PRACTICAL NEURO-OPHTHALMOLOGY

An Exercise in Problem-Based Learning

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SESSION 1: VISION LOSS

I. THE PRINCIPLES OF LOCALIZATION

In neurology and neuro-ophthalmology, once you know where the lesion is, you will often know what caused it. Perhaps the realtors (the people who sell homes) are correct when they say that the most important thing is “location, location, location!”

In this course, you will apply a three-step diagnostic approach: 1) decide which are the abnormal findings; 2) determine where the abnormal process is taking place and whether it is unifocal, multifocal, or diffuse; 3) offer a list of what is causing the abnormal process, placing the most likely—and most important—causes highest on the list.

Confronted with a patient who complains of a problem with vision, your first job is to decide whether the problem is OPTICAL (FIGURE 1) or NEURAL (FIGURES 2, 3). Optical defects include: 1) uncorrected refractive errors and 2) imperfections of the ocular media—the cornea, lens, and vitreous. Neural defects include lesions of the retina, optic nerve, optic chiasm, optic tracts, lateral geniculate body, optic radiations, primary visual cortex, and vision-related cortex.

If the problem is neural, you must determine it derives from the TOPOGRAPHICAL part of the pathway (retina to primary visual cortex (FIGURE 2)) or the PERCEPTUAL part of the pathway (primary visual cortex to vision-related parietal and temporal cortex (FIGURE 3)). If the problem lies in the perceptual visual pathway, you must determine if it derives from the occipital-parietal pathway, which deals with VISUAL SPATIAL concepts (the “where” of vision), or the occipital-temporal pathway, which deals with VISUAL RECOGNITION concepts (the “what” of vision).

Of course, a patient may report visual problems and have no organic disorder! In other words, the visual problems are the result of a PSYCHOLOGIC or BEHAVIORAL disorder. To make this part simpler, we will combine psychologic and behavioral disorders under the title PSYCHOGENIC.
II. THE PROCESS OF LOCALIZATION

A. OPTICAL DISORDERS. We depend on three tools to diagnose an optical disorder: 1) pinhole; 2) refraction, including retinoscopy; and 3) examination of the ocular media.

1. Pinhole. This device will correct most optical disorders by selecting a narrow central path for light rays so that they do not need to be focused by the eye’s refractive elements and will not be disturbed by imperfections in the ocular media. However, the pinhole may not fully correct optical disorders because patients may have difficulty seeing through the small holes and limited light. Children, the elderly, and demented patients have particular difficulty using the pinhole.

2. Refraction. This process may not fully correct refractive errors because: 1) the ocular media are unclear or irregular so that retinoscopy is difficult and not precise; or 2) the patient cannot provide consistent guidance in the subjective part of refraction.

3. Examination of the ocular media. This process usually provides important information to skilled examiners, but sometimes it is difficult to estimate how much visual loss is caused by ocular media imperfections.

B. NEURAL TOPOGRAPHICAL DISORDERS. Locating lesions within this part of the visual pathway depends mainly on examination of: 1) pupils, 2) retina and optic disc; and 3) visual fields. Examination of color vision is occasionally useful. Also, special tests that are not part of the regular clinical examination are sometimes useful, including: 1) electroretinography and dark adaptation; 2) optical coherence tomography (OCT); 3) fluorescein angiography; 4) ultrasound; 5) computed tomography (CT), and 6) magnetic resonance imaging (MRI).

1. Pupils. The pupil size is governed by a reflex that has two parts: 1) an AFFERENT part that is carried in the neural visual pathway toward the lateral geniculate nucleus; before it
reaches that nucleus, it leaves the optic tract to form a synapse in the midbrain pretectum, where it links with the parasympathetic part of the third cranial nerve; 2) an **EFFERENT** part that begins with the parasympathetic portion of the third cranial nerve nucleus and travels with that nerve to the ciliary ganglion, where it forms a synapse and then travels to the iris sphincter muscle. (FIGURE 4)

The examination of pupils includes three measurements: 1) size of pupils in dim illumination; 2) extent of constriction to direct light; and 3) swinging light test.

The measurement of the size of the pupils in dim illumination does not provide any information about the afferent (input) visual pathway; it tells only about the function of the efferent pathway from the third cranial nerve nucleus to the iris sphincter.

The measurement of the constriction of the pupils to direct light provides information about either the afferent or efferent pathway; you can only distinguish between an afferent and efferent malfunction by performing the third step—the swinging light test.

The swinging light test (FIGURE 5) involves shining the light on the right eye and observing the constriction to light and then moving (swinging) it across the nose to shine on the left eye and observing its constriction to light. Then you must swing the light back across the nose to shine on the right eye and observe its constriction to light. You must continue in this way, swinging the light back and forth between the eyes, looking for a consistent dilation of one pupil, which is called a **relative afferent pupil defect** (RAPD). You may not see a consistent dilation of one pupil, but instead a consistent difference in the degree of constriction to the two pupils, which would suggest a mild form of RAPD.

If you find a RAPD, you should conclude that the patient has: 1) an ipsilateral optic neuropathy; or 2) an asymmetric optic neuropathy, worse on the side of the RAPD; or much less commonly, 3) an ipsilateral extensive retinopathy or 4) a contralateral optic tract lesion.

A retinal lesion that is responsible for a RAPD must damage at least ¾ of the retinal area. A **unilateral foveal lesion that severely impairs visual acuity usually does not cause a RAPD.** (We do not understand why mild or moderate retinal lesions fail to produce a RAPD, but there are several interesting theories!) The usual explanation for a contralateral RAPD in optic tract lesions is that more than 50% of retinal ganglion fibers cross in the human optic chiasm.
2. Ophthalmoscopy. Ophthalmoscopic examination in patients with visual acuity loss is directed at finding structural abnormalities of the fovea and optic disc. However, foveal abnormalities that impair visual acuity are not always visible even to very skilled examiners. If other parts of the examination do not show evidence of an optic neuropathy or other retrobulbar visual pathway lesion, then it may be necessary to use ancillary tests (autofluorescence photography, angiography, electroretinography, optical coherence tomography) to study the fovea.

In viewing the optic disc, you should recall that it is a collection of axons coming from retinal ganglion cells, and that it also contains blood vessels and a glial support system. There are four main abnormalities of the optic disc: 1) pallor; 2) elevation; 3) excavation; and 4) hypoplasia.

Optic disc pallor indicates that axons within the optic nerve have died. (The explanation for why axon death causes the optic disc to become pale is not certain.) The delay from the time of axon death to the appearance of optic disc pallor depends on where the lesion lies within the optic nerve. If the lesion lies near the optic disc, pallor may appear within 2 weeks; if the lesion is closer to the optic chiasm, pallor may not appear before 6 weeks. Of course, visual impairment may occur from many types of lesions in the optic nerve without causing axon death (or optic disc pallor). The chance that visual recovery will occur is better if the optic disc is not pale.

Optic disc pallor may be diffuse or focal (segmental). An important cause of focal disc pallor is ischemic optic neuropathy, which may cause pallor limited to the upper, lower, or temporal segments. Toxic, nutritional, and metabolic optic neuropathies typically cause pallor limited to the temporal region of the optic disc in both eyes.

Optic disc elevation indicates that the axons are crowded. This phenomenon may be congenital or acquired. Congenital optic disc elevation occurs when the scleral canal, through which the optic nerve exits from the eye, is relatively small, as in hyperopia. Another congenital cause of optic disc elevation is drusen, calcified mitochondria that surround optic disc axons. The cause of drusen is not certain, but current belief is that the optic nerve axons are not healthy and some are dying. In some cases, optic nerve function may progressively fail and produce enlarging nerve fiber bundle visual field defects.
Acquired optic disc elevation may occur in many optic nerve disorders, but there are 4 main causes: 1) ischemia, 2) inflammation, 3) infiltration by neoplastic cells, and 4) increased intracranial pressure.

Ischemia of the optic nerve usually causes the sudden development of optic disc elevation, which may be diffuse or segmental. The elevation may be hyperemic (red) or pallid (white), and there may be optic disc hemorrhages.

Inflammation of the optic nerve is called optic neuritis. The optic neuritis associated with multiple sclerosis produces little if any optic disc elevation; the optic neuritis associated with infections or immune disorders other than multiple sclerosis may cause considerable elevation.

The optic disc elevation caused by cancerous infiltration may be mild or severe.

Optic disc elevation caused by increased intracranial pressure is called papilledema. Current belief is that the optic disc elevation in papilledema is produced mostly by axonal swelling which results from axoplasmic stasis, but we are not certain how the high intracranial pressure causes this. Perhaps the pressure compresses the optic nerve axons as they exit from the eye or, alternatively, perhaps the pressure causes ischemia of these axons and reduces axoplasmic flow by impairing axon metabolism.

Papilledema is usually present when intracranial pressure has been high for at least one week. You should grade papilledema on the basis of its severity and its chronicity. Severity is graded as mild, moderate, and severe. Chronicity is graded as acute, subacute, and chronic. Another important observation is whether the elevation is mixed with pallor. Pallor is a sign that some axons have died. We call the mixture of elevation and pallor atrophic papilledema. It means that visual loss from axon death has already occurred.

Optic disc excavation means that the optic disc cup has expanded beyond its normal limits. Another way to think of excavation is that neuroretinal rim tissue has been lost. Once excavation has occurred, careful measurement of the visual field will show that there are deficits. These visual field deficits will be minimal until the excavation is advanced. Excavation is usually judged by the cup-to-disc ratio, the ratio of the diameter of the optic disc cup to the diameter of the optic disc. The cup-to-disc ratio is extremely variable in the normal population. Therefore, it is better to look directly at the neuroretinal rim and judge whether it is generally thin or focally thin.
The most common cause of optic disc excavation is *primary open angle glaucoma*. Current belief is that glaucoma causes death not only of axons but also of their glial support system. Other optic neuropathies rarely cause much excavation, perhaps because they do not damage the glial support system. The most common exception is *ischemic optic neuropathy caused by giant cell arteritis*. Perhaps the reason this condition sometimes causes excavation is that the ischemia is so severe that it produces death of all optic nerve tissue—axons and glia. One way to distinguish between glaucoma and other optic neuropathies as a cause of excavation is to look at the remaining neuroretinal rim tissue: if it is pale, the cause is not glaucoma!

*Optic disc hypoplasia* means that the optic disc has an abnormally small diameter because its axons never developed. It is a sign that the lesion is congenital. But optic disc hypoplasia may occur with congenital tumors of the optic chiasm like craniopharyngiomas or optic nerve/chiasm pilocytic astrocytomas that can continue to grow and damage vision long after birth.

3. **Visual fields**. The power of visual field examination in locating the cause of impaired vision is based on the fact that the shape of the visual field defect often tells where the lesion lies in the neural visual pathway and sometimes tells what kind of lesion it is.

All visual field defects may be divided into three kinds of shapes: 1) nerve fiber bundle, 2) hemianopic, and 3) nonspecific.

*Nerve fiber bundle defects*. (FIGURES 6-11) These defects arise because the optic nerve or the retinal nerve fiber layer (FIGURE 6) has been damaged. There are four kinds of nerve fiber bundle defects: 1) central; 2) cecocentral; 3) arcuate/altitudinal; and 4) temporal wedge. (FIGURE 11)

Central and cecocentral defects (FIGURES 7, 8) result from damage to the axons that serve the fovea and the retina between the fovea and the optic disc. These axons make up the papillomacular bundle. Toxic, nutritional, and metabolic optic neuropathies are common causes of these defects.

Arcuate and altitudinal defects (FIGURE 9) result from damage to the axons that bend around the papillomacular bundle in the temporal retina and enter the optic discs in their upper and lower regions. Arcuate defects almost always have a prominent border aligned to the horizontal meridian in the nasal visual field. Altitudinal defects are simply
more extensive arcuate defects that occupy most of the inferior or superior half of the visual field. Such defects are common in ischemic optic neuropathy. Papilledema, inflammatory, compressive, infiltrative neoplastic, and congenital dysplastic optic neuropathies can also cause them.

**Temporal wedge defects** (FIGURE 10) result from damage to the axons arising in the nasal retina and entering the nasal half of the optic disc. These defects are uncommon, but may arise in congenital dysplastic and advanced acquired optic neuropathies.

*Hemianopic defects.* Hemianopic defects are visual field defects that have a prominent border aligned to the vertical meridian of the visual field. These defects may occupy the nasal or temporal hemifield. Hemianopic defects are caused by lesions at or near the optic chiasm or in the retrochiasmal visual pathway that travels from the optic chiasm through the optic tracts and optic radiations to the primary visual cortex.

There are three types of hemianopic defects that arise from damage to the region of the optic chiasm or to the optic nerve immediately in front of the optic chiasm: 1) bitemporal, 2) unilateral temporal; and 3) junctional. (FIGURE 12)

**Bitemporal hemianopic defects.** (FIGURE 12a) These hemianopic defects lie in the temporal fields of both eyes. They are the most common defects associated with disease affecting the optic chiasm. They result because the axons that arise from the nasal retinal ganglion cells, which cross in the optic chiasm, are especially vulnerable to any kind of pathologic process affecting the region of the optic chiasm. Very often the defects are small, so they may be difficult to recognize. Most diseases that affect the optic chiasm are tumors that can be successfully treated to prevent further visual loss or even restore lost vision, so you must be watching for these defects!

**Unilateral temporal hemianopic defects.** (FIGURE 12b) These hemianopic defects lie in the temporal field of only one eye. The other eye has a normal visual field. These defects indicate a lesion in the optic nerve near the optic chiasm. As the optic nerve axons approach the chiasm, those that originate in the nasal retina begin to separate from those that originate in the temporal retina. The axons arising in the nasal retina are especially vulnerable, for reasons that we do not understand. Such defects
are always accompanied by a relative afferent pupil defect (RAPD) in the eye with the visual field defect.

**Junctional hemianopic defects.** (FIGURE 12c) These defects consist of a mixture of temporal hemianopias and nerve fiber bundle defects. They indicate a lesion at the junction of the optic nerve and optic chiasm.

When the lesion damages the visual pathway behind the optic chiasm (the pathway from the optic tract to the primary visual cortex), it usually creates a homonymous hemianopia. In a homonymous hemianopia, the defects are present in both eyes and occupy the same hemifield in both eyes—either on the right side or the left side. In other words, there is a hemianopic defect in the nasal field of one eye and a hemianopic defect in the temporal field of the other eye.

When the homonymous hemianopia is complete, you know that the lesion lies in the retrochiasmal visual pathway, but you cannot tell in which part of that pathway it lies! (FIGURE 13)

On the other hand, incomplete hemianopic defects sometimes contain shape features that allow you to locate the lesion within a particular part of the retrochiasmal visual pathway. Here is a guide to some of those features:

1) Incomplete homonymous hemianopias that are very different in size in the two eyes, called incongruous homonymous hemianopias, are probably caused by lesions of the optic tract. (FIGURE 14 left)

2) Incomplete homonymous hemianopias that are the same in size in the two eyes, called congruous homonymous hemianopias, are usually caused by lesions in the posterior optic radiations or primary visual cortex. (FIGURE 14 right)

3) Wedge-shaped defects in the superior visual field (FIGURE 15) indicate a lesion in Meyer’s loop in the anterior temporal lobe.

4) Homonymous hemianopias with defect borders aligned to both the vertical and horizontal meridians, called homonymous quadrantanopias, indicate a lesion in or near the primary visual cortex. (FIGURE 16ab)
5) Homonymous paracentral scotomas, small but visually debilitating visual field defects restricted to the central 10 degrees, are caused by lesions that affect only the posterior 50% of primary visual cortex. (FIGURE 17a). These defects can be explained by the fact that the field of vision is mapped onto the primary visual cortex so that the central 10 degrees of the field are mapped onto the posterior 50% of the visual cortex. (FIGURE 18)

6) Macula-sparing macular-sparing homonymous hemianopias, which spare the central 10 degrees, are caused by lesions that damage only the anterior 50% of primary visual cortex (FIGURE 17b). The explanation for these defects is that the visual field outside the central 10 degrees is mapped anteriorly within the primary visual cortex. (FIGURE 18)

7) Temporal crescent scotoma, a defect that is present only in the visual field of the eye contralateral to the lesion (FIGURE 17c), is caused by a lesion that affects only the most anterior part of primary visual cortex. The explanation for this defect is that the visual field of the unpaired temporal crescent is mapped onto the most anterior 10% of the primary visual cortex. (FIGURE 18) (An interesting fact: this is the only visual field defect associated with a lesion of the retrochiasmal visual pathway that is not hemianopic and appears only in the visual field of one eye!)

Nonspecific defects. Visual field defects that contain neither nerve fiber bundle nor hemianopic features are called nonspecific. Perhaps they are so small or so big that nerve bundle or hemianopic features are not evident. Alternatively, they may be caused by optical defects (corneal scar, cataract, vitreous hemorrhage) or lesions of the outer retina.

Performing visual field examination. We test visual fields informally by displaying fingers in the visual field quadrants. This technique is called finger confrontation. It is quick to do, but it is useful only for detecting very large defects.

A slightly more sensitive way to detect visual field defects is to have the patient draw the defects on a piece of paper. This task is easier if it is done on a grid of lines (Amsler grid). But patients can only draw these defects if they are aware of them. Unfortunately, many patients are not aware of having these defects, especially if they have arisen slowly, are diffuse, or are located far away from fixation.

The most sensitive way to detect and define visual field defects is called perimetry. In perimetry, you place the patient’s head inside a white bowl and display bright white spots of light of varying intensity to one eye at a time. You tell the patient to press a button to make a noise
when a light is seen. The stimuli can be stationary (static) or moving (kinetic). The static method has become the preferred way to perform formal visual fields because it is more sensitive and more reproducible than the kinetic method.

Once the visual fields have been performed, you must interpret the results in this way:

1. *Is the result normal or abnormal?* This is sometimes a difficult determination. Perimetry depends on patient cooperation; some patients are better at doing this test than others. Minimal defects may be important if there is other clinical evidence to suggest a lesion.

2. *Is the patient’s performance reliable?* The test contains standard reliability measures (reliability indices) that can help you decide this question. But even if the reliability indices are normal, the patient may not be providing honest results.

3. *Is there a defect that provides information about the location of the lesion?* Look first for hemianopic features. If they are not present, look for nerve fiber bundle defect features. Then decide whether defects contain additional features that help refine the localization.

4. *What disease is causing the defect?* The shape of the defect may help you, but you will have to combine this information with other clinical observations.

C. NEURAL PERCEPTUAL DISORDERS

See Part III. The Disorders.

D. SPECIAL NEURAL DISORDER: AMBYOPIA

Amblyopia is reduced visual acuity caused by lack of exposure of the fovea to a focused image during the first years of life. This reduced exposure leads to atrophy of regions of the lateral geniculate body and visual cortex that receive inputs from the affected fovea. Amblyopia usually affects only one eye. It occurs in three circumstances: 1) anisometropia: one eye has a high uncorrected refractive error; 2) strabismus: the eyes are not aligned, and one eye
constantly fails to fixate the viewed target; and 3) optical imperfection: a cataract, corneal scar, or eyelid ptosis prevents a clear image from reaching the retina.

Because amblyopia has no direct diagnostic markers, the diagnosis depends finding evidence for one of the three circumstances that promote amblyopia and excluding other causes of reduced visual acuity by meeting ALL of these four criteria: 1) pinhole and refraction do not substantially improve visual acuity in the affected eye; 2) there is no RAPD; 3) there is no structural or electrophysiologic abnormality of the fovea; 4) there is no refixational eye movement in the affected eye when a 4 prism-diopter prism is placed before it.

**E. PSYCHOGENIC DISORDERS**

See Part III. The Disorders.

**III. THE DISORDERS**

If you have been able to locate the lesion, you will probably have a good idea of what might be causing it. But to make an even stronger diagnosis, you should have some knowledge of the disorders that affect these parts of the brain. Here is some basic information about the main disorders that affect the optic nerves, optic chiasm, retrochiasmal neural visual pathway, and the perceptual pathways that extend from the primary visual cortex to parietal and temporal lobes.

**OPTIC NERVE AND CHIASM DISORDERS**

**A. OPTIC NEURITIS.** In optic neuritis, the optic nerve and sometimes the optic chiasm are attacked inappropriately by the body’s immune system. The principal target is myelin, and so it is called a demyelinating disorder. There are two forms of optic neuritis—typical and atypical.

Typical optic neuritis is a demyelinating disorder of unknown origin that is often associated with multiple sclerosis. Atypical optic neuritis is an inflammation of the optic nerve in
which an underlying disorder other than multiple sclerosis can often be identified (infection, sarcoidosis).

In typical optic neuritis, most patients are women less than 40 years old. The visual loss develops over several days, usually in one eye. The visual deficit ranges from extremely mild to very severe. It is often accompanied by pain around the affected eye that is made worse by eye movement. Although visual acuity may be normal, nerve fiber bundle defects are present in the affected eye. A relative afferent pupil defect (RAPD) will be present unless the optic nerve in the fellow eye has been previously damaged. Ophthalmoscopy may be normal or show optic disc elevation.

Optic neuritis may be the first manifestation of multiple sclerosis, or the patient may already have symptoms or neurologic findings typical of this disease. Brain MRI will sometimes show signal abnormalities in the affected optic nerve and in the cerebral white matter.

Treatment trials have shown that corticosteroid (intravenous methylprednisolone at 1 gm per day for 3 days followed by prednisone 1 mg/kg for 14 days) accelerates visual recovery slightly but does not alter final visual outcome. If MRI shows white matter abnormalities, and there is clinical evidence of other neurologic deficits, patients may be advised to start preventive treatment for MS.

Even without treatment, most patients who have typical optic neuritis recover vision substantially if not completely over several weeks.

In atypical optic neuritis, the optic nerve may become inflamed as part of a systemic autoimmune or infectious disorder, or from an adjacent inflammation in the meninges, orbit, or sinuses. Imaging is helpful in making this diagnosis. Treatment is aimed at the underlying disorder.

B. ISCHEMIC OPTIC NEUROPATHY. In this condition, the optic disc becomes infarcted. There are two forms--arteritic and non-arteritic.

Arteritic ischemic optic neuropathy is part of temporal arteritis. It generally affects men and women aged over 70 years. Many victims have no systemic symptoms, but others report headache, stiffness and pain in the shoulder and pelvic joints, malaise, fatigue, and poor appetite for weeks to months (polymyalgia rheumatica). Other patients describe scalp
tenderness or pain with chewing (jaw claudication) which is caused by ischemia in the domain of the external carotid artery. Sedimentation rate and C-reactive protein are often elevated.

Vision loss is acute, monocular, severe, and painless. The optic disc is swollen. Some patients present with both eyes affected. If only one eye is affected, the other eye can become infarcted within days.

Diagnosis is based on ophthalmic and systemic clinical findings, supported by an elevated sedimentation rate and C-reactive protein, and a positive histology on temporal artery biopsy (giant cells, fragmented internal elastic membrane).

Treatment consists of high doses of corticosteroids usually administered intravenously. There is no hope of improving the vision in the affected eye, so treatment is directed at preventing vision loss in the unaffected eye. Corticosteroid treatment is often continued orally for a year after diagnosis, when the chance of recurrent optic neuropathy is very low.

**Non-arteritic ischemic optic neuropathy** is at least 100 times more common than arteritic ischemic optic neuropathy. It is probably caused to poor perfusion through ciliary arterioles that have been narrowed by arteriosclerosis. Most patients are aged between 40 and 75 years, and they have systemic hypertension, diabetes, abnormal blood lipids, or they are heavy smokers or have a strong family history of arteriosclerosis.

Vision loss is usually monocular and acute without warning but less severe than in the arteritic form. There are typically no new systemic manifestations. The affected optic disc is swollen; there is an RAPD in the affected eye. An arcuate/altitudinal nerve fiber bundle defect is usually present. Vision loss generally stops getting worse within 5 days and does not affect the fellow eye. However, the fellow eye is at a 10-20% risk for a similar event within the next 10 years.

Diagnosis is based on the ophthalmic findings in the proper setting. There is no effective treatment. Management is directed at excluding arteritis and other causes of optic neuropathy, and at reducing arteriosclerotic risk factors. Vision does not recover very much.

**C. COMPRESSIVE OPTIC NEUROPATHY AND CHIASMOPATHY.** The optic nerve can be compressed by a tumor—a neoplasm, aneurysm, cyst, abscess, or malformation. Compression of the optic nerve interferes with its ability to conduct visual information.
Visual loss is usually slowly progressive, but may be sudden in onset if the mass rapidly expands (aneurysm, hemorrhage, cyst). Any degree of visual loss may occur, together with any type of nerve fiber bundle defect. The optic disc may appear normal unless axon death has occurred, in which case the disc will be pale.

Diagnosis is based on imaging. Treatment is aimed at the underlying mass.

When the main site of compression is the optic chiasm, as is the case with pituitary tumors and craniopharyngiomas, the visual field defect will usually have hemianopic features.

Visual recovery following treatment of compressive masses depends on the degree of pre-existing damage. Usually the sooner the mass is discovered, the better the outcome. So you see the importance of early diagnosis!

D. INFILTRATIVE OPTIC NEUROPATHY. Any form of cancer that enters the subarachnoid space can penetrate the optic nerve and destroy its function. Common causes are leukemia and lymphoma, and lung and breast cancer, but any cancer can do this.

Visual loss develops over several days, in one eye or both, usually painlessly. Most patients have symptoms of cancer elsewhere in the nervous system or a known history of cancer. Visual loss is usually severe. The optic disc may be elevated or normal.

Diagnosis depends on imaging of the brain (which often shows meningeal or parenchymal abnormalities), imaging of the body (which often shows a primary tumor or other metastatic lesions), and lumbar puncture (which often discloses elevated protein and neoplastic cells).

Treatment consists of corticosteroids, which often restore vision--at least temporarily--and radiation and chemotherapy. Unfortunately, prognosis for survival is poor--typically less than one year after diagnosis.

E. TOXIC, NUTRITIONAL, AND METABOLIC OPTIC NEUROPATHIES. These three types of optic neuropathies all produce slowly progressive, symmetrical central or centrocecal scotomas in the two eyes.
Among the many toxins that have been implicated in causing optic neuropathy, the most common is ethambutol. A widely used and effective treatment for mycobacterial diseases, it becomes toxic to the optic nerves when prescribed at greater than 15 mg/kg/day for more than 6 months. Damage is often irreversible. Therefore, careful ophthalmologic monitoring is useful to detect the earliest signs of damage—reduced visual acuity and cecocentral scotomas.

A similar pattern of visual loss is seen in severe alcohol abuse. The cause is believed to be poor nutrition (especially deficiency of thiamine) and direct toxicity of alcohol. The target appears to the mitochondrion, and damage is usually irreversible. Sometimes vision can be at least partially restored if alcohol intake stops and if treatment with thiamine and other vitamins is carried out successfully. Recent evidence suggests that this optic neuropathy may occur in individuals who also have a mutation in mitochondrial DNA also found in Leber Hereditary Optic Neuropathy. Treatment with anti-oxidants is common but its efficacy is unverified.

Optic neuropathy of this pattern has also been documented with ingestion of methanol (usually as a substitute for ethanol) and in B12 vitamin deficiency.

The metabolic condition most often associated with optic neuropathy is a mitochondrial disorder called Leber Hereditary Optic Neuropathy (LHON). Transmitted by mothers via a mutation in mitochondrial DNA at one of three principal sites, LHON causes subacute visual loss first in one eye and, weeks to months later, in the fellow eye. Onset is usually between age 15 and 40 years, mostly in men. However, patients at any age can be affected. There are usually no other clinical deficits. A curious feature of LHON is that there may be no RAPD at a time when only one eye has suffered visual loss. The explanation for this phenomenon is debated.

The only clinical feature that distinguishes this optic neuropathy from optic neuritis is the appearance of dilated optic disc blood vessels and a thickened nerve fiber layer surrounding the optic disc. On fluorescein angiography, the optic disc does not leak, indicating that the swelling is not caused by vasogenic edema. Brain imaging is usually normal. Visual loss is usually profound and irreversible. Diagnosis is confirmed by a blood test that identifies the mutation. Sadly, there is no treatment.

**F. OPTIC NEUROPATHY OF INCREASED INTRACRANIAL PRESSURE (PAPILLEDEMA).** If intracranial pressure (ICP) rises high enough for long enough, the optic
discs will often become edematous (papilledema) because the high pressure in the subarachnoid space around the optic nerves interferes with axoplasmic flow. However, papilledema does not develop until many days after a sudden rise in ICP. On the other hand, if you do not see papilledema, you can safely conclude that chronically high intracranial pressure is not the cause of headache or other neurologic manifestations.

**RETROCHIASMAL DISORDERS**

The most common conditions that produce persistent retrochiasmal visual loss are infarction, neoplasm, hemorrhage, malformation, inflammation, and infection. Some type of homonymous hemianopia will be present on visual field examination. When the lesion is acute or enlarging, the patient may report various abnormal visual experiences, such as seeing distortions in the shape of viewed objects (cerebral metamorphopsia), seeing multiple copies of a viewed object (cerebral polyopia), or seeing objects that are no longer in view (palinopsia). If the lesion extends to the parietal or temporal regions, patients may have perceptual disorders as well as visual field defects.

Brain imaging nearly always shows the lesion, but there are some exceptions: 1) status epilepticus (the electroencephalogram should show this); 2) metabolic encephalopathy (especially diabetic nonketotic hyperglycemia); and 3) mild encephalitis. The region of the optic tract and lateral geniculate nucleus may be affected by trauma and demyelination without showing very prominent abnormalities on brain imaging, so you must look carefully in this region!

**TRANSIENT VISION LOSS**

Ophthalmologists and neurologists are often faced with patients who report temporary (transient) visual loss. The examination is often normal and so diagnosis will depend on the patient’s history!

One of the most difficult challenges in such patients is to determine if the transient visual loss affected one eye (monocular transient visual loss) or both eyes (binocular transient visual loss).
There are four pieces of information that help you to distinguish monocular from binocular transient visual loss in the patient’s description:

1) if the patient covered one eye during the event and had impaired vision with the other eye, and then covered the other eye and vision remained normal, then the transient visual loss was monocular;

2) if the patient had impaired vision with both of his eyes open, but is known to have normal baseline vision in both eyes, then the transient visual loss was binocular;

3) if the patient believes that the impaired vision involved the temporal hemifield of one eye, then the transient visual loss was probably binocular;

4) if the patient believes that the impaired vision included scintillations that progressed across the visual field, the transient visual loss was binocular.

Transient monocular transient visual loss is caused by reduced perfusion of the eye from: 1) local occlusive disease of the retinal or optic nerve arteries; 2) embolic disease from the cervical carotid arteries, aortic arch, or heart; 3) systemic hypertension or hypotension with fluctuating blood pressures; or 4) papilledema. Evaluation must include a careful history and examination to exclude systemic and ocular factors.

Transient binocular visual loss is caused by migraine, transient ischemic attacks, or seizures.

Migraine usually starts in youth (second to fourth decade) and is distinctive in having a typical visual aura--a jagged scintillation that expands across the visual hemifield in 20-30 minutes. Headache usually follows the aura, but not always! Migraine visual manifestations without headache are especially common in patients aged over 50 years. The diagnosis of migraine is firm if the aura changes sides in successive attacks.

Transient ischemic attacks of the retrochiasmal visual pathway cause loss of vision that lasts no longer than a few minutes. They may be accompanied by scintillations that y consist of stationary bright dots or streaks of light. The visual loss may affect one or both hemifields. Because the ischemia is based on reduced perfusion within the vertebrobasilar arterial system, the patient may also have symptoms of ischemia to the brain stem (diplopia, dizziness, dysphagia, weakness). Vascular imaging is often normal. You must direct your attention at the heart, arteriosclerotic risk factors, and systemic blood pressure.
Seizures are a rare but important cause of transient binocular visual loss. The visual loss is almost always accompanied by stationary scintillations that may consist of dots and streaks but also geometric forms and even scenes. These scintillations, which are of variable duration, may occupy one hemifield or both. Visual field examination usually discloses a homonymous hemianopia. In nearly all cases, brain imaging discloses the underlying lesion.

Patients who report seeing objects or figures that are not actually present (formed visual hallucinations) probably do not have seizures. The more likely cause is: 1) poor vision in both eyes (“Charles Bonnet syndrome”); 2) medication-induced or metabolic encephalopathy; 3) a sleep disorder; or 4) psychosis.

PERCEPTUAL DISORDERS

For more than 25 years, neuroscientists have known that visual information passes from primary visual cortex along two separate pathways: 1) occipital-parietal (telling the viewer where things are) and 2) occipital-temporal (telling the viewer what things are). Lesions can selectively damage either of these pathways.

Occipital-parietal disorders damage the ability of the brain to apply attention appropriately to visual information and to locate it in space. The deficit is considered to be a combination of impaired distribution of visual attention and impaired spatial relations.

When the lesion is confined to one cerebral hemisphere, the disorder is called hemispatial neglect, in which the patient is not attentive to visual stimuli in the contralateral hemifield. In most cases, the lack of attentiveness applies to auditory and tactile stimuli as well as visual stimuli. In fact, the patient may make no motor gestures into the neglected hemifield and will not acknowledge that the parts of his body located in that hemispace belong to him.

It is often difficult to distinguish between hemispatial neglect, an attentional disorder, and homonymous hemianopia, a topographical disorder. My favorite ways to make this distinction are:

1) Patients with hemispatial neglect usually have impaired attention for all three sensory modalities--vision, hearing, and touch sensation on the skin. They will extinguish those stimuli on the neglected side if the stimuli are presented simultaneously on both sides. This phenomenon does not occur in homonymous hemianopia.
2) Patients with hemispatial neglect will shift their sense of space away from the neglected side. The best way to test for this feature is ask the patient to cancel line segments distributed in both hemifields or to copy a drawing that has identical elements in both hemifields. A patient with hemispatial neglect will not cancel line segments in the defective hemifield, but most patients with homonymous hemianopia will learn to explore the defective hemifield and complete this test perfectly—or nearly perfectly!

When the lesion affects the parietal regions of both cerebral hemispheres, the disorder is called the Balint-Holmes syndrome. In this disorder, patients are unable to distribute attention appropriately between fixation and the peripheral visual field on both sides! They also do not appreciate the spatial relationships of objects in their entire visual environment. As a result of these deficits, they often do not see more than one object at a time because they cannot disengage their attention from an object viewed at fixation to look at objects in their visual field periphery. They reach inaccurately for objects and they behave as if they had very constricted visual fields. They are much more visually impaired than patients who have constricted visual fields from optic neuropathy or retinopathy!

**Occipital-temporal disorders** impair recognition, that is, the ability to identify familiar objects or symbols. The term agnosia is applied to such disorders, but the terminology is not consistent.

A common agnosia is pure alexia (alexia without agraphia), in which patients cannot read, but they can spell and write perfectly! The lesion lies in the left cerebral hemisphere. It usually damages the left distal optic radiations and the left part of the splenium of the corpus callosum, so that it causes a right homonymous hemianopia and disconnects the intact right hemisphere primary visual cortex from the left hemisphere language centers. Patients will report difficulty with vision, but they may not be aware that they also cannot read!

Another disorder is topographical agnosia, in which patients lose their ability to navigate in familiar surroundings. The lesion is always in the right temporal lobe.

A less common disorder is prosopagnosia, in which patients do not recognize familiar faces. The lesion is usually in both occipital-temporal lobes. If the bilateral lesion is very extensive, patients may also have visual object agnosia, an inability to recognize familiar
objects. The best way to test for this deficit is to display familiar objects to the patient. If the patient cannot name them, allow the patient to feel the objects with his hands. If he recognizes them by their shape, the diagnosis is visual object agnosia. If he does not recognize them, he has a global cognitive disturbance.

**PSYCHOGENIC DISORDER**

In this disorder, the patient is pretending to have a visual impairment. Such a disorder is very common and must be identified promptly in order to avoid inappropriate, expensive, and sometimes dangerous diagnostic tests.

Patients can pretend that they have any degree of visual acuity loss and nearly any type of visual field defect. Your strategy should be based on the following principles: 1) test until the patient finally displays normal visual function; 2) uncover inconsistencies in the history and examination that make an organic cause very unlikely.

For a decision-tree approach to abnormal visual acuity, look at Figure 19.
Figure 1. The optical part of the visual pathway (From Trobe JD. The Neurology of Vision.)
Figure 2. The neural topographical part of the visual pathway. (From Trobe JD. The Neurology of Vision.)
Figure 3. The perceptual part of the visual pathway. (From Trobe JD. The Neurology of Vision.)
Figure 4. The pupil reflex pathway. (From Trobe JD. The Neurology of Vision)
Figure 5. The swinging light test. In a normal subject (left column), the pupils are equal in size in dim illumination (top row). A bright light shined into the right eye causes both pupils to constrict (second row). When the light is moved over to shine directly on the left eye, the pupils do not change in size (third row). When the light is moved back to shine directly on the right eye, the pupils do not change in size (fourth row). In a patient with a left relative afferent pupil defect (right column), the pupils are equal in size in dim illumination (top row). A bright light shined into the right eye causes both pupils to constrict (second row). When the light is moved over to shine directly on the left eye, the pupils dilate (third row). When the light is moved back to shine directly on the right eye, the pupils constrict (fourth row). (From Trobe JD. The Physician's Guide to Eye Care.)
Figure 6. Schematic representation of the retinal nerve fiber layer of the right eye. It has been divided up into three compartments. 1 = papillomacular compartment; 2 = arcuate compartment; 3 = nasal radial compartment. Injury to the retinal ganglion cells or their axons from each of these compartments causes nerve fiber bundle visual field defects of characteristic shapes. (From Trobe JD. The Neurology of Vision)
Figure 7. Central scotoma. The retinal nerve fiber layer (left) is shown as having lost axons from the region of the fovea. Therefore, a central scotoma (right) is created that covers the fixation area. (From Trobe JD. The Neurology of Vision)

Figure 8. Cecocentral scotoma. The retinal nerve fiber layer (left) is shown as having lost axons from the region of the fovea and the region between the fovea and the optic disc. Therefore, a cecocentral scotoma (right) is created that extends from fixation to the physiologic blind spot. (From Trobe JD. The Neurology of Vision)
Figure 9. Arcuate scotoma. The retinal nerve fiber layer (left) is shown as having lost axons from the superior arcuate compartment. Therefore, an arcuate scotoma (right) is created that extends inferiorly from the nasal horizontal meridian to the physiologic blind spot. (An altitudinal defect is simply a larger arcuate defect!) (From Trobe JD. The Neurology of Vision)
Figure 10. The retinal nerve fiber layer (left) is shown as having lost axons from the region of the nasal radial compartment. Therefore, a temporal wedge scotoma (right) is created that extends from extends outward temporally from the physiologic blind spot. (From Trobe JD. The Neurology of Vision)
Figure 1.  The four kinds of nerve fiber bundle defects that occur when the left optic nerve is damaged. (Humphrey visual field gray scale display.) a = central scotoma. b = cecocentral scotoma. c = arcuate scotoma; d = temporal wedge scotoma. (From Trobe JD. The Neurology of Vision)
Figure 12. Visual field defects from damage to the optic chiasm and to the optic nerve near the optic chiasm.  

- **a** = bitemporal hemianopia.  
- **b** = unilateral temporal hemianopia.  
- **c** = junctional hemianopia.  

(From Trobe JD. The Neurology of Vision)
Figure 13. Complete right homonymous hemianopia. When the visual field defects are COMPLETE, you cannot determine where within the retrochiasmal visual pathway the lesion lies. (From Trobe JD. The Neurology of Vision)
Figure 14. Incongruous left homonymous hemianopia from an optic tract lesion (left) and congruous left homonymous hemianopia from an optic radiation lesion (right). (From Trobe JD. The Neurology of Vision)
Figure 15. Superior wedge right homonymous hemianopia from a lesion in Meyer’s loop in the anterior temporal lobe. (From Trobe JD. The Neurology of Vision)
Figure 16. Visual field defects caused by lesions of the primary visual cortex. a = Superior quadrantanopia. b = inferior quadrantanopia. (From Trobe JD. The Neurology of Vision)
Figure 17. More visual field defects caused by lesions of the primary visual cortex. A = homonymous paracentral scotomas. B = macular-sparing homonymous hemianopia. C = temporal crescent defect discovered by Goldmann kinetic perimetry. Note that this defect will not be found by conventional static perimetry unless test points are located in the visual field periphery. (From Trobe JD. The Neurology of Vision)
Figure 18. The mapping of the visual field onto the primary visual cortex. Top. The primary visual cortex is located on the upper and lower sides of the occipital fissure. Middle. The letters A-F designate the areas of primary visual cortex that correspond to the areas of visual field (Bottom). Notice that the most anterior part of primary visual cortex (A, B) decodes visual information from the temporal crescent of the visual field (A, B in bottom drawing); the middle part of primary visual cortex (C, D) decodes visual information from the intermediate part of the visual field (C, D in bottom drawing); the posterior part of primary visual cortex (E, F) decodes visual information from the paracentral ("macular") part of the visual field (E, F in bottom drawing). (From Trobe JD. The Neurology of Vision)
Figure 19. Decision-tree for abnormal visual acuity.
SESSION 2: DIPLOPIA

I. WHAT CAUSES DIPLOPIA?

Diplopia, or double vision, is the sensation of seeing two copies of a viewed object. It occurs when there is a defect in the optics of the eye (monocular diplopia) or when the two eyes are not in normal alignment (binocular diplopia).

A. MONOCULAR DIPLOPIA. Monocular diplopia usually occurs when the eye’s refracting system is defective and it produces more than one focused image on the retina. Patients report seeing one clear image and at least one unclear, overlapping (“ghost”) image. The common causes are an uncorrected refractive error, a corneal surface irregularity or opacity, an iris hole, or a cataract.

If an optical defect is present only in one eye, then occluding that eye will eliminate diplopia, but occluding the unaffected eye will not. If there are optical defects in both eyes, and monocular diplopia is present in both of them, then occluding either eye will not eliminate diplopia.

The ghost images should disappear when the patient views the object through a pinhole because the pinhole selects a narrow optical path that bypasses refractive errors and ocular surface irregularities. If the diplopia disappears when the pinhole is placed in front of the affected eye, you have diagnosed an optical problem. Now you must perform a refraction and a biomicroscopic examination to determine which optical problem is the cause of this monocular diplopia.

The pinhole is not a useful screening test in children and mentally impaired or older adults because they have difficulty using it.

If the patient reports monocular diplopia, but the pinhole does not eliminate it, the symptom is probably psychogenic.

An uncommon cause of monocular diplopia is an abnormality in cerebral visual processing called cerebral polyopia, in which patients with a stroke or tumor in the occipital
region report seeing two or more duplicate images. Pinhole does not eliminate the illusion. Neither does covering one eye at a time because the illusion is binocular. Unlike the illusion created by an optical problem, it is identical in the two eyes! Patients usually also have homonymous hemianopia and visual perseveration (palinopsia), distortion of viewed objects (cerebral metamorphopsia), or visual hallucinations.

A common misconception is that foveal disorders (such as epiretinal membranes) cause monocular diplopia. They do not! Foveal disorders may cause binocular diplopia because the images formed by the two eyes are different in size or shape. As a result, the brain cannot blend them into one image, and the fusional forces responsible for maintaining ocular alignment fail.

**B. BINOCULAR DIPLOPIA.** When the eyes are in normal alignment, the fovea of each eye fixates the viewed target. No diplopia occurs. (FIGURE 1) But when one eye is deviated out of normal alignment, the fixating eye views the object with the fovea and the deviating eye views it with the parafoveal retina. As a result, the image viewed with the deviating eye will appear displaced. (FIGURE 2) Even if the deviating eye has normal visual acuity, it will not provide a distinct image of the viewed object because the parafoveal retina has poor image resolution. Covering either eye will eliminate diplopia.

When one eye is deviated inward, the misalignment is called esodeviation. When one eye is deviated outward, it is called exodeviation. When one eye is deviated vertically, it is called hyperdeviation, no matter whether the deviation is upward or downward. (FIGURE 3)

You must describe these deviations from normal alignment according to whether or not they are present under normal viewing conditions. The word tropia is used if the misalignment is present when both eyes are open and looking at the target under normal binocular viewing conditions. If the eyes are inwardly misaligned under such conditions, the term is esotropia. If the eyes are outwardly misaligned, the term is exotropia. If the eyes are vertically misaligned, it is hypertropia.

If the misalignment is present only under abnormal viewing conditions that weaken the brain’s natural force of fusion designed to keep the eyes aligned, the term is phoria. For example, if you alter the viewing conditions of one eye as the subject views a target, and that eye drifts inward, the patient has an esophoria. If interrupting binocular viewing causes one eye
to drift outward, that is an \textit{exophoria}. If one eye drifts upward or downward, that is a \textit{hyperphoria}.

Because tropias occur under normal binocular viewing conditions, they are called manifest ocular misalignments. Phorias, which occur only when the brain’s fusional forces are weakened, are considered latent ocular misalignments. Phorias are very common and are not considered pathologic unless they are becoming much more frequent or are incomitant (this term will be defined later in the text). Phorias can easily evolve into tropias if the brain’s level of consciousness is altered by sleepiness, sedative medication, or encephalopathic disease states. Tropias are always considered pathologic.

A patient with ocular misalignment may not report diplopia! There are seven possible reasons for this:

1) \textit{Very poor vision in one or both eyes}.

2) \textit{Suppression of the image from the non-fixating eye}. Such suppression is common if ocular misalignment occurs within the first decade of life. (This suppression process is often accompanied by amblyopia, see section C below.)

3) \textit{A visual field defect in the deviating eye}. The image is not seen by the deviating eye because it falls within the field defect.

4) \textit{Small ocular misalignment}. The deviating image is displaced so minimally from the fixating eye that the patient cannot distinguish a second image. In such cases, the patient may report that vision is indistinct but not necessarily diplopic. For example, patients who have skew deviation typically report blurred vision rather than double vision because the misalignment is small.

5) \textit{Large ocular misalignment}. The image from the deviating eye is displaced so far away from fixation that the patient does not notice it.

6) \textit{Impaired cognition}. The patient cannot appreciate diplopia.

7) \textit{Impaired language or other communication}. The patient is unable to report the sensation of diplopia.
C. AMBLYOPIA describes reduced visual acuity that develops in an eye that has not received a focused image on its fovea. Amblyopia occurs only during infancy and early childhood when the visual pathway is still in a developing phase and depends for its maturation on receiving coherent visual stimuli.

The development of amblyopia is based on the early competition between the two eyes in the laying down of neural circuitry. So, if one eye is foveating clearly and the other is not, the cells of the lateral geniculate body and the ocular dominance columns of the primary visual cortex that receive inputs from the eye with unfocused imagery will lose out to those of the eye with focused imagery. Because of this concept of competition between the two eyes, amblyopia is usually limited to one eye—the disadvantaged eye. Amblyopia develops in three settings:

1) *Ocular misalignment that develops before the age of about 5 years.* In order to avoid the unpleasant symptom of diplopia created by having the eyes out of alignment, the youthful brain blocks the awareness of the displaced image that comes from the deviating eye. This suppression process, which is incompletely understood from a neurophysiologic point of view, becomes less effective as the brain matures.

2) *A large uncorrected refractive error in one eye (anisometropia).* In this circumstance, the fovea of the eye with a large uncorrected refractive error will not receive a focused image. If anisometropia persists beyond a certain amount of time, amblyopia will develop just as it does in early childhood ocular misalignment.

3) *Eyelid ptosis or ocular media opacities.* Eyelid ptosis that covers the visual axis prevents a focused image from reaching the fovea. Media opacities such as corneal scars or cataracts have the same effect.

Amblyopia can often be corrected if the foveal imagery of the amblyopic eye is improved and if the non-amblyopic eye is placed at a temporary viewing disadvantage by blurring or blocking its foveal image. Thus, besides correcting misalignment, refractive error, ptosis, or media opacities, an important step in amblyopia therapy is to put the non-amblyopic eye at a viewing disadvantage by patching it or instilling parasympatholytic eyedrops that interfere with focusing on near targets.
There is some controversy about the upper age limit for effective reversal of amblyopia. Recent studies suggest that at least some visual acuity can be restored even if amblyopia therapy is begun as late as age 13 years.

II. EVALUATING BINOCULAR DIPLOPIA

Your ability to make a diagnosis in patients with binocular diplopia depends on four components: 1) taking a **history**; 2) assessing the **range of eye movements**, 3) measuring the **pattern of misalignment**; and 4) detecting accompanying **neuro-ophthalmic abnormalities**.

A. HISTORY. You should ask the following questions of the patient:

1) **Are the two images separated horizontally, vertically, or torsionally with respect to one another?** This information helps to suggest whether the problem affects principally the horizontally-acting, vertically-acting, or torsionally-acting extraocular muscles. In many cases, the images will be separated in both the horizontal and vertical planes, a phenomenon termed oblique diplopia. Torsional displacement of images suggests superior oblique muscle weakness.

2) **Does the separation of the two images change as gaze shifts to different directions?** In asking this question, you are trying to anticipate whether the misalignment is comitant, that is, the same degree in the various positions of gaze, or incomitant, that is, of different degree in the various positions of gaze. You should also ask if the separation of images changes between distance viewing and reading.

3) **Has the separation of the two images changed over time?** This information helps determine the clinical course of the deficits.

B. RANGE OF EYE MOVEMENTS. Ask the patient to follow your moving light with his eyes so you can measure the conjugate pursuit movements of the two eyes (called **ocular versions**). When the eyes are moved in the horizontal plane, the white canthal region of the eyes should normally disappear behind the lids. When the eyes are moved in downgaze, nearly
all of the cornea should disappear under the lower lid. When the eyes are moved in upgaze, 1/3 of the cornea should disappear under the upper lid.

If ocular versions show reduced amplitude, test the range of the ocular pursuit movement of each eye tested individually by covering the other eye (called **ocular ductions**). If versions are incomplete, you must measure ductions because if the eyes are misaligned, the non-fixating eye will often not execute a full rotational movement unless the fixating eye is covered.

The information you get from testing the range of pursuit eye movements may give you a clue to the misalignment pattern. But the range of pursuit eye movements may be completely normal and yet the eyes are still out of alignment. Therefore, the next step is to measure alignment.

**C. OCULAR ALIGNMENT.** There are two approaches to measuring ocular alignment:

1) **Subjective approach.** With this approach, you must have the cooperation of the patient to tell you the position of the image seen by each eye. Therefore the patient must be aware of diplopia. But the patient does not make fixational eye movements.

2) **Objective approach.** With this approach, you do not need the cooperation of the patient to tell you the position of the image seen by each eye. But the patient must make fixational eye movements.

**Subjective approach: the Single Maddox Rod Test.** (FIGURES 4, 5) The Single Maddox Rod Test is the most practical method of testing ocular misalignment subjectively. It consists of a round stack of transparent red cylinders.

You must place the Maddox rod in front of the right eye and tell the patient to look at a bright light displayed at a distance of about 6 meters (20 feet). The left eye sees a white spot of light and the right eye sees a red line whose orientation is perpendicular to the plane of the cylinders.

To assess horizontal alignment, place the Maddox rod with its cylinders stacked horizontally. (FIGURE 4) The patient should see a vertical red line and a spot of white light. If
the light spot appears displaced horizontally from the red line, use prisms to quantify the degree of misalignment. Place the prisms over the right eye until the red line appears to intersect the white spot. The size of the prism necessary to produce this intersection becomes the degree of misalignment (measured in prism-diopters) in that gaze position.

If the patient sees the red line to the left of the light, the patient has an exodeviation. If the patient sees the red line to the right of the light, the patient has an esodeviation. You must now perform this procedure in all relevant positions of gaze.

To test vertical misalignment, repeat these steps with the Maddox rod cylinders stacked vertically. (FIGURE 5) If the patient sees the red line below the light, then the patient has a right hyperdeviation. If the patient sees the red line above the light, then the patient has a left hyperdeviation.

Subjective approach: the Double Maddox Rod Test. You should measure torsional misalignment with two Maddox rods placed into a trial frame. (FIGURE 6) Position the rods so that the cylinders are stacked vertically. The patient should see two lines. If they appear parallel to one another, there is no torsional misalignment. If they do not appear parallel, tell the patient to turn a knob on the trial frame that adjusts the axis of the Maddox rod positioned in front of the right eye. Once the patient reports that the two lines have become parallel, you should read the new axis (in degrees away from the vertical plane) and record that interval as the amount of torsional misalignment. If the dial has been turned counterclockwise, the patient has an excyclodeviation (extorsion); if it has been turned clockwise, the patient has an incyclodeviation (intorsion). Fourth cranial nerve palsy produces an excyclodeviation.

The Maddox Rod Tests will fail in adults with impaired cognition or language because they will not be able to communicate what they are seeing. But in cooperative adults, it has great value because:

1) You can measure small amounts of ocular misalignment. Such small amounts are difficult to measure with objective methods.

2) You need not depend on fixational movements of the eyes. Such fixational movements cannot be made by some patients with severe paretic or restrictive ocular motility disorders. Therefore, the objective tests that use the cover test (see below) will not work.
3) You can measure horizontal and vertical misalignments separately. You cannot do this easily with the objective approaches of measuring ocular misalignment (see below).

**Objective approach:** Cover-uncover test. Tell the patient to look at a target placed at a distance of 6 meters. Place an occluder in front of the right eye and observe whether the left eye makes a fixational movement. If there is no movement, place the occluder over the left eye and observe the right eye for a fixational movement. If covering either eye produces a fixational movement, the patient has a manifest misalignment, called a tropia.

You can measure the size of the tropia by placing prisms of increasing strength over the deviating eye until no further fixational movement occurs. Repeat these steps with the eyes placed into all positions of gaze and in straight ahead gaze with the patient’s head tilted toward the right shoulder and then toward the left shoulder. Finally, measure the alignment with the eyes viewing a target at reading distance.

If the cover test produces an inward fixational movement, the patient has an exotropia. If it produces an outward fixational movement, the patient has an esotropia. If it produces a downward eye movement in one eye and an upward movement in the other eye, the patient has a hypertropia, defined by the eye that moves downward.

**Objective approach:** The Alternate Cover Test. If the cover-uncover test does not reveal a tropia, use this test to detect a latent ocular misalignment, called a phoria.

Place the occluder over the right eye and quickly swing it across to cover the left eye and back to cover the right eye. Continue to swing the occluder back and forth to cover one eye at a time. If you observe fixational movements in the uncovered eye, yet you observed no fixational movements during the Cover-Uncover Test, the patient has a phoria. Use prisms to quantify the misalignment in all relevant positions of gaze. In order for the Cover Tests to work, the patient must have the ability and the understanding to make a fixational eye movement. It will fail if you do not instruct the patient to move the eyes to make the image clear. Also, you cannot use the Cover Tests in patients who have who have severe restrictive or paretic ocular motor conditions, or in patients who have poor vision, cognition, or cooperation because they cannot make reliable fixational eye movements. The Cover Test is not effective in detecting very small ocular misalignments because tiny fixational eye movements will be hard for you to see.
**Objective approach: The Corneal Reflex Test.** When patients cannot cooperate with the Maddox Rod or Cover Tests, you can obtain a crude estimate of ocular alignment with the Corneal Reflex Test. From a distance of 1 meter, shine your light into the patient’s eyes and observe the position of the corneal light reflection in both eyes. When the eyes are aligned, the reflection should appear slightly nasal to the center of the two pupils. If the reflection is displaced temporally, the patient has an esotropia. If the reflection is displaced nasally, the patient has an exotropia. A downwardly displaced reflection indicates a hypertropia. (FIGURE 3)

The Corneal Reflex Test is not very sensitive to small ocular misalignments, as it takes 7 degrees of ocular misalignment to see a 1 mm shift of the corneal reflection.

**Interpreting the Examination Results.** If the amount of ocular misalignment is equal in all gaze positions, then the diplopia is **comitant**. If the amount of misalignment varies from one gaze position to another, the diplopia is **incomitant**.

Is the distinction between comitant misalignment and incomitant misalignment important? Yes, very important! Comitant misalignment is usually caused by disturbances of vergence, whereas incomitant misalignment is usually caused by disturbances of extraocular muscles, neuromuscular transmission, ocular motor cranial nerves, or brain stem pathways.

**III. COMITANT DISORDERS**

Comitant disorders of ocular misalignment are usually caused by a vergence disturbance. Most of these disorders occur early in life, but some may occur in adults.

**A. INFANTILE ESOTROPIA OR EXOTROPIA.** Comitant ocular misalignment that is detected at birth or within the first year of life is probably caused by an imbalance between convergence and divergence.

**B. ACCOMMODATIVE ESOTROPIA.** Esotropia that is detected between the first and third years of life is often caused by excessive accommodation in patients with hyperopia.
C. SENSORY ESOTROPIA OR EXOTROPIA. Esotropia or exotropia may arise within the first decade of life if there is poor sight in one eye or both. In these conditions, the patient does not usually report diplopia because vision is poor in at least one eye.

D. ESOTROPIA OR EXOTROPIA CAUSED BY AN INTRACRANIAL DISORDER. If comitant esotropia or exotropia is present in a patient with diplopia, you must consider the possibility that the brain’s ability to maintain fusion has been weakened by meningitis, encephalitis, increased intracranial pressure, or a brain tumor.

E. CONVERGENCE INSUFFICIENCY. In this common condition that affects mostly young adults, patients report diplopia or blurred vision only at reading distance. It is usually related to poor convergence effort by the patient. It is almost never neurologically important.

F. SPASM OF THE NEAR REFLEX. In this condition, the patient reports intermittent diplopia and you will find esotropia together with excessive accommodation and constriction of the pupils. This condition is caused by anxiety or malingering.

IV. INCOMITANT DISORDERS

Incomitant disorders of ocular alignment are usually caused by disturbances of the extraocular muscles, neuromuscular junction, ocular motor cranial nerves, or brain stem pathways.

A. EXTRAOCULAR MUSCLE DISORDERS. In these conditions, the extraocular muscle is weak or tight. If the muscle is weak, the agonist muscle does not contract properly. If the muscle is tight (from scarring) or trapped (within orbital scarred tissue), it does not permit the antagonist muscle to move the eye properly. In the early phase of inflammation or trauma, extraocular muscles swell and do not contract properly. In the chronic phase, the extraocular muscles become shortened and tight.

Important examples of extraocular inflammation are Graves disease, idiopathic orbital inflammation, and orbital cellulitis. Other important conditions that affect the extraocular muscles
are muscular dystrophies, mitochondrial myopathies, blunt trauma, and arteriovenous fistulas of the cavernous sinus.

B. NEUROMUSCULAR JUNCTION DISORDERS. The most common neuromuscular junction disorder that affects the eyes is myasthenia gravis. Botulism, which prominently affects the autonomic nervous system, is also a consideration. Eaton-Lambert myasthenic syndrome rarely affects eye movements.

In myasthenia gravis, any pattern of diplopia and misalignment may occur. Because the medial rectus is often most affected, this condition may produce unilateral or bilateral adduction deficits and resemble internuclear ophthalmoplegia. Because the muscles become weakened with effort, diplopia is often variable in degree and typically lessens or disappears after sleeping or resting the eyes. Ptosis and orbicularis oculi weakness are usually present. The iris sphincter muscle, which is supplied by the autonomic nervous system, is always spared. Associated neurologic findings include bulbar, limb, and trunk weakness.

In botulism, diplopia occurs in about 50% of patients, but never without autonomic abnormalities, including dry eyes, mydriasis, impaired pupil constriction to light, and impaired accommodation. The diplopia is typically horizontal and the ductional deficits are mild. Dry mouth, constipation, dysphagia, and nausea are usually more prominent symptoms than diplopia.

In Lambert-Eaton myasthenic syndrome, diplopia and ductional deficits are rare and mild. They occur late in the course of the illness and are minor compared to limb weakness.

C. OCULAR MOTOR CRANIAL NERVE PALSIES. A palsy of the third, fourth, and sixth cranial nerves may occur alone or in combination.

In third cranial nerve palsy, the patient will report vertical or horizontal or oblique diplopia with or without ptosis or mydriasis. In a complete third nerve palsy, the eye will appear turned out and slightly down due to weakness in adduction, supraduction, and infraduction, and there will be ipsilateral ptosis and an unreactive, dilated pupil (mydriasis). Incomplete third cranial nerve palsy will cause variable deficits in adduction, supraduction, or infraduction with variable
ptosis and mydriasis. Alignment testing will show a hypertropia and or exotropia, depending on gaze position.

In *fourth cranial nerve palsy*, the patient will report vertical diplopia and one of the images may appear tilted. The diplopia is worse on gaze contralateral to the lesion and with the head tilted toward to the side of the lesion. To eliminate diplopia, the patient will often tilt his head in the direction opposite to the side of the lesion. In unilateral lesions, the eye ipsilateral to the damaged nerve may appear deviated upwards, as injury to this nerve results in impaired infraduction. There may be no visible ocular ductional deficit. If a ductional deficit is present, it will be evident when the ipsilateral eye looks downward and inward.

Alignment testing will show an ipsilateral hypertropia that becomes greater on gaze contralateral to the lesion and with the head tilted toward the ipsilateral shoulder. Double Maddox Rod testing will show an excyclodeviation of less than 10 degrees. In bilateral fourth cranial nerve palsies, the patient may have only a minimal hypertropia in primary gaze position because the two palsies nearly cancel out the vertical misalignment. But there will be a right hypertropia on left gaze and a left hypertropia on right gaze. In such cases, the excyclodeviation usually exceeds 10 degrees.

In *sixth cranial nerve palsy*, the patient will report horizontal diplopia that is often present only with distance viewing. The images will appear farther apart in gaze ipsilateral to the lesion. To eliminate diplopia, the patient will often adopt a face turn toward the side of the lesion. The eye ipsilateral to the lesion appears deviated inward due to weakness in abduction. There is usually an ipsilateral abduction deficit but it may be minimal. Alignment testing will usually show an esotropia in straight ahead gaze that becomes greater in ipsilateral gaze and less in contralateral gaze.

An important principle in the evaluation of suspected ocular motor cranial nerve palsies is whether the palsy is the only pertinent deficit (*isolated palsy*) or whether it is one of several pertinent deficits (*non-isolated palsy*). In adults, non-traumatic isolated third and sixth cranial nerve palsies are most often caused by reversible ischemia to the extra-axial portion of the nerve. However, isolated third cranial palsies may also be caused by intradural aneurysm, a condition that must be detected before catastrophic rupture. Isolated sixth cranial nerve palsies may be caused by cranial base tumors. Isolated fourth cranial nerve palsies usually results from ischemia of the nerve or from a congenital weakness of the superior oblique muscle that eventually becomes apparent in adulthood. Isolated ocular motor palsies may also be caused
by meningeal processes such as inflammation, cancer, head trauma, and vascular malformations.

*In children, ischemia is rarely a cause of ocular motor cranial nerve palsy, so you must consider inflammation or cancer as more likely causes.*

When more than one ocular motor cranial nerve palsy is present at the same time, or in combination with other neurologic deficits or a history of cancer (non-isolated palsy), you must always think of lesions of the superior orbital fissure, cavernous sinus, cranial base meninges, or brain stem. With cavernous sinus lesions, there is often involvement of the first two sensory divisions of the trigeminal nerve. Lesions in the cavernous sinus often spare the inferior division of the third cranial nerve, producing only ptosis and a supraduction deficit. With lesions of the brain stem, there will often be extremity weakness, ataxia, or paresthesias.

*Acute and chronic cranial polyneuritis (Guillain-Barré syndrome, Fisher syndrome)* often causes symmetrical or nearly symmetrical deficits of ocular movement. As a result, the ocular misalignment may be minimal. Ptosis and mydriasis are sometimes present, and you may find ataxia, weakness, and deep tendon areflexia.

**D. BRAIN STEM DISORDERS.** Lesions that interrupt brain stem pathways to the ocular motor cranial nerve nuclei are important causes of diplopia. There are two important conditions: *skew deviation* and *internuclear ophthalmoplegia*.

*Skew deviation.* This condition arises from interruption of the connections between the vestibular pathways and the ocular motor brain stem nuclei. Lesions can lie in the brainstem or, less commonly, the vestibular nerve or labyrinths. Patients complain of vertical diplopia but not of a tilted image. Ductional testing will reveal full ductions or impaired infraduction of the higher eye. The vertical misalignment is usually incomitant, but it may be comitant. Associated features include saccadic pursuit, nystagmus, and ataxia.

*Internuclear ophthalmoplegia.* This condition results from lesions in the medial longitudinal fasciculus, the pathway that connects the sixth cranial nerve nucleus to the contralateral third cranial nerve nucleus so that horizontal gaze can occur. The patient will report blurred vision or horizontal diplopia on lateral gaze away from the side of the lesion.
Ductional testing will reveal impaired or slow adduction of the ipsilateral eye and usually a jerk nystagmus of the abducting contralateral eye.

As you analyze a patient with diplopia, you may find it useful to follow a decision-tree (FIGURE 7).
Figure 1. Normal ocular alignment. The corneal reflections appear in the center of both pupils (top). The foveas of both eyes are fixating the visual target (bottom). There is no diplopia.
Figure 2. Abnormal ocular alignment. The right eye is deviated inward (esotropia). The viewed target forms an image on an eccentric (nasal) part of the retina of the right eye and so the target is seen as displaced toward the right side. (Modified from Trobe JD. The Physician’s Guide to Eye Care)
Figure 4. The Single Maddox Rod Test in esodeviation. A. The Maddox Rod is placed over the right eye so that its cylinders are stacked horizontally while the subject views a bright light (not seen here). B. The subject sees a bright white spot with his uncovered left eye and a vertical red line displaced to his right, indicating an esodeviation. C. The prism bar is placed over the right eye and moved up or down until the strength of the prism is enough to move the vertical red line so that it intersects the bright white spot (D). The examiner notes the strength of the prism
required for “neutralization” of the esodeviation in that gaze position. (From Warden K and Trobe J. Diplopia. Neurology Medlink.)

Figure 5. The Single Maddox Rod Test in right hyperdeviation.  A. The Maddox Rod is placed over the right eye so that its cylinders are stacked vertically while the subject views a bright light (not seen here).  B. The subject sees a bright white spot with his uncovered left eye and a vertical red line displaced below the light, indicating a right hyperdeviation.  C. The prism bar is placed over the right eye and moved up or down until the strength of the prism is enough to
move the horizontal red line so that it intersects the bright white spot (D). The examiner notes the strength of the prism required for “neutralization” of the hyperdeviation in that gaze position. (From Warden K and Trobe J. Diplopia. Neurology Medlink.)

Figure 6. The Double Maddox Rod Test in cyclodeviation. Maddox Rods are placed in a trial frame so that their axes are vertical and aligned to the zero degree mark. B. The subject, who has a cyclodeviation, should report that he sees one horizontal line and one tilted line. C. The examiner tells the subject to adjust the dial on the right lens until the two lines are parallel. The examiner then reads the new position of the right dial in degrees away from zero as the amount of cyclodeviation.(From Warden K and Trobe J. Diplopia. Neurology Medlink.)
Figure 7. Decision-tree for Diplopia
SESSION 3: ABNORMAL EYE MOVEMENTS

I. TYPES OF ABNORMAL EYE MOVEMENTS

In Session 2, you learned about conditions that cause binocular diplopia because the eyes are out of alignment. In this session, you will learn about conditions in which the eyes do not move properly, but they remain in normal alignment. The four types of abnormal eye movements are:

1) Gaze deficits: absent or markedly reduced eye movements

2) Gaze deviations: conjugate deviations of the eyes

3) Nystagmus

4) Saccadic intrusions

In order to understand why certain brain lesions cause abnormal eye movements, you must first be familiar with the pathways in the brain that govern eye movements.

II. OCULAR MOTOR PATHWAYS

There are four main systems that govern eye movements:

1) Saccadic system (FIGURES 1-4)

2) Pursuit system (FIGURE 5)

3) Vergence system

4) Vestibulo-ocular system (FIGURE 6)

Here are the main points about the pathways that govern these eye movement systems:
1) The saccadic, pursuit, and vestibulo-ocular systems control conjugate eye movements, in which the eyes move in the same direction. These movements are called versions.

2) The vergence system controls disconjugate eye movements, in which the eyes move in opposite directions in the horizontal plane. These movements are called vergence.

3) The saccadic, pursuit, and vergence systems control eye movements that are under voluntary control. These are called volitional eye movements. They are mostly generated in the cerebrum. (FIGURES 1, 3, 5)

4) The vestibulo-ocular system controls eye movements that are not under voluntary control. These movements are called non-volitional, or reflex, eye movements. They are generated in the labyrinth, saccule, and utricle of the inner ear. (FIGURE 6) (There are saccadic eye movements not under voluntary control; they include the corrective fast eye movements of jerk nystagmus and the rapid eye movements of sleep. They are probably generated within the brainstem.)

5) Horizontal volitional eye movements (FIGURES 1-4) are generated in the frontal and parietal lobes and the signal reaches the paramedian reticular formation and eventually the sixth cranial nerve nucleus in the pons.

6) Vertical volitional eye movements are generated in the frontal and parietal lobes and the signal reaches the third and fourth cranial nerve nuclei in the midbrain. Upgaze eye movements have a signal that passes through the posterior commissure in the dorsal midbrain (FIGURE 4); downgaze eye movements have a signal that passes through the tegmental midbrain. (FIGURE 4)

7) The cerebral signal for horizontal saccades moves the eyes to the opposite side; the cerebral signal for horizontal pursuit moves the eyes to the same side. The pontine paramedian reticular formation and sixth cranial nerve nuclei move the eyes to the same side; the vestibulo-ocular pathway (labyrinth, saccule, vestibular nerve, nucleus, tegmental pontomedullary pathway) moves the eyes to the opposite side.

With this information, you can understand the following clinical phenomena:
1) A unilateral cerebral lesion impairs volitional gaze to the opposite side and causes gaze deviation to the same side. It spares non-volitional gaze.

2) A unilateral pontine lesion impairs volitional and non-volitional gaze to the same side and often causes gaze deviation to the opposite side.

3) A midbrain/thalamic lesion impairs vertical gaze. A dorsal midbrain lesion impairs upgaze and may also cause downgaze gaze deviation; a ventral midbrain lesion impairs downgaze and may cause upgaze deviation.

4) A unilateral labyrinthine, vestibular nerve, or vestibular nuclear lesion causes a gaze drift to the same side which is seen as nystagmus with its fast phase toward the side opposite to that of the lesion.

I. GAZE DEFICITS

Gaze deficits are caused by disease that affects any part of the ocular motor system that extends from the cerebrum to the extraocular muscles. To help you in localizing the process, try to determine if there are signs suggesting an extraocular muscle disorder (orbital disease, myasthenia gravis), multiple cranial nerve palsies (ptosis, pupil dysfunction), brainstem disease (ataxia, nystagmus, weakness), or cerebral hemisphere disease (sparing of reflex gaze, hemiparesis, hemisensory loss, cognitive or language dysfunction).

A. HORIZONTAL GAZE DEFICITS. When the eyes do not move normally in the horizontal plane, but they move normally in the vertical plane, the lesion is either in the pons or the cerebrum.

If the deficit was present in early childhood and the patient makes head thrusts when he shifts his gaze, then the diagnosis is probably congenital ocular motor apraxia. The cause of this condition is poorly understood and the location of the lesion has not been identified. It often improves by the second decade of life.

If the deficit affects only horizontal gaze to one side, then the lesion lies either in the contralateral cerebrum or in the ipsilateral pons. If non-volitional gaze is spared, the lesion (stroke, tumor, inflammation) lies in the contralateral cerebrum; if non-volitional gaze is affected, the lesion lies in the ipsilateral pons.
If the horizontal gaze deficit affects both directions of gaze, and does not spare non-volitional gaze, you must consider a diencephalic or extensive brain stem lesion (tumor, infarction, hemorrhage), Wernicke encephalopathy, other metabolic or dystrophic encephalopathies, botulism, Guillain-Barré syndrome, myasthenia gravis, or inflammation, trauma, or dystrophy of the medial and lateral rectus muscles.

If the horizontal gaze deficit affects all directions, but spares non-volitional gaze, the diagnosis is probably progressive supranuclear palsy if the process has been slowly progressive, or bilateral cerebral infarction if the process has been acute.

B. VERTICAL GAZE DEFICITS. Upgaze deficits usually come from lesions of the thalamus, pineal gland, or midbrain. Upgaze deficits can also be caused by acute obstructive hydrocephalus, inflammation or trauma of the extraocular muscles, or progressive supranuclear palsy.

C. HORIZONTAL AND VERTICAL GAZE DEFICITS. If horizontal and vertical gaze are both impaired, and the onset was acute, you must consider bilateral cerebral, thalamic, or brain stem infarctions or hemorrhages, Wernicke encephalopathy, cranial polyneuritis, neoplastic meningitis, bilateral cavernous sinus lesions, myasthenia gravis, botulism, and bilateral inflammation or trauma of the extraocular muscles.

If the onset of the gaze deficits was very slow, you should think more of progressive supranuclear palsy, spinocerebellar ataxia, and mitochondrial disorders, as well as myasthenia gravis and chronic orbital myositis.

III. GAZE DEVIATIONS

Gaze deviations are sustained conjugate rightward, leftward, upward, or downward shifts of both eyes. They usually result from an acute imbalance within the central nervous system that causes the eyes to be driven in one direction within the orbit. There is almost always a gaze deficit in the direction opposite to the gaze deviation.
Nearly all gaze deviations are caused by central nervous system disorders. But they can rarely be seen in patients who have tight extraocular muscles from chronic inflammation or trauma. Use the principles of localization that you applied for gaze deficits.

A. HORIZONTAL GAZE DEVIATIONS. There are four cerebral causes: 1) ipsilateral cerebral hemispheric lesion; 2) contralateral pontine lesion; 3) thalamic lesion; 4) focal cerebral seizure.

Cerebral hemispheric and some thalamic lesions will spare the non-volitional (reflex, vestibulo-ocular) eye movements. Pontine lesions will impair all ipsilateral eye movements. Gaze deviation in focal seizure is usually accompanied by head deviation to the same side and sometimes convulsive movements of the ipsilateral face, arm, and leg.

B. UPGAZE DEVIATIONS. There are five causes: 1) acute brain stem ischemia, especially in systemic hypotension; 2) seizure; 3) oculogyric crisis; 4) transient phenomenon in newborns; 5) psychogenic phenomenon.

C. DOWNGAZE DEVIATIONS. There are three causes: 1) acute hydrocephalus; 2) thalamic infarction or hemorrhage; 3) extraocular myopathy.

IV. NYSTAGMUS

A. DEFINITIONS. Nystagmus is a rhythmic oscillation of the eyes that begins with a slow drift of the eyes. The second, or correcting, phase of the oscillation may be a slow eye movement or a fast eye (saccadic) movement. If the oscillation includes two slow phases, it is called pendular nystagmus. If the second half of the oscillation is a fast movement, it is called jerk nystagmus.

A common imitator of nystagmus is a saccadic intrusion, in which ocular fixation is interrupted by a fast conjugate movement of the eyes that takes them away from the viewed target. Saccadic intrusions and nystagmus are caused by different sets of disorders (see below).
You should describe nystagmus according to the path of the eyes: is it horizontal, vertical, or rotary (torsional)? You should describe the amplitude of the oscillations as high or low.

Although jerk nystagmus begins with a slow phase, it is named by the direction of its fast phase. For example, a nystagmus whose fast phase is to the right is called a right-beating nystagmus. If the trajectory is torsional, you should describe the nystagmus as if the fast phase were clockwise or counterclockwise on a clock face superimposed on the patient's eyes.

B. PHYSIOLOGIC NYSTAGMUS. Nystagmus may exist as a normal variant called physiologic nystagmus. It is sometimes hard to distinguish this physiologic nystagmus from pathologic nystagmus. Here are the four distinctive features of physiologic nystagmus:

1) Present only in the far extremes of horizontal gaze
2) Persists for no more than four beats
3) Trajectory is horizontal or horizontal-torsional
4) Amplitude is low and identical in both directions of gaze

C. PATHOLOGIC NYSTAGMUS: WHY DOES IT OCCUR?

Pathologic nystagmus has four main underlying causes:

1) Poor vision. To cause nystagmus, the poor vision must begin within the first decade of life. It must be caused by a lesion in the eyes, optic nerves, or optic chiasm. Lesions behind the optic chiasm do not cause nystagmus! The poor vision should affect both eyes, but sometimes poor vision in one eye will cause nystagmus in that eye.

2) Vestibular imbalance. A lesion that damages one labyrinth or vestibular nerve will create a slow drift of the eyes toward the side of the lesion, followed by a corrective fast phase away from the side of the lesion.

3) Impaired brain stem neural integrator function. The neural integrator is a medullary brain stem center that is responsible for maintaining the eyes in
eccentric gaze. When it does not work properly, there is a jerk nystagmus in extremes of gaze. Poor function of the neural integrator may be the cause of infantile nystagmus and probably of acquired nystagmus caused by brain stem disorders, systemic metabolic disorders, and medications.

4) *Extraocular muscle weakness.* When an extraocular muscle does not function properly, it may be unable to keep the eye in full eccentric gaze, so that the eye will drift back toward the center. The cause may be a lesion of one of the ocular motor cranial nerves, the neuromuscular junction, or the extraocular muscles.

D. PATHOLOGIC NYSTAGMUS: WHAT ARE THE SYMPTOMS?

There are two symptoms associated with nystagmus: blurred vision and oscillopsia. Patients who developed nystagmus *within the first five years of life* will report that their vision is blurred. Patients who developed nystagmus *after the first five years of life* will also report blurred vision. But if the amplitude of the pendular phase of the nystagmus is large, they may also report that viewed objects seem to be moving, a symptom called oscillopsia. Those who have *pendular* nystagmus will report that the target moves back and forth. Those who have *jerk* nystagmus will report that the target moves repetitively in the direction of the fast phase.

E. PATHOLOGIC NYSTAGMUS: WHAT ARE THE MAIN TYPES?

1. *Infantile nystagmus.* This nystagmus is noticed within the first six months of life. In straight ahead gaze, the nystagmus may be jerk or pendular, but in extremes of gaze, it is always jerk. The nystagmus remains horizontal in all fields of gaze. Some patients have an underlying lesion of the eyes, optic nerves, or optic chiasm that causes poor vision (sensory infantile nystagmus). Other patients have no identifiable lesion (motor infantile nystagmus). Some patients have a face turn because their nystagmus has its lowest amplitude (null zone) in eccentric gaze and their visual acuity is optimal when they position their eyes in that null zone.

2. *Spasmus nutans.* This is a high-frequency, low-amplitude pendular nystagmus that appears within the first year of life and is often accompanied by head nodding and torticollis. The nystagmus may seem to affect only one eye, but closer inspection reveals it to be binocular. Diagnostic studies, including brain imaging and lumbar puncture, are negative.
There is no treatment and the condition always resolves without trace within three years of onset. The cause of this condition remains unknown.

3. **Peripheral vestibular nystagmus.** This is a horizontal-torsional jerk nystagmus that may be present in right, center, and left gaze. Its fast phase will be toward the side opposite to an acute lesion of the labyrinth or vestibular nerve. The nystagmus amplitude will be enhanced by covering the eyes. The best way to enhance peripheral vestibular nystagmus is to close one eye of the patient and observe the fundus of the other eye through a direct ophthalmoscope. A standard way to evoke this kind of nystagmus is to reposition the patient’s head vigorously. Many patients will also have vertigo and imbalance, and sometimes tinnitus and hearing loss. Saccades and pursuit are preserved but sometimes difficult to evaluate because of the nystagmus and the patient’s distress. The nystagmus diminishes rapidly within a few days of onset.

4. **Acquired pendular nystagmus.** This pendular nystagmus affects both eyes but may be of higher amplitude in one eye. The nystagmus may be in the horizontal, vertical, or torsional plane. Sometimes the motion of the eyes follows a complex pattern. The lesion is always in the brain stem. Many diseases can cause this form of nystagmus, most commonly multiple sclerosis. There are three distinctive forms of acquired pendular nystagmus:

   1) **seesaw nystagmus:** the nystagmus is vertical and torsional, and one eye moves upward while the other eye moves downward. The lesion, often a tumor, is in the diencephalon or midbrain.

   2) **oculopalatal tremor:** the nystagmus is mostly vertical, and the eyes move synchronously with the palate and perhaps other facial muscles and the diaphragm. The lesion may be in the upper or lower brain stem. This form of nystagmus is distinctive because it develops many months after the original brain stem damage has occurred.

   3) **oculomasticatory myorhythmia:** the eyes display oscillatory convergence and divergence in synchrony with contraction of the muscles of mastication. The lesion is in the high brain stem and is usually caused by Whipple disease.

5. **Sidebeat, upbeat, and downbeat nystagmus.** In these forms of nystagmus, there is a jerk nystagmus in the direction of gaze, either in the horizontal or vertical plane. In sidebeat nystagmus, the eyes have the fast phase on sidegaze in the direction of gaze. In upbeat nystagmus, the eyes have the fast phase on upgaze. In downbeat nystagmus, the eyes have
the fast phase in downgaze. In these forms of nystagmus, the lesion is in the brain stem, and the cause may be inflammatory, ischemic, hemorrhagic, neoplastic, or metabolic-toxic. In downbeat nystagmus, the damage is sometimes disclosed by brain imaging as being in the cerebellum or medulla.

6. **Nystagmus of internuclear ophthalmoplegia.** A lesion of the medial longitudinal fasciculus (very common in multiple sclerosis but also in ischemic stroke) produces an ocular motor abnormality called internuclear ophthalmoplegia, in which there is impaired adduction of the ipsilateral eye and a jerk nystagmus of the abducting contralateral eye. Current belief is that the abducting eye overshoots, and that the nystagmus is an attempt at correcting this overshooting.

7. **Extraocular muscle weakness.** Nystagmus can sometimes occur when the extraocular muscles are not working well enough to keep the eyes in eccentric gaze. Such nystagmus may occur with lesions of the cranial nerves, neuromuscular junction, or extraocular muscles. Sometimes the nystagmus is in the eye with the weak muscle. At other times, the nystagmus is in the contralateral agonist muscle, which overshoots and drifts back repeatedly. This nystagmus is often incorrectly believed to be coming from a central nervous lesion!

V. **SACCADIC INTRUSIONS**

A. **DEFINITION.** Some oscillatory conditions of the eyes look like nystagmus—and are often mistaken for nystagmus—but are not nystagmus because they begin with a fast eye movement (saccade). This fast eye movement interrupts fixation, so it is called an intrusion. Because the brain suppresses vision during a saccade, the patient with saccadic intrusions does not usually report any visual symptoms. However, if the intrusions are very frequent, they will interfere with stable fixation and cause blurred vision.

B. **TYPES OF SACCADIC INTRUSIONS**

1. **Superior oblique myokymia.** In this condition, the patient reports episodes of intermittent twitching of the affected eye and indistinct or double vision. The episodes are apparently unprovoked and there are no other pertinent symptoms. During an episode, the affected eye makes low-amplitude, brief intorsional movements. There are no other
abnormalities. Diagnostic studies, including brain imaging, are usually normal. Current belief is that this manifestation is caused by an instability of the fourth cranial nerve axon or the superior oblique muscle membrane. Axon and muscle membrane stabilizing medications are sometimes effective.

2. **Square wave jerks.** These are horizontal saccades that move the eyes conjugately away from fixation and then, after a brief interval, back to fixation. The movements are continuous but not perfectly rhythmic. If the amplitude of the saccades is 5 degrees or less and the frequency is less than 10 per minute, these eye movements may be physiologic. Otherwise they represent a nonspecific disorder of the brain stem. The patient has no visual symptoms from these abnormal eye movements. They are particularly common in progressive supranuclear palsy and after severe blunt head trauma. Current belief is that they are caused by disinhibition of the pontine saccade generator.

3. **Ocular flutter and opsoclonus.** In this ocular motor oscillation, the eyes are making frequent conjugate saccades in the horizontal plane (ocular flutter) or in the horizontal and vertical planes (opsoclonus). Because the eyes are always moving, patients complain that they cannot see clearly, but they do not describe oscillopsia. Some patients also have a tremor, myoclonus, or ataxia of the limbs and trunk and a delirium. In children, the common causes are a paraneoplastic syndrome related to metastatic neuroblastoma or viral encephalitis. In adults, the common causes are a paraneoplastic syndrome related to lung or gynecologic cancer or viral encephalitis. Toxicity from medication may also occasionally cause this disorder.

4. **Volitional flutter.** In this condition, the patient deliberately generates an ocular oscillation that looks exactly like ocular flutter! This disorder is usually found in patients who are seeking rewards for a medical condition or are seeking attention. You can distinguish volitional flutter from non-volitional (true) flutter by the fact that patients producing volitional flutter can only keep it going for seconds at a time and they have no other abnormal aspects to their neurologic examination.

5. **Ocular dysmetria.** In this condition, small, brief horizontal saccadic oscillations occur as patients make refixational eye movements. If you watch carefully, you will see that the oscillations have progressively diminishing amplitude as the eyes settle on a fixation target. However, it is often difficult to notice that the oscillations begin with a refixational eye movement because such movements may be of very small amplitude. Many of these patients also have extremity or trunk ataxia. It is very difficult to distinguish ocular dysmetria from ocular flutter.
Therefore, if tremor, myoclonus, or ataxia is present, it is best to evaluate the patient for flutter/opsoclonus.

6. **Convergence-retraction.** When the patient makes an attempt at looking upward, the eyes converge and move backwards into the orbits intermittently. Each attempt at upward gaze provokes 2 or 3 convergence-retraction cycles. The basic disturbance is an inability to perform upward saccades. The convergence-retraction is a substitution for the impaired upward saccades. Lid retraction, skew deviation, esotropia, exotropia, and light-near dissociation of pupil constriction (see Pupil Section, below) may also be present. The lesion is always in the dorsal midbrain, which may be compressed by a dilated posterior third ventricle in acute hydrocephalus or by a thalamic or pineal lesion.

7. **Ocular bobbing.** In this condition, the eyes move conjugately upward and then downward. The frequency of the cycles varies from moment to moment, and there may be periods when there is no oscillation. In the most common form, the eyes move downward quickly from the center position and then return slowly to the center position. In less common forms, the eyes either move slowly downward from center or move slowly or quickly upward from center. In some patients, the lesion is in the pons and in others it is severe metabolic or hypoxic-ischemic damage to the cerebrum. The mechanism by which ocular bobbing occurs is not understood. Perhaps it is, like Cheyne-Stokes respiration, a release (de-efferentation) phenomenon; that is, the midbrain is released from the natural inhibition of the cerebrum or the pons.

8. **Ping pong gaze.** In this condition, the eyes oscillate very slowly from one side to the other. This ocular motor disorder is always associated with severe hypoxic-ischemic damage to the cerebrum. Its mechanism is unknown, but like ocular bobbing, it may represent de-efferentation phenomenon; in this case, the release is of a periodic generator of horizontal ocular oscillations in the pons.

For a decision-tree approach to ocular oscillations, look at Figure 7.
Figure 1. Brain pathways for control of horizontal saccades. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 2. Brain stem pathway for control of horizontal saccades. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 3. Brain pathways for control of vertical saccades.(From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 4. Brain stem pathways for control of upward and downward saccades. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 5. Brain pathways for control of pursuit. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 6. Brain stem pathway for control of horizontal vestibulo-ocular reflex. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 7. Decision-tree for Ocular Oscillations
SESSION 4: PUPILS

I. THE COMMON PROBLEM: ANISOCORIA

The most common problem of the pupils is anisocoria, in which one pupil is larger than the other. When anisocoria is the only pertinent finding, it is usually not a serious medical problem. Anisocoria becomes a concern only when there are other findings, such as ptosis, diplopia, weakness, ataxia, or impairment of consciousness.

The most efficient approach to analyzing anisocoria is to discover first whether the pupils constrict normally to a light shined directly at each eye. But in order to understand why this approach is logical, you must be familiar with the two neural pathways that control the pupils.

II. THE PUPIL PATHWAYS

A. THE PARASYMPATHETIC PATHWAY. (FIGURE 1) The afferent, or input, part of the pupil reflex pathway is made up of axons from the retinal ganglion cells. They are stimulated partly by light passing from photoreceptors through bipolar cells, and partly by light that directly activates melanopsin-containing ganglion cells. The axons pass through the optic nerves, optic chiasm, and optic tracts. In the distal optic tract, they diverge to enter the midbrain tectum, where they synapse several times on both sides. Neural signals then pass to the parasympathetic part of the third cranial nerve nuclei on both sides of the midbrain tegmentum. Light information from each eye is equally distributed to the two third cranial nerve nuclei. Therefore, lesions of this afferent part of the pupil reflex pathway do not cause anisocoria!

The efferent, or output, part of this reflex is carried from the third cranial nerve nucleus by the fascicles of the third cranial nerve ventrally in the midbrain and through the subarachnoid space to the cavernous sinus and then through the inferior division of the third cranial nerve to the ciliary ganglion. Most of the axons synapse in the ciliary ganglion and pass as the short
ciliary nerves to the iris sphincter. The efferent part of the third cranial nerve is called its pre-
ganglionic segment. The efferent part from the ciliary ganglion to the iris sphincter is called its post-ganglionic segment. Anisocoria may result from damage to either segment of the efferent part. But if anisocoria is the only abnormality, and the affected pupil does not constrict properly to light, the most likely place to look for the lesion is in the post-ganglionic segment of this pathway--in the distal orbit or the eye.

B. SYMPATHETIC PATHWAY. (FIGURE 2) This pathway begins in the hypothalamus. Axons travel through the brain stem in a dorsolateral position. In the medulla, they are frequently damaged by a stroke caused by occlusion of the vertebral artery and its first branch, the posterior inferior cerebellar artery. The descending oculosympathetic axons synapse in the intermediolateral lower cervical spinal cord and leave the spinal cord to travel upward along a path near the spinal column. These axons travel through the neck and synapse in the superior cervical ganglion at the level of the angle of the jaw. The axons then travel along the internal carotid artery as it enters the skull base and the cavernous sinus, where they are close to the sixth cranial nerve. The axons enter the orbit through the superior orbital fissure and reach the iris dilator and Muller's muscle, which elevates the upper lid. Some fibers also synapse on a retractor of the lower lid.

Lesions of the sympathetic pathway may occur in its central segment (from hypothalamus to cervical spinal cord), its pre-ganglionic segment (from the paravertebral to the superior cervical ganglion), or its post-ganglionic segment (from the cervical internal carotid artery to the eye). If anisocoria is the only abnormality, and the pupils constrict properly to light, the most likely places to look for a lesion are the pre-ganglionic segment in the chest/ lower neck and the post-ganglionic segment in the upper neck.

III. EVALUATING PUPIL ABNORMALITIES

A. CLINICAL EXAMINATION. The examination of the pupils has three basic steps:
1) *Measurement of pupil size in the dimmest possible illumination.* A difference in pupil size of more than 1mm may be pathologic.

2) *Measurement of the constriction of each pupil to direct light.* Constriction should be quick and equal in the two eyes. However, the degree of constriction normally varies widely from one person to another.

3) *The swinging light test.* This test is designed to uncover a relative afferent pupil defect which would usually indicate a lesion of one optic nerve or asymmetric lesions of both optic nerves. (The swinging light test is reviewed in Session #1: Visual Loss.)

If the pupil does not constrict properly to direct light, you must look for three important features:

1) *Segmental constriction.* Observe the iris carefully at the slit lamp to see if some portions are actually constricting less completely than others. If you observe this, you should diagnose *segmental constriction*, a feature that occurs mostly with lesions of the ciliary ganglion, ciliary nerves, or the sphincter muscle itself.

2) *Light-near dissociation.* Compare pupil constriction to direct light with pupil constriction to a target viewed at reading distance. If you observe that the pupil does not constrict to direct light but does constrict to a target placed at reading distance, you should diagnose *light-near dissociation*, a feature that occurs with lesions of the optic nerves and chiasm, dorsal midbrain, and ciliary ganglion or ciliary nerves, but not usually with lesions of the pre-ganglionic segment of the third cranial nerve.

3) *Tonicity.* Observe how quickly the pupil constricts to direct light and how quickly it dilates as the patient changes fixation from a target held at reading distance to a target viewed at far distance. If the constriction or dilation is slow, you should diagnose a tonic pupil. A tonic pupil occurs only with lesions of the ciliary ganglion or ciliary nerves, but does not develop until at least 8 weeks have elapsed from the time of the damage.
B. PHARMACOLOGIC EXAMINATION. You can use topically-applied pharmacologic agents to help you diagnose pupil abnormalities:

1) *Pilocarpine*. Concentrations of 0.5% or higher of this parasympathomimetic agent will constrict the normal pupil. Such concentrations will not constrict a pupil when the iris sphincter has been injured by trauma or has been exposed to a parasympatholytic agent. Concentrations of 0.1% will constrict a pupil on the side of a ciliary ganglion or ciliary nerve lesion, a phenomenon called *denervation supersensitivity*, which develops within days of the onset of damage to the ciliary ganglion or its nerves. However, denervation supersensitivity also occurs from a lesion in the pre-ganglionic segment of the third cranial nerve! Therefore, instilling 0.5% pilocarpine into the eye is useful in differentiating between a denervated iris sphincter and a pharmacologically blocked or traumatized iris sphincter. It is not useful in differentiating between a pre-ganglionic and a post-ganglionic third cranial nerve lesion.

2) *Cocaine*. Concentrations of 4% or higher of this sympathomimetic agent will dilate the normal pupil. They will poorly dilate the pupil on the side of damage to any segment of the oculosympathetic pathway, even if the damage occurred within the past few hours. If anisocoria of >1mm remains 1 hour after instillation of cocaine, Horner syndrome is a likely cause. The weaknesses of cocaine as a diagnostic agent are that it is not readily available in eyedrop form, and that it is a weak dilator even of the normal pupil.

3) *Apraclonidine*. Concentrations of 0.5% or 1% of this sympathomimetic agent will not dilate the normal pupil but will dilate the pupil on the side of a Horner syndrome. As a result, the anisocoria will reverse sides! This agent will also reverse the ptosis of Horner syndrome. Therefore, apraclonidine is useful in determining whether a Horner syndrome is present, but it may not work until several days have elapsed from the time of damage. Its advantages over cocaine are that it is readily available and will readily dilate the affected pupil while not dilating the normal pupil, and it will
IV. IMPORTANT PUPIL ABNORMALITIES

A. PHYSIOLOGIC ANISOCORIA. Anisocoria of less than 1 mm occurs in many normal subjects. But to make this diagnosis, you must be certain that both pupils constrict normally to direct light and that there is no diplopia, ptosis, or ocular ductional deficit. You may have to distinguish physiologic anisocoria from Horner syndrome by observing the response of the pupils to instillation of cocaine or apraclonidine.

B. HORNER SYNDROME. This is a lesion of the oculosympathetic pathway. It creates anisocoria of 1 to 2 mm and usually ipsilateral ptosis, which is rarely more than 2 mm. The diagnosis can be confirmed by finding that after instillation of topical cocaine 4%-10%, there is a residual anisocoria of more than 1 mm or by finding that instillation of apraclonidine 0.5%-1% eliminates the anisocoria or causes the smaller pupil to become the larger pupil.

When Horner syndrome develops quickly, and if the patient reports pain in the neck or face, the cause is probably a dissection of the ipsilateral carotid artery. Diagnosis is urgent because the patient may develop a stroke if she is not treated with aspirin or warfarin. When Horner syndrome develops slowly, and the patient does not report any other symptoms, you should look for a tumor in the upper chest or neck. Horner syndrome can also be caused by injury to the sympathetic pathway following placement of an internal jugular cannula or other surgical procedures on the neck and chest.

C. TONIC PUPIL. This pupil is abnormal because its iris sphincter is not receiving normal signals from a damaged ciliary ganglion or ciliary nerves. The affected pupil is usually larger than the normal pupil and not perfectly round because only a portion of its sphincter is not working. The affected pupil will not constrict to light or it will constrict only in a portion of the sphincter, a feature called segmental constriction. Several weeks after the time of damage, the
pupil will constrict slowly to a target viewed at reading distance and will dilate slowly when the
patient is asked to fixate a distant target after viewing a target at reading distance, a feature
called *tonicity*. Pilocarpine 0.1% will cause constriction of the affected pupil (but not the
unaffected pupil), a feature called *denervation supersensitivity*. You may also discover some
other abnormalities, including loss of accommodation, and absent deep tendon reflexes and
corneal sensation. Many months after the onset of the tonic pupil, it may become the smaller of
the two pupils. In some cases, the other eye will later develop the same abnormality.

In most cases, the cause of a tonic pupil is unknown, but current belief is that it results
from a viral infection. Diagnosis depends on finding segmental constriction and tonic dilation.
Dilute pilocarpine is often used to discover denervation supersensitivity, but this phenomenon
can also occur in pre-ganglionic lesions of the third cranial nerve.

**D. ANISOCORIA IN PRE-GANGLIONIC THIRD CRANIAL NERVE PALSY.** Anisocoria
with a poorly constricting pupil can also be part of a pre-ganglionic third cranial nerve palsy.
However, *anisocoria is never the only manifestation of a third cranial nerve lesion!* If the third
cranial nerve has been damaged, you should expect to find some amount of ptosis and
ductional deficits on the side of the dilated pupil.

**E. TECTAL PUPILS.** In this condition, a lesion in the region of the dorsal midbrain
interrupts the connection between the afferent and efferent parts of the pupillary reflex. As a
result, the pupils are abnormally large and do not constrict properly to direct light. However,
they may constrict when a visual target is placed before the eyes at reading distance, a
phenomenon called *light-near dissociation*. Light-near dissociation occurs with lesions of the
dorsal midbrain because the pathway that controls pupil constriction to a target placed at
reading distance passes through the ventral midbrain, not through the dorsal midbrain.

With midbrain tectal lesions, these pupillary abnormalities never exist without some other
manifestations, such as deficient upgaze, skew deviation, convergence-retraction, and lid
retraction.
F. PHARMACOLOGICAL ANISOCORIA. Many medications and plants contain parasympathomimetic and sympathomimetic substances. If the patient’s eyes are contaminated by these substances, pupil size and constriction may be altered. Scopolamine patches used to prevent seasickness and aerosols used in pulmonary care are the most common examples, but patients can also instill medications normally used to dilate pupils without telling the truth to their doctors! If the contamination is from a parasympatholytic agent, the affected pupil will be dilated and will not constrict properly to light. If the contamination is from a sympathomimetic agent, the affected pupil will also be dilated and it may or may not constrict properly to light.

Diagnosis depends mainly on discovering the exposure. If you suspect a parasympatholytic blockade, you could prove it by instilling pilocarpine 0.5% in both eyes and finding that the normal pupil constricts less than the affected pupil, or not at all! There is no effective way to use eyedrops to confirm anisocoria caused by exposure to topical sympathomimetic agents.

G. ANISOCORIA OF TRAUMATIC IRIDOPLEGIA. In this condition, trauma to the iris sphincter causes the affected pupil to be abnormally large and poorly constricting to light. The pupil shape is often irregular and slit lamp examination will show marginal tears, dialysis, synechiae, lens surface pigment, or iris transillumination defects. There should be a history of blunt trauma or intraocular surgery.

If there are no clear findings of trauma on slit lamp examination, you could prove iris sphincter damage as the cause of the pupil abnormality by instilling pilocarpine 0.5% and observing reduced or segmental pupil constriction in the affected eye.

H. BENIGN EPISODIC ANISOCORIA. In this condition, the patient will report observing that one pupil was larger than the other for a period of time. The patient may also say that vision in that eye was impaired during that time.

When patients have been examined during such episodes, their affected pupils have sometimes constricted poorly or normally to light. Current belief is that this phenomenon is an episodic abnormality of autonomic function, involving either the parasympathetic pathway or the
sympathetic pathway. It may be part of migraine, or an autonomic cephalalgia such as cluster headache, or a seizure.

To make this diagnosis, you should be certain that there are no other neuro-ophthalmologic abnormalities.

For a decision-tree approach to anisocoria, look at Figure 3.
Figure 1. The parasympathetic pathway that controls the pupil sphincter muscle. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 2. The sympathetic pathway that controls the iris dilator muscle. (From Burde, Savino, and Trobe, Clinical Decisions in Neuro-Ophthalmology, 3rd Edition.)
Figure 3. Decision-tree for Anisocoria.

**APPENDIX:**

**INTERPRETING MAGNETIC RESONANCE BRAIN IMAGING**

We cannot go far in making a diagnosis in neuro-ophthalmology without using magnetic resonance imaging (MRI). Interpreting MRI scans is difficult, but it is based on simple ideas:

1) locating the signal abnormalities

2) deciding what the signal intensities tell us about the nature of the abnormality
We rely on two pulse sequences: T1 and T2. The signal intensities on T1 and T2 range from very high (white) to very low (black). There are many shades of gray in between.

We can inject a contrast agent (gadolinium) during the T1 sequence in order to see areas where blood flow is abnormally high or where the blood-brain-barrier has been disrupted. In those areas, there will be an abnormally high (white) signal.

T2 images allow us to see where there is an abnormally high amount of moving protons, as occurs in most lesions of the central nervous system.

When we compare the signal intensity on T1 and T2, we can get a good idea of the lesion (FIGURE 1):

1. **Black on pre-contrast T1, white on T2.** Most lesions of the brain and spinal cord contain an abnormal amount of mobile protons in free water, so they will be black on T1 and white on T2. Examples are **cyst fluid, abscess, edema, encephalomalacia, demyelination, and necrosis. Normal cerebrospinal fluid (CSF)** will also look like this.

   An important modification of the T2 sequence is the fluid attenuation inversion recovery (FLAIR) sequence. It is designed to reduce the high T2 signal of tissues with freely flowing water, such as CSF, cysts, and large areas of encephalomalacia. With this modification, lesions that have abnormally high amounts of interstitial and intracellular water, which does not flow freely, become more visible as white areas.

2. **Black on pre-contrast T1, black on T2.** This appearance is caused by air, dense calcium, cortical bone, rapidly flowing blood, dense fibrous tissue, iron, and hemosiderin (from parenchymal hemorrhage of more than one week’s duration).

   Air, dense calcium, cortical bone, and dense fibrous tissue produce a very black signal on T1 and T2 because they have no moving protons. (Lower densities of calcium show variable and unpredictable signals.)

   Blood that flows rapidly produces a very black signal because its protons are flowing out of the scanned slice. This phenomenon is called “flow-related signal void”.

   Hemosiderin and iron are strongly paramagnetic and will therefore be very black on T2 and nearly black on T1.
3. White on pre-contrast T1, black on T2. Tissue with this combination of signals contains melanin, intracellular methemoglobin (resulting from hemorrhage of 3-7 days' duration), or fat.

Fat appears black on T2 on spin echo T2 sequences that are not in common use today. On the newer sequences, fat appears gray or white.

4. White on pre-contrast T1, white on T2. This combination of signals results from extracellular methemoglobin (brain hemorrhage of 1-4 weeks' duration), slowly flowing blood, or fat.

Fat appears white on T2 on current turbo/ fast spin echo sequences. Because fat and extracellular methemoglobin both cause white signal on T1 and T2, you must use a fat-suppression sequence to distinguish between them (fat will appear black and extracellular methemoglobin will remain white).

Slowly flowing blood, usually in veins and sometimes from arteries, causes white T1 and T2 signals because its protons are moving so slowly that they remain trapped within the scanned slice.

When the protein of a body fluid becomes high, the fluid becomes less like water, so its T2 signal goes from white to gray and its T1 signal goes from black to gray. (This happens in meningitis.) The same thing occurs when the fibrous content, cell density, or nuclear-cytoplasmic ratio of tumors becomes high.

Special T2 sequences called “gradient echo scans” improve the ability to detect calcium and hemosiderin. These substances become blacker and larger on this pulse sequence than on ordinary T1 or T2.

Fungal infections create signal intensities that will be gray on T1 and T2 if protein content is high, but black if they contain paramagnetic or ferromagnetic material. Chronic densely concentrated mucosal secretions, which may contain no mobile protons, may also produce black T1 and T2 signals.

The MRI signal from brain and spinal cord parenchymal hematoma evolves as the clot is degraded (FIGURE 2). Signal intensity depends on protein concentration, red blood cell hydration, size, and shape, hematocrit, clot formation and retraction, inflammatory response, and magnetic field strength.
A relatively recent valuable addition to the pulse sequences of MRI is diffusion-weighted imaging (DWI). Lesions in which the interstitial spaces have become crowded will restrict the diffusion of water molecules and produce a high (white) signal on DWI. Examples are recent infarction, abscess, epidermoid cyst, tumors with tight cellular density, and exuberant inflammation with cell death (some forms of multiple sclerosis, progressive multifocal leukoencephalopathy). To be sure that the high signal on DWI is not a reflection of the high signal on T2 ("T2 shine through"), you must make sure that the high signal on DWI is matched by a corresponding low signal on the apparent diffusion coefficient (ADC) map.
<table>
<thead>
<tr>
<th></th>
<th>WHITE on T2</th>
<th>BLACK on T2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLACK on T1</strong>*</td>
<td>Cerebrospinal fluid</td>
<td>Air*</td>
</tr>
<tr>
<td></td>
<td>Cyst</td>
<td>Dense calcium*</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
<td>Cortical bone*</td>
</tr>
<tr>
<td></td>
<td>Demyelination</td>
<td>Rapidly flowing blood#</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>Iron</td>
</tr>
<tr>
<td></td>
<td>Encephalomalacia</td>
<td>Hemosiderin</td>
</tr>
<tr>
<td></td>
<td>Necrosis</td>
<td></td>
</tr>
<tr>
<td><strong>WHITE on T1</strong>*</td>
<td>Extracellular methemoglobin</td>
<td>Melanin</td>
</tr>
<tr>
<td></td>
<td>Slowly flowing blood+</td>
<td>Intracellular methemoglobin</td>
</tr>
<tr>
<td></td>
<td>Fat**</td>
<td>Fat**</td>
</tr>
</tbody>
</table>

Figure 1. Types of lesions in the central nervous system and the MRI signal intensities they produce.

*T and T2 signal is black because there are no mobile protons

**White on T2 turbo/fast spin echo; black on T2 conventional spin echo

***These boxes all refer to T1 signal without the injection of contrast material ("pre-contrast or "non-contrast"). Intravenous injection of contrast material is used with T1 pulse sequences ("post-contrast" T1). It will generate a whiter signal than on pre-contrast T1 in tissues that have an especially dense arterial blood flow or when the dye has escaped across an absent or deficient blood-brain barrier to linger in the tissue.

#Rapidly flowing blood causes black T1 and T2 signal because the protons have escaped the scanned slice.

+Slowly flowing blood, usually venous, causes white T1 and T2 signal because the protons move too slowly to escape the scanned slice.
<table>
<thead>
<tr>
<th>Phase</th>
<th>Time from Bleed</th>
<th>Stage of Hemoglobin</th>
<th>T1***</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>&lt;6 hours</td>
<td>Oxyhemoglobin</td>
<td>Gray</td>
<td>White</td>
</tr>
<tr>
<td>Acute</td>
<td>6-72 hours</td>
<td>Deoxyhemoglobin</td>
<td>Gray</td>
<td>Black</td>
</tr>
<tr>
<td>Early subacute</td>
<td>3-7 days</td>
<td>Intracellular methemoglobin</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Late subacute</td>
<td>1-4 weeks</td>
<td>Extracellular methemoglobin</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Early chronic</td>
<td>&gt;4 weeks</td>
<td>Extracellular methemoglobin with hemosiderin rim</td>
<td>White</td>
<td>White with black rim</td>
</tr>
<tr>
<td>Late chronic</td>
<td>Months to years</td>
<td>Hemosiderin</td>
<td>Black</td>
<td>Black</td>
</tr>
</tbody>
</table>

Figure 2. The MRI signal intensities of different phases of abnormal blood in central nervous system tissue.

***The T1 signal is without contrast injection ("pre-contrast" or “non-contrast”).
Bibliography