoot the endpoint; i.e., produce an RAPD in the normal (covered) eye. The examiner should then rebleach the retina of that eye and perform the swinging flashlight test with another filter at the next lower amount. Several ''rules of thumb'' in measuring the RAPD for various conditions are found in Table 15.1.

Although some authors (53) have used a grading scale for the RAPD based on the initial pupillary constriction and how quickly the pupil redilates (e.g., Grade I: weak initial constriction followed by greater redilation; Grade II: a slight ''stall'' in movement, followed by a definite dilation; Grade III: immediate pupillary dilation [i.e., pupillary escape]; Grade IV: pupillary dilation during prolonged illumination of the contralateral eye for 6 seconds, followed by constriction; Grade V: immediate pupillary dilation and no signs of constriction), these systems are subject to inter-observer errors and are affected by pupillary size; e.g., the small pupil may not show a detectable initial constriction.

There is some correlation between the severity of an RAPD and the size of a peripheral field defect in the eye

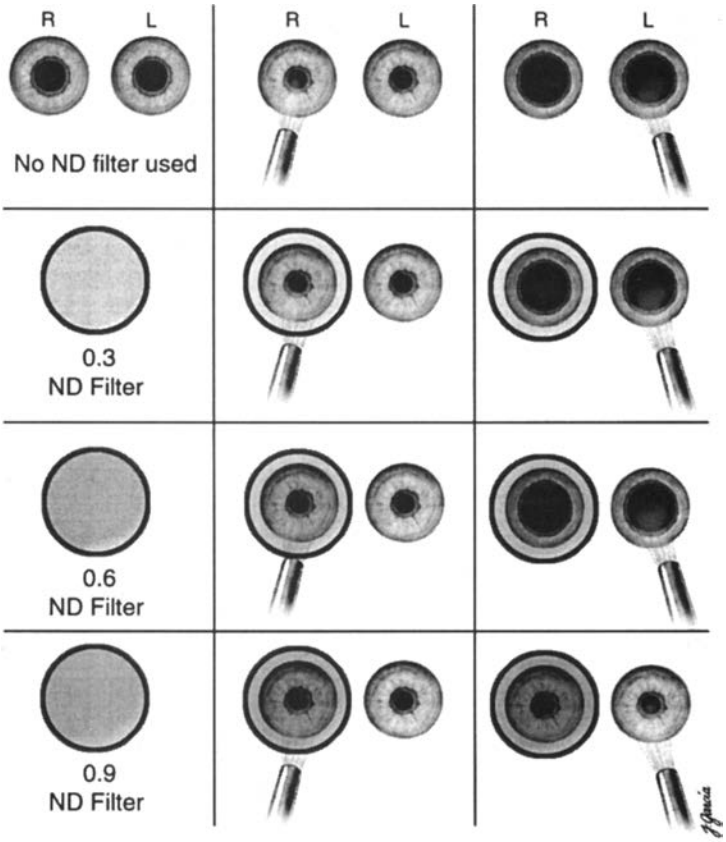


Figure 15.8. Quantification of the relative afferent pupillary defect (RAPD) using neutral density filters and the swinging flashlight test. Neutral density filters of increasing density are placed in front of the normal eye in a patient with a contralateral RAPD, and a swinging flashlight test is performed until the RAPD disappears. In this case, the RAPD is balanced with a 0.9 log unit filter.

Figure 15.9. The equipment needed to quantify or bring out a relative afferent pupillary defect includes a bright handheld light source, a pupil gauge, and a set of photographic neutral density filters in 0.3, 0.6, 0.9, and 1.2 steps.

Table 15.1
Expected Relative Afferent Pupillary Defect in Various Settings

Condition	Expected RAPD	Comment	References
Optic nerve	0.3–3 log units	If no RAPD, either no optic neuropathy or bilateral disease	22,143
Chiasm	Only if asymmetric		
Optic tract	0.4–0.6 log units in the eye with the temporal visual field defect (contralateral to the tract lesion)	From asymmetry of the pupillomotor fibers (more crossed fibers than uncrossed)	144–146
Pretectal lesion	Contralateral RAPD without associated loss of visual acuity, color vision, or visual field		147
Visual field defect	RAPD correlates with severity of visual field loss		55
Central visual field defects	Greater pupillary escape		148
Peripheral visual field defects	Greater sustained pupillary response		25
Amblyopia	$<$0.5 log unit	If $>$1.0 log unit, look for other explanation	22,149
Anisocoria	0.1 log unit for every 1 mm difference; $<$3 mm of anisocoria induces RAPD that may be difficult to measure	Must assess in light	150
Macular disease	If visual acuity $>$20/200, RAPD of $\leq$0.5 log units	Even worst macular disease causes RAPD of $<$1.0 log unit	22,151
Central serous choridopathy	$<$0.3 log units		152
Central retinal vein occlusion	Ischemic: 0.9–1.2 log units; Nonischemic: $<$0.6 log units		153
Retinal hemorrhage	Small: none; large: major intraocular can produce RAPD of $\leq$1.2 log units	Depends on amount of light blocked	154
Retinal detachment	1 quadrant: 0.3 log units; 2 quadrants: 0.6 log units; macula: 0.9 log units. Total: 2 log units		46,155,156
Retinitis pigmentosa	$\leq$0.3 log units		157
Cataract	$\leq$0.3 in opposite eye but only if cataract very dense	From upregulation of photoreceptors in eye with cataract	158,159
Patching; dark adaptation	$\leq$1.5 log units in nonoccluded eye	Maximum RAPD in 30 minutes; reverses in 10 minutes	160,161
Glaucoma	Usually none unless unilateral or markedly asymmetric	Corresponds with remaining neuroretinal rim	162,163
Refractive error	None		164
Nonorganic visual loss	None		22,39

RAPD, relative afferent pupillary defect.

detected by kinetic perimetry (54). There is less convincing evidence of a correlation between the pupillary response and a central field defect in the eye detected by static perimetry (55).

Tests other than the swinging flashlight test can be used to detect a relative afferent pupillary defect. Kestenbaum proposed a test that is loosely based on the Gunn phenomenon, in which the patient fixes in the distance with one eye, while the other eye is occluded by the palm of the hand (56). The examiner holds a handlight with fresh batteries 1 inch from the uncovered eye for 5 seconds to allow the pupils to stabilize. The size of the uncovered pupil is then measured with a pupil gauge to the nearest 0.25 mm. The size of the opposite pupil is then measured in the same fashion, and the difference between the two eyes is determined after correcting for any initial anisocoria. This result is called ''Kestenbaum's number.''

Jiang and Thompson measured the RAPD in a group of patients using the swinging flashlight test with neutral density filters (57). They compared the results with the results of the Kestenbaum test and found a distinct relationship between the severity of the RAPD measured with neutral density filters and Kestenbaum's number ($r = 0.86$). The major problem with the Kestenbaum test includes the need for two intact iris sphincters and the problem of miosis of the elderly and hippus in the young (57).

A highly sensitive way to detect an RAPD is by using pupillography (58,59). Pupillary reactions that occur during stimulation of an eye with a damaged retina or optic nerve have a prolonged latent period and a shortened duration and diminished amplitude of constriction. These parameters can be evaluated by pupillography. For example, inflammatory diseases of the optic nerve and optic atrophy are associated with significant prolongation of the latent period, ischemic optic neuropathy produces a lesser prolongation, and acute papilledema does not affect latency at all (60). Furthermore, portable pupillography units can detect and measure large RAPDs quickly, even in a clinical setting (61), and such devices can be linked to computerized systems to test the visual field (62,63).

Tests used to detect an RAPD, particularly the swinging flashlight test, are sensitive tests for optic nerve dysfunction; however, they represent only one type of test used to determine whether or not a patient has an optic neuropathy and, if so, the degree of severity of the optic nerve dysfunction. Other tests of optic nerve function are reviewed in Chapter 4 of this text.

Other Clinical Tests of Pupillary Function

The swinging flashlight test provides only relative information regarding the visual sensory system of the two eyes, because the pupillary light response of one eye is compared with that of the other eye. In order to assess the pupillary light reflex of each eye separately, however, one can evaluate the number of pupillary oscillations that occur over a fixed amount of time or determine the time it takes for a pupil to oscillate a specific number of times when stimulated by light (64–66). In this test, a thin beam of light (0.5 mm wide) is placed horizontally across the inferior aspect of the pupillary margin (Fig. 15.10). The light induces pupillary constriction that moves the light out of the pupil. The pupil then redilates until the beam is once again at the edge of the pupillary margin, whereupon the pupil again constricts, creating a cycle. A set number of cycles (usually 10, 20, or 30) are then timed by a stopwatch to the nearest 0.1 second, and the time of the cycle—the **edge-light pupil cycle time**—is calculated as msec/cycle. Alternatively, the number of cycles that occur during a fixed period of time, usually 1 minute, are counted. In both cases, the results are compared with results from normal control subjects. For instance, normal pupils generally cycle at a rate of 900 msec/cycle.

Unfortunately, the edge-light pupil cycle time is not a particularly sensitive indicator of optic nerve disease compared with the swinging flashlight test or visual evoked potentials. In addition, it may be difficult or impossible to induce regular oscillations in some patients and, as with other tests of pupillary constriction, the edge-light pupil cycle time is affected by the efferent arm of the pupillary light reflex (e.g., oculomotor nerve function). Nevertheless, it is a potentially useful initial diagnostic test in one-eyed patients or in patients with presumed bilateral symmetric retinal or optic nerve disease (67,68).

Pupil Cycle Induction Test

The **pupil cycle induction test** is a variation of the edge-light pupil cycle time (69). It is used to assess the difficulty in producing regular and sustained light-induced pupillary oscillations. In this test, a beam with a thickness of 0.45 mm or less is placed horizontally at the lower edge of the pupil-

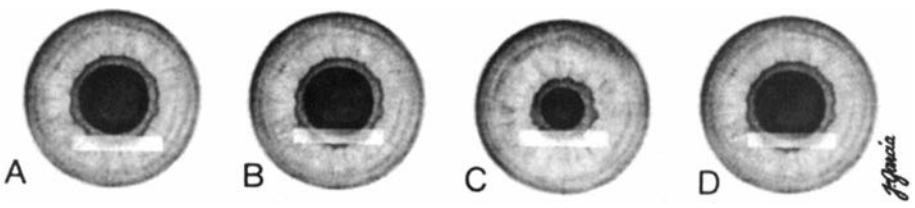


Figure 15.10. Testing the edge-light pupil cycle time. The pupil can be induced to cycle at the slit lamp by placing a horizontally oriented slit beam on the lower pupil margin. The beam is then moved slightly upward, inducing pupillary constriction that moves the light out of the pupil. The pupil then redilates until the beam is once again at the edge of the pupillary margin, whereupon the pupil again constricts, creating a cycle.

Table 15.2
Pharmacologic Testing in Diagnosing Common Pupil Conditions

Agent	Setting/Purpose	Dose	Time	Lighting	Measure	End Point	Caution
Testing for denervation supersensitivity							
Dilute pilocarpine (165–167)	Dilated, poorly reactive or nonreactive pupil to distinguish tonic pupil from 3rd nerve palsy pupil or pharmacologic blockade	0.0625–0.1% (168)	30 min	Dim light or darkness	Change in pupil diameter	>0.5 mm difference between two eyes *or* the larger abnormal pupil becomes the smaller pupil	Limited usefulness-bilateral Adie pupil; normals can react variably to medication; cannot reliably distinguish between 3rd nerve palsy and tonic pupil (167)
Testing for Pharmacologic Blockade							
Pilocarpine	Dilated, fixed pupil to distinguish pharmacologic blockade from tonic pupil or 3rd nerve palsy pupil	2%	40 min	darkness	Change in pupil diameter	Pupil that is pharmacologically blockaded should not constrict at all or should constrict minimally	Other causes of dilated pupil may prevent constriction; e.g., traumatic or post-herpetic iridoplegia; angle-closure glaucoma; fixed pupil after cataract surgery (154)
Testing for Horner Syndrome							
Cocaine (169)	Anisocoria with normal pupillary reactions to light to determine if sympathetic defect present	2–10%	40–60 min	Light	Larger pupil dilates; smaller pupil either dilates poorly or not at all	>0.8 mm inequality is positive; <0.3 negative	If the affected pupil dilates >2 mm to cocaine, be wary (170); keep patient alert because sleep may give a false-negative test; always assess test result in dark
Hydroxyamphetamine (and Tyramine) (171)	In proven Horner syndrome to differentiate between first/second order and third order Horner syndrome	5%	50–60 min	Light	Dilation of Horner pupil indicates first or second order Horner syndrome; dilation of normal pupil but not of Horner pupil indicates third-order syndrome	>1 mm change in anisocoria **OR** a change of anisocoria (difference in pre to post-anisocoria) of >0.5 mm suggests post-ganglionic (171); increased size of smaller pupil over normal pupil suggests preganglionic defect (154)	Should not be performed on same day as cocaine test; some authors suggest waiting 3 days; not always accurate in congenital Horner syndrome because of trans-synaptic degeneration (154)
Apraclonidine (172,173)	Anisocoria with normally reactive pupils; to determine if sympathetic defect present	0.5–1%	60 min	Light	Dilation of the smaller pupil (reversal of anisocoria)	Dilation of smaller pupil with reversal of anisocoria (normal pupils never dilate >0.5 mm)	Helpful when cocaine not available, but does *not* differentiate pre- and postganglionic Horner syndromes
Phenylephrine 2.5%	To confirm a Horner syndrome and to exclude a small immovable pupil causing a positive test	2.5%	30–60 min	Light	Pupillary size after treatment	The Horner pupil should dilate as well as or more than other pupil	A normal pupil will also dilate

lary margin in much the same way as in testing the edge-light pupil cycle time. The pupils of almost all eyes with normal optic nerves can generally be induced to cycle at regular intervals, whereas the pupils of almost all eyes with optic nerve disease show altered responses, such as complete failure to cycle or prolonged pauses in the cycle. We have found the results of testing edge-light pupil cycle time and pupil cycle induction difficult to interpret, not particularly reproducible, and less sensitive than the results of a simple swinging flashlight test. We thus use these tests only when assessing monocular patients.

PHARMACOLOGIC TESTING

A few cautionary comments should be made regarding the interpretation of pupillary responses to topically instilled drugs.

First, the test variables must be carefully controlled whenever possible, both before and after pharmacologic testing. This means that the ambient lighting should be optimal for the test performed, the patient must fixate in the distance for at least 1 minute to minimize miosis and relax the pupil, and the patient should be alert throughout the test, because the psychic state of the individual can influence pupillary size (e.g., the pupils tend to be miotic in persons who are tired or listless and mydriatic in patients who are upset or anxious) (70).

Second, the pupil sizes must be measured as accurately as possible. The CU-5 camera manufactured by the Polaroid Company allows the direct measurement of pupillary size; however, one can simply paste or tape a ruler on the patient's brow and then use any camera to obtain photographs from which accurate measurements can be made. Pupillometers also provide accurate measurements but are not well suited to most clinical practices.

Third, it is ideal, whenever possible, to use the presumably normal pupil as an internal control. For instance, if a judgment is to be made about the dilation or constriction of one of the pupils in response to a drop of some topical agent, such as 0.1% pilocarpine, 10% cocaine, or 5% hydroxyamphetamine (see Chapter 16), the drug should be placed in **both eyes** so that the responses of the two eyes can be compared. When the condition is bilateral, no such comparisons are possible, but an attempt should be made to make certain that the observed response is indeed caused by the instilled drug. In such cases, the drug may be placed in one eye only so that the responses of the medicated and unmedicated eyes can be compared. Occasionally, in patients with presumed bilateral pupillary abnormalities, we and others (22) place drops in both of the patient's eyes and also in one of our own, to serve as a type of external control.

Finally, the drug should always be placed in the eye of concern **first** and then placed in the contralateral eye so that if there is no response in the presumably abnormal eye, one cannot blame squeezing or tearing as the cause.

Problems can occur when performing pharmacologic testing of the pupil using topical drugs. The drug may be outdated and thus more or less potent. The patient may develop sufficient tearing that the strength of the drug is altered by dilution, or it is washed out of the inferior conjunctival sac before it can be absorbed. The patient may squeeze the eyes tightly during instillation of the drug, thus preventing a sufficient amount of drug from being placed in the inferior conjunctival sac. Penetration of the drug through the cornea may be altered, especially if other topical medications have been used; e.g., anesthetics for testing of intraocular pressure, or if the integrity of the corneal epithelium has been altered by manipulation of the cornea during tonometry or testing of corneal sensation. One must also consider individual variations in the action of the drug on patients of different ages or with different colored irides.

Determining the results of pupillary testing can also be difficult depending on the initial size of the pupil. Differences in pupillary diameter or area can have profound results on the ultimate outcome in pharmacologic testing (Table 15.2).

Finally, it is important to remember why a particular test is being performed in the first place (Table 15.2). The correct drug must be used and placed in the eyes in the proper fashion.

ASSESSMENT OF ACCOMMODATION, CONVERGENCE, AND THE NEAR RESPONSE

Most visual problems associated with accommodation occur because accommodation is too great, too little, or too slow. Disturbances of the other two components of the near response—convergence and pupillary miosis—also can be of importance if they are too active or if they have reduced activity.

HISTORY

The symptoms of patients with disturbances of accommodation tend to be nonspecific but some aspects of the history may be important. Patients with accommodative insufficiency, for instance, usually complain of blurred vision at near but not in the distance. Patients with the most common problem with accommodation—**presbyopia**—may report that the farther away they hold an object, the better they can see it. Some patients with accommodative insufficiency report monocular diplopia; others complain of discomfort during attempted reading, a noticeable delay in focusing when changing fixation from a distant to a near or a near to a distant object, or a combination of these symptoms. Some patients report headache, light intolerance, and other asthenopic symptoms (71). Frequently, presbyopia and other accommodative insufficient states can be precipitated with medications having anticholinergic effects.

Accommodative excess or spasm is typically associated with clear vision at near and poor distance vision. Objects may look larger or smaller (macropsia or micropsia) than normal in this setting. In addition, patients with accommodative excess or spasm often complain of brow ache (72). When convergence also is affected, other symptoms may be present. For example, convergence excess often is associated with diplopia in the distance, blurring of vision, oscillopsia,

and/or pain; whereas convergence insufficiency most often is associated with trouble reading, diplopia at near, blurred vision that clears when either eye is covered, and pain or discomfort during near tasks.

In patients with **spasm of the near reflex**, symptoms are related to dysfunction of all three components. Such patients have accommodative spasm (up to 8–10 diopters), extreme miosis, an esotropia in primary position, and apparent but inconsistent bilateral limitation of abduction. These patients tend to complain of blurred or dim vision, binocular horizontal diplopia at both distance and near, temple or diffuse headache, pain in the eyes, and even trouble walking (73,74). Spasm of the near reflex is discussed in detail in Chapter 16 of this text.

EXAMINATION

Accommodation is the ability of the lens to change its refractive power in order to keep the image of an object clear on the retina. The primary stimulus for accommodation is blurring (75), and most tests of accommodation depend on producing or eliminating blur. There are, however, stimuli for accommodation other than blur, including chromatic aberration and perceived nearness (76), and these can also be used to test accommodation.

General Principles Related to the Components of the Near Triad

Accommodation is part of a complex triad that maintains clear near vision and is called the **near response** or the **near reflex**. Even though the components of the near response—accommodation, convergence, and pupillary miosis—normally work together during near viewing, each component can be tested separately. For example, one can weaken the stimulus to accommodation with plus lenses or strengthen the stimulus to accommodation with weak minus lenses without stimulating convergence or miosis. One can use weak base-out prisms to stimulate convergence without changing accommodation. Under certain conditions, one can test accommodation without inducing pupillary constriction (77). In addition, even in presbyopia in which accommodation fails, convergence and miosis continue. Furthermore, if one paralyzes accommodation with drugs, convergence remains intact. **Relative accommodation** is the term used to describe the amount of accommodation that is unrelated to convergence; **relative convergence** describes the amount of convergence unrelated to accommodation (78).

Depth of focus is slightly different from accommodation. It is the distance for any given accommodative state that an object can be viewed without a change in acuity or generation of blur. Depth of focus is more dependent on pupillary size and amount of illumination than is accommodation. For example, accommodation is not significantly affected by miosis and bright illumination; however, in patients with small pupils and bright illumination, the depth of focus is increased. Thus, a patient over 60 years of age will have very little, if any, accommodation; however, if one compares two patients, one with large pupils and the other with small pupils, the patient with the smaller pupils will have an increased depth of focus, and this increased depth of focus may be mistaken for accommodation. Many traditional tests of accommodation thus may overestimate the amount or range of accommodation in a patient because the tests cannot distinguish true accommodation from combined accommodation and depth of focus (79).

Accommodation

There are actually three aspects of accommodation: the near point of accommodation, the accommodative amplitude, and the range of accommodation. The **near point of accommodation** (NPA) is the point closest to the eye at which a target is sharply focused on the retina. The **accommodative amplitude** is the power of the lens that permits such clear vision. This power is measured in units called diopters (D) and is calculated by dividing the NPA in centimeters into 100. The accommodative amplitude is thus simply the reciprocal of the NPA (e.g., a patient with an NPA of 25 cm has an accommodative amplitude of 100/25 = 4 D). The **range of accommodation** is the distance between the furthest point an object of a certain size is in clear sight and the nearest point at which the eye can maintain that clear vision.

Convergence

Convergence is a vergence adduction movement that increases the visual angle to permit single binocular vision during near viewing. Convergence can be voluntary but need not be; i.e., no stimulus need be present to elicit it. It is also reflexive and a co-movement in the near response. Accommodation and convergence are related; a unit change in one normally causes a unit change in the other (80).

Convergence may be separated into four subtypes: (*a*) tonic convergence; (*b*) accommodative convergence; (*c*) fusional convergence; and (*d*) voluntary convergence.

The eyes normally tend to diverge. Keeping the eyes straight thus requires increased tone in the medial rectus muscles. This tone is **tonic convergence** (81).

Accommodative convergence is the amount of convergence elicited for a given amount of accommodation. The relationship between accommodation and convergence is usually expressed as the ratio of accommodative convergence in prism diopters (PD) to accommodation in diopters: the AC/A ratio. Because accommodation decreases with age, the AC/A ratio increases with age (72,82). Just as convergence can be stimulated by accommodation, so accommodation can be stimulated by convergence. The ratio of convergence accommodation in diopters to convergence in PD is called the CA/C ratio.

Fusional convergence is convergence that is stimulated not by changes in accommodation but by disparate retinal images (81). It is thought to be used to ''fine tune'' normal convergence. Pupillary constriction can occur with fusional vergence, but the amplitude of this form of convergence is not as great as that of accommodative convergence.

Voluntary convergence is measured by determining the near point of convergence (NPC)—the nearest point to which the eye can converge. It is closer to the eyes than

the near point of accommodation and, in general, does not deteriorate with age as does the NPA. The NPC usually is 10 cm or less.

Miosis

The pupil constricts when changing fixation from distance to near. This movement can occur in darkness, is slower than the light reflex, and is maintained as long as the near reaction is maintained. Miosis improves the range through which an object is seen clearly without any change in accommodation; i.e., the depth of field (see above). The miotic response to the near effort is directly dependent on that effort. Normal persons usually need a visible target to view to reach maximal pupillary miosis and accompanying accommodation. This miotic response also can be inadvertently stimulated by forceful eyelid closure (83). In patients with presbyopia, pupil size continues to decrease even when accommodation has reached its maximum. This probably occurs because aging changes limit alterations in the lens or ciliary muscles, whereas the pupillary sphincter is still functional and responsive to stimulation (84). On the other hand, artificially induced miosis (e.g., pharmacologic) reduces the amplitude of accommodation (85).

In testing accommodation and the near vision response, the above relationships must be remembered. Furthermore, one must remember that accommodation is never measured or tested in an absolute sense, but rather in response to how it changes under certain testing conditions (86).

Testing Techniques

The techniques one uses to determine the range and amplitude of accommodation, degree of convergence, etc. depend in part on the setting and the questions to be answered.

Accommodation

The principal handicaps in the clinical application of adequate tests of accommodation are the subjective nature of the end points and the number of variables that must be controlled. The first step in any testing of components of accommodation or the near triad, is to perform an adequate refraction for both distance and near viewing. For children and some adults, a cycloplegic refraction with an agent such as cyclopentolate (Cyclogyl) is needed to prevent the patient from accommodating and thus increasing the degree of myopia requiring correction during the refraction (87,88). Indeed, this ''pseudomyopia'' may be the first clue to accommodative spasm. Conversely, excellent distant vision and poor near vision may indicate accommodative insufficiency or presbyopia.

The NPA is most easily measured clinically using a scale device such as the Prince, Krimsky, or Berens rules (89–91). These instruments are simply rulers with markings in both centimeters and diopters on which there is a small sliding chart containing Snellen letters (Fig. 15.11). The technique of testing accommodation with them is called the ''push-up method'' (92) and is performed as follows.

Wearing an optimum distance refraction and with the opposite eye occluded, the patient fixes on small (usually 5 point) type on a card that is attached to the rule and that can be slid forward and backward. The size of the type is important, because the smallest type will evoke the strongest accommodative response (93). The zero point of the rule should be 11–14 mm in front of the cornea. This corresponds to the approximate position of the spectacle correction. The card is moved from a distance to the closest point at which the patient can see the print before it starts to blur. This is the NPA and, as noted above, is expressed in centimeters. The maneuver is repeated several times until the test gives reproducible results.

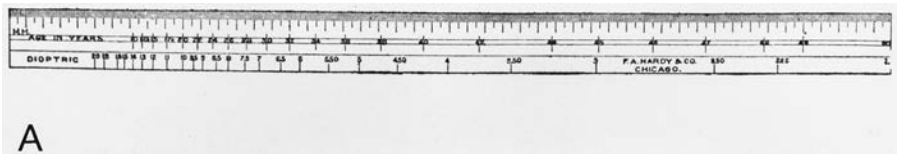
Once the NPA is determined, the accommodative amplitude in diopters, as indicated above, is calculated by dividing 100 by the NPA in centimeters. Using the push-up method, Duane (94) developed age-related normative data for the accommodative amplitude that are still in use today (Fig. 15.12).

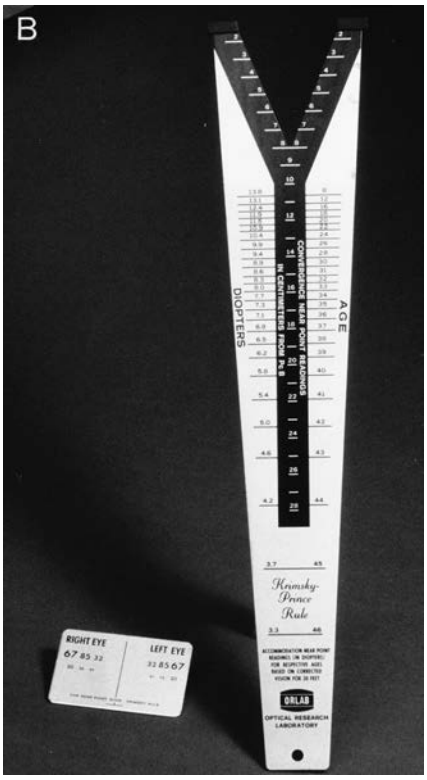
Although the push-up method of determining the NPA and the accommodation amplitude has the disadvantage of overestimating accommodation, it is the most widely used method, the quickest in clinical practice, and the most popular. When interpreting the results of testing of accommodation using the push-up method, the examiner must be sure that the patient fully cooperated with the testing. Nevertheless, if, on repeated testing, the NPA (and thus the accommodative amplitude) is consistently out of the range considered to be normal for age, the results should be considered truly abnormal (94).

Adequate room lighting obviously must be available when testing accommodation, and it usually is recommended that the light be directed over the right shoulder when testing the right eye and over the left shoulder when testing the left eye. Indeed, illumination is a critical factor in performing the test. By increasing illumination from 1 to 25 foot-candles, the accommodative range can be increased by 28% in nonpresbyopes and by 73% in presbyopes (95).

The range of accommodation can be tested in a fashion similar to that used to test the accommodative amplitude. The patient is instructed to indicate when the object blurs at near (the near point or NPA) and when it blurs in the distance (the far point). The range of accommodation is then calculated by determining the far point and near point in diopters (i.e., dividing each of the distances in centimeters into 100) and by subtracting the far point from the near point. For an emmetrope, the range of accommodation corresponds to the accommodative amplitude because the far point is at infinity. For a myope whose near point is 10 cm and whose far point is 50 cm **in front** of the eye, the range of accommodation is $100/10 - 100/50 = 10 - 2 = 8$ D. For a hyperope with a near point of 10 cm and a far point of 25 cm **behind** the eye, the range of accommodation is $100/10 - (-100/25) = 10 - (-4) = 10 + 4 = 14$ D. If the patient is too presbyopic or myopic to do the test, corrective lenses should be used. One must then adjust the results to reflect the correction. If a minus lens has been used, the diopter power of the lens is added to the result; if a plus lens has been used, the diopter power is subtracted.

The push-up method of measuring the NPA and the ac-





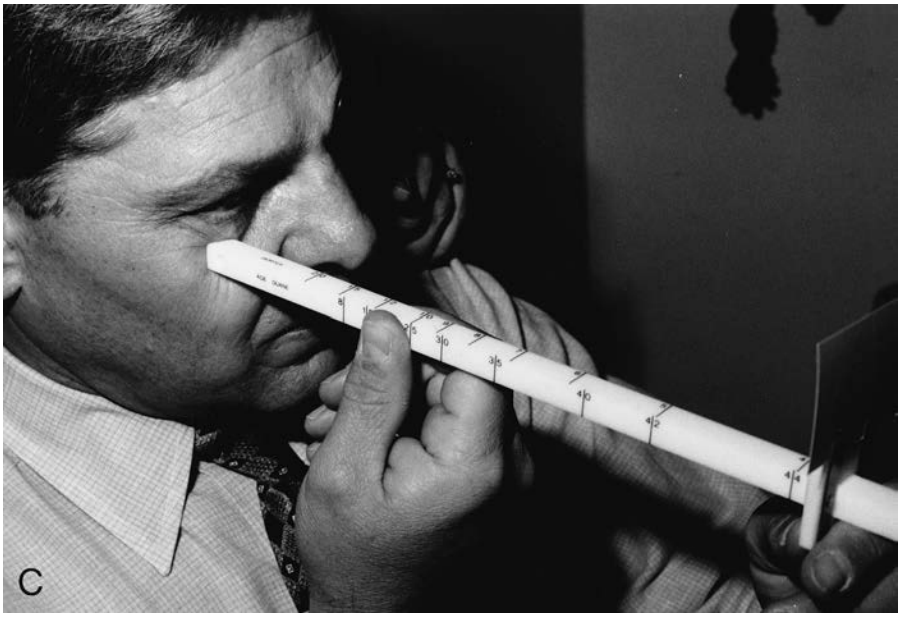


Figure 15.11. Photographs of accommodative rules. *A*, The Prince Rule. *B*, The Krimsky-Prince Rule. *C*, The Berens Rule. (*A,* From Wood CA. The American Encyclopedia and Dictionary of Ophthalmology. Chicago, Cleveland Press, 1919: 10961. *B,* Photo courtesy Paul Montague, CRP.)

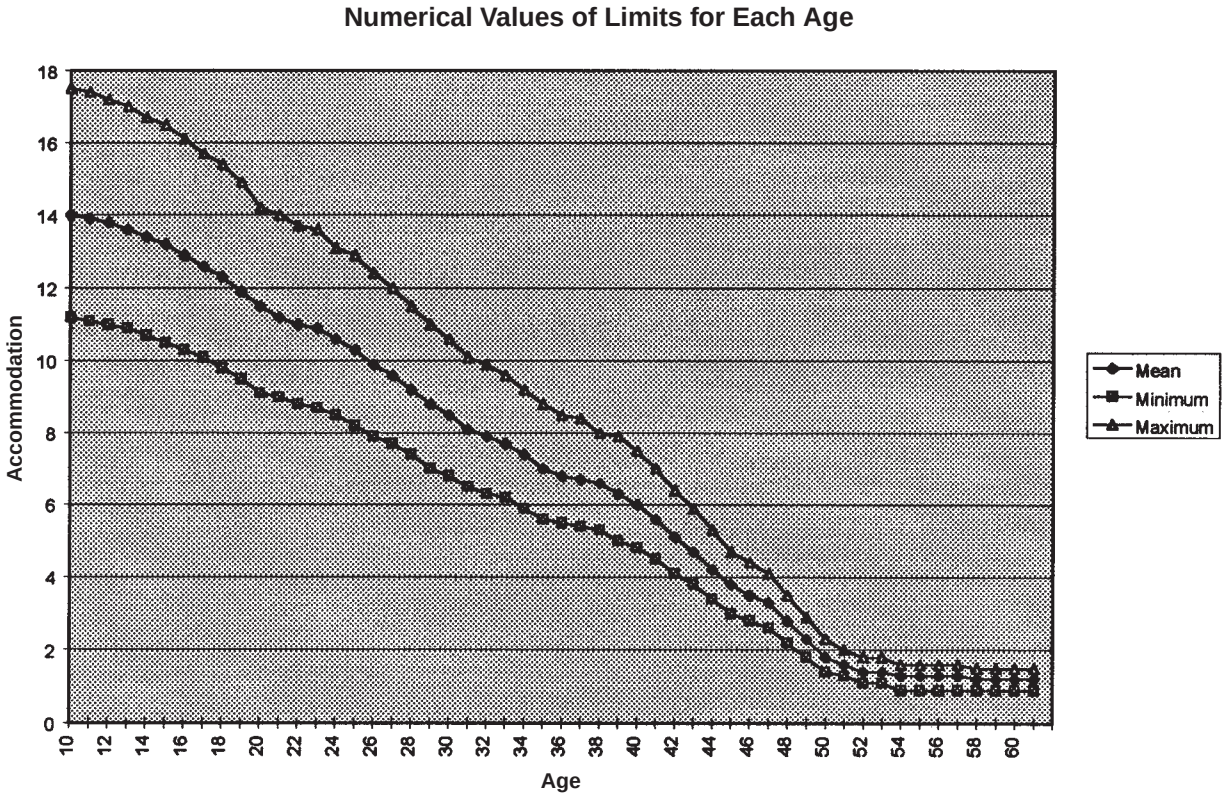


Figure 15.12. The relationship between accommodation and age. Note the relatively linear decrease in accommodation with age until about age 52, when almost all accommodation has been lost. (Graph data from Duane A. The accommodation and Donders curve and the need of revising our ideas regarding them. JAMA 1909;52:1992–1996.)

commodative amplitude is not the only one that can be used. A second method is the **method of the spheres**. In this test, the patient fixates on a reading target at 40 cm, and accommodation is stimulated by progressively adding minus (i.e., concave) lenses until the print blurs. Accommodation is then relaxed by adding stronger plus (i.e., convex) lenses until the print again blurs. The sum of the lenses is the measure of the accommodative amplitude. For example, if a patient accepts up to a -4.0 D sphere before print blurs and then accepts the addition of $+2.50$ D sphere before print again blurs, the total accommodative amplitude is 4.0 D + 2.5 D = 6.50 D (72). Like the push-up method for determining the NPA and the accommodative amplitude, the method of the spheres depends on patient cooperation.

The most objective method of measuring accommodation is the use of refractometers (96,97). Most of these machines use increasingly minus lenses to stimulate accommodation and measure the accommodative response. Alternatively, one can stimulate accommodation not with lenses but pharmacologically by using a topical agent muscarinic agonist like pilocarpine and measure the response using a refractometer (98).

Convergence

Like accommodation, there is a near point of convergence (NPC), a convergence amplitude, and a range of convergence. In general, however, the only measurement of importance is the NPC. This measurement usually is determined by having the patient fixate on an accommodative target held 33 cm from the eyes. The target then is moved toward the nose, with the patient being instructed to try to keep the target in focus. The end-point of the test is when the patient reports horizontal diplopia. The distance at which this occurs is then measured with a millimeter ruler placed alongside the patient's nose.

The NPC also can be determined by placing a red glass over one eye and moving a light forward until the patient experiences diplopia (99) or, more objectively, by performing the above test and noting the distance from the nose at which one of the inward turning eyes is observed to turn suddenly outward. In normal persons, the NPC is usually between 5–10 cm (100). An NPC greater than 30 cm indicates convergence insufficiency.

Yet another way to determine if convergence is normal is to perform a cover-uncover test (see Chapter 18) while the patient is reading. This is helpful only if the patient has full versions and no previous strabismus.

In addition to determining the NPC, it may be useful to determine if a patient's convergence is sufficient for the amount of accommodation; i.e., the AC/A ratio. There are two different methods for measuring the AC/A ratio.

The **gradient method** determines the AC/A ratio by the

change in deviation in prism diopters (PD) that occurs when a lens of a specific power is placed over both eyes to stimulate or relax accommodation (101). An accommodative target must be used, and the working distance is held constant. Plus or minus lenses are used to vary the accommodative requirement, and the difference between the ocular alignment with and without the lens, divided by the power of the lens, is the AC/A ratio. For example, a patient's ocular alignment is measured with the patient viewing the accommodative target at a specific distance such as 33 cm, and the patient is found to have an esophoria of 2 PD. A −1.00 D spherical lens is placed over each eye, and ocular alignment is again measured with the patient viewing the same target at the same distance. The patient is now found to have an esophoria of 6 PD. The difference between the ocular alignment with and without the lens, divided by the power of the lens, is the AC/A ratio and is $6 - 2/1 = 4/1 = 4$. This means that when 1 diopter of accommodation was stimulated in this patient by placing a −1.00 D spherical lens in front of the eyes, the patient's convergence, measured at the same distance from the eyes, increased from 2 to 6 PD. In another patient, a +3.00 sphere might be used to reduce accommodation, and a change in deviation from an exotropia of 4 PD to an exotropia of 10 PD might be noted. The AC/A ratio then would be $10 - 4/3 = 6/3 = 2$.

The second method for determining the AC/A ratio is the **heterophoria method**. This method uses the distance-near relationship to determine the AC/A ratio. Instead of measuring ocular alignment at near with and without a specific power lens, ocular alignment is measured at distance and near, and the difference in alignment in PD between distance and near viewing is divided by the fixation distance used for near viewing as expressed in diopters. Normal persons should have the same ocular alignment when viewing both distant and near objects. If a patient is more exotropic or less esotropic at near compared with distance, this indicates less convergence, or a low AC/A ratio; if the patient is more esotropic or less exotropic at near compared with distance, this indicates a high AC/A ratio. For example, if a patient has an exophoria of 5 PD at distance and an esophoria of 4 PD at 33 cm, the AC/A ratio is $5 - (-4)/3 = 9/3 = 3$.

The normal AC/A ratio is between 3 and 6, regardless of the method of testing that is used (72). It should be noted, however, that the AC/A ratio varies from person to person and from day to day or hour to hour in a given individual depending on that person's level of fatigue or alertness. In addition, the AC/A ratio rises sharply after the age of 40 as accommodation begins to be lost but convergence remains stable (102). Nevertheless, values above 6 usually indicate an excess of convergence per unit of accommodation, whereas values below 3 suggest convergence insufficiency. An elevated AC/A ratio in a cooperative child is a risk factor for the rapid onset of myopia (103).

Testing convergence accommodation; i.e., the CA/A ratio, requires that the patient experience no blur during the test. This can be accomplished by the use of a pin hole device (104), performing the test in dim illumination (105), or using a Gaussian target (106). In this test, accommodation is measured as convergence is produced using progressively stronger base-out prisms. Unlike accommodation, convergence does not decline significantly with age (102). Thus, just as the AC/A ratio increases with age, the CA/C ratio decreases with age (102,105).

ASSESSMENT OF LACRIMATION

The most anterior optical surface of the eye, the **tear film**, is also one of the greatest optical powers of the eye, and a deficient tear film thus is one of the most common causes of fluctuating blurred vision in clinical practice. In fact, optical aberrations caused by an early break-up of the tear film have been shown objectively to diminish image quality (107).

The tear film is a trilaminar structure consisting of a superficial lipid layer, an aqueous middle component that accounts for over 90% of the film, and a mucin component in the innermost layer. In order to discern a problem of the tear secretion, one must attempt to determine if only one layer is affected or all the layers are affected.

The main function of the lipid layer is to retard evaporation of the tear film. Removal of this layer causes a 19-fold increase in evaporation (108,109).

The aqueous layer, being the thickest component of the tear film, contributes the most to its volume, and most of the tests that measure the quantity of the tear film test this layer. The aqueous layer of the tear film is produced by both the primary lacrimal gland located in the lacrimal fossa in the superior lateral orbit and the accessory lacrimal glands of Krause and Wolfring that are similar in structure to the main lacrimal gland but are much smaller in size. The glands of Krause are located in the upper fornix, whereas the glands of Wolfring are situated further down on the eyelid, above the tarsus. The relative importance of the main and accessory lacrimal glands in the maintenance of normal tear secretion is somewhat controversial. It generally is accepted that the main lacrimal gland, having an efferent parasympathetic innervation, functions primarily during **reflex** tear secretion, whereas the accessory lacrimal glands provide **basal** tear secretion (110,110a).

The mucin layer is a biphasic layer that allows the aqueous component to adhere to the hydrophobic cornea epithelium. This layer thus helps to maintain the integrity of the aqueous component of tears and the quality of the tear film. Abnormalities in this layer (and also in the oil layer) can create tear film disturbances despite good aqueous tear production. The mucin layer is produced by goblet cells located in the conjunctiva.

The normal basal tear volume is 5–9 μL, and the normal flow rate averages 0.5 to 2.2 μL/min (111). In general, neither basal tear volume nor flow changes with increasing age, but reflex tearing decreases with age (112).

The main disturbances of lacrimation relate to excess or insufficient tear production and to obstruction of the normal passage of tears through the lacrimal drainage apparatus. Thus, the assessment of patients with difficulties should be oriented to an evaluation of tear production and drainage.

HISTORY

Excessive drying of the eyes occurs in several settings, including reduced production, increased evaporation, and excessive drainage of tears. **Epiphora**—excessive tearing—also occurs under several different circumstances, including increased production of tears, an obstructed lacrimal drainage system, or excessive dryness of the eyes caused by a deficiency of normal basal tearing from hypofunction of the glands of Krause and Wolfring. In this last setting, the excess tearing is reflexive in nature and results from stimulation of the primary lacrimal gland in response to dryness and irritation of the cornea. Indeed, epiphora and irritation from dry eyes is one of the most common ocular problems in the United States (113) and the world (114).

The causes of dry eyes initially may be suspected from the results of a validated short questionnaire developed by Schein et al. (115) (Table 15.3). This questionnaire consists of six major questions. Even though these questions do not significantly correlate with tests of reduced tear function (e.g., lower Schirmer scores or abnormalities on Rose Bengal testing; see below), the questions nevertheless seem to be able to identify patients likely to have dry eyes.

Like dryness of the eyes, epiphora may cause blurred vision that is present during both distance and near viewing. Patients with epiphora should be asked about recent trauma to the eyelids or nose and about previous surgery in this area. They also should be queried about any symptoms or signs of recent infections or inflammations.

EXAMINATION

The examination of a patient with a disturbance of lacrimation is directed toward three main abnormalities: decreased tear production, increased tear production, and partial or complete obstruction of the lacrimal drainage apparatus.

Lid function is critical to spreading the tear film and should be assessed in any patient suspected of having an abnormality of tear function. Disturbances of eyelid structure and function can be detected both by simple external examination and by slit-lamp biomicroscopy. Slit-lamp examination can also detect punctate staining of the inferior cornea related to dry eyes, exposure (lagophthalmos), or a lid abnormality (112).

Table 15.3
Questions to Ask to Diagnose Dry Eyes

1. Do your eyes ever feel dry?
2. Do you ever have a gritty or sandy sensation in your eyes?
3. Do your eyes ever have a burning sensation?
4. Are your eyes ever red?
5. Do you notice much crusting on your lashes?
6. Do your eyes ever get stuck shut in the morning?

(From Schein OD, Hochberg MC, Munoz B, et al. Dry eye and dry mouth in the elderly: A population-based assessment. Arch Intern Med 1999;159:1359–1363; and Brewitt H, Sistani F. Dry eye disease: The scale of the problem. Surv Ophthalmol 2001;45[Suppl 2]:S199-S202.)

Tests of the tear film may be separated into those that test a particular part of the tear film or a particular function of the tears, those that measure the amount of tear secretion, and those that detect obstruction of tear drainage (115a).

The lipid layer can be studied using optical interference patterns, matching the color interference with known color controls. This method is used mainly for research purposes; however, lipid layer thickness measurements were strongly correlated with an assessment of fluorescein break-up time and the Schirmer 1 test in a series of patients evaluated by Isreb and colleagues (116) (see later). Thus, it would appear that a deficiency of the lipid layer of the tear film can be associated with clinical tests of tear film production and function.

An examination of the aqueous layer should begin with an assessment of the tear meniscus, which should be observed for evidence of protein precipitates and debris. A normal tear meniscus is about 1 mm; less than 0.3 mm is abnormal (117). At the same time, the relation of the tear meniscus to the lower eyelid can be assessed. The eyelids and lashes should be observed for evidence of entropion, ectropion, and stray lashes, and for the position and integrity of the lower lacrimal punctum, because such abnormalities may cause disturbances that simulate those caused by abnormal tear production.

Specific tests of the mucin layer of the tears include a conjunctival biopsy to determine if goblet cells are present and, if so, in what number. A qualitative test for mucin also can be performed. In this test, a cotton strip (3 mm $\times$ 10 mm) is placed in the inferior cul de sac of an unanesthetized eye for 5 minutes. The strip is then placed on a glass slide and stained with the periodic acid-Schiff (PAS) stain. If the stain is positive, mucin is present (112).

Impression cytology also can be used to determine if goblet cells are present and in what numbers. In this simple technique, cellulose acetate filter strips are placed on the conjunctival epithelium and then transferred to a glass slide where they are stained with hematoxylin and PAS. This procedure can be used to diagnose not only dry-eye conditions but also vitamin A deficiencies (118).

Other qualities of the tear film can be tested individually. For example, the tear film contains various proteins including albumin, immunoglobulins, and lysozyme (119). Lysozyme, an enzyme that lyses bacterial walls and is reduced in dry-eye syndromes, can be detected using the lysozyme lysis test. This test is said to be more reliable and sensitive than the Schirmer test (discussed later); however, the lysozyme lysis test requires gels, broth cultures, and measurements after incubating tear-soaked filter papers in the gel for 24 hours, whereas the Schirmer test requires only a strip of filter paper and a topical anesthetic. Other assays, such as an assay for tear lactoferrin (120), also may be useful in diagnosing such conditions as keratoconjunctivitis sicca (121). The osmolarity of the tear film can be measured. An increasing osmolarity may be diagnostic of keratoconjunctivitis sicca (122).

In patients with symptoms suggesting insufficient tear production, the most common tests performed are nonspecific tests of tear secretion. The sensitivity and specificity

Table 15.4
Sensitivity and Specificity of Tests for Tear Production

Test Name	Basis of Test	Reference Values	Sensitivity	Specificity
NIBUT	Noninvasive test of tear stability	<10 seconds suggests unstable tear film	82%	86%
Rose Bengal	Assess ocular surface damage	<3 sec, <1 sec	95%, 92%	96%, 86%
Schirmer 1	Assess reflex tear flow	≤5.5 mm, ≤3 mm, ≤5 mm, ≤10 mm	85%, 10%, 25%, 79%	83%, 100%, 90%, 97%
Schirmer 2	Assess reflex tear flow			
Phenol red thread	Assess tear volume	<6–10 mm	Unknown	Unknown

NIBUT, noninvasive tear breakup timen.
(Adapted from Mainstone JC, Bruce AS, Golding TR. Tear meniscus measurement in the diagnosis of dry eye. Curr Eye Res 1996;15:653–661; and from Versura P, Cellini M, Torreggiani V, et al. Dryness symptoms, diagnostic protocol and therapeutic management: a report on 1200 patients. Ophthalmic Res 2001;33:221–227.)

of these tests vary greatly (Table 15.4), depending on the specific test used and the reference criteria for normal values.

Judging the height of the tear meniscus may predict the amount of tear production and secretion as may assessment of radius of curvature, height, width, and cross-sectional area; however, there is little correlation between the results of this technique and the results of more objective tests of tear production (e.g., the Schirmer test) unless quantitative measurements of the meniscus are made (123).

The **noninvasive tear film break-up time** test is perhaps the simplest test used to determine the adequacy of the tear film (124). In this test, the examiner touches the conjunctiva of an unanesthetized eye with a fluorescein strip or places a small drop of fluorescein on the cornea of the eye. The fluorescein stains the mucin layer of the tear film and spreads across the cornea, which is then assessed using the cobalt blue filter of the slit lamp. The patient is asked to blink once, then look straight ahead without blinking. A normal test is characterized by the persistence of the fluorescein over the cornea for 10 seconds or longer. A break up and disappearance of the fluorescein in less than 10 seconds is abnormal and indicates an abnormality in one of the layers of the tear film (125). This simple test has relatively good sensitivity (82%) and specificity (86%) for adequacy of the tear film (126).

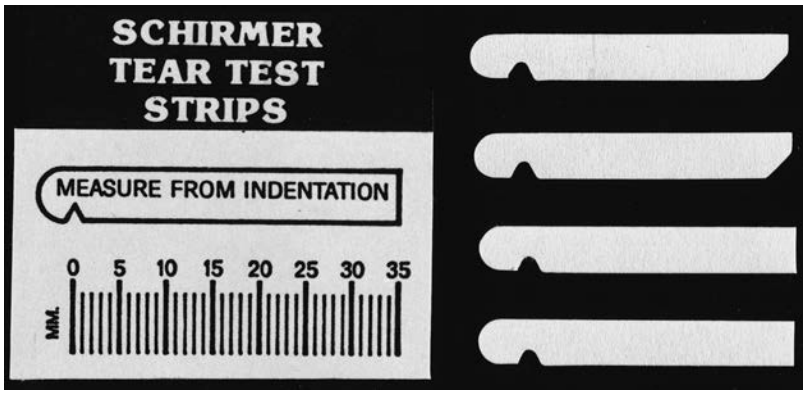
Another test of tear function is the **Rose Bengal test**. In this test, the eye is first anesthetized with a 5% solution of proparacaine, and a small drop of a 1% solution of Rose Bengal is placed either directly on the cornea or just superior to it. This solution stains dead and degenerating cells. Normal patients should have little if any staining of the conjunctiva and cornea, whereas patients with a dry eye or a poor mucin layer will have mild to severe staining of both (112). Some authors have found that Rose Bengal staining in nonexposure zones of the bulbar conjunctiva characterize tear deficiencies caused by an abnormality of the lipid layer and help to differentiate it from dry-eye syndromes caused by a deficiency of the aqueous component of the tear film (127).

As noted above, tear secretion may be classified as basal, reflex, or total. Tests of tear secretion can be separated into those that test basal tear production (i.e., from the glands of Krause and Wolfring) and those that test reflex tear production (i.e., from the primary lacrimal gland).

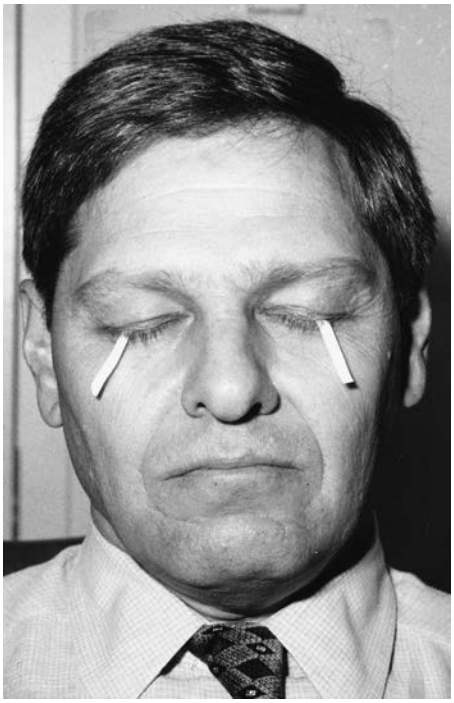
The **Schirmer test** was first described in 1903 (128) and remains a simple and practical clinical test of tear secretion (125). Total tear secretion usually is tested first, because no anesthetic drop is applied to the eye in this test, often called the Schirmer 1 test. In this test, the patient sits in a dimly lit, quiet room. After drying the inferior conjunctival fornices on both sides with a cotton-tipped applicator or the edge of a tissue, the examiner places a strip of special absorbent filter paper in the lower conjunctival sac on both sides, with care being taken to keep the strip from touching the cornea by placing it either medially or laterally (Fig. 15.13). The strips are stabilized by folding the indented end over the lid margin. The patient is then advised to look straight ahead or slightly upward for 5 minutes, during which time he or she can blink normally. After 5 minutes, the strip is removed, and the amount of wetting is measured from the folded end. Because the eyes have not been anesthetized, the irritation from the filter paper produces wetting of the filter paper from both basal tear secretion and reflex secretion.

A variant of the Schirmer 1 test can be performed by anesthetizing the eyes with a topical drug such as proparacaine 0.5%. Topical cocaine should not be used as an anesthetic, because it irritates the cornea and inflames the eye. Once the eye has been anesthetized, the paper strips are placed as indicated above, and the nasal mucosa is stimulated using a cotton-tipped applicator or a tissue or piece of cotton that has been soaked with benzene or a similar trigeminal stimulant (129). This test provides a more consistent means of stimulating reflex tear secretion (in addition to the basal secretion that occurs). Regardless of the technique used, normal persons have a total tear secretion (e.g., wetting of the filter paper) of 10–30 mm in 5 minutes (112).

Basal tear secretion is determined using the Schirmer 2 test. In this test, a topical anesthetic is placed in the inferior conjunctival sac of both eyes. After a minute or so, the examiner uses a small piece of cotton or filter paper to dry the inferior fornices as in the Schirmer 1 test and its variant described above. The paper strips are then placed in the manner of the Schirmer 1 test, and the patient is given instructions identical with those given for the Schirmer 1 test. After 5 minutes, the strips are removed, and the amount of wetting is measured. The wetting in this test should represent only the basal tear secretion, because the topical anesthetic should prevent stimulation of the main lacrimal gland. In addition, by subtracting the amount of basal tear secretion obtained from the Schirmer 2 test from the total secretion



A



B

Figure 15.13. *A*, Schirmer filter strips and measuring scale on packet of strips. *B*, Patient with Schirmer strips properly placed laterally in inferior fornix of both eyes.

measured in the Schirmer 1 test or its variant, one should obtain the amount of reflex tearing (see later, however).

The **phenol red thread test** also assesses tear volume and deficient aqueous. It uses a cotton thread that has been soaked with phenol red. This substance is actually yellow but is sensitive to the pH of tears and will change from yellow to red when soaked with tears. One end of the thread is placed in the inferior conjunctival sac with the other end hanging over the edge of the lid, and the length of thread that has changed color is measured after 15 seconds. A change of color from yellow to red of less than 6 mm is diagnostic of dry eyes (125).

All of the tests of tear secretion described above have their proponents and detractors. Korb surveyed practitioners as to their preferred diagnostic method for the determination of dry-eye syndrome (130). Besides a complete history and use of the dry-eye questionnaire developed by Schein et al. described above (115), most practitioners used the fluorescein tear film break-up time or Rose Bengal test as their first test. In fact, a study that compared the Schirmer 1 and 2 tests, the Rose Bengal test, the tear film break-up time test, and the assay for lactoferrin level in patients with Sjögren syndrome reported that the best balance between sensitivity and specificity was achieved by performing both a Rose Bengal test and a Schirmer 1 test (131).

Fluorophotometric methods can be used to measure both tear volume and flow. These techniques are not clinically applicable, however, and are best used as research tools (132). Corneal sensitivity testing does not correlate with dry eyes (133).

Patients who have epiphora, particularly those in whom the epiphora is unilateral, should be evaluated not only for excess or reduced tear production but also for possible blockage of the tear drainage system. The punctae should be examined to see if they are patent, and the examiner should gently press on the lacrimal sac to see if there is regurgitation of

contents through the punctae, indicating a block at the nasolacrimal duct.

The patency of the drainage system can be assessed using the **fluorescein dye disappearance test**. The test is performed by instillation of one drop of 2% fluorescein dye into the inferior conjunctival sac of both eyes. The conjunctival sacs of the two eyes are then assessed after 5 minutes for any difference between the two eyes of residual fluorescein in the sac and on the sclera, as indicated by a difference in color intensity (134). A slightly more quantitative version of this test is to instill the dye in both inferior conjunctival sacs and to place a small cotton pledget, cotton-tipped applicator, or strip of Schirmer filter paper in the nose on each side just beneath the inferior turbinate (135,136). The pledgets, applicators, or strips are removed 1–5 minutes later and examined to see if they are stained with dye that should have passed through the lacrimal punctae into the lacrimal canaliculi and then to the lacrimal sac, eventually exiting the lacrimal duct just below the inferior turbinate. If no dye is present, a **secondary dye test** can be performed by flushing the lacrimal system with clear saline checking the fluid emanating from the nose for fluorescein staining (135). If there still is no dye, the nasolacrimal apparatus can be probed. If, after probing, dye is present at the inferior turbinate, incomplete blockage exists, and the lacrimal pump is functioning. If, however, there is clear fluid at the inferior turbinate, a nonfunctioning pump exists, and a complete block is present (112,129).

In addition to the tests described above, lacrimal scintillography has been used to test lacrimal flow. This technique uses technetium-99 combined with specific scanning techniques, allowing abnormal secretion and abnormal tear flow patterns to be identified (137). The procedure is useful for research but is impractical for the daily assessment of patients in the clinic. Finally, taste tests in which a specific substance, such as saccharin or Chloromycetin, is placed in the inferior conjunctival sac, can be used to determine if there is an intact lacrimal drainage system; however, these tests give results that are not reproducible and that have not been standardized (112).

Dacryocystography is a radiologic evaluation of the lacrimal drainage system in which contrast is placed into the lower fornix on the side of the presumed obstruction, and radiographs, computed tomographic scans, magnetic resonance images, or angiographic images are obtained to determine if and where the contrast material hangs up, thus localizing the obstruction (138). This test may be helpful in selected patients, particularly those in whom a structural lesion is suspected.

Just as in testing for dry eyes, sometimes a combination of testing is necessary for the evaluation of patients with epiphora (139). The physician involved with such patients should be aware of the tests that can be performed as well as their relative sensitivities and specificities.

ACKNOWLEDGMENTS This work was supported in part by a grant from Research to Prevent Blindness, Inc., New York, NY, to the Department of Ophthalmology, University of Utah.

REFERENCES

1. Loewenfeld I. The Pupil. Boston, Butterworth-Heinemann, 1999.
2. Jacobson DM. Benign episodic unilateral mydriasis. Ophthalmology 1995;102: 1623–1627.
3. Murray RB, Adler MW, Korczyn AD. The pupillary effects of opioids. Life Science 1983;33:495–509.
4. Weir REP, Whitehead DEJ, Zaid FH, et al. Pupil Blown by a Puffer. Lancet 2004;363:1853.
5. Bienfang DC. Neuro-ophthalmology of the pupil and accommodation. In Albert DM, Jakobiec FA, eds. Principles and Practice of Ophthalmology. Philadelphia, WB Saunders, 1994:2470–2482.
6. 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.
7. Loewenfeld IE. The Pupil. Boston, Butterworth, 1999:833–839.
8. Czarnecki JSC, Pilley SFJ, Thompson HS. The analysis of anisocoria. Can J Ophthalmol 1979;14:297–302.
9. Wachler BSB, Krueger RR. Agreement and repeatability of infrared pupillometry and the comparison method. Ophthalmology 1999;106;319–323.
10. 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.
11. Loewenfeld IE. The Pupil. Boston, Butterworth, 1999:869–894.
12. Loewenfeld IE. Pupillary changes related to age. In Thompson HS, ed. Topics in Neuro-Ophthalmology. Baltimore, Williams & Wilkins, 1979:124–150.
13. Ettinger ER, Wyatt HJ, London R. Anisocoria: Variation and clinical observation with different conditions of illumination and accommodation. Invest Ophthalmol Vis Sci 1991;342:501–509.
14. Thompson HS. The pupil and accommodation. In Lessell S, van Dalen JTW, eds. Neuro-Ophthalmology. Amsterdam, Excerpta Medica, 1980:226–240.
15. Lam BL, Thompson HS, Corbett JJ. The prevalence of simple anisocoria. Am J Ophthalmol 1987;104:69–73.
16. Rosenberg ML. Physiological anisocoria: A manifestation of physiologic asymmetry of sympathetic tone. Invest Ophthalmol Vis Sci 1988;29(Suppl):79.
17. Cheng MMP, Catalano RA. Fatigue-induced familial anisocoria. Am J Ophthalmol 1990;109:480–481.
18. Wilhelm H, Wilhelm B. Clinical applications of pupillography. J Neuroophthalmol 2003;23:42–49.
19. Lowenstein O, Loewenfeld IE. Influence of retinal adaptation upon the pupillary reflex to light in normal man. II. Effect of adaptation to dim illumination upon pupillary reflexes elicited by bright light. Am J Ophthalmol 1961;51:644–654.
20. Lowenstein O, Loewenfeld IE. Influence of retinal adaptation upon the pupillary reflex to light in normal man. I. Effect of adaptation to bright light on pupillary threshold. Am J Ophthalmol 1959;48:536–549.
21. Ellis CJK. The pupillary light reflex in normal subjects. Br J Ophthalmol 1981; 65:754–759.
22. Thompson HS. The pupil. In Hart WM, ed. Adler's Physiology of the Eye. Ed 9. St Louis, Mosby Year Book, 1992:412–441.
23. Sun F, Stark L. Pupillary escape intensified by large pupillary size. Vision Res 1983;23:611–615.
24. Thompson HS. Afferent pupillary defects: Pupillary findings associated with defects of the afferent arm of the pupillary light reflex arc. Am J Ophthalmol 1966;62:860–873.
25. Bergamin O, Kardon RH. Greater pupillary escape differentiates central from peripheral visual field loss. Ophthalmology 2002;109:771–780.
26. Semmlow J, Stark L. Pupil movements to light and accommodative stimulation: A comparative study. Vision Res 1973;13:1087–1100.
27. Loewenfeld IE, Newsome DA. Iris mechanics. I. Influence of pupil size on dynamics of pupillary movements. Am J Ophthalmol 1971;71:347–362.
28. Sun F, Tauchi P, Stark L. Dynamic pupillary response controlled by pupil size effect. Exp Neurol 1983;82:313–324.
29. Lowenstein O, Friedman ED. Pupillographic studies. Arch Ophthalmol 1942; 27:969–993.
30. Bergamin O, Kardon RH. Latency of the pupil light reflex: sample rate, stimulus intensity and variation in normal subjects. Invest Ophthalmol Vis Sci 2003;44: 2597–2605.
31. Lowenstein O. Alternating contraction anisocoria. Arch Neurol Psychiatr 1954; 72:742–757.
32. Price MJ, Thompson HS, Judisch GF, et al. Pupillary constriction to darkness. Br J Ophthalmol 1985;69:205–211.
33. Frank JW, Kushner BJ, France TD. Paradoxical pupillary phenomena. Arch Ophthalmol 1988;106:1564–1566.
34. Riley FC, Moyer NJ. Experimental Horner's syndrome: a pupillographic evaluation of guanethidine-induced adrenergic blockade in humans. Am J Ophthalmol 1970;69:442–447.
35. Pilley SFJ, Thompson HS. Pupillary ''dilation lag'' in Horner's syndrome. Br J Ophthalmol 1975;59:731–735.
36. Alward WL, Munden PM, Verdick RE, et al. Use of infrared videography to detect and record iris transillumination defects. Arch Ophthalmol 1990;108: 748–750.

37. Smith SA, Smith SE. Bilateral Horner's syndrome: detection and occurrence. J Neurol Neurosurg Psychiatry 1999;66:48–51.
38. Hirschberg J. Neuritis retrobulbaris. Zentralbl Prakt Augenheilkd 1884;8: 185–186.
39. Gunn RM. Functional or hysterical amblyopia. Ophthal Rev 1902;21:271–280.
40. Gunn RM. Discussion on retro-ocular neuritis. Lancet 1904;4:412.
41. Kestenbaum A. Clinical Methods of Neuro-Ophthalmological Examination. New York, Grune & Stratton, 1946:288–291.
42. Levatin P. Pupillary escape in disease of the retina or optic nerve. Arch Ophthalmol 1959;62:768–779.
43. Levatin P, Prasloski PF, Collen MF. The swinging flashlight test in multiphasic screening for eye disease. Can J Ophthalmol 1973;8:356–359.
44. Enyedi LB, Dev S, Cox TA. A comparison of the Marcus Gunn and alternating light tests for afferent papillary defects. Ophthalmology 1998;105:871–873.
45. Thompson HS. Pupillary signs in the diagnosis of optic nerve disease. Trans Ophthalmol Soc UK 1976;96:377–381.
46. Thompson HS. Putting a number on the relative afferent pupillary defect. In Thompson HS, Daroff R, Frisén L, et al., eds. Topics in Neuro-Ophthalmology. Baltimore, Williams & Wilkins, 1979:157–158.
47. Thompson HS, Corbett JJ, Cox TA. How to measure the relative afferent pupillary defect. Surv Ophthalmol 1981;26:39–42.
48. Borchert M, Sadun AA. Bright light stimuli as a mask of relative afferent pupillary defect. Am J Ophthalmol 1988;106:98–99.
49. Kawasaki A, Moore P, Kardon RH. Variability of the relative afferent pupillary defect. Am J Ophthalmol 1995;120:622–633.
50. Thompson HS, Jiang MQ. Letter to the Editor. Ophthalmology 1987;94: 1360–1362.
51. Thompson HS. 12th Pupil Colloquium. Am J Ophthalmol 1981;92:435–436.
52. Fineberg E, Thompson HS. Quantitation of the afferent pupillary defect. In Smith JL, ed. Neuro-Ophthalmology Focus 1980. New York, Masson, 1979:25–30.
53. Bell RA, Waggoner PM, Boyd WM, et al. Clinical grading of relative afferent pupillary defects. Arch Ophthalmol 1993;111:938–942.
54. Thompson HS, Montague P, Cox TA, et al. The relationship between visual acuity, pupillary defect, and visual field loss. Am J Ophthalmol 1982;93: 681–688.
55. Kardon RH, Hauper CL, Thompson HS. The relationship between static perimetry and the relative afferent pupillary defect. Am J Ophthalmol 1993;115: 351–356.
56. Kestenbaum A. Clinical Methods of Neuro-Ophthalmological Examination. Ed 2. New York, Grune & Stratton, 1961:420–456.
57. Jiang MQ, Thompson HS, Lam BL. Kestenbaum's number as an indicator of pupillomotor input asymmetry. Am J Ophthalmol 1989;107:528–530.
58. Lowenstein O, Loewenfeld IE. Electronic pupillography: A new instrument and some clinical applications. Arch Ophthalmol 1958;59:352–363.
59. Kawasaki A, Moore P, Kardon RH. Long-term fluctuation of relative afferent pupillary defect in subjects with normal visual function. Am J Ophthalmol 1996; 122:875–882.
60. Alexandridis E, Argyropoulos TR, Krastel H. The latent period of the pupil light reflex in lesions of the optic nerve. Ophthalmologica 1981;182:211–217.
61. Volpe NJ, Plotkin EES, Maguire MG, et al. Portable pupillography of the swinging flashlight test to detect afferent papillary defects. Ophthalmology 2000;107: 1913–1922.
62. Kardon RH, Kirkali PA, Thompson HS. Automated pupil perimetry. Pupil field mapping in patients and normal subjects. Ophthalmology 1991;98:485–495.
63. Kardon RH. Pupil perimetry. Curr Opin Ophthalmol 1992;3:565–570.
64. Stern HJ. A simple method for the early diagnosis of abnormality of the pupillary reaction. Br J Ophthalmol 1944;28:275–276.
65. Miller SD, Thompson HS. Edge-light pupil cycle time. Br J Ophthalmol 1978; 62:495–500.
66. Miller SD, Thompson HS. Pupil cycle time in optic neuritis. Am J Ophthalmol 1978;85:635–642.
67. Weinstein JM, Van Gilder JC, Thompson HS. Pupil cycle time in optic nerve compression. Am J Ophthalmol 1980;89:263–267.
68. Milton JG, Longtin A, Kirkham TH, et al. Irregular pupil cycling as a characteristic abnormality in patients with demyelinative optic neuropathy. Am J Ophthalmol 1988;105:402–407.
69. Safran AB, Walser A, Roth A, et al. Pupil cycle induction test: A way of evaluating the pupillary light reflex. Ophthalmologica 1981;183:205–213.
70. Lowenstein O, Loewenfeld IE. The pupil. In Davson H, ed. The Eye. Vol. 3. New York, Academy Press, 1969:255–337.
71. Duke-Elder WS. System of Ophthalmology. St Louis, CV Mosby, 1970: 476–479,
72. Michaels DD. Visual Optics and Refraction, St Louis, CV Mosby, 1985.
73. Cogan DG, Freese CG. Spasm of the near reflex. Arch Ophthalmol 1955;54: 752–759.
74. Goldstein JH, Schneekloth BB. Spasm of the near reflex: A spectrum of anomalies. Surv Ophthalmol 1996;40:269–278.
75. Kruger PB, Pola J. Stimuli for accommodation: Blur, chromatic aberration and size. Vision Res 1986;26:957–971.
76. Kotulak JC, Morse SE. The effect of perceived distance on accommodation under binocular steady-state conditions. Vision Res 1995;35:791–795.
77. Stakenburg M. Accommodation without pupillary constriction. Vision Res 1991; 31:267–273.
78. Duke-Elder WS. Text-Book of Ophthalmology. St Louis, CV Mosby, 1949: 4415–4450.
79. Glasser A, Kaufman PL. Accommodation and presbyopia. In Kaufman PL, Alm A, eds. Adler's Physiology of the Eye, Ed 10. St Louis, CV Mosby, 2003: 197–233,
80. Schor CM. A dynamic model of cross coupling between accommodation and convergence: Simulations of step and frequency responses. Optom Vis Sci 1992; 69:258–269.
81. Von Noorden G. Binocular Vision and Ocular Motility, Ed 4. St Louis, CV Mosby, 1990:85–100.
82. Bruce AS, Atchison DA, Bhoola H. Accommodation-convergence relationships and age. Invest Ophthalmol Vis Sci 1995;36:406–413.
83. Loewenfeld IE. The Pupil. Boston, Butterworth, 1999:317.
84. Alpern M. Testing distance effect on phoria measurement at various accommodation levels. Arch Ophthalmol 1955;54:906–915.
85. Hennessy RT, Iida T, Shiina K, et al. The effect of pupil size on accommodation. Vision Res 1975;16:587–589.
86. Miller RJ. Pitfalls in the conception, manipulation and measurement of visual accommodations. Hum Factors 1990;32:27–44.
87. Egashira SM, Kish LL, Twelker JD, et al. Comparison of cyclopentolate versus tropicamide cycloplegia in children. Optom Vis Sci 1993;70:1019–1026.
88. Mutti D, Zadnick K, Egashira S, et al. The effect of cycloplegia on measurement of the ocular components. Invest Ophthalmol Vis Sci 1994;35:515–527.
89. Prince AE. A combined age and refraction scale. Arch Ophthalmol 1897;16: 24–27.
90. Krimsky E. A modified Prince rule. Am J Ophthalmol 1960;49:827–829.
91. Berens C, Sells SB. Experimental studies on fatigue of accommodation. Am J Ophthalmol 1950;33:47–58.
92. Duane A. Studies in monocular and binocular accommodation with their clinical applications. Am J Ophthalmol 1922;5:865–877.
93. Atchison DA, Capper EJ, McCabe KL. Critical subjective measurement of amplitude of accommodation. Optom Vis Sci 1994;71:699–706.
94. Duane A. The accommodation and Donders curve and the need of revising our ideas regarding them. JAMA 1909;52:1992–1996.
95. Ferree CE, Rand G. Intensity of light in relation to the examination of the eye. Br J Ophthalmol 1936;20:331–346.
96. Schaeffel F. Wilhelm H, Zrenner E. Inter-individual variability in the dynamics of natural accommodation in humans: relation to age and refractive errors. J Physiol 1993;461:301–320.
97. Mathews S. Scleral expansion surgery does not restore accommodation in human presbyopia. Ophthalmology 1999;106:873–877.
98. Wold JE, Ju A, Chen S, Glasser A. Subjective and objective measurement of human accommodative amplitude. J Cataract Refract Surg 2003;29:1878–1888.
99. Mazow ML, France TD, Finkleman S, et al. Acute accommodative and convergence insufficiency. Trans Am Ophthalmol Soc 1989;87:158–173.
100. Von Noorden GK. Binocular Vision and Ocular Motility. St Louis, CV Mosby, 1990.
101. Morgan MW. A comparison of clinical methods of measuring accommodative convergence. Am J Optom 1950;102:385–396.
102. Heron G, Charman WN, Schor CM. Age changes in the interactions between the accommodation and vergence systems. Optom Vis Sci 2001;78:754–762.
103. Mutti DO, Jones LA, Moeschberger ML, et al. AC/A ratio, age, and refractive error in children. Invest Ophthalmol Vis Sci 2000;41:2469–2478.
104. Fincham EF. The proportion of ciliary muscular force required for accommodation. J Physiol 1955;128:99–113.
105. Wick B, Currie D. Convergence accommodation: Laboratory and clinical evaluation. Optom Vis Sci 1991;68:226–231.
106. Tsuetaki TK, Schor CM. Clinical method for measuring adaptation of tonic accommodation and vergence accommodation. Am J Optom Physiol Optom 1987;64:437–439.
107. Tutt R, Bradley A, Begley C, et al. Optical and visual impact of tear break-up in human eyes. Invest Ophthalmol Vis Sci 2000;41:4117–4123.
108. McCulley JP, Shine WE. The lipid layer: The outer surface of the ocular surface tear film. Biosci Rep 2001;21:407–418.
109. McCulley JP, Shine W. A compositional based model for the tear film lipid layer. Trans Am Ophthalmol Soc 1997;95:79–88.
110. Rolando M, Zierhut M. The ocular surface and tear film and their dysfunction in dry eye disease. Surv Ophthalmol 2001;45(Suppl 2):S203–S210.
110a. Dartt DA. Dysfunctional neural regulation of lacrimal gland secretion and its role in pathogenesis of dry eye syndromes. Ocular Surface 2004;2:76–91.
111. Mishima S, Gasset A, Klyce SD, et al. Determination of tear volume and tear flow. Invest Ophthalmol 1966;5:264–276.
112. Doughman DJ. Clinical tests. Int Ophthalmol Clin 1973;13:199–217.
113. Schaumberg DA, Sullivan DA, Buring JE, et al. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136:318–326.
114. Chia EM, Mitchell P, Rochtchina E, et al. Prevalence and associations of dry eye syndrome in an older population: The Blue Mountains Eye Study. Clin Exp Ophthalmol 2003;31:229–232.

115. Schein OD, Hochberg MC, Munoz B, et al. Dry eye and dry mouth in the elderly: A population based assessment. Arch Intern Med 1999;159:1359–1363.
115a. Dogru M. Tsubota K. New insights into the diagnosis and treatment of dry eye. Ocular Surface 2004;2:59–75.
116. Isreb MA, Greiner JV, Korb DR, et al. Correlation of lipid layer thickness measurements with fluorescein tear film break-up time and Schirmer's test. Eye 2003;17:79–83.
117. Nichols KK, Nichols JJ, Lynn Mitchell G. The relation between tear film tests in patients with dry eye disease. Ophthalmic Physiol Opt 2003;23:553–560.
118. Newman NJ, Capone A, Leeper HF, et al. Clinical and subclinical findings with retinal deficiency. Ophthalmology 1994;101:1077–1083.
119. Mircheff AK. Lacrimal fluid and electrolyte secretion: A review. Exp Eye Res 1989;8:607–617.
120. McCollum CJ, Foulks GN, Bodner B, et al. Rapid assay of lactoferrin in keratoconjunctivitis sicca. Cornea 1994;13:505–508.
121. Da Dalt S, Moncada A, Priori R, et al. The lactoferrin tear test in the diagnosis of Sjögren's syndrome. Eur J Ophthalmol 1996;6:284–286.
122. Lemp MA. Recent developments in dry eye management. Ophthalmology 1987; 94:1299–1304.
123. Mainstone JC, Bruce AS, Golding TR. Tear meniscus measurement in the diagnosis of dry eye. Curr Eye Res 1996;15:653–661.
124. Norn MS. Desiccation of the precorneal tear film. I. Corneal wetting time. Acta Ophthalmol 1969;47:856–880.
125. Bron AJ. Diagnosis of dry eye. Surv Ophthalmol 2001;45(Suppl 2):S221–S226.
126. Mengher LS, Pandher KS, Bron AJ. Non-invasive tear film break-up time: Sensitivity and specificity. Acta Ophthalmol 1986;64:441–444.
127. Lee SH, Tseng SCG. Rose Bengal staining and cytologic characteristics associated with lipid tear deficiency. Am J Ophthalmol 1997;124:736–750.
128. Schirmer O. Studien zur physiologie und pathologie der tränenabsonderung und tränenabfuhr. Albrecht von Graefes Arch Ophthalmol 1903;56:197–291.
129. Jones LT. Anatomy of the tear system. Int Opthalmol Clin 1973;13:3–22.
130. Korb DR. Survey of preferred tests for diagnosis of the tear film and dry eye. Cornea 2000;19:483–486.
131. Vitali C, Moutsopoulos HM, Bombardieri S. The European Community Study Group on diagnostic criteria for Sjogren's syndrome: Sensitivity and specificity for ocular and oral involvement in Sjogren's syndrome. Ann Rheum Dis 1994; 53:637–647.
132. Afonso AA, Monroy D, Stern ME, et al. Correlation of tear fluorescein clearance and Schirmer test scores with ocular irritation symptoms. Ophthalmology 1999; 106:803–810.
133. Bjerrum KB. Test and symptoms in keratoconjunctivitis sicca and their correlation. Acta Ophthalmol Scand 1996;74:436–441.
134. Zappia RJ, Milder B. Lacrimal drainage function. 2. The fluorescein dye disappearance test. Am J Ophthalmol 1972;74:160–162.
135. Zappia RJ, Milder B. Lacrimal drainage function. 1. The Jones fluorescein test. Am J Ophthalmol 1972;74:154–159.
136. Toprak AB, Erkin EF, Kayikcioglu O, et al. Fluorescein dye disappearance test in patients with different degrees of epiphora. Eur J Ophthalmol 2002;12: 359–365.
137. Hurwitz JJ, Victor WH. The role of sophisticated radiological testing in the assessment and management of epiphora. Ophthalmology 1985;92:407–413.
138. Rubin PA, Bilyk JR, Shore JW, et al. Magnetic resonance imaging of the lacrimal drainage system. Ophthalmology 1994;101:235–243.
139. Guzek JP, Ching AS, Hoang TA, et al. Clinical and radiologic lacrimal testing in patients with epiphora. Ophthalmology 1997;104:1875–1881.
140. Loewenfeld IE. Pupillary changes related to age. In Thompson HS, ed. Topics in Neuro-Ophthalmology. Baltimore: Williams & Wilkins, 1979:124–150.
141. Bitsios P, Prettyman R, Szabadi E. Changes in autonomic function with age: A study of pupillary kinetics in healthy young and old people. Age and Aging 1996;25:432–438.
142. Thompson HS. Pupillary signs in the ophthalmologic diagnosis of optic nerve disease. Trans Ophthalmol Soc UK 1976;96:377–381.
143. Cox TA, Thompson HS, Corbett JJ. Relative afferent pupillary defects in optic neuritis. Am J Ophthalmol 1981;92:685–690.
144. Bell RA, Thompson HS. Optic tract lesions and relative afferent pupillary defect. In Thompson HS, ed. Topics in Neuro-Ophthalmology. Baltimore, Williams & Wilkins, 1979:164–168.
145. Newman SA, Miller NR. The optic tract syndrome: Neuro-ophthalmologic considerations. Arch Ophthalmol 1983;101:1241–1250.
146. Schmid R, Wilhelm B, Wilhelm H. Naso-temporal asymmetry and contraction anisocoria in pupillomotor system. Graefes Arch Clin Exp Ophthalmol 2000; 238:123–128.
147. Forman S, Behrens MM, Odel JG, et al. Relative afferent pupillary defect with normal visual function. Arch Ophthalmol 1990;108:1074.
149. Portnoy JZA, Thompson HS, Lennarson L, et al. Pupillary defects in amblyopia. Am J Ophthalmol 1983;96:609–614.
150. Lam BL, Thompson HS. An anisocoria produces a small relative afferent papillary defect in the eye with the smaller pupil. J Neuroophthalmol 1999;19: 153–159.
151. Newsmen DA, Milton RC, Gass JDM. Afferent pupillary defect in macular degeneration. Am J Ophthalmol 1981;92:396–402.
152. Han DP, Thompson HS, Folk JC. Differentiation between recently resolved optic neuritis and central serous retinopathy. Arch Ophthalmol 1985;103:394–396.
153. Servais GE, Thompson HS, Hayreh SS. Relative afferent pupillary defect in central retinal vein occlusion. Ophthalmology 1986;93:301–303.
154. Kardon R. The pupil. In Kaufman P, Alm A, eds. Adler's Physiology of the Eye. Ed 10. St Louis, CV Mosby, 2003:713–743.
155. Folk JC, Thompson HS, Farmer SG, et al. Relative afferent pupillary defects in eyes with retinal detachment. Ophthalmic Surg 1987;18:757–759.
156. Bovino JA, Burton TC. Measurement of the relative afferent pupillary defect in retinal detachment. Am J Ophthalmol 1980;90:19–21.
157. Jiang MQ, Thompson HS. Pupillary defects in retinitis pigmentosa. Am J Ophthalmol 1985;99:607–608.
158. Sadun AA, Bassi CJ, Lessell S. Why cataracts do not produce afferent pupillary defects. Am J Ophthalmol 1990;110:712–714.
159. Lam BL, Thompson HS. A unilateral cataract produces a relative afferent pupillary defect in the contralateral eye. Ophthalmology 1990;97:334–338.
160. Lam BL, Thompson HS. Relative afferent pupillary defect induced by patching. Am J Ophthalmol 1989;107:305–306.
161. DuBois LG, Sadun AA. Occlusion-induced contralateral afferent pupillary defect. Am J Ophthalmol 1989;107:306–307.
162. Kohn AN, Moss AP, Podos SM. Relative afferent pupillary defects in glaucoma without characteristic field loss. Arch Ophthalmol 1979;77:294–296.
163. Jonas JB, Zach FM, Naumann GO. Quantitative pupillometry of relative afferent defects in glaucoma. Arch Ophthalmol 1990;108:479–480.
164. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. Arch Ophthalmol 1982;100:135–146.
165. Thompson HS. Adie's syndrome: some new observations. Trans Am Ophthalmol Soc 1977;75:587–626.
166. Drummond PD. The effect of light intensity and dose of dilute pilocarpine eye drops on pupillary constriction in healthy subjects. Am J Ophthalmol 1991;112: 195–199.
167. Jacobson DM, Olson KA. Influence of pupil size, anisocoria, and ambient light on pilocarpine miosis. Ophthalmology 1993;100:275–280.
168. Leavitt JA, Wayman LL, Hodge DO, et al. Pupillary response to four concentrations of pilocarpine in normal subjects: Application to testing for Adie tonic pupil. Am J Ophthalmol 2002;133:333–336.
169. Kardon RH, Denison CE, Brown CK, et al. Critical evaluation of the cocaine test in the diagnosis of Horner's syndrome. Arch Ophthalmol 1990;108:384–387.
170. Wilhelm H. Neuro-ophthalmology of papillary function: Practical guidelines. J Neurol 1998;245:573–583.
171. Cremer SA, Thompson HS, Digre KB, et al. Hydroxyamphetamine mydriasis in Horner's syndrome. Am J Ophthalmol 1990;110:71–76.
172. Morales J, Brown SM, Abdul-Rahim AS, et al. Ocular effects of apraclonidine in Horner syndrome. Arch Ophthalmol 2000;118:951–954.
173. Brown SM, Aouchiche R, Freedman KA. The utility of 0.5% apraclonidine in the diagnosis of Horner syndrome. Arch Ophthalmol 2003;121:1201–1203.
174. Brewitt H, Sistani F. Dry eye disease: the scale of the problem. Surv Ophthalmol 2001;45(Suppl 2):S199–S202.
175. Versura P, Cellini M, Torreggiani V, et al. Dryness symptoms, diagnostic protocol and therapeutic management: Report on 1,200 patients. Ophthalmic Res 2001;33:221–227.