Neuro-Ophthalmology

CLINICAL SIGNS AND
SYMPTOMS

Fourth Edition

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Neuro-Ophthalmology

CLINICAL SIGNS AND SYMPTOMS

Fourth Edition
TO SALLY
A basket of love for her understanding
Medical textbooks are of several types and purposes. Some are encyclopedias of a particular subject, and such books are excellent sources of reference. At the other end of the spectrum is the so-called introductory text, which frequently is so abbreviated that the physician is led only halfway toward an appropriate diagnosis. Between these two extremes, a gap exists in the neuro-ophthalmic literature. What is required is a clinically useful textbook for the practicing as well as the resident ophthalmologist, and I have striven to fill that need in this book.

My focus has been on the practical application of well-accepted diagnostic techniques and the interpretation of clinically relevant information needed to form sound differential diagnoses. Since this textbook is intended for use in a clinical situation, I have assumed that the reader is familiar with the discipline of ophthalmology.

On that basis, I have covered the most important aspects of the field of ophthalmology succinctly, but sufficiently to enable the practitioner to determine an appropriate diagnosis and course of treatment. With respect to rare and unusual diseases, I have included only those that are especially critical to the patient’s vision or general health.

As the title indicates, the book discusses neuro-ophthalmology in terms of its signs and symptoms. Thus, each chapter deals with either a symptom that leads the patient to seek medical attention or a sign that is demonstrated on physical examination. Each chapter is written in the form of a monograph. Although this practice leads to some repetition, it permits the reader to research a sign or symptom by reference to one chapter and eliminates checking numerous page references in the index. For this reason also, cross references have been kept to a minimum. I believe that this format will give the physician who is less familiar with certain conditions a better chance of arriving at a correct diagnosis. Besides diagnoses, in each chapter I have suggested diagnostic tests and techniques that I have found particularly useful with the type of condition being discussed.

One of the essentials of having several coauthors in a textbook with this approach is that all contributors see the book and their subject in the same light as does the senior author to give the book a certain cohesiveness. I feel that my coauthors have achieved this while adding their own particular expertise in their subject of interest. Some of the chapters are also a basic review of laboratory subjects, such as radiology and electrodiagnosis. These chapters are meant to give readers a firm grounding in what these tests can do in making a diagnosis and when they are likely to be employed.

The responsibility of taking care of patients does not end with making the proper diagnosis. That is only the beginning of patient care. The physician must direct the patient to any additional workup and then on to proper care under his or her guidance or in a referral to other specialists. To know what new diagnostic tests and treatments are available, we have incorporated chapters on electrical testing, imaging, neuro-otology, and neurosurgery. These chapters are not meant to make the reader an expert in these
diverse specialties but to give reasonable
guidance. Headache, for example, can be
due to many causes and, rarely, ophthalmic.
Papilledema and diplopia are also very di-
verse in medical specialties that are in-
volved. That is why the physician who is
managing neuro-ophthalmic patients needs
to have a broad background of medical in-
formation. This allows physicians to manage
the patient's workup properly and also to
evaluate the competence and current level
of competence of the physicians to whom
they refer patients.

The previous editions have concentrated
primarily on neuro-ophthalmic diagnosis and
not treatment. In this edition, we have ex-
panded our therapeutic discussions not only
in some of the ancillary chapters but in the
treatment of optic neuritis and migraine
headache and the treatment of pseudotumor
cerebri.

Rather than covering ancillary data in
depth in the text, I have supplied pertinent
bibliographic references to facilitate further
research by either those who seek additional
evidence for the conclusions reached on a
particular subject or those who would like to
explore a subject further in the literature.

New Haven, CT

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true measure, but I will try to make special
mention of a few.

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Neuro-ophthalmologic History and Neurologic Examination

Jonathan D. Wirtschafter

The accuracy of clinical diagnosis depends on the history and examination, an adequate fund of knowledge, and correct diagnostic reasoning. The patient who is referred for a neuro-ophthalmologic problem is different from most patients seen by either the ophthalmologist or the neurologist. For the ophthalmologist who is used to making a diagnosis by examination of a transparent organ, the neuro-ophthalmologic patient requires more investment of time and talent to obtain a better history and to arrange alternative and supplementary examinations. For the neurologist who is accustomed to emphasizing the history, the neuro-ophthalmologic patient requires the mastery of additional examination techniques and their interpretation. This eclectic and anecdotal chapter highlights some of the aspects of the neuro-ophthalmologic history and nonocular neurologic examination. Some of the newer technologies are mentioned briefly, but the details are left for other chapters in this volume or reviews of the current medical literature. Only after the clinical diagnostic assessment has been made should the clinician order specific laboratory and imaging studies to test the hypotheses that follow from the history and examination.

PURPOSE OF THE HISTORY AND EXAMINATION

The examiner attempts to answer several questions during the neuro-ophthalmologic examination. The relationships of the questions are easily stated, but the answers may come in any order.

1. Does the patient have one or more organic or functional disorders?
2. What is the topographic localization of the organic lesions?
3. What is the cause of the disorder?
The neuro-ophthalmologist frequently is confronted by multiple diagnoses in the same patient. For example, the patient may have not reported the best visual acuity when tested; the patient may need a refraction to improve the acuity; a posterior subcapsular cataract may be interfering with vision when the patient is tested looking at a near visual acuity chart in bright illumination; there may be macular degeneration, and the patient may have alexia. When one or more problems occur along a single neurologic pathway, they are said to be linearly localized. Conversely, when the problem can be specified as occurring at only one location along a pathway, it is described as point localized. For example, a patient first identified as having a visual pathway lesion could have visual fields leading to point localization of a chiasmal syndrome. It is axiomatic that any point localization in the anterior visual pathway could be mimicked by lesions at one or more other locations. One of the reasons for performing multiple examination procedures on the same patient is to avoid the risks of faulty topographic localization and diagnosis.

ANSWERING THE PATIENT’S CONCERNS

The patient's own diagnostic assessment, insight, and concerns are an important part of the neuro-ophthalmic agenda. In my experience, the final outcome of about one-third of neuro-ophthalmic workups is to reassure the patient that the problem is likely to be static or to improve spontaneously after some period of time. Moreover, it may be desirable to limit the further expenditure of health care resources on the problem. These issues cannot be approached unless the examiner knows if the patient is concerned about specific diagnostic possibilities such as brain tumor or multiple sclerosis. Alternatively, the patient may be concerned about the relationship of his or her symptom to a disease present in a relative or friend. A medicolegal issue may be pending, and information should be specifically sought about whether all litigation and disability claims have been settled or whether such action is pending or contemplated. In this regard, it is also important to establish in the medical record whether the patient is seeking consultation for medical care or has been referred by an attorney or insurance company. In medicolegal cases I generally include a sentence stating whether the patient was cooperative and helpful in giving the history and performing the tests requiring patient cooperation. Because many attorneys are concerned about knowing if a physician may be biased by specializing in either plaintiff or defense cases, you may wish to demonstrate your impartiality by maintaining some records concerning the ratio of these two types of cases.

HISTORY OF THE PRESENT ILLNESS

The importance of the history in the evaluation of the awake neurologic patient cannot be overemphasized. Much of the examination can be omitted or minimized if the review of neurologic symptoms is negative and the patient is not deceiving, confused, or suffering from loss of memory or intellectual ability. Conversely, objective examination techniques are required if the patient is not able to provide a good history or cooperate for various subjective tests.

Certain diagnoses can only be made on the basis of the patient's history. Migraine headaches are an example. Many patients will be surprised to know that migraine episodes can occur without headache (acephalic migraine). It is usually possible to use the patient's description to distinguish the flashing lights that may result from classic migraine (a cortical symptom), vitreous traction on the retina (a mechanoneural transmission symptom), or amaurosis fugax (a neural symptom). It is important to try to distinguish between symptoms of carotid artery stenosis or embolism and symptoms of verteobasilar artery stenosis, because
carotid artery disorders are more likely to require further differentiation as a prelude to surgery.

The multiplicity of the times of occurrence and types of past neurologic symptoms may cause you to suspect that the patient has multiple sclerosis. An ophthalmologist must remember to ask about urinary incontinence, anorexia, and gait disturbance, as these are among the most frequent complaints of patients with multiple sclerosis.

**Communicating with the Patient**

The chief complaint and history of the present illness may need to be elicited more than once. If several problems exist, they should be identified separately and ranked in their importance to the patient. Not infrequently, you will have to teach patients some facts and have them report after a subsequent attack of an episodic phenomenon. For example, you may explain the differences between (a) the left eye and the left visual field of each eye, (b) monocular and binocular diplopia, (c) crossed and uncrossed diplopia, and (d) ghost, blurred, and double images. Sometimes you will want to give patients a pinhole oculler or a red celluloid lens to take home so they can better describe an intermittent symptom. A patient can look through the pinhole during an attack of blurring to determine whether this simple "universal lens" relieves the symptom, thus demonstrating a refractive or accommodative problem. You can give patients a red lens so that they can demonstrate the extent and direction of intermittent diplopia. You can also ask the patient to have a friend call you during an attack of apparent movement of the environment and describe the patient's eye movements while observing them under your direction.

You will frequently be frustrated by the patient ascribing different meanings to words than you would. Examples of this occur in the language used to describe headache. Patients may use the terms "migraine" or "sinus" to describe a symptom of greater occipital neuralgia. Often the patient's finger gesture illustrating the pain describes a circular course from front to back, along the origin of the temporalis muscle; this is characteristic of pain of greater occipital neuralgia. Sometimes the patient will describe orbital pain but point to the anterior part of the origin of the temporalis muscle when the diagnosis is "myofascial pain syndrome."

The term "dizzy" may be used to mean "feeling faint or lightheaded" or to mean "oscillospsia," the apparent movement of the environment. Oscillospsia and nystagmus can occur simultaneously or independently.

Yet another example of the difference between your language and the patient's relates to use of drugs and medications. They may not define "drugs" as including aspirin, scopolamine patches, vitamin A preparations, or birth control pills, just to name a few.

**Onset and Recurrences of Symptoms**

The onset of symptoms is important in the evaluation of trauma, infection, and postinflammatory events. In addition to external events, time of day or the posture of the patient may be associated with the onset or the recurrence of a symptom. Certain events may be more likely to begin during sleep. It has been suggested that the cerebral blood flow may decrease at night and lead to thrombosis, whereas embolism from an ulcerated plaque may occur more frequently during hours of greater activity. Postural changes at night may increase the cerebrospinal fluid pressure, giving rise to headaches. Patients with papilledema resulting from increased intracranial pressure frequently report that they have transient obscurations of vision immediately after standing. A colloid cyst of the third ventricle may produce sudden headache, owing to increased cerebrospinal fluid pressure resulting from a ball-valve action at the aqueduct of Sylvius or the foramen of Monro. This symptom was precipitated recurrently in one
of our patients each time he crawled through an apartment window to visit a
woman who was married to someone else. Changes in head position may also con-
tribute to many other neuro-ophthalmic symptoms, including paroxysmal positional
vertigo, head pain associated with posterior fossa tumors, and the amplitude of intracra-
nial bruits.

You must use caution in accepting the pa-
tient's interpretation of the mechanism or
time of onset of a symptom. The accidental
covering of each eye may lead to the dis-
covet of a longstanding condition that the
patient believes has just begun. The sudden
onset of bilateral blindness may result from
an acute hemianopia in one hemifield in a
patient with an unrecognized longstanding
contralateral hemianopia. We have one pa-
tient who had an automobile accident in-
volved in the hemianopic visual field resulting
from the "old stroke" before he went blind
with the "new stroke." In this patient, the
pupillary light reflex was normal, demonstrat-
ing the retrogeniculate nature of the
blindness.

We have encountered patients in whom
blindness in one or both eyes was recog-
nized one or more days after general, car-
diovascular, or orthopaedic surgery. In some
patients it is unlikely that the visual loss re-
sulted from an intraoperative event; in such
cases potentially reversible ocular ischemia
may have occurred during the postoperative
period when the patient was unable to rec-
ognize or report the problem. This suggests
that visual acuity is a vital sign that ought to
be tested and recorded.

Other events that seem to provoke recur-
rent symptoms also should be addressed. Pa-
tigue may increase the symptoms of myas-
thenia gravis, and exercise and increased
body temperature may produce visual loss or
other neurologic symptoms in multiple sclero-
sis, a response known as the Uhthoff phe-
nomenon. The relationship between menses
and migraine should be probed.

Foods may play an important role as re-
current causes of headaches of several vari-
esties. Migraine may be precipitated by alco-
hol in general and red wine in particular,
other foods associated with migraine include
chocolate and hard cheeses. Caffeine with-
drawal and hypoglycemia are other dietary
causes of headache.

Reading is blamed for many symptoms,
and you will need to examine the circum-
stances surrounding this activity in some de-
tail. Try to determine what activities have
been given up or are being performed less
well as a result of the illness. It may be
worth asking whether there are difficulties
seeing the stairs (in patients with severe con-
striction of the visual field or vertical dip-
lopia), using the rearview mirror of an auto-
mobile (in diplopia), finding the curb or the
bathroom in the dark (in retinal degen-
ervations), or seeing the highway when driving
in bright light (in posterior subcapsular
cataracts). Patients with retinal cone dys-
trophies and degenerations usually prefer to
read in dim (mesopic) light.

One of the most difficult symptoms to
evaluate is loss of depth perception, espe-
cially of moving objects such as baseballs or
automobiles, following the loss of vision in
one eye. Patients who have been monocular
for years do not have similar complaints.
Usually these symptoms resolve within a
few months, but adaptation to monocular vis-
ual loss is not fully understood. Patients
complain much less frequently of loss of
stereopsis when viewing small objects;
when they do so, the cause is usually related
to loss of visual acuity in one or both eyes
rather than to an acquired abnormality of oc-
ular alignment. Acquired misalignment is
more likely to cause diplopia. The author is
particularly sympathetic to the disabling ef-
fects of loss of stereopsis experienced by a
dentist who loses vision in one eye.

Try to get some external confirmation of
the patient's assertions. Family members can
report unusual behavior such as appropriate
responses to abnormally perceived visual
stimuli, as occurs in Alzheimer's disease or
other dementias. For example, the patient
may walk up to and try to straighten a door
frame that is misperceived as warped. Old
photographs of the patient can often be used
to find unremembered ptosis or anisocoria. The social and economic functional status of the patient is frequently important. A simple approach is to ascertain what previously performed activities the patient has recently abandoned. Using blepharospasms as an example, a patient may report limiting his or her reading time, decreasing driving (or driving with one hand on the steering wheel while the other hand holds an eyelid open), or becoming reclusive because friends think he or she is winking at them or is sleepy.

**Prior Imaging and Electrophysiologic Examinations**

Previously performed diagnostic studies are becoming increasingly important and confusing in the practice of neuro-ophthalmology. Unfortunately, many of the patients you see will report that they have had computed tomographic (CT) scans or magnetic resonance imaging (MRI) scans and that the results were “normal.” Do not be misled by this. Many of these scans never included the optic canals or the sellar region. The superior orbital fissure, which is 3 cm in height, is easily mistaken for the optic canal, which is only 3 mm in height. In axial sections, the optic nerve can appear anterior to the superior orbital fissure, which has been misinterpreted as the optic canal. In thick axial sections, the superior rectus and levator palpebrae superioris muscles can be averaged with the optic nerve, which can mistakenly be interpreted as enlarged or even neoplastic. The information obtained from direct conventional arteriograms and from digital subtraction angiograms differs significantly; the latter technique may provide adequate information about the extracranial circulation but insufficient information concerning the intracranial vessels. In cases where intracranial information may be needed to plan surgery, a standard arteriogram may be required. MRI angiography requires no intravenous contrast agent and may soon replace many of the studies previously performed with conventional angiography using iodinated contrast media. MRI studies performed without contrast media may need to be repeated with contrast media, particularly in the evaluation of neoplasms. With this technique, we have been able to identify metastatic tumors involving the falk when all prior studies had been normal.

Unless you have confidence in the report and technique, it is best to review all previous scans yourself with a neuroradiologist before accepting them as normal. Skepticism may be justified concerning the results of other past diagnostic studies, including “normal” visual fields and “abnormal” cerebrospinal fluid pressures. While discussing past diagnostic studies with patients, you should determine whether any problems occurred (e.g., allergic reactions to the intravenous contrast material). It may be necessary to prompt patients concerning various diagnostic studies they have had done and have forgotten or not understood. Many patients are not yet familiar with any of the electrodiagnostic tests except the electroencephalogram. It may require some effort to determine whether the patient was examined for any of the evoked responses (visual, brainstem auditory, or somatosensory) or by electroretinography, electro-oculography, or electronystagmography.

**Past and Present Medications**

The response to prior treatment(s) may be of value in determining or ruling out various pathogenic mechanisms. This information may also tell when and to what extent the symptom bothers the patient. The medications presently used by the patient may provide etiologic clues because they may be the direct cause of the patient's symptoms or they may reveal a diagnosis not considered by the patient to be relevant to the neuro-ophthalmic symptom. Examples of the latter include medications for hypertension, diabetes mellitus, or hypothyroidism following treatment for hyperthyroidism. Thus the patient who presents with diplopia from a re-
restrictive myopathy may have once had a hyperthyroid condition and now may have Graves' disease. Of course, medications can cause dysfunction of the ocular motor system (nystagmus, paresis, impaired smooth pursuit movements, and dysmetria), ocular autonomic system (particularly affecting accommodation), and the afferent visual system (optic neuropathies and retinopathies). The systemic effects of present ocular medications also should be considered; for example, asthma can be produced by systemic absorption of beta-blockers. Fraunfelder and Grant have each compiled texts listing the ocular effects of systemic medications and the systemic effects of ocular medications.

**Review of the Ocular History and Symptoms**

The review of ocular history and symptoms is mandatory. Since most patients date their ocular problems from when they were examined for glasses, it may be best at least to record when they obtained their first and most recent lenses. The frequency, amount, and effectiveness of prescription changes can be helpful in the diagnosis of structural changes in the eye. Frequent changes of refraction suggest the diagnosis of diabetes mellitus. It is important to document when glasses ceased to correct the problem fully. It can be useful to obtain the prescription for the lenses from the patient, because sometimes it may not be appreciated that the patient is wearing a "hidden" progressive bifocal or a prism, either of which may explain diplopia. A high amount of astigmatic correction with an axis of more than 15° from the vertical or horizontal meridians may be associated with the "tilted disk syndrome" and a visual field defect spilling out of the superior temporal quadrant.

After obtaining the refraction history, one can ask about prior ocular surgery, patching for amblyopia, orthoptic exercises, topical eye drops, and systemic medications for glaucoma or inflammation.

**Transient Loss of Vision.** Transient loss of vision is defined according to the time involved and the extent and depth of the loss. Transient obscurations of vision may last only a few seconds when they are caused by papilledema and increased intracranial pressure. Bilateral loss of vision with vertigo may last only a few seconds at a time with vertebrobasilar artery disease and hypotensive episodes. Monocular hypoperfusion episodes may last seconds to minutes and are often associated with the sensation that a curtain has come down before the affected eye. Emboli from the carotid artery and other sources usually obscure vision for 3 to 5 minutes at a time, while uniocular migraine may last 10 to 20 minutes. Classic ophthalmic migraine with a positive scotoma may last 20 to 30 minutes and is usually followed by a headache. Sometimes the visual loss may not be followed by a headache. Patients are surprised to learn that there is a phenomenon called "acephalic migraine."

**Qualitative Loss of Vision.** Qualitative loss of vision is a frequent complaint in monocular optic neuropathies. The patient may report that objects appear less bright or colors less intense than they are with the opposite eye. Objective visual acuity may be normal, so that more subtle tests such as the determination of contrast sensitivity or the visual evoked potential are required to confirm the patient's subjective complaint. When qualitative loss of vision occurs in both eyes, the patient may complain of difficulty in recognizing faces or in driving at night.

**Visual Field Defects.** Visual field defects may be noted by the patient when they are binocular or large or interfere with specific activities. A patient with a large visual field defect may be able to note and even be annoyed by a target moving within the defective field. This ability to recognize moving but not static targets is called staticokinetic dissociation, or the Riddoch phenomenon. Although it was first thought to be a specific characteristic of occipital lobe lesions, the phenomenon has been demonstrated throughout the retrobulbar visual...
pathway. Automated perimetry primarily relies on static perimetry because it is so effective at locating depressions in the pericentral visual field.

**SCOTOMA.** Most visual field defects are not perceived by the patients as a scotoma (a dark spot). It is thus necessary to perform visual field examinations because patients are not aware of areas where the vision is always absent or reduced. It is only when the situation is constantly in flux that the patient becomes aware of a scotoma. As perceived by the patient, a scotoma may be positive (something perceived as dark and lying in the way of seeing the object), or negative (something perceived as bright or dazzling and lying in the way of seeing the object), or both (a frequent symptom in classic migraine). Negative scotomas, also called photopsias, are considered a formed hallucination. Frequently, positive and negative scotomas coexist. Patients may also report symptoms of tachistopsia with a wall of fog or steamy and wavy lines separating them from the object of regard. When the patient reports a moving positive scotoma, its direction, velocity, and duration should be recorded. For example, patients with carotid artery stenosis may report a reversible curtain coming down from above.

**PHOTOPHOBIA.** Photophobia is an aversion to light and depends on a combination of optic and trigeminal nerve stimuli. It does not occur in blind eyes. Irritation of the eyes, nasal mucous membrane, and structures at the base of the skull can all act as stimuli. Photophobia and photopsia have been reported to coexist in optic neuropathies.

**METAMORPHOPSIS.** Metamorphopsia is a distortion of vision. The most common form—micropsia—occurs in macular disease. It does not change much from day to day. Refractive surgery of the cornea may also induce distortions. Rapidly changing distortions are usually caused by diffuse disorders of the visual pathway.

**ENTOPTIC PHENOMENA.** Entoptic phenomena are flashes of light that originate in the retina, probably from direct traction by the vitreous.

**HALLUCINATIONS.** Visual hallucinations are experiences that have no basis in external reality. The patient with an organic hallucination (e.g., a whiskey bottle tied to the leg) may respond appropriately (e.g., "cut the whiskey bottle off my leg"), whereas the patient with schizophrenia may not. Formed hallucinations usually result from disorders involving the temporal lobes of the brain, whereas unformed hallucinations reflect occipital and parietal lobe disorders.

**ACQUIRED READING DIFFICULTIES.** Acquired reading difficulties may result from visual field defects, specific and localized disorders involving alexia, or nonspecific loss of cerebral function. It is useful to ask patients to read aloud and interpret material appropriate to their interests and educational accomplishments. We are sometimes surprised to find that patients with progressive supranuclear palsy do not (yet) have an acquired loss of higher cortical visual function, but instead cannot get their eyes depressed into the field of the bifocal. Giving them a prescription for single-focus reading glasses is the greatest thing you may ever do for these patients.

**DIPLOPIA.** Diplopia may vary with time of day or use of the eyes. The most valuable clue here may be the coexistence of ptosis, which strongly suggests myasthenia gravis. Most of the slowly progressive systemic or ocular myopathies are not associated with diplopia. It is critical to determine whether the diplopia is monocular (seen with one eye or each eye independently) or binocular.

It used to be thought that most monocular diplopia was caused by psychogenic factors, with a few cases resulting from intraocular conditions such as a partially dislocated lens. Now it is recognized that most of these cases are caused by problems in the optical alignment of the cornea and lens and that patients can be shown how to eliminate monocular diplopia by the use of a pinhole occluder. Multiple pupils or a peripheral iridectomy will not produce a second image if a normal lens is properly located within the eye or if the patient is aphakic. Patients often have difficulty in distinguishing low
degrees of diplopia as such and instead describe blurring of images. Binocular diplopia results from deviation of the visual axes of the two eyes.

Horizontal and vertical diplopia may interact in ways that can distract attention from the main diagnosis. For instance, a patient who should complain of vertical diplopia owing to a paralysis of the superior oblique muscle may complain of a large-amplitude secondary horizontal deviation. Only when the patient is given a horizontal prism is the true diagnosis made. Cyclodeviations may also be difficult to detect when taking the history or even during the examination process unless red and white Maddox rods are placed in trial frames in front of the eyes. It is even more difficult to detect such a problem when the examiner is not thinking about the possibility of a bilateral superior oblique paresis.

**Neurologic History**

The review of a neurologic history and symptoms can often be brief, but it is best to have a pattern to ensure completeness. A good approach is to ask about prior neurologic and psychiatric diagnoses, then the dysfunctions of the major structural and functional groups of the nervous system, and then about neurologic and psychiatric symptom complexes such as pain, headache, seizures, and abnormalities of mental function.

**REVIEW OF CRANIAL NERVE SYMPTOMS**

The review of neuro-ophthalmologic symptoms begins with the cranial nerves. Loss of smell is sometimes a feature of olfactory groove meningiomas or other tumors extending into the prechiasmal region, but in neuro-ophthalmologic practice, anosmia most often follows severance of the olfactory nerves during surgical exploration of the region of the optic chiasm. Anosmia may result from severe head trauma in the syndrome of anosmia-agnosia or, more rarely, from tumors that invade the orbit.

Trigeminal nerve symptoms or dysfunctions are frequently important. The onset and severity of anesthesia or pain of the head or face should be explored. The patient may not be aware of corneal anesthesia, but may have blurred vision from minor corneal abrasions. Alternatively, the patient may complain of a red eye and conjunctival discharge, unaware that the cornea is being injured. Numbness and paresthesia occur more frequently than pain when the preganglionic portion of the trigeminal nerve is involved at the superior orbital fissure, the cavernous sinus, or Meckel’s cave. Herpes zoster is the most common disorder of the gasserian ganglion, and you should inquire whether the patient has had the characteristic vesicular rash.

Pain occurring when the eyes are moved is often associated with idiopathic or demyelinating types of optic neuritis, but you should be aware that inflammation of the ethmoid or other sinuses may also be associated with pain during ocular movements. In about 20% of cadavers, the ethmoid sinus mucosa is in direct contact with the dura of the optic nerve, so that impaired vision and painful ocular movements may occur for more than one reason.

The electric shock-like pain of trigeminal neuralgia usually results from vascular compression in the root entry zone at the lateral border of the pons. More rarely, it occurs from primary demyelinating disease or tumors in this region. Trigeminal neuralgia in young women is more likely to be the result of multiple sclerosis than a premature presentation of the idiopathic variety. Pain that is not typical for tic douloureux or that cannot be ascribed to an obvious peripheral cause should be described as “atypical facial neuralgia,” with the implication that repeated examinations may be required to exclude tumors invading the skull.

It is also important to remember that the first division of the trigeminal nerve projects centrally to the second or possibly lower cervical levels through its descending tract.
and nucleus, so that misreferral of pain can extend anywhere from the neck to the eye. Irritation of sensory nerve roots in the neck can cause eye pain. Pain from intracranial vascular structures can also be referred to the eye. Common problems causing misreferral of pain to the eye are greater occipital neuralgia, intracranial tumors, temporomandibular joint and myofacial pain syndromes, and diseases of the paranasal sinuses. Although photophobia usually results from corneal irritation, it may result from stimulation anywhere within the trigeminal distribution, particularly the nasal mucosa and the dura in the parasellar region. The greater occipital nerve (derived from the second cervical level) can become a source of neuralgia that is frequently detected by getting the patient to point with one finger to the location of the pain. The patient makes a sweeping motion from the lateral portion of the orbit backward along the parietal bone. The patient may not connect the motion to the occipital bone, so that you will have to demonstrate the local sensitivity during the physical examination. Disease of the motor branch of the nerve can result in difficulty chewing. Myofacial pain syndrome is a benign problem related to chewing. Temporomandibular joint pain is often referred to the lower portion of the orbit.

The facial nerve may give rise to numerous ocular symptoms because of impaired closure of the eyelids. The history should focus on the onset of the facial palsy, the amount of any previous recovery of function, and the degree of further recovery that is anticipated. For example, surgery for an acoustic neuroma may traumatize but not sever the facial nerve, so that the neurosurgeon may have told the patient that further recovery is expected. This information could alter your treatment. When involvement of the more proximal regions of the facial nerve is suspected, you might also ask whether sounds are abnormally loud in one ear (stapediaus nerve paresis) or whether tear production is deficient in one eye (greater superficial petrosal nerve paresis). The combination of trigeminal and facial nerve dysfunction is particularly dangerous for the cornea and may cause you to follow the patient more closely.

Depending on the patient’s complaints, you may wish to ask about excessive and episodic closure of the eyelids as occurs in benign essential blepharospasm, which is usually bilateral, or in hemifacial spasm, which is usually unilateral. In blepharospasm, you will wish to know whether only the eyelids or more of the face is involved. In hemifacial spasm, you need to find out whether there is weakness, usually of the lower facial muscles, that interferes with smiling, chewing, kissing, or whistling.

Sometimes benign essential blepharospasm has an asymmetric onset with greater involvement of one side of the face. Conversely, patients with hemifacial spasm may sympathetically blink the opposite eye. In circumstances where it is difficult to distinguish these two conditions, it is useful to observe the mentalis muscle carefully, which is frequently involved in hemifacial spasm but almost never in essential blepharospasm. Hemifacial spasm continues during sleep in contrast to the movement of benign essential blepharospasm. Observations from a bed partner can be helpful in making this distinction.

The eighth cranial nerve is composed of the acoustic and vestibular nerves. Symptoms involving both nerves suggest extraxial problems within the temporal bone or at the pontocerebellar angle. Questions concerning hearing should concentrate on whether any loss is bilateral or unilateral, whether it came on gradually or suddenly, and whether it is progressive. Patients presenting with a complaint of tinnitus (with or without vertigo) are not common in neuroophthalmology because these patients usually enter the health care system at other points.

If patients have vertigo, you should determine whether it is postural (resulting from standing) or positional (resulting from a change in head position). Ask whether the vertigo persists or quickly fatigues. In neurologic patients with unexplained blurred
vision, you may wish to ask questions directed toward an overactive vestibulo-ocular reflex. Patients with this problem may note that their vision is blurrier in a moving automobile than in a stationary one. Moreover, these patients find that they can read the labels of goods on the shelves of a grocery store much better when they stand still than when they are walking.

The caudal cranial nerves and bulbar muscles can be considered as a group. Questions concerning taste sensation have a disappointing yield, but questions concerning chewing and swallowing can be rewarding. Patients with bulbar myopathies and neuropathies often report that attempts to swallow liquids may result in water coming out of the nose. Alternatively, patients may report that solid foods such as meat or a toasted peanut butter sandwich cannot be swallowed without additional liquids. The patient is not usually a good source of information about the volume and quality of his or her speech, and these questions are best addressed to family members. When blepharospasm is a part of a facial dystonia the voice can become very hoarse or windy due to spasm of the vocal cord adductors or abductors.

**REVIEW OF GENERAL NEUROLOGIC SYMPTOMS**

After reviewing the cranial nerve symptoms, you should review the sensory, motor, and autonomic symptoms. Questions about sensory symptoms seek to reveal numbness and paresthesia that may have been forgotten because of their lack of prominence compared with other complaints, as well as current dysfunction. If positive answers are obtained, then try to localize the symptom to the peripheral nerves, a spinal cord level, or a more rostral location. Ask the patient whether there is any focal or generalized weakness. Occasionally, you will want to ask about involuntary movements, myotonia, or fasciculations. More frequently, you will want to ask about incoordination or difficulty with gait or balance. Urinary incontinence was mentioned earlier as a frequent sign of multiple sclerosis, although it may occur in a wide variety of neurologic disorders such as normal pressure hydrocephalus. Changes in menses and in sexual drive and performance should be considered because of the close proximity of the neuroendocrine structures to the optic nerves, chiasm, and tracts.

**NEUROLOGIC AND PSYCHIATRIC SYMPTOM COMPLEXES**

The neurologic history may conclude with a review of neurologic and psychiatric symptom complexes such as pain, headache, seizures, and abnormalities of mental function. You may already have formed an opinion about the patient's memory, intelligence, and affect. If not, you may wish to explore these subjects further by asking questions about falling performance in school, in business, or in homemaking. You will probably have to initiate questions concerning illusions, hallucinations, metamorphopsia, and other complex visual problems. Patients are embarrassed to bring these topics up and may fail to do so. We have seen patients with Alzheimer's disease who have enough insight to recognize that people will think that they are mentally ill if they reveal the chaotic visual world they are experiencing.

**Prior Medical History**

The prior medical history is reviewed in the usual manner, but you need to guard against the possibility that the patient is editing the history to omit information such as the previous removal of a tumor of the lung, breast, or prostate. The general review of symptoms is routine except that you may concentrate on the symptoms of any particular diagnosis or syndrome that have come into consideration.

**Family History**

Frequently, the family history is not productive and can be confusing; for example,
many persons have a positive family history of migraine. When the family history is positive, however, it can help to make the diagnosis and define the prognosis. At a minimum, you should ascertain that the patient's parents are not related except by marriage and that no other person in the family has a similar illness. Frequently, you may need to contact the physicians caring for other family members, but it is best to examine the family yourself. You can often obtain a dilated fundus examination of the parents who have brought a child to your office. Ethnic history also can be valuable, as some disorders are concentrated in certain ethnic groups (e.g., progressive oculopharyngeal muscular dystrophy in families of French-Canadian background).

Social and Occupational History

A patient's habitual use of alcohol can give rise to alcoholic optic neuropathy, cranial nerve palsies, nystagmus, and Wernicke's encephalopathy. We have found that it is well to overestimate the amount of alcohol that the patient may consume and use that as a basis for questioning (e.g., “Do you buy more than one bottle of whiskey a week?”). A spouse may be helpful in confirming the patient's alcohol use, unless they drink in excess together. The interviewing technique called the "CAGE questions" are many times more sensitive than the best laboratory tests in the detection of chronic alcoholism. The questions are arranged in the following order to permit the use of the mnemonic CAGE. Have you (a) felt the need (b) cut down drinking; (c) ever felt annoyed by criticism of drinking; (d) have a guity feeling about drinking; (e) ever taken a morning eye-opener? You should record the amount of tobacco use, although the role of tobacco in tobacco-alcohol optic neuropathy is controversial. In considering the toxic-metabolic causes of neuro-ophthalmic disorders, it may be necessary to ask about the possibility of vitamin deficiency resulting from prior surgery or other disorders of the upper gastrointestinal tract. So-called recreational drugs may become a source of ocular problems when they are taken intravenously.

Acquired immune deficiency syndrome (AIDS), its precursor human immune deficiency virus (HIV) infection, and its sequelae including intraocular cytomegalovirus (CMV) infection have created an epidemic affecting the entire society. The medical and social history should include questions that relate to HIV exposure and prior testing. The physician must be aware that AIDS can coexist with and reactivate other neuro-ophthalmologic disorders such as syphilis.

The social history needs to include questions related to geographic exposures to disease. For persons living within the United States, it may be appropriate to ask questions relating to Lyme disease and coccidioidomycosis. It also is useful to determine whether national origin or travel experiences may have resulted in unconsidered exposures to other parasitic or infectious diseases.

NONOCULAR ASPECTS OF THE PHYSICAL EXAMINATION

Examination of the Head, Face, and Neck

You will find it useful to have a system for examining the head, face, and neck. Observation may be all that is necessary, although palpation and auscultation may also be required. As you begin observation, be certain that you have considered all of the devices used to hide the true condition of the head. Caps must be removed. Wigs may hide alopecia, surgical scars, abnormal skin, nevi, and inflamed temporal arteries. Hair dyes or tints may mask a white forelock. Cosmetics may cover the butterfly rash of the collagen vascular diseases or the port-wine stain of Sturge-Weber syndrome. The vessels giving rise to the port-wine stain of Sturge-Weber
syndrome are now being obliterated by laser, thus making diagnosis more difficult. In tuberous sclerosis, cosmetics may cover flat depigmented spots or elevated lesions such as the more common erythematous angiofibromas and the less common maculopapular fibromas. Lipstick may disguise the signs of Sturge-Weber syndrome, Osler-Weber-Rendu syndrome, and neurofibromatosis. Unopened lips may cover what would otherwise be obvious findings of the buccal surface, gums, teeth, and tongue in a number of neuro-opthalmologic disorders. A high collar may hide a thickened sternocleidomastoid, which turns the head in torticollis, or an overacting trapezius muscle, which may tilt the head in dystonia. A long neck has been noted in mental retardation syndromes, a short neck occurs as a result of malformation of the cervical vertebrae, and a webbed neck is a characteristic of Turner syndrome. A simple necklace may mask the scar of thyroid surgery or a scar that would explain Horner syndrome. Also look for scars where tags of skin may have been removed from the external ear.

The shape and symmetry of the head can be noted, particularly with regard to the vertical midfacial line. The other important vertical lines are those through the medial and lateral canthi. The medial intercanthal distance is normally one-third of the lateral intercanthal distance. If it varies from this, hypertelorism or hypotelorism may be present and associated with a neurologic syndrome. The distance between the medial and lateral canthi is short in fetal alcohol syndrome.

Traditionally, the face has been divided into three segments by horizontal lines at the level of the medial canthi and by diagonal lines passing from the corners of the mouth to the aural points where the most anterior portion of the upper ear connects with the face. The upper segment includes the cranium, and the lower segment includes the face. With the recent emphasis on the embryology of the neural crest-derived mesoderm, some authorities now describe the face as developing in two portions: a medial portion derived from the frontonasal process and a lateral portion derived from the branchial clefts. The medial aspects of the orbits and nose and the central portion of the upper lip arise from the neural crest.

Abnormalities of the configuration of the cranial vault can result from primary or secondary suture abnormalities. Increased intracranial pressure is the major cause of visual loss in such patients. Microcephaly and macrocephaly are recognized first by measuring the skull circumference. In the infant referred for apparent blindness, simple transillumination of the skull in a darkened room may diagnose loss of substance as occurs in hydranencephaly or congenital occlusion of the middle cerebral arteries.

Excessive amounts of hair in the eyebrows, synophrys, and excessive frontal hair are seen in infants with chromosomal and metabolic disorders. Premature frontal balding occurs in myotonic dystrophy.

The eyes, nose, and ears are the major features of the middle face. The tilt of the lid fissures is controlled by the relative growth of the first branchial arch laterally to the frontonasal process medially. Thus, the A-shaped tilt or antimongoloid slant of the eyelids frequently occurs when development of the first branchial arch is defective.

Proptosis may be bilateral or unilateral and is measured with an exophthalmometer. Enophthalmos is usually unilateral. Sometimes, an abnormally large or small globe can simulate proptosis or enophthalmos. One clue to this may be the diameter of the cornea or a high refractive error. Ultrasonography can measure the axial length of the globe without radiation to the patient. Palpation of the orbit may reveal tenderness, bony depressions, masses, crepitus, or pulsation. Palpation lateral to the orbit can be used to recognize enlarged preauricular nodes or salivary glands.

Abnormalities (particularly widening) of the proximal portion of the nose are associated with many important neuro-opthalmologic diagnoses. You may conclude that the ears are low set if the aural points are below a line through the medial canthi and if the lowest aspects of the ear are below the bot-
tom of the nose when the patient is viewed from the front. Such patients are likely to have developmental abnormalities of the first branchial arch. Large ear lobules occur in the mucopolysaccharidoses.

Abnormalities of the lip and palate are the most important congenital abnormalities of the lower facial segment. Their association with severe neurologic abnormalities, such as optic nerve hypoplasia, is greatest if the nose is also involved and least if there is a small midline defect. Tenting of the upper lip occurs in longstanding bilateral facial weakness, as in Möbius syndrome, and pursed lips occur in myotonic dystrophy, perhaps as an effort to keep the mouth closed. The suggested readings include several sources that are useful for identifying specific syndromes of the head, face, and mouth.

The neck may be inspected and palpated for evidence of enlargement of the thyroid gland and lymph nodes or for other abnormalities.

Auscultation of the carotid arteries or of the head may be performed. When you attempt to confirm the presence of a bruit, it is best to have the patient assume the position in which he or she hears it. To avoid the artifact induced by movement of the eyes or eyelids, have the patient close both eyes, place the bell of the stethoscope gently over one eye, and then have the patient open the other eye. You will then be able to recognize when eye movement occurs.

**Examination of the “Other” Cranial Nerves**

It is difficult to make a strict division between the ophthalmologic and nonophthalmologic portion of the neuro-opthalmologic examination; however, it is helpful to list those aspects that may not be covered in the routine ophthalmologic examination. For example, I find it convenient to keep a packet of instant coffee in my “neurology drawer.” It can easily be brought out, smelled, and replaced.

If your office routine calls for most return patients to have their vision and intraocular pressure measured before “routine” dilatation of the pupil, you will have to make allowances for the neuro-opthalmologic examination. The pupils should be checked for a relative afferent pupillary defect; accommodation and near visual acuity may need to be determined, and corneal sensation must be determined; and corneal sensation must be tested before mydriatic, cycloplegic, and anesthetic solutions are instilled.

**TRIGEMINAL NERVE.** An esthesiometer is rarely required for quantitative testing of the corneal reflex. What is most important is avoiding a response to threat rather than to corneal pain. First, place the cotton fiber on the perilimbal conjunctiva, and then drag it across the limbus. The nasal response to a tickle with a cotton swab is a useful way to confirm asymmetry of trigeminal nerve function. Unilateral depression of the nasolacrimal reflex has been reported to be the only physical sign in some cases of meningioma of the temporal fossa.

Each of the three divisions of the trigeminal nerve is tested for pin and touch, and the responses are recorded, if necessary, on a diagram of the face. It is sometimes useful to test for sensation of the infraorbital nerve by lifting the lip and touching the gingiva above the canine tooth with the broken wooden portion of a cotton-tip applicator. This will also allow you to identify and get above the margin of any dentures the patient may have. I find it much easier to confirm anesthesia here than on a swollen lip in a patient who has sustained an orbital floor fracture and other facial trauma. Although the corneomandibular reflex may occur in 10% of normal subjects, patients with supranuclear paralysis of the trigeminal nerves may have a brisk corneomandibular reflex of movement of the mandible away from the side of stimulation.

Chronic unilateral peripheral trigeminal denervation causes atrophy of the temporalis muscle, thus flattening the contour of one side of the face above and below the zygomatic arch. Acute unilateral motor paralysis can be detected by deviation of the jaw to-
ward the paralyzed side. Myotonic dystrophy causes bilateral atrophy of the temporalis muscle. Patients whose myotonic dystrophy has progressed to the point that they have symmetric cataracts usually also have recurrent paretic dislocation of the jaw; when these patients speak, they do so with one hand under their jaw, ready to replace it.

Electrophysiologic testing of the blink reflex is rarely indicated. Exceptions may include the need to confirm subjective anesthesia or to decide whether a problem is inside or outside of the brainstem (intraxial or extraxial). The test is performed by recording the electromyogram bilaterally from the orbicularis oculi muscles, following a unilateral stimulus given alternately to each side of the face. Normally, there will be an early monosynaptic ipsilateral reflex and a late polysynaptic bilateral reflex.

**Facial Nerve.** The function of the facial nerve fibers distal to the stylomastoid foramen can be determined by inspection. While taking the history, you can observe the functions of the superior and inferior groups of the facial muscles. The superior group is involved in movements of the eyebrows, forehead, scalp, and ears, whereas the inferior group is involved in smiling and other movements of the lips. Flattening of the nasolabial fold is characteristic of facial nerve weakness. The intermediate group of muscles that are responsible for tightly squeezing the eyelids must be specifically tested in the awake patient. With tight squeezing, the bases of the eyelashes should become hidden or "buried." The patient should be able to overcome the examiner's gentle effort to force the lids open. If one of the groups appears weak, you should compare the relative strength of all three groups on both the ipsilateral and contralateral sides of the face. The patient should then be asked to elevate the eyebrows, to wrinkle the nose, to show the teeth, and to whistle. In some patients with impaired cerebral functions, you may need to look for an infranuclear paresis by using a glabellar tap to test the orbicularis oculi reflex. Supranuclear palsies may dissociate the voluntary from the involuntary action of the facial muscles; thus, the nasolabial fold may be flat except when the patient is induced to smile.

Localization and electrophysiologic studies are important in the management of an idiopathic, total, or progressive Bell's palsy. Three tests can localize the problem satisfactorily in most cases. A Schürer's test revealing a unilateral absence of reflex tear production localizes lesions proximal to the geniculate ganglion, because the greater superficial petrosal nerve leaves the facial nerve at the ganglion. Crocodile tears or gustatory lacrimation results from misregeneration of the facial nerve following proximal lesions.

The second test for facial nerve function, the stapedius reflex, is used to test the function of the stapedius nerve, which arises just distal to the junction of the horizontal and top of the vertical portion of the facial canal. In this procedure, fluid is placed in the ear and the pressure is measured with a tympanometer. A loud noise is then made to provoke the stapedius reflex, and the small movement of the tympanic membrane results in a change in the pressure recorded by the tympanometer. If the stapedius reflex persists, the problem is distal to the pyramidal eminence of the mastoid bone. The clinical symptom of an absent stapedius reflex is the impression that sounds are too loud on the affected side.

The third test for facial nerve function is electrophysiologic. It involves bipolar stimulation of the facial nerve at the stylomastoid foramen. If the threshold for muscle contraction is 3.5 mA higher on the side of the facial palsy than on the opposite side, surgical decompression of the facial canal is often performed. Usually, the loss of responsiveness to electrical testing for more than 48 hours makes it unlikely that there will be a complete recovery of function without synkinesis. Unless contraindicated, steroids are generally used in the patients with Bell's palsy who do not require surgical decompression.

One can test the function of the chorda tympani nerve to reveal the status of the fa-
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cial nerve in about the middle of the vertical portion of the facial canal. Because this test is subjective, it is not as frequently used as the tests listed above. This nerve provides taste sensation to the anterior two-thirds of the tongue. Cannulation of the ducts from the submandibular glands can be used to compare the reflex secretion of each side following stimulation with lemon juice.

Pain and sensory loss may accompany facial paralysis from all causes. It is important to remember that tumors invading the base of the skull can involve the cranial nerves. The cutaneous distribution of the sensory fibers of the facial nerve is represented by the Ramsay Hunt syndrome of geniculate herpes zoster. The vesicles may appear within and behind the opening of the external auditory canal on the external ear. They may also be seen on the tympanic membrane and on a small patch of skin above the tip of the mastoid.

Chronic, recurrent, unilateral or bilateral swelling of the face and facial palsy occur in an idiopathic condition known as Meltzerma syncope.

Observation of abnormal movements in the distribution of the facial nerve reveals several patterns. The most frequent and least troublesome is known as benign facial myokymia. It tends to occur when a person is tired and primarily involves the eyelids. Occasionally, waves of incoordinated contractions are seen passing over the face in a more serious facial myokymia associated with pontine disorders. In recent years, it has been shown that hemifacial spasm is frequently caused by compression of the proximal portions of the facial nerve by vascular loops, particularly of the anterior inferior cerebellar artery. This produces progressive weakness of the facial nerve together with the episodic spasm. In advanced cases, the patient cannot keep food out of the buccal region and cannot whistle or kiss. Benign essential blepharospasm and its more severe counterpart involving the entire face, the Brenigg syndrome, seem to be caused by disorders of the basal ganglia and are similar to drug-induced tardive dyskinesia. There is increased interest in these disorders, partially resulting from improvements in medical and surgical therapy. Injection of botulinum A toxin into the eyelids produces temporary chemodenervation lasting about 3 months. Orbicularis myectomy removes most of the offending orbicularis oculi muscle.

**VESTIBULOCOUSTIC NERVE.** The vestibulocoustic nerve has two divisions, which share the proximal portion of the internal auditory canal with the facial nerve. Thus, any patient with facial nerve findings should at least have a minimal examination of hearing function and at most have formal audiology and electronystagmography.

**Hearing.** Hearing is more easily examined than vestibular function. A tuning fork is used to determine whether the patient has equal hearing in each ear. The C tuning fork is used. It is preferable to use a 512-Hz tuning fork rather than a 256-Hz tuning fork, which can be felt to vibrate as well as be heard. The Weber test is used to determine whether one ear has impaired bone conduction from the tympanic membrane to the cochlea or whether one ear has impaired perception owing to abnormalities of cochlear apparatus and nerve. The vibrating tuning fork is placed in the center of the forehead, and the patient indicates the ear that hears best. The louder sound is heard on the affected side in conductive deafness and on the unaffected side in perceptive deafness. In the Rinne test, the vibrating tuning fork is placed against the mastoid process until the patient no longer hears it; it is then placed in air near the ear, where it should be heard about twice as long, unless the patient has conductive deafness. Other tests of hearing require an audiologist.

**Vestibular Function.** Vestibular function testing is performed for various purposes. For example, caloric stimulation can be used to demonstrate unilateral vestibular nerve dysfunction, assuming that the brainstem and ocular motor system are intact, or to demonstrate brainstem function, assuming the vestibular nerve is intact. The details of these tests are not described here except to point out that irritation of the external audi-
otory canal in a patient with a basilar skull fracture and blood in the canal may contribute to intracranial infection. Irrigation should not be performed when there is a defect in the tympanic membrane.

The other tests of vestibulo-ocular function that I perform most often are (a) observation of spontaneous nystagmus with Frenzel (+30 diopter) spectacles; (b) determination of whether the patient can use the smooth pursuit system to visually suppress the vestibulo-ocular reflex; and (c) demonstration of positional and postural nystagmus. Frenzel lenses are used primarily when nystagmus is suspected but cannot be observed owing to visual suppression. The ophthalmoscope is an alternative way to observe spontaneous nystagmus. The examiner focuses light on the optic disc and has the patient use the opposite eye to look at a target. The opposite eye is then covered, and the spontaneous movements of the first eye can be observed as magnified by the ophthalmoscope.

The vestibulo-ocular reflex is tested by placing the patient in an examining chair that can rotate in a wheel chair. A fixation target is suspended about 25 cm in front of the patient’s eyes and arranged so that it will rotate with the patient’s head. A metal coat hanger may be compressed so that it will fit around the head, and a piece of tape placed over the hook which is bent at right angles to its usual position. The tape makes the wire of the tip thick enough to constitute an easily seen target. The vestibulo-ocular reflex is induced by rotating the patient about 30° to one side, waiting at least 5 seconds, and then rotating the patient in the opposite direction. The patient should be able to keep his or her eyes on the target. If there were no target moving with the head and the vestibulo-ocular reflex (VOR) gain were normal, the eyes would move an equal amount opposite to the direction of the head movement. Disorders of the vestibulocerebellar connections increase VOR gain in the horizontal plane whereas disorders of the midbrain horizontal tectum decrease VOR gain in the vertical plane. Thus, a patient who shakes his or her head faster than once per second while attempting to read a near vision chart may lose several lines of acuity. This test must be done with both horizontal and vertical head shaking. It requires an electronystagmography laboratory to measure VOR gain, but the two tests described can tell whether vision stimuli can cancel out the gain.

Positional nystagmus is tested using the Bannay-Nylen maneuver, having the patient sitting on an examining table. The head is turned 45° toward the right shoulder and rapidly guided over the edge of the table so that the head hangs at a 45° angle from the table and the eyes are observed. Frenzel lenses may be used. Nystagmus may appear after a 10-second latent period. While the patient gazes toward the downturned ear, predominantly rotary eye movements result; while the patient gazes toward the upturned ear, predominantly vertical movements occur. Repeated testing usually fatigues the nystagmus in benign paroxysmal positional vertigo, which seems to be caused by dysfunction of the posterior semicircular canal. Failure to fatigue may indicate a posterior fossa lesion. The test must also be performed with the head turned left. Postural nystagmus may be observed when the patient suddenly rises from a reclining position to a sitting or standing position.

Bony fistulas of the semicircular canals can produce ocular motor symptoms. The response to auditory stimuli is known as Tullio’s phenomenon, the response to air pressure is known as Hennebert’s sign.

Tests of vestibulospinal function may also test the cerebellar systems and the spinal tracts. The tests I perform conveniently in an office setting include (a) the Romberg test (performed with the shoes off, feet together, and the eyes closed), (b) walking toward a target (for convenience, I follow this with the tandem walk test), and (c) a past pointing test. The past pointing test consists of requesting that the patient’s finger be repeatedly moved between the examiner’s finger and the patient’s nose. The examiner’s finger is kept at arm’s length and is moved into each direction of gaze.
CAUDAL CRANIAL NERVES. The neuro-ophtalmologic examination may include an assessment of the caudal cranial nerves. It is not practical to test taste sensation on the posterior third of the tongue. The pharyngeal motor functions of the glossopharyngeal and vagus nerves are tested primarily by observing for deviation of the uvula to one side while the patient attempts to say "th" or by demonstrating loss of the gag reflex. Bilateral vagal paralysis is accompanied by loss of speech and difficulty swallowing. The distinction between a bulbar (infranuclear) palsy and a pseudobulbar (supranuclear) palsy is made on the basis of the absence or presence of a gag reflex.

The laryngeal function of the vagus nerve is best demonstrated by direct laryngoscopy, which should be performed if the patient is house. The somatic sensory function of the vagus nerve is limited to a small portion of the external auditory canal and auricular concha. Loss of vagus function may cause a tachycardia not responsive to carotid sinus compression or the oculocardiac reflex.

The accessory nerve supplies both the sternocleidomastoid and the upper portion of the trapezius muscles. Both muscles are affected by lesions at the jugular foramen, but the most common injuries to the nerve occur more distally and spare the sternocleidomastoid.

The hypoglossal nerves supply the tongue muscles. Obvious atrophy of one side of the tongue follows hypoglossal-facial anastomoses. More subtle bilateral involvements occur in disorders of the cranial base or in myringobulbia.

Examination of Sensation

A basic examination of touch, pin, and vibratory sensations can be performed while the patient has the shoes and stockings removed. Graefestesia can also be tested.

Examination of Mental Functions

Toward the completion of the examination, you should have a good grasp of the patient's mental function and should record any abnormalities. Formal testing of orientation, memory, or ability to calculate is rarely needed. You may want to ask again about recurrent ideas or abnormal sensory experiences.

General Observations

Although you may decide to refer the patient for a "complete physical examination," you may wish to pursue a few leads selectively at this time. I have found that some of the most rewarding efforts include (a) looking at prior photographs of the patient, (b) completely undressing infants to look for other congenital abnormalities, (c) examining the skin and nails, (d) listening for cardiac murmurs, and (e) observing the patient suspected of malingering after he or she believes that the examination is completed.

Examination of Muscles, Motor Functions, and Reflexes

It is not my goal in this chapter to describe a complete neurologic examination, but to describe what I actually do with some patients. If I am concerned about a myopathy, I will look carefully at the gag reflex for loss of function of the pharyngeal muscles. There may be a droopy appearance without sharp angles at the pharyngeal pillars. I would then look for weakness of the neck and proximal muscles of the arms and legs. The hands are inspected for atrophy and tested for strength. If myotonic dystrophy is suspected, you will want to test for percussion myotonia of the thenar eminence. The calves and the feet can be inspected while examining the deep tendon reflexes. The plantar reflex is examined and recorded. The heel-shin test of coordination may be conveniently performed at this point. The examination is adjusted and motor milestones recorded if the patient is an infant.
SUGGESTED READINGS
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Recog...
Papilledema

Thomas J. Walsh

Recognition of papilledema as a sign of increased intracranial pressure awaited the invention of the ophthalmoscope by Hermann von Helmholtz and the fundus observations of Albrecht von Graefe. Although the luminescence of the pupils of certain animals was noted as early as Roman times, the first direct observation of the optic nerve and retinal vessels was not reported in the medical literature until 1704. This was accomplished by Jean Mery when he held a cat under water until the anoxia dilated the pupil of the cat; the optical effect created by the water unexpectedly revealed the optic nerve and retinal vessels. This experiment, obviously, could not be performed on humans; demonstration of the luminescent quality of human eyes was finally achieved in 1846 by William Cummings.

The first primitive ophthalmoscope was developed in 1847 by Charles Babbage, who did not grasp its clinical significance. Babbage's paper describing his work, "About the Light of the Eyes," was read by a friend, DuBois Raymond, on December 6, 1850, before the German Physical Society. The only written report on Babbage's discovery was in 1854 by an English ophthalmologist, who discouraged him from continuing his work.

The importance of this discovery, however, did not escape von Helmholtz, then a young professor, who developed the first clinically practical ophthalmoscope in 1851.

During the next decade, many reports of retinal signs were published. In 1860 von Graefe reported his observations in four patients with brain tumor and a swelling of the optic nerve head; he called the observation stauungspapille. Parsons coined the English term papilledema in 1906. Von Graefe's conclusion about what he saw was correct. It was indeed fortunate for all of ophthalmology that all four cases reported by von Graefe were brain tumors. He did not recognize in his first report the broad differential diagnosis of a swollen nerve head. It remained for Paton and Holmes in their paper in 1911 to differentiate between papilledema with increased intracranial pressure and optic neuritis. Their basic differentiation was based on visual function. Edema of the nerve head with decreased vision was considered optic neuritis; edema of the nerve head without decreased vision was papilledema secondary to increased intracranial pressure. As experience has taught us, decreased vision also occurs as a result of chronic papilledema secondary to increased intracranial pressure and subsequent optic nerve atrophy.

After the initial observations of those early pioneers, the use of the retinal examination spread rapidly in all branches of medicine. Hughlings Jackson said, "I think it is the luckiest thing in my medical life, that I began the scientific study of my profession in an ophthalmic hospital." In his lectures, Charcot often referred to the use of the ophthalmoscope. "Gentlemen," he once said, "I could not too strongly recommend to you to seek in the application of the Helmholtz mirror the invaluable assistance which it is capable of yielding."
PATHOPHYSIOLOGY

It has been said that many things will be constantly rediscovered in medicine if we do not read the old literature. In the words of Celsius, "Though we should not refuse to give modern authors due credit for their discoveries and happy imitations, it is none-the-less just to restore to the ancients what properly belongs to them." Von Graefe interpreted the optic nerve swelling as a result of intracranial pressure on the intracranial vascular structures, such as the cavernous sinus. This would result in fluid stasis in the eye, which he termed stauungspapille. His particular interpretation does not fit the facts we know today. For example, obstruction of the cavernous sinus does not always lead to signs in the fundus, and obstruction of the venous return from the eye into the intracranial vault via the cavernous sinus may produce a picture of decreased venous flow and increased venous tortuosity but not frank papilledema. Nonetheless, von Graefe's explanation has some merit, and many subsequent investigators have offered variations on it.

After the discovery by Schwalbe of the perineural space and its relationship to the subarachnoid space, it was proposed that optic disc edema was in reality subarachnoid fluid. According to this explanation, increased intracranial pressure forced subarachnoid fluid out into the lower-pressure perineural space and intracocular nerve. We know from further anatomic studies that this is not correct.

Hayreh found that merely decompressing the optic nerve would reduce the disc edema even when the intracranial pressure was not reduced. This observation suggested that the intracranial pressure rather than the subarachnoid fluid was transmitted. This pressure in turn caused some effect on structures in the nerve and at the nerve head, resulting in a blockage of fluid.

Weiss and Hiscott brought to our attention the flow of subcellular and molecular particles along the axons of the nerves that is now widely recognized as axoplasmic flow.

Further refinement of the components of this flow have been outlined by Lasel, Watson, and others. We now know that at least three types of axoplasmic flow exist; these occur simultaneously and somewhat independently and are affected by different pathologic processes.

The electron microscopic findings of papilledema vary depending on the locations within the optic nerve head. The specific location for the accumulation of axoplasm is the lamina retinalis and peripapillary retina. However, in these first two areas of the lamina choroidalis and scleralis there is no axonal swelling, probably because of the rigid nature of the connective tissue in these locations.

One component of axoplasmic flow is an orthograde rapid flow, which moves along the axon at a rate of 200 to 1000 mm/day and is thought to serve synaptic transmission. The second component is an orthograde slow flow, which moves at 0.5 to 3 mm/day. Its function is to maintain the growth and metabolic stability of the axon. The third component of axoplasmic flow is a retrograde flow that moves at 50 to 75 mm/day. This component allows the axon to sample its environment and send information back to the cell body.

Different mechanisms of insult differentially affect the axoplasmic flow components. Ischemia predominantly blocks rapid axoplasmic flow, whereas compression of an axon blocks slow axoplasmic flow. The former situation occurs in anterior ischemic optic neuropathy, and the latter in increased intracranial pressure. Whether the rapid component is also affected by increased intracranial pressure has not been resolved.

The axoplasmic flow theory fits another observed fact of increased intracranial pressure. In such disorders as Foster Kennedy syndrome, the atrophic nerve does not swell, while the other nerve is grossly swollen from increased intracranial pressure. It seems logical that an atrophic nerve would have no axon left and thus no axoplasmic flow. Therefore, the increased intracranial pressure could not obstruct what is not flowing.
In the past, routine microscopic examination of the edematous optic nerve head revealed interstitial fluid. Axonal swelling was also described, and it was felt that this resulted from absorption of the interstitial fluid. Recent electron microscopic studies have revealed that this swelling is really an obstruction of axoplasmic flow and not vascular obstruction as envisioned by von Graefe.

That movement of certain particles in the axon is restricted to specific components of axoplasmic flow was established by the use of radioactively labeled proteins that move with either orthograde slow, orthograde fast, or the retrograde flow component. Tritiated leucine is used as a tracer of the slow component and orthograde rapid component. Electron microscopic studies by Anderson and Hendrickson of optic nerve heads swollen secondary to increased intracranial pressure revealed an accumulation of mitochondria, an important component of axoplasm, in the axon. They also demonstrated that tritiated leucine accumulates at the nerve head in papilledema secondary to increased intracranial pressure. This finding suggests that the slow component of axoplasmic flow is obstructed.

Obstruction of axoplasmic flow may be accomplished by hypoxia, ischemia, constriction, and the injection of local drugs such as local anesthetics. Neuroleptic drugs (e.g., chlorpromazine) increase the rate of axoplasmic flow. When an axon is severed, axoplasmic flow continues for a while in both segments, with a buildup of axoplasm at both ends. Different types of injury to the axon impede the different components of axoplasmic flow at different rates. It now seems certain that increased intracranial pressure impedes the orthograde slow component most of all, whereas ischemic processes impede the rapid component. Whether these two mechanisms of impeding a particular axoplasmic flow have some influence on the other components is not completely settled.

Ischemic changes in the retinal nerve fiber layer that disrupt axoplasmic flow create a backup of axoplasm. When this occurs, we can see ophthalmoscopically cotton-wool spots that represent a collection of mitochondria. If there is only mild ischemia without death of axons, then we see the appearance of retinal edema and not the white cotton-wool spots. McLeod and colleagues demonstrated this by laser coagulation studies. This information has been used to distinguish ischemic papillitis from papilledema secondary to increased intracranial pressure. Not only is the clinical appearance of the nerve head different in the two conditions but so is the electron microscopic picture with degenerated axons and the radioactive tracer element studies.

Slow transport is impaired but not completely blocked in both papilledema and hypotony. Some of the slow axoplasmic flow component progresses in the orbital and intracranial optic nerve. In these same experiments, some obstruction of rapid axoplasmic flow occasionally occurs. Anderson has suggested that the swelling of axons from impairment of slow transport causes disruption of axons similar to that found in an ischemic situation and this results in some rapid flow obstruction.

The status of optic nerve function should be considered in evaluating the types of axoplasmic flow obstruction in different clinical situations. The general clinical rule of thumb is that optic disc swelling with good visual function is papilledema secondary to increased intracranial pressure, whereas optic disc swelling with loss of vision or field is optic neuritis. Another clinical situation is characterized by very high intraocular pressure and obstruction of rapid axoplasmic flow. This obstruction may result either from an intraocular pressure that is high enough to stop all flow or from the ischemia secondary to the increased intraocular pressure. Whatever the mechanism, the axon no longer receives its nourishment from the rapid axoplasmic flow and dies. The result is loss of neural function, and the eye no longer sees. Since only the slow component is apparently obstructed to any significant degree in increased intracranial pressure, the rapid component must not be significantly
affected, and neural function continues. This is what we see clinically. However, long-standing increased intracranial pressure such as occurs in pseudotumor cerebri not infrequently causes loss of vision if left untreated for a prolonged period of time.

In this chapter, the term papilledema is used to describe disc edema associated with increased intracranial pressure. The term papillitis is used to describe inflammations of the optic nerve associated with a decrease in vision or field. All other swellings of the disc are referred to as disc edema.

Ophthalmologists are frequently asked whether a disc is edematous and, if it is, whether the cause of the edema is increased intracranial pressure. The decision to call a disc edematous is often based on the presence of a combination of signs rather than on any one specific sign. To illustrate, a disc may be blurred (owing to drusen) and have a flame-shaped hemorrhage associated with it. The association of drusen and hemorrhage is recognized although rare, and a diagnosis of papilledema should not be made merely because hemorrhage is present. Frequently, a disc may be grossly edematous but not because of increased intracranial pressure—hemorrhage and marked nerve-head edema may be seen in cases of severe hypertension or venous occlusive disease.

Thus, the ophthalmologist must first decide whether the signs are of true papilledema or of pseudopapilledema and then whether a diagnostic workup is indicated. If the condition is diagnosed as disc edema, the ophthalmologist must then decide whether it is secondary to increased intracranial pressure or to one of the other conditions that give a similar appearance. This last decision is as important as the first ones, since certain tests are pertinent to specific diagnoses, and mistakes may cause delay in instituting proper treatment or may cause the patient to undergo unnecessary, expensive, or dangerous tests.

Increased intracranial pressure can cause asymmetric or even unilateral papilledema. This has been thought to be due to different degrees of adhesion between the optic nerve and perineural sheath and changes at the lamina cribrosa.

**FUNDUS SIGNS OF PAPILLEDEMA**

**Hyperemia**

Hyperemia is caused by capillary dilatation in the nerve head. The age of the patient must be taken into consideration since the color of the disc varies with age. In the infant, the disc frequently is pale and hyperemia is more easily seen, whereas in the young or middle-aged adult, the disc is frequently pink to hyperemic in appearance. In the person 70 years of age or older, the disc color is more waxy, and hyperemia is more noticeable when it occurs. Hyperopic discs look more hyperemic, whereas myopic discs appear paler, particularly in the temporal sector.

**Venous Distention**

An impression of an increase in diameter of the retinal veins may be spurious. An observer who uses only the arteriovenous ratio as an index is assuming that the arterial size is normal; however, the arteriovenous ratio may be increased because of decreased arterial size, as in hypertension. Venous distention may also be seen in conditions that cause increased venous pressure and slowing or swelling of the blood column. If these signs are present, consideration should be given to the possibility of diabetes, dysproteinemias, glaucoma, or vascular shunts with increased venous pressure, as in carotid cavernous sinus fistula.

Retinal veins may be enlarged because of increased shunting of blood, as in arteriovenous fistula in the orbit or the cavernous sinus. If either type of fistula is present, bruits or pulsations of the globe may be present.
The pulsations of the globe may not be easily seen on external inspection, but they can be readily observed if the fundus is examined with an ophthalmoscope. The subtle pulsation is manifested by a sharpness and then blurring of focus of the retina that is synchronous with the pulse at the wrist.

In diagnosing diabetes as a cause of venous distention, a formal glucose tolerance test must be performed, not just a random blood glucose evaluation. A carotid cavernous sinus fistula has the clinical signs of ocular bruits, pulsations of the globe, ophthalmoplegia, hypalgnesia of the first division of the fifth cranial nerve, and evidence of venous distention of the lids, orbit (exophthalmos), and external surfaces of the globe.

**Filling in of the Optic Cup**

Since the presence or absence of a cup, as well as its size, varies from patient to patient, its absence is difficult to ascribe to edema unless the patient's cup size was determined in a previous examination. The fundus contact lens is of little value in distinguishing between absence of the cup and filling in of the cup by edema.

**Blurring of the Disc Margin**

Blurring of the disc margin is more difficult to detect in the hyperopic eye than in the myopic eye, in which a choroidal pigment line frequently demarcates the disc margin; however, blurring always begins on the nasal margin. If the temporal margin is more blurred, a local process, such as juxtapapillary choroiditis or a tumor, should be suspected. Since the degree of blurring may look much different with the indirect ophthalmoscope than with the direct one, both instruments should be used in the evaluation (Fig. 2.1).

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*Figure 2.1.*

Early papilledema. Notice peripheral elevation of nerve and beginning blurring of disc margins.
Paton's Lines

Recognition of Paton's lines (Plate 2.1A) is difficult only because it is a subtle sign that will probably be missed if the observer does not specifically check for it. It is one of the surest signs of true disc edema. The lines appear only on the temporal side of the disc and are in a vertical direction concentric with the disc. As the disc swells, a slight displacement of the retina away from the temporal edge of the disc occurs, causing the retina to fold back on itself. Folds may be seen at the rim of the disc. Any case of true disc edema should have such folds. Any case of disc edema should be followed for any evidence of such folds. Folds may develop in association with disc edema.

**Plate 2.1**

- **Plate 2.1A**
  Paton's lines. The lines appear as several concentric reflexes seen on the temporal side of the disc and extending considerably above and below it.

- **Plate 2.1B**
  Macular star. This sign denotes longstanding increased intracranial pressure from any cause. (Courtesy of Lee Jampol.)

- **Plate 2.1C**
  Roth's spots. The hemorrhage is flame-shaped owing to its location in the nerve fiber layer, and it has a small white center of malignant or inflammatory cells. (Courtesy of Lee Jampol.)

- **Plate 2.1D**
  Drusen. These excrescences can be seen as isolated refractive bodies in the substance of the disc.
retina to fold on itself, or corrugate. This folding, in turn, causes a variation of the reflection from the internal limiting membrane, which is seen as Paton's lines. As the edema increases, this area becomes edematous and Paton's lines are no longer seen. Any cause of edema can produce Paton's lines, so their presence signifies only edema. They are not seen with such entities as drusen of the nerve head. The appearance of horizontal lines in the macula, on the other hand, signifies tumors of the muscle cone, thyroid disease, or brawny scleritis.

Edema may also spread from the disc along the arcuate fibers, making them more prominent. This appearance is not a clear-cut sign of edema; it may be seen also in cases of mild myelination of the fibers, which is difficult to differentiate from edema.

**Spontaneous Venous Pulse**

Many people do not have a spontaneous venous pulse at times, an absence that is frequently normal. It has been shown experimentally, however, that when the spinal fluid pressure reaches 200 mm of spinal fluid or water, the venous pulse disappears. It has been my experience that this is a reliable sign. Other investigators, such as Williamson-Noble, Hayreh, and Levin, have evaluated this concept and found it to be not only experimentally but clinically valid. The most recent clinical review of the subject was by Levin, who reviewed 33 patients with increased intracranial pressure. Van Uitert and Eisenstadt in commenting on Levin's experience disagree that the presence of a venous pulse rules out significantly increased intracranial pressure. In their comments they cite four cases of their own in which there was a spontaneous venous pulse at the same time as they measured a significantly increased intracranial pressure. All previous reports of such an occurrence have been anecdotal and not supported by simultaneous fundus observation and spinal fluid pressure measurements. No test in medicine is perfect or without exceptions; however, given the surrounding clinical facts, the presence of venous pulse is one more piece of evidence to support the clinical diagnosis of no significantly increased intracranial pressure above 200 mm of spinal fluid. It is a clinical sign that has been valuable to me over the years and I will continue to use it in my evaluation of a swollen disc.

Although some observers consider a light touch to bring out the pulse valid, I do not think it advisable since it might introduce a significant error. Since the lightness of the touch is an unknown quantity and since intraocular pressure is measured in millimeters of mercury and not of water, the touch introduces an error of 13.5 to 1 for each millimeter of digital increase in ocular pressure. A collapsing of the vein, even if incomplete, is the sign to be observed (rather than a moving of the vessel caused by adjacent arterial pulsations). Collapsing of the vein is best seen deep in the disc or as the vein crosses the disc margin.

**Deflection of Vessels**

The location of vessels coming off the disc into the vitreous and then back to the level of the retina is not an unusual anomaly. It does not represent papilledema because the disc can be seen at a different level from that of the elevated vessels. The presence of vessels elevated by a swollen disc, however, suggests papilledema.

**Hemorrhages and Exudates**

The presence or absence of hemorrhages does not indicate either the cause or the severity of the edema. If the hemorrhages are caused by increased intracranial pressure, their quantity does not change the gravity of the condition. A small number of hemorrhages should not provide a sense of security.
Certain types or locations of hemorrhages and exudates, however, may be of diagnostic help. Disc edema associated with hemorrhages and exudates that are not only located at the posterior pole but also found all the way out to the equator suggest hypertension rather than papilledema. Exudate in the macular, such as a macular star, has no etiologic significance but denotes chronicity (Plate 2.1B). If hemorrhage is an overwhelming feature and the veins are engorged, central retinal vein obstruction is more likely. Hemorrhage located in the subhyaloid area, particularly over the disc or macula, suggests a subarachnoid hemorrhage such as results from a ruptured cerebral aneurysm (Fig. 2.2).

Hemorrhages with white centers are called Roth’s spots (Plate 2.1C). They suggest septic embolization, leukemia, lupus erythematosus, or pernicious anemia.

**Vision Changes**

The rule is that disc edema with a loss of vision signifies optic neuritis and that papilledema with normal vision signifies increased intracranial pressure, but this rule does not always hold. Occasionally, optic neuritis occurs with good visual acuity. One of the signs of optic neuritis is the afferent
papillary defect (Marcus Gunn pupillary escape phenomenon), which indicates damage to the conduction system. Axial optic neuritis with a central scotoma and full peripheral field is the common defect, but field defects with good visual acuity can also occur.

Loss of acuity can occur with papilledema or disc edema from any cause when hemorrhages occur in the macula, as in hypertension, or in the subhyaloid area, with subarachnoid hemorrhages. Longstanding increased intracranial pressure may cause decompensation of the optic nerve, with resulting loss of acuity. This decompensation is one complication of prolonged pseudotumor cerebri and one of the principal reasons for surgical intervention when medical therapy fails.

Cells in the Vitreous Humor

In cases of papillitis or of retrobulbar optic neuritis in close proximity to the globe, cells can occasionally be seen in front of the disc. This phenomenon is detected only with the fundus contact lens and is rarely seen even when expected. Cells can appear in the vitreous humor as a result of other inflammatory conditions, but they are not as discrete or as localized as in papillitis or retrobulbar optic neuritis.

Height of the Disc Edema

The referring physician frequently requests information about the height of the disc edema. Unfortunately, the information causes more problems than it solves, because of the misplaced emphasis that some people put, for example, on 1 diopter of elevation as opposed to 5 diopters, as if the urgency regarding hospitalization and diagnostic tests varied with the height of the edema. Once the diagnosis of papilledema is made, prompt evaluation is mandatory, because of the increased intracranial pressure.

When measuring the degree of disc edema, the observer measures from the highest part of the edematous disc down to the normal nonedematous retina. The difference in dioptic power is read on the ophthalmoscope. If one is to record disc edema in millimeters of elevation, 2 diopters of disc elevation denote 1 mm of elevation in the phakic person, and 3 diopters of disc elevation denote 1 mm of elevation in an aphakic person (Fig. 2.3).

Optociliary Shunt Vessels

Optociliary shunt vessels in association with poor vision or blindness and pale disc edema are highly suggestive of the diagnosis of anterior optic nerve sheath meningioma. They have also been reported in association with optic disc drusen, central retinal vein obstruction, arachnoid cysts, gliomas, and coloboma of the optic nerve.

The reason for the development of venous shunt vessels may be increased pressure in the optic nerve sheath. The relationship of pressure in the sheath to disc edema was shown by Hayreh in his experimental work on monkeys. When he incised one optic nerve sheath in monkeys with increased intracranial pressure, the disc edema resolved only on that side. The other side maintained the papilledema when the intracranial pressure was maintained at preoperative levels. A clinical report on two patients by Perlmutter et al. seems to support this finding. These two patients had pseudotumor cerebri and developed optociliary shunt vessels. In one of the patients, one optic nerve was decompressed; within 3 days, the disc edema disappeared, and the shunt vessels were markedly reduced. This is in keeping with the results in the monkey experiments by Hayreh (Fig. 2.4).
- **Figure 2.3.**

Advanced papilledema with multiple hemorrhages, filling in of the optic cup, and total blurring of disc structures.

- **Figure 2.4.**

Shunt vessels of the optic disc.
NONFUNDUS SIGNS OF PAPILLEDEMA

Enlargement of the Blind Spot

Measuring the blind spot may be difficult either because the patient may not be fully conscious or because it is the first field examination of a neuro-ophthalmologic patient, who may be frightened or confused and thus not completely cooperative. The blind spot may even be enlarged before any gross evidence of edema of the disc appears. Enlargement of the blind spot is not an entirely dependable sign of early papilledema since the enlargement in itself may not be pathologic, as can be seen in patients who are slow responders or who want to be extra sure of their observations.

The cause of enlargement of the blind spot as a sign of papilledema has been debated since the time of Knapp's description. Retinal displacement and retinal elevation of peripapillary elements and the Stiles-Crawford effect are three of the more traditional explanations. More recently, a report suggesting a relative scotoma on the basis of induced hyperemia has been suggested by Corbett et al. The hypothesis is that edematous elevations of the peripapillary elements away from the blood supply of the choroid makes results in a decrease in sensitivity. A purely mechanical displacement of the retinal peripapillary elements, as pointed out by Corbett et al., would produce an absolute not a relative scotoma. A relative scotoma is the defect produced by papilledema. This may not be true if the disc edema results from some other cause such as ischemic optic neuritis in which the retinal or optic nerve tissues have some additional insult that alters their function. Corbett et al. found that in most cases the scotoma could be reduced by using plus lenses.

Their refractive theory as a cause of field defects is supported by the work of Young, Walsh, and Knox on tilted discs. In the tilted disc, there is a bitemporal hemianopia, which can be reduced by using minus lenses. Whatever the explanation, these authors point out an important basic principle in performing field examinations: Unless the perimetrist pays scrupulous attention to the patient's refractive error, false-negative or false-positive responses can be produced.

Transient Visual Obscuration

Transient visual obscuration (TVO) is a loss of vision lasting 10 to 20 seconds; in contrast, amaurosis fugax can last up to 10 or 20 minutes. This symptom may occur in one eye or in both simultaneously. Bilateral obscuration of vision is the usual visual presentation. This symptom has been exclusively associated with increased intracranial pressure and not just edema of the disc; it is not seen for instance with papillitis. However, Sadun, Currie, and Lessell reported four patients with TVO in the absence of increased intracranial pressure. The cases were disc edema with vitritis, optic nerve sheath meningioma, Fuch's coloboma, and intrapapillary drusen. One explanation of these cases is that vessels in the laminar and prelaminar area are a low-pressure system; thus perfusion of that part of the nerve depends on the difference between the intraocular pressure and tissue pressure. Small increases in intraocular pressure can reduce flow in that part of the nerve without changes in the retinal blood flow.

Patients with TVO often do not mention the symptom. By the time they wipe their glasses or clear the tears from their eyes, the phenomenon is over. The physician should ask patients whether they have episodes of bilateral blurring or graying out of vision. During the blurring episodes, no visible fundus change occurs. Increasing obscurations are a forewarning of decompensation of the optic nerve, which may lead to blindness. The tissue pressure is elevated by the increased intracranial pressure and backed up axoplasmic flow. One method of alleviating the tissue pressure has been optic nerve
sheath fenestration. Sadun, Currie, and Lessell postulated that in all of their cases, the optic nerve tissue pressure was increased, causing ischemia and the symptoms of transient visual obscurations. The obscurations are followed by an adjustment of the autoregulation system. Although interesting, the explanation of these rare cases of Sadun, Currie, and Lessell does not necessarily apply to cases of increased intracranial pressure in which TVO is much more common.

**Pupillary Abnormalities**

When disease affects the conducting mechanism of one optic nerve, the afferent pupillary defect may be present. It may be caused by optic neuritis, vascular disease of the optic nerve, tumor, or any other optic nerve lesion.

Increased intracranial pressure, on the other hand, causes no direct pupillary signs. Supratentorial masses, however, as they encroach on the tentorial notch, compress the third cranial nerve and cause pupillary abnormalities. The abnormality may vary from a slightly dilated and/or sluggish pupil, at one end of the spectrum, to a fixed maximally dilated pupil, at the other.

In supratentorial tumor herniation, an ipsilateral pupillary abnormality is often associated with contralateral motor signs, owing to cerebral peduncle compression. Occasionally, the pupillary and motor signs are ipsilateral, owing to compression of the other cerebral peduncle, producing a Kernohan notch syndrome. This syndrome sometimes causes confusion in determining on which side the lesion is located. A good rule of thumb is to trust the pupil to point out the appropriate side.

**State of Consciousness**

The patient's level of consciousness is a nonspecific sign. Consciousness may be altered in any disease that affects cerebral metabolism, a category that includes most causes of increased intracranial pressure, with the notable exception of pseudotumor cerebri. Significantly increased intracranial pressure, however, does not always cause changes in consciousness, whereas hypertensive encephalopathy frequently does.

**Headache**

Headache is another nonspecific symptom. It can be related to increased intracranial pressure, or it can be a symptom of associated tension or anxiety. One feature of headache, however, is specific to increased...
Intracranial pressure. When the intracranial pressure is increased, such as with the Valsalva maneuver, the headache becomes worse. Vascular headaches are frequently improved by the Valsalva maneuver, and tension headaches are not affected at all. The classic morning headache is also rare, as is projectile vomiting (Fig. 2.5).

**PSEUDOPAPILLEDEMA**

**Drusen**

The excrescences termed drusen (Pl. 2.1D) are a frequent cause of blurred disc, particularly in children. Drusen may cause enlarged blind spots, as well as other field defects, most commonly, inferonasally. Drusen may be buried deep in the disc and not easily seen in children, especially when the ophthalmoscope light is shined directly on the disc. Shining the light at the edge of the disc causes retroillumination of the disc structures and frequently makes the yellow crystalline body more visible. Diagnosis is made more difficult when hemorrhages occur with the drusen.

Drusen tend to be less of a diagnostic problem in patients in their late teens and older, perhaps because drusen increase in number or migrate forward in the disc and become more visible as patients get older. Examining the pediatric patient's parents or older siblings for evidence of drusen may be helpful in identifying a familial tendency.

Kamin, Hepler, and Foo reported two children with decreased vision secondary to optic nerve drusen. This loss of vision is extremely rare in children, since most of us see
this problem in that age group as part of the differential diagnosis of a blurred disc rather than as loss of vision. Drusen have been regarded as a curiosity of ophthalmoscopy for the most part. Our understanding of the pathology of drusen has been changed by the work of Spencer and Tso. Their work on the role of axoplasmic transport in the production of papilledema and drusen has radically changed our thinking. Although drusen uncommonly cause symptomatic defects, they are not all that benign. Of 38 eyes studied by Newman, using red free fundus photography, 97.2% had an abnormal appearance to the nerve fiber layer, and 75% had abnormal fields. The most interesting finding was an abnormal visually evoked potential (VEP) response in 97.2% of the study.

When losses of vision and field occur, drusen may be even more difficult to accept as the only cause of disc blurring. If only one eye is involved, other causes must be evaluated to rule out the possibility that a retrobulbar tumor is compressing the nerve and causing loss of vision and field. If both eyes have loss of vision and field, the diagnosis is easier, since field loss in both eyes does not fit into a recognized neurologic picture. However, a suprachiasmatic mass should be considered and evaluated with special studies, such as roentgenograms of the sella turcica and computed tomography (CT). CT scans and magnetic resonance imaging (MRI) have essentially replaced the air study. This is even more true today with the use of contrast material and thinner computer scan slices.

Hemorrhages associated with drusen are occasionally seen by ophthalmologists. They may occur more frequently than we suspect because they usually produce no symptoms recognizable to the patient and, therefore, are not seen by a physician at the time they occur. Drusen as the cause of a hemorrhage on or near the disc has been reported many times and is a well-recognized entity. Sanders, Gay, and Newman divided hemorrhages associated with drusen into three classes because they felt that each had a different significance in regard to sequelae. The hemorrhages in the first group occur in the superficial nerve fiber layer. They rarely cause symptoms but can cause field defects that resolve. Vitreous hemorrhages cause a more dramatic loss of vision, particularly if they occur anterior to the fovea. These usually also resolve unless vitreous complications occur. The hemorrhages in the last group occur in association with optic nerve drusen and choroidal neovascularization. Patients with this type of hemorrhage have acute visual symptoms and seek consultation. Henkind, Atterman, and Wise felt that such patients would develop permanent visual loss and require vigorous treatment. Harris, Fine, and Owens, however, recently reported on four patients (seven eyes) with drusen, hemorrhage, and subpigment epithelial neovascularization. All but one of these four patients did well with no treatment. The follow-up evaluation ranged from 1 to 10 years. It would seem that this group of hemorrhages associated with drusen and a choroidal neovascular membrane should be looked at more seriously even though they also appear to have an excellent prognosis.

It is still true that, over all, drusen of the optic disc is a benign ophthalmoscopic finding; however, in view of the new reports on changes in the nerve fiber layer, VEP, and complications associated with neovascular membranes, more cautious observation is indicated in anyone with optic nerve drusen.

Myelination of Nerve Fibers

Although the ophthalmologist sees myelination of the nerve fibers from time to time, this anomaly is not usually a problem in the differential diagnosis of papilledema. The condition is caused by myelination that has continued past the lamina cribrosa on to the retina itself but usually does not cover the entire disc (Plate 2.1/1A). The myelin appears white and solid, with an irregular feathery border, in contrast to the appearance of an
PLATE 2.II

- Plate 2.IIA
  Medullated nerve fibers. The appearance is of uniform whiteness, with an irregular, feathery, sharp border.

- Plate 2.IIB
  Epipapillary membrane. This normal variant of the retinal blood vessels may be mistaken for disc edema.

- Plate 2.IIC
  Hypertensive retinopathy. Anemic arteries and papilledema are more prominent than hemorrhages; the reverse is seen in central retinal vein occlusion.

- Plate 2.IID
  Central retinal vein occlusions. Hemorrhage is the most prominent feature, with papilledema only a secondary aspect.
edematous disc, which blends into the surrounding retina.

The myelin may extend along the arcuate fibers to a lesser degree, giving the appearance of edema in the fibers. The only field defect that may occur is enlargement of the blind spot. Myelination does not cause the other signs of papilledema. If they are present, another process must also be considered.

Since the presence of myelin is presumed to depend on the integrity of a healthy axon, the reverse should also be true. The disappearance of myelin would be expected to occur if optic atrophy of these axons occurs. This combination of events is rare, and it is even rarer to have the before and after pictures to document such an event. Schachat and Miller reported such a case in a man with anterior ischemic optic neuropathy. Therefore, patients with myelinated fibers should have them photographically documented. If they return with visual complaints, the appearance of early disc atrophy may be masked by the white appearance of the disc, owing to the myelin. The reduction in the extent of the myelinated fibers may be the only early diagnostic sign. Myelinated fibers otherwise cause no clinical signs or symptoms, such as optic nerve drusen can.

**CAUSES OF PAPILLEDEMA AND DISC EDEMA (FIG. 2.6)**

**Hypertension**

The disc edema caused by group 4 hypertension and that caused by increasing intracranial pressure appear essentially the same. The problem arises in trying to differentiate increased intracranial pressure with secondary hypertension from group 4 hypertension with papilledema and hypertensive encephalopathy. The papilledema secondary to increased intracranial pressure is limited to the posterior pole, whereas that caused by hypertension is accompanied by marked hypertensive changes that extend to the peripheral retina (Plate 2.11C).

**Subarachnoid Hemorrhage**

A small group of patients with papilledema have preretal hemorrhages that may be located in front of the disc or the macula (Fig. 2.1). This type of hemorrhage in adults almost always indicates subarachnoid hemorrhage. In infants, it suggests subdural hemorrhage. If the hemorrhage is located in front of the macula, it causes a severe decrease in vision. Unless it breaks into the vitreous humor, however, it will be absorbed, and previous vision will return. I have also seen these hemorrhages with posterior vitreous detachment.

Intraocular hemorrhages secondary to subarachnoid hemorrhage occur in about 20% of patients. The presence of these hemorrhages is highly significant in predicting...
Figure 2.6.
Evaluation of true nerve edema.

The mortality rate from ruptured aneurysms. The mortality rate is about 60% when fundus hemorrhages are present but only 27% when they are absent according to Manschot, Richardson, and Hyland, and Fahmy. Mechanisms for the production of fundus and optic nerve sheath hemorrhages have been put forward by Ballantyne, Walsh and Hedges, and Muller and Deck. Some authors, like Ballantyne, believe these hemorrhages are caused by venous obstruction owing to increased intracranial pressure on intracranial venous structures draining the eye and orbit. Walsh and Hedges believe that the cause is intracranial pressure transmitted to orbital structures. Muller and Deck evaluated 46 eyes and their orbits and optic canals in patients with increased intracranial pressure, 87% had optic nerve sheath hemorrhage, and 37% had intraocular hemorrhages. These authors concluded that orbital hemorrhages came from optic nerve sheath vessels. These hemorrhages probably do not result from increased intracranial pressure being transmitted to the orbital venous structures. Also, any increased orbital venous pressure can be dissipated by alternate venous drainage into the facial and pterygoid vessels. These two facts militate against optic nerve sheath hemorrhages resulting from intracranial subarachnoid blood being pushed into the optic nerve sheath. Hemorrhages can be found on the optic nerve sheath in cases of increased intracranial pressure without subarachnoid hemorrhage. These hemorrhages in the nerve sheath occur predominantly in the subdural rather than the subarachnoid space. Muller and
Deck believe that the hemorrhages in the sheath may be caused by the rupture of pial vessels when the sheath is rapidly expanded during a sudden severe rise of intracranial pressure.

Muller and Deck stated that intraocular hemorrhages have a different mechanism. These hemorrhages result from sudden increases in venous ocular pressure at a level in the nerve that precludes its dissipation by alternate drainage into the facial and pterygoid vessel systems.

Vitreous hemorrhages in subarachnoid hemorrhage were first described by Terson. Vitreous hemorrhages in this clinical setting are rare. They may occur initially as large hemorrhages breaking out into the vitreous or secondarily from a subhyaloid hemorrhage that subsequently breaks the posterior vitreous face and invades the vitreous body. Hemorrhages of this magnitude represent even more serious consequences from the intracranial disease than just preretinal hemorrhages. If the patient survives, the vitreous hemorrhage will clear, which may take up to a year.

Subhyaloid hemorrhage may occur from neovascularization of the retina, as in diabetes, or from the neovascularization following a central retinal vein occlusion. The retinal diagnostic clues in diabetes, such as the exudates, are readily seen. In an old central retinal vein occlusion, the vein looks white, with vessels sprouting from the site of the obstruction.

Central Retinal Vein Occlusion

The predominant picture in central retinal vein occlusion (Plate 2.ID) is one of blood, not edema or exudate. The branch retinal vein occlusions are more readily diagnosed by those unfamiliar with the fundus picture, because the hemorrhages are limited to one quadrant of the retina.

The decrease in visual acuity associated with central retinal vein occlusion is usually marked and rapid in onset. This decrease in acuity is not seen with increased intracranial pressure, except over a long period of time and with a gradual onset. The disc in central retinal vein occlusion is plethoric. The disc in papilledema with vision loss shows a glotic grayish appearance with white sheathing of the vessels. Papillophlebitis as initially described by Linn and Hoyt should not be confused with papilledema secondary to increased intracranial pressure. Papillophlebitis occurs unilaterally in young healthy adults. The fundus picture is usually much worse than the patient’s complaints of minimal blurriness. The edema and hemorrhages on the disc and in the retina are more consistent with a vein occlusion than with papilledema. Unlike vein occlusions in adults, this entity has a good prognosis. Like vein occlusion in adults, however, there is no effective treatment unless some systemic cause is revealed.

The diseases to be considered in determining the cause of central retinal vein occlusion are glaucoma, diabetes, dysproteinemias, multiple myeloma, and polycythemia vera. The evaluation of diabetes requires a formal glucose tolerance test rather than a postprandial blood glucose determination. The dysproteinemias, such as Waldenström’s macroglobulinemia, are best diagnosed by an electrophoresis of the patient’s blood serum.

Leukemia and Septic Chorioretinitis

These disorders are discussed together because of the sign they have in common—Roth’s spots (hemorrhages with white centers) (Plate 2.1C). In leukemia the white centers are tumor cells, whereas in septic chorioretinitis they are inflammatory white cells. Both diseases may cause disc edema. Many hemorrhages are present but usually only a few Roth’s spots. When Roth’s spots are present, they are located at the posterior pole and need not be looked for at the equator or beyond. The white centers in
Roth's spots are transient, and when they are looked for the next day, they may be filled in with blood and look like an ordinary retinal hemorrhage. Roth's spots are seen in other diseases, including subacute bacterial endocarditis, pernicious anemia, scurvy, lupus erythematosus, and sickle-cell anemia. Usually, these conditions do not cause disc edema.

**Optic Neuritis**

As a rule, disc edema with a decrease in visual acuity suggests optic neuritis. The appearance of the papillitis is not diagnostic, as some patients with optic neuritis have good visual acuity. In these, the field defect may be so subtle that the patient is not aware of it; it must be looked for carefully.

A useful diagnostic test for evaluating papillitis with good visual acuity is the afferent pupillary defect, which indicates unilateral optic nerve disease. This phenomenon may be seen when damage to the nerve occurs for any reason, causing a conduction defect, even in cases of neuritis with good visual acuity. The test is performed in the following way. The physician shines a light in the affected eye, and the pupil in that eye responds, as expected, by constricting. A consensual reaction also occurs. The light is then moved quickly from the affected eye to the other eye—and the degree of pupillary constriction in both eyes comes down more. The light is then moved quickly back to the affected eye, whereupon the pupil of the affected eye dilates significantly, as does the pupil in the fellow eye. The light must be moved rapidly from one eye to the other so as not to lose the constrictor effect from the normal eye. The test should be done several times to differentiate the condition from a dilatation of the pupil owing to hippus.

Cells in the vitreous humor in front of the disc are an inconsistent sign of papillitis or a retrobulbar optic neuritis. They can be seen only with the fundus contact lens, and they are not seen grossly with the ophthalmoscope. Cells in the vitreous humor can be seen in a variety of conditions—pars planitis, chorioretinitis, and cyclitis. In all these disorders, the cells cause a visible haze or debris in the vitreous humor and are not localized to the disc area.

The Hardy, Rand, Ritter (HRR) color plates are a useful screening device. Even in optic neuritis with good visual acuity, the ability to recognize the plates may be markedly different in each eye. This finding can be carried over into the field examination, in which a field defect may be more easily detected with colored test objects than with small white ones.

**Infiltration of the Optic Nerve**

Infiltration of the optic nerve head may give the appearance of papilledema on casual inspection. Fortunately, infiltration of the disc is rare and usually occurs unilaterally, which should alert one to an alternative diagnosis to true papilledema. Infiltration or masses on the nerve head can be seen with several disorders, such as tuberculous sclerosis, sarcoid, and lymphoma (Plate 14.1D).

The eye and orbit are affected in about 25% of cases of systemic sarcoid. The perivascular and surface appearance of the retinal vasculitis is well known.

The four different manifestations of optic nerve involvement in sarcoid are optic atrophy, optic neuritis, optic nerve granuloma, invasion of the nerve, and papilledema.

The papilledema may occur secondary to infiltration of the peripapillary areas or as papillitis. It may also occur secondary to true increased intracranial pressure from a mass effect or, more rarely, from direct infiltration of the disc. A patient reported by Jampol, Woodfin, and McLean and seen by us responded dramatically to systemic steroids (Plate 14.1B).

Intracranial involvement occurs in about 5% of cases of systemic sarcoid. These cases may present as cranial nerve involvement, of which seventh nerve paresis is the most
common, or with hypothalamic involvement and symptoms of diabetes insipidus. Walsh and Smith have reported a case of a suprasellar tumor causing a mass effect. This mass produced diabetes insipidus, bitemporal hemianopia, and papilledema. The mass was biopsied and showed a typical non-caseating granuloma. The mass responded to steroids, and all of the symptoms and signs were relieved or markedly improved.

A firm diagnosis is difficult to establish without a biopsy. A computed tomogram is said to show a characteristic appearance. This has not held up in a series of cases reviewed by Powers and Miller. An increase in the serum angiotensin-converting enzyme has also shown promise as a laboratory aid in the diagnosis, but it is not universally elevated in all cases of sarcoid.

Other infiltrations of the optic nerve can be seen, as in lymphoid reticulum cell sarcoma. We have seen lymphoma produce this ocular presentation on several occasions; however, these patients were well known to us as patients with lymphoma and did not have optic infiltration as their initial systemic complaint. The optic nerve masses resolved under therapy but left an infarcted nerve from the infiltration (Plate 14.1D).

Reticulum sarcoma usually presents as a uveitis associated with subretinal and choroidal infiltrates and, occasionally, with disc hyperemia mimicking early papilledema.

**Tumors**

Orbital and optic nerve tumors can cause disc edema through obstruction of ocular venous drainage. They may also cause decrease in visual acuity, field defects, decrease in motility, and proptosis. The exophthalmos may be subtle, and exophthalmometer measurements should be part of the evaluation of unilateral papilledema or loss of acuity.

Digital exploration of the periorbital area may reveal a mass accessible to biopsy. Tumors that are truly retro-orbital or are in the muscle cone are the most difficult to diagnose, but they can be diagnosed by the ultrasound technique or CT. CT or MRI with and without contrast and with coronal views are necessary.

Thyroid disease may cause unilateral loss of vision, exophthalmos, disc edema, and horizontal striae in the macular area. Although these conditions also suggest orbital tumor, a positive forced duction test and lid retraction point toward thyroid disease as the primary cause.

Intracranial tumors, particularly those along the sphenoid ridge, can cause changes that are more marked in one eye than in the other. In disc edema caused by venous compression in the superior orbital fissure, the veins appear to be disproportionately larger than in papilledema caused by increased intracranial pressure. This venous stasis may also be seen as a caput medusa (dilated veins) on the globe. As the tumor enlarges and the intracranial pressure increases, the relationship of papilledema and venous engorgement is more typical of true papilledema. A variation of this condition is the Foster Kennedy syndrome, in which the tumor, usually a frontal lobe glioma or an olfactory groove meningioma, compresses the optic nerve, causing optic atrophy. The atrophy occurs before the tumor takes up a significant amount of intracranial space. Then as the tumor grows, increased intracranial pressure develops, and the other nerve shows papilledema while the atrophic side does not. When the Foster Kennedy syndrome occurs in persons 65 years of age or older, however, it is commonly caused by vascular disease.

Longstanding increased intracranial pressure from any cause and tumor of the chiasm both bring about a bilateral decrease in acuity. Bilateral papilledema with a decrease in acuity can be confused with bilateral optic neuritis, a mistake that is likely to occur when the CT and MRI of the sphenoid ridge and sella turcica are reported as normal. Slow progressive loss of acuity is not caused by optic neuritis, however, so a compressive lesion must be considered. Suprasellar masses, such as meningioma, craniopharyngioma, or aneurysm, may cause compression of the
nerves without evidence of bony changes, even with adequate tomograms of the sella turcica. A CT examination with a contrast medium should be used to rule out a suprasellar mass. Careful inspection of the plain roentgenograms may reveal subtle calcification in some cases of meningioma and aneurysm. Suprasellar calcification can be seen in more than 85% of childhood craniopharyngiomas, but it is uncommon in the adult variety. If the Foster Kennedy syndrome is caused by an olfactory groove meningioma, anosmia ipsilateral with the optic atrophy also occurs.

The association of a spinal cord tumor and increased intracranial pressure is well known but occurs uncommonly. The mechanism is also poorly understood. When no intracranial reason for the papilledema can be found and before pseudotumor cerebri is accepted as the diagnosis, investigation for a spinal cord tumor should be considered. The usual lower extremity symptoms should dismiss serious consideration of pseudotumor cerebri. MRI with contrast of the lumbar region may show atrophy and widening of the interpedicular distance. This, then, suggests a more definitive evaluation by myelography. The cause of the papilledema is not necessarily mechanical obstruction of cerebrospinal fluid flow as has been shown by myelography. Since increased cerebrospinal fluid protein is a constant finding in these cases, the protein may obstruct the turnover of cerebrospinal fluid as occurs in the Guillain-Barré syndrome.

**Brain Abscess**

Brain abscess usually causes focal neurologic deficit, but occasionally it produces papilledema.

**Juxtapapillary Choroiditis**

A focal chorioretinitis next to the disc may be hard to see because of overlying inflammatory exudates. The focal nature of the changes suggests the diagnosis, since the rest of the nerve looks normal. Since juxtapapillary choroiditis most frequently occurs on the temporal side of the disc, it is unlikely to be papilledema, which occurs first on the nasal side.

**Posterior Scleritis**

Posterior scleritis, usually referred to as brawny scleritis, causes retinal edema with horizontal striae in the macula as well as low-grade disc edema. The best way to see the thickened choroid is with the fundus contact lens. Brawny scleritis is usually idiopathic, but it can be associated with thyroid disease.

**Ocular Hypotension Secondary to Intraocular Operation**

Cataract operation, even when it is uncomplicated and when the depth of the anterior chamber is normal, may be associated with a low intraocular pressure—in the range of 2 to 4 mm. The low pressure causes mild swelling of the disc and macula, with chronic loss of vision caused by macular disease. A dilated fundus examination using the indirect ophthalmoscope is necessary. A detailed view of the ciliary body may reveal ciliary body detachment, with secondary decrease in aqueous production. Seidel's test with fluorescein should be done, and the physician should look for a leak of the wound if an obvious filtering bleb is not present.

**Ischemic Optic Neuropathy**

**TEMPORAL ARTERITIS (ARTERITIC).**

This condition is usually thought of as occurring in older people who show signs of headache and a temporal artery that is prominent, very tender, and noncompressible.
The usual history is one of sudden loss of vision without warning or associated symptoms. If asked about any previous signs and symptoms, the patient may admit to them but dismiss them as "just old age" or "wearing out." Frequently, temporal arteritis causes disc edema, but it is of the pale and ischemic variety, with small vessels, rather than the plethoric type seen with increased intracranial pressure. The diagnosis of temporal arteritis should be considered in a patient over 55 years of age, particularly one over 65 years of age, when sudden loss of vision occurs in one or both eyes. Temporal arteritis has been reported and confirmed by biopsy in much younger people, but only rarely. The condition usually attacks one eye at a time, but since the other eye may be affected within days, a diagnosis should be made promptly, and therapy begun immediately. Temporal arteritis is a true ophthalmic emergency.

The physician should strongly suspect temporal arteritis whenever the blood sedimentation rate is elevated. The usual elevation is 45 mm or more, but even minimal elevations (in the range of 30 mm) warrant a temporal artery biopsy. In a positive biopsy, the typical multinucleated giant cells are present. If the condition is strongly suspected because of an elevated sedimentation rate, systemic steroid therapy should be started immediately, even if the biopsy cannot be done for as long as 48 hours. Such a brief course of steroid therapy does not affect the biopsy, and it may protect the other eye. Since temporal arteritis is a segmental disease, it is imperative to get serial sections done on the specimen because the pathologic area may be missed. It is important to get a positive biopsy early so that patients who do not require steroid therapy will not continue to receive it. Since they are in the age group that tolerates steroids poorly and is prone to such diseases as diabetes and hypertension, a positive biopsy also puts the treatment on a firmer basis. It has been suggested that doing a temporal artery arteriogram will show the occluded areas more precisely and thus increase chances of a positive biopsy. This has generally not worked out. When a sudden loss of vision with ischemic disc edema occurs, an important differential diagnosis is infarction of the nerve immediately behind the disc from emboli, particularly from an atheromatous condition of the carotid or aortic arch.

**SMALL VESSEL OPTIC NEURITIS (ANTERIOR ISCHEMIC OPTIC NEUROPATHY) NONARTERITIC.** Anterior ischemic optic neuropathy (AION) is associated with ischemic disc edema more often than is temporal arteritis. The loss of vision in patients with AION is gradual rather than cataclysmic; it tends to be a piecemeal loss of vision. In persons with AION, the other eye tends to be affected more consistently, although usually not simultaneously. AION is not associated with an increased sedimentation rate, and the temporal artery biopsy is negative.

The cause of this condition is considered to be small ciliary vessel occlusive disease, and the condition is not favorably affected by anticoagulant or steroid therapy. Although no effective specific therapy exists, associated conditions that decrease the vascular perfusion ratio of the eye should be evaluated. These conditions are increased ocular pressure, decreased blood pressure, such as occurs in too sudden and too severe treatment for hypertension, and decreased carotid pressure owing to silent carotid occlusive disease, as evidenced by a decrease in ophthalmodynamometry.

**ACUTE ANEMIA.** Acute blood loss, such as occurs in gastrointestinal and uterine hemorrhages, does not commonly cause loss of vision or disc edema. When it does, the edema is of the pale ischemic variety, with attenuated vessels. About 25% of those who develop disc edema do so immediately, and the remainder develop it in the next few days or weeks. The loss of vision is usually unilateral, and it may be complete or partial or even present as a field defect, such as an altitudinal hemianopsia. The visual loss may be made worse by antecedent carotid occlusive disease or small vessel disease in the optic nerve or in the retina, which has already decreased the perfusion of the eye.
**CHRONIC ANEMIA.** Chronic anemia is also an infrequent but established cause of visual loss and disc edema. In the United States, it usually occurs in women who have begun a pregnancy with a low hemoglobin level and then compounded the problem with no prenatal care, thus making the hemoglobin level drop even lower. The edema is low grade and closer to the ischemic variety than the edema in increased intracranial pressure. The diagnosis is easily made by hemoglobin and hematocrit determinations. Whatever visual loss ensues can be made worse by an associated eclampsia or hypertension that causes further ischemia.

**Idiopathic Intracranial Hypertension**

The many causes of intracranial hypertension all have serious consequences for the visual system. At some point in the course of the disease, intracranial hypertension may require specific and aggressive treatment (e.g., surgery, shunting, or optic nerve decompression) to prevent those serious visual consequences. One such disease process that requires cautious and prolonged observations is idiopathic intracranial hypertension, also called pseudotumor cerebri. Despite its name, this disease can be anything but benign.

**PATHOLOGY**

Increased intracranial pressure results from only a limited combination of factors: an increase in cerebral mass, an increase in vascular volume, or an increase in fluid in the subarachnoid space. Sabs and Joyner did brain biopsies on 10 patients and found an increase in intracellular edema. Other investigators have identified the microvasculature as the source of the problem with secondary tissue swelling. The role of increased fluid in the subarachnoid space was suggested by Bergaw and Greer. They injected 131I RISA in two patients and found a decrease in absorption from the spinal fluid compartment into the intravascular compartment. In view of the varied disease processes that have been associated with idiopathic intracranial hypertension, there may well not be one underlying pathologic picture for this disease.

**ETIOLOGY**

The disease initially called serous meningitis by Quicke and now referred to as idiopathic intracranial hypertension has many different associations with a varied group of disease processes that do not appear to have anything in common. It has been repeatedly reported in patients taking vitamin A, tetracycline, nalidixic acid, and penicillin. There is also an association in patients with plumbism, carbon dioxide retention, hypoparathyroidism, and lupus erythematosus. The disease is seen most commonly in obese young females with menstrual irregularities and in the first trimester of pregnancy. At one time it was also commonly seen in female patients on the pill, but this is a rare association now. Idiopathic intracranial hypertension is also seen as a consequence of cerebral sinus thrombosis either spontaneously, secondary to mastoid disease, or postpartum. Unless specific invasive diagnostic tests are performed, this particular finding is only inferential depending on the clinical setting (e.g., mastoid disease or postpartum). These patients have one symptom that may help in the diagnosis. In the presence of the venous flow disturbance in cerebral sinus thrombosis, these patients hear a noise; it is not a bruit, but rather is called a venous souffle. This noise cannot be heard by the physician with a stethoscope. It is only heard by patients and not all the time. Usually they will hear it when the surrounding environment is quiet. They report it as a blowing sound or whisper rather than the loud roaring sound of a bruit. It may even be dampened or enhanced depending on which side they are lying. As a result of this variability and apparent inconstancy, patients may not mention this symptom, and the astute clinical historian must seek it. The dural sinus thrombosis is best demonstrated by MRI (Fig. 2.7, A and B).
- Figure 2.7.
A and B. Case of pseudotumor cerebri secondary to multiple sinus thrombosis.
The association of pseudotumor cerebri with vitamin A toxicity is not usually seen in adults. I have seen it in one 19-year-old girl who chronically ingested an excess of vitamin A to treat her acne. Vitamin A toxicity can be acute or chronic. The acute variety occurs when the patient ingests food with a high vitamin A content such as polar bear meat or shark liver. The toxicity is manifested by headache, nausea and vomiting, a decreased sensorium, and irritability. Acute toxicity in children may be caused by an accidental overdose of vitamins that the infant had access to. Chronic intoxication is a more common presentation with the signs and symptoms of idiopathic intracranial hypertension.

Hydrocephalus and increased intracranial pressure have also occurred in vitamin A-deficient babies in association with other neurologic signs such as increased reflexes and a bulging fontanel. Administration of vitamin A in these patients quickly reverses the process. It is important to consider this entity in infants, who cannot speak and give a history.

DIAGNOSIS

The usual criteria for establishing the diagnosis of pseudotumor cerebri are signs of increased intracranial pressure confirmed by lumbar puncture. The spinal fluid, except for increased pressure, should be entirely normal or show a slight decrease in spinal fluid proteins, a finding that has been reported in as many as 70% of cases. The ventricles are of normal size or small. In the past, invasive studies such as a pneumoencephalogram were required to demonstrate ventricular size. Now the CT scan has replaced the pneumoencephalogram. In the absence of neurologic signs and before the advent of CT examinations, the possibility of a posterior fossa tumor made lumbar spinal taps dangerous in the face of increased intracranial pressure. However, a CT examination can rule out a posterior fossa tumor or aqueduct stenosis with secondary enlargement of the ventricles. This allows a safe spinal tap from below to establish the diagnosis of pseudotumor cerebri.

A negative neurologic examination is also essential except for signs and symptoms secondary to the increased intracranial pressure (e.g., sixth-nerve paresis, headache, and transient loss of vision). The headache is generalized, nonlocalizing, and made worse by increasing the intracranial pressure such as during a Valsalva maneuver. Headache is usually present in benign intracranial hypertension and frequently is the reason patients seek medical consultation. However, headache is not always present despite the increased intracranial pressure and may come and go despite constant increased intracranial pressure. The lack of or cessation of a headache, therefore, does not always mean a decrease in intracranial pressure and is not a reason for complacency. It is during the neurologic examination that papilledema is discovered and the rest of the diagnosis is considered.

Another type of pain less commonly seen is facial pain or paresthesia. The mechanism for this is not known. One theory is that a swollen brain with displacement causes trigeminal nerve stretching over the petrous bone or compression of the nerve root at the petrous apex as it is about to enter the trigeminal cistern and become the gasserian ganglion. Macular pigmentary changes have been reported in papilledema secondary to pseudotumor cerebri. The reason for these pigmentary changes is probably secondary to retinal edema.

The diagnosis of pseudotumor cerebri usually is suggested by a finding of papilledema corroborated by increased spinal fluid pressure on a spinal tap. Although these two findings would seem interchangeable—if you have one, you have the other—this does not hold in all cases. Many reports indicate that in idiopathic intracranial hypertension, there is wide fluctuation in intracranial pressure; thus, at any given moment, a tap may show normal, borderline, or elevated pressure. For example, in one series of patients whose spinal fluid pressure was monitored over 24 hours, the pressure...
ranged from 186 to 520 mm of spinal fluid. A low tap in the face of papilledema creates a diagnostic dilemma; an elevated spinal fluid tap in the absence of papilledema is equally confusing. Both situations can exist and severely test the acumen of the most astute physician.

The situation of increased intracranial pressure without papilledema is particularly important in judging when the course of idiopathic intracranial hypertension is over. Even after the papilledema disappears, severe visual consequences may occur if the intracranial pressure is still elevated or the idiopathic intracranial hypertension recurs without the production of papilledema.

Pseudotumor that occurs in the young pediatric group differs from cases we see in teenagers and older persons. A review of Lessell's cases revealed no female sex predilection, nor was obesity a factor. The usual presentation in teens and older patients is headache. In the pediatric group, changes in personality like apathy, somnolence, irritability, dizziness, and ataxia were the usual presenting signs. In this group the fontanels are frequently open, and the sutures are not set; as a result papilledema is infrequent.

PROGNOSIS

Visual loss with this disease is quite common. In several groups of patients, up to 40% have had some field or acuity loss. The problem has been to establish what factors predict those patients at risk for visual loss. Several decades ago, Walter Dandy, the famous neurosurgeon, had four criteria—all visual—for surgical intervention in this disease: decreasing visual acuity, progressive contraction of the field, glossis of the disc, and increasing transient obscuration. These criteria are still valid today. My own experience and the reports by Corbett et al., by Orcutt, Page, and Sanders, and by Wall, Hart, and Burde provide additional information about prognostic factors in benign intracranial hypertension.

The degree of edema does not reflect the degree of the increased intracranial pressure. Therefore, we cannot assume that a minor amount of edema is less serious than 4 diopters of papilledema. Neither does the duration of the papilledema predict the final visual result. Visual loss can occur late or early in the course of the disease, although the amount of visual loss does increase with the duration of the disease. However, this finding is of little help in the management of an individual case. In more chronic cases, peripapillary subretinal hemorrhage secondary to neovascularization occurs and is a bad prognostic sign for visual loss. Macular stars do not portend visual loss but only substantiate the chronicity of the process. Anemia of a significant degree appears to affect visual loss. There is diverse opinion about the significance of vascular hypertension. However, a combination of anemia and hypertension may increase the chances of visual loss because of the increased ischemic effect of the two together. High myopia appears to increase the patient's prognosis for visual loss.

TREATMENT

Many patients with idiopathic intracranial hypertension have mild symptoms and do not require treatment. However, they need to be followed just as closely as those who have severe complaints, because of possible visual system deficits. Repeated spinal fluid taps have been advocated but are not very pleasant for the patient. Since the spinal fluid pressure usually restores itself to the previous level in about 2 hours, I am not convinced of the rationale for its use in a chronic disease. There is also the risk of infection with multiple taps. Repeated taps may cause tears in the dura, with chronic leaking of spinal fluid and perhaps worsening of the headache.

The use of carbonic anhydrase inhibitors such as acetazolamide decreases the production of cerebral spinal fluid just as they reduce aqueous production in the eye. An intravenous bolus of 1 g has been shown to decrease cerebral spinal fluid secretion for 2 hours. The usual maximum dosage recom-
mended by the manufacturers is far below what has been shown to be effective in reducing intracranial pressure, which has been projected at 4 g/day. Side effects at this dosage level or even less include gastrointestinal symptoms, disturbances in acid-base balance, and perioral and digital paresthesia. Methazolamide theoretically may be preferable to acetazolamide because it crosses the blood-brain barrier better than acetazolamide. No studies have been performed to compare the two drugs. Diuretics in classes other than carbonic anhydrase inhibitors do not work as well.

Since Diamox belongs to the sulfonamide family, agranulocytopenia can occur, although rarely. It has also been reported to be teratogenic in pregnant females. However there are only two cases of this in the literature, and it appears to be a safe drug after the 20th week of pregnancy. Another feature of chronic use is the production of metabolic acidosis. This can predispose to calcium oxalate deposition and renal stones. However, furosemide has been reported as a fair substitute. I cannot speak from personal experience. An uncontrolled study also suggests chlorothalidone as another substitute.

Steroids are another therapeutic possibility. Steroids in themselves have serious side effects and have been implicated in causing benign intracranial hypertension in association with the nephrotic syndrome. Most physicians treating benign intracranial hypertension recommend only a short course of steroid treatment, usually lasting no more than several weeks.

If the disease process does not abate and the medical treatment is not effective in stopping visual loss, then surgical intervention must be considered. The surgical treatment falls into two groups. The first is the lumbo-peritoneal shunt, which has the advantage of rapidly normalizing the intracranial pressure and reducing the papilledema. Although any competent neurosurgeon can do this surgery, the operation, like all operations, is not perfect. The shunt may fail with return of increased intracranial pressure; at the other extreme, it may filter excessively and lead to increased headache due to shifting of the intracranial contents and stretching of the nerves.

The second surgical choice is an optic nerve decompression (Fig. 2.8). This technique has been effective in reversing visual loss from increased intracranial pressure, although the exact mechanism of its effect is not well understood. Some workers contend that opening up the optic nerve sheath reduces pressure in the nerve and allows for better vascular perfusion of the nerve. Others contend that the dural window in the optic nerve sheath acts as a draining point for cerebrospinal fluid and, therefore, helps reduce the intracranial pressure. The report of Kaye, Galbraith, and King on a 51-year-old female with a 14-month history of papilledema and pseudotumor cerebri addresses this controversy. Hayreh's fenestration experiments revealed fibrous adhesions to the nerve as a late finding. This scarring appears to shift the pressure away from the low pressure vascular system at the laminar cribrosa. This would explain the ipsilateral eye but not cases with contralateral improvement from unilateral fenestration. However, multiple explanations may be needed to explain all the cases. Because of worsening symptoms, increasing papilledema, and increasing transient obscurations, bilateral optic nerve sheath decompression was performed. Intracranial pressure was measured continuously postoperatively, and no significant lowering of the intracranial pressure was recorded. However, the papilledema and symptoms decreased, and the patient was normal 2 months postoperatively. Therefore, optic nerve sheath decompression appears to preserve optic nerve function but does not apparently treat the underlying cause of the increased intracranial pressure by draining the subarachnoid fluid. The treatment of increased intracranial pressure is discussed further below.

The surgical procedure is fairly standard, with some small individual variations that each surgeon has learned from experience.
Figure 2.8.
There is no preoperative pupil dilatation, since intraoperative monitoring of pupil function is vital for surgical safety. Some surgeons prefer local, and others like myself prefer general anesthesia. Local anesthesia may interfere with pupil function, and there is always the problem of a retrobulbar hemorrhage, which could make a marginal functioning nerve worse as well as postpone surgery beyond an optimal time. The degree of globe manipulation and compression of orbital contents are easier under general anesthesia. However, the disadvantage of general anesthesia is that too much compression can be used in an attempt to increase visualization. To reduce orbital pressure the patient is placed in slight reverse Trendelenburg position. I do this for cataract surgery as well. The anesthesiologist must be told to not let the patient's blood pressure drop at all during the procedure. A drop in blood pressure may add to any lack of nerve perfusion from the previous problem and the operative manipulations.

A medial orbital approach is used to facilitate the temporal retraction of the globe. A generous lateral canthotomy is preferred. A wire speculum is used because it creates less pressure on the orbital contents. The larger blade-type speculum can force the lids wider apart but may create more orbital pressure. Pupillary size must be monitored during the entire procedure. If the pupil dilates more than 2 mm, relax all pressure points. A conjunctival peritomy is then performed beginning 4 mm from the limbus over the medial rectus muscle. It is important to start the peritomy 4 mm back rather than at the limbus so the conjunctival repair at the end of the procedure can be tight and nonleaking. The peritomy extends from over the medial rectus to beyond the superior and inferior rectus muscles. The medial rectus is now isolated as in any standard disinsertion of the muscle with 6-0 Vicryl sutures placed in the lateral aspects of the muscle in a locking configuration. The superior and inferior rectus muscles are isolated, and 4-0 silk sutures are used as traction sutures. A 6-0 Vicryl suture is inserted in the scleral stump of the medial rectus muscle insertion in a baseball-type stitch. Be sure it encompasses the entire stump; any asymmetric attachment may cause torsion of the globe and make the nerve harder to visualize. At this point, bring in the microscope and focus it in the most advantageous position for observation. As you go deeper into the orbit, look for the ridge on the sclera that identifies the long ciliary artery. Use this as a landmark and keep it in the center of the field. The conjunctiva and tenons capsule are now dissected up by blunt dissection to reduce bleeding. Keep the dissection between the cortex veins. Farther on, you encounter orbital fat, and this is retracted by either a small blunt malicable retractor or a cotton-tip applicator. When the optic nerve is isolated, gently displace the posterior ciliary artery to prevent injuring it. Locate an avascular area on the nerve. Also locate a dilated area which is most likely to have a fluid level between the sheath and optic nerve. Pick up the sheath with fine neurosurgical microforceps. Cut a hole in the sheath using a Beaver surgical blade M.V.R. Unitome 5560. Then extend the incision with a Beaver sickleblade. This blade is easier to use than scissors because of the limited space. As you cut dura, some of the arachnoid can be seen and needs to be incised to release the perineural fluid. Don't incise the pia on the nerve. Any bleeding is usually slight and handled by tamponade. At this point some surgeons prefer multiple longitudinal slits and others a window as generous as surgically possible. I prefer the window technique. A Fisher tenotomy hook is moved carefully without pressure longitudinally along the nerve to free up any adhesions. At this point, if there is no bleeding, then reinsert the medial rectus muscle and remove the sutures on the vertical recti. The conjunctiva is then closed watertight with 6-0 plain catgut. Antibiotic ointment and a nonpressure dressing is applied.

The patient should be relatively quiet for 24 hours to reduce chances of bleeding in the orbit or sheath, which can compromise optic nerve function and or the surgical
result. The most serious complication of this procedure is further damage to the optic nerve. Diplopia and pupillary abnormalities have also been noted but appear to be more common in the lateral surgical approach.

Carotid Cavernous Sinus Fistula

Among younger patients, carotid cavernous sinus fistula is more often seen in men and after trauma. Among older patients, it is more often seen in women and secondary to arteriosclerotic rupture of an intracavernous aneurysm. The increased venous flow to the eye, as well as the increased venous pressure, may cause only edema of the disc and fullness of the retinal veins without dilated veins on the conjunctiva, sclera, and lids. If the fistula is present long enough, the edema may become bilateral. Rarely, disc edema may even begin in the contralateral eye if a superior ophthalmic vein thrombosis occurs ipsilateral with the fistula. The associated signs of ocular bruits and ophthalmoplegia should be evaluated.

Pulsations, unless marked, may be missed. They are best seen by looking at the eye from the side rather than straight ahead. The more subtle pulsations are diagnosed when the physician uses direct ophthalmoscopy, noting that the fundus is going in and out of focus synchronously with the pulse at the wrist. If the applanation technique is used, the tonometer sign may be missed. The variation of the tonometer reading may be interpreted as unsteadiness of the patient in the headrest of the slit lamp. With the Schiotz tonometer, however, the arm has wide rhythmic swings in the range of six scale readings rather than the usual two to three scale readings.

Peripheral Ocular Disease

Peripheral uveitis or pars planitis may cause a vitreitis that, in turn, causes disc edema and macular edema. Examination of the far periphery of the fundus with the indirect ophthalmoscope is indispensable. Fundus contact lens examination of the vitreous humor reveals cells. The cellular reaction is more generalized than that seen in papillitis located just in front of the disc.

Unilateral Neck Dissection and Lung Disease

In radical neck dissection, a procedure for extensive carcinoma, the possibility that a particular dissection is incomplete with later metastasis to the brain is of real concern. If the patient later has a mild disc edema and engorged veins, the question of cerebral metastasis with increased intracranial pressure is raised. The physician may not consider the possibility of decreased venous drainage from the head and presume that the other jugular system is able to drain the head adequately. The other system is not always competent, however, and disc edema may result.

The theory behind ligation of the internal jugular vein or in removing it totally in a radical neck dissection is that the rich collateral venous system draining the head will compensate. These collaterals include the orbital, occipital, pharyngeal, piriform, and emissary venous systems, to name only a few. However, these systems may not always work adequately on demand. They may also work to different degrees. For instance, left jugular compression usually causes a more pronounced rise in cerebral spinal fluid pressure than does right jugular compression. This type of response probably explains the increase in intracranial pressure that follows radical neck dissections and the increased cerebral venous pressure from chronic chest pathology.

With such patients, the usual studies—skull roentgenograms, brain scan, CT, MRI, neurologic examination, complete ophthalmologic examination including field examination—must be performed. If the other
signs of increased intracranial pressure are present, contrast studies must be considered.

Disc edema caused by severe pulmonary disease, such as emphysema, can also be seen. It may be caused by decreased venous drainage from the head into the chest, or it may be secondary to an increase in blood \( PO_2 \).

Chronic lung disease is a well-known cause of increased intracranial pressure. Despite the large numbers of people whom we see with various grades of chronic obstructive pulmonary disease (COPD), the occurrence of papilledema is rare. The cause is believed to be the increased \( CO_2 \) that results from the COPD. Kety showed that by raising the level of \( CO_2 \) in the blood, secondary vascular dilation occurs, resulting in increased intracranial pressure. The secondary anoxia these patients suffer over a long period rarely causes optic nerve ischemia and decreased vision. If another complicating factor occurs, such as a reduction in optic nerve perfusion pressure, then decrease in vision can occur. The chronic anoxia increases erythropoiesis, and a secondary type of polycythemia occurs. This hyperviscosity of the blood may cause sludging and vascular congestion at the nerve head, with the appearance of papilledema. The increased volume of the blood also causes an increase in the intravascular space in the cranial vault, further increasing the intracranial pressure.

Papilledema can also occur with other causes of respiratory compromise such as the Pickwickian syndrome.

**FLUORESCINE TEST**

Fluorescein dye injections are useful for separating true disc edema from pseudopapilledema. Fluorescein testing does not, however, distinguish among the different causes of disc edema. Moreover, in many cases of mild papilledema, no true leakage of the dye from the disc occurs, although one would expect this result. The fluorescein test can be done without a photographic setup. The main requirements are a cobalt blue filter for the indirect ophthalmoscope and access to the fluorescein dye. Detailed study of the fluorescein photographs is desirable. Whenever possible, the test should be performed in conjunction with retinal photography rather than as a casual office procedure.

**SUGGESTED READINGS**


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FUNCTION AND ANATOMY
OF THE PUPIL

The Latin word for pupil is pupilla. A translation of this is doll- or imagelike. This can be interpreted as the image that is reflected in the pupil when the cornea has its normal, crystal clear, mirrorlike quality. Pupil function begins at about the fifth month of fetal life and is active at the sixth month of fetal life. The pupil performs many functions. It regulates the amount of light entering the eye. By not dilating to its fullest extent, it reduces the spheric and chromatic aberration induced by the peripheral lens. By becoming small, it increases the depth of focus. The change in pupil size from 1.5 mm to 8 mm is equivalent to a camera lens aperture from F13 to F2.5 or a 30/1 difference in admitted light. All these pupillary phenomena can be observed by the physician who puts a miotic or a mydriatic in his or her own eye.

The sphincter muscle is innervated by parasympathetic fibers that come to the eye with the third cranial nerve. Pupillary dilatation is occasionally the earliest sign of third cranial nerve paralysis. The dilator muscle innervation comes in mainly by way of the ophthalmic nerve trunk through the superior orbital fissure.

Rare cases of congenital mydriasis exist. Pupils with this disorder respond to light but not to convergence or accommodation. They constrict in the presence of 4% pilocarpine, confirming that a sphincter is present. These pupils also react to 10% phenylephrine hydrochloride, confirming a functioning dilator muscle. There is no reaction to potent cholinesterase inhibitors, suggesting an abnormality in the activity of acetylcholine.

ANATOMY

Gross Anatomy

The gross anatomy of the iris can be divided into four layers. The first is the anterior border layer. The second contains the stroma and the sphincter muscle. The third is the anterior epithelium, which differentiates into the dilator muscle. The fourth is the posterior pigmented epithelium, which gives most of the color to the iris. The further development of a brown iris depends on the progressive increase in stromal melanosomes. When there are few melanosomes, the shorter blue wavelengths pass through the stroma and are reflected as blue from the posterior pigmented layer, which does not absorb them. As the melanosomes of the stroma increase, the color progresses to gray and then brown. The development of the melanosomes occurs during the first year of life and depends
on sympathetic innervation. Lack of this sympathetic stimulation leads to the heterochromia that is a part of congenital or neonatal sympathetic paralysis (Horner syndrome).

Parasympathetic System

The ocular motor complex in the mesencephalon contains a paired group of cells called the Edinger-Westphal nucleus. These are the visceral nuclei and are located dorsal medial to the somatic nuclei. They contain preganglionic parasympathetic cell bodies that send processes to synapse in the ciliary body. Between these two paired columns of somatic cells is the nucleus of Perlia. The anterior medial nuclei are located ventral to the complex and are near the midline. Preganglionic pupillary fibers not only arise from this complex but also may come from Perlia's nucleus. The exact part of the preganglionic fibers contributed by Perlia's nucleus is not certain. There is still a controversy over which part of the Edinger-Westphal nucleus supplies the pupil and which part accommodates. The parasympathetic fibers follow the course of the oculomotor nerve (see Figs. 6.15, 6.16, 6.17, and 6.18) from the brainstem, exit in the interpeduncular fossa, and travel with the oculomotor nerve all the way into the cavernous sinus. During its course, the parasympathetic fibers are located in the peripheral superior part of the oculomotor nerve. In the cavernous sinus, the parasympathetic fibers travel with the inferior division of the third nerve into the orbit and then enter the ciliary ganglia, where most of the fibers are preganglionic parasympathetic. Other fibers from a branch of the oculomotor nerve to the inferior oblique muscle also enter and synapse with cell bodies in the ciliary ganglion. All these fibers now become postganglionic fibers and become the short ciliary nerves that pass forward between the sclera and the choroid and innervate the iris sphincter and ciliary body.

Other fibers pass through the ciliary ganglion without synapsing. These are postganglionic sympathetic fibers from the superior cervical ganglion. They pass through the ciliary ganglion without synapsing and continue on also as short ciliary nerves. These fibers then act as vasomotor fibers for the iris vessels, and a very small number innervate the dilator muscle.

Ninety-four percent of the fibers that synapse in the ciliary ganglion go to the ciliary body. The ratio of pupillary fibers to the light reaction to those to accommodation appears to explain the preference of fiber regeneration for the near reflex over that to the light reflex, as seen in Adie's pupil.

The short ciliary nerves that contain postciliary ganglion parasympathetic fibers pass forward in the space between the choroid and sclera mix and form into a complex that innervates the iris sphincter, ciliary muscle, and vasomotor responses in the iris vessel walls. This complex appears to innervate the muscles in a random manner. However, Thompson and others feel that there is a more direct and specific fiber to muscle cell relationship. In general, the postganglionic fibers from the ciliary ganglion innervate the ciliary muscle and the iris sphincter.

Sympathetic System

The first neuron of the sympathetic fibers begins in the posterior hypothalamus, traverses the midbrain and reticular substance of the pons, and ends in the anterior lateral gray substance of the spinal cord (Fig. 3.6). It synapses somewhere between C-8 and T-2, in what is referred to as the ciliocerebral center (Hudge's center). The second neuron begins when the fibers leave the spinal cord via the white ramii communicantes of C-8 to T-2, traveling through the stellate ganglion and vertical sympathetic trunk to synapse at the superior cervical ganglion, where the second neuron is completed. The work of Palmubo suggests that the preganglionic neurons controlling the pupil enter the upper one-half of the stellate ganglion by a separate paravertebral root. The stellate ganglion contains the fibers from the lower cervical and first thoracic ganglia. He noted that
Unlike taking the entire stellate ganglion, when he resected the preganglionic root and only the lower one-half of the ganglion, he did not produce a Horner's pupil in 93% of the cases. He concluded that the pupillary fibers must travel by a separate root to only the upper half of the ganglion.

The third neuron is composed of fibers that form a plexus around the carotid artery. As the carotid artery bifurcates, the fibers suberving sweating follow the external carotid artery, a fact that is important in the localization of the lesion producing Horner's syndrome. The main fibers go with the internal carotid artery into the carotid canal, in which a thin-walled structure separates the carotid artery from the tympanic cavity. The sympathetic fibers penetrate the carotid, tympanic wall and form the caroticotympanic nerve, which runs submucosally in the middle ear. They then pass through the cranial vault near the pterygoid canal and enter the cavernous sinus. Passing over the gasserian ganglion, they enter the orbit via the superior orbital fissure. The sympathetic fibers that innervate the dilator muscle branch with the nasal ciliary nerve, bypass the ciliary ganglion, and then branch into the long ciliary nerves and innervate the dilator muscle. These enter the suprachoroidal space nasally and temporally beneath the horizontal recti muscles to join the anterior neural plexus. The other sympathetic fibers pass through the ciliary ganglion without synapsing and travel with the short ciliary nerves to become vasomotor fibers for the iris vessels.

Another group of fibers that pass through the ganglion without synapsing is the long sensory root that leaves the ganglion to travel with the nasociliary nerve of the opthalmic division of the trigeminal nerve.

The afferent pupillary fibers are not retinal specific and are believed to begin with photoreceptor cells. They travel with the axons of the optic nerve and branch off just short of the lateral geniculate body. The fibers subserving the pupillary light reflex branch off the optic tract before the lateral geniculate body and travel in the brachium of the superior colliculus, where they synapse in the pretectal region of the mesencephalon. Stereotaxic stimulation studies by Ranston and Magoun demonstrated pupillary constriction when this area was stimulated and lack of constriction when this area was bilaterally destroyed.

Change in accommodation is produced by movement of the ciliary body with a resultant change in shape of the lens from contraction or relaxation of the zonules. The ciliary muscle is divided into three segments: meridional, radial, and circular portions. Convincing evidence demonstrates a dual innervation for the ciliary muscle. One of our group, R. Fenton, examined the ciliary muscle of a patient with a congenital ocular motor nerve palsy and found only the circular muscle hypoplastic. Similar findings are seen in cases of sympathetic paralysis in the longitudinal and radial portions of the ciliary muscle. These parasympathetic fibers appear to originate in the caudal portion of the parasympathetic nucleus in the mesencephalon, as suggested by the stereotaxic work of Bender. There is some evidence put forth by Burde that there may also be a more direct parasympathetic route to the ciliary muscle, bypassing the ciliary ganglion.

**PUPILLARY SIZE AND PHYSIOLOGY**

Sometime during the first 6 months of life, the pupils begin to increase in size, reaching their maximum size during early adulthood. Occasionally adolescent patients complain that their pupils are too large. Largeness of pupils is not significant if the pupils are equal in size and if they contract equally well. In older people the pupils become small.

We are always concerned about anisocoria as well as pupil function. There is a condition of benign anisocoria. The difference in pupil size is usually about 0.5 mm or less. Lowenfeld identified this difference in about 20% of the patients in his series. No other abnormality in function or pharmacologic
response was noted. Her explanation is that there is an unequal supranuclear control of the dorsal mesencephalic visceral nuclei on the pupillary function.

The sympathetic and parasympathetic systems control the movement of the pupil. However, this is too simplistic a summary of pupillary movement. Many parts of the brain possess some control over pupillary function via the autonomic system. These include the frontal and occipital cortex, the hypothalamus, and, some suggest, a retinohypothalamic pathway.

The sympathetic and parasympathetic systems both have preganglionic fibers with acetylcholine as the transmitter substance. The postganglionic transmitter substance in the sympathetic system is norepinephrine and in the parasympathetic system is acetylcholine. This fact is clinically important in the pharmacologic testing of different pupil abnormalities discussed below.

Recent studies suggest that pupil-sparing third nerve palsy may not be as sparing as once thought. The pupil cycle time was found to be abnormal in cases of diabetic ophthalmoplegia. However, pupil abnormalities in diabetes are well known, particularly to any cataract surgeon who need to dilate a pupil preoperatively. There is not uncommonly some autonomic dysfunction of the iris.

It appears that, just as Hering’s law applies to yoke muscles serving motility and levator function, it also applies to accommodation. For example, if one paralyzes the pupil and accommodation in one eye with a cycloplegic drug, and the person then tries to fix his or her vision up close with the cycloplegic eye, there is excessive miosis and accommodative response in the eye without cycloplegia. Alternatively, if a mydriatic drug is instilled in one eye and the patient now fixes with this eye, the accommodative response is normal in that eye, and the fellow eye does not show the excessive responses that occur when a cycloplegic drug is used. These findings appear to support the application of Hering’s law to accommodation; that is, the accommodative function of the near reflex can be separate from the miotic component.

NORMAL PUPILLARY REFLEXES

Three normal pupillary reflexes deserve discussion.

PHYSIOLOGIC PUPILLARY UNREST. This normal pupillary movement goes on constantly, even when the stimulation of the pupil does not vary. The movement varies from very active to barely perceptible. Both extremes may be (and usually are) normal. Abnormally active pupillary movement is said to represent a pathologic state. I have not found the separation of pupillary motion into physiologic movement and hippus valuable or valid.

CILIOSPINAL SKIN REFLEX. This phenomenon is frequently tested, but its mechanism is often misunderstood. Pinching the skin at the neck should dilate the pupils. In the unconscious patient the test is useful for determining the depth of coma and intactness of brainstem pathways. The reflex is mediated by the pain fibers of the descending branch of the fifth cranial nerve and is not (as was once thought) initiated by squeezing the sympathetic chain in the neck.

PUPILLARY LIGHT REFLEX. The degree of pupillary contraction does not always indicate the state of vision. It is not unusual, for instance, for a patient to have finger-counting vision caused by central chorioretinitis and still maintain not only a good pupillary light reflex but also one that is equal to the reflex pupillary contraction to light of the uninjured eye. If, however, one pupil is sluggish to light (compared with its fellow eye) but better to accommodation, a defect in the afferent arc of the light reflex is indicated. If the loss of vision is severe enough, an afferent defect or pupillary escape phenomenon may be present.

We are all familiar with the pupil constricting to light and dilating when that stimulus is removed. This phenomenon also occurs physiologically when you go from a
lighted environment to a darker one. There are rare cases in which the pupil constricts to darkness. The mechanism is not well understood. This response was first proposed as a sign of retinal disease such as congenital stationary night blindness and congenital achromatopsia. However, it has also been reported in albinism, Best’s disease, optic nerve hypoplasia, retinitis pigmentosa, and leber’s congenital amaurosis.

TOURNAY PHENOMENON. The Tournay phenomenon refers to the dilation of the pupil in the abducting eye on sustained lateral gaze. This reaction does not occur immediately, but after a few seconds of sustained gaze. Sharpe and Glaser studied 30 patients, using infrared photography, and found no instances of the Tournay phenomenon. Loewenfeld, Friedlander, and McKennon, in studying 150 patients, found the phenomenon occasionally and suggested that it may occur in up to 10% of people.

IRREGULARITY OF THE PUPIL

Another consideration in pupillary function, irregularity of the pupil, may be due to an old inflammation that has caused posterior adhesions (synchiae) to the lens. The condition may prevent adequate dilatation in the dark or adequate contraction in the light in one or more quadrants, depending on the extensiveness of the synchiae. Colobomas of the iris are always in the area of the fetal cleft, which is to the temporal side of the 6 o’clock position. Surgery, iris tumors, and blunt trauma can also distort the iris. If the blunt trauma tears the sphincter, the pupil is peaked. If the trauma tears the base of the iris, the tear may not be seen without a gonioscopic examination. A tipoff that the condition exists, however, is that a segment of the iris is displaced centrally and the pupil is flattened in the same area. Gonioscopic examination shows the tear at the base of the peripheral iris. A history of significant blunt trauma to the eye, such as a hyphema or a blow-out fracture of the orbital floor, would indicate enough force to cause such a tear.

GENERAL EXAMINATION TECHNIQUES

The first step in the pupillary examination is to determine if anisocoria is present, which may not be as easy as it sounds. If you do not detect anisocoria in bright illumination, test for it in semidarkness, observing the other conditions for correct pupil testing. A carefully taken history may explain this pupil abnormality. Eye drops, trauma, or neck operation that has injured the sympathetic chain may produce anisocoria.

The mechanics of testing are not difficult, but they must be scrupulously employed. Do not stand in front of the patient and do not shine the light directly at the patient. Stand with the light off to one side, and have the patient look off at a distance to eliminate factors that might stimulate accommodation and invalidate the testing. Be sure that the beam of light is small enough that only one eye at a time is stimulated. Check the light reflex several times to be sure that the pupillary contraction is the result of the light and not of physiologic pupillary unrest.

The second step in the examination is comparing the reaction of the pupil to light and accommodation so that you can decide whether it is the larger or the smaller pupil—whether both pupils are abnormal. Signs of fatigue may be a more subtle indication of a pupillary defect. Fatigue may not be apparent with one testing of the light reflex, and multiple restesting may be of value.

Traumatic mydriasis and iridoplegia can be complete, incomplete, or segmental. The causes of these findings after blunt eye trauma can be multiple. The sphincter can be torn or mechanically stunned. If the trauma is severe enough to cause recession of the angle, branches of the short ciliary nerve may be injured at the iris root. Lastly, retrobulbar hemorrhages may damage the ciliary ganglion or the short ciliary nerves.

The final step, particularly if function is intact and only anisocoria is present, is checking for associated signs, such as ptosis, muscle imbalance, heterochromia, or pupil cycling time.
The pupil cycling time can be determined by focusing a small beam of light, such as a slit lamp beam, at the pupil margin and measuring the average period of pupil oscillations with an infrared video pupillometer or a stopwatch. The clinical usefulness of pupil cycling time versus afferent pupillary defect may not be worth the effort to measure it. Some authors, however, believe that pupil cycling abnormalities indicate specific diseases. For instance, in demyelinating optic nerve disease, pupil cycling may be absent or at least abnormal (i.e., irregular in amplitude or just intermittent), even if there is a normal light response. They feel this abnormality is not seen in normal persons or in other diseases of the optic nerve.

Figures 3.1 and 3.2 outline the causes of miosis and mydriasis and provide information in a compact form that will help in the differential diagnosis (Figs. 3.3, 3.4, 3.5).

**TONIC PUPIL**

A tonic pupil (Adie’s pupil) is of interest because of the diseases that may be confused with it. When a tonic pupil appears to be nonreactive, it may be confused with a third cranial nerve paralysis that is secondary to an aneurysm—a mistake that results in unnecessary hospitalization and usually in an arteriogram. When a tonic pupil shows light-near dissociation, the patient may be labeled syphilitic. The tonic pupil has several clinical features that easily distinguish it from third cranial nerve paralysis and from syphilis. It is usually unilateral, occurring bilaterally in only about 10% of cases. Involvement of the second pupil, when it occurs, usually happens later and not simultaneously with the first pupil. The condition occurs predominantly in women between 20 and 40 years of age; it is uncommon in males.

There are two groups of tonic pupils. The first group is related to orbital disease that affects the ciliary ganglion. The cause for most of these cases is unknown (true Adie’s pupil) and carries with it no long-term bad prognosis for life or vision. A small number of orbital cases can be secondary to severe orbital trauma or orbital infections. The second group is neuropathic in cause and can be seen in association with diabetes, autonomic neuropathies (e.g., Ross syndrome), and Guillain-Barré syndrome.

**Light-Near Dissociation**

The initial complaint in a patient with a tonic pupil is usually that one pupil is larger than the other. The patient may or may not experience blurring but will have some visual complaints owing to the large pupil. On casual examination, the pupil does not appear to react to light or near. In addition, the patient may have a tension-related headache. The combination of internal ophthalmoplegia or partial third cranial nerve paralysis and headache immediately suggests an aneurysm. The diagnosis may be difficult if the pupil is truly unresponsive, and it may be unresponsive very early in the course of the disorder. A tonic pupil initially may be frozen to any light or to accommodation, no matter how prolonged the stimulus. Within days or several weeks, however, the more typical light-near dissociation phenomenon appears. The light-near dissociation pupil differs from the true Argyll Robertson pupil in that the true Argyll Robertson pupil does not have the tonic light and near response that an Adie’s pupil has.

When initially evaluated, many patients demonstrate light-near dissociation, a factor that simplifies the diagnosis. Some persons who have a tonic pupil also have cycloplegia, which adds to the confusion that the defect is a third cranial nerve paralysis. The cycloplegia is transient, and near-normal accommodation returns. In examining for pupillary reactions, use a prolonged stimulation by a bright light, such as that from an indirect ophthalmoscope. An excellent approach is to seat the patient in front of the slit lamp and to use that light to examine the eyes. The slit lamp is a bright-light source, and the magnification aids in the observation of pupillary narrowing.
## Pupillary Abnormalities

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Argyll Robertson</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Pseudo Argyll Robertson</td>
<td>Pseudotubes pituitinias; pseudotubes diabetic; third cranial nerve misdirection; periaque ductal syndrome</td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>Congenital; cluster headache; Rader paragenninal syndrome; migraine headache; carotidynia</td>
</tr>
<tr>
<td>Drug-induced (topical)</td>
<td>Glaucoma medication</td>
</tr>
<tr>
<td>Drug-induced (systemic)</td>
<td>Narcotics; barbiturates</td>
</tr>
<tr>
<td>Posterior synechiae</td>
<td>Iritis; hyphema</td>
</tr>
<tr>
<td>Punctum (coma)</td>
<td></td>
</tr>
</tbody>
</table>

### Types and causes of mydriasis.

<table>
<thead>
<tr>
<th>Types</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor paralysis</td>
<td>Aneurysm; diabetes; trauma; tumor; syphilis</td>
</tr>
<tr>
<td>Tonic pupil</td>
<td>Mydriatics</td>
</tr>
<tr>
<td>Drug-induced (topical)</td>
<td>Drug-induced (systemic)</td>
</tr>
<tr>
<td>medication</td>
<td>Traumatic</td>
</tr>
<tr>
<td>Drug-induced (systemic)</td>
<td>Essential iris atrophy</td>
</tr>
<tr>
<td>medication</td>
<td>Absent sphincter muscle</td>
</tr>
</tbody>
</table>

### Figure 3.2.
Types and causes of mydriasis.

### Figure 3.3.
Approach to pupil evaluation, part 1.

![Pupil Diagram](image-url)

- Anisocoria
- Pathologic
- Normal reaction (light and near)
- Smaller pupil
- Sympathetic paralysis
  - Acquired - Pupil increasing accommodates, Anisocoria more obvious in dark initally
  - Decreasing sweating with 3rd neuron
- Congenital - all above and increased ptosis
- Larger pupil
- Partial 3rd nerve palsy (internal)
- Constricts to 0.25% Pilocarpine
- Test - 2.5% Neo-Synephrine Hydroxylamphetamine 1/1000 aqueous adrenaline
• **Figure 3.4.**
Approach to pupil evaluation, part 2.

• **Figure 3.5.**
Approach to pupil evaluation, part 3.
The keys to diagnosing tonic pupil are for the physician to have an index of suspicion, particularly when the patient is a young female, and to look for the typical clinical signs. A partial third cranial nerve paralysis should not show any light-near dissociation. Lack of ptosis or of any vertical muscle imbalance in any field of gaze, although not absolute proof, is strong evidence against third cranial nerve paralysis.

**Tonic Movement**

Movement to light or accommodation is also typical in tonic pupil. Observe the patient at the slit lamp or with some magnification, such as a loupe or hand magnifier, and stimulate the pupil reflex steadily. The pupil contracts, but it does so slowly, giving the appearance of a light reflex in slow motion. If the condition were a partial third cranial nerve paralysis, the remaining pupillary reflex, although diminished in amplitude, would be brisk. In tonic pupil, the movements of the sphincter are not only slow but also irregular. The pupil contracts in segments, rather than simultaneously, for 360°, giving the appearance of a bag of worms moving. This phenomenon is not seen in third cranial nerve paralysis or syphilis except as a manifestation of third cranial nerve misdirection. This irregular contraction is due to segmental paresis of the iris sphincter. This seems to imply that one sector of the iris is innervated by one nerve with no lateral spread of innervation. This distribution may also be true in the Edinger-Westphal nucleus as suggested in the case report of Selhorst, Hoyt, and Feinsod on midbrain corectopia.

In the area of the cornea corresponding to the sector of iris paresis, there may be associated decreased corneal sensation.

Initially accommodative paresis is common, with gradual improvement over time. Just as there is tonicity of pupillary function, there is also tonicity of accommodation. This can cause asymmetric accommodation, giving rise to complaints of blurred vision, depending on which is the fixing eye. The contraction of the ciliary muscle may be somewhat segmental just as iris contraction is segmental owing to segmental paresis. There is clinical evidence in support of this phenomenon. In one-third of patients, astigmatism is induced when accommodation is stimulated.

One author suggests that tonic pupils can occur after third nerve palsy. Abnormal regeneration can cause segmental iris contraction, but tonic redilatation does not occur as in true Adie's pupil, which is probably due to supersensitivity to acetylcholine.

**Size**

A tonic pupil is usually larger initially than its fellow pupil. When reinnervation of the tonic pupil occurs, the pupil becomes somewhat smaller, but anisocoria remains. Occasionally on examination, the tonic pupil is smaller than its fellow pupil. The tonic nature of the pupil is also seen when it is redilating, as well as when it is contracting. Thus, if a patient to be examined has been reading in the physician's waiting room for a period of time, both pupils will have contracted. The physician examining the patient observes that the unaffected eye quickly redilates, but the tonic pupil remains small for a while—a phenomenon that may persist throughout the examination. Such a pupil is likely to be confused with a miotic pupil because it is small.

**Mecholyt Test**

The more peripheral the lesion is in a nerve, the more likely it is to develop supersensitivity to the motor endplate excitor substance. The lesion in the tonic pupil is just behind the globe, in the ciliary ganglion. A patient with a tonic pupil develops supersensitivity to a 2.5% mecholyt solution, whereas the normal pupil does not contract with even a 15% solution. The supersensitivity is often not present initially, and if the test results are negative, the test should be repeated at a later date.
To perform this test, measure both pupils at distance fixation and then instil one drop of a 2.5% methacholine solution in each eye. Dismiss the patient for 45 minutes, telling her not to read or do any other close work. When she returns, measure the pupils again at distance fixation under the same lighting conditions. The tonic pupil will be smaller than before and frequently smaller than the pupil of the normal eye. If both pupils are tonic, both react; thus the physician cannot be sure that the patient is not one of those rare people who react to a 2.5% methacholine solution. (Methacholine sensitivity can also be seen in the Riley-Day, Goldenhar, and cri-du-chat syndromes, all of which are easily differentiated from the tonic pupil.)

If methacholine is not available, a 0.125% pilocarpine solution can be used. The normal pupil will react with less miosis to a 0.125% pilocarpine solution than will the tonic pupil. It is not important if the normal pupil also constricts to 0.125% pilocarpine; the tonic pupil will constrict proportionately more.

The site of the lesion for Adie’s tonic pupil and the subsequent supersensitivity to weak parasympathomimetic substances is in the postganglionic area of the ciliary ganglion. However, some cases of ocular motor palsy show some parasympathetic supersensitivity in the preganglionic area. This finding suggests that there may be direct parasympathetic fibers from the midbrain to the eye without synapsing in the ciliary ganglion. Laboratory confirmation of this was demonstrated by Jaeger and Benevento and confirmed by Parelman, Fay, and Burde. Even though a postganglionic lesion is the most likely cause of a positive methacholine test, the examiner should keep an open mind for other locations should the other clinical signs fit.

**Tonic Pupil Syndrome**

Some patients with a tonic pupil also have loss of knee and ankle reflexes. Other reflexes, such as those in the arms, can be absent or depressed also. This condition is known as the tonic pupil syndrome. The loss of the reflex may be unilateral or bilateral, and it is not necessarily ipsilateral with the abnormal pupil. Since the patient is asymptomatic, loss of the reflex is not brought out in the history; however, the reflexes can be tested easily. The reason for the association of tonic pupil and loss of reflexes is not understood. The reflex loss does support the tonic pupil diagnosis if the pupil is in the early phase of no reaction to light or accommodation.

**Significance**

The important feature of the tonic pupil syndrome and of the isolated tonic pupil is that neither condition is related to any ocular or nervous system disease that needs to be evaluated and treated. It is important, however, to inform the patient about the condition so that she in turn may inform any future physician of her eye and reflex changes and thus prevent another physician from trying to fit them into another diagnosis. The patient should also carry some medical identification so that, should she ever become unconscious, the tonic pupil will not be considered a sign of a subdural hematoma and hence lead to a craniotomy.

**ARGYLL ROBERTSON PUPIL**

**Classic Signs**

The pupillary phenomenon of Argyll Robertson, or light-near dissociation, has been known since 1869, but its chief "super"—syphilis—is as old as man. A light-sensitive retina and miosis are the essential features. An amaurotic eye also has a pupil that is rigid to direct light stimulation and that contracts to an imaginary target at near. The true Argyll Robertson pupil does contract to near but usually not normally. It is
also smaller than a tonic pupil. A longstanding Adie's pupil may also become small but not as small as an Argyll Robertson pupil. The Argyll Robertson pupil is usually bilateral, but if it is initially unilateral, it is the smaller of the two pupils. Before-and-after pupil photographs under the same lighting and distance fixation circumstances are important to accurately document the results of the examination.

Irregularity of the pupil, a phenomenon frequently noted, is not one of the basic criteria. Argyll Robertson pupils become irregular because iritis occurs and posterior synechiae or iris atrophy from chronic inflammation develops. Argyll Robertson pupils also dilate poorly with atropine; however, this sign is difficult to evaluate and is not useful clinically.

**Light-Near Dissociation**

The classic signs of Argyll Robertson pupil, therefore, are rigidity to light and contraction to accommodation. In the past, these signs indicated tertiary syphilis 99% of the time. Since the advent of antibiotics, however, syphilis is less prevalent, and light-near dissociation is now more commonly a sign of Adie's pupil or tonic pupils caused by diabetic or alcoholic neuropathies.

In the 1800s, the bright lights of the indirect ophthalmoscope or the slit lamp were not available. Many of the then light-rigid pupils perhaps would not be considered rigid today. Therefore, I prefer to use the criterion of light-near dissociation. The small amount that the pupil reacts to light is normal and not slow as in the tonic pupil.

**Causes**

The fact that Argyll Robertson pupil represents tertiary syphilis means that the usual blood tests may be negative. If they are, an IFA-ABS test should be done. Argyll Robertson pupil may be (and often is) present without other signs of tertiary syphilis. Once syphilis is suspected, the physician should look for other ocular signs of the disease, such as peripheral chorioretinitis. If congenital syphilis is a possibility, the physician should look for salt-and-pepper retinopathy, as well as the ghost vessels of interstitial keratitis. The ghost vessels should be looked for at the superior cornes beneath the upper lid, since they may be subtle and missed unless the lid is elevated when the slit lamp examination is performed.

Although the Argyll Robertson pupil has long been associated with tertiary syphilis, on rare occasions, it has been seen with herpes zoster, sarcoid, von Recklinghausen encephalitis, diabetes, Lyme disease, and Wernicke's encephalopathy. The exact location of the lesion has not been absolutely identified. However, a discrete lesion to the Edinger-Westphal nucleus in the area of the periaqueuctal gray has been identified on magnetic resonance imaging (MRI) in cases of sarcoid and multiple sclerosis. The Edinger-Westphal nucleus has a caudal and a rostral area. The rostral portion controls the reflex to light, and the caudal portion regulates accommodation. A lesion in the rostral area would affect pupillary response and no accommodation, which is what we see in Argyll Robertson pupil. Tonic pupils also can occur in syphilis. The lesion in Adie's pupil is usually accepted as occurring in the postganglionic parasympathetic pathway. Recent cases of Thompson and Sharpe would suggest a similar site for syphilitic tonic pupil.

Mass lesions in and around the aqueduct of Sylvius, between the third and fourth ventricle, can cause Argyll Robertson pupils. The lesions frequently cause other signs, such as paralysis of up-gaze and retraction nystagmus. If retraction nystagmus is not obvious, it can be elicited by bringing optokinetic targets from above down. In this way, the quick component of the nystagmus is up and reinforces the retraction nystagmus, which is brought out in up-gaze or
attempted up-gaze. The patient under consideration is obviously not a syphilitic patient.

**Pseudo Argyll Robertson Pupil**

Pseudo Argyll Robertson pupil is seen in pseudotabes punitaria, pseudotabes diabetica, and third cranial nerve misdirection. In pseudotabes punitaria, the light reaction is poor because of the underlying disease, in which the optic nerves are affected at the chiasm. In pseudotabes diabetica, the poor light reaction is secondary to either poor vision or neuropathy of the short ciliary nerves.

Third cranial nerve misdirection is not common, but it can be mistaken for unilateral Argyll Robertson pupil. It is the unilateral nature of the pseudo Argyll Robertson pupil that should bring third cranial nerve misdirection to mind. The pupillary reaction to near occurs not because the pupil contracts on near gaze but because the medial rectus muscle is stimulated on near gaze. The stimulation is due to a misdirection after recovery from third cranial nerve paralysis, in which some relationship develops between the medial rectus muscle and the pupillary fibers. The pupillary reaction can also be demonstrated by observing the pupil when the patient is looking at a distant point and turning his or her gaze to the right or left so as to stimulate the appropriate medial rectus muscle. This procedure causes contraction of the pupil, just as in convergence, and differentiates the condition from a true Argyll Robertson pupil. The significance of the sign is that it occurs more commonly after a traumatic third cranial nerve paralysis or because of an aneurysm and rarely with tumors or syphilis, and it has never been reported after diabetic third cranial nerve paralysis. Therefore, if a patient has third cranial nerve misdirection and diabetes, the previous third cranial nerve paralysis was caused not by the diabetes but by something else—in the absence of a history of severe trauma, most likely it is an aneurysm.

Some clinicians describe a pupil that is large and does not react to light but does contract to near (and is associated with a positive blood test) as an Argyll Robertson pupil.

**FIXED PUPIL**

**Amaurotic Pupil**

The diagnosis of an amaurotic pupil is often made incorrectly because all four of the criteria for the condition are not evaluated. The observer frequently relies only on the fact that the pupil does not react to light. The criteria are (a) the blind eye has no direct reaction to light, but (b) it does react consensually, (c) the normal eye has a good direct reaction to light, but (d) it does not react consensually from a light shone in the amaurotic eye. If one were to use the lack of direct reaction to light as the only criterion, Argyll Robertson and tonic pupils would be considered blind—and obviously they are not. If the affected eye lacks both direct reaction and consensual reaction, both limbs of the pupillary arc are involved. This involvement suggests an orbital apex syndrome, since the third cranial nerve, as well as the optic nerve, are affected.

A more difficult situation arises when the patient complains of blurred vision and has a large nonreactive pupil. The initial impression may suggest optic nerve involvement also. However, the distance vision may be blurred because of an uncorrected refractive error, and the near vision may be blurred because of the loss of accommodation that becomes manifest with cycloplegia. In addition, a good consensual reaction exists in the normal eye.

**Drug-Induced Cycloplegia**

The possibility that the patient has either accidentally or intentionally put a cyclo-
Pupillary Abnormalities

Pupillary drug in the eye should be considered. Accidental dilatation and cycloplegia can come about through the use of unlabeled eye drops that were prescribed for other eye diseases. Rubbing the sap of certain plants and flowers can also result in cycloplegia. Most of the night-blooming flowers contain scopolamine. The physician who is confronted either with no background or with a negative neurologic examination should put one drop of a 0.5% pilocarpine solution in the affected eye. If no reaction occurs in either eye, then the test is inconclusive concerning pharmacologic blockade. In these cases and particularly in brown eyes, 1% pilocarpine may be needed. If the patient's mydriasis is drug-induced, the motor endplates will not react to such a dilute pilocarpine solution. If the condition represents a partial third cranial nerve paralysis, however, the motor endplates are intact and will respond with the appropriate miosis.

In addition to the weak pilocarpine test for proving blockade, there may be systemic symptoms and signs that suggest a diagnosis. These include hyperpyrexia, urinary retention, dry flush skin and dry mucous membranes, psychiatric agitation, confusion and disorientation, ataxia incoordination, and visual and auditory hallucinations.

AFFERENT PUPILLARY DEFECT

One of the functions of the pupil is regulation of the amount of light falling on the retina. Too much or too little light prevents the retina from working at peak efficiency.

**Eliciting the Sign**

If the amount of light shining into a pupil is reduced, both pupils dilate to gather in more light. If the intensity of the light is not reduced and the optic nerve has developed a conduction defect, less light is transmitted, a phenomenon that the brain interprets as less light getting onto the retina. The response to this light "reduction" is the same as that in the first instance—both pupils dilate to an appropriate amount.

The afferent pupillary defect (Marcus Gunn pupillary escape phenomenon) depends on the light-reduction response that occurs in the presence of a conduction defect in the optic nerve. In attempting to demonstrate the afferent pupillary defect in a patient, the physician shines the light into each eye separately. Both pupils respond, even though one optic nerve has a conduction defect. A difference may exist in the quality of the response of each pupil to direct light, but the difference cannot usually be appreciated clinically unless the optic nerve is severely affected. However, when the light is brought quickly from the normal pupil to the side with the conduction defect, both pupils dilate (swinging flashlight test). The brain interprets the decrease in signals from the nerve with the conduction defect as it would if the intensity of the light were reduced.

The afferent pupillary defect is more easily seen in dim illumination with distance fixation. The observer must be careful not to stimulate accommodation by standing in front of the patient or by putting a light directly in front of the pupil. Sometimes it is even valuable to quantitate this sign, which can be done by use of progressive neutral density filters. Increase the neutral density filter over the normal eye as you do the swinging flashlight test until the least neutral density filter is found that neutralizes the afferent pupillary defect. If a pupil responds more slowly to light than usual, do the test more slowly to better see the retardation, and vice versa for a pupil that responds rapidly.

**Causes**

A conduction defect in one optic nerve causes the afferent pupillary defect, but it does not account for unequal pupils, which
is a separate entity that requires additional explanation if it occurs.

The afferent pupillary defect (APD) is seen only in unilateral optic nerve disease. It is not generally a useful sign when the chiasm is involved. It can occasionally be seen in chiasmal disease if one nerve is more involved. An APD can also occur on a retinal basis, but only when extensive destruction has occurred. Such lesions as those in macular degeneration or the large macular lesions in toxoplasmosis can cause it. A lesion such as diffuse diabetic retinopathy, with proliferation and loss of most of the retinal architecture, or a complete retinal detachment can cause an APD. Therefore, a patient who has some minor retinal disease and exhibits the APD has two diseases, one in the retina and one in the optic nerve.

APD has also been seen in cases of strabismus, but this is rare, and concomitant optic nerve disease should be seriously considered.

In a patient with a dense unilateral cataract, the afferent pupillary response may be falsely positive. If this test is repeated in a dark background environment, the test becomes negative if no other optic nerve disease coexists. The usual explanation for no APD is that even with decreased light transmission there is an increase in scattering of light that makes up for it. Sadasiv believes that it is due to retinal compensation over the period of time it takes the cataract to develop.

The main use of the APD is in evaluating the patient who complains about the vision in one eye but who has a normal ophthalmoscopic examination. The APD is a valuable diagnostic sign in retinobulbar neuritis, particularly in patients with relatively good vision. It can be elicited even in cases of optic neuritis with only one Snellen line difference in acuity between the two eyes.

The afferent pupillary escape phenomenon has been seen in tract lesions with a complete homonymous hemianopia. One author (O'Connor) has seen it in cases of partial homonymous hemianopias. Behr first noted a decreased contralateral pupillary response in tract lesions. The proposed reason is that there is a greater field defect in the contralateral eye, with the temporal field defect.

The APD attests to the presence of the conduction defect, not to its time of onset. This defect lasts as long as there is a conduction difference between the two eyes.

**THIRD CRANIAL NERVE PARALYSIS**

An early sign of third cranial nerve disease may be simply mydriasis. However, careful evaluation may show that other functions of the third cranial nerve are also affected. Look for a small vertical muscle imbalance that may be seen only on up-gaze, for a slight ptosis, or for an ipsilateral decrease in accommodation. Repeated testing of the pupil with light may show pupillary fatigue in the abnormal eye, whereas the fellow eye continues to constrict normally, even when repeatedly tested.

Partial internal ophthalmoplegia has the same differential diagnosis and serious implications as described for total third cranial nerve paralysis. The most serious and urgent implication is an aneurysm. Pupil-sparing oculomotor paralysis secondary to internal carotid-posterior communicating aneurysms was once considered rare. Now this sign is seen in about 8% of such cases.

Kerr and Hollowell confirmed Sunderland’s work on the location of the pupil fibers in the third nerve. They are located dorsomedially and medially in the nerve. This has particular significance in predicting the ability to produce mydriasis with pressure on the third nerve. It takes less pressure on the medial aspect of the nerve than on the dorsal or lateral aspect to cause mydriasis. For instance, displacement of the brain with compression of the third nerve against the tentorial edge readily causes mydriasis, whereas increased intracranial pressure with pseudotumor cerebri does not.
It is important, therefore, to identify other causes that can produce internal ophthalmoplegia. Infections, such as varicella and botulism, on occasion have been reported to cause internal ophthalmoplegia. Internal ophthalmoplegia has also been reported after panretinal photocoagulation. The probable mechanism created by the photocoagulation is damage to the short ciliary nerves traveling anteriorly in the sclera.

Accommodation problems have been reported to occur during the regulation of diabetes. This is besides the usual refractive error so commonly encountered. These findings are not associated with pupillary or motility signs. The accommodative changes are usually mild and often missed. However, they can be severe on occasion, and their possible association with diabetes should be remembered. The cause is unknown, but it is suggested that a similar mechanism that affects the resiliency of the lens during changes in blood sugar also accounts for changes in accommodation.

Aberrant regeneration of the third cranial nerve can also affect only pupillary fibers. The aberrant association of pupillary contraction with innervation of the medial rectus has been well described by Ford, Walsh, and King.

Czarnecki and Thompson described three other pupillary signs of misdirection: (a) contraction of the iris sphincter to eye movements similar to that described by Ford, Walsh, and King but only in certain sectors of the iris, suggesting not only aberrant but partial regeneration of the third cranial nerve; (b) also similar sector contractions to light stimulation; and (c) in the dark and in the absence of light stimulation and with pupils that had no light reaction, there was miosis but asynchronous with the normal eye. Since there is no afferent arc to stimulate the pupil, one explanation is that fibers intended for the third cranial nerve muscle group now innervate the pupil.

Recent studies suggest that pupil-sparing third nerve palsy may not be as sparing as once thought. The pupil cycle times were found to be abnormal in cases of diabetic ophthalmoplegia. However, pupil abnormalities in diabetics are well known. There is not uncommonly some autonomic denervation of the iris as well.

HORNER SYNDROME

Horner syndrome, which affects the eye and eyelids, is caused by paralysis of the cervical sympathetic nerves.

Anatomic Considerations

Discussion of the many syndromes involving the long sympathetic nerve chain to the eye requires at least a cursory knowledge of the relevant anatomy (Figs. 3.6, 3.7).

Signs

PTOSIS. Ptosis is never severe in Horner syndrome, since the levator portion of the third cranial nerve does most of the lid elevation. The ptosis varies, depending on how tired or alert the patient is. It is not uncommon to observe a ptosis when the patient is evaluated after admission in the evening (when tired) and to find it has improved in the morning. This improvement is not real, since the levator and frontalis muscles and uninjured sympathetic fibers act to overcome the ptosis. Occasionally, no ptosis exists in the presence of sympathetic fiber damage, namely when the fiber to Müller's muscle has already branched off in the orbit proximal to the site of injury. Müller's muscle may also be spared in cases of slight damage to the sympathetic fibers. I feel that this sparing is rare. The lack of ptosis makes the diagnosis of Horner syndrome more difficult, but its absence or presence does not usually help much in determining the anatomic location, since the other factors just mentioned influence the degree of ptosis.

An additional problem in diagnosing the ptosis of Horner syndrome occurs in the elderly patient who may also have pseudo-
**Figure 3.6.**
Course of sympathetic nerves from hypothalamus to the eye and adjacent anatomic structures.

1st Neuron—Associated symptoms of brain-stem involvement, such as dizziness, vertigo, transient ischemic attacks suggestive of hemianopsia with or without long tract signs.
- Hydroxyamphetamine—Dilates both pupils
- Phenylephrine—Dilates both pupils
- Cocaine—Horner's pupil dilates more poorly than normal pupil

2nd Neuron—Chest mass with arm pain, phrenic nerve paralysis, supraventricular nodules, neck mass, thyroid enlargement, neck surgery, neck injury, cervical osteoarthritis with bone spurs.
- Hydroxyamphetamine—Dilates both pupils
- Phenylephrine—Dilates both pupils
- Cocaine—Horner's pupil dilates more poorly than normal pupil

3rd Neuron—History of vascular headache (migraine, Reeder's, cluster), carotid artery disease with ipsilateral visual loss and contralateral motor and sensory signs. Sweating present if above bifurcation of carotid artery and absent if below bifurcation.
- Hydroxyamphetamine—Horner's pupil dilates less or not at all
- Phenylephrine—Horner's pupil dilates more
- Cocaine—Horner's pupil dilates more poorly or not at all

**Figure 3.7.**
Clinical differences of three sympathetic neurons.

ptosis secondary to blepharochalasis. In such a case, attention should be directed to the lower lid, which also has sympathetic innervation. I prefer to call this reaction Kears' lower lid sign, since it was Kears who pointed out to me the significance of sympathetic innervation of the smooth muscle of the lower lid. This innervation normally holds the lower lid down and against the globe. When the muscle is paralyzed, the lid rides up slightly (Fig. 3.8, A and B). The test for the lower lid sign is performed by having the patient fixate on a hand light and then moving the light up until the side with the suspected Horner syndrome has the 6 o'clock position of the cornea barely touching the lower lid. Then the other eye is observed. Instead of its being in the same
MIOSIS. Miosis may seem to vary in Horner syndrome. The brightness of the background light in which the patient is examined may make the anisocoria difficult to detect. The same can be said of the physician standing in front of the patient during the examination and thereby stimulating the patient's accommodation and reducing the size of both pupils. To overcome these two problems, the patient should be examined in a semidark room with his or her gaze at a distant point and the observer off to one side. Because of the slowness of the affected pupil to dilate in the dark, the anisocoria is greater during the first 5 seconds of dark adaptation than at 15 seconds.

The miosis may also vary according to the extent of the defect, patient alertness, extent of reinnervation, and degree of denervation sensitivity. As a result of denervation supersensitivity, a patient may complain of an occasionally larger pupil on the side on which the physician observes a smaller pupil. This situation rarely occurs, but it probably represents the patient's supersensitivity to circulating epinephrine, a phenomenon that can be elicited by the instillation of one drop of a 1:1000 aqueous epinephrine solution topically onto both corneas. In the patient with Horner syndrome, the pupil that has developed supersensitivity dilates, whereas the other pupil shows no reaction.

Systemic drugs such as barbiturates and narcotics can also cause miosis, but without ptosis. A notable exception to the rule is glutethimide (Doriden), which tends to enlarge the pupils, particularly when taken in toxic doses. Topical medications (including most of the antiglaucoma drugs) also cause miosis.

Miosis is greater in postganglionic lesions than in preganglionic ones.

OCULAR HYPOTONY. The intraocular pressure on the side of a Horner syndrome is at least 5 mm less than the pressure in the fellow eye.

HETEROCROMIA. The human iris is blue or slate gray at birth. Those irises that become brown do so by the end of the first year of life, a change that involves sympa-
thetic innervation. Therefore, the iris of a patient with congenital or neonatal Horner syndrome usually remains lighter, since no sympathetic stimulation occurs to make it darker blue or brown than the iris of its fellow eye. This phenomenon is obvious if the other eye is brown and the eye with the Horner syndrome is blue. It is not as apparent in blue-eyed patients, in whom the difference may be more subtle and can easily be overlooked. The difference is more easily seen in daylight than in artificial indoor light. Depigmentation is said to occur in acquired adult Horner syndrome, but for all practical purposes it can be considered a rare phenomenon. Therefore, Horner syndrome with heterochromia has a congenital or neonatal onset—a fact that may be of value in medicolegal testimony (Fig. 3.9).

**INCREASE IN ACCOMMODATION.**

Cogan demonstrated that an increased amplitude of accommodation occurs on the side with Horner syndrome. He also proved that the increase is caused not by the miosis but by change in the ciliary muscle that amounts to 0.5 to 1.5 diopters. It is difficult to use the phenomenon as a test in patients under 35 years of age because young people can read almost up to their nose; thus any variations in accommodation are difficult to detect clinically. In examining someone who needs glasses, be sure that the patient is wearing the correct distance prescription, with an equal reading prescription over it. With the use of the near reading card, you will find that the patient reads significantly closer on the side with Horner syndrome.

**ANHIDROSIS.** Lesions from the posterior hypothalamus to the bifurcation of the carotid artery result in ipsilateral loss of sweating ability on the face. If Horner syndrome occurs above the carotid artery bifurcation, the sweating mechanism is intact, a good localizing sign. However, demonstrat-

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**Figure 3.9.**

One example of congenital Horner's with heterochromia. Right eye has brown iris, and left iris is hazel with smaller pupil. Right iris is brown and left iris blue, but in this case the pupils were dilated prior to the picture. (Pictures courtesy of Dr. Caleb Gonzalez.)
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ing the loss of sweating ability or eliciting a history of it from the patient is not easy.

**DIPLOPIA.** Horner syndrome with con-tralateral diplopia suggests a trochlear nerve palsy on the opposite side that is found in a brainstem lesion. If the trochlear nerve paren-als is on the same side as the Horner lesion, consider the cavernous sinus or superior orbital fissure as the anatomic location.

**Chemical Tests**

The clinical usefulness of cocaine and epinephrine was outlined by Foerster and Gagel. These authors believed that using either a 4% cocaine solution or a 1:1000 aqueous epinephrine solution can differentiate the neurons anatomically. Cocaine prevents the reuptake of norepinephrine at the motor endplate and thus prolongs its action on the effector cell. If the sympathetic pathways are interrupted, norepinephrine should not be released, and therefore, a mydriatic effect should not occur. Epinephrine, on the other hand, works directly as a stimulator of the motor endplate. A 1:1000 aqueous epinephrine solution should not dilate a normal pupil; however, if supersensitivity exists (as can occur in postganglionic third-neuron lesions), the pupil will dilate. Therefore, Foerster and Gagel believed that the scheme shown in Figure 3.10 was a good one for localizing a Horner syndrome to one of the three sympathetic neurons; however, the scheme usually does not work.

Third-neuron Horner syndrome rarely shows supersensitivity to 1:1000 aqueous epinephrine. It is better to use 1 or 2% phenylephrine. This drug may dilate both pupils but will have a greater effect on the supersensitive pupil. It is important to document both pupil signs before and after the test to evaluate the relative effectiveness of the drug on both pupils. In theory, cocaine should not dilate any Horner syndrome pupil, no matter what neuron is involved, since no impulse comes to the motor endplate to release norepinephrine in the first place. If the Horner syndrome pupil does dilate, it is probably because the Horner syndrome is incomplete or because a small amount of norepinephrine has been released at the endplate constantly without direct central nervous system stimulation. Thompson and Mensher have modified Foerster and Gagel’s scheme by the use of hydroxyamphetamine, which works differently from the other two agents by releasing endogenous norepinephrine from an intact motor endplate. If the condition is a third-neuron Horner syndrome and the nerve and endplate have degenerated, epinephrine is not present and thus no mydriasis occurs with hydroxyamphetamine.

If the condition involves a first or second neuron, the third neuron is left intact, with the norepinephrine stores present. Even though no central nervous system innervation exists, hydroxyamphetamine releases the norepinephrine, and the pupil should dilate. My experience with the hydroxyamphetamine test makes it seem valuable. I

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on Pupil When Lesion is Central (First-Neuron)</th>
<th>Effect on Pupil When Lesion is Postganglionic (Third-Neuron)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>Normal mydriasis</td>
<td>No dilatation</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>No dilatation</td>
<td>No dilatation</td>
</tr>
</tbody>
</table>

**Figure 3.10.** Effects of cocaine and epinephrine on the pupils in Horner’s syndrome (Foerster and Gagel schema).
think that it has good theoretic points to recommend it and that it should be tried. Maloney, Younge, and Moyer evaluated the hydroxyamphetamine test and found it 84% accurate in predicting and 96% accurate in confirming a third-neuron Horner syndrome. Grimson and Thompson agreed that the test may be inconclusive in 15 to 20% of cases, and this number rises unless photographs are taken. The test is particularly unreliable in cases of congenital Horner syndrome. My experience with the test has been more limited than that of these authors, but I find it more useful than cocaine and 1:1000 aqueous epinephrine.

The cocaine test should be discussed further. The cocaine should be in a 4% solution and not a 10% solution as some advocate. A 10% solution adds nothing to the test, and copious use may do some transient damage to the epithelium. Changing the corneal tear film or epithelium by drops or corneal sensitivity testing only alters the topical pharmacologic sensitivity tests such as epinephrine and methacholyl and hydroxyamphetamine.

Causes and Significance

A usual question is, Why bother about Horner syndrome since most patients are not symptomatic or, at the worst, have only a slight ptosis? The reason for bothering is that Horner syndrome may be the tip of an iceberg, indicating a more serious condition.

In determining the cause of Horner syndrome, the usual approach is to try to localize it to a specific neuron. In older patients, one of the most common causes of Horner syndrome is a vascular infarct of the sympathetic chain. The lesion may occur along the first neuron in the brainstem, owing to the obstruction of the small penetrating vessels from the basilar artery. A lesion also may occur along the distribution of the third-neuron sympathetic chain associated with the carotid artery. The latter has been shown by Sears, Kier, and Chavis to occur experimentally.

The congenital variety of Horner syndrome is considered by most to be caused by neck injury from manipulation during a difficult forceps or breech delivery. Trauma is the most frequently found cause in those beyond infancy and under the age of 21. Patients older than 20 years of age, and particularly those over 50 years of age, with second-neuron Horner syndrome, should be investigated for the presence of tumor (usually malignant) when the onset of an isolated Horner syndrome occurs. The most common tumors are metastatic and bronchogenic carcinoma, particularly apical, or Pancoast tumors. Benign tumors, such as neurofibromas and thyroid adenomas, are less common.

The causes of isolated Horner syndrome have changed somewhat since the report of Giles and Henderson. Third-neuron Horner syndrome carries a high incidence of nonmalignant disease as the cause. Third-neuron Horner syndrome is more likely caused by a headache syndrome (e.g., Reeder's, cluster), trauma (e.g., basal skull fracture), or inflammations (e.g., Tolosa-Hunt, otitis media, herpes zoster, epidural anesthesia, and carotid artery dissection).

I have seen Horner syndrome in dissection of the internal carotid artery. Several of these have been from chiropractic manipulation. Carotid angiography can usually identify the problem. Some may be missed by this imaging technique such as in a case reported by Brown et al. They identified the dissection by MRI in which the subject demonstrated an area of hyperintensity.

The second-neuron Horner syndrome still carries a high incidence of tumors as the cause, as was pointed out by Giles and Henderson and confirmed in the subsequent reviews by Grimson and Thompson and by Maloney, Younge, and Moyer. Grimson and Thompson stated that the incidence is as high as 50%, and Maloney, Younge, and Moyer found that 72% of the tumors causing a Horner syndrome were along the second-neuron distribution. Younge makes an additional observation: Most of the tumors in
their series were Pancoast type, and Horner syndrome was rarely the presenting sign. Their patients also had arm pain, which should serve as a clue to the real cause of the Horner syndrome.

**Workup**

How does the physician evaluate Horner syndrome once the diagnosis has been made? The time of onset may be difficult to establish. The time the patient says it started may only be the time he or she noticed it. One of the best ways to establish the time of onset is by examining old photographs of the patient, particularly job, army, or passport identification photographs. Such photographs are usually unretouched, and often the pupils can be seen with a magnifying glass or the large indirect ophthalmoscope lens. If these types of photographs are not available, ask the patient to supply some high school or college yearbook pictures or some wedding pictures. The fact that a Horner syndrome has been present for 10 years or more points to a benign cause, even when the exact reason for the condition remains obscure.

Ask the patient about any neck operation (e.g., a thyroid surgical procedure) that might have injured the sympathetic chain. Scars from such operations can easily be overlooked. Ask also about a chest or heart operation, which could also account for Horner syndrome. In the past, when more carotid arteriograms were done using the direct carotid artery injection route, both permanent and transient Horner syndromes were sometimes seen.

Question the patient carefully about any neck trauma as a youth. If the patient played sports, ask whether a neck collar was worn for several months because of an athletic injury. Photographs showing the patient's pupils around that time, when any miosis would have been more evident before reinnervation, may document the time of onset. Horner syndrome can also be seen in severe whiplash injuries, such as those occurring in automobile accidents.

The examination should include palpation of the neck for masses, thyroid nodules, or supravacular nodes. Apical views of the lung to visualize a Pancoast tumor, as well as skull and cervical roentgenograms, should be ordered. Hematologic evaluation to rule out lymphomas or Hodgkin's disease is also indicated.

**Types**

**FIRST-NEURON HORNER SYNDROME.** The most common cause of first-neuron Horner syndrome is vertebral-basilar insufficiency as in Wallenberg syndrome. A Horner syndrome may be the only residual sign of a transient ischemic episode. Severe osteoarthritis of the neck, with obvious bony spurs visualized on roentgenographic examination, is known to have caused compression of the sympathetic fibers as they leave the cervical canal. I have also seen Horner syndrome occur with severe whiplash injury without other obvious neurologic deficits. Horner syndrome can be transient or permanent, and it may be the only evidence of the severity of the injury, particularly when the patient has multiple posttraumatic complaints.

Neurologic signs that appear to be on opposite sides of the nervous system suggest multiple sites of origin. One such combination is a Horner syndrome on one side and a fourth nerve palsy on the other side. However we must remember that the fourth nerve is the only crossed cranial nerve. The left fourth nerve is on the right side before it crosses in the anterior medullary velum. Therefore, this left fourth nerve before it crosses is near the right sympathetic nerve and can give this crossed arrangement of signs from one lesion.

**SECOND-NEURON HORNER SYNDROME.** Among the most common causes of second-neuron Horner syndrome is apical lung cancer (such as Pancoast tumor), which
is best demonstrated by apical views of the lung. Mediastinal tumor is also a cause, but it is not as easily detected.

**PHRENIC NERVE SYNDROME.** A new triad involving a Horner syndrome has been reported: Horner syndrome, a hoarse voice, and paralysis of the hemidiaphragm. This triad involves the second neuron of the sympathetic chain, the phrenic nerve, and paralysis of the recurrent laryngeal nerve. The only place these three nerves are in close apposition is at the level of the sixth cervical vertebra. This syndrome occurs with local or recurrent tumors to this area. The three cases reported by Rowland Payne involved recurrences of breast carcinoma.

**THIRD-NEURON HORNER SYNDROME—GROUP ONE.** Third-neuron Horner syndrome can be broken down into two groups. The first group includes patients with Raeder’s paratrigeminal syndrome, cluster headaches, and migraine. These three conditions may be aspects of the one disease, but each condition is worthy of comment because of its individual characteristics.

**Raeder’s Paratrigeminal Syndrome.**Raeder’s paratrigeminal syndrome is essentially a painful Horner syndrome; the major complaint is pain over the first and second divisions of the trigeminal nerve. The patient shows all the signs of Horner syndrome, except that the sweating mechanism is intact because the lesion is located above the bifurcation of the carotid artery. There may be a small area of anhidrosis on the ipsilateral forehead. This area is supplied by terminal frontal branches coming in with the carotid artery. This is a variable sign. Raeder’s syndrome occurs overwhelmingly in men, usually in those in their forties. The major consideration is that the condition is benign. The pain subsides, but frequently the Horner syndrome remains. The first reported case of Raeder’s syndrome involved a meningioma of the gasserian ganglion, but most subsequent reported cases have been benign. Davis, Daroff, and Hoyt reported one case associated with an extracranial aneurysm. Law and Nelson also had one case of a supraclinoid aneurysm, and Cohen, Zakov, and Solanga reported two cases associated with fibrous dysplasia.

Raeder’s syndrome can be broken down into two groups. Group 1 exhibits Horner syndrome, trigeminal pain, and other paraspinal cranial nerve involvement and is not benign. Group 2 exhibits the first two signs but lacks paraspinal nerve involvement. Group 2 is usually caused by a vascular or inflammatory mechanism affecting the sympathetic chain and sensory fibers that run in the carotid artery sheath and is benign. If the pain is atypical or persists more than 3 months, these patients should be investigated even in the absence of other cranial nerve involvement. No specific treatment exists.

**Cluster Headaches.** Patients with third-neuron Horner syndrome may have headache as a primary finding. These patients are also usually in their forties. The headache is not steady, and it is predictable as to time of day and duration (usually several hours). These patients also have tearing and ocular hyperemia, as well as ipsilateral nasal stuffiness. The associated Horner syndrome may be transient. The condition is benign. At one time it was treated with histamine desensitization, but this treatment has fallen out of favor. In any case, it is usually a self-limited process, although episodes do recur (hence the name cluster headaches).

**Migraine.** In any form, even with a typical homonymous scotoma, migraine may affect the carotid artery and result in Horner syndrome. The condition is usually self-limited.

**THIRD-NEURON HORNER SYNDROME—GROUP TWO.** The second group of third-neuron Horner syndrome involves the facial sweating mechanism. The syndromes are (a) idiopathic hemifacial hyperhidrosis, (b) postsympathectomy facial hyperhidrosis, and (c) hemifacial anhidrosis.

**Idiopathic Hemifacial Hyperhidrosis.** The patient with idiopathic hemifacial hyperhidrosis syndrome complains only of increased sweating on one side of the face, particularly on the forehead. Usually, the
condition is aggravated by eating spicy foods. No other signs of Horner syndrome are present. The increased sweating is caused by the overactivity of the sympathetic fibers that subserve sweating, and it disappears with sympathetic nerve block. This condition probably results from aberrant regeneration of the sudomotor fibers along the external carotid.

**Postsympathectomy Facial Hyperhidrosis.** After a complete cervical sympathectomy, anhidrosis is present in the ipsilateral affected area. Then after a long time, adjacent autonomic fibers from the vagus nerve sprout to innervate the sympathetic nerves. Thereafter, patients sweat and tingle when they eat. Since sweating is cholinergic and tingling is caused by pilomotion, which is adrenergic, the vagus nerve must make preganglionic connections where all fibers are of the cholinergic variety. No associated pupillary or palpebral signs are present.

**Homofacial Anhidrosis.** Sweating over the ipsilateral face is lost with sympathetic interruption below the bifurcation of the vertebral artery, where the facial sweat fibers leave the artery. Occasionally, however, sweating may be preserved on the forehead because some sympathetic fibers have gone with the orbital division, innervating the forehead directly. Therefore, anhidrosis of the face below the eye and above the upper lip has the same significance, even if the sweating mechanism remains intact in regard to the forehead.

Just as destructive lesions of the sympathetic chain cause a Horner syndrome, there are rare cases in which those same lesions can stimulate the sympathetic nerve. This produces mydriasis either intermittently or permanently. Less frequently, there can also be lid retraction rather than ptosis, and more rarely, hyperhidrosis. This syndrome has been reported with malignant lung tumors and cervical cord disease. In the few cases that I have seen, this finding of stimulation is transient and becomes a destructive lesion with the signs of a Horner syndrome in a very brief period of time.

Another form of intermittent pupillary dilatation is that in a patient who had a third-neuron Horner syndrome and now has supersensitivity to the circulating effective substance. Supersensitivity can develop as early as 2 to 3 weeks after sympathetic paralysis. The pupil supersensitivity will decrease as the sympathetic axons regenerate or sooner if there is reinnervation by lateral sprouting of axons, which is most common in the autonomic system.

The first case of this I noted was in my own secretary. She arrived at the office one Monday morning with a severe headache, minimal left hypertropia, about 1 mm larger left pupil, and ptosis. I diagnosed a third nerve palsy and arranged for the neurosurgeons to evaluate her. They did this and confirmed my diagnosis of an aneurysm. They operated successfully, and she had a full asymptomatic recovery. She was aware that an enlarged pupil was a sign of a third nerve palsy and an aneurysm. A few months later she noted intermittent dilatation of that same pupil without any other signs or symptoms. She was concerned that the aneurysm clip was slipping and that her aneurysm was again causing symptoms. The neurosurgeons and I worked her up and reassured her this was not the case. When we explored the history further, she noted that she would occasionally notice this pupillary difference while examining herself in the mirror. We surmised that she became anxious and produced more adrenaline, which then further dilated her pupil. She tested positive to 1/1000 aqueous adrenaline. Our conclusion was that at the time of her aneurysm compressing the third nerve, there must have been sympathetic injury that was masked by the mydriasis and ptosis of the partial third nerve palsy. She improved and has had no further problems.

**HETEROCROMIA**

As noted above, congenital Horner syndrome is usually associated with heterochromia; that is, one iris differs in color from its fellow. If all patients with congenital Horner
syndrome had one brown eye and one blue eye, detection of this condition would be simple. However, in some blue-eyed patients, the color difference between the irises is quite subtle and difficult to detect. Iris color should be checked in daylight (by the office window) rather than in fluorescent light. The difference thus revealed is often striking.

Both darker-eye and lighter-eye heterochromia are seen, although the latter is more common than the former. These symptoms can indicate several disorders other than Horner syndrome. Larger-sector pigmented areas are never and do not represent true heterochromia.

Darker-Eye Heterochromia

A diffuse iris melanoma is best evaluated with the slit lamp, since the darker brown area is a mass rather than simply as pigmented iris stroma. In neurofibromatosis, associated signs help identify the disorder. A thorough physical examination is called for, with the physician looking for other neurofibromas and, particularly, for café au lait spots. If the physician finds five café au lait spots that measure more than 2 cm in diameter or each, the diagnosis of neurofibromatosis is almost certain, even if the patient lacks other signs and symptoms. A single café au lait spot may point to neurofibromatosis, but it is not conclusive evidence.

If hemosiderosis is present, a carefully taken history of trauma or ocular penetrations, as well as slit-lamp, indirect ophthalmoscopic, and gonioscopic examinations, is mandatory.

Hemochromatosis of the iris is associated with a history of repeated bleeding in the anterior chamber.

Lighter-Eye Heterochromia

Lighter-eye heterochromia is seen more frequently than darker-eye heterochromia because the iris does not become pigmented until late in the first year of life. Iris pigmentation requires sympathetic stimulation. Congenital or neonatal sympathetic paralysis is a leading cause of heterochromia. The lack of pigmentation is not universally present.

Waardenburg syndrome is a variation of congenital Horner syndrome. In addition to lighter-eye heterochromia, the patient has a prominent white forelock, lateral displacement of the medial canthus, deafness, hypertrichosis, a broad nasal root, and lighter pigmentation of the ipsilateral fundus.

Peachs' heterochromic cyclitis is worthy of comment because of its resistance to therapy. Most prolonged cases of iris cause atrophy of the iris stroma and result in secondary heterochromia. Pech's iris has specific corneal endothelial deposits that are stellate in shape. It has a low level of activity and is resistant to therapy of any kind. Secondary glaucoma and cataract also may develop, but they can be treated as the need arises.

Essential iris atrophy is a rare but interesting problem that occurs predominantly in young women. It is progressive. Since secondary glaucoma is the main complication, patients should be examined for glaucoma periodically.

SUGGESTED READINGS
Pupillary Abnormalities


Keen FW, Holloway OW. Location of pupillomotor and accommodation fibers in the oculomotor nerve. Experimental observations on paralytic mydriasis. J Neurosurg Psychiatry 1964;27:473.


Pupillary Abnormalities


The diagnosis and management of orbital disease has improved enormously with the advancements in imaging techniques. With the improvement in computed tomography (CT) scanning and magnetic resonance imaging (MRI), the physical diagnostic abilities of the examining physician have become far less important. However, a careful history can be helpful in categorizing orbital disease.

**HISTORY TAKING AND PHYSICAL EXAMINATION**

Most patients with orbital disease present to an ophthalmologist with complaints involving either appearance, discomfort with the eyes, blurring of vision, or double vision. The initial evaluation of any such patient involves documentation of past ophthalmic history as well as physical examination including visual acuity, manifest refraction, visual fields, color perception, motility examination, and ophthalmoscopy. In many cases, additional history will be beneficial concerning the onset of presenting symptoms, the temporal course of symptoms, presence or absence of pain, and the localization of diplopia regarding fields of gaze.

Patients with orbital disease should be specifically evaluated for globe displacement in all three dimensions. The ophthalmologist is familiar with anterior-posterior displacement of the globe, but vertical displacement as well as horizontal displacement should be evaluated. The displacement of the globe leads very directly to the location of the orbital mass. Orbital masses will push the globe directly opposite the location of the origin of the mass; i.e., muscle cone masses push the globe forward, superior nasal orbital masses push the globe inferotemporally. Recognition of the location of the mass can often help to exclude or exclude certain types of tumor from the differential diagnosis.

A sensitive way to determine anterior displacement of the globe is to visualize the patient in a marked, chin-up position. A good observer can estimate as little as 1 mm of asymmetry in the forward protrusion of the corneal apex in this position. This proposal can be quantitated with the exophthalmometer, the most common being the Hertel instrument. However, these instruments are notoriously inaccurate when used to document change in propulsors. Horizontal displacement is determined by measuring from the midline of the nasal dorsum to the midline of the pupillary axis or the medial
limbus. Vertical dystopia (vertical displacement of the globe) is harder to quantitate but can be recognized by holding a ruler horizontally across the face and resting the ruler at the lower edge of one pupil or the lower limbus and comparing it with the position of the other pupil or limbus. This will often help to point out small amounts of vertical displacement that might otherwise be missed.

Cranial nerve function is evaluated first, assessing motor nerves by evaluating the ductions and versions of both globes, as well as the excursion of the eyelids. The evaluation of eyelid function is well described in the chapter on ptosis in this textbook. Finally, fifth cranial nerve function is assessed by determining sensory aspects of the cornea.

Examination of the orbit should involve auscultation with the bell of the stethoscope. Vascular lesions, both chronic and acute, can be diagnosed. The bell is placed over the forehead, cheek, and finally the globe, with the eyes closed, comparing the left with the right side. Palpation for abnormal lymph nodes is particularly important in the preauricular and submandibular areas.

Once again, the vast majority of patients will present to the ophthalmologist with a relatively limited number of complaints: (a) the acute onset of redness, pain, and pain of the eyelids and/or the eye, often accompanied by diplopia, (b) change in appearance, most often related to vertical or anterior displacement of the globe, (c) diplopia, and (d) irritation, excessive tearing, or photophobia as a result of the orbital disease.

**IMAGING OF THE ORBIT AND SKULL**

Any patient with the acute onset of orbital disease or evidence of a space-occupying orbital mass warrants imaging of the orbital structures. The ability to image the orbital structures has been enormously enhanced by the development of and the improvements in the technologic aspects of CT scanning and MRI. While an in-depth discussion of CT and MRI is beyond the scope of this chapter, the clinician should understand the potential advantages and disadvantages of each of these imaging modalities. Since MRI is more recent in development, there is a tendency to think that MRI will routinely provide information that is not available with the CT scan. Indeed, the vast majority of primary orbital diseases are better imaged with CT scanning, using thin sections and contrast, than with MRI. It is my preference in any patient with evidence of an orbital mass to first obtain a CT scan, 2- to 3-mm sections, both axial and coronal, with and without contrast. If the presenting symptom is visual loss without evidence of a primary orbital mass, then the MRI is probably the best imaging study as a first step.

**CT CONTRAST AGENTS**

The presence of a large amount of fat within the orbit with its low density relative to the adjacent extracocular muscles, globe, and bone generally allows excellent delineation of anatomic detail. An intravenous indinated contrast agent is not always necessary to provide appropriate images. Contrast is rarely of value in trauma but is frequently extremely valuable in orbit inflammatory disease as well as neoplastic lesions. Graves' thyroid orbital disease fits somewhere in between trauma and primary orbital lesions in terms of the usefulness of contrast. Radiation exposure can be limited by obtaining only contrast CT scans rather than preceding these with noncontrast scans. If the nature of the lesion is in doubt, the original studies should probably include both noncontrast and contrast images.

**PATIENT COOPERATION**

A certain amount of self control and patient cooperation is necessary to obtain opti-
nal imaging of the orbit. Most adults are capable of such self-control. If, in your initial evaluation, you feel that a given patient is unlikely to be able to demonstrate the necessary self-control, preimaging sedation may be required. This should be communicated to the radiology department. Provocative measures such as the Valsalva maneuver can often be helpful in diagnosing intermittently filling vascular lesions such as the orbital varix. MRI may provide additional valuable information when compared with CT scans in particular clinical settings. MRI is particularly useful in distinguishing lesions that have high blood flow or are cystic in nature. In addition, MRI is far superior to CT scanning when evaluating lesions of the optic nerve, particularly lesions that may extend into the optic canal or extend intracranially. MRI has also been proven to be superior to CT scanning in localizing nonmetallic foreign bodies of the orbit. Gadolinium enhancement with fat suppression can add significantly to the resolution of orbital apex lesions.

**INDICATIONS FOR CT SCANNING**

CT scanning should be the first choice for orbital imaging in the following clinical settings: (a) presumed metallic orbital foreign body; (b) blunt trauma to the orbit; (c) Graves’ disease (when imaging of the orbit is required); (d) presumed primary or metastatic orbital mass (except optic nerve meningioma, optic nerve glioma, or mass that could be clinically localized between the orbital apex and the optic chiasm); (e) presumed sinus disease; (f) presumed primary tumor of the lacrimal drainage system; and (g) unexplained enophthalmos.

**INDICATIONS FOR MRI**

MRI should be the primary imaging modality when the following presumed diagnoses have been made: (a) optic nerve sheath meningioma; (b) optic nerve glioma; (c) visual loss that is clinically compatible with an intracranial pre- or postchiasmal lesion; (d) presumed high-flow vascular lesions of the orbit (CC fistula, orbital varix, AV malformation); and (e) orbital abscess.

**CONTRAINDICATIONS FOR CT AND MRI**

CT imaging has no absolute contraindications. The relative contraindications are related to the radiation dosage. The CT scan tends to be a more tolerable imaging study for patients who are claustrophobic. MRI is definitely contraindicated in any patient who may have a magnetic foreign body within the eye or orbit, patients with cardiac pacemakers, magnetic intracranial aneurysm clips, and cochlear implants. The safety of MRI for the fetus during pregnancy is not known. Consequently, first-trimester MRI studies should be avoided if possible.

**ORBITAL OR PERIORBITAL LESIONS THAT DO NOT REQUIRE IMAGING STUDIES**

The rather common cystic dermoid tumor of the lateral orbit seen in infants is typically palpable, slightly compressible, and partially movable in the zygomatic frontal suture line, was recognized soon after birth, and has slowly increased in size. Imaging studies of the orbit are invariably of no assistance in the management of these lesions. Although there may be some slight erosion of the bone, particularly in older children, there is never penetration through bone with this lesion. Consequently, CT scanning or MR scanning is a waste of time and money. This same tumor is much less frequent but can occur in the superior medial portion of the orbit. In this location, the clinical description is similar to that of the lateral lesion. However, because of the risk of such a lesion...
being an encephalocoele, CT scanning of this lesion is probably indicated.

The CT scan evaluation of patients with a presumed diagnosis of orbital cellulitis is probably an appropriate initial study. However, follow-up evaluations are often done far too frequently. In the typical example of a young child with orbital cellulitis secondary to pansinusitis, there is no need to perform a secondary CT scan until at least a month after the initial episode or after clinical exacerbation of the disease. The CT scan evaluation of the sinuses tends to lag significantly behind the clinical resolution of the infectious orbital cellulitis.

An adult patient with anterior (preseptal) cellulitis that appears clearly to be related to an insect bite or a skin wound or injury probably does not need a CT scan of the orbit for appropriate diagnosis and management. If the cause of the cellulitis is unclear, then clearly the CT scan is the preferable test to evaluate the status of the sinuses.

**ORBITAL BIOPSY**

With very few exceptions, a histologic diagnosis is not generally possible on the basis of CT scanning or MRI. However, the deep cystic orbital dermoid tumor can be accurately and precisely diagnosed with an appropriate CT scan. This is the only nontraumatic mass lesion whose contents are lighter than air. Consequently, the Hounsfield units in measuring the x-ray attenuation of the interior of the mass will be in minus numbers. A clinical diagnosis on the basis of imaging studies and clinical findings can often be approximated without biopsy. However, the large majority of orbital lesions are going to require biopsy for definitive treatment. Many of the unsuspected mass lesions of the orbit, primarily cavernous hemangiomas that are found as a result of cranial imaging studies, probably require no treatment or surgical biopsy. If a well-circumscribed lesion is found within or outside the muscle cone in an orbit with a normally functioning globe, there is significant question as to whether or not the histopathologic nature of this lesion must be determined. It is generally safe to say that cavernous hemangiomas are cosmetic lesions unless they are creating optic nerve dysfunction. If the optic nerve dysfunction has progressed to significant loss of vision by the time the lesion is diagnosed with an imaging study, one must consider the risks versus the potential benefits of surgery for a given patient. Age, health, and status of the other eye all play a role in such decision making. It is safe and accurate to say that the mere presence of a mass within the orbit is not an indication for surgical acquisition of tissue for histologic diagnosis.

The most appropriate surgical approach to an orbital mass depends upon the location of the mass within the orbit. Whether the goal is complete excision or incisional biopsy does not greatly affect the general outlines listed below. Orbital tumors can generally be classified in a sagittal plane as being anterior, deep, intraconal, or orbital apex. In a coronal plane, they can be classified as superior medial, superior, superior lateral, inferolateral, inferior, and inferior medial.

There are a relatively limited number of skin incisions that allow access to the orbit. In order of frequency used for access to the orbit they are (a) superior lid crease incision; (b) inferior fornix incision with lysis of the inferior crus of the lateral palpebral tendon; (c) lateral canthal incision with or without removal of the lateral orbital rim; (d) the Lynch incision; and (e) craniotomy, which may be frontal or subfrontal.

Masses in the anterior to midorbit located superior medially, superiorly, and laterally are best approached through a lid crease incision. Masses in the anterior to midorbit located in the inferior medial, inferior, and inferolateral orbit, are best approached through an inferior fornix incision with lysis of the inferior crus of the lateral palpebral tendon. Direct lateral anterior masses are probably best approached through a lateral canthal incision. Deep orbital masses and orbital apex masses, lateral and inferior to the optic nerve, are best approached through a
lateral canthal incision with removal of the lateral orbital rim. Deep medial and medial orbital apex lesions are best reached with lateral canthal incision to allow removal of the lateral orbital rim and subsequent dissection of the medial rectus muscle for mid-orbital masses, superior lid crease incision for midorbital masses, and an extended Lynch incision for deep medial orbital apex lesions. Superior orbital apex lesions are often best exposed through a frontal or subfrontal craniotomy.

Fine needle aspiration biopsy of the orbit has not been widely accepted as a preferred method for obtaining tissue from the orbit. In the hands of a relatively few people, this appears to be a safe and highly effective way of obtaining tissue with less morbidity from particularly deep orbital masses. However, even among those who have had the most success with this modality of tissue acquisition, complications have occurred, including perforation of the globe. Fine needle aspiration is probably most appropriate in an orbit that has a presumed metastatic lesion and an eye that has reduced visual acuity, where the anticipated method of treatment is radiation therapy and where other metastatic lesions are not more accessible.

The handling of tissue obtained from orbital biopsy is a critically important step in the diagnostic continuum of a given patient. With any given specimen, tissue may be used for histopathology, immunocytochemistry, electron microscopy, and flow cytometry. Each of these techniques requires different tissue handling. Consequently, it is extremely important that the pathologist be involved in the handling of the tissue as soon as possible. It is probably never appropriate to submit all of the tissue already fixed in formalin. If possible, the pathologist should come to the operating room to be clinically aware of the location and the nature of the tumor and personally be responsible for the delivering of the tissue to the pathology laboratory, where the tissue can be divided so that any and all of the above-listed studies can be performed. This is generally not a problem in institutions that have a well-trained ophthalmic pathologist. It can be a significant problem for those who are in institutions where appropriately trained ophthalmic pathologists are not available. If you are in doubt about the handling of the tissue following the biopsy, it is always essential to speak with a well-trained ophthalmic pathologist prior to obtaining this material, even if such a person is not available in your institution.

**HISTOPATHOLOGY**

Formalin is the appropriate fixative for routine histopathology. However, once the sample is fixed in formalin, it may be of limited or no value for performing other diagnostic studies.

**IMMUNOCYTOCHEMISTRY**

The use of immunocytochemical methods of study can greatly add to the diagnostic capabilities of the pathologist and thereby enhance the clinical information for the surgeon. The ability to perform these studies can be lost or significantly hindered by improper tissue handling and fixation. Once again, the value of consulting a pathologist about the most appropriate method for handling tissue cannot be overemphasized.

**SURFACE MARKERS**

Surface markers are used primarily to determine phenotypic monoclonality of lymphocytes. Monoclonal cells express the same surface antigens that are derived from a single cell or cell line.

Genotypic monoclonality (i.e., all cells contain the same DNA) can now be determined for lymphocytes by use of DNA hybridization techniques. In years past, it was hoped that these studies would be of great value in the diagnosis of and the prognostication for patients with lymphocytic orbital
lesions. Unfortunately, these tests do not support significant clinical conclusions because the presence of a clonal population of lymphocytes does not absolutely indicate lymphoma.

**CYTOPLASMIC MARKERS**

Numerous cell-type or organ-specific antibodies are available to the pathologist. Paraffin-embedded sections are exposed to an antibody against a specific antigen. Through a series of amplification steps, the marker becomes visible where the antigen was present on the tissue section. A panel of antibodies is tested because individual antibodies alone may demonstrate no sensitivity. The results of immunocytochemistry must be interpreted on the basis of the clinical information and histopathology available to the pathologist. One should never rely exclusively on immunocytochemistry for diagnosis.

Antibodies are commercially available to specific intermediate filament proteins, actin, cytoskeletal proteins, neural-associated antigens, mesenchymal antigens, organ-specific antigens, and lymphoid antigens.

**INTERMEDIATE FILAMENT PROTEINS**

Intermediate filaments are cytoplasmic cytoskeletal proteins present in all cells. Intermediate filaments have the fortunate characteristic of demonstrating antigenically distinct epitopes in different cell types or tumors derived from these cell types. Five distinct intermediate filaments have been described.

Vimentin is an intermediate filament protein present in all mesenchymal cells, including lymphocytes, histiocytes, fibroblasts, endothelial cells, and Schwann cells. It is not expressed in mature muscle cells. As with all useful markers, antigenicity is retained in the neoplastic transformation, so tumors derived from mesenchymal cells (e.g., sarcomas) express vimentin.

Desmin is an intermediate filament expressed in all smooth, striated, and cardiac muscle cells. Desmin and vimentin can be coexpressed in poorly differentiated muscle tumors such as rhabdomyosarcoma and leiomyosarcoma. The coexpression of vimentin and desmin is therefore diagnostically helpful for rhabdomyosarcoma and leiomyosarcomas.

Cytokeratins are a heterogeneous group of proteins present in epithelial cells. Cytokeratins of high and low molecular weight can be recognized, and their presence can help in determining the cell of origin, particularly when differentiating carcinomas of squamous or ductal origin.

Gial fibrillary acidic protein (GFAP) is an intermediate filament protein expressed in astrocytes and ependymal cells, but not in neurons, microglia, or oligodendrocytes. GFAP is expressed only in central nervous system neural tumors, with the notable exception of lactimal and salivary pleomorphic adenomas. Neurofilament is an intermediate filament found in well-differentiated neural cells. Primitive neural cells express neurofilament minimally, making its usefulness in tumor diagnosis limited. One exception is the primitive-appearing esthesioneuroblastoma, which expresses neurofilament.

Actins compose a family of proteins forming filaments within the cytoplasm of virtually all cells. Six different isoforms of actin have been described, four are muscle-specific types and two are nonmuscle types. Expression of muscle-specific actin is most useful in the diagnosis of muscle tumor such as rhabdomyosarcoma.

**Neural-Associated Antigens.** Several neural-associated antigens are useful in diagnosing certain tumors. The most noticeable of these are S-100 antigen, chromogranin, and synaptophysin. These neural-associated antigens can be helpful in the diagnosis of melanoma and neuroendocrine tumors such as pheochromocytomas, islet cell and melanomas.
cell carcinomas, parathyroid carcinomas, and carcinoid tumors.

**Mesenchymal Antigens.** Various mesenchymal markers can help subclassify tumors derived from connective tissue cells.

**Vasoformative Tumors.** Vasoformative tumors (e.g., hemangiomas, angiosarcomas, hemangioendotheliomas) express markers such as factor VIII–related antigens and ulex lectin.

**TUMOR- AND ORGAN-SPECIFIC ANTIGENS**

HMB45 is a cytoplasmic antigen found only in melanoma cells and junctional nevus cells. The presence of this antigen appears to be specific and sensitive for the diagnosis of melanoma as well as for determining depth of invasion.

Antibodies to prostate-specific antigen specifically mark prostate cells. The presence of this antigen can be helpful in the diagnosis of metastatic prostate cancer.

GCDFP15 is an antibody that defines membrane-associated glycoprotein specific for breast, salivary gland, and sweat gland epithelium. Its major use appears to be in distinguishing metastatic breast carcinoma from poorly differentiated adenocarcinomas from the lung or gastrointestinal tract.

Thyroglobulin is present in the vast majority of primary and metastatic thyroid carcinomas. This is most useful in distinguishing metastatic thyroid from nonthyroid carcinomas.

**LYMPHOID ANTIGENS**

Many new antibodies to lymphoid antigens have been developed in recent years. Their primary use is in distinguishing lymphomas from other poorly differentiated tumors. In addition, the presence or absence of certain lymphoid antigens allows the definitive separation of Hodgkin's cells from non-Hodgkin's lymphoma cells.

**ELECTRON MICROSCOPY**

Electron microscopy is primarily reserved for obtaining additional information that may lead to an appropriate classification of otherwise unidentifiable tumors.

**FLOW CYTOMETRY**

Flow cytometry provides information regarding cell multiplication rates, cell size variability, and multiple cellular populations. At the present time, flow cytometry appears to be of greatest value in providing prognostic information regarding a given tumor.

**CLINICAL UNDERSTANDING OF ORBITAL DISEASE**

It is well beyond the scope of a single chapter in a neuro-ophthalmology text to discuss comprehensively the wide variety of inflammatory, infectious, and neoplastic diseases that involve the orbit selectively or as part of a systemic disease. However, certain orbital disease processes are set apart from other orbital disease processes in importance because of their incidence or severity. Graves' thyroid orbitopathy, the most common disease process involving the orbit as part of a systemic disease, is the orbitopathic process associated with thyroid gland abnormalities.

Although the first clinical description of this disease was published by Perry in 1825, it was the publication by Robert Graves, M.D., in 1834, that has been most remembered. Consequently, this disease remains firmly entrenched as Graves' disease. In most populations of the world, this disease has an incidence of 15 per 100,000 in the female population, and 3 per 100,000 in the male population. The age of onset ranges from early childhood to the eighth decade of life. The ocular and orbital findings may precede or follow the onset of the glandular
dysfunction. No matter which presents first, the thyroid glandular dysfunction or the orbital ocular findings, the other aspect of the disease will present within six months in 85% of patients. In the other 15% of patients, the relationship between the thyroid gland and the orbitopathic changes can be more drawn out and more complicated. Approximately 90% of patients with Graves' disease will be hyperthyroid, 10% hypothyroid, 3 to 4% will have Hashimoto's thyroiditis, and 5 to 6% will be euthyroid. A large percentage of these patients will present to the ophthalmologist with vague or subtle complaints and findings. The appropriate diagnosis by the ophthalmologist can save many of these patients months of medical testing and diminished quality of life while the appropriate thyroid diagnosis is being made. Consequently, it is of immense importance that the ophthalmologist be constantly aware of the typical presenting symptoms and findings of Graves' disease. It has often been said that astute clinicians see and hear those things for which they are looking and listening.

The most frequent symptoms of Graves' disease patients presenting to the ophthalmologist are, in order of frequency, pain or ocular discomfort, increased lacrimation, photophobia, diplopia, and blurred vision. The most frequent early ocular and orbital findings are dilatation of conjunctival vessels, particularly in the horizontal axis, chemosis, and swelling of fullness of the eyelids. Once the disease becomes more established, the most frequent diagnostic findings are eyelid retraction, eyelid lag and/or lagophthalmos, proptosis, restricted extraocular muscle movements, and optic nerve dysfunction.

The ophthalmologist should play an active role in the early diagnosis of the hyperthyroidism in patients presenting with the above symptoms and findings. The thyroid-stimulating hormone (TSH) assay has replaced all other thyroid function tests as the most appropriate screening test. If the TSH is normal, it is quite appropriate for the ophthalmologist to be the physician who continues to follow patients suspected of developing Graves' disease. If the TSH is abnormal, the patient should immediately be referred to an endocrinologist.

CT scanning is generally of much greater value than MRI in evaluating suspected Graves' disease patients. However, the CT scan is just another diagnostic test. If the appropriate diagnosis can be made on the basis of symptoms, findings, and a depressed TSH, then a CT scan may very well not be necessary in the early diagnosis and/or management of Graves' disease patients. If the clinical picture is not clear or the patient presents with significant asymmetry of proptosis, then a CT scan would be appropriate to help aid in the diagnosis of Graves' disease and rule out the possibility of primary or secondary orbital mass.

Retrospective studies have indicated an adverse relationship between radioactive iodine treatment for hyperthyroidism and progression of the orbitopathy. Consequently, many endocrinologists are pursuing pharmacologic suppression of the thyroid gland much more extensively than in the past. In patients who fail to tolerate pharmacologic suppression of the thyroid gland, a choice must be made between radioactive iodine and subtotal thyroectomy. Deciding between these two choices can be difficult and is often based upon the age of the patient, the cosmetic concerns of the patient, and the orbital ocular status prior to radioactive iodine or thyroectomy.

The vast majority of Graves' disease patients can be managed with oral, non-steroidal anti-inflammatory drugs, topical anti-inflammatory drugs including corticosteroids, diuretics, and frequent application of ice. Oral corticosteroids should be reserved for those patients who develop compressive optic neuropathy. However, rarely can patients be managed throughout the course of their compressive optic neuropathy with oral corticosteroids. The treatment often becomes worse than the disease for patients with prolonged oral corticosteroids. Consequently, most patients with progressive optic neuropathy will require radiation treatment of the orbital apex or surgical decompression of the orbital apex.
Radiation treatment in the 2000 to 2500 Gy range will certainly reduce orbital inflammation, feelings of pressure, and orbital vascular congestion. However, radiation treatment rarely has any significant effect on motility changes or proptosis.

Consequently, patients who have what they consider to be cosmetically disfiguring proptosis, patients who have corneal exposure problems secondary to proptosis and eyelid retraction, and patients who have functionally significant restrictive myopathy are going to require a combination of surgical orbital decompression, extraocular muscle surgery, and repositioning of the eyelids, always done in this order.

Graves' disease is indeed an autoimmune disease involving the T-cell lymphocytes. Antibodies are produced, which bind presumably to the TSH receptor sites of the thyroid gland cellular membranes and orbital fibroblasts. Many of the orbital ophthalmic changes associated with Graves' disease are created by the overproduction and deposition of glucosamine glycans within the extraocular muscles and orbital fat. One hopes the future will bring a therapeutic modality that will allow these binding sites to be blocked early in the course of the disease, prior to the development of significant orbitopathy. It is quite clear that for most patients with Graves' disease, the hyperthyroidism is a transient inconvenience. However, the orbitopathy may lead to a lifelong devastating change in the quality of their lives.

Nonspecific orbital inflammatory disease can usually be differentiated from Graves' orbitopathy by its typically unilateral presentation with severe pain and marked changes of one or more extraocular muscles with typical involvement of the tendinous insertions. Orbital fat can appear rather infiltrated, and scleral thickening is not uncommon.

Primary and metastatic orbital tumors are almost always unilateral and often create nonaxial proptosis, compared with the axial proptosis expected with Graves' orbitopathy. Significant pain and inflammation are unusual with orbital tumors, except for adenoid cystic carcinoma, which primarily occurs within the lacrimal gland. Consequently, it is generally possible to differentiate between Graves' orbitopathy and orbital tumors on the basis of clinical information. Clearly, unilateral proptosis is going to lead to imaging studies of the orbit, which will make the definitive differentiation. Orbital infections, whether bacterial or fungal, are almost always unilateral. In infants, they can often be of acute onset. In adults, they can vary between acute and very indolent in onset. The inflammatory response can vary from mild to severe, as can the pain. The vast majority of orbital infections are associated with or caused by sinus infections. Far less common is the hematogenous spread of infectious agents to the orbit from other distant focal sites of infection. Almost always these patients will have some other underlying health problem, frequently diabetes mellitus. Consequently, the unilaterality of the process will lead to orbital imaging, which will in most cases make the appropriate diagnosis.

Cavernous sinus fistulas, particularly those of low flow, can lead to unilateral, somewhat indolent onset of orbital findings and symptoms. The conjunctival vessels assume an arterialized appearance, and an orbital bruit is frequently present. Pain is rather mild, and many of these patients have a history of orbital or head trauma.

**CASE STUDIES**

*Case 4.1*

A 62-year-old white male presented with gradual development of proptosis of the right upper eyelid over the past several months. The patient was evaluated for other vague abdominal and urinary tract symptoms. No specific diagnosis has been made. Orbital imaging studies revealed a poorly localized mass in the area of the right lacrimal gland. Lateral orbitotomy revealed a mass that diffusely involves the lacrimal gland. Biopsy revealed a monoclonal lymphocytic mass,
• Figure 4.1A.
Coronal section, 3-mm cut with contrast, showing a poorly defined, large superior lateral mass in the right orbit, displacing the right globe inferiorly, with no evidence of bony erosion of the orbital roof.

• Figure 4.1B.
T2-weighted images of the MR scan on the same patient. One can see that there is essentially no information gained from the MR scan that was not available on the CT scan.
confirming the diagnosis of orbital lymphoma (Fig. 4.1, A and B)

- **Case 4.2**

A 1-week-old white male with known Kartagener's syndrome underwent imaging studies of the head, revealing a large orbital mass on the right side. Imaging studies showed a large superior orbital mass. The presumed diagnosis was rhabdomyosarcoma. The tumor was biopsied through the upper eyelid crease. The histologic diagnosis was a malignant nerve sheath neoplasm (Fig. 4.2).

- **Case 4.3**

A 63-year-old white male presented with vague symptoms of fullness of the right orbit. Clinical evaluation led to the suspicion of Graves' disease. TSH was normal, and imaging studies revealed a well-circumscribed intracranal mass, lateral to the optic nerve. This mass was removed through a right lateral orbitotomy, which confirmed the diagnosis of cavernous hemangioma (Fig. 4.3, A and B).

- **Case 4.4**

A 65-year-old black female presented with the diagnosis of Graves' disease. She was a smoker with significant chronic obstructive pulmonary disease and an insulin-dependent diabetic. Over the past several months she had noted progressive dimming of her visual acuity bilaterally, as well as loss of color perception. Visual fields and VEP demonstrated defects compatible with optic nerve compression. Imaging studies, CT scanning of the orbit, revealed massive enlargement, particularly of the posterior medial rectus muscle bellies. She underwent radiation with 2500 cGy to both orbital apices with no improvement in visual function. Over a period of months following the radiation, her visual acuity continued to decline with further

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**Figure 4.2.**

Axial section, 3-mm cut of a CT scan with contrast, showing a diffuse mass through the superior and temporal orbit on the right side. There is evidence of bony erosion along the lateral orbital rim and wall.
Visual fields were decreased medially; a small visual field defect was noted nasally at 2 degrees. (Fig. 4.4)

- Case

A 60-year-old man presented with a 3-month history of gradually decreasing visual acuity in the right eye. He had no history of trauma, inflammation, or recent illness. Examination revealed a best-corrected visual acuity of 20/20 in the right eye and 20/15 in the left eye. Fundus examination showed a small, yellow, subretinal lesion in the right eye, consistent with a serous retinal detachment. Treatment with corticosteroids and photodynamic therapy was initiated.

- Figure 4.3.

A. Axial section, 5-mm cut of a CT scan with contrast, showing a well-circumscribed, spherical mass that enhances and is of relatively uniform density, located in the lateral muscle cone. B. Axial sections of the T1-weighted images of an MR scan showing the same muscle cone lesion. Once again, there is no information obtained from the MR scan that is not present on the CT scan.
visual field loss. Consequently, both orbits were decompressed through an inferior and medial approach to the orbital floor and medial wall. Visual acuity has been stable now at 20/40 and 20/30 for the past 3 years (Fig. 4.4).

● Case 4.5

A 60-year-old white male presented with slowly progressive proptosis and mild discomfort involving the left eye, together with what was later recognized as slight proptosis. Imaging studies revealed massive enlargement of the inferior rectus muscle with involvement of the tendinous portion of the muscle. TSH was normal. The patient was treated with oral corticosteroids with minimal improvement. Consequently the mass was biopsied; the pathologic findings were polyclonal lymphocytic mass, confirming the diagnosis of nonspecific orbital inflammatory disease. He was later radiated with 2500 rads to the inferior rectus muscle, with slight improvement in the motility and discomfort of the left eye (Fig. 4.5).

● Case 4.6

A 22-year-old black female had been treated intermittently for upper respiratory tract infection complicated by sinusitis. She had undergone two courses of oral antibiotic therapy with a continuing feeling of malaise and recent onset of headaches. She had slight proptosis on one side, with diminished motility. Imaging studies revealed extensive left pansinusitis with frontal brain abscess. Frontal craniotomy was performed to drain the brain abscess, and the sinuses were drained and cleared of abnormal tissue. Cultures revealed anaerobic streptococci (Fig. 4.6).

● Figure 4.4.

Axial sections, 3-mm cuts of a CT scan showing massive enlargement of the horizontal rectus muscles at the orbital apex, leading to compression of the optic nerve as it exits through the optic canal.
**Figure 4.5.**
Coronal section, 3 mm thick, with contrast. CT scan showing marked enlargement of the left inferior rectus muscle and questionable enlargement of the left medial rectus muscle. The MR scan provided no information that was not available on the CT scan.

**Figure 4.6.**
Coronal sections, 3 mm thick, with contrast enhancement of the CT scan, showing diffuse opacification of all sinuses on the left and significant opacification of sinuses on the right. There is diffuse enhancement of the superior medial orbital fat contents with variation in densities, suggesting the presence of air within the superior medial orbit. In addition, there is an enhancing area in the left frontal lobe that is less dense centrally, suggesting a brain abscess.
SUGGESTED READINGS


Ptosis

Thomas J. Walsh

Blepharoptosis, usually referred to as ptosis, can be described as the condition in which the upper lid is at a lower position over the cornea than normal. The question arises, What is the normal position? The usual adult position, with the eyes straight ahead, is for the lid to be about 1.5 mm below the upper limbus of the cornea. It is usually not this low in infants, and it is frequently lower in older persons. It may be lower in some people as a familial trait. If the ptosis is unilateral or asymmetric, the diagnosis is usually made more easily. In some diseases, however, both bilateral and symmetric ptosis occur, making the diagnosis of ptosis more difficult. (A normal form of bilateral and symmetric ptosis is the condition referred to colloquially as bedroom eyes.)

Two groups of muscles and nerves elevate the upper lid. The major contributor is the levator muscle, which is innervated by the third cranial nerve. This muscle extends as a broad band and inserts into the anterior surface of the cartilaginous tarsal plate. A secondary system inserts into the upper border of the tarsus; it is called Müller's muscle, and it has an associated pupillary sign. Müller's muscle is innervated by the sympathetic nervous system. A peculiar feature of anatomy, which requires understanding, is the intimate relationship between the superior rectus muscle, which elevates the eye, and the levator muscle. Both muscles come from the same anlage, at Zinn's ligament.

Not infrequently, both are affected, particularly when trauma is involved.

EXAMINATION TECHNIQUES

Measure the distance between the two lid margins by measuring the lid fissures with a millimeter ruler, with the patient's eyes looking straight ahead. This method is more accurate than measuring how much of the lid is below the theoretically normal lid position, which, as mentioned, can vary. In planning any surgical correction, it is also important to know where the other normal lid sits in relation to the cornea.

Another feature to consider is the function of the levator muscle. Using the millimeter ruler again, observe the excursion of the lid from eyes in the full down-gaze position to the full up-gaze position. Normal excursion is about 15 mm. A major error in evaluating the amount of ptosis can occur when a patient overcomes the ptosis by employing the frontalis muscle. If you observe a wrinkling over one eye and not over the other, suspect a slight ptosis that is being overcome by the use of the frontalis muscle, giving some lift to the ipsilateral lid. Have the patient close the lid, and press your thumb over the center of the patient's eyebrow. Do not push up—and thus do the same thing the patient's frontalis muscle does—or push down, thereby depressing the lid and causing a ptosis. Press in
toward the bone to prevent the frontalis muscle action on the skin overlying the lid. This maneuver should also be done when measuring excursions of the lid.

True ptosis is due to a neuropathic process either in the third cranial nerve innervation to the levator muscle or in the sympathetic innervation to Müller’s muscle or to one of several myopathic processes.

PSEUDOPTOSIS—TYPES AND CAUSES

Protective Ptosis

Pseudoptosis has many manifestations, the most common one being protective ptosis associated with an irritated eye. The irritation may be an internal inflammation, such as iritis. Photophobia is an early sign of iritis, and frequently it is present before any external inflammatory sign, such as redness. Photophobia may also be seen with inflammation in the posterior segment of the eye but not as consistently as in iritis. The possibility of a corneal foreign body, abrasion, or retained foreign body under the upper lid should be considered. Careful inspection of the upper lid when everted, particularly when doubly everted over a Desmarres retractor, is a necessity.

Hysterical Ptosis

Hysterical ptosis is usually unilateral, and the wrinkling of the orbicularis muscle can be seen as the cause. Cases of flaccid hysterical ptosis do occur, but they are rare.

Enophthalmos

The lid may be ptotic because of lack of support from the globe, a condition that occurs with enophthalmos secondary to a loss of orbital fat. The loss of fat occurs most often after blunt trauma with orbital hemorrhage or after trauma causing a blowout of the orbital floor with damage to the orbital contents.

Microphthalmia and Phthisis Bulbi

In congenital microphthalmia, the lid is not supported properly. A more common variety of microphthalmia is phthisis bulbi, a shrinking of a normal eye after total blindness occurs and internal disruption of all functions such as in end-stage glaucoma or severe disorganization after trauma.

Blepharochalasis

A common finding, and one that may mask an associated subtle but true ptosis, such as exists in Horner syndrome, is the blepharochalasis of the elderly. This condition results from loss of fascial attachments of the overlying skin to the levator muscle, causing the skin to fall down and cover the lid margin. Usually the skin can be gently lifted by pushing up on the brow, and the lid margin may then be found to be in a normal position.

Ptosis after Operation

Minimal ptosis may occur after cataract or retinal detachment operation, with traction sutures under the superior rectus muscle, or after temporary removal of that muscle.

Vertical Muscle Imbalance

The most subtle type of ptosis, and one that is frequently overlooked, is that caused by vertical muscle imbalance. If the patient fixes with the lower eye, the action causes the other eye to move up and places the lid
lower on the cornea, thereby giving the appearance of ptosis. To detect this condition, alternately cover one eye and then the other. Two observations can be made. The apparently ptotic side will have that eye come down to fix when the cover is moved to the other eye. When each eye fixes, each lid will be in the same position in reference to the pupil and the cornea. The measurement of the fissures will also be found equal (Fig. 5.1, A and B).

**Apraxia of Lid Opening**

Apraxia of lid opening is not true ptosis. A patient with this disorder has difficulty in opening the lids after forced closure. The condition is not related to blepharospasm, and the patient shows no contraction of the orbicularis muscle. Characteristically, to initiate movement, the patient may thrust the head back, as if to break some neuronal connection inhibiting lid opening. No ptosis occurs between attacks, which are associated with a variety of supranuclear lesions, including Huntington's chorea.

**TRUE PTOSIS (FIGS. 5.2, 5.3)**

**Congenital Ptosis**

Most kinds of congenital ptosis are not hereditary, with one notable exception. The ptosis associated with epicanthus inversus and blepharophimosis, which is usually bilateral, is frequently familial and may be a dominant characteristic. The other kinds of congenital ptosis have no familial association (and the ptosis is unilateral in 70% of the cases).

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**Figure 5.1.**

Patient with a right hypertropia. **A.** She is fixing with the hypertropic eye, and no difference in the lids is noticed. **B.** She is fixing with the hypertropic eye, causing the left eye to look down and the left lid also to be down, giving the impression of a ptosis. The relative position of the pupil as a result of a tropia will influence which eye appears to have a pseudoptosis.
Figure 5.2.
Ptosis evaluation, part 1.

Figure 5.3.
Ptosis evaluation, part 2.
SUPEIOR RECTUS MUSCLE WEAKNESS

A feature often overlooked in congenital ptosis—and sometimes in acquired ptosis—is an associated weakness of the superior rectus muscle (found in about 10% of the cases). This feature must be considered in evaluating a patient for correction of ptosis. It is also important to evaluate the patient’s Bell’s phenomenon. Failure to recognize a superior rectus muscle weakness or an inadequate Bell’s phenomenon may result in a corneal exposure problem that may be more serious than the original ptosis. Once a corrective surgical procedure has been performed on the lid, the superior rectus muscle weakness may be a greater cosmetic problem than the ptosis ever was. The patient may complains that the now obvious vertical displacement of the eye was caused by the operation. Improper selection of operative procedure may make the vertical problem worse.

LEVATOR APONEUROSIS DEHISCENCE

In congenital ptosis, the distance from lid sulcus to lid margin is normal. The congenital ptotic lid is the higher not the lower lid on down-gaze because of structural changes that keep the lid from relaxing on down-gaze (Fig. 5.4). In cases of levator dehiscence, this impediment is absent, and the ptotic lid is the lower lid on both up-gaze and down-gaze (Fig. 5.5).

* Figure 5.4.
Patient with congenital ptosis. Note that the ptotic left lid is higher on down-gaze than the normal lid.
HORNER SYNDROME

Horner syndrome has ptosis as one of its prime signs. Just as the ptosis may be overlooked because of associated frontalis muscle assistance, incompleteness of Horner syndrome or the degree of alertness of the patient may cause the miosis to be overlooked if all the pupil-influencing factors are not considered. A detailed description of these factors is given in Chapter 3. The presence of heterochromia on the side of the ptosis should alert one to look even harder for a smaller pupil on that side, since it goes along with a congenital Horner syndrome (Fig. 5.6). Heterochromia is seen only in a ptosis caused by sympathetic paralysis with a congenital or neonatal onset.

CYCLIC THIRD CRANIAL NERVE PARALYSIS

Cyclic paralysis of the third cranial nerve may be complete or incomplete. This rare condition usually begins in childhood, remains throughout life, and is benign. It is gradual in onset until a certain point, and then it gradually recovers without any deficit. An entire episode lasts only a few minutes. After pupillary involvement, ptosis is one of the most constant features of this syndrome. The inclusion of other parts of the third cranial nerve varies from patient to patient. Lid twitching prior to the onset of each new phase is a characteristic sign. The extraocular muscles are infrequently involved and then only the medial rectus muscle. The onset in
childhood, repetitiveness of course, and lack of residual deficit essentially differentiate this disorder from third cranial nerve paralysis associated with diabetes or aneurysm, which comes on later in life. The cause is unknown, as is the treatment.

**Acquired Ptosis**

Hereditary ptosis coming on later in life is not common. The main example that I see is that associated with chronic progressive external ophthalmoplegia. The leading initial sign of the condition is ptosis, and it may be the only sign for many years. Observing other members of the patient’s family, either in person or from photographs, is important. Many patients either suppress a family history or are truly unaware of it; since all members look alike, nobody thinks to comment about it. The Tensilon test is negative and excludes myasthenia gravis. The normal pupil and normal accommodation absolve the third cranial nerve.

**Myasthenia Gravis**

Ptosis is usually the first sign of myasthenia gravis in young people, just as it is in chronic progressive external ophthalmoplegia. The ptosis caused by myasthenia gravis, however, responds to a Tensilon injection. In addition, no pupillary or accommodative abnormalities exist, and the ophthalmoplegia that usually comes on later is similar to other myopathies, with the elevation of the eye being primarily affected. Keeping the eyes in sustained up-gaze for 1 to 2 minutes causes the ptosis to get worse. This factor is almost pathognomonic of myasthenia gravis and is not seen in Horner syndrome or third cranial nerve disease.

When the cause of the ptosis is still in doubt, the lid peek sign may be useful. Just as the levator is weakened to hold the upper lid in its proper position, the orbicularis is also weak in keeping the fissure closed for a prolonged period. When a patient is asked to close the eyes and keep them closed, the fissure opens up in a few seconds because of the orbicularis weakness. This phenomenon needs to be differentiated from motor in persistance, which is part of the syndrome of the nondominant hemisphere or which occasionally can be seen in bilateral hemisphere lesions. The associated hemisphere signs and symptoms should easily differentiate it from the lid peek sign of myasthenia gravis.
In contrast to ptosis, lid retraction in myasthenia gravis is uncommon. When it occurs, three different types are categorized by the duration of the lid retraction. The most common form is the lid retraction associated with weakness of the contralateral levator muscle, which may be prolonged. This type of lid retraction is an example of Hering's law of equal innervation to yoke muscles at work. Hering's law can be temporarily altered toward the more normal side during the Tensilon test. During this test, less effort is required of the myasthenic lid, and no lid retraction develops in the other lid. The second type of lid retraction is Cogan's lid twitch sign. The upper lid overshoots when the eyes are moved rapidly from down-gaze to a position straight ahead. There is no sustained lid retraction in these instances. The third type of lid retraction was reported by Pulkkin, Sacks, and Boshes in a small series of myasthenic patients. This type of lid retraction is over in a few seconds and is caused by posttetric facilitation of the levator, seen particularly after prolonged up-gaze. A similar mechanism was postulated for a comparable phenomenon in the small muscles of the hand of myasthenic patients.

In patients with only ptosis or ocular signs of myasthenia gravis, the acetylcholine receptor antibody is positive in 65% of cases but in over 90% of patients with generalized myasthenia gravis. Medications can induce a myasthenic syndrome. These include curare, pancillamine, and the aminoglycosides such as gentamicin, neomycin, and tobramycin. These drugs appear to work at the myoneural junction.

**THIRD CRANIAL NERVE PARALYSIS**

One of the major causes of acquired ptosis is third cranial nerve paralysis owing to an aneurysm. If the ptosis is associated with diplopia or, more significantly, with a pupillary abnormality, aneurysm as the cause must be the first consideration. The condition requires prompt evaluation and treatment because of its catastrophic characteristics. Not all third cranial nerve paralyses come on with marked involvement of all parts of the third cranial nerve. In the overwhelming majority of patients with aneurysms causing third cranial nerve paralysis, however, the pupil is affected to some degree. Subtle changes in pupil size in dim illumination with distance fixation should be scrupulously evaluated. The extraocular muscle weakness may not be apparent or considered, since the patient does not complain of diplopia. When the patient is examined with the eyes in the extremes of gaze, particularly with the affected eye turned up and out in the field of action of the superior rectus muscle, a small hypotropia may be seen that is not present in the opposite field of gaze.

The other prime cause of third cranial nerve paralysis, diabetes, does not always spare the pupil and accommodation. In about 20% of cases of diabetic third cranial nerve paralysis, the pupil is involved; and these cases cannot be differentiated clinically from those caused by aneurysm, even when the urine gives a 4+ reaction for sugar. A third cranial nerve paralysis with the pupil involved must be considered to be caused by an aneurysm until that is adequately ruled out. Some degree of ptosis is almost always present in third cranial nerve paralysis from any cause.

Adults with acquired Horner syndrome do not have the heterochromia associated with congenital Horner syndrome (Chapter 3). In any case of ptosis, examination of the pupils for size abnormalities is essential. When in doubt as to the equality of pupils, observe the pupils in dim light with the patient's gaze directed at a distance. The other test is to measure the near point of accommodation or the point at which the patient begins to notice blurring. The side with Horner syndrome will read considerably closer. Measure with the patient's glasses on for full distance correction and an equal amount of bifocal correction if needed. The procedure is most effective with patients over 40 years of age who require reading glasses. The high degree of residual accommodation in the young person makes the measurement difficult in those under the age of 55.
TRAUMA

Any injury often causes either direct damage to the levator muscle or damage to its oculomotor innervation. Since the superior rectus muscle has a common origin with the levator muscle, it is also frequently injured, with a resultant muscle imbalance. The damage may not be immediately apparent if the ptosis is severe enough to cover the pupil and prevent diplopia. The recovery from ptosis may take many months, and no corrective surgery should be considered until at least 6 months have elapsed with no improvement. Resorption of edema of the lids should not be interpreted as improvement of ptosis. Be conservative and do not overestimate the final outcome to the patient.

EXTERNAL TUMORS OF THE LID

Any external lid tumors large enough to pull the lid down are readily visible. Those that are in the superior orbit or in the upper fornix between the lids and the globe may not be appreciated on simple inspection. Diagnosis may require digital palpation of the area beneath the superior bony orbital rim, as well as double eversion of the upper lid and observation beneath it. Plexiform neuromas of the lid feel like a bag of worms rather than a single mass, and they frequently extend laterally beneath the skin of the cheek and into the temporal fossa. These neuromas are associated with generalized neurofibromatosis and have other signs, such as café au lait spots and epilepsy.

STRABISMUS OPERATION

When an operation to correct strabismus shortens the superior rectus muscle, it may also pull the levator muscle down, causing ptosis. Such an operation, if carried too far posteriorly, may cause damage to the nerve going to the levator muscle (because the nerve passes through the superior rectus muscle on its way to the levator muscle). Ptosis thus caused would come on at the time of the surgical procedure, of course, and not months or years later.

MYOTONIC DYSTROPHY

Myotonic dystrophy does not start with ptosis and therefore is not usually a problem in diagnosis. The other muscular signs of myotonia, as well as the age of the patient at onset, make the diagnosis rather easy. Cataracts of all types are seen in association with myotonic dystrophy, but the Christmas tree cataract is pathognomonic. It is seen only with the slit lamp, and it appears as multiple scattered red and green crystalline dots throughout the lens.

SYNKINETIC PTOSIS

In synkinetic ptosis, the change in degree of ptosis is related to some other facial movement, such as that of the nostril, ear, or jaw. Those cases of synkinetic ptosis associated with jaw movement (referred to as the Marcus Gunn, or jaw-winking, phenomenon) are the only ones of clinical significance.

The patient exhibiting the Marcus Gunn phenomenon moves the lid up and down by opening and closing the mouth, with associated contraction of the masseter muscle. The same lid action can be achieved by contracting the masseter muscle when the jaw is moved from side to side. The lid movement can be brought out by having the patient chew gum or suck on a hard candy. As long as the masseter muscle is contracted, the ptosis is improved. The jaw-winking component seems to disappear with age in many patients, but the ptosis does not. The reason for this difference is not known.

CEREBRAL PTOSIS

Cerebral ptosis is a rare but recognized clinical entity. The exact anatomic location of the lesion causing this phenomenon is unknown. Other CNS lid problems, such as apraxia of lid opening and blepharospasm, are also a mystery. Cerebral ptosis appears to be more common with right hemisphere
Hering's Law of Equal Innervation

Hering in 1868 first proposed the idea of equal innervation to extracranial yoke muscles. This phenomenon allows the two eyes to move smoothly and together in all types of eye movements. It maintains binocular vision during these ocular excursions. Later investigations have applied Hering's equal innervation theory to the levator muscle as well.

Unilateral lid retraction is well recognized occurring when there is contralateral ptosis. This is a frequent result of additive lid support from the frontalis muscle and should be looked for when examining for ptosis. A small ptosis may be overcome by the frontalis support and may be missed by the casual observer.

Clinical evidence for equal innervation is the presence of lid retraction in the eye contralateral to a ptosis. Further evidence in support of this innervation hypothesis is obtained when the lower of the two lids is manually lifted. This maneuver reduces innervation to the lifted ptotic lid and also to the retracted lid. Because innervation to the retracted lid is now less, it assumes a normal innervation and position in reference to the globe. This same result can be achieved by covering the eye with the ptotic lid and forcing the patient to fix with the eye that has the retracted lid.

If Hering's law of equal innervation can be applied at the nuclear level rather than peripherally, it is equally appealing. This is because of the close proximity of the levator subnuclei to the other subnuclei of the third nerve nucleus. We know that there is some interrelationship between the ocular motor nuclei in the area of the superior rectus muscle.

Other nerves also play a role in lid position, including the facial nerve, which controls closing of the lid by innervating the orbicularis muscle. In addition to the levator muscle lifting the lid via oculomotor innervation, the sympathetic system innervates Müller's muscle. All of these muscles are not always subject to Hering's law. In fact, it is easy to open or close one eye, smile on one side of the face, or wink. However, unless we consciously do these things, there is bilateral symmetrical movement such as when we blink or smile.

There are many cases of lid retraction that have no relationship to Hering's law. These entities are discussed below.

Third Cranial Nerve Misdirection

Synkinetic retraction may be seen in third cranial nerve misdirection between the levator muscle and the inferior rectus muscle; they are referred to as the pseudo-von Graefe's sign. After third cranial nerve paralysis owing to trauma or aneurysm, a misdirection phenomenon may occur between the levator muscle and the inferior rectus or medial rectus muscle. When the eye is moved in the direction of either of these muscles, the lid may be innervated, causing lid retraction.

Lid Retraction

A consideration of lid retraction should be included in any discussion of ptosis. When looking at a patient with ptosis, the physician must decide whether one lid is ptotic or
the other lid is retracted, regardless of which lid the patient thinks is abnormal. Patients interpret their condition according to what is more cosmetically disturbing to them. If retraction is present, a small white area of sclera appears between the lid and the upper cornea, a phenomenon that is always abnormal.

Retraction of the lower lid also occurs in thyroid ophthalmopathy even without proptosis, just as it occurs in the upper lid. Retraction of the upper lid does not occur with proptosis resulting from orbital tumors. The upper lid stretches and goes forward with the globe as it is pushed out. This movement should be expected, since we see a large excursion of the lid synchronous with the globe in vertical gaze. It is also helped by gravity and capillary attraction to the conjunctival surface of the globe. The lower lid does not move in the same manner or at least not to the same degree as the upper lid. The inferior rectus muscle has attachments to the lower lid. Since this is one of the major muscles affected by thyroid disease, it can cause retraction of the lower lid. Lower-lid retraction can also be seen after recession of the inferior rectus muscle and as an early sign of facial nerve paresis.

The sympathetic innervation involves the lower lid also. In Horner syndrome, the lower lid moves up in the form of a reverse ptosis. This sign may be particularly useful in cases with other anatomic variations of the upper lid (e.g., blepharochalasis) that obscure whether there is ptosis or not. A fuller description of this sign is presented in Chapter 3.

**Thyroid Disease**

Although the causes of lid retraction are numerous, over 90% of the time the condition represents thyroid disease. As pointed out by McLean and Norton, the sign may be unilateral, and it may occur prior to the onset of systemic and chemical signs of thyroid disease. A discussion of the chemical tests that are most valuable currently for the diagnosis of thyroid disease are discussed more fully in Chapter 6, Diplopia.

**Collier's Lid Retraction**

The next most common cause of lid retraction is Collier's sign in midbrain disease occurring particularly at the posterior commissure. Usually, no problem exists in differentiating patients with this condition from those with thyroid disease.

**Hydrocephalus**

The setting-sun sign of hydrocephalus in children is not well explained; possibly it is a variant of Collier's sign and is caused by transmitted pressure.

**Third Cranial Nerve Misdirection**

Third cranial nerve misdirection may produce a combination of ptosis and lid retraction. It occurs predominantly after trauma or aneurysm—and never results from diabetes, which fact is the reason for observing this sign. If a patient has developed third cranial nerve misdirection after a third cranial nerve paralysis, it must be concluded that even if the patient has diabetes, the cause of the misdirection was either trauma or an aneurysm that was unsuspected. Diabetes causes third cranial nerve paralysis but never misdirection. When the third cranial nerve recovers, there may be a slight ptosis or none at all. As the eye is adducted, the lid retracts because of a new relationship established between the innervation of the medial rectus muscle on adduction and the lid. This sign is best seen in examining the horizontal excursion of the eye in question on down-gaze rather than in the straight-ahead position. A similar relationship may occur between the...
levator muscle and the inferior rectus muscle on down-gaze.

**Adverse Seizures**

Frontal lobe or adverse seizures have associated ocular signs that are of interest. When one frontal lobe is stimulated, the head and eyes are driven toward the other side and the upper lids retract. Between seizures, the lids and the gaze mechanisms are normal.

**Lid Retraction after Operation**

Previous operation for ptosis with secondary overcorrection or a surgical procedure for laceration of the lid with contraction of the scar in a vertical direction may result in retraction of the lid. These causes of lid retraction may be identified readily from the history or from simple inspection.

**Claude Bernard Syndrome**

Claude Bernard syndrome is the opposite of Horner syndrome. In this rare syndrome, lesions stimulate the sympathetic chain, causing ipsilateral lid retraction. The lesions that cause Horner syndrome also cause Claude Bernard syndrome. Occasionally, a patient voices complaints typical of those made in Claude Bernard syndrome but on examination will be found to have a slight Horner syndrome rather than lid retraction and enlarged pupils. Such a patient may have a peripheral Horner syndrome in which a supersensitivity to his or her own circulating epinephrine has developed. This possibility is confirmed by placing a 1:1000 aqueous solution of epinephrine in both eyes and observing them 30 minutes later. The side the patient has complained about will show a larger pupil and a variable amount of upper lid retraction.

**Voluntary Subluxation of the Globe**

In this frightening spectacle, the patient is able to markedly retract the upper and lower lids to near the equator of the globe. At the same time, the patient subluxates the globes enough to get the lids behind the equatorial plane. He or she then squeezes the orbicularis muscle and closes the lids, thus pushing the globes farther out. The patient can usually reverse the process unless the lids go into spasm or secondary swelling occurs. At this point, the patient may require a partial, partial or total, nerve block to release the lid spasm and replace the globes.

**Myotonic Lid Lag**

There are cases of myotonic lid lag in both hypo- and hyperkalemic periodic paralysis that initially look like lid retraction. Myotonic lid lag is more common in the hyperkalemic form but can occur in the hypokalemic form, making the institution of potassium therapy sometimes puzzling.

**TESTS FOR OCULAR MYASTHENIA GRavis**

**Tensilon Test**

Any ptosis that is not of obvious origin deserves a Tensilon test, which is given as a 1-mL intravenous injection. Traditionally, it has been advised that an adequate dose of atropine be given to the patient prior to injection. A problem involved in giving the atropine dose is that the medication lasts much longer than is required for the test and becomes uncomfortable to the patient. Another problem is that most patients are given the atropine intramuscularly and then almost immediately—before it has a chance to work—are given the Tensilon test. Many
physicians feel that the use of atropine is unnecessary but that it should be available.

To do the Tensilon test, give the patient 0.1 mL of Tensilon as a screening dose while looking for any overreactions to the drug. If none occur within 1 minute, then give the rest of the dose in 0.2-mL doses per 30 seconds. An improvement in the ptosis should be seen within 30 seconds; the entire effect will pass within 3 minutes. The important part of the test is to find the area of maximum ocular deficit, either in extraocular muscle imbalance or as ptosis, before giving the test. Then examine that entity or position during the test period. A positive response reflects significant improvement in these areas and pinpoints the cause as myasthenia gravis. Ptosis is more easily evaluated with the Tensilon test than is diplopia.

Quinine Challenge

Before the Tensilon test came into use, an opposite approach was in vogue, namely, seeing whether one could make the myasthenia worse. The physician gave the patient quinine, which reduced the sensitivity of the motor endplate and thus aggravated the myasthenia. This approach is no longer taken, but the reaction to quinine may still be seen in two other situations: (a) a patient who drinks tonic water may ingest enough quinine to cause a worsening of any myasthenia and (b) quinine given to many older people as a treatment for night leg cramps may at the same time aggravate a myasthenic process.

Electromyography

In my experience, electromyograms for ocular myasthenia gravis are not useful. The electrical pattern obtained may be typical of myasthenia gravis but not entirely diagnostic. Furthermore, the technique is inadequate because the recording needle is frequently inserted in the levator aponeurosis rather than in the muscle, which is farther back in the orbit. Testing other muscles, such as the biceps muscle, may give false-negative results if the patient has only the ocular form of myasthenia gravis.

Biopsy

Biopsy is also of limited diagnostic value because, first, one has to get some muscle and not the aponeurosis, and second, the specific features that are diagnostic of myasthenia gravis are not commonly seen in biopsy specimens. The basic defect is not in the muscle anatomy, but is a biochemical defect in the number of packets of acetylcholine in the motor endplate. The biochemical deficit is evaluated by the Tensilon test. The pathologic changes are indirect evidence of the disease. None of the other myopathic processes involve significant enough differential pathologic changes to warrant a biopsy. Drachman points out that one cannot differentiate a neuropathic process from a myopathic one by a biopsy. In addition, good experimental evidence now exists that an antigen-antibody reaction at the motor endplate also interferes with the motor endplate function.

TREATMENT OF PTOSIS

Treatment of ptosis depends on the problems involved. If the ptosis causes skeletal deformity owing to head position or if the lid covers the pupil in a child in whom amblyopia may develop, repair must be undertaken early.

If the ptosis is caused by recent trauma, delay and careful observation for many months are indicated before embarking on a surgical procedure. If the condition is a myopathy and up-gaze is affected—or may be affected in the future—surgical caution is the word because severe corneal exposure owing to inadequate Bell’s phenomenon and the associated orbicularis muscle weakness during sleep) becomes a problem. Cautious
Surgical Treatment

The type of operation varies according to the degree of ptosis, the amount of levator muscle function, and the judgment of the surgeon. In-depth discussion of the possibilities is best left to surgical texts. The two approaches I recommend are the tarsal conjunctival approach of Hoffer for a small ptosis (3 mm or less) and the skin approach of Berke for a larger one. For ptosis associated with the Marcus Gunn phenomenon, the frontalis sling, along with the cutting of the innervation to the lid so as to prevent the recurrence of jaw-winking, is recommended. Crutch glasses can be used, but they seldom are tolerated by the patient.

Corticosteroid Therapy

Oral corticosteroids have been used in the treatment of ocular myasthenia gravis for several years. Despite the lack of universal agreement as to the efficacy of this treatment in purely ocular cases, certainly it may be worthwhile in a number of cases, particularly when the patient does not have an adequate response to anticholinesterase drugs. In addition, some evidence suggests that long-term anticholinesterase therapy may destroy some of the smaller nerve terminals and therefore may not be the best treatment over long periods of time.

TREATMENT OF LID RETRACTION

The treatment of lid retraction is the treatment of the underlying process. In the case of thyroid disease, the lid retraction usually does not go away completely with control of the hyperthyroidism, but it can be further improved by lateral and, if necessary, a small medial tarsorrhaphy. In extreme cases, a reverse ptosis procedure can be performed, in which part or all of the tarsal attachments of the smooth and striate muscles are detached.

The use of topical guanethidine to create a chemical Horner syndrome was first reported by Gay and his associates and subsequently popularized in the British literature. It has not been useful in my hands and has a history of ocular irritation. Recent studies with topical 0.5% thymoxamine have been more promising but also have the same irritating effects when applied topically. The thymoxamine is an alpha-adrenergic blocker and, therefore, ideal to effect abnormal stimulation of Müller's muscle. Thymoxamine does relieve about 2 to 3 mm of lid retraction even if thickened muscles are demonstrable on computerized tomography. It does not work on stable, longstanding thyroid eye disease. It also does not affect normal persons, nor does it work in a variety of other neuromuscular diseases. It is in this latter category, as a diagnostic agent to confirm thyroid disease and rule out other neuromuscular diseases that thymoxamine may find its greatest use.

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Diplopia (dip, double; ops, see), or double vision, is seeing the same object in two different places or simply seeing double. The essence of double vision is seeing one clear, or at least clearer, image and a second less-clear image displaced from the first. In most cases, it is fairly easy for the individual with diplopia to recognize the "real thing" when looking at a stationary object in familiar or nonthreatening surroundings. This double vision can be very annoying but can be dealt with by patching or dosing one eye when watching television, reading, or carrying out routine activities in a familiar place. However, when a person is in a more demanding situation (e.g., driving) or around moving objects in an unfamiliar situation, the second image, especially at distance fixation, may produce a great deal of consternation, uncertainty, and even danger. An individual with double vision also loses the more subtle but definite advantage of stereoscopic depth perception when dealing with near objects. From the standpoint of comfortable, effective vision and personal safety, diplopia can play an important role in visual and personal health. Diplopia is usually acquired in visual adulthood and may be caused directly or indirectly by one or more sometimes significant systemic or local conditions.

MECHANISM OF NORMAL BINOCULAR VISION AND DIPLOPIA

To see double, it is necessary to have vision in both eyes. The vision need not be equal or even good in the eye responsible for the second image, but in general, the symptoms of diplopia are more likely to be bothersome if the second image creates enough awareness to be competitive and, therefore, annoying. To better understand diplopia, it is necessary to understand the mechanism of single binocular vision.

Retinal Correspondence

Each eye provides the brain with a more or less complete view of what is in front of it. In normal humans, the two eyes relate to one another in such a way as to produce a single image from two "pictures," a right-hand picture and a left-hand picture. This union of images is carried out through a complex neurologic organization beginning with corresponding retinal points. The most notable of the corresponding retinal points are the two foveas. When the fovea of each eye is stimulated indepen-
Diplopia

The brain registers that the object "seen" by each fovea is in the same place regardless of the direction the eyes are pointing. The two foveas in the normal situation can be considered the principal corresponding points. The fovea is also the retinal location responsible for the best visual acuity. Away from the fovea, the two retinas relate so that each point in the right retina has a corresponding point in the left retina. Specifically, the right nasal retina contains points that correspond to their counterpart in the left temporal retina, and vice versa. By this scheme, the two eyes produce a single cycloplus eye, which can be envisioned as being centered around the occipital cortex, with the two foveas being the only truly binocular as well as sensorially corresponding points and with the nasal-temporal and temporal-nasal retinal relationships existing elsewhere in the right and left hemispheres.

The binocular visual field, which is made up of stimuli from both eyes, is slightly smaller in its peripheral extent than either monocular visual field. The reason for this phenomenon is that the lower temporal field of each eye is seen only by the ipsilateral eye because the nose blocks the contralateral eye.

When stimulation of corresponding retinal points or areas produces single vision, normal retinal correspondence is said to be present. Conversely, when stimulation of corresponding retinal points produces diplopia or when stimulation of noncorresponding retinal points produces single vision, anomalous retinal correspondence is present. Anomalous retinal correspondence may be harmonious or nonharmonious, depending on whether the angle of anomaly is equal to (harmonious) or less than (nonharmonious) the angle of strabismus. Nonharmonious retinal correspondence, which serves no apparent purpose, may be only a testing artifact whose presence gives a clue as to the depth of the sensorial adaptation. Strabismus in early life followed by suppression and then sensory reorientation is the basis of anomalous retinal correspondence. This response can be considered an innate, binocularly functioning antidiplopia mechanism.

Suppression

The physiologic solution to the diplopia potential that occurs when the two eyes send the brain an independent picture is fusion, which is the normal binocular state. An expedient response when fusion is not possible is suppression of one image. Suppression of the image from one eye is for the most part relative; that is, even in the case of profound suppression a person can be made aware of the second image if a more intense stimulus is presented to the suppressed eye. That is, in most instances the suppression can be overcome if sufficient stimulus is given to the nonpreferred eye. Nonetheless, suppression, which occurs at the cortical level, is an effective mechanism for eliminating diplopia.

When strabismus produces the potential for double vision in infants or children, who have an immature visual system, suppression occurs rapidly, is profound, and causes a permanent breakdown in the normal binocular fusion process. This profound suppression may be alternating so as to maintain normal vision in the eye that happens to be used at the moment for fixation. On the other hand, the suppression may habitually affect just one eye; in this case, there is fixation preference for the other eye, and amblyopia occurs in the habitually suppressed eye.

The earlier the onset of strabismus and the longer it is left untreated, the more profound the suppression will be. Suppression may be reversed in most cases with timely and effective occlusion therapy. Both the establishment of suppression, with or without amblyopia, and the reversal of suppression through occlusion and other amblyopia treatments occur during the immature or plastic period beginning shortly after birth and persisting until ages 6 to 9 years. Treatment of amblyopia with timely and persistent occlusion of the preferred eye can be effective. There is no specific treatment that directly enhances fusion. At present, the only effective strategies to enhance fusion are indirect methods intended to equalize vision, such as patching...
and alignment of the eyes by means of surgery or hyperopic optical correction and/or the use of bifocals in a few selected cases as early in life as possible.

When suppression exists, harmonious anomalous correspondence is usually present. This means that the suppressed, or actually partially suppressed, eye is being used to fill in the visual picture more or less as a "helper." The misaligned picture that the suppressed eye sends to the brain is sensorially modified by the anomalous correspondence. This phenomenon can be confirmed by noting the difference in size between the monocular and binocular visual fields. For example, in an exotropic individual who has right-eye vision of 20/20 and left-eye vision of 20/200, the suppressed eye of the exotrope, particularly in the peripheral monocular field, contributes significantly to the visual field; this contribution can be plotted with binocular visual field testing. With facultative, or alternating, suppression, either eye may be used for fixation while the other eye is suppressed momentarily and acts as a "helper." The instantaneous sensorial adaptation seems clinically to be as profound in facultative suppression as in habitual suppression with amblyopia but differs in that it occurs on an instantaneous and alternating basis. That is, the suppressed eye has the capability for reversal to become the fixating eye at any time.

A clinical situation that stresses the importance of binocularity in the presence of suppression occurs in the adult who has exotropia and who also has serviceable vision in each eye, with or without alternation. This type of strabismus individual will have an expanded binocular visual field. A person with large-angle exotropia may be able to see peripheral objects out to 180° or more on the side of the deviating eye. Using noncorresponding retinal points united in harmonious anomalous retinal correspondence at least in part, these patients enjoy an expanded, and to a certain extent useful, visual field without diplopia. When these adult, large-angle exotropic patients with an enlarged binocular visual field have their eyes straightened surgically, they should be warned that they will, at least for a short time, experience what they may interpret as "tunnel vision." This sensation is experienced as the individual reverts from an expanded to a normal binocular field. Such patients can be reassured that the early postoperative, uncomfortable feeling always goes away, and therefore reverting from an expanded to a normal visual field should not be a deterrent to having their eyes straightened.

**Physiologic Diplopia**

Normal persons with no strabismus when provoked experience physiologic diplopia because all objects except the object of regard (what we are looking at) are seen by noncorresponding retinal points and thus produce double images. Objects closer than the object of regard are seen by the noncorresponding temporal retina of each eye; such near objects produce doubled and crossed images (crossed, or heteronymous, diplopia). Objects farther than the object of regard, provided the object of regard is inside infinity (inside 20 feet for practical purposes), are seen by the noncorresponding nasal retinas of each eye; such distant objects produce uncrossed double images (direct, or homonymous, diplopia). Fortunately, normal humans have the innate capacity to ignore the panorama of potential double images and to be visually aware only of what is useful and comfortable. In the pathologic manifest strabismic state, exotropia produces uncrossed diplopia, and exotropia produces crossed diplopia.

It should be emphasized both to normal individuals and to those with strabismus from a variety of causes that a person with two seeing eyes can always experience diplopia. The normal person is the one who with proper motivation can successfully avoid diplopia and maintain comfortable, effective, single binocular vision. Avoidance of physiologic diplopia by normal individuals is aided by the fact that psychologically they
know what they are looking at, and the doubled images are seen by retinal areas with poorer resolution.

**Panum's Fusional Space**

The horopter is defined as the sum of points in space that stimulate corresponding retinal points along the horizontal plane and are seen singly. Panum's fusional space includes the area slightly farther from the person that stimulates binasal retinal areas and the area slightly closer to the person that stimulates bitemporal retinal areas. The summation of these stimuli, seen singly and with depth, produces stereoscopic vision. Normal binocular vision with stereopsis and binocular vision without stereopsis should be distinguished. For example, a patient with 30° of alternating esotropia has binocular vision, as evidenced by an enlarged binocular field; an esotropic patient also exhibits binocular vision, although it is less obvious and less important clinically. However, such patients, who are binocular in the broader sense, will be unable to appreciate stereopsis, which is the ultimate reward of binocular single vision.

**Posttreatment and Other Types of Diplopia**

In the clinical situation when adult patients with longstanding strabismus are being considered for surgery to straighten the eyes, they can be tested for the likelihood of postoperative diplopia by placing fully correcting prisms in front of the eyes while a distant object is fixated. They are then asked whether they see singly or not. Although this may be a useful technique to anticipate transient postoperative diplopia and to show patients what diplopia will look like if they do not already know, it is seldom a reliable predictor of persistent bothersome postoperative diplopia. Thus, preoperative diplopia testing is definitely a limited clinical tool.

A special type of posttreatment diplopia is worth mentioning. This is the intractable diplopia that can occur after prolonged patching of one eye for amblyopia in the presence of small-angle strabismus, even microtropia. We have seen several young patients with minimal amblyopia of 20/20 in one eye and 20/40± in the other eye who underwent extensive amblyopia treatment with both patching and active stimulation. Such patients may improve a line or so in the amblyopic eye, but in the process the suppression is broken down, and diplopia occurs because nonsuppressed, noncorresponding retinal points now are competing on a more-or-less equal footing in the absence of suppression or effective anomalous correspondence. Because these patients lack fusion potential, they cannot be successfully treated with a prism or glasses. This same phenomenon can also occur spontaneously in adults with amblyopia who change the way they use their eyes. For example, such an individual may be given a new job that requires prolonged attention to fine detail such as reading blueprints or reading fine calipers. This form of "autopleoptics" can cause adult-onset diplopia in susceptible patients in the same way that prolonged patching causes it in a child. There is no adequate treatment for this type of diplopia except time and possibly altered use of the eyes, so that prolonged scrutiny of small objects is avoided.

In paradoxical diplopia, a patient with an esodeviation reports crossed diplopia, or a patient with an exodeviation reports direct diplopia. This rare and transient phenomenon occurs when there is a change in the strabismus angle that is not accompanied by an appropriate and compensating suppression and/or alteration in retinal correspondence. Monocular diplopia can result from a variety of abnormalities of the media, including corneal opacities and irregularities, polycoria, cataract, subluxated lenses, and vitreous opacities. Maculopathy can also cause monocular diplopia. In differentiating a media cause from a retinal cause for monocular diplopia the patient is asked to look through a pinhole. If the monocular
Diplopia disappears while looking through a pinhole, a media cause for the monocular diplopia can be inferred. If the monocular diplopia persists when the patient looks through a pinhole, a maculopathy is the most likely cause for the monocular diplopia.

Receptor problems have occasionally been reported with pituitary tumors that bisect fixation and with hemorrhages in the occipital cortex that spread the receptor elements of the visual cortex. When monocular diplopia is present, binocular triplopia can occur if the visual axes are misaligned.

Motor Fusion

The two eyes move about in the frontal plane under the influence of six pairs of extracocular muscles that function in a yoked manner. The ultimate role of the extracocular muscles is to move the eyes together toward, and then to enable the eyes to maintain fixation upon, the object of regard. These two functioning units, right eye plus extracocular muscles and left eye plus extracocular muscles, initially meet at the occipital cortex. Their binocular vision capability is consummated through integration in the brainstem and, finally, is expressed through the cranial nerves, which supply the extracocular muscles. The purpose of this visual motor feedback mechanism is to maintain alignment of the visual axes on the object of regard while the person viewing and/or the object of regard is either changing positions or still. Fixation is maintained through a series of conjugate movements of the eyes whereby they move "together" in the various directions—right, left, up, and down, or a combination of these movements. Binocular yoked eye movements are called versions.

Yoke muscles receive equal, distributed innervation according to Hering's law. Antagonist muscles receive reciprocal innervation according to Sherrington's law. When an object is brought from far to near, the eyes undergo convergence with an emphasis on medial rectus contraction and lateral rectus relaxation; when an object is moved from near to far, the opposite occurs.

During accommodation, the central stimulus for fusion occurs in the occipital cortex where retinal image disparity is recognized and where a "correction" stimulus to effect alignment of the object of regard is initiated. This stimulus to bring the images together by motor fusion is mediated through the brainstem. Damage to this axis from trauma, surgery, or other causes can lead to central disruption of fusion. Patients with this problem can fuse momentarily, but they have no capacity to maintain this fusion and, therefore, have intractable diplopia. Two other conditions are somewhat like this: horror fusionis and persistent secondary deviation. In horror fusionis, the two foveae act like similar poles of a magnet and actually repel one another, producing a constant diplopia. In persistent secondary deviation, such as occurs with bilateral sixth or fourth nerve palsy or with third nerve palsy especially with aberrant regeneration, a secondary deviation drives the visual axes apart in nearly any field of gaze. These conditions may be slight variations on the constant theme of damage to the CNS regulating mechanisms.

EVALUATION OF THE DIPLOPIA PATIENT

The use of diagnostic diagrams can be both helpful and restrictive. They may be very simple and easy to follow, but they don't cover the subject adequately. The other approach is to cover the entire subject, which results in a very involved and difficult diagram to follow and understand. We are all looking for a simple solution to a complex problem. It would be so easy to have a computer program that outlines the appropriate differential diagnosis. You then feed in the results of the examination and the laboratory data, and the computer prints out the proper diagnosis. Medical history-taking, however, is more an art than a science,
which skill is honed over years of practice and experience. The diagnostic trees are a less sophisticated approach to the problem than the computer but can be helpful. If they are used, knowing their limitation, then they serve a real purpose. We have tried to strike a balance between the two extremes of design and to develop one that is practical.

History (Fig. 6.1)

The proper investigation of a patient with the complaint of diplopia is truly a test of the physician's history-taking ability. The primary part of the patient interview is to determine if the patient is using the term "double vision" correctly. True binocular diplopia resulting from the malalignment of the two eyes requires a different workup than monocular diplopia (Fig. 6.2). If the patient still claims to see double with either eye closed or that diplopia is still present when one particular eye is closed and the other is open, then we have monocular diplopia. As simple a differentiation as that may seem unimportant, but most patients have not examined their problem that specifically. If the problem is monocular and due to some opacity in the media, ask the patient if the "double vision" is more like a ghost image on TV with one clear image and another more faded outline around it? The distortion of the transmitted image from the ocular media can be a corneal scar, keratoconus, cataract, vitreous opacities, or macular disease. Distortion of images has been reported on a cerebral basis but is extremely rare and will be equal in both eyes. Distortion due to

![Diagram of History of Chief Complaint]

- Diplopia
- Blurred vision
- True binocular diplopia
  - Intermittent
  - True intermittent
- Constant
  - One field only
- Monocular
  - One eye
  - Both eyes

1. Other neurologic complaints
2. Hypertension, diabetes, other systemic diseases
3. Malignancy
4. Ocular surgery old or recent
5. History nonsurgical treatment strabismus
6. Trauma

1. Same in each eye
2. Characteristic of one eye
3. Decreased vision or distorted (e.g., smoked glass)

**Figure 6.1.**
Diplopia history.
macular disease is frequently described by patients as double. Ask the patient if the image is like a view seen in a cracked mirror. True binocular diplopia images are usually two images equally clear. This may not be always true if there is a secondary problem in one of the eyes, such as a cataract.

Once the history denotes monocular diplopia, then tests such as a pinhole, careful refraction, keratometry, Amsler grid, slit lamp examination, contact lens evaluation, and careful fundus examination are the directions the workup should take.

If the history denotes true binocular diplopia, then the next step is to find out if it is constant or intermittent. This may not be as straightforward a question as it seems. If it is intermittent, inquire about the circumstances under which it occurs. Does it develop later in the day and do the images get further apart as the day progresses? If it does, then myasthenia gravis is high on the list of differential diagnoses. Myasthenia gravis is an even stronger consideration if there is a ptosis and the patient is a young female. The patient may notice weakness in her shoulders when combing her hair, which is highly suggestive of the diagnosis. The evaluation of a patient with this list of symptoms takes a different direction. This includes the clinical fatigue test, EMG studies, blood assay for acetylcholine receptor antibody, and the edrophonium test (Tensilon).

If the diplopia occurs in separate episodes, then inquire under what circumstances it occurs. Ask particularly if there are any other neurologic symptoms such as weakness, sensory changes in an arm or a leg, periorbital paresthesias, or difficulty finding a word or a period of unconsciousness that occur at the same time as the diplopia. This type of diplopia probably represents a transient is-
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Thrombosis. Evaluation of cardiac status with an echocardiogram, blood pressure monitoring, and carotid ultrasound evaluation is appropriate. However, before ordering such tests, at least listen to the patient's heart for a gross arrhythmia, check the blood pressure and listen for a carotid bruit. Even though diplopia is a sign of posterior circulation disease, that is no guarantee that the arteriosclerotic disease is limited only to that portion of the vascular system. Listening to carotid bruits may therefore be quite revealing. Another form of intermittent diplopia may be in a situation where the diplopia is in only one direction and therefore appears to occur intermittently. This is commonly seen in partial sixth and fourth nerve palsies. This may be apparent to the examiner in how the patient holds his or her head during the interview. The patient may not even be aware of a compensating head position.

Intermittent diplopia can result from the breakdown of a phoria. The clinical clue is that the muscle measurements are comitant, which suggests an old problem or a phoria converted to a tropia. This breakdown of a phoria can occur after head trauma, severe illness, or fever. How often have we heard about the measles settling in the patient's eyes and causing strabismus.

Patients often use the term double vision in such situations as convergent spasm and momentarily having blurred or double vision when refixing at distance. Students can have a similar complaint at near with prolonged reading, which is covered under the title of vergence insufficiency. At best this is a very obvious diagnosis with good history taking.

If the diplopia is constant, then ask whether the images are vertically or horizontally separated. If the patient response is horizontal, then the diagnosis of the offending muscle is much easier. It represents either a lateral rectus or, less commonly, a medial rectus muscle paresis. If the medial rectus is an isolated problem, it rarely represents a partial third-nerve paresis. The latter is more commonly due to a myopathy such as myasthenia gravis. It is less commonly due to thyroid disease, which primarily affects vertical muscles initially. The medial rectus palsy may also be due to a central mechanism such as internuclear ophthalmoplegia. In a similar circumstance, skew deviation represents the vertical counterpart of a central mechanism causing diplopia rather than a final common pathway.

Evaluation of vertical diplopia is much more complicated than that of horizontal diplopia. Invariably when patients are asked if the diplopia is horizontal or vertical, they answer that it is both or oblique in nature. This is because there are multiple muscles involved or an underlying horizontal phoria that is now revealed. The three-step test is the usual method of identifying which is the appropriate muscle. This test is described below.

**Monocular Diplopia Examination (Fig. 6.3)**

Once the question leads to a monocular form of blurred vision, it is not uncommon for the patient to have trouble realizing it any more specifically. The pinhole test is one of the easier tests to start the evaluation. If the pinhole test significantly improves the patient's vision, then a careful refraction is the next test to perform. Since refractive errors are very common and usually not pathologic causes of blurred vision, it frequently solves the problem without further workup. If the test is performed at a phoropter, the solution may not be the refraction but rather the relative pinhole effect and constriction of the field resulting from looking through a small aperture. This can be avoided by transferring the prescription from the phoropter to a trial lens arrangement where the constrictive field is not a compensatory factor.

A true pinhole test can be done with a single or multiple pinhole technique. Multiple-hole technique is usually easier for the new patient. Even with the multiple pinhole test, some patients cannot perform very well and
Figure 6.3.
Monocular diplopia evaluation, part 2.

give an answer as though it was a negative response. Decreased vision from refractive disease is improved with a pinhole, while macular disease is the same or usually worse. Nerve disease usually remains about the same with or without the pinhole.

The Amsler grid is a valuable test for showing macular distortion to a patient, as is illustrated in Chapter 17 (Figs. 17.3, 17.4, 17.5). Show these two illustrations to patients who have difficulty in interpreting what they see. It is also helpful to let patients with a monocular complaint compare the one normal eye with the abnormal eye. A response of distortion usually indicates macular disease, but cataracts such as irregular cortical spokes or posterior subcapsular opacities can cause distortion. Small changes in the patient’s lens may not be impressive on ophthalmoscopy or even on biomicroscopy. An irregular reflex on retinoscopy may be more suggestive of the problem. Small changes can be especially bothersome in irregular corneal astigmatism such as is seen with keratoconus.

The patient’s blurred vision complaint may be a poorly expressed description of a field defect. These defects are usually paramacular and may be vascular, edematous, inflammatory, or hemorrhagic and found on a careful fundus examination. If the defects are the same in both eyes, an occipital lobe location may be the source of the problem. Glaucoma defects are usually negative scotomas and not noticed by patients. However, when an arcuate scotoma comes very close or directly into fixation, the patient will report an acute complaint. The central involvement is usually a late sign of glaucoma. When this event occurs, you expect to see advance cupping, which would be the clue to the diagnosis. In low-pressure glaucoma,
central defects occur early, and as such, cupping is not as obvious.

Subtle macular disease, such as central serous retinopathy or retinal epithelial detachment, is best seen with a fundus contact lens or a 90 diopter lens.

Pupil examination is important to help differentiate optic nerve disease from other causes. This is particularly helpful when the cause for the reported decrease in vision is not obvious during the examination. The possibility of functional disease comes to mind as part of the differential diagnosis when no obvious cause is found. However, a relative afferent pupillary defect removes that diagnosis from consideration and identifies the optic nerve as the source of the decrease in vision.

**Binocular Diplopia Examination (Figs. 6.4, 6.5)**

In a case of true binocular diplopia, instruct the patient to move the eyes in the cardinal directions of gaze. Restriction of an eye in one of these cardinal directions will usually identify the affected muscle. The investigation from this point takes two directions. The first test is to measure the horizontal and vertical deviations in the cardinal fields of gaze. In the face of a large horizontal deviation, a small hyperdeviation may be missed unless measurements are made. This is even more important to define when the ductions are full and the affected muscle is not obvious. If the eye restriction is obvious, then you need to differentiate a neuropathic from a myopathic or restrictive cause. A restrictive cause is best diagnosed by a forced duction test. Adequate topical anesthesia is applied to the eye and a tooth forceps is used to move the affected eye in the direction it does not move voluntarily. The best area to pick up with the forceps is next to the limbus. Farther away from the limbus, the conjunctiva is loose and can be moved without moving the eye. The test conclusion in that situation would be inconclusive. Did the eye not move because of restriction or because the loose conjunctiva just moved and didn't create enough force to move the globe? I find that the usual topical anesthetics are not enough for total anesthesia in the perimacular area to have the patient relax during the test. Since I am a neuro-ophthalmologist, I have cocaine in the office, which at one time I used for doing pupil testing. I don't use it for that purpose anymore, but I find it useful in forced duction tests. Put the cocaine on a cotton-tip applicator and apply it to the area of the conjunctiva that you plan to pick up with the forceps. This technique reduces the amount of cocaine absorbed by the patient and lessens any serious allergic reaction. It is always best to put a drop of any other topical anesthetic in the eye before applying the cocaine, since cocaine is more uncomfortable before total anesthesia occurs. An adequate forced duction test is one in which you can move the eye freely or there is obvious resistance. The question to be asked is whether the resistance is from a primary orbital or muscular process or if the patient is resisting. The way to differentiate is to look at the normal moving eye for reference. When the patient has a problem moving the left eye out totally, observe the right eye on left gaze. If there is restriction of left eye movement but the right eye is in full adduction, this restriction of the left eye is real. If the patient does not move the right eye, then the restriction may be from lack of cooperation and not from a restriction. The technique of using an anesthetic coated cotton-tip applicator for moving the eye is adequate if the eye moves freely. It is difficult to evaluate the results if there is limited movement, since the applicator has no firm grip on the ocular tissues. As a first attempt, it is worth doing if the eyes move freely, and it is certainly less traumatic than using forceps.

If the ductions are normal and there is still double vision, the cover test is the first step toward the solution. The alternate-cover test determines whether there is any muscle imbalance. This test can be misleading if the examiner is not wary. If there is a phoria or tropia, you would expect to see some cor-
Figure 6.4.
Binocular diplopia evaluation, part 1.

Effective movement of the eye as it comes out from under the cover. However, a patient who is not alert or paying attention may not move the recently uncovered eye and bring fusion into play. This gives the false impression of no muscle imbalance. There are two ways to avoid this mistake. If the test is being done with gaze at distance, have the patient look at a series of letters and read them as each eye is uncovered. When the cover is moved from one eye to the other, the patient must move the newly uncovered eye toward the next letter on the screen to see and name it. If the patient reports the correct letter and did not move the newly uncovered eye to see it, there is no phoria or tropia. The patient has to move that eye to pick it up if he or she has a phoria or tropia. When the test is done at near, use a light or small object for the patient to fix on or maybe even his or her own finger. Before moving the cover from one eye to the other, move the object of regard back and forth slowly. Observe whether the patient is following it as instructed. You then stop the movement of the fixation object. This is followed immediately by moving the cover over the other eye and observing any corrected eye movement. This alternate-cover test merely shows a muscle imbalance and does not reveal whether it is a phoria or a tropia.

The cover-uncover test is used to differentiate a phoria from a tropia. A phoria is a deviation of the eyes that is kept under control by the fusional mechanism. It becomes manifest when fusion is interfered with, as during the alternate-cover test. The tropia is a manifest deviation that fusion can't overcome. The cover-uncover test reveals whether the deviation found on the alter-
Diplopia

BINOCULAR DIPLOPIA EXAMINATIONS

Ductions

Normal

Cover Tests

Phoria

Decompensating old phoria
Physiologic phoria
Spasm near reflex
Psychogenic
(prior fusion tests)

Tropia

Prism, red lens, Maddox
rod measurement

Horizontal Muscle

Cyclovertical

Medial Rectus

Three-Step Test

Lateral Rectus

INO
Miosis-parity
Thyoma

3rd Nerve
4th Nerve
Skew

Figure 6.5.

Binocular diplopia evaluation, part 2.

An alternate-cover test is a phoria or a tropia. When the cover is taken off one eye rather than switched over to the other eye, there are several responses possible. If there is no movement from either eye, there may be no phoria or tropia. However, we noticed some movement in the alternate-cover test. The lack of eye movement now means that the deviation is a tropia and that the eye originally not behind the cover is still the fixing eye. Confirmation is seen when the cover is moved onto the other fixing eye without interfering with the potential fusional mechanism. If you move the cover onto the second eye by moving directly to the other eye, you always have one eye covered and never allow fusion to work if it can. To prove it is a tropia, take the cover off the first eye and then cover the other eye, leaving an interval for fusion to work when both eyes are uncovered. Now the second eye picks up fixation while the first eye, which was originally fixing, moves in or out or up or down the exact amount the fixing eye moves to pick up fixation.

An example will help to illustrate this test. The alternate-cover test reveals an esophoria or tropia defect. Cover the left eye and the patient must fix with the right eye. Remove the cover and the right eye continues to fix. The left eye, now uncovered, moves in or moves out to align itself with the steady fixing right eye. Uncovering the second eye allows it to move in an appropriate direction and to align itself with the other, which does not move. It proves that fusion plays an important role in aligning the eyes and that the deviation is an esophoria. If there is no movement in the left eye when it is uncovered, then it is a tropia, and the right eye
remains the fixing eye. The alternative response is that as it is uncovered, the left eye moves out to pick up fixation, and the right eye that was fixing moves in the exact amount that the left eye moves out to pick up fixation. That deviation is called a tropia because fusion did not overcome it. No matter what the response, it should be repeated several times to be sure of it. It should be done in the cardinal directions, since the deviation may be in only one field of gaze and not the other. Any abnormal or compensating head position should be corrected during these measurements.

Once the deviation is identified as a tropia, then it is easier to switch back to an alternate-cover test when doing it with prisms to measure the extent of the deviation. As the alternate-cover test is repeated, put progressively stronger prisms in front of either eye to compensate for the deviation. The prism is placed so that the apex of the prism points in the direction of the deviation. When an adequate prism is used to compensate for the deviation, no further movement is seen on alternate-cover testing. The test is then performed in the cardinal directions to identify where the defect is the greatest. It is not uncommon in cyclovertical muscles to use compensating prisms in both a horizontal and a vertical direction. We can overcome a fair amount of muscle imbalance in the horizontal direction but very little in the vertical direction. If a patient has a large horizontal phoria, that may be the presenting picture to the examiner. When the examiner finds the horizontal deviation comitant, he or she is led to believe that the deviation is old. For instance, in the presence of a horizontal comitant deviation of 20 dipters, a small vertical tropia of 3 prism dipters can very easily be missed. It is this last vertical diplopia that caused the separation in the eyes and made the latent horizontal deviation so obvious. Since fusion cannot overcome the vertical deviation, it no longer can overcome the horizontal deviation either. An examiner who makes the determination on the basis of the comitant deviation will miss the real culprit, which is the new subtle vertical deviation.

The three-step test to identify the vertical muscle involved is outlined below. Sometimes the patient is confused with identical images when asked which one disappears when one eye is covered. If the images are far apart, sometimes the patient will ignore the other image and not be aware of diplopia. A red lens can be used over one eye to try to bring the patient's attention to the problem. The patient sees two objects in different colors and can identify two separate objects. Sometimes the red object is not seen. This may occur if the patient suppresses the image or if the red lens is in front of the poorer-seeing eye. In either case, switch the red lens to the other eye, and the patient may then appreciate a red and white image. If the diplopia is intermittent, it is appropriate to do away with the fusional mechanism while doing the mechanism measurements. The red lens can do this, but frequently the patient can force fusion even with a red lens in front of one eye. This intermittent complaint can be seen particularly in myasthenia gravis and may not be uncovered by the red lens test. The Maddox rod changes a single point of light into a bar. The two dissimilar images of a bar seen by one eye and a point of light presented to the other cannot be overcome by the fusional mechanism. Once the preliminary test identifies a tropia, the next logical step is identifying which muscle. This is done using the three-step test.

Identification of Muscles Involved

When it is determined that true diplopia is present, the offending muscle must be identified. To do this, examine each eye separately, instructing the patient to follow a hand light into all the cardinal fields of gaze (duction) while one eye is covered. If a muscle is severely affected, some limitation of movement may be seen in the oculocephalic reflex (doll's eyes).
of movement will occur in one or more fields, which will facilitate identification of the offending muscle. If limitation is not obvious, the muscle is weak only in regard to maintaining fusion with the other eye (version). Since ductions are stronger than versions, muscular weakness affects fusion first.

Limitation of movement can be caused by structural changes in the muscles that prevent their stretching, such as a tumor mass or hemorrhage. Tumor or hemorrhage may cause diplopia for several reasons, including neuropathic or myopathic changes and displacement of the globe. Blowout fractures of the orbital floor with entrapment of the muscle tendons also produce diplopia.

The forced duction test as described above is a simple, easily performed, and useful diagnostic technique for evaluating limitation of ocular rotation and determining whether lack of innervation or some other condition is responsible.

**Horizontal Diplopia**

Horizontal movement of the eye is accomplished by means of the medial rectus muscle, which is innervated by the third cranial nerve, and by means of the lateral rectus muscle, which is innervated by the sixth cranial nerve. The medial rectus muscle moves the eye toward the nose; the lateral rectus muscle turns the eye out. Diplopia involving these muscles is purely horizontal. When the medial rectus muscle is involved, the images are crossed; that is, the left image disappears when the right eye is covered.

Diplopia involving the lateral rectus muscle produces homonymous, or uncrossed, images and may be evident only when an attempt is made to look into the field of action of that muscle. Therefore, examination should include right and left as well as straight ahead gaze.

With right lateral rectus muscle weakness, diplopia may not occur in left gaze. However, an uncrossed diplopia will occur in right gaze, and the right image will disappear when the right eye is covered.

**Vertical Diplopia**

Four muscles produce vertical diplopia (Fig. 6.6). Three of these, the superior rectus and the inferior oblique muscles, which move the eye up, and the inferior rectus muscle, which moves it down, are controlled by the third cranial nerve. The fourth muscle, the superior oblique muscle, which moves the eye down, is innervated by the fourth cranial nerve.

Unlike the medial and lateral rectus muscles, which have a single function, these muscles cause the eye to intort or extort and, in addition, assist the medial and lateral rectus muscles to move the eye medially or laterally. Because of these secondary functions, vertical diplopia is rarely just vertical; the images are usually obliquely located, at least to some degree (Figs. 6.7, 6.8).

The terms intorsion and extorsion refer to the rotation of the eye around an imaginary axis running from the posterior orbital apex through the center of the globe and out

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Vertical Actions</th>
<th>Torsions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior rectus</td>
<td>Elevation</td>
<td>Intorsion</td>
</tr>
<tr>
<td>Inferior rectus</td>
<td>Depression</td>
<td>Extension</td>
</tr>
<tr>
<td>Inferior oblique</td>
<td>Elevation</td>
<td>Extension</td>
</tr>
<tr>
<td>Superior oblique</td>
<td>Depression</td>
<td>Intorsion</td>
</tr>
</tbody>
</table>

*Figure 6.6.* Actions of cyclovertical muscles.
Binocular Vertical Movements in Oblique Positions

![Diagram of binocular vertical movements](image)

*Figure 6.7.*
Binocular vertical movements. (Courtesy of Dr. Caleb Gonzalez, Strabismus and Ocular Motility, Williams & Wilkins, 1984.)

Binocular Torsional Movements in Oblique Positions

![Diagram of binocular torsional movements](image)

*Figure 6.8.*
Binocular torsional movements. (Courtesy of Dr. Caleb Gonzalez, Strabismus and Ocular Motility, Williams & Wilkins, 1984.)
through the cornea when the head is tilted toward either shoulder. This movement keeps the visual axis parallel to the ground (Fig. 6.9).

The principal function of these muscles is elevation or depression of the eye, primarily in one position. The superior oblique muscle, for instance, is a depressor only when the eye is adducted. When it is abducted, the muscle acts as an intortor, rotating the eye toward the nose. The primary vertical function of the superior and inferior rectus muscles takes place when the eye is abducted. The primary vertical action of the inferior oblique muscle occurs when the eye is adducted.

**VERTICAL DIPLOPIA TESTING**

Evaluation of vertical diplopia involves three steps.

**STEP 1.** Since four muscles in each eye may be implicated, it must first be determined in which eye the visual axis is deviated.

---

*Figure 6.9.*

Anatomic paths for torsional gaze. (Courtesy of Dr. Caleb Gonzalez, Strabismus and Ocular Motility, Williams & Wilkins, 1984.)
upward. The answer is easily ascertained by the cover-uncover test while the patient fixes on a light. If it is determined that the condition is a true tropia and not a phoria, one can use the alternate-cover test, which is easier and quicker to perform. As each eye is covered alternately, one will come up and the other come down to fix. The one that comes down is the higher or hypertropic eye. Even if the other eye is suspected of being the affected eye, the eye that comes down to fix should be selected for this evaluation. From the eight muscles that could cause vertical diplopia, all the combinations of muscles that could cause the test results should be considered. In the higher eye, weak depressor muscles, such as the inferior rectus and superior oblique muscles, may be responsible. On the other hand, the elevator muscles in that eye can be eliminated, since only overactions secondary to weak antagonists—not primary muscle overactions—should be considered. Another possibility is that there are weak elevators in the hypotropia eye, which suggests the superior rectus and inferior oblique muscles. Possible muscle involvement has been reduced from eight to four muscles, two in each eye, and all different.

STEP 2. In step 2, the degree of diplopia in right and left gaze is examined. The vertical muscles function most strongly in one field of gaze. When they are weakened, the greatest vertical separation will be in that field. The vertical action of the superior and inferior oblique muscles occurs primarily in adduction. In abduction, the superior and inferior rectus muscles come into play. If the diplopia is worse in right gaze than in left gaze, select from muscles isolated in step 1. The muscle in each eye that would have the greatest vertical effect in right gaze should be selected.

At this point, it should be determined whether the two muscles chosen are intortors or extortors. If one is an extorter and one an intorter, the error is in muscle selection. Then the diagnostic steps must be checked.

STEP 3. The Bielschowsky head-tilt test (Fig. 6.10) is now used to determine torsional malfunction of the vertical muscles. Because of the partial or complete paresis of one muscle, extra innervation is given to it to help the muscle perform its torsional function.

When the head is tilted to the left, the left eye intorts and the right eye extorts; when the head is tilted to the right, the right eye intorts and the left eye extorts. If the diplopia worsens in left head tilt, either a weak intorter in the left eye or a weak extorter in the right eye is responsible. The fact that both muscles chosen in step 2 were either intortors or extorters facilitates selection of the muscles to be considered in step 3. If both intorters were selected in step 2 and the diplopia is worse on left head tilt, both intorters involved are those in the left eye. Since the two intorters selected in step 2 were in different eyes, the intorter in the left eye is the offending muscle.

To compensate for the double vision, we adjust the position of the head, face, and chin and place all three in a position in which fusion may be restored (Fig. 6.11). Depressing or elevating the chin compensates for vertical

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Hypertropic Eye</th>
<th>Direction of Head Tilt to Increase Diplopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right superior rectus</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Right superior oblique</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>Left superior rectus</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Left superior oblique</td>
<td>Left</td>
<td>Left</td>
</tr>
</tbody>
</table>

*Figure 6.10.* Bielschowsky head-tilt test.
### Table

<table>
<thead>
<tr>
<th>Paretic Muscle</th>
<th>Face Turn</th>
<th>Chin</th>
<th>Head Tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left medial rectus</td>
<td>Right</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>Left</td>
<td>—</td>
<td>—</td>
</tr>
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<td>Right</td>
</tr>
<tr>
<td>Left superior oblique</td>
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<td>Down</td>
<td>Right</td>
</tr>
<tr>
<td>Left inferior rectus</td>
<td>Right</td>
<td>Down</td>
<td>Left</td>
</tr>
<tr>
<td>Left inferior oblique</td>
<td>Left</td>
<td>Up</td>
<td>Left</td>
</tr>
</tbody>
</table>

#### Figure 6.11.
Compensatory head positioning.

...movement. Turning the face to the right or left compensates for a lack of abduction or adduction. Head tilting compensates for the torsional component. In the case of the medial and lateral rectus muscles, only the face turn is necessary, since there is no vertical or torsional component. In theory, the head positioning should be universally adapted. It is not. In fact, it is most commonly seen with paresis of the lateral rectus and superior oblique muscles. Even then, patients may not adopt a compensatory head position or may even assume a reverse head position. This latter type choosing lets the eyes drift further apart, since it may be easier to suppress widely separated images than to fuse images in an uncomfortable position. Knowing the three functions of the vertically acting muscles of elevation or depression, adduction or abduction, and incyclorversion and excyclorversion is enough to decide the correct head position.

To bring this diagnostic method into focus, let us consider two hypothetical cases in which this type of testing would be standard procedure.

### CASE STUDIES

#### • Case 6.1 Paralysis of the Superior Oblique Muscle

In step 1, a patient complaining of diplopia is found to have the left eye higher on the alternate-cover test (Fig. 6.12). Possibly involved are the weak depressor muscles (the superior oblique and the inferior rectus muscles) in the left eye, or the weak elevators (the superior rectus and the inferior oblique muscles) in the right eye.

In step 2, the diplopia is determined to be worse in right gaze. Of the four muscles selected in step 1, the only ones having maximum vertical action in right gaze are the left superior oblique and the right superior rectus muscles. Both are intortors.

In step 3, the diplopia is found to be worse on left head tilt, which brings into play the left eye intortors and the right eye extorters. Since only intortors were selected in step 2, malfunction of the left superior oblique muscle is indicated, because the other intortor in that eye (the left superior rectus muscle) was eliminated in step 1.

#### • Case 6.2 Paralysis of the Superior Rectus Muscle

In step 1, a patient with a vertical diplopia is found on alternate-cover testing to have the left eye higher (Fig. 6.13). The muscles involved must be either the weak elevators of the right eye (right superior rectus and right inferior oblique muscles) or the weak depressors of the left eye (the left superior oblique and left inferior rectus muscles).

In step 2, the diplopia is determined to be worse in right gaze. Of the muscles selected in step 1, the only purely vertical muscles in right gaze are the left superior oblique and the right superior rectus, both of which are intortors.
<table>
<thead>
<tr>
<th>Muscles Possibly Involved</th>
<th>Muscles Selected - Step 1</th>
<th>Muscles Selected - Step 2</th>
<th>Muscles Selected - Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right superior rectus</td>
<td>Right superior rectus</td>
<td>Right superior rectus</td>
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<tr>
<td>Right superior oblique</td>
<td>Right superior rectus</td>
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<tr>
<td>Left inferior rectus</td>
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- Figure 6.12.
Three-step test for paralysis of the left superior oblique muscle.

<table>
<thead>
<tr>
<th>Muscles Possibly Involved</th>
<th>Muscles Selected - Step 1</th>
<th>Muscles Selected - Step 2</th>
<th>Muscles Selected - Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right superior rectus</td>
<td>Right superior rectus</td>
<td>Right superior rectus</td>
<td></td>
</tr>
<tr>
<td>Right superior oblique</td>
<td>Right superior rectus</td>
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<td>Right inferior rectus</td>
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<td>Left superior rectus</td>
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<td>Left inferior oblique</td>
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<tr>
<td>Left inferior rectus</td>
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</tbody>
</table>

- Figure 6.13.
Three-step test for paralysis of the right superior rectus muscle.

In step 3, the diplopia is found to be worse on right head tilt, which involves the right eye intortors and the left eye extortors. Since only intortors were selected in step 2, the intortor of the right eye, the right superior rectus, must be the muscle at fault.

The foregoing cases illustrate the most common forms of isolated paralysis to which the three-step evaluation method is applicable. A similar program can be worked out for the inferior rectus and inferior oblique muscles. However, these muscles are more commonly involved in cases of local disorders of the orbit, such as inflammation, tumors, and blowout fractures of the floor; only rarely are they causative factors in iso-
Diplopia

Right Superior Oblique Palsy

Right Superior Rectus Palsy

Right Interior Oblique Palsy

Right Interior Rectus Palsy

*Figure 6.14.*
Position of eyes in head-tilt position with paresis. (Courtesy of Dr. Caleb Gonzalez, Strabismus and Ocular Motility, Williams & Wilkins, 1984.)

...luted paralysis owing to a neuropathic process (Fig. 6.14).

The diagnosis of vertical diplopia is not always easy. Not infrequently, more than one muscle may be involved, as in a partial third cranial nerve paralysis. Where diplopia is minimal, failure to make sure that the patient's head is in the correct erect straight-ahead position is a common error. A mild degree of vertical and oblique diplopia can be compensated for by unconscious head tilting on the part of the patient, which may obscure results. On the other hand, head tilting is much more common in superior oblique, than in superior rectus, muscle paralysis, and observation of abnormal head posture prior to formal testing may facilitate diagnosis.

The oblique character of diplopia tends to confuse the diagnostic program, and it will be totally misleading if it is simultaneously considered in the course of the evaluation. When both vertical and oblique separation of images occurs, only the vertical component should be considered. If so much horizontal separation exists that it is difficult or impossible to determine whether the vertical component is greater in left or right gaze or to evaluate the significance of the torsional component in step 3, the horizontal displacement should be removed by prism correction. The extent of this correction should be such that on testing, the vertical movement of the eyes is more apparent to both patient and observer. Such a correction is more easily done with loose prisms than with the prism bar, which is cumbersome to move correctly when testing in the various cardinal fields of gaze.
If the vertical diplopia is not of recent onset, steps 1 and 2 of the testing procedure will fail in line, but step 3 will usually be inconclusive, because the head-tilt test may not separate the last two malfunctioning muscles. Smoothing out or development of concomitance is common and may come on soon after the onset of the initial paralysis. In such an event, an indication of which muscle is involved may be derived from the patient's history, which may reveal local trauma to one eye, associated proptosis with a superior rectus muscle weakness, or a previous third cranial nerve paralysis on one side.

With vertical diplopia testing, it is difficult to follow the three-step diagnostic procedure while keeping the correct muscles in mind. Thus it is recommended that the three primary observations be made and noted but that the muscle selection for each step be deferred until the testing is completed. At that time, results based on primary observations can be checked and rechecked more simply and efficiently.

During the alternate-cover test, some cases of diplopia are not grossly obvious because the diplopia may be caused by minimal paralysis of the muscle or fusion will overcome or obscure the problem. In these cases, the red lens test can sometimes be of great help. When a red lens is put over one eye as the patient looks at the hand light in the extremes of gaze, he or she sees two images, because the red lens helps to break up fusion. The image as the patient sees it will be in position opposite to that of the position of the eye. Thus, if the red lens is over the right eye and the patient sees the red image as the lower of the two images, the right eye is the higher eye in terms of the straight-ahead position.

If the patient maintains fusion even with the red lens in position, the Maddox rod, which changes a beam of light into a line by multiple prisms, should be used. With the Maddox rod, the patient sees a bar of light in one eye and a pinpoint of light in the other and obviously cannot fuse these two dissimilar images. If the rod is red, this feature further helps the patient to discriminate between the two objects. The Maddox rod can be rotated so that the line of light is vertical in one situation, thus allowing the patient to experience horizontal separation of images. The Maddox rod can then be rotated 90° to measure the vertical separation.

**Fourth-Nerve Diplopia**

Torsion represents a special aspect of diplopia. Recognition of the presence of torsion can lead to more accurate diagnosis of fourth cranial nerve paralysis, the most common cranial nerve palsy affecting ocular motility seen by the strabismologist. When taking the history of a patient with diplopia, complaint of spontaneous torsional diplopia should raise the suspicion that bilateral fourth cranial nerve palsy may be present. Finding a "V" pattern and noting a left hypertropia on head tilt to the left and a right hypertropia on head tilt to the right confirms the presence of bilateral fourth-cranial-nerve palsy. Because this condition may be masked or partially masked, one should maintain suspicion when significant vertical diplopia symptoms including report of torsional diplopia are present, even if the head-tilt response is equivocal.

Spontaneous torsional diplopia also occurs with superior oblique myokymia. In this condition, the patient will observe a rhythmic or pulsating incyclidiplopia caused by repetitive, purposeless contraction of one of the superior oblique muscles. This condition is usually self-limiting. When symptoms persist, treatment consists of Tegretol therapy and surgery; simultaneous superior oblique tenectomy and inferior oblique myectomy has been advocated as a surgical treatment.

Torsion with or without spontaneous diplopia can be measured after dissociation is produced by placing a Maddox rod, one red and one white, in front of each eye. The rods are placed with the long axes vertical to produce a horizontal image of the fixation light on the retina. Either the patient or the examiner adjusts the axis of the rod until the two lines are seen to be parallel or superimposed; when this occurs, the line(s) from each lens along the retina is diagnostic of torsional diplopia. The strabismologist can then determine the direction and amount of torsion as well as the amount of hyper- or hypotropia.
Diplopia

Each light produced by the Maddox rod falls along the principal horizontal meridian of the retina. It may be necessary to rotate both lenses to produce parallel lines. The following is a rough rule of thumb for differential diagnosis of fourth-nerve palsy: (a) the clinical picture of fourth cranial nerve palsy including head tilt usually with a fuller face on the side opposite the direction of the tilt and noncomitant hypertropia but no cycloplegia on testing with the double Maddox rods, clean-cut history of trauma, and a vague time of onset indicates probable congenital superior oblique palsy; (b) the clinical picture of fourth-nerve palsy with a history of trauma or a sudden unexplained onset of torsion measuring less than 15° with the double Maddox rod but no subjective torsion probably is acquired superior oblique palsy; and (c) a history of vertical diplopia and head trauma in a patient with torsion measured at more than 15° with the Maddox rod and/or subjective torsional diplopia, a "V" pattern, and chin-down position indicates probable bilateral superior oblique palsy.

A quick method for differentiating superior oblique palsy from other vertical muscle palsies employs an extension of the Bindschadler head-tilt test, which is carried out as follows:

1. When a patient presents with a vertical tropia in the absence of restriction (free ductions in both eyes), the lateral versions are evaluated first. The adducted eye during the lateral version that produces greater vertical tropia points to the ipsilateral oblique muscle and the contralateral rectus muscle as the two potentially paretic muscles.

2. The patient's head is then passively tilted 45° to the right and to the left. If the vertical deviation increases with the head tilted toward the higher eye, the oblique muscle is paretic; if the vertical deviation is greater with the head tilted toward the lower eye, the rectus muscle is paretic.

There are four vertically acting muscles in each eye. Two are elevators, the inferior oblique and the superior rectus, and two are depressors, the superior oblique and inferior rectus. By carefully following the above scheme, it is possible to isolate the single most likely vertically acting paretic muscle in just a few seconds. The clinical reality is that in almost every case when this test is applied, the superior oblique is paretic. When results are equivocal, a bilateral superior oblique palsy is often the most likely diagnosis. It is less common to find isolated paresis of one of the vertical rectus muscles or of the inferior oblique muscles, although these do occur and can be found on occasion. However, in most instances when the diagnosis is something other than a fourth-nerve palsy, some other contributing cause usually is present, such as prior surgery or trauma.

Sixth-Nerve Diplopia

Paresis of the sixth cranial nerve may be more common in a neuro-ophthalmology practice than fourth cranial nerve palsy, which is seen primarily in a strabismus practice. Unilateral sixth-nerve palsy produces diplopia only when looking in or toward the field of action of the paretic muscle. Of course, the strabismus is an esodeviation, because the weakness is in an abducting muscle. In the very young, the differential diagnosis of this esodeviation includes essential infantile esotropia, which is usually constant and does not produce diplopia. A more difficult differentiation includes type I Duane syndrome, which is actually a form of sixth-nerve palsy (sixth-nerve nuclear hypoplasia) with aberrancy of the third nerve in the orbit. Type I Duane syndrome usually has malalignment in the field of action of the underacting lateral rectus, restricted passive adduction, and narrowing of the fissure in adduction both in the involved eye. Most patients with type I Duane syndrome have good fusion with stereopsis when looking slightly away from the involved side. Patients with bilateral type I Duane syndrome may have straight eyes in the primary posi-
tion with fusion or may have esotropia in the primary position. When doll's head or oculovestibular testing produces full abduction in any of the early-onset esodeviations, sixth-nerve palsy can be ruled out.

The diplopia of unilateral sixth-nerve palsy can be treated with a patch, preferably over the fixating eye, at least part of the time, or with a prism when the angle is small. Nowadays, many ophthalmologists prefer to inject the antagonist medial rectus with 1.5 to 5 units of botulinum A toxin, usually under EMG control, in the acute phase (within 3 months of onset) to avoid contracture of the antagonist. This treatment is also used in conjunction with extraocular muscle transfer to avoid the need to resect the medial rectus muscle in chronic sixth-nerve palsy.

Third-Nerve Diplopia

Third cranial nerve palsy falls into two main categories, congenital and acquired. The congenital variety causes no trouble with diplopia because of early compensatory sensorial adaptations. Acquired third-nerve palsy produces diplopia that is extremely difficult for the patient to overcome. Even in the absence of aberrant regeneration, the combination of muscles involved in the third-nerve palsy makes it difficult to find an area of single binocular vision. With aberrant regeneration this is virtually impossible. Suppression of the involved eye is without doubt the best solution to the diplopia of persistent acquired third-nerve palsy. If suppression is not achieved, occlusion with a patch or frosted lens or use of an opaque contact lens may be the treatment of choice.

Diplopia after Cataract Surgery

In recent years, an increasing number of patients have complained of diplopia after cataract surgery. Cataract surgery often is performed on only one eye, producing good acuity in an eye that had been unused for a long time. If fusional facility has broken down, the potential for double vision definitively exists after monocular cataract surgery. Good vision with the second eye after cataract surgery also may uncover a preexisting mild, but bothersome, Graves' ophthalmopathy, which produces diplopia. However, in most cases, it is believed that a toxic or mechanical effect or both associated with injectable anesthetics used in the orbit produces myopathy leading to paresis and/or restriction. Whatever the cause or causes of diplopia after cataract surgery, this condition has become a greater problem recently. Some of these diplopia patients can be treated with prism. If the deviation is large and noncomitant or if the patient does not wish to wear glasses, surgery can be done. These patients can be ideal candidates for adjustable suture surgery done with local anesthesia on an out-patient basis.

Diplopia with Mechanical Restriction

Various causes of mechanical restriction (e.g., thyroid myopathy, blowout fracture, Brown's syndrome, postretinal detachment repair, and orbital mass) can produce diplopia. In almost every case, this restriction produces a noncomitant strabismus. This type of noncomitant strabismus with mechanical restriction can be evaluated by means of passive duction testing and generated muscle force testing.

Generated muscle force testing can be done only with the awake patient. The eye is anesthetized in a manner similar to that for passive duction testing. The patient is first asked to look away from the direction of the field to be tested. The examiner grasps the eye at the limbus on the opposite side of the direction that the eye is to be moved. The patient is then asked to look
gradually in the direction of the field to be tested while the examiner stabilizes the eye. Movement of the fellow untested eye into the field of action to be tested is evidence that the patient is putting forth neural input in the eye being tested. This is a manifestation of Hering’s law. A pull or tug on the forceps experienced by the examiner during this maneuver is evidence that generated muscle force is present in the tested muscle. Generated muscle force can also be measured in the face of restricted passive reductions by noting an increase in intraocular pressure when ocular movement is attempted in the restricted field. If there is no increase in intraocular pressure in the presence of restricted movement, decreased generated force can be inferred. Comparing saccadic velocity either by observation of eye movement or with use of an EOG with recording can identify decreased muscle contraction as evidenced by decreased saccadic velocity in the tested eye compared with saccades in the fellow eye.

Accurate appraisal of the state of active and passive eye movements can direct the ophthalmologist toward more appropriate treatment. For example, mechanical restriction must be relieved before other surgical straightening is undertaken. Also, resection of a “dead” muscle will not help movement in the field of action of that muscle. Instead, a muscle transfer may be indicated.

PRISM THERAPY

Prism therapy can be useful in the short term as well as the long term as a remedy for diplopia. Fresnel press-on membrane prisms can be applied in the office for temporary relief of diplopia. Prism therapy is also useful in cases of diplopia in which the angle is changing and when the diplopia is thought to be only temporary. In general, prism therapy, either temporary or permanent, is limited to 10 prism diop ters per eye. With Fresnel prisms, vision is reduced as prism power goes up. With permanent prisms, weight and unsight-

NEUROPATHIC CAUSES

Third Cranial Nerve Paralysis

OCULOMOTOR NEUROANATOMY

[FIGS. 6.15–6.19]

The oculomotor nerve is the most complex of the three nerves that control ocular movement. It contains synaptic motor fibers for eye movement and visceral parasympathetic fibers that innervate the intrinsic muscles of the eye. The topographic organization of the oculomotor nucleus has been examined by Bernheimer, Brower, Warwick, Bender and, more recently, by Burde. The oculomotor nerve lies in the mesencephalon in the inferior periaqueductal gray matter and is about 6 to 8 mm long. The neurons that innervate the superior rectus muscle originate in a subnucleus and innervate most of the opposite superior rectus muscle. The superior rectus muscle is innervated by a central caudal nucleus. In the dorsal caudal location is the Edinger-Westphal nucleus.

As the fibers leave the oculomotor nucleus, they form a fascicle. The diagnosis of a fascicle lesion depends on what structure it is near when affected. The syndromes are well known. Roth's syndrome demonstrates an oculomotor palsy and contralateral cerebellar ataxia. It is contralateral, since it is above the decussation of the motor tracks. Benedikt's syndrome demonstrates contralateral abnormal movements due to its proximity to the red nucleus, with an oculomotor palsy. As the oculomotor nerve progresses more ventrally in the mesencephalon, it passes the motor tracks in the cerebral peduncle, producing a crossed hemiparesis syndrome called Weber's syndrome. The above three syndromes usually
• Figure 6.15.
Anatomy of oculomotor nerve, part 1. (Courtesy of William Stewart.)

• Figure 6.16.
Anatomy of oculomotor nerve, part 2. (Courtesy of William Stewart.)
produce a complete oculomotor palsy, but on rare occasion the pupil is spared. As the oculomotor nerve emerges from the mesencephalon in the interpeduncular fossa it can also produce a Weber's syndrome identical to an intrinsic brainstem Weber's. The oculomotor nerve passes between the posterior cerebral and superior cerebellar artery. This location is important since it is an alternative location for an oculomotor palsy from an aneurysm. It then crosses through the dura and enters the cavernous sinus, passing the posterior cerebral artery and internal carotid artery, which is the more common location for involvement with an aneurysm. Its position in the cavernous sinus is above the fourth nerve and first, sometimess second, division of the trigeminal nerve. Parkinson described the blood supply to the oculomotor nerve in the cavernous sinus. It is supplied
by the dorsal meningeal, tentorial, and inferior hypophyseal branches of the meningo-hypophyseal branch. In the anterior cavernous sinus it divides into two divisions. The superior division controls the levator superioris and superior rectus muscles. The inferior division supplies all the other muscles of the oculomotor complex and pupillary fibers. Both divisions pass into the orbit through the annulus of Zinn. The superior division runs anteriorly in the superior rectus muscle, while the fibers for the levator pass along the lateral border of the superior rectus and upward to pass through the belly of the levator muscle. The pupil fibers leave the inferior division to synapse in the ciliary ganglion. The pupil fibers in the subarachnoid portion of the oculomotor nerve are located on the superior portion of the nerve.

**GENERAL TESTING SIGNS**

The third cranial nerve (oculomotor nerve) has many functions. It supplies innervation (a) to the levator muscle, which lifts the lid, (b) to the superior rectus and inferior oblique muscles, which elevate the eye, and (c) to the inferior rectus muscle, which depresses the eye. Accommodation and pupillary constrictions also depend on the third cranial nerve.

When a patient is being examined for possible third cranial nerve paralysis, all the areas innervated by the third cranial nerve must be tested. If ptosis is present, the diplopia may not be evident to either patient or physician when the patient is tested in the straight-ahead position; however, when the patient is instructed to look up and laterally in the field of the vertical action of the superior rectus muscle, the imbalance may be obvious to both patient and observer. This subtle finding may also be true of the other muscles as well as the pupillary and accommodation reactions. Owing to their common origin at the annulus of Zinn, a combination of ptosis and superior rectus muscle weakness is the most frequently occurring of all possible associations within the third cranial nerve. Isolated ptosis and isolated superior rectus muscle weakness are usually of traumatic or congenital origin.

**THIRD CRANIAL NERVE MISDIRECTION.** Although the physician does not often look for third cranial nerve misdirection, it is of real significance because it occurs after recovery from a third cranial nerve paralysis; however, it may not be obvious for 6 months to a year after the onset of, and recovery from, the paralysis. Several signs of this condition must be looked for, any one
of which may occur alone and be as significant as multiple signs of misdirection. The most common form of misdirection is the pseudo-von Graefe's sign. When the patient looks down, the upper lid retracts and the superior sclera is exposed (as in thyroid disease). In another form of misdirection, lid gaze dyskinesia, the lid is elevated when the patient moves the eye medially and innervates the medial rectus muscle on pure horizontal gaze. When the patient looks laterally, the lid returns to normal position. Lid gaze dyskinesia may be missed when the affected eye is examined in the horizontal plane, and is best seen in horizontal movements of the eye in down-gaze (Fig. 6.19). (In a normal eye, no elevation or depression of the lid should exist in pure horizontal gaze excursion.) If lid gaze dyskinesia is present, pupillary signs frequently are seen. The pupil becomes smaller in near gaze on innervation of the medial rectus muscle as well as in horizontal gaze, when the patient turns the eyes toward the nose, again innervating the medial rectus muscle. This reaction is termed a pseudo-Argyll Robertson pupil, referring to a lack of pupillary response to light but a better reaction to accommodation-convergence. In patients with the misdirection phenomenon, however, the pupil is contracted, not because of the accommodation reflex, but because of some crossover innervation between the medial rectus muscle and the pupil. This phenomenon can be demonstrated by making the medial rectus muscle work on distant horizontal gaze movement and show the same contraction of the pupil as would occur via the accommodation-convergence mechanism. (This phenomenon also differentiates the condition from one related to tertiary syphilis.)

Third cranial nerve misdirection (a) occurs more frequently after third cranial nerve paralysis owing to trauma or after an aneurysm, (b) is infrequently caused by tumor or syphilis, and (c) has not been reported after third cranial nerve paralysis owing to diabetes. Therefore, if a diabetic patient shows third cranial nerve misdirection, it is likely that a subclue aneurysm has been overlooked and should now be considered in the absence of a significant history of trauma.

The mechanism by which misdirection occurs is far from settled. In an experiment on chimpanzees in which misdirection was created, Bender found that the regrowth of fibers involved a random distribution to all extracocular muscles. Lang and Lipschutz first postulated misdirection of facial nerve fibers as a reason for the synkinesis mass movements of the facial nerve. Bielschowsky then applied that concept to the oculomotor nerve. Peripheral orbital traumatic cases would tend to support this theory. Lepore and Glaser argued against that explanation, stating that "neuromuscular junctions formed by ectodermal muscle of the iris sphincter and axons formerly innervating striated muscle probably would not be functional." Instead, they postulated ephaptic transmission as the mechanism for synkinesis. Other explanations for the synkinesis movements are central reorganization and supersensitivity.

Sunderland's work demonstrated that the endoneurium must be interrupted—not just the axon—for misdirection to occur. If the endoneurium is left intact, then the injured axons follow their normal route during the regeneration process. This phenomenon is supported clinically by pathologic examination of an ocular motor palsy with misdirection from an aneurysm and an ocular motor palsy without misdirection from diabetes. In the former case, there is axon degeneration and disruption of the endoneurium; in the latter case, there is axon degeneration but the endoneurium is intact. These findings seem to support the misdirection theory experimentally, pathologically, and clinically.

There are cases, however, of intracavernous lesions that create synkinesis but never develop an oculomotor paresis; these cases seem inconsistent with the misdirection explanation of synkinesis. Some other pathologic studies also appear to cast doubt on the misdirection theory. Kerns excised an oculomotor nerve specimen from a patient who had developed a paresis from an aneu-
rysm and after recovery had demonstrated synkinesis. He found fewer axons on the involved side rather than more, which would be expected if there was misdirection of fibers. Another possible interpretation of these findings is that there is an increase in the number of small axons, suggesting regeneration.

The most difficult cases to explain in this anatomic rewiring scheme are the cases of reversible synkinesis. If some fibers grow to the wrong terminal and innervate, causing the signs of synkinesis, why do they stop? One explanation is that the normal and misdirected fibers compete for preferential innervation of a muscle and that the normal fibers eventually win out. There is experimental evidence by Kufler to support this view.

A second explanation for synkinesis is interaxonal, or epiphaptic, transmission. The myelin sheath acts as an insulation between axons. When the axon is injured and the myelin sheath is interrupted or becomes defective, then interaxonal stimulation may occur. This phenomenon was initially demonstrated by Hering. Monuzzi in 1944 observed that action currents can alter the electric activity in nearby axons. If a myelin defect allows electric "cross talk" to occur, then healing or isolation of that defect in the axon should stop it. VonUexkuell observed that he could reduce such cross talk by putting saline at the injured site. Normally, saline is an excellent conductor of electrical impulses and thus might be expected to enhance the cross talk. However, in these experiments, the saline may have caused swelling of the tissues at the injury site, thereby isolating the nerve and its electric transmission. Clinical evidence of epiphaptic transmission in a case of chronic nerve compression was demonstrated by Thomasulo.

Another theoretical explanation of synkinesis was put forth by Fuchs. He postulated that after a peripheral nerve is injured, not only is there regeneration of the nerve, but also there may be some reorganization centrally that would explain synkinesis. Study of pathologic specimens has shown that when a nerve is injured, changes do occur in the cell body. If the nerve regenerates normally, these changes disappear. The more severe the injury, the more changes are seen in the cell body. The question remains whether the nucleus defect can cause the peripheral fibers to regenerate in a misdirected fashion. The other side of the argument is that anatomic changes do not necessarily result in functional change. The most convincing argument against this reorganization theory is diabetic ocular motor palsies. If peripheral injury is the initiating factor for central reorganization, then what distinguishes trauma, tumor, and aneurysm from diabetic injury such that the latter does not cause misdirection?

Denervation supersensitivity is a well-known phenomenon. The more peripheral the nerve that is damaged, the more sensitive it becomes to its own effector substance. The pharmacologic tests to demonstrate Adie's or Horner's pupil are based on this phenomenon. The diabetic cases are again the main stumbling block to accepting this mechanism to explain oculomotor synkinesis.

There is also a syndrome called primary misdirection without apparent oculomotor paresis. This has infrequently been seen with an intracavernous lesion such as meningioma or aneurysm. The cases of aneurysm at the junction of the internal carotid and posterior communicating artery usually present with oculomotor palsies. Subsequent to that, third-nerve misdirection can occur. They rarely cause primary misdirection. As mentioned above, a lesion of the anterior cavernous sinus can interfere with only one division of the third nerve, as it separates into the superior and inferior divisions. An isolated lesion of the superior division of the oculomotor nerve is much more commonly seen in the orbit than in the anterior cavernous sinus. However, in the face of no orbital disease to account for the superior division paresis, look in the anterior cavernous sinus.
Congenital Oculomotor Palsy

Congenital oculomotor palsy can be due to absent or partial nerve development. Many cases have miotic not mydriatic pupils, which suggests a misdirection phenomenon in a peripheral nerve location.

ANATOMIC TYPES (FIG. 6.20)

Once diplopia has been diagnosed as being caused by dysfunction of the third cranial nerve, the next step is to determine what part of the nerve is affected and what disease is the cause. For the purpose of this discussion, disorders of the third cranial nerve have been grouped into six categories according to anatomic location.

NUCLEAR LESIONS (FIG. 6.15, 1). Even though the two third cranial nerve nuclei are separate, they show some interaction. Most authors believe that the fibers of the superior rectus muscle are the ones that are interdependent. Therefore, in identifying an isolated third cranial nerve paralysis as being nuclear in location, the following should be helpful. Total third cranial nerve paralysis affecting one eye but with no limitation of upgaze in the other eye rules out a nuclear lesion as the causative factor. In paralysis owing to a nuclear lesion, the contralateral superior rectus muscle would have to be limited because of interdependence. Vascular disease is the most frequent cause of this type of paralysis.

FASCICULAR LESIONS (FIG. 6.15, 2, 3). Disease in the fascicular fiber bundle, which is also intrinsic to the brainstem, involves two well-recognized syndromes. A disorder in the dorsal fascicular area produces the syndrome

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**FIGURE 6.20.**
Clinical approach to third-nerve paralysis.
of Benedikt, with ipsilateral third cranial nerve paralysis and a contralateral hemitremor that is produced by proximity to the red nucleus. Disorder in the ventral fascicular area produces the syndrome of Weber, with ipsilateral third cranial nerve paralysis and contralateral hemi-ataxia. The degree of involvement of the third cranial nerve and the severity of the tremor or paralysis vary from mild to severe. Once again, vascular disease, particularly arteriosclerosis, is the main cause of these symptoms. The syndrome of Weber may also occur as an extrinsic brainstem phenomenon owing to lesions in the interpeduncular fossa, where the third cranial nerve exits from the brainstem, but it cannot be differentiated from the intrinsic variety on clinical grounds alone. In addition to vascular disease, venous malformation and tumors may also cause this condition in the interpeduncular fossa.

**SUBARACHNOID LESIONS (FIG. 6.15, 3).** The subarachnoid space is the most common location for third cranial nerve paralysis, particularly if the pupil is involved, no matter how minimally. When the pupil is involved, the major cause to be considered is an aneurysm at the junction of the internal carotid and posterior communicating arteries. If aneurysm proves to be the cause, other signs of subarachnoid hemorrhage usually occur, such as pain, stiffness of the neck, photophobia, and a change in the level of consciousness. These additional symptoms are not always present, however, and their absence does not rule out an aneurysm if the pupil is involved. Pupillary involvement owing to an aneurysm is usually significant; the pupils usually are large and fixed; however, any change in size and function is equally significant. Absence of pupillary involvement used to be considered rare, occurring (according to Rucker) in about 3% of cases owing to aneurysm. More recent studies by Kissel et al. and Nadeau and Trobe indicate that absence of pupillary signs is not all that rare, particularly in partial third-nerve paresis. In this case, pupillary response may initially be normal, but the patient should be observed for subsequent development of pupillary signs (Fig. 6.16, 1, 2, Fig. 6.21).

Diabetes is the second most common cause of third cranial nerve paralysis in the

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**Figure 6.21.** Basilar aneurysm compressing area between posterior cerebral and superior cerebellar artery.
Diplopia

In third cranial nerve paralysis secondary to diabetes, the pupillary function is usually unimpaired, owing, theoretically, to collateral circulation from the ophthalmic artery to the peripheral part of the nerve, where the pupil fibers are located. On the other hand, studies by Cogan and Goldstein and by Rucker indicate that pupillary involvement may occur in up to 20% of cases of diabetic ophthalmoplegia, and that pain indistinguishable from that associated with aneurysm can occur in up to 50%. Therefore, the physician must consider the possibility of aneurysm even if the patient is known diabetic. Cleanness of spinal fluid does not rule out an aneurysm, since evidence of subarachnoid hemorrhage is not always present. The 2-hour postprandial serum glucose test is not sufficient for identifying diabetes as the underlying cause of third cranial nerve paralysis. In most such cases, it will be found that the patient has occult diabetes that may be suggested only by a formal glucose tolerance test. Since the treatment for third cranial nerve paralysis secondary to diabetes is to do nothing, the physician may be tempted to wait the 6 or 8 weeks it takes almost all cases to clear up. By delaying, the physician can differentiate between a condition owing to diabetes and one owing to an aneurysm, since the latter is unlikely to improve. Such an approach is still foolish and dangerous because the time of peak incidence for spontaneous rebleeding from an aneurysm is within 12 to 14 days, a period well short of the healing time for diabetic third cranial nerve paralysis. Moreover, some aneurysms do not progress and the third cranial nerve returns to normal—thus, a potential time bomb is left untreated. The best rule is to regard an isolated third cranial nerve paralysis with pupillary involvement as being caused by aneurysm until it is proven otherwise.

Diabetic oculomotor palsy has been identified in a few pathologic specimens. They occur at the interface of separate vascular supplies to the nerve. This usually occurs from recurrent collateral branches of the ophthalmic artery anteriorly and branches of the posterior cerebral, posterior communicating, and basilar artery posteriorly. Pupil sparing is considered possible from the standpoint of several different explanations. If a mass lesion is intrinsic to the oculomotor nerve, it will grow steadily, occasionally displacing and preserving the small pupil fibers that are more pressure resistant. Lesions that compress the nerve from below are away from the pupil fibers, which are in the superior part of the nerve. A lesion in the cavernous sinus can affect the superior division of the nerve, which does not carry pupil fibers. The same lesions that damage pupil function and subsequently develop aberrant regeneration can give a false sense of pupil function. These last two reasons for pupil sparing are not nearly as valid when examined clinically as are the other previous causes. Lesions in the cavernous sinus can affect the parasympathetic and sympathetic fibers' control of the pupil. This gives the impression of pupil sparing. That is only relatively true for size and not true for function. There are rare cases of preganglionic parasympathetic hypersensitivity found in cavernous sinus lesions as recorded by Slamovitz.

Vascular occlusive disease may also result in isolated cranial nerve dysfunction. Some cases present catastrophically as a subarachnoid hemorrhage or as a compressive lesion without evidence of a subarachnoid hemorrhage suggesting a tumor. Recent studies by Milisavljevic of the microvascular relationships to nerves III, IV, and VI suggest another type of vascular presentation. In these studies, he found that 40% of the oculomotor nerves are penetrated by small arteries such as the long or short circumflex mesencephalic artery or a branch of the interpeduncular perforating arteries. If these vessels dilate, they can compress parts of the oculomotor nerve either in the periphery, causing pupil involvement, or in the intrinsic portion, sparing the pupil. Similar microvascular studies of the abducens nerve found such an arteriolar relationship rare. However, the abducens nerve not uncommonly is penetrated by a contralateral pon-
tine vein or tributary of the anteromedian pontine vein. The pupil fibers run in the superior peripheral part of the oculomotor nerve. In a vascular lesion such as diabetes, the vessels affecting the nerve may be one of the penetrating branches, thus sparing the peripheral part of the nerve, which may also derive some blood supply from the nearby pal vessels.

Compressive lesions may not initially affect the pupil portion of the oculomotor nerve; an example is a basilar aneurysm that compresses the nerve from below. It is also not uncommon for aneurysmal compression of the oculomotor nerve to compress the upper division of the nerve, leaving the inferior division until later. This occurs commonly in the cavernous sinus where the oculomotor nerve divides into superior and inferior divisions. Sometimes there is apparent pupil sparing due to pupil contraction in addition to the aberrant regeneration syndrome. Another cause for diagnostic error occurs when there is involvement of the sympathetic nerves in the cavernous sinus, giving the impression of a normal-size pupil. This type pupil, however, does not react normally to stimulation by light or near reflex tests.

The rule of thumb that an isolated oculomotor palsy with the pupil spared is diabetes mellitus and that an isolated oculomotor palsy with the pupil involved is an aneurysm at the junction of the internal carotid and posterior communicating arteries is a good general rule. However, it is not perfect and has many exceptions. Even though diabetes usually spares the pupil, it involves the pupil often enough not to be worthy of a case report. Pupil involvement of the oculomotor nerve with an aneurysm is also the rule, but pupil sparing, once thought to be extremely rare, is now being reported more and more commonly in the literature. O'Connor surveyed 646 neurosurgeons and found that 30.8% of them had seen such pupil sparing with an aneurysm. In many pupil-sparing cases, further observation over the following several days will reveal eventual pupil involvement. Since we now know that oculomotor palsy secondary to both diabetes and aneurysms can present with and without pupillary involvement, the general rule outlined above is sometimes difficult to apply in an individual patient. However, because of the potential lethal consequences of an aneurysm, the differential diagnosis is particularly critical in such cases.

Aneurysms are a deadly disease because of the severe consequences of bleeding and the lack of warning to prevent it. The frequency of an aneurysm is estimated at between 1 and 8% of the population, with subarachnoid hemorrhage occurring in 10 to 15 people per 100,000 population. These figures are the result of the combined aneurysm study. Up to 60% of these people die before they are hospitalized. If they make it to the hospital 37% of them will die and 17% will have a severe disability.

Aneurysms are usually symptomatic later in life but develop from inherent weakness at branching of major arteries. Since they become symptomatic decades later, other hemodynamic factors play a role in causing them to rupture, such as hypertension and arteriosclerosis. There are medical diseases that are commonly associated with aneurysm. These include polycystic kidney disease, Moya-Moya disease, and fibromuscular dysplasia. Diseases that weaken the arterial wall such as Ehlers-Danlos syndrome, Marfan syndrome, and pseudoxanthoma elasticum also contribute to aneurysm formation. The cooperative study noted that 26% of symptomatic aneurysms rupture within 5 years, while the asymptomatic ones have a rate of 2.6 percent. The cooperative study also noted that between 40 and 50% of patients have some warning, such as a minor hemorrhage or expansion of the aneurysm. It is the latter that confronts the neuro-ophthalmologists more frequently with compression of the third nerve and occasionally the optic nerve.

One of the more serious factors that influence recovery is the arterial spasm. Early operation can cause an increase in that vascular spasm. However, delayed operation can allow reruption. Therefore, controlling factors
motor palsy secondary to aneurysm can present differently in individual patients. The potential lethal nature of aneurysms is differentially critical in such cases because of bleeding and the risk of morbidity and mortality.

The description of an aneurysm depends on the size of the dome. A broad-based aneurysm is less than 1.5 cm. A globular one is 1.5 to 2.5 cm, and a giant aneurysm is larger than 2.5 cm. The smaller the aneurysm, the less likely it is to bleed. Viewed in this way, magnetic resonance imaging (MRI) can usually visualize an aneurysm 5 mm or larger. Unfortunately, this is only a good step forward in diagnosis and is not as good as arteriography. Treatment options will not be discussed here. Some of the newer modalities include interventional neuroradiology as a treatment for some aneurysms. An overview is presented in a chapter on neuroradiology below.

As noted above, diabetics and the elderly have a higher incidence of aneurysms due to higher mortality rates. Aneurysms are present in 10 to 15% of people older than 70 years, with a prevalence of 15% in people older than 80 years. The risk of aneurysm aneurysm is higher in patients with diabetes, especially those with poorly controlled diabetes.

Aneurysms are classified as either fusiform or saccular. Fusiform aneurysms are more common in older patients and are usually determined by pressure or dilatation. Saccular aneurysms are more common in younger patients and are usually determined by rupture.

The diagnosis of an aneurysm is usually made through imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). These studies can show the size and location of the aneurysm and help determine the best therapeutic approach.

The treatment of an aneurysm depends on its size, location, and patient factors. Options include observation, endovascular coiling, surgical clipping, or a combination of both. In the case of a giant aneurysm, surgical clipping is typically the preferred treatment.

An isolated oculomotor nerve palsy in patients under age 20 is another matter. The overwhelming majority of patients under 10 years of age with an aneurysm present with a subarachnoid hemorrhage. At least three cases of teenage patients presenting with third-nerve palsy, headache, and stiff neck have been reported. Of the more than 6000 aneurysms reviewed by Patel, Laitinen, Matson, and Locksley, only 12 cases (0.2%) were children under 10 years of age, and only 42 were under age 20. We cannot ignore the diagnosis of aneurysms in younger patients with oculomotor palsy, but other causes such as ophthalmoplegia migrane, inflammation, postinfectious ophthalmoplegia, and missed trauma should be considered.
kept in mind. All of these statistics change if there is evidence of subarachnoid hemorrhage or other associated neurologic signs, whether in a child or in an adult. In a review of childhood aneurysms, Matson, Patel, and Harwood-Nash found only one instance of an aneurysm arising from the posterior communicating artery, which is the typical site for adult aneurysms producing third-nerve palsies.

Infrequently, subarachnoid involvement of the third cranial nerve can be caused by cranial arteritis. I have rarely found this situation, but Meadows has found subarachnoid involvement of the third nerve in 12 to 15% of the cases of temporal arteritis he has seen.

In 40% of cases involving patients with third cranial nerve ophthalmoplegia owing to tumor, the tumor is metastatic. In two large series on ophthalmoplegia, nasopharyngeal carcinoma was found to be the most common metastatic tumor.

Infection accompanying third cranial nerve paralysis is not common; however, varicella and botulism have been reported as causing isolated internal ophthalmoplegia involving accommodation and pupillary function and thus deserve special mention. At one time, diplopia was a frequent cause of isolated pupillary paralysis, but today diplopia is rarely reported.

CAVERNOUS SINUS INVOLVEMENT (FIG. 6.17-3). Another form of paralysis can occur where the third cranial nerve runs through the cavernous sinus—the point at which it is associated with the fourth and sixth cranial nerves, the first and second divisions of the fifth cranial nerve, and the ocular sympathetic nerves. An isolated third cranial nerve paralysis in this location is rare; but it can occur; however, signs of cavernous sinus involvement soon become evident on repeated examination.

An intracavernous aneurysm underlying third cranial nerve paralysis is readily differentiated from other cerebral aneurysms. An important distinction is that even if an intracavernous aneurysm ruptures, bleeding occurs into another vascular compartment rather than into the subarachnoid space; thus the signs and symptoms of a subarachnoid hemorrhage are absent. However, this is not 100% true. Kuppersmith found that in 79 cases, 1.3% ruptured into the subarachnoid space. The usual complication was optic and cranial nerve neuropathy. Pain is usually intermittent and not a prominent feature of an intracavernous aneurysm, which frequently develops a fibrous coat as it enlarges and progressively compresses the cavernous sinus nerves. One of the earliest signs associated with third cranial nerve paralysis owing to a disorder in the cavernous sinus is depression of the ipsilateral corneal reflex. Presence of a cephalic murmur that can be altered by carotid compression may help in differential diagnosis.

Symptoms of an intracavernous aneurysm generally occur when the patient is over age 50, whereas aneurysms located on the internal carotid artery produce symptoms at least 10 years earlier. Intracavernous aneurysms occur later in life than aneurysms in other parts of the internal carotid artery; the secondary exophthalmos usually is moderate, and chemosis frequently is absent. All of these symptoms differentiate intracavernous aneurysm from arteriovenous cavernous sinus fistula. Optic atrophy owing to enlargement of the aneurysm and compression of the optic nerve is of major concern.

Arteriovenous fistulas are of two varieties—those caused by trauma and those that are spontaneous and arteriosclerotic. Nowadays, more than 75% of such cases are caused by trauma suffered in automobile and motorcycle accidents and are seen mostly in young men, as might be expected. The remainder are spontaneous and arteriosclerotic in origin, occurring primarily in elderly women.

Arteriovenous fistulas can affect the third cranial nerve as well as other nerves of the cavernous sinus. Exophthalmos and chemosis may be much more prominent than in cavernous sinus aneurysm. Dilated veins around the cornea give the appearance of a caput medusa. Bruits are easily heard by both physician and patient; the ability to change their character by carotid
compression varies and depends on the degree of collateral circulation.

Schiotz’s tonometer can be a valuable tool in diagnosing arteriovenous cavernous sinus fistula. Normal pulsations in the eye cause the arm of this instrument to move 2 or 3 mm while readings on the average, but the wider pulse swings of an arteriovenous cavernous sinus fistula may cause the arm to swing 10 mm or more. (This wide swing may occur without the physician’s having noted any obvious pulsation on simple inspection.) Abnormal pulsation of the globe can be seen with applanation tonometry as well, although not as easily as with Schiotz’s tonometer.

Another subtle feature of pulsation may be seen during direct ophthalmoscopic examination of the fundus. As the fundus is observed, the disc and vessels go in and out of focus synchronously with the pulse at the wrist. This phenomenon is distinct from the variation in focus that occurs with variation in accommodation. The pulsations just described are more easily perceived with the direct, than the indirect, ophthalmoscope. Both types of ocular pulsation may be seen when gross movement of the globe is not apparent.

Both secondary glaucoma and ischemic optic atrophy are of major concern in patients suffering from arteriovenous fistula and are the usual reasons for a decision to operate. The results of an operation can be disastrous, however, and the desirability of surgical intervention is presently being widely debated. The conservative view expressed by Spencer, Thompson, and Hoyt and by Sanders and Hoyt is that present surgical techniques tend only to increase the ischemia in many cases and thus make matters worse. The detachable balloon technique has become popular for treatment of arteriovenous fistulas and does not produce the severe consequences seen with previous surgical approaches. Miller has even used the superior ophthalmic vein as a route of injection. The newer interventional neuroradiologic techniques have improved the results significantly.

Carotid cavernous sinus fistula (CCSF), which is an uncommon medical occurrence, occurs in two forms. The first involves a direct flow from the intracavernous carotid artery into the cavernous sinus and exhibits high flow and marked signs. The second involves a connection between a smaller dural artery and the cavernous sinus, it exhibits minimal signs. If fistulas of the second type are low grade, they are frequently missed or at least treated as chronic conjunctivitis because of a persistent red eye. The red eyes in these patients show dilated vessels with clear conjunctiva between the vessels, with or without chemosis. In true infectious conjunctivitis, the vessels are prominent, but the intervening conjunctiva is pink or red and not clear. Neither type of fistula is usually life threatening, but the high-flow type may threaten vision. The most common complication of the smaller fistula is open-angle glaucoma, which is the most likely cause for the increase in episcleral venous pressure seen in such cases.

Tumor invasion of the cavernous sinus occurs in two different ways: (a) by intracavernous growth of a metastatic tumor and (b) by lateral extension of a pituitary tumor into the cavernous sinus with or without the bitemporal field loss usually associated with this condition. In the latter disorder, termed pituitary apoplexy, the onset is usually sudden, and the patient appears quite ill. The third cranial nerve is rarely solely involved, and the optic nerve on the same side may also be involved owing to extension of the tumor forward into the optic nerve sheath. The fact that most persons exhibiting this syndrome have not had a known pituitary tumor prior to the onset of the apoplexy may delay a proper diagnosis.

**SUPERIOR ORBITAL FISSURE INVOLVEMENT (FIG. 6.18, 3).** Tumors impinging on the superior orbital fissure can also cause third cranial nerve paralysis. Because the nerves involved are the same as those involved in disorders located in the cavernous sinus, differentiation usually cannot be made on clinical grounds alone; however, indications of bony changes owing to tumor pro-
provide a clue to diagnosis. The most common tumor in this area is a sphenoid ridge meningioma that frequently causes prominent changes readily discernible on even the plain roentgenogram.

Tolosa-Hunt syndrome is a condition entirely unrelated to other disorders causing ophthalmoplegia. Pain usually precedes the ophthalmoplegia and is usually steady rather than throbbing or episodic. The ophthalmoplegia may involve the third, fourth, and sixth cranial nerves separately or in combination. Symptoms may last for several weeks or longer and then usually remit spontaneously, although some residual ophthalmoplegia may continue. It is not unusual to have a remission of the syndrome involving the third cranial nerve, followed by a quick relapse with involvement of the sixth or fourth cranial nerve. Bilateral involvement is rare but not unheard of in these cases.

In diagnosing Tolosa-Hunt syndrome, all other possible causes of this symptom complex must be ruled out. The diagnostic approach usually includes roentgenograms of the sinuses (to exclude infection) and the sphenoid ridge, MRI, or computerized tomograms of the retro-orbital structures, and perhaps cerebral arteriograms. Diagnosis of Tolosa-Hunt syndrome is by exclusion and should therefore be made only after exhaustive evaluation.

**ORBITAL LESIONS (FIG. 6:18-3)**. Ophthalmoplegia affecting the third cranial nerve in the orbit involves not only the same nerves as in the superior orbital fissure and cavernous sinus but also the optic nerve. As a consequence, the patient may experience loss of vision and perhaps exhibit exophthalmos. In the orbit, the third cranial nerve separates into two divisions, so a partial third cranial nerve paralysis of one or the other division is possible. The upper division innervates the lid and the superior rectus muscles; all the other third cranial nerve functions are in the inferior division.

Involvement of the superior division of the oculomotor nerve usually is located in the orbit or anterior cavernous sinus. Although it used to be thought that such involvement could occur in the nucleus, nuclear involvement producing isolated third-nerve palsy without other neurologic signs has been reported by Keane. Cases of palsy of isolated muscles innervated by the oculomotor nerve have also been reported by Pusateri as occurring due to selected lesions in the oculomotor nucleus. If the superior division of the oculomotor nerve is involved, there is ptosis and difficulty in elevation in abduction. If this elevation disorder results from a supranuclear lesion, it should be equal in abduction and adduction and orthophoric. The studies of Warwick have provided information on the detailed organization of the oculomotor nucleus. Miller has suggested that the division of the oculomotor nucleus into a superior and inferior division may be actually functionally organized in the nerve all the way back to its exit from the brainstem. There is no direct anatomic evidence for this, but strong inferential evidence. Such an anatomic organization of function from the brainstem has been demonstrated for the facial nerve.

A decrease in vision or merely an afferent pupillary defect on the affected side may be enough of a clue to lead to a diagnosis of third cranial nerve paralysis in the orbit. Among possible causative factors, orbital tumor and congestive sinus disease, such as mucocele, tumor, or infection, should receive major consideration. Infection may not be immediately obvious if the patient has no sinus symptoms and does not appear toxic; however, progressive pain and exophthalmos should suggest this possibility, and appropriate roentgenographic evaluation is indicated. Since roentgenograms of the sinus area are frequently difficult to read, expert opinion should be sought (a) as to the views to be taken and (b) in the interpretation of the roentgenograms or MRI.

**OTHER CAUSES**

**MIGRAINE.** Ophthalmoplegic migraine is an uncommon phenomenon that presents in children. Miller found only two admissions
O'Doherty suggested compression of adjacent nerves by a swollen carotid artery secondary to migrainous ischemia. Vijayan suggested that the ophthalmoplegia resulted from an ischemic neuropathy. The work of Mijasavilevic, mentioned earlier, suggests that both theories can be applied. Thus, penetration of the third cranial nerve by small arteries, which is common, can cause compression or ischemia of nearby structures.

KERNOHAN NOTCH SYNDROME. The Kernohan notch syndrome is a variation of a frequently occurring condition. Ordinarily, supratentorial pressure from a tumor or subdural hematoma compresses the third cranial nerve as it crosses the tentorial edge. Since the pupillary fibers are in the peripheral superior medial part of the nerve, these fibers are frequently affected first, without significant involvement of other parts of the third cranial nerve. The ipsilateral cerebral peduncle is compressed at the same time, and signs of ipsilateral pupillary enlargement and contralateral hemiparesis can be observed.

In the Kernohan notch variation, compression of the ipsilateral third cranial nerve is associated with cross-compression of the contralateral cerebral peduncle, resulting in ipsilateral third cranial nerve paralysis and ipsilateral hemiplegia. This situation leads to confusion as to which side of the head the expanding lesion is on, since these two signs are normally crossed. In determining the location of the lesion, a rule of thumb is to rely on the pupillary sign rather than on the hemiparesis.

ORBITAL FRACTURES. Orbital bone fractures can trap muscles and result in diplopia. The most common fracture is one that occurs in the orbital floor, trapping the inferior oblique and inferior rectus muscles as they form into Lockwood's ligament. Rare cases also exist of simulated superior oblique tendon sheath syndrome with a floor fracture. Medial wall fractures can trap the medial rectus muscle and may look like a lateral rectus palsy; however, the globe retracts with attempts at lateral gaze. This entrapment and pseudo-lateral rectus palsy can be
diagnosed by a forced duction test and by saccadic velocity testing.

Orbital roof fractures are less common but have their own set of complications. These complications may be insidious and delayed in onset and are therefore often missed. The most serious of these complications are meningitis and brain abscess secondary to a connection between the intracranial space and the frontal sinuses.

**MISCELLANEOUS CAUSES.** Herpes zoster ophthalmoplegia occurs when the skin lesions over the first division of the fifth cranial nerve are almost healed. The diagnosis is obvious, since all the signs and symptoms of the herpetic disease are present. The ophthalmoplegia will clear slowly without therapy.

Congenital third nerve palsies are generally considered to be traumatic in origin because of the high incidence of misdirection that occurs in the peripheral nerve. They tend to be an isolated neurologic event without other brainstem signs.

Third cranial nerve paralysis occurs infrequently in connection with lupus erythematosus, encephalitis, amyloidosis, Hodgkin's disease, temporal arteritis, tetanus, sarcoidosis, and rarely, after dental anesthesia. The mechanism in dental anesthesia may be retrograde flow of the anesthetic. More rarely, fat emboli can cause blindness owing to arterial obstruction. Multiple sclerosis rarely causes ophthalmoplegia, and when it does, it is usually in the form of a sixth cranial nerve paralysis. The acquired immune deficiency syndrome has also produced oculomotor paresis, occasionally as a presenting sign. Facial nerve involvement, however, is more common.

The cause of an unresolved oculomotor palsy in children that is not identified by initial studies should be followed up at intervals by repeat imaging studies. Since high-resolution computed tomography (CT) and MRI often allow adequate review of the brainstem without invasive studies, there is little excuse for not pursuing such cases at repeated intervals. Abdul-Rahim and Savino reported on five such cases that revealed tumors of the oculomotor nerve, probably schwannomas, on subsequent studies years later.

**Convergence Insufficiency**

Convergence insufficiency is a very common problem causing reading complaints in students. Acquired convergence insufficiency or convergence paralysis has been associated occasionally with a diverse group of causes. I have found a significant relationship between this condition and head trauma. In many of my cases, patients who were prepresbyopic before trauma, had convergence insufficiency or paralysis after cerebral trauma, but no medial rectus paralysis on ductions. Many also had a marked presbyopia and no pupillary involvement. Some of these cases resolve with time, but most do not. The exact location of the lesion is unknown. Recent studies by Buttnery-Emmevar enlarged on the anatomic division of the subnuclei of the oculomotor nerve. He believes that the rostral portion of the medial rectus group of cells controls convergence movements. So far no lesion has been identified in this area on imaging studies, but MRI may pinpoint the lesion in the near future.

**Fourth Cranial Nerve Paralysis**

**ANATOMY (FIG. 6.22)**

The trochlear nerve nucleus develops adjacent to the oculomotor nerve in the floor of the fourth ventricle. The trochlear nerve is the only crossed cranial nerve (Fig. 6.22, D). The fascicle then travels dorsally before crossing in the anterior medullary velum (Fig. 6.22, D). This is a site often suggested in bilateral trochlear nerve palsies. The fourth nerve emerges from the dorsal surface of the brainstem and travels between the posterior cerebral and superior cerebellar artery as does the oculomotor nerve (Fig. 6.16, D). The nerve then passes the cerebral peduncle and enters the cavernous sinus where it lies in the substance of the lateral wall adjacent to the oculomotor nerve (Fig. 6.17, D). It then passes out of the cavernous sinus, into the superior orbital fissure, and into the orbit but
outside the annulus of Zinn (Fig. 6.18, 3). The nerve then crosses over the superior rectus muscle and moves immediately to innervate the superior oblique muscle.

Unlike the third cranial nerve, the fourth cranial nerve (trochlear nerve) innervates only one muscle, the superior oblique, which causes the eye to intort and turn down. Minimal weakness in this muscle may result in symptoms, since the eye is much less able to overcome vertical than horizontal imbalance. In paralysis of the oblique muscle, the versions are mostly affected; theuctions are frequently full.

A frequent error in testing for a minimal defect in motility is permitting the patient's head to be tilted during testing, which masks the defect. Testing should be done with the patient's head-erect, even if it has to be supported manually.

**COMPENSATORY HEAD TILT**

In general, the head-tilt test is useful in distinguishing paralysis of the superior oblique muscle in one eye from paralysis of the superior rectus muscle in the other, since, for all practical purposes, isolated paralysis of the inferior oblique and inferior rectus muscles is uncommon. As noted earlier, the Bielschowsky head-tilt test is positive if further separation of the images occurs when the head is tilted to the side of the affected superior oblique muscle. For instance, in paralysis of the left superior oblique muscle that causes a left hypertropia, the diplopia increases with left head tilt.

In describing a compensatory head position, it is important to describe three facets of the position rather than just the shoulder toward which the head is tilted: (a) whether the chin is elevated or is depressed in an
attempt to overcome the vertical aspect of the imbalance, (b) whether the face is turned to the right or turned to the left to overcome weakness in adduction or abduction, and (c) whether the head is tilted toward the left shoulder or toward the right shoulder to overcome torsional weakness. A description of these three head positions represents the attempt to compensate for the three functions of the vertically acting muscles (Table 6.11). For example, in paralysis of the left superior oblique muscle, the chin is tilted down to overcome the weak depression effect of the left superior oblique muscle; the face is turned to the right to overcome the weak abductions; and (last but not least) a right head tilt causes the left eye to extort, thereby overcoming the weak intorsion effect of the paralysis of the left superior oblique muscle.

Exceptions to the foregoing rules are rare, but they do occur. Although a patient presumably chooses a head position to maintain fusion, on rare occasions the patient may elect the reverse position to further separate the images, thus making it easier to suppress the more distant image. Actual testing will show that the head tilt assumed makes the images move farther away rather than nearer. Thus the head position initially seen should not be considered absolutely indicative of the muscle involved.

Sandifer syndrome, an unusual form of head tilting, is seen in children with a short esophagus. In such cases, the head can be easily lifted manually (suggesting no contraction of neck muscles), but the tilt to one shoulder will be resumed as soon as the supporting hand is removed. No muscle imbalance is found on repeated motility testing, which rules out the two common causes of head tilting. A child who is old enough may be able to describe gastrointestinal disturbances that are relieved when the head is tilted and depressed, thus shortening the esophagus. Patients with this condition are best referred to a pediatric surgeon, who can readily diagnose hiatus hernia by use of a barium swallow and treat it.

TESTING OF FOURTH CRANIAL NERVE PARALYSIS IN PRESENCE OF THIRD CRANIAL NERVE PARALYSIS

In evaluating any third cranial nerve paralysis, it is important to detect any associated defects in the fourth and sixth cranial nerves, which may place the lesions in the cavernous sinus or superior orbital fissure. Since third cranial nerve paralysis prevents the eye from being adducted, another form of testing must be chosen to test the vertical action of the superior oblique muscle. The patient should be instructed to attempt to look down and in with the paretic eye while the examiner confirms the effort by observing the fellow eye, which should move down and out. A small intorsing maneuver of the affected eye, not vertical depression, is an indication of good fourth cranial nerve function in an eye that cannot be adducted because of third cranial nerve paralysis. The intorsion, which reflects the action of the superior oblique muscle when it is not in the abducted position, is small, and it must be looked for specifically. Watching the movement of a horizontally located conjunctival vessel makes the intorsion easier to see.

CONGENITAL PARALYSIS

Congenital paralysis, a fairly common defect, frequently goes undetected. Many patients' features are cosmetically acceptable, and congenital paralysis of the fourth cranial nerve does not usually involve amblyopia; thus, such patients usually remain undiscovered until they have a routine eye examination. Types of congenital paralysis diagnosed in children of preschool age are either cosmetically obvious or accompanied by a head tilt that suggests a muscle imbalance requiring evaluation.

Brown's syndrome, which involves restriction of the muscle and sheath as it slides through the trochlea, is not innervational but mechanical, and it is therefore an entirely different problem. In a typical case, as the eye is adducted in up-gaze, it turns down and in as if an inferior oblique muscle paralysis
existed. The forced duction test easily differentiates this movement from that occurring in inferior oblique muscle paralysis; it is positive when the examiner attempts to move the eye up and in.

ACQUIRED PARALYSIS (Fig. 6.23)

Trauma is the leading cause of acquired superior oblique muscle paralysis. The trauma can be local, with damage to the trochlea, or more severe, with intracranial damage.

A form of trauma that does not appear to be severe at first glance occurs as the result of a rear-end automobile collision. The history has been similar in the cases I have seen. The stopped car in which the patient was seated was hit from behind, causing a typical whiplash movement, with sudden hyperextension of the head and neck. In some instances, the head struck the steering wheel or dashboard. Usually, the patient was neither rendered unconscious nor sustained more than a bump on the head. Onset of diplopia was immediate. On examination, the eye was neither red nor swollen, indicating little if any local injury to the

| I | Congenital (decompensation) |
| S | Trauma |
| O | Acquired Brown’s syndrome (pain over trochlea) |
| L | Skew (no cycloversion) |
| A | Ischemic (Diabetes, hypertension) |
| T | Idiopathic |
| E | Other |
| D | Tumor |
| 4TH | Hydrocephalus |
| N | Giant Cell Arteritis |
| E | Aneurysm (rare) |
| R | Demyelinating (rare) |
| V | E |
| P | A |
| R | A |
| A | L |
| L | Y |
| S | I | S |

*Figure 6.23.*

Differential diagnosis of fourth-nerve paralysis.
In the orbit, or to the superior oblique muscle in the orbit. The muscle imbalance was minimal and usually cleared over a period of 3 to 6 months.

If the patient has large fusional amplitudes, then consider a congenital palsy that has now decompensated. This can happen as a result of minor trauma, from illness, and for no obvious reason. When the measurements vary from examination to examination or no adequate reason is forthcoming, then consider myasthenia gravis and do a Tension test. A ptosis is an extremely common presentation of myasthenia gravis, although it is not 100%, and its absence does not rule out myasthenia gravis. Vasculopathic causes such as diabetes and hypertension are quite common; less common are infectious diseases such as herpes zoster. If none of these causes are present and there are not very wide fusional amplitudes or other neurologic signs developing with worsening of the fourth-nerve palsy, then imaging studies such as MRI are indicated. Imaging is not required for the isolated palsy.

As many as 30% of cases of acquired trochlear nerve paralysis are bilateral. The second trochlear nerve palsy may be more subtle than the first and is frequently missed until it shows up after surgery for the first palsy. To properly identify the bilateral nature of this condition, first neutralize the horizontal deviation with prisms during the examination. Then a right hypertropia in left gaze will become a left hypertropia in right gaze. If it is subtle, be sure to examine the motility in the oblique fields.

Superior oblique myokymia is a rare phenomenon. The cyclovertical torsion of the eye causes oscillopsia. This condition was first reported by Hoyt, and all cases appear to be benign. The cause is unknown, and treatment if any is Tegretol. Surgical correction has not been particularly satisfactory and may even cause diplopia.

Lesions in the cavernous sinus or superior orbital fissure can cause a combination of trochlear nerve palsy and ipsilateral Horner syndrome. However, lesions in the brainstem can cause ipsilateral Horner syndrome and contralateral trochlear palsy. A skew deviation is an alternative reason for the diplopia, but appropriate measurements of the hypertropia and head tilt confirm a trochlear palsy and brainstem location.

In cases of acquired paralysis of the fourth cranial nerve, the exact location of the injury to the nerve is uncertain. However, a clue may be gleaned from three bilateral cases that I have seen in which the headache was slightly more serious. Two of these patients had experienced a period of unconsciousness, but in all three, superior oblique muscle paralysis was the only sign of intracranial trauma, despite the severity of the head blow. Since both fourth cranial nerves come together only in the anterior medullary velum where they cross, it seems likely that the injury occurred in this area. Of further note, the bilateral cases that I have seen have not cleared spontaneously but have required a surgical procedure to resolve the problem. The sign that suggests bilateral fourth nerve involvement is the alternating hypertropia. There is a left hypertropia in right gaze and a right hypertropia in left gaze. The Bielschowsky head-tilt test also changes from side to side if one looks to the right or to the left when performing the test.

In certain surgical approaches to frontal sinus disease, the trochlea is moved and may be damaged; however, these procedures are now rarely used. Other causes of superior oblique muscle paralysis, such as vascular disease and diabetes, have been diagnosed, but trauma is by far the most frequent cause. Although isolated fourth cranial nerve paralysis owing to diabetes is uncommon, a glucose tolerance test is indicated in certain patients.

A form of intermittent Brown's tendon sheath syndrome occurs in adults. The usual complaint is intermittent diplopia immediately preceded by what is described as a popping sensation in the area of the trochlea, sometimes accompanied by mild pain and tenderness. The diplopia may last from minutes to days or weeks. The same forcedduction findings seen in a true Brown's syndrome are found while the patient is symptomatic.
Although the cause of this disorder is unknown, systemic steroids seemed to help in two cases that I have treated. I have not tried local injection of steroids.

Other inflammatory causes such as rheumatoid arthritis, herpes zoster, cysticercosis, and Tolosa-Hunt syndrome have been infrequently responsible. If the vertical deviation does not fit a trochlear nerve paresis or there is no cycloversion or it varies from examination to examination, consider a skew deviation.

**Sixth Cranial Nerve Paralysis**

**ANATOMY (FIGS. 6.24, 6.25)**

Differentiation of the sixth nerve nucleus occurs between the fourth and sixth week of gestation. This is coincidental with the development of the fourth and third nerve nuclei.

The sixth nerve nucleus develops in the floor of the fourth ventricle (Fig. 6.24, I). It appears somewhat elevated because of the passage of the seventh nerve around it. The neighboring structures are the medial longitudinal bundle, which lies medial. The sixth nerve nucleus also lies dorsal and medial to the vestibular nuclei. These are important structures since lesions of the sixth nerve in this location will cause signs that identify the anatomic lesion as intrinsic to the brainstem. The fascicle travels ventrally and exits at the pontomedullary junction. The nerve then passes vertically in close approximation to the anterior inferior cerebellar artery (Fig. 6.16, 2). It continues through the subarachnoid space to pierce the dura. The dura is folded over the petrous bone and is called Gruver's ligament (Fig. 6.25, 4). The nerve passes beneath it through a space called...
Dorello’s canal and enters the cavernous sinus (Fig. 6.17, 6). The sixth nerve lies in the cavernous sinus near the carotid artery rather than in the wall of the sinus like the oculomotor and the trochlear nerves. It then travels through the superior orbital fissure and through the annulus of Zinn to innervate the lateral rectus muscle.

Like the fourth cranial nerve, the sixth cranial nerve (abducens nerve) innervates only one muscle, the lateral rectus, which moves the eye laterally. Unlike the superior oblique muscle, the lateral rectus muscle has no secondary or tertiary function. It comes into play primarily when the eye is fixed on a distant object. Many a case of minimal sixth cranial nerve paralysis has been missed because the patient was asked to look at a light 3 feet distant rather than 20 feet distant during the alternate-cover test.

Just as head positioning can mask a fourth cranial nerve paralysis, so a head turn can mask a minimal sixth cranial nerve paralysis if the patient is examined only in the straight-ahead or near position. The diplopia that occurs with lateral rectus muscle paralysis is homonymous owing to the esotropia that is created. That is, when two images are seen, the ipsilateral image disappears when the ipsilateral eye is covered.

The measurement of horizontal vergences reveals the ability of a muscle to overcome stress. Some people can overcome 30 prism dioptries of muscle imbalance, which permits certain muscle weaknesses to be overcome before diplopia is experienced. This compensation is different from that of muscles innervated by the fourth cranial nerve, which work primarily in a vertical direction and may overcome only 1 or 2 prism dioptries of imbalance. If a patient has a progressive weakening of the lateral rectus muscle, as may occur with increasing intracranial pressure, it will show up in the distance muscle balance. In successive examinations (either days or weeks apart) of the distance phoria, the measurements increase significantly toward the esophoric side. The first readings may be an esophoria of 2 dioptries, indicating a small degree of esophoria at distance that will become moderate as the intracranial pressure increases. The increase in measurement will take place before the occurrence of frank diplopia, owing to the ver-

gence rest mechanism. Usually useful is the problem of days, the c distance p time a frank developed shown to increased int

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Although paralysis is possibl e specific an physician dromes and minor, th

The ref now perm in the ab could not particula rly or the brainst doma, chx suspected, bone wind for bone o way to id possible c to identify isolat ed c causes suc als, and di common c occur after Therefore workup sl tion rate, o and thyroi clear, th formed. A p
gence reserve of the horizontal fusional mechanism. This testing technique is particularly useful in deciding whether a blurred disc is true papilledema. While the disc problem is being evaluated, over several days, the change in the measurements of the distance phoria may be significant. By the time a frank sixth cranial nerve paralysis has developed or both sixth cranial nerves are shown to be involved, the diagnosis of increased intracranial pressure is obvious.

Synkinetic phenomena of the third cranial nerve are well known and not rare, whereas synkinetic phenomena involving the sixth cranial nerve are rare. I have not seen a case, but Spaeth reported on a small series in 1950.

Although isolated sixth cranial nerve paralysis is not uncommon, it is almost impossible to adequately identify its cause or specific anatomic location. Therefore, the physician must be familiar with the syndromes and associated signs, both major and minor, that may help to identify either the location or the cause of this disorder.

The refinement of imaging techniques now permits identification of lesions—even in the abducens fascicle—that previously could not be detected. MRI has proven particularly useful in examining for lesions in the brainstem and parenchyma. If a choroida, chondrosarcoma, or meningioma is suspected, then a computed tomogram with bone windows should be ordered to look for bone erosion or hyperostosis. The best way to identify the anatomic location and possible causes of a sixth nerve paralysis is to identify the neurologic company it keeps. Isolated cases are mostly due to vascular causes such as hypertension, arteriosclerosis, and diabetes. Tumors are a much more common diagnosis in children, unless they occur after upper respiratory tract infections. Therefore in isolated cases, the initial workup should include a CBC, sedimentation rate, collagen vascular battery of tests, and thyroid studies. If the diagnosis is not clear, then a Tensilon test should be performed. A CT or MRI study may be done initially or postponed for 2 to 3 months, by which time most vascular cases will be recovered. If no improvement occurs within 3 months, imaging studies with views along the course of the sixth nerve are necessary. Bone scans at the base of the brain are also indicated as well as a lumbar puncture and nasopharynx investigation. If the sixth nerve palsy is progressive and no cause can be identified, a forced duction test should be done. The progression may be due to contraction of the medial rectus muscle rather than to some progressive disease of the sixth nerve. If surgical correction of the sixth nerve palsy is contemplated, botulinum toxin injection of the medial rectus muscle should be tried.

If the cause of the sixth nerve paresis remains unknown, the diagnostic studies should be repeated at 6 months. Experience teaches us that tumors progress and cause increasing compression and unrelenting signs and symptoms. However, there are several explanations for sixth nerve palsies that spontaneously recover in such a clinical setting: remyelination, axonal regeneration, displacement of the nerve off a growing mass, and restoration of blood flow to the nerve.

CONGENITAL PARALYSIS (Fig. 6.26)

Möbius syndrome involves complete bilateral paralysis of the sixth and seventh cranial nerves. Its cause is unknown, but a carefully taken drug history may be revealing. I had two patients whose mothers had taken thalidomide during pregnancy. In most cases, however, the cause is unknown.

Duane syndrome is one form of congenital sixth cranial nerve paralysis. There are three types with different electromyographic responses. Type 1 reveals limited or absent abduction and normal adduction. Type 2 has limited or absent adduction and normal abduction. The third type has limited abduction and limited adduction. Since most patients with this condition are not esotropic in the primary straight-ahead position, the condition is frequently not discovered early in life. When it is finally diagnosed, whether the sixth cranial nerve paralysis is old or of
| I | Congenital |
| S | Trauma (orbit head) |
| Q | Lateral series thrombosis |
| L | Postpartum |
| T | 2nd to mastoiditis |
| A | Gradening syndrome |
| T | Idiopathic |
| E | Intracranial pressure |
| D | (Pseudotumor, tumor) |

6TH

| N | Stroke |
| E | Nasopharyngeal malignancy (along with 2nd division |
| R | 5th nerve dysesthesia |
| V | Wernicke-Korsakoff syndrome (ataxia of gait, nystagmus, confabulations) |

| P | Spinal puncture (anesthesia or myelography) |
| A | Tolosa-Hunt syndrome (associated pain) |
| R | Ischemic (diabetes, hypertension, arterosclerosis) |

| A | Tumors (Meningiomas, pontine gliomas, metastasis, cavernous sinus mass) |
| Y | Nuclear aplasia (Duane's syndrome) |
| S | Miscellaneous (MS, migraine, sarcoidosis, giant cell arteritis) |

**Figure 6.26.**

Differential diagnosis of sixth-nerve paralysis.

Recent origin becomes a serious question. Bilateral paralysis of recent onset may be caused by increased intracranial pressure or brainstem glioma. Bilateral Duane syndrome is rare (Fig. 6.27 A, B, and C).

Examination for the additional signs of Duane syndrome assists the observer in differentiating between this condition and an acquired sixth cranial nerve paralysis. Patients with Duane syndrome are not usually esotropic in the primary position, and they do not develop anophoria as a rule. If they look into the field of the paretic muscle, no diplopia results, because this movement brings into play a mechanism called facultative anophoria rather than the anophoria ex anopsia usually seen with esotropia. The key sign, however, is a narrowing of the lid fissure on adduction and return of the fissure to normal when the eye reverts to the straight-ahead position. In at least some cases, lid narrowing is caused by simultaneous innervation of the lateral and medial rectus muscles. This has been confirmed by electromyographic studies and autopsy material reported by Hoyt and Nachtigaller and again by Hotchkiss, Miller, Clark, and Green. Auditory evoked material, as reported by Jay and Hoyt, further suggests a primary brainstem malfunction rather than a peripheral cause. On adduction, therefore, the medial and lateral rectus muscles cocontract, causing enophthalmos and narrowing of the lid fissure. Once lid narrowing is observed, the malfunction can be diagnosed as congenital, and further diagnostic procedures are un-
\textbf{Figure 6.27.}

Patient with bilateral Duane syndrome. A. Straight and primary position. B. Right Duane with decrease in right lateral rectus function and left superior oblique overaction.
and further diagnostic procedures are unnecessary.

In rare circumstances, Duane syndrome can be acquired. I have seen one case caused by trauma, and at least one case has been reported in a patient with rheumatoid arthritis. The electromyographic studies are different in these cases from those in the congenital form, which shows cocontraction of the lateral and medial rectus muscles. In addition, superior or inferior oblique muscles may overact.

ACQUIRED PARALYSIS

VASCULAR OCCLUSION. Vascular accidents involving the brainstem occur frequently. The two syndromes that usually accompany such accidents are (a) Foville syndrome, which combines sixth and peripheral seventh cranial nerve paralysis with homolateral gaze paralysis, and (b) the Millard-Gubler syndrome, which consists of sixth and peripheral seventh cranial nerve paralysis and contralateral hemiplegia.

In elderly patients, spontaneous isolated sixth cranial nerve paralysis can occur and frequently disappears within several months. One explanation of this malfunction, proposed as far back as Cushing's time, holds that it is caused by compression of the sixth cranial nerve on the anterior surface of the pons by the lateral branches of the basilar artery, particularly the anterior inferior cerebellar artery.

Sixth cranial nerve palsies can also be caused by temporal arteritis and polyarteritis nodosa. Both these conditions can be diagnosed by a temporal artery biopsy. The sedimentation rate is also elevated in both diseases. The pathology is the differentiating feature.

GRADENIGO SYNDROME. Gradenigo syndrome is rarely seen in this age of antibiotics. The inflammation often involves severe otitis media and mastoiditis with secondary petrositis, in the course of which the area of the petrous bone called Dorello's canal is affected, and the sixth cranial nerve becomes

...
Lateral Sinus Thrombosis. Lateral sinus thrombosis is frequently idiopathic. The resulting inflammation extends to the inferior petrosal sinus, which is adjacent to the sixth cranial nerve, thus causing malfunction of this nerve. Thrombosis may occur postpartum or from distant emboli, as, for example, in venous stasis of the legs.

**Superior Orbital Fissure Syndrome.** Also called Tolosa-Hunt syndrome, superior orbital fissure syndrome may begin as an isolated sixth cranial nerve paralysis. The course, diagnosis, and treatment of this syndrome are discussed above.

In treating patients with symptoms located at the superior orbital fissure, the physician must be careful not to err by failing to rule out all the diseases possible in the cavernous sinus, superior orbital fissure, and posterior orbit. The same rule applies to suspected lesions in the cavernous sinus, such as arteriovenous fistulas and tumors. It is unusual to see only an isolated sixth cranial nerve paralysis without symptoms relating to the other cavernous sinus nerves; however, the literature includes several cases of a sixth cranial nerve paralysis in the cavernous sinus, with further signs developing only 6 months after onset of the paralysis.

**Cerebellopontine Angle Tumors.** Although cerebellopontine angle tumors cause paralysis of the sixth cranial nerve, other prominent signs frequently precede the onset of this paralysis. The seventh and eighth cranial nerves are affected, and frequently, anesthesia of the cornea is present. All three nerves should be tested when an obscure sixth cranial nerve paralysis is seen. Sixth cranial nerve paralysis is not the presenting sign of an angle tumor, but it may be the complaint that leads the patient to seek medical attention. Selective audiograms, and a CT/MRI study outlining the cerebellopontine angle will demonstrate an acoustic neuroma, the type of tumor most commonly found in that area. Of cerebellopontine angle tumors, 90% are acoustic neuromas. The most common causes of the remaining 10% are meningiomas and cholesteatomas. In the case of meningiomas, radiographic studies may show osteoblastic changes in adjacent bones. In the case of cholesteatomas, contrast studies demonstrate a scalloped edge to the tumor unlike the smooth surface of an acoustic neuroma. A facial tic is also more common with cholesteatmos. Although not 100% accurate, spinal fluid protein tends to be normal rather than markedly elevated as it is in other tumors located in that area of the angle, which obstruct the flow of cerebrospinal fluid as do acoustic neuromas (Fig. 6.28).

**Spinal Anesthesia.** Transient sixth cranial nerve paralysis following spinal anesthesia is a rare but definite occurrence. In a review of 10,400 cases involving spinal anesthesia, Phillips et al. found that transient sixth cranial nerve paralysis had occurred in eight patients. Thorsen felt it was more common, with an incidence of 1 in 400 procedures. This condition is much less common in my experience. Although this transient paralysis appears to be more common with the injection of contrast material than with a simple spinal tap, the incidence is too small to demonstrate this conclusively.

One explanation for this paralysis is that it represents a toxic response to the injected material. This is unlikely, since there is a delay of 1 or 2 weeks before the symptoms develop. A second explanation is more plausible. The patients that have experienced lateral rectus paresis have other post-spinal tap symptoms, such as headache in the erect position. These symptoms have generally been considered to be caused by chronic leakage of spinal fluid from the tap site, with displacement of the brain and traction on pain-sensitive structures. It is not hard to extrapolate this theory to include traction on the sixth nerve with compression of firm structures such as the petrous bone.
Spinal fluid examinations to determine the presence of a cellular reaction indicative of arachnoiditis are not usually performed. Paralysis owing to spinal anesthesia clears rapidly (within days or a week or two) and requires no further investigation if the rest of the neurologic examination is normal. In summary, the cause of this type of nerve malfunction is obscure, and the treatment is to do nothing.

**WERNICKE-KORSAKOFF SYNDROME.** When associated with chronic alcoholism, Wernicke-Korsakoff syndrome includes several eye signs, among which are nystagmus of a nonspecific character, horizontal gaze paralysis, sixth cranial nerve paralysis, and, rarely, vertical gaze paralysis. If a patient with sixth cranial nerve paralysis has a history of alcoholism, Wernicke-Korsakoff syndrome is frequently the diagnosis; however, the physician should not fail to rule out the possibility that an alcoholic patient may have sustained some intracranial trauma, and that the sixth cranial nerve paralysis could be the result of increasing intracranial pressure from a subdural hematoma. In addition, the patient may suffer from ataxia of gait and from somnolence, the other two symptoms in the triad described originally by Wernicke. The confabulation symptom of the Korsakoff syndrome was added later, and although it is frequently seen, it is not an essential feature of the Wernicke syndrome.

**TOXIC DRUG REACTIONS.** In cases of sixth cranial nerve paralysis, always consider toxic drug reactions and take a careful drug history. Lateral rectus muscle paralysis has been reported in connection with such drugs as furaltadone and iodochlorhydroxyquin. Optic neuritis is a much more common problem with iodochlorhydroxyquin, but sixth cranial nerve paralysis has also been reported.

**INCREASED INTRACRANIAL PRESSURE.** Sixth cranial nerve paralysis secondary to increased intracranial pressure is well known. What produces paralysis is not completely understood—stretching of the nerve with bony impingement owing to downward displacement of the brainstem? compression by branches of the basilar artery? The early sign of this condition, increasing esophoria, is discussed above. An unusual but dramatic form of sixth cranial nerve paralysis is one that is transient but occurs suddenly and repeatedly. Patients with this disorder develop sudden headaches that are accompanied by paralysis of one or both lateral rectus muscles. All symptoms disappear within minutes or hours. While the signs are present, patients are usually active rather than lethargic, and they frequently shake or hit their heads as if to push out whatever is causing the symptoms. This maneuver suggests that some ball-valve mechanism may be causing sudden changes in intracranial pressure. A colloid cyst of the third ventricle that is intermittently closing off the aqueduct can do this.

Compared with tumor, pseudotumor cerebri is a relatively infrequent cause of increased intracranial pressure. If this condition is to be ruled out as a causative factor, however, (a) diagnostic tests should reveal signs of increased intracranial pressure; (b) the results of a spinal fluid examination should be negative except for increased opening pressure; (c) the neurologic examination should be totally negative, except for the possible presence of a sixth cranial nerve paralysis if the intracranial pressure is high enough; and (d) a CT examination should reveal a normal size ventricular system. If there were a small lesion near to and compressing the aqueduct, then the ventricles would be enlarged, suggesting a non-communicating hydrocephalus.

Most cases of pseudotumor cerebri are idiopathic. Some are related to specific causes such as chronic vitamin A intoxication, tetracycline overdose, postpartum dural sinus thrombosis, and the institution or withdrawal of steroids in treating nephrosis or are a complication of Addison’s or hypoparathyroid disease. Treatment, if any, varies, but it usually consists of steroid therapy over a period of several weeks.

Pseudotumor cerebri is self-limited, but it may persist for months. The real danger of a
Figure 6.28.
A. Patient presents with sixth-nerve paresis from cholesteatoma. B. Same patient with extensive bone erosion.

A prolonged course is secondary atrophy of the optic nerve. Thus, vision and fields should be checked frequently, and the disc should be observed for beginning gliosis—all of which indicate optic nerve decompensation and suggest the need for more vigorous treatment of the intracranial pressure.

**NASOPHARYNGEAL MALIGNANCY.** Nasopharyngeal malignancy (Godtfredsen syndrome) is an uncommon disease that often
affects the sixth cranial nerve. For example, in a series of 53 cases reviewed by Smith and Wheliss, sixth cranial nerve paralysis was present in 29. A significant feature of this type of sixth cranial nerve paralysis is associated pain or paresthesia over the second division of the fifth cranial nerve. This combination of signs should impel the physician to look for other signs that suggest nasopharyngeal malignancy.

The main presenting complaints usually include cervical lymphadenopathy, pain in the ear, pain in the face, and symptoms of nasal obstruction. Most patients have also experienced unexplained weight loss prior to seeking medical attention, at which time a mild or frank sixth cranial nerve paralysis may be present. The third and fourth cranial nerves may also be affected initially, but not as frequently as is the sixth cranial nerve. Usually, by the time multiple orbital nerves are involved, exophthalmos is also present. Mention of serous otitis media, another significant symptom of this disorder, may be omitted by the patient as of minor importance compared with the diplopia and pain being experienced. Intermittent blockage of the eustachian tube, causing a popping sensation or a blocked ear, is another and more subtle symptom of this disease.

Even when a nasopharyngeal malignancy is suspected, it may be difficult to establish. Examination is frequently misleading, since the tumor initially arises submucosally in the nasopharynx. It then grows intracranially but extradurally, affecting one cranial nerve after another before becoming a significant space-occupying lesion. Therefore, a biopsy is indicated even if the nasopharyngeal mucosa looks normal. A good location for biopsy is in the area called Rosenmüller's fossa, which is a common site for this type of tumor.

Special roentgenographic views may reveal another feature of a nasopharyngeal malignancy. A nasopharyngeal tumor usually gains entrance to the cranium by way of the basilar foramina. The usual skull series does not include these openings; therefore, roentgenographic views of the basilar foramina should be ordered specifically, since they may reveal significant erosion of one or more foramina.

On the basis of cell type, lymphoepithelioma is the most common form of tumor found in the nasopharyngeal area. Such tumors are relatively radiosensitive, and radiotherapy may result in a temporary amelioration of symptoms; however, the 5-year survival rate for patients with this type of malignancy is only about 25%. Although malignant nasopharyngeal tumors are rarely seen in the United States, this condition is the leading cause of cancer among males in mainland China. It is not common among people of Chinese descent living in enclaves in Hawaii and San Francisco.

Dental Anesthesia

Sixth-nerve palsies have infrequently incurred with local dental anesthesia. One explanation is injection of the anesthetic into the superior or inferior alveolar artery. The anesthetic travels by retrograde flow or from the pressure of the injection into the maxillary artery and then into the middle meningeal artery and its orbital branch, which anastomoses with the lacrimal branch of the ophthalmic artery.

SIXTH CRANIAL NERVE PARALYSIS IN CHILDREN

When sixth cranial nerve paralysis develops suddenly in an otherwise normal child, it is certainly cause for concern about the possible presence of a serious disorder. Such disorders as increased intracranial pressure or a pontine glioma are always a possibility.

In 1967, Knox, Clark, and Schuster reported on a series of children with spontaneous sixth cranial nerve paralysis that occurred about 7 to 21 days after a nonspecific illness. Spinal fluid tests were usually negative, and no attempt was made to establish that the paralysis was infectious in origin. The patients developed no other symptoms, and the paralysis cleared within several weeks. I have practice, and well if no od

Spasm of the ocular muscles is a condition that may present with small pupils. The patient may have vision at distance and near which is cons

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Weeks. I have seen two such cases in my practice, and I believe that it is proper to wait if no other signs of increased intracranial pressure exist and the remainder of the neurologic examination is normal. Some noninvasive studies such as CT and MRI may be performed, but the invasive studies may be deferred a week or two, provided that the foregoing criteria are met. A spontaneous sixth cranial nerve paralysis begins to clear in a week or two, whereas a pontine glioma does not. Nevertheless, a week's delay probably does not affect the outcome of a pontine glioma.

**Spasm of the Near Reflex**

Spasm of the near reflex is not a common syndrome but will be seen by all ophthalmologists from time to time. The patient presents with convergence of the eyes, small pupils, and increased accommodation. The patient reports diplopia and blurring of vision at distance. These are signs of an exaggerated expression of the near reflex, which is convergence, increased accommodation, and miosis. The clue to a functional cause is found with observation. Functional patients cannot maintain this condition for more than 1 or 2 minutes. Just look at them, and they will then stop doing it. They will usually cover their eyes as if in pain, because they cannot maintain the convergence spasm and do not want to reveal that fact. This may be a conscious or subconscious effort. For confirmation, retinoscopy and refract to good vision without cycloplegia, and you will find that these patients are quite myopic. After cycloplegia, the same vision can be attained with considerably less myopic correction or even a plano prescription.

Pathologic cases have been reported with intracranial infection, labyrinthine disease, brain tumors, and trauma. The clinical circumstances of these cases are quite different and are not usually confused.

**MYOPATHIC CAUSES**

**Thyroid Disease**

**SIGNS AND SYMPTOMS**

It is widely understood that Graves' disease is inherited. However, why one person develops the disease at one age and another years later, even when they are related, is not known. The disease probably needs other factors to activate it. Recently, some studies have suggested smoking as a risk factor. Studies of those who do smoke reveal abnormal lower-activity T-suppressor lymphocytes, and therefore smoking makes a patient immunosuppressed.

Signs of a thyroid disorder can be seen in the eye at different stages of the disease. Symptoms may include some of the signs of hyperthyroidism (e.g., in Graves' disease), in which case the diagnosis is obvious. More frequently, the patient consults an ophthalmologist, complaining of lid retraction and mild exophthalmos before the onset of the systemic signs of hyperthyroidism or before results of laboratory tests are positive. The most frustrating form of eye involvement is that which sometimes occurs after ablation of the hyperactive thyroid gland, when all the systemic signs and laboratory tests have returned to normal.

Although exophthalmos is the best-known symptom of thyroid disease, it may not always be obvious. Even though the condition is present, some patients neither look nor measure particularly exophthalmic owing to the position of their eyes. In such cases, comparison of the patient's present appearance with that in old photographs may be of help. Conversely, some patients who appear exophthalmic may have appeared that way all their lives; prominent or protruding eyes may be a family characteristic. More rarely, patients may complain of unilateral exophthalmos, the condition most obvious to them, when in reality they may have enophthalmos on the other side owing to an old orbital cellulitis or they may have suffered trauma with orbital hemorrhage and
perhaps a fracture of the orbital floor. All of these conditions can cause absorption of orbital fat and enophthalmos.

Exophthalmic measurements are not difficult, but practice with the instruments involved is required to get reliable results. I prefer the Krimb instrument because of the lining-up mechanism that is built into the system. The part of this instrument that brackets the eye includes mirrors with a millimeter scale. This device permits measurement of the anterior surface of the cornea. In addition, the mirror has two red lines that must be lined up before the observer takes this reading, which ensures that the testing circumstances will be the same for every examination. A measurement of 19 mm represents the upper limit of normal for the anterior surface of the cornea; 95% of the population have measurements below this value. However, as previously indicated, a patient who normally measures 16 mm and now measures 19 mm is becoming exophthalmic.

Ophthalmoplegia is a prominent feature of thyroid disease, whereas diplopia is not. If diplopia is present, the patient will probably mention it; however, the patient will usually not compensate for it by putting a patch over one eye or closing an eye as does a patient who has experienced the sudden onset of a sixth cranial nerve paralysis. Limitation of ocular motion is usually in the upward direction and is caused by restriction of the globe by the inferior muscles rather than by weakness of the elevator muscles. This condition can be confirmed by finding restriction of the globe in the forced duction test, which is a particularly significant test when the extraocular muscles are affected before exophthalmos or lid retraction indicates the nature of the disease. Since the inferior muscles are primarily affected, an attempt at up-gaze causes compression of the globe owing to restriction caused by these muscles. This compression in turn raises the intraocular pressure and creates a false impression of glaucoma. Measurement of the intraocular pressure with the eye in down-gaze and in up-gaze should demonstrate a difference in pressure (Fig. 6.29, A and B).

Lid retraction, as has been pointed out by McLean and Norton, may be unilateral and precede all other signs of hyperthyroidism by years. Moreover, lid retraction may occur even in the absence of exophthalmos. The lid is considered retracted when the sclera shows between the upper lid margin and the superior limbus. The fact that the sclera is showing above the limbus indicates that that eye is more likely to be the affected one rather than that the other eye has a proptosis. An exception to this rule occurs when one eye is hypotrophic to the other eye, which is fixing. This condition may leave sclera showing above in the hypotrophic eye.

Periorbital edema may be caused by several conditions in addition to thyroid disease. As the lid tissues become more relaxed with age, some patients, particularly women, may complain of swelling that is worse on arising in the morning. Periorbital edema also occurs in association with orbital infection, trichiasis, renal disease, and myxedema. In early thyroid disorders, the skin edema is usually pale and soft, rather than red and brawny, as it usually is in severe infection. In Graves' disease, which is marked by the rapid onset and progression of exophthalmos, the edema is firm and the eyes red and swollen. The more severe the exophthalmos and the more acute its onset, the greater the chemosis, redness, and congestion of the globe.

Prominent conjunctival vessels over the lateral rectus muscles are often seen before significant chemosis and congestion of the rest of the ocular vessels occur.

Foreign-body sensation is a common complaint, particularly in patients with a combination of up-gaze defect, exophthalmos, and lid retraction—all of which lead to corneal exposure, which is most easily seen in the inferior cornea. Examination following application of fluorescein is best done with the slit lamp, because the punctate staining will be superficial and mild in contrast to the obvious staining usually seen in the case of an outright abrasion. Patients frequently complain of foreign-body sensation early in the course of thyroid disease, even though no staining is evident. Photophobia is also a fre-
Figure 6.29.
Enlarged muscles due to thyroid disease. A. Axial view makes muscles appear as a mass. B. Coronal view shows all muscles enlarged.
quent complaint in thyroid disease, even with minimal corneal involvement.

Severe corneal exposure can lead to corneal ulcers, to infection, and, eventually, to scarring or perforation. Extreme exophthalmos requires constant observation and appropriate treatment to prevent such complications. On occasion, the treatment may even include surgery to decompress the orbit.

Optic nerve involvement as evidenced by decreased visual acuity is seen in the most severe cases of exophthalmos; it is most likely to develop when the exophthalmos is rapidly progressive and accompanied by numerous inflammatory signs. Optic neuropathy is certainly not caused by mechanical stretching of the optic nerve. The intraorbital portion of the nerve measures about 30 mm, whereas the distance from the posterior aspect of the globe to the beginning of the optic canal is 18 mm. Thus, there is 12 mm of play in this S-shaped nerve before mechanical stretch occurs—far in excess of the 7 to 10 mm of exophthalmos seen in the most severe cases. Decreased acuity may be caused by compression of the nerve and its vascular supply by enlarged muscles. A decrease in acuity can also be ascribed to changes in the corneal epithelium owing to a lack of adequate preocular tear film or to punctate epithelial changes.

Brawny scleritis, which causes a decrease in acuity owing to macular involvement, can also occur as a consequence of hyperthyroidism. Dilation of the pupil and examination with the fundus contact lens may reveal horizontal retinal macular striae and a thickened elevated choroid in the posterior pole.

**THYROID FUNCTION TESTS**

(FIG. 6.30)

The three most common causes of hyperthyroidism are (a) Graves’ disease—stimulation of the thyroid by circulating thyroid stimulating immunoglobulins, (b) toxic nodular goiter—autonomous production of hormone by one or more nodules within the thyroid, and (c) thyroiditis—leakage of stored thyroid hormone from an inflamed gland. All three may be associated with eye signs including lid retraction, stare, and lid lag. Exophthalmos and diplopia, on the other hand, are specifically associated with Graves’ disease and are caused by an autoimmune process involving the extracocular muscles and orbital connective tissues.

Whenever the possibility of Graves’ ophthalmopathy is raised by complaints related to proptosis or diplopia, one must evaluate the patient for hyperthyroidism. Since the thyroid disease and the ophthalmopathy are separate components of the underlying auto-
Diagnosis of Graves' Ophthalmopathy

**Figure 6.30.**

In the immune process, the hyperthyroidism may precede, occur simultaneously with, or follow the ocular pathology. Therefore, the patient with proptosis or diplopia may have (a) diagnostic elevations of routine thyroid function tests, (b) "borderline" levels of thyroid hormone with or without hyperthyroid symptoms, or (c) normal thyroid tests. Each of these conditions will require a different diagnostic and therapeutic approach (Fig. 6.30).

**Overt Hyperthyroidism.** A simple and inexpensive set of routine thyroid function tests is usually all that is necessary to confirm the diagnosis of hyperthyroidism in a symptomatic patient. This includes measurement of the serum thyroxin (T<sub>4</sub>) level, measurement of the serum-binding capacity for (e.g., the T<sub>3</sub> resin-uptake test, T<sub>3</sub>RU), and calculation of a free thyroxin index (FTI). An elevated FTI in a patient with hyperthyroid symptoms plus ophthalmopathy is sufficient to make a diagnosis of Graves' disease.

The rationale for measuring both T<sub>4</sub> and T<sub>3</sub>RU is as follows: Most of the T<sub>4</sub> in serum is bound to large carrier proteins and therefore cannot enter the cells. The bound T<sub>4</sub> is in equilibrium with a tiny amount of free (and therefore active) hormone. Unfortunately, it is difficult to measure the free T<sub>4</sub> level directly; in addition, free T<sub>4</sub> is affected by variations in the concentration of the binding proteins. Assessment of the serum binding capacity for T<sub>4</sub> allows one to adjust for alterations in binding proteins. Multiplying the T<sub>4</sub> level by the T<sub>3</sub>RU yields the FTI, which roughly parallels the actual free T<sub>4</sub> in serum and, therefore, reflects the thyroid status of the patient.
BORDERLINE HYPERTHYROIDISM. When routine thyroid function tests reveal a T4 level and an FTI that are at the upper limit of normal or only slightly elevated, additional tests are required to evaluate the thyroid status. Two approaches are possible.

First, one can measure the serum level of thyroid-stimulating hormone (TSH). Ultra-sensitive TSH assays have become the standard in most clinical laboratories. Unlike older methods, these can reliably distinguish low normal levels from frankly low levels. Overproduction of T4 and triiodothyronine (T3) by the thyroid, as in Graves' disease, suppresses TSH secretion by the pituitary. A level of TSH below the normal range strongly suggests hyperthyroidism.

Second, one can measure the level of T3 in serum by means of a specific radioimmunoassay (RIA). T3 is the most potent thyroid hormone, but it circulates at much lower concentrations than T4. The level of T3 is routinely elevated in hyperthyroid patients; in Graves' hyperthyroidism, the T3 is usually elevated out of proportion to the T4 level. Therefore, in a patient with ophthalmopathy and a borderline high T4 and FTI, the detection of an unequivocal elevation of T3 by RIA would strongly support a diagnosis of Graves' disease.

EUTHYROID GRAVES' DISEASE. Graves' ophthalmopathy may precede all signs and symptoms of hyperthyroidism, occasionally by many years. Therefore, one may be faced with a patient with diplopia and/or exophthalmos but with a normal routine FTI and T4 by RIA. In these cases, ancillary tests may be used, or one may make the diagnosis by excluding other possibilities.

Graves' hyperthyroidism is caused by the production of thyroid-stimulating immunoglobulin (TSI) as part of an autoimmune process. Assays for TSI are now commercially available and, in theory, could confirm a diagnosis of Graves' disease even in the absence of biochemical hyperthyroidism. However, TSI may be detectable in only half of all patients with euthyroid Graves' ophthalmopathy. In addition, this test is expensive and difficult to perform. A more useful approach is to obtain a CT scan of the orbits; the demonstration of bilateral extraocular muscle thickening would favor a diagnosis of Graves' ophthalmopathy, whereas unilateral thickening or mass effect would suggest an alternative diagnosis.

TREATMENT

In all forms of thyroid disease, restoration of a euthyroid state is the ultimate goal. In regard to ocular involvement, treatment falls into both the medical and surgical categories.

MEDICAL TREATMENT. The aim of medical treatment is to minimize the patient discomfort that accompanies thyroid disease with ocular involvement. Severe periorbital swelling in the morning can be lessened somewhat if the patient sleeps with the head elevated. Corneal exposure owing to severe exophthalmos or paralysis of up-gaze is a problem, taping the lid shut or filling the palpebral fissure with some bland ointment at night can be of value. Lid taping may not be totally successful, however, because the partially open palpebral fissure may allow the tape to scrape the cornea. Should this problem occur, creating a moisture chamber by taping the edges of a piece of plastic wrap (e.g., Saran) to the skin at the orbital rim may afford some relief. The frequent use of some form of artificial tears can help to alleviate the foreign-body sensation as well as the symptoms of mild superficial punctate keratitis. Occasionally, the physician must resort to rather thick artificial tears in the form of a 1% solution of methylcellulose. I usually reserve this type of medication for the most severe cases, since it is rather sticky and esthetically repugnant to the patient.

Lid retraction is probably the sign most obvious to patients and the one that bothers them the most cosmetically. A method of treatment devised by Gay involves the use of topical guanethidine to create a chemical Horner syndrome with slight ptosis. Although this treatment aroused considerable interest in England, it is not standard accepted treatment in the United States. I have tried Gay's method on several patients but found it of little value in facilitating normal
lid function, particularly if the lid retraction was longstanding, with fibrotic changes in the levator tendon. The use of systemic steroids should be reserved for cases of diplopia in which the onset is rapid and progressive and for exophthalmos accompanied by significant inflammatory signs. The differentiation for the lid retraction in thyroid disease from Collier's sign in midbrain disease is usually not a problem when the entire clinical picture is considered. However, the lid retraction of thyroid disease stays elevated in down-gaze.

Surgical Treatment. In my opinion, surgical treatment should be restricted to cases in which the ocular involvement is severe.

In some patients, the eyes appear paralyzed with respect to up-gaze, when in fact, changes in the inferior muscles are restricting the upward movement of the globe. Surgical correction of this defect primarily involves weakening the depressor muscles, which are really the main offenders.

Surgical procedure to improve the appearance of patients with exophthalmos and lid retraction should be considered only if these two signs are stable. If they are, a small lateral tarsorrhaphy may be performed to reduce the prominent appearance of the eye. (A too-aggressive lateral tarsorrhaphy may give the eyes a squashed appearance.) Most patients are grateful for an improvement in their appearance, even though the lids have not been brought down to a fully normal position.

Cases of severe progressive exophthalmos with loss of vision, severe recurrent corneal ulcers, and exposure keratitis require careful treatment to prevent permanent loss of vision. In the past, a lateral Krönlein resection to decompress the orbit was the standard procedure. More recently, there has been some interest in combining the lateral Krönlein procedure with the creation of a surgical blowout fracture, thus, it is hoped, improving both the exophthalmos and the vision. On the other hand, many cases involving acutely progressive signs can be managed with systemic steroids, constant care of the corneal exposure problem, and a little patience.

Myasthenia Gravis

As Drachman et al. have so well pointed out, the pathologic differences between neuropathic and myopathic processes are not as clear-cut as was once believed. Myasthenia gravis is a chronic disease marked by weakness of the voluntary muscles, particularly the muscles involved in facial expression, mastication, swallowing, movement of the proximal limb girdle, and lid and ocular motility. Myasthenia gravis affecting ocular and lid motility can occur first as an isolated prosthesis owing to a weak levator muscle. Biopsy of the affected muscle is rarely helpful in diagnosing myasthenia gravis, since it seldom reveals the specific changes that occur as a result of this disease. Moreover, because the biopsy is performed on the levator tendon rather than the muscle itself, the test is often inconclusive.

Signs and Symptoms

Although myasthenia gravis affects many muscle groups, the ocular signs, particularly ptosis, are frequently the earliest indication of the presence of this disease. In fact, ocular symptoms are the only sign in at least 15% of patients. Ptosis without ophthalmoplegia may be present for some time before weakness of the extraocular muscles is detectable. This gives a false sense of the disease as if limited to only a few muscles. However, a biopsy of other asymptomatic uninvolved muscles will reveal a reduced number of receptors. This suggests that myasthenia gravis is a more diffuse immunologic disease that is expressed in different degrees in different muscle groups.

Some patients may mask or partially overcome a minimal ptosis (as in Horner syndrome) by contracting the frontalis muscle (frowning the brow). A patient suffering from myasthenia gravis is usually unable to frown the brow, since the frontalis muscle is just as weak as the levator muscle. A rare
exception occurs in cases of asymmetric myasthenia gravis. When patients with this condition attempt to contract the frontalis muscle, no correction for the ptosis occurs on the abnormal side. On the unaffected side, the contraction of the frontalis muscle causes the lid to retract. This action may lead to an erroneous diagnosis of thyroid myopathy.

The application of Hering’s law has been one of the more popular explanations for lid retraction, but it does not explain all cases. For example, cases that demonstrate lid retraction briefly after prolonged up-gaze are explained by postetamonic facilitation. Hering’s law also does not apply to those with lid retraction after demonstrating Cogan’s lid twitch sign. In those who show more permanent lid retraction, consider concomitant thyroid disease, since it appears in 10% of myasthenics. A patient who prefers fixing with the eye that has the ptotic lid may retract the other lid in an effort to lift the ptotic lid to adequately clear the pupil. This is an application of Hering’s law. A way to test this hypothesis is to manually lift the ptotic lid, so no innervation is necessary, and watch the retracted lid on the other side drop down.

The Tensilon test is helpful in the diagnosis of asymmetric myasthenia gravis, because after the injection of this drug, the lid on the ptotic side retracts immediately. With the Tensilon test, lid retraction may occasionally be observed on the normal side also, even though the patient is not contracting the frontalis muscle. This retraction indicates some bilateral, although asymmetric, levator weakness.

Up-gaze is the direction in which the patient initially develops symptoms of diplopia. Weakness of convergence, particularly during extensive reading, also causes symptoms to develop. These symptoms are frequently misinterpreted as signs that the patient needs stronger eyeglasses. Thus, many different strengths of eyeglasses, even some with prisms, are prescribed before myasthenia gravis is discovered as the true cause of the diplopia. In an attempt to strengthen weakening convergence, the entire near-reflex may be invoke, causing an increase in accommodation. This will cause a pseudo-mydriasis.

Since weakness of up-gaze may not be manifest on primary gaze, the patient should be instructed to rotate the eye well up and to sustain it in that position. Sustained up-gaze tends to make the ptosis clearly evident and may also reveal a diplopia that may not be obvious on simple inspection. Some physicians prefer to have patients move their eyes up and down rapidly and to open and close their lids quickly to fatigue the muscles. I find the sustained up-gaze maneuver to be equally successful. Blinks during the test may be sufficient to overcome the fatigue phenomenon. Patients may not be aware that they are suffering from weak ocular motility, since the ptosis that has led them to seek treatment may cover the pupil in extremes of up-gaze and therefore obscure the diplopia.

The worsening of the diplopia and ptosis seen on exercising the ocular muscles in myasthenia gravis does not occur in patients with partial third cranial nerve paralysis, regardless of how long they sustain a gaze in the field of action of the weak muscles.

The key sign differentiating myasthenia gravis from third cranial nerve paralysis is the absence of pupillary signs in myasthenia gravis. If pupillary signs are present, either two disease conditions are present or the diagnosis of myasthenia gravis is incorrect. If spasm of the near reflex causes paralysis of abduction, look for pupillary signs consistent with the diagnosis of third cranial nerve paralysis. The ophthalmic signs of myasthenia gravis are all external, sparing pupil and accommodation functions. There have been reports by Herishanu and by Dutton that describe pupillary fatigue and sluggish light response. These patients will also improve with anticholinesterase medications. If the extracocular muscles appear normal, electromyographic studies will still show abnormal saccadic velocities. The stapedius is rarely involved; its weakness causes hyperacusis.
In contrast to the good orbicularis muscle function but weak elevator muscle function typical of third cranial nerve paralysis, a patient with weak elevator muscles owing to myasthenia gravis may also have weak orbicularis muscles. Ignoring this fact, particularly in view of the possibility that the patient may have some difficulty with up-gaze, may lead to a severe corneal exposure problem if a surgical procedure for ptosis is attempted. (The orbicularis muscle can be tested by forcing the lids open after the patient has been instructed to squeeze them shut.)

The myasthenic crisis is one of the most feared complications of myasthenia gravis. Over-treatment of myasthenia gravis with cholinergic drugs results in clinical findings similar to those in the myasthenic crisis. The most serious complication of both conditions is respiratory paralysis, with tracheotomy sometimes required.

Myasthenia gravis takes three forms in infancy and childhood. All of them respond to anticholinesterase medication. All three also show similar and appropriate EMG responses of a decrement in motor units in response to repetitive nerve stimulation. Other features of the disease serve to differentiate the causes of all three types.

The neonatal form is seen in infants born of myasthenic mothers and is probably secondary to the transfer of antibodies to the acetylcholine receptors. Symptoms occur during the first day of life and in over 70% of cases, which differs from the original description. The most common sign is a poor sucking reflex despite an alert infant eager to eat. Eye signs, such as ptosis and motility disturbances, which are so common in adult-onset myasthenia, occur in only about 15% of neonatal myasthenia.

The second type is the congenital form, which probably results from a genetically transmitted disease rather than a circulating antibody. A prominent sign is extracocular muscle abnormalities with a minor amount of generalized weakness, which is the reverse of the neonatal form.

The third form is called Juvenile; its onset is usually after 1 year of age, and most cases occur after the age of 10. As in the adult form, ptosis and diplopia are the prominent initial features.

An autoimmune response is suggested as the mechanism in the juvenile and adult forms, and an antiacetylcholine receptor antibody can be identified in a high percentage of cases. No antibody to the acetylcholine receptor is found in the congenital form, which is genetically transferred.

The normal vesicle contains 10,000 acetylcholine molecules. In the Eaton-Lambert syndrome, the production and availability of acetylcholine as well as the number of molecules per vesicle are normal. The problem is in releasing these molecules to produce a muscle response. In myasthenia gravis, there is a reduction in the number of acetylcholine receptors because of antibody interference.

**EATON-LAMBERT SYNDROME.** Eaton-Lambert syndrome is a myasthenia gravidalike condition that occurs as a consequence of carcinoma elsewhere in the body. Isolated eye signs, however, have not been reported; therefore, Eaton-Lambert syndrome need not be considered if the presenting symptom is isolated ophthalmoplegia or isolated ptosis. The significant features are absent or decreased deep tendon reflexes, proximal muscle weakness, and increasing (rather than decreasing) muscle strength after voluntary exercise. Electromyography serves to definitely distinguish the Eaton-Lambert syndrome from true myasthenia gravis. In the Eaton-Lambert syndrome, a recruitment of motor units occurs with continual stimulation, rather than the dropout that occurs in myasthenia gravis.

The myasthenic syndrome of Eaton-Lambert affects many different muscle groups but, remarkably, spares the ocular muscles, unlike true myasthenia. There have been isolated reports of diplopia, but these are extremely rare. A remote effect of carcinoma has been the development of polyneuropathies that develop slowly over months and are predominantly distal, symmetric,
and sensorimotor in type. These patients develop severe weakness and atrophy, arexia, and sensory loss in the limbs. A mixed sensorimotor form of myasthenic syndrome is five times more common than a pure sensory form; usually, there is no remission and steady progression. This is seen in 2 to 5% of all patients with malignancy. Carcinoma of the lung accounts for 50% of the sensorimotor form and 75% of the pure sensory form. There is also a type that takes the form of polymyositis; this syndrome, secondary to carcinoma, is seen in about 15% of all patients with polymyositis and typically appears after the age of 50. The proportion of these cases owing to bronchogenic carcinoma is higher than in other forms of carcinoma. In cases of Eaton-Lambert syndrome not resulting from oat cell carcinoma, either the DR3 or HLA B8 antigen is found. Either of these antigens is also found in the Eaton-Lambert cases secondary to carcinoma. They appear to be immunologically connected and may have crossovers in therapy.

MYASTHENIA-LIKE SYNDROMES SECONDARY TO MEDICATION. The mechanism of drug-induced myasthenic syndromes varies from drug group to drug group. With d-penicillamine, an antiacetylcholine receptor antibody develops. With antibiotics such as neomycin, streptomycin, kanamycin, polymyxin B sulfate, dihydrostreptomycin, viomycin sulfate, and colistin sulfate, neuromuscular blocking effects occur for other reasons. These effects may not be related only to the use of these medications; they have been more frequently reported after general anesthesia. They also may not necessarily be related to the stress of surgery but rather to other factors influencing neuromuscular transmission, such as neuromuscular blocking agents (e.g., succinylcholine), or to a decrease in serum and tissue calcium.

As ophthalmologists, we rarely see serious systemic problems develop from the medications we prescribe. However, timolol can be absorbed enough to change pulse rates and cause psychiatric symptoms. This drug, which is a beta-adrenergic blocker, can also precipitate congestive heart failure, hypotension, and asthma. There are also cases of timolol making myasthenia gravis worse; the exact mechanism of this effect is not known, although beta-adrenergic blockers are known to have a depressor effect on the neuromuscular junction.

TESTS FOR MYASTHENIA GRAVIS

When evaluating patients suspected of having myasthenia gravis, the major procedure is the Tensilon test, which is specific for myasthenia gravis. Tensilon is an intravenous medication that competes with acetylcholine for the enzyme acetylcholinesterase at the myoneural junction. This allows increased effectiveness of acetylcholine at that junction and improvement of muscular function. There have been infrequent reports of a positive Tensilon test with compressive lesions. These patients also have improved symptomatology with anticholinesterase medications. However, results of the Tensilon test are not always positive, even in obvious cases. It is also true that the Tensilon test may not be positive at the onset of the disease but may become positive as the condition progresses. For this reason, the test should be repeated at intervals if results are negative early in the course of the disease.

The Tensilon test should be done in three stages. Initially the patient should be free of all cholinesterase inhibitors. The patient should then be given an injection of atropine to prevent undue vagal responses. I do not do this routinely, and a recent survey of neuro-ophthalmologists revealed that most do not use atropine but have it on hand. The amount given is usually inadequate and is given too close to the actual test to be of any therapeutic value. The first part of the test is to give a 0.1-mL dose of Tensilon intravenously and observe the reaction over 2 to 3 minutes. Patients may experience salivation, mild sweating, perioral vesiculation, and nausea, but rarely bradycardia and hypotension. If no change is noted in the lid or motility defects, then more Tensilon is given. The best response to look for is in the lid position rather than motility. Fascicula-
tions of the lids is common and does not represent a positive response. Instead of giving 0.9 mL in one bolus, it is better to give it in 0.2-mL increments at 30-second intervals. Occasionally with the higher 0.9-mL dose, the defects appear to get worse, not stay the same or get better. Sometimes an improvement in motility abnormality may not reflect improvement in a myasthenic muscle but rather weakening of its antagonists. The reason for this is that the ocular muscles have two types of motor endplates, called en grappe and en plaque. In myasthenia gravis, one type of fibers may be affected more than the other. In this situation, one set reacts positively to Tensilon and the other is made worse by Tensilon.

Since a positive response to Tensilon usually occurs in about 30 seconds and is over within 1 to 3 minutes, the precise ocular function to be tested should be determined before the testing procedure is begun. A total ocular motility examination should not be attempted during the short period in which Tensilon is effective, since the key signs of a positive reaction may be missed. Ptosis is the most obvious sign of myasthenia gravis, improvement in this condition is the sign to look for during the first 2 or 3 minutes of the testing procedure. A positive response to Tensilon is usually diagnostic of myasthenia gravis, although false-positive tests have been rarely reported in pontine glioma, orbital apex syndrome, polymyositis, ocular myositis, and botulism.

The Tensilon test is not positive nearly as often as we suspect the diagnosis of myasthenia gravis. For confirmation, Miller, Morris, and Maguire use intramuscular neostigmine with detailed orthoptic measurements before and during the test. This procedure in association with electromyographic studies is said to yield a higher number of positive results for myasthenia than Tensilon alone.

Before Tensilon became available, small doses of curare were used to test for myasthenia gravis. Patients with myasthenia gravis are supersensitive to curare; however, this difficult and dangerous drug was all but abandoned with the advent of Tensilon.

Another once-popular test that has fallen by the wayside involved the use of quinine—a drug that made the myasthenic process worse. Although quinine is no longer used in the testing procedure, this drug may still subtly alter the results of other tests, because many patients drink quinine water or take quinine compounds, which aggravate the myasthenia gravis symptoms. Therefore, unless history taking includes a specific question about the use of quinine in any form, the physician may remain unaware that such a practice is making the myasthenia gravis worse or at least making treatment more difficult. The theory behind quinine ingestion is that the drug lessens the sensitivity of the motor endplate and thus holds the firing of the muscle neurofibrils to a minimum. It is commonly given for night leg cramps.

The Tensilon test may also be done in conjunction with tonography. In fact, this modification is recommended for patients who respond negatively to the Tensilon test. In this procedure, the patient is given an intravenous drip of normal saline solution. The tonometer is placed on the eye, and the normal slope of the tonography curve is followed. A small amount of saline solution is then injected into the tubing, following which, the slope of the curve is again observed. The saline injection should cause no change. Tensilon is now injected into the same tubing. If the muscles are normal, no reaction occurs. A positive reaction, which consists of a sudden increase in the pressure in the eye, owing to cocontraction of the extraocular muscles, is diagnostic of myasthenia gravis.

Another variation of the Tensilon test involves cooling the eye muscles to 29°C for several minutes to decrease the activity of acetylcholinesterase. This is done by putting ice in a rubber glove and placing it over the closed eye for 2 minutes. Then the Tensilon test is repeated. This procedure increases the chances for a positive response.

In recent years, an assay for antiacetylcholinesterase receptor antibodies has become available. This assay is positive in 88% of generalized myasthenia gravis cases but
drops to a disappointing 60% in purely ocular cases.

Investigation of the thymus gland is also essential because of its relationship to the disease. The removal of the thymus gland except in cases of thymoma is still controversial. A CT scan of the thymus gland sometimes can be too good and give positive results that are not confirmed with a thymic gland biopsy. Therefore, a linear tomogram can be useful.

Electromyographic studies can be quite useful. The problem in testing ocular muscles or the levator is a difficult technique. Failure to get a record may be the result of placing the recording needle in the tendon rather than the muscle. There are several types of recording techniques. There is evaluation of neuromuscular jitter by single fiber recording and a repetitive maximal motor nerve stimulation technique.

The affected fibers are distinctive with a Gomori trichrome stain and are called ragged red fibers. This results from a deposit between myofibrils and adjacent to the plasma membrane of mitochondria.

**TREATMENT**

In the treatment of myasthenia gravis, anticholinesterase medications, such as Prostigmin, are a group of drugs. The main problem with this group of drugs is the possibility of an overdose and consequent cholinergic crisis. Moreover, the use of these drugs is particularly difficult when the myasthenia gravis is confined to the ocular muscles. As a result, a therapeutic dose for the ocular muscles may be too toxic for normal skeletal muscles.

Steroids are now being used to treat advanced cases of myasthenia gravis that are not responding well to anticholinesterase medication. Such patients are started on steroids in daily doses of up to 100 mg per day and maintained at that level until symptoms stabilize. The dosage is then reduced to a minimal amount on an alternate-day program until the medication can be discontinued, perhaps after many months.

Thymectomy in women or removal of solitary thymomas is still appropriate and efficacious therapy. In some clinics, thymectomies are being performed with good success even on men without thymomas.

In myasthenic patients, a surgical procedure for ptosis should be approached with extreme caution. A perfect ptosis repair may leave the cornea exposed during the day, because of a weak orbicularis muscle, and at night, because of inadequate Bell's phenomenon owing to ophthalmoplegia. If the ptosis is severe and the lid covers the pupil, a surgical procedure may be considered; however, the amount of ptosis should be stable, the degree of Bell's phenomenon reasonable, and the ptosis repair less than complete.

**Progressive External Ophthalmoplegia**

Once a myopathy with ptosis as the most prominent feature has been diagnosed, the differential diagnosis is essentially either myasthenia gravis or progressive external ophthalmoplegia (PEO).

The onset of PEO can be between infancy and 50 years of age, but PEO commonly begins in persons over 20 years of age. Frequently, a family history of this condition exists. Because of the variable expression of the disease, examine other family members for evidence of the disease. The initial family history is frequently negative.

The pigmentary retinopathy is not like retinitis pigmentosa. A bone spicule appearance and equatorial location is not seen in the Kearns-Sayre syndrome. This pigmentary retinopathy is more like salt and pepper and is located at the posterior pole. The ERG is not as abnormal as in retinitis pigmentosa patients.

As in myasthenia gravis, a long interval may elapse between the development of ptosis and involvement of the extraocular muscles. The muscles controlling up-gaze are the first group involved in both myasthenia gravis and progressive external ophthalmoplegia.
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ais muscle, and at
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y be considered.
ptosis should be
phenomenon reap-
air less than com-
nia gravis and PEO. In contrast to myas-
nia gravis, PEO is associated with a nega-
tive Tension test and the absence of diar-
nal variation or relation to fatigue.

The two syndromes discussed in the fol-
owing paragraphs are not simply other
forms of PEO. Although they all have PEO
part of the clinical picture, they also have
abnormalities of the nervous, cardiac, and
hematopoietic systems that differentiate
them from PEO. When PEO is diagnosed, it
is essential that these other diseases be ruled
out because they are more serious than PEO
and are, in fact, life threatening.

Oculopharyngeal dystrophy of Victor,
which may occur sporadically or be inher-
ted as a dominant trait, involves external
ophthalmoplegia and pharyngeal weakness.
Facial and limb girdle weakness have also
been reported in association with this condi-
tion.

Kearns-Sayre syndrome is made up of
PEO, retinitis pigmentosa, and heart block in
young people. Therefore, in all cases of
PEO, a good opthalmoscopie examination
and electrocardiogram should be performed;
if the PEO is associated with the Kearns-
Sayre syndrome, death from heart block is a
possibility.

Hassen-Kornzweig syndrome consists of a
broad mixture of signs, one of which in-
cludes PEO. Diarrhea owing to poor absorp-
tion of lipids from the gastrointestinal tract
may precede the onset of PEO by a few
weeks to several years. Patients with this
syndrome are also deficient in serum cholesterol
and beta-lipoproteins. Pigmentary degenera-
tion of the retina is seen in some cases. Some
patients have a positive Babinski reflex, sen-
ory loss, ataxia, optic atrophy, and an in-
crease in cerebrospinal fluid protein. Acan-
thocytosis of the red blood cells is another
laboratory sign that is of assistance in diag-
nosing Hassen-Kornzweig syndrome.

Raffson syndrome, which is rather uncom-
mon, should be suggested by a combination
of PEO, retinitis pigmentosa, and polyneu-
ropathy. Presence of these conditions should
prompt a test for phytanic acid level, which
is elevated in this disorder. Less significant
diagnostic signs are cerebellar ataxia, hear-
ing loss, anosmia, ichthyosis, and epiphysyal
dysplasia.

**Pseudotumor of the Orbit**

In addition to chemosis, pain, and exoph-
thalmos, pseudotumor of the orbit has an in-
flammatory sign similar to that which occurs
in orbital cellulitis. The congestion of the
vessels is usually not as prominent as in cel-
ulitis, but the difference is difficult to evalu-
ate. Pseudotumor of the orbit is usually uni-
lateral, and the ophthalmoplegia is usually
marked. Onset can occur at any age, but I
usually see it in women between 30 and 50
years of age. Occasionally, the inflammatory
signs are minimal, and diplopia is present,
with involvement of only one muscle and
pain on motion—a combination that makes
diagnosis more difficult. In early cases of
pain in the orbit, exophthalmometer read-
ings on each visit may reveal a gradual de-
velopment of exophthalmos. This changing
pattern facilitates diagnosis of pseudotumor
of the orbit before the frank signs of this
condition become obvious. The usual diffe-
rential diagnoses of cellulitis or an infiltrat-
ing lesion must be ruled out because no spe-
cific tests are available to establish the presen-
tence of these diseases. On the other
hand, the possibility of a lymphoma of the
orbit should be considered.

Patients with pseudotumor of the orbit re-
spond very well to systemic steroids; how-
ever, discontinuance of steroid therapy often
leads to recurrence of the disease. I have
had to keep many of my patients on steroid
medication for months, and in some cases
up to a year. Even when steroid medication
is apparently withdrawn successfully, the
disease can recur months or years later.

**Myositis**

Myositis has the same signs and symptoms
as pseudotumor of the orbit, and it is treated
with steroids with the same degree of effectiveness.

**Trichinosis**

Trichinosis is uncommon in the United States, and in the few cases that occur, a carefully taken history will reveal that the patient has recently eaten pork. In addition to the gastrointestinal problems and eosinophilia that are symptomatic of trichinosis, the main ocular symptoms are periorbital swelling, marked pain on movement, and, occasionally, diplopia. Examination of the globe itself does not reveal the inflammatory signs usually associated with pseudotumor or myositis. Petechial hemorrhages of the conjunctiva are frequently seen.

**Myotonic Dystrophy**

Although diplopia is not a sign of myotonic dystrophy, this disease is discussed in this chapter because it is a myopathic process. Patients suffering from myotonic dystrophy frequently have ptosis, which is also an early sign of myasthenia gravis and PEO. Therefore, prior to the onset of diplopia in ptotic patients, the possibility of myotonic dystrophy should be considered in the course of the differential diagnosis.

Ptosis is certainly not the earliest sign of myotonic dystrophy. However, in known cases, ptosis is part of this syndrome and should be so regarded in the absence of other signs of third cranial nerve paralysis, such as pupillary involvement. Restriction of gaze occurs less frequently but is also a sign of myotonic dystrophy. Other associated eye signs are a positive Schirmer's test, keratitis sicca, ocular hypertony averaging 10 mm of mercury, decreased corneal sensitivity, decreased dark adaptation as shown by the electroretinogram, and, in a small number of cases, a starlike retinal pigmentary degeneration.

The handclasp sign is easily elicited and dramatic. After a firm handshake, the patient is unable to release his or her grasp. Similarly, after forced closure of the lids, the patient may be unable to open the eyes on command (or at will).

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Neuro-otology is a subspecialty that encompasses disorders of the peripheral and central auditory and vestibular systems. Neuro-otology is a field similar to neuro-ophthalmology in that it is defined by its practitioners. Most neuro-otologists have come from the field of otorhinolaryngology. The focus has been on the organs that are presumably abnormal, that is, the ear. This emphasis resembles the early history of neuro-ophthalmology, which concentrated primarily on the eye; only later, when central visual and ocular motor connections and symptomatology were considered, the field began to involve those dealing with the brain, namely neurologists. Similarly, neuro-otology initially concentrated upon the primary functions of the ear, vestibular and auditory, without reference to central auditory processing within the central nervous system (CNS) or to those neurologic conditions that could produce unsteadiness, dizziness, and vertigo, as well as alterations in hearing. When the multiple symptoms of dizziness or disequilibrium are considered, it is clear that there are neurologic and systemic conditions that can produce disorders of balance. Thus, neurologists have become increasingly involved in the evaluation of patients reporting dizziness. Just as retinal disorders remain primarily the province of the ophthalmologist, so hearing disorders, which are primarily peripheral, remain largely the province of the otolaryngologist.

We have divided this chapter into two major sections: the first on vestibular disorders, and the second on auditory disorders. Each section reviews the essential aspects of the history and the office examination. Because vestibular symptoms are often accompanied by auditory complaints, neurologists who choose to deal with dizzy patients should be familiar with both vestibular and auditory testing. Therefore, we include a brief review of pertinent tests for vestibular and auditory disorders. Finally, we introduce therapeutic strategies for patients with dizziness and hearing loss.

VESTIBULAR DISORDERS

History

Vertigo, strictly defined, refers to an hallucination of movement. When the symptom complex is one of spinning or rotation, the cause is almost always the inner ear or peripheral vestibular system. Although some patients experience a definite sense of environmental spin or self-rotation, most do not present solely with true spinning vertigo. The most common complaint is dizziness, a term that represents a variety of symptoms (Table 7.1). The examiner should elicit an exact description of what the patient is experiencing. Is it a spinning sensation that could be characterized as vertigo, pointing
Table 7.1. SYMPTOMS ENCOMPASSED BY THE TERM DIZZINESS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Term</th>
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<tbody>
<tr>
<td>Vertigo</td>
<td>Bouncing</td>
</tr>
<tr>
<td>Unsteadiness</td>
<td>Falling</td>
</tr>
<tr>
<td>Imbalance</td>
<td>Swimming</td>
</tr>
<tr>
<td>Spinning</td>
<td>Staggering</td>
</tr>
<tr>
<td>Floating</td>
<td>Weaving</td>
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<tr>
<td>Painting</td>
<td>Moving</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>Pawing out</td>
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<tr>
<td>Swaying</td>
<td>Tiltiing</td>
</tr>
<tr>
<td>Twisting</td>
<td>Leaning</td>
</tr>
<tr>
<td>Blurring vision</td>
<td>Rocking</td>
</tr>
<tr>
<td>Disorientation</td>
<td>Oscillating</td>
</tr>
<tr>
<td>Poor equilibrium</td>
<td>Rolling</td>
</tr>
</tbody>
</table>

to the peripheral vestibular apparatus? Is it a sensation of falling without rotation? Is it a sensation of unsteadiness or imbalance? Is there a particular direction in which the patient tends to fall? When the patient's complaint is actually incoordination or clumsiness, the cause may be cerebellar dysfunction or peripheral neuropathy. When the symptom complex is "lightheadedness" or "swimming-headedness," the examiner should think of presyncope or syncope and consider systemic factors such as postural hypotension, vasodepressor syncope, or cardiac arrhythmia.

After trying to define the true qualitative nature of the symptom complex, one must proceed to a consideration of temporal factors. Is the patient's experience a continuous one? Are there episodes of severe symptomaticity with symptom-free intervals? If the symptoms are episodic, do they occur only when the patient is upright?

Patients often have difficulty describing their symptoms. Initially, it is important to have patients provide their own descriptions before the examiner biases the outcome by suggesting descriptive phrases. Some patients are asked to describe their symptoms without using the word "dizziness" cannot further characterize the symptoms.

In addition to determining whether the symptom complex is episodic, one should define duration, length of symptoms, and any associated complaints such as tinnitus, hearing loss, double vision, slurred speech, numbness, or paralysis. A history of episodic disequilibrium accompanied by diplopia, slurred speech, perioral numbness, dimming of vision, and occasional drop attacks would suggest transient vertebrobasilar ischemia. Are there associated symptoms such as headache, and have these occurred at earlier times? If the patient experienced severe episodes of imbalance in early life, followed by occipital or generalized headaches, especially throbbing, the history would suggest basilar artery migraine. Did the dizziness follow head trauma, a systemic illness accompanied by aminoglycoside antibiotic therapy, or a mild upper respiratory infection? Episodic positional vertigo with brief episodes of spinning while turning over in bed suggests a common condition, benign paroxysmal positional vertigo (BPPV). Did the symptom complex occur following ear surgery or infection, deep-sea diving, or a concussive blow to the ear? Such a history, with or without hearing loss, would suggest a perilymph fistula.

There are a significant number of patients whose balance disorders are aggravated or even caused by anxiety. If the disequilibrium or dizziness is of long duration, it is often difficult to tell whether the symptom complex is caused by anxiety or depression or whether the anxiety or depression are secondary to the dizziness. One always tries to make a positive diagnosis of a neurosis or chronic anxiety disorder on the basis of other symptomatology and historic information. There may be a history of previous episodes of serious depression or anxiety attacks, and these should be elucidated before concluding that dizziness is secondary to anxiety.

Neurologists and neuro-otologists follow a large number of patients with chronic vertiginous sensations who remain undiagnosed. These patients complain of constant or intermittent disequilibrium, often aggravated by position change, as well as by visual stimuli such as moving traffic and patterned wallpaper or by passing food displays in supermarkets. Many of these patients have become agoraphobic; they hesitate to leave their homes and particularly fear driving a car that
will be passed by other automobiles. Some of these persons have had a single attack of acute peripheral vestibulopathy but have never made appropriate central compensation or adapted to their peripheral abnormality. Although mechanisms for compensation remain unclear, most patients, particularly those younger than 30, rapidly recover from an acute peripheral vestibulopathy. Elderly patients or patients with a previously existing intrinsic brainstem abnormality will rarely make adequate compensation for an acute peripheral vestibulopathy. These patients continue to complain of severe disequilibrium and have exacerbated symptoms with a variety of visual inputs. They often have completely normal examinations and vestibular tests.

Figures 7.1 and 7.2 illustrate what might happen following an acute peripheral vestibular abnormality. In some individuals, as diagramed in the right-hand panel of Figure 7.2, there is decreased ability to compensate for peripheral vestibular abnormality. One possibility would be a congenital inability to make CNS compensation, but others include (a) an acquired central inability to compensate due to CNS lesions, as from multiple sclerosis or previous brainstem stroke; (b) a fluctuating peripheral vestibular problem, as in Ménière’s disease; (c) relative inactivity without much afferent input; and (d) a peripheral vestibular apparatus providing inaccurate, although nonfluctuating, afferent information. Careful history taking may reveal childhood meningitis, a remote head injury, or particular susceptibility to motion sickness in childhood. During history taking, these possibilities should be explicitly sought.

**Examination of the Dizzy Patient**

**GENERAL EXAMINATION**

Every patient with a disorder of equilibration or true vertigo should have a screening general physical examination. Patients who

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**Figure 7.1.**

*Left:* Vestibular afferent input during normal horizontal head rotation to the right. Increased firing rate from right peripheral vestibular apparatus. Ocular deviation shows slow-phase deviation to the left. *Nav* vestibular nuclei. (Adapted from Baxi 1984 and Daroff 1977.) *Right:* Acute left peripheral vestibulopathy with resultant acute vestibular sensation simulating head rotation to the right. Slow-phase ocular deviation to the left (small arrow) and fast phase of nystagmus to the right (bold arrow) and away from the side of the peripheral vestibular injury.
Normal central compensation

Abnormal central compensation

CNS Plasticity

(No vertigo, no spontaneous nystagmus)

(Vertigo ± spontaneous nystagmus)

**Figure 7.2.**

*Left.* Normal adaptation for prior left peripheral vestibulopathy. Despite a reduced firing rate from the left side, the central nervous system (CNS) has compensated for the disparity, and there is no nystagmus or vertigo. *Right.* Abnormal compensation for prior left peripheral vestibulopathy. The patient continues to experience vertiginous sensations and may have nystagmus with a fast phase to the right (solid arrows).

-exhibit symptoms suggesting presyncope or actual syncope must have particular attention paid to their cardiovascular systems. Not only should patients have their blood pressure measured in the resting, sitting, and standing position, but they also should have their blood pressure measured at 1-minute intervals up to 5 minutes after assuming the upright position, as delayed postural hypotension is not uncommon. Exercise-induced hypotension is an important observation and should lead to consideration of conditions such as the Shy-Drager syndrome, diabetic autonomic neuropathy, and cardiac defects such as aortic stenosis and obstructive cardiomyopathy. Whenever episodic symptomatic episodes are associated with a question of alteration of consciousness or lightheadedness, particular attention should be paid to the possibility of cardiac dysrhythmia. Most patients with cardiac dysrhythmias do not report associated sensations of irregular heartbeat, thumping in the chest, or fluttering; however, examination may reveal an irregular cardiac rhythm or cardiac murmur.

During the general examination, attention should be paid to systemic conditions that could give rise to a general feeling of malaise or weakness interpreted by the patient as a disorder of balance. Conditions leading to sudden syncope may be revealed on the general physical examination. Patients with suspected extracranial vascular disease not only should have the head and neck auscultated for bruits, but also should have a general examination of the peripheral vascular system, including the cranial and carotid pulses and evaluation for significant varicose veins that might lead to venous pooling and hypotensive episodes.

The neurologic examination should be directed by the patient's history. In patients with clear-cut episodic vertigo, the neurologic examination will usually be normal, with the exception of the ocular motor findings to be described. However, when the patient's symptom complex is more vaguely
defined and includes disequilibrium or unsteadiness, particular attention must be paid to examination of the motor system, reflexes, sensation, and cerebellar function.

All patients with undiagnosed disorders of equilibration, however described, should have a complete neurologic examination. Portions of the neurologic examination are described briefly below, followed by suggestions of which entities might cause abnormality.

MENTAL STATUS EXAMINATION

Signs of diffuse alteration in consciousness may suggest overmedication, metabolic encephalopathy, or an acquired debilitating process. Focal disturbances in intellectual function, such as a subtle aphasia, may lead to the consideration of multi-infarct dementia with accompanying brainstem infarctions or of a mass lesion in the dominant hemisphere.

CRANIAL NERVE EXAMINATION

Alterations in visual sensory function can be a primary or exacerbating cause of disequilibrium. Even the recent addition of a new refractive correction, particularly lenses for presbyopia, may be an added or primary cause of imbalance. Visual field defects such as unsuspected bitemporal or homonymous field defects from infarcts or tumors may cause patients to run into objects or feel disoriented in space. The presence of papilledema or absent venous pulsations on funduscopy should be an immediate clue to raised intracranial pressure. Altered corneal sensation can be the clue to a previously unsuspected cerebellar pontine angle mass. Simple auditory screening tests may reveal a previously unsuspected hearing loss and should always lead to formal audiologic testing. Abnormalities on examination of cranial nerves IX through XII raise the differential diagnosis of multiple cranial neuropathies caused by collagen-vascular disease, tumors of the base of the skull, or nasopharyngeal carcinoma.

OCULAR MOTOR EXAMINATION

The presence of spontaneous or induced nystagmus is of critical importance in the diagnosis of peripheral, central, or systemic causes of imbalance. Nystagmus types of particular note are described in the section on the directed neuro-otologic examination. Defective downward gaze is often the first sign of progressive supranuclear palsy, a condition often accompanied by disequilibrium. The presence of asymmetric slowing of the adducting eye indicating an internuclear ophthalmoplegia is a subtle but important clue to the presence of brainstem multiple sclerosis, brainstem infarction, or mass lesion of the posterior fossa.

MOTOR SYSTEM EXAMINATION

The examination of motor function can reveal focal or diffuse weakness indicating CNS or neuromuscular disorders. A subtle hemiparesis may be the true cause of the patient's balance complaint. Diffuse hyperreflexia reflects cerebellar or spinal cord dysfunction and, in combination with cerebellar abnormality, might lead to the diagnosis of a spinocerebellar degeneration.

SENSORY EXAMINATION

Examination of sensation can reveal a significant peripheral neuropathy leading to a diagnosis of diabetes or toxic neuropathy. Selective loss of sensory modalities conveyed by the posterior column, such as proprioception and vibration, may indicate that the patient has vitamin B12 deficiency or early tabes dorsalis. Such patients are relatively steady during the Romberg test with eyes open but rapidly lose balance and fall in any direction when visual compensation is eliminated by eye closure.

CEREBELLAR SYSTEM EXAMINATION

Obvious limb or body ataxia should be an immediate clue to the CNS abnormality as the cause for the patient's imbalance. Unsteadiness during Romberg testing with eyes open and only slight exaggeration on eye closure indicates a cerebellar abnormality. Cerebellar dysfunction is usually accompanied by abnormality during gait testing or even difficulty maintaining balance while seated. Patients with symptomatic peripheral
vestibulopathy tend to fall toward the side of the abnormality during eye closure with the head straight ahead. Unilateral limb ataxia is almost always an indicator of focal posterior fossa abnormality, such as infarct, demyelination, abscess, or tumor.

DIRECTED NEURO-OTOLOGIC EXAMINATION

A directed neuro-otologic examination should be performed, particularly when there are abnormalities of the auditory, ocular, motor, and vestibular systems. Audiologic testing is discussed below. During the neurologic examination, there may be subtle signs of peripheral vestibular dysfunction indicated by nystagmus. On external examination, the nystagmus fast phase is away from the ear with the vestibular abnormality. During the funduscopic examination, particular attention should be paid to the movement of the optic disc. A rhythmic, subtle, horizontal, slow- and fast-component nystagmus is frequently present in patients with new peripheral vestibular dysfunction. The nystagmus is brought out by reducing fixation during the funduscopic examination. For example, with the patient staring at a dimly lit target in the distance, the presence of a slow ocular drift to the left and a fast phase to the right of the optic disc should indicate to the examiner that the patient has a subtle left beating nystagmus in the primary position. The findings indicate a right peripheral vestibular abnormality. Fast, upward, rhythmic, vertical movement of the optic disc seen during funduscopic examination signifies the presence of downbeat nystagmus. The examiner should then search carefully for the presence of downbeat nystagmus during examination of oblique and downward gaze. The need to search for presence of any type of nystagmus during the directed neuro-otologic examination cannot be overemphasized. The directed neuro-otologic examination should include a detailed otoscopic examination of the external auditory canal and the tympanic membrane. The presence of a retracted or scarred eardrum suggests prior middle ear infection. The presence of a blue mass behind the tympanic membrane points to a glomus jugulare tumor.

The patient should be tested for balance during standing, walking, and turning, and for the presence of past-pointing. Past-pointing is a tendency for the repetitively elevated and lowered outstretched fingers to drift unidirectionally. Past-pointing is a clear indication of tonic imbalance in the vestibular system. If, during Romberg testing, the patient tends to fall in a certain direction, can this direction be altered by changing head position? The ability to alter the direction of the fall during Romberg testing by head turning indicates a peripheral vestibular abnormality. For example, a patient with an acute left peripheral vestibulopathy will tend to fall to the left during eye closure with the head straight ahead, but will fall backward (toward the abnormal ear) with the head turned left, and will fall forward during eye closure when the head is turned to the right.

The physician should test for the presence of an intact vestibulo-ocular reflex (VOR) and observe whether the patient is able to maintain steady ocular fixation during funduscopic examination as the head is gently rotated from side to side. The patient with an intact VOR can still maintain fixation on distance objects during head turn. The absence of this ability produces an apparent nystagmus, most easily observed during funduscopic examination, which is good evidence for a defective VOR. A different test of vestibulo-ocular control is for the patient to fix on his or her own thumb while rotating the head in the same direction. During this maneuver, the patient must suppress the vestibulo-ocular response to permit combined head and eye tracking. The loss of this ability may be a subtle clue to cerebellar system dysfunction. The patient should also be examined for the presence of nystagmus when visual fixation is reduced by wearing Frenzel glasses, which blur the patient's vision. The lenses also magnify the eye, allowing better detection of low-amplitude nystagmus.

If the patient has no cervical problems, a head-shaking test can be performed. The pa-

Differe
t of Dizziness

Because the symptom of dizziness often is misinterpreted as presyncope, significant dizziness is usually classified into the categories of peripheral, central, and mixed. There is a term central dizziness, used to describe the symptoms that are due to dysfunction of the cerebellum, brainstem, or peripheral vestibular system. The terms peripheral dizziness, or vertigo, refers to those symptoms that are due to dysfunction of the peripheral vestibular system. The term central dizziness, or cerebellar dizziness, refers to those symptoms that are due to dysfunction of the cerebellum, brainstem, or both.

Peripheral dizziness is usually caused by lesions of the vestibular nerves, which are part of the eighth cranial nerve. Lesions of the vestibular pathway can be caused by lesions of the eighth cranial nerve, which is a sensory nerve that innervates the inner ear. Lesions of the vestibular pathway can also be caused by lesions of the cerebellum, which is a structure in the brain that is involved in the control of movement. Lesions of the cerebellum can be caused by a variety of conditions, including tumors, infections, and degenerative diseases.
Differential Diagnosis of Dizziness

Because ongoing or episodic conditions accompanied by vertigo, unsteadiness, or presyncope are produced by multiple and often subtle causes, it is not surprising that a significant number of patients cannot be readily diagnosed. A major differential diagnostic classification would include broad categories such as (a) peripheral vestibulopathy, (b) central neurologic disorders, and (c) systemic or medical conditions. There is some ambiguity in the use of the term central, which has been used by otolaryngologists to include causes that are central or proximal to the vestibular end-organ and therefore include the vestibular portion of the eighth nerve. Neurologists, however, consider conditions that affect the vestibular nerve, such as tumors, as peripheral in location because they are on a cranial nerve and are extraaxial. Because masses or neoplasms can enlarge to involve other structures in the cerebellopontine angle, particularly the brainstem, conditions that affect the eighth nerve are discussed for convenience in the central category.

Peripheral Causes of Vertigo

Peripheral causes result from dysfunction of vestibular end-organs (semicircular canals, utricle, and saccule) (Table 7.2).

**PERIPHERAL VESTIBULOPATHY**

Peripheral vestibulopathy encompasses terms such as vestibular neuritis, labyrinthitis, and viral neuro labyrinthitis. Such terms imply an inflammatory mechanism, which is unwarranted. Vestibular neuritis, strictly speaking, is characterized by single or recurrent sudden episodes of true vertigo lasting from hours to days and often associated initially with vomiting. When the condition is associated with hearing loss, the entire labyrinth is assumed to be involved, and the term labyrinthitis is used. Despite this technical distinction, many neuro-otologists, otologists, and neurologists use the terms vestibular neuritis and labyrinthitis interchangeably, whether or not auditory symptoms are present. In such patients the vertiginous sensation may be provoked by head movement, but not necessarily by a particular head position.

Whether isolated viral involvement of the vestibular nerves is a cause of acute or episodic vertigo is controversial. Many prefer the term acute or recurrent peripheral vestibulopathy. In the acute phase, many patients present with sudden severe vertigo, nausea, and vomiting, without any hearing disturbance or facial weakness. The acute symptoms usually resolve in a few days to a week but may recur in weeks or months. If true vertigo is part of the symptom complex, the condition is most likely to be associated with some disorder of the peripheral end-organ. However, patients with either acute peripheral vestibulopathy or, more commonly, recurrent attacks may experience...
only a sensation of lightheadedness or floating or a feeling of "walking on tennis balls." Even if the patient has had hundreds of episodes, it is important to determine whether any of them were associated with spinning vertigo. Over time, the nature of the patient's symptom complex may change, even with peripheral vestibulopathy, from vertiginous sensations to those of pure unsteadiness or disequilibrium.

Epidemic and seasonal outbreaks of acute vertigo have suggested an infectious origin due to viral disease, but this largely remains unproved. Viral labyrinthitis can also be part of a systemic viral infection such as mumps, measles, infectious mononucleosis, or upper respiratory tract viral infections. Isolated viral infections of the labyrinth are also believed to cause the sudden onset of hearing loss and/or vertigo in both children and adults. Otitic herpes zoster is an infection characterized by pain in the ear, followed in 1 to 10 days by a vesicular eruption in the external ear. When the seventh and eighth nerves are affected, there is a combination of facial weakness, hearing loss, and vertigo known as the Ramsay Hunt syndrome. Whenever vertigo is associated with severe ear pain or facial pain, one must consider this possibility. A dysesthetic area of skin may precede by many days the appearance of the skin eruption.

**Table 7.3.** CHARACTERISTICS OF PERIPHERAL VS. CENTRAL POSITIONAL VERTIGO

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>Peripheral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (time to onset of vertigo or nystagmus)</td>
<td>0-40 seconds (mean 7.8)</td>
<td>No latency</td>
</tr>
<tr>
<td>Duration (duration and symptoms of single episode)</td>
<td>less than 1 minute</td>
<td>Begin immediately</td>
</tr>
<tr>
<td>Fatigability (fatigability)</td>
<td>Yes</td>
<td>Symptoms may persist</td>
</tr>
<tr>
<td>(increasing signs and symptoms with repetition of provocative maneuvers)</td>
<td>87%</td>
<td>No</td>
</tr>
<tr>
<td>Nystagmus direction</td>
<td>Direction fixed, torsional, up, upper pole of eyes toward ground</td>
<td>Direction changing, variable</td>
</tr>
<tr>
<td>Intensity of signs and symptoms</td>
<td>Severe vertigo, marked nystagmus, systemic symptoms such as nausea</td>
<td>Usually mild vertigo, less intense nystagmus, rare nausea</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>Inconsistent</td>
<td>More consistent</td>
</tr>
</tbody>
</table>

*BENIGN POSITIONAL VERTIGO*

Benign positional vertigo refers to a symptom complex classically described as indicating benign peripheral (end-organ) disease. These symptoms, differentiated from central neurologic symptoms, are outlined in Table 7.3. The signs and symptoms of benign positional vertigo are transient and rarely last longer than 40 seconds. They frequently occur when a certain position is assumed, such as lying down or turning in bed. Other causes of vertigo are also intensified by position change. Depending on whether the symptom (vertigo) or sign (nystagmus) is being emphasized, this condition is termed paroxysmal positional vertigo (BPPV) or benign paroxysmal positional nystagmus (BPPN). In a major review of 240 cases, Baloh and associates described the clinical and eye movement-recording features in patients with BPPV. In each case, after a rapid position change from sitting to head-hanging position, a stereotyped torsional paroxysmal nystagmus was observed. The time to onset of the nystagmus, the latency, was from 0 to 40 seconds, with an average of approximately 8 seconds. The initial phase of the nystagmus was rotary and upward, with the upper pole of the eye beating toward the ground on visual inspection. From the examiner's observation, the nystagmus should appear counterclockwise,
with the left ear down. The average age of onset was 54 years, and the most common identifiable causes were head trauma (17%) and viral neuraklabyrinthitis (15%).

Troost and Patton described historic factors that should lead to the consideration of BPPV: (a) symptoms associated with certain head positions; (b) rotational vertigo of episodic nature; (c) an antecedent episode of severe rotary vertigo, with or without nausea and vomiting, associated with upper respiratory infection that suggests prior viral neuraklabyrinthitis; (d) a history of head trauma before attacks of vertigo; (e) most severe symptomatology early in the day, with lessening symptoms as the day progresses; and (f) a relative absence of spontaneous symptoms without head movement or positional change. Physical examination findings include (a) vertical-rotary BPPN produced by provocative maneuvers (Fig. 7.3); (b) latency to onset of symptoms once precipitating head position is achieved; (c) short-duration nystagmus (3 to 30 seconds); and (d) adaptation of nystagmus and symptoms (i.e., disappearance with repeated maneuvers). Additionally,
**Figure 7.4.**

In benign paroxysmal positional nystagmus, the nystagmus fast phase is horizontal-rotary directed toward the uppermost ear when gaze is directed toward the lowermost ear (upper panel). The nystagmus slow phase is upward toward the forehead when gaze is directed to the uppermost ear (middle panel). With the eyes in the central orbital position, the nystagmus fast phase is vertical upward and rotary toward the down ear (bottom panel). (From Troost BT, Patton JM. Exercise therapy for positional vertigo. *Neurology* 1992;42:1441–1444.)

BPPN is not a constant feature of the physical examination, being present on some examinations but absent at other times. Typical nystagmus upon assumption of certain head postures is considered the single most important physical finding in making the diagnosis of BPPN (Fig. 7-A).

Posttraumatic vertigo immediately follows head trauma in most cases, implying end-organ damage in the absence of other CNS signs. The interval between injury and onset of symptoms can, however, be days or even weeks. The mechanism for the delay of symptoms is uncertain but includes hemorrhage into the labyrinth, with later development of serous labyrinthitis. Another mechanism for delayed posttraumatic positional vertigo is cupulolithiasis, in which the calcareous deposits (otoconia) of a damaged organ of the labyrinth are displaced to a sensitive region of the posterior canal, making it more susceptible to stimulation in certain head positions. In posttraumatic vertigo, the symptoms may be those of general peripheral vestibulopathy or benign positional vertigo. Generally, the prognosis is good, with symptoms gradually resolving within weeks to months. As pointed out by Baloh and colleagues, vertigo is a recognized outcome of head injury, and in the absence of specific pathologic findings, the diagnosis should be considered in cases where no other cause for vertigo can be found.
colleagues, disabling persistent positional vertigo unresponsive to medical therapy occurs more commonly than was previously recognized. Many patients respond to exercise therapy, as described below, and rarely need selective section of the nerve to the posterior semicircular canal.

**DRUG TOXICITY**

Patients with dizziness produced by vestibulotoxic drugs are presumed or documented to have persistent injury to the peripheral end-organ. Among the agents causing such end-organ injury are the aminoglycosides. Streptomycin and gentamicin are most detrimental to the vestibular end-organ; kanamycin, tobramycin, and neomycin cause more damage to the auditory end-organ. Patients usually report progressive unsteadiness, particularly when visual input is diminished, as happens at night or in a darkened room. Vestibular testing documents a progressive bilateral loss of vestibular function. The aminoglycosides are concentrated in the endolymph and perilymph; thus the hair cells are exposed to high concentrations of the drugs. Extreme caution should be used in patients with renal disease, because most of these agents are primarily eliminated by the kidney. This type of end-organ toxicity should be contrasted with that produced by the large group of drugs with widespread reversible central and peripheral nervous system effects (Table 7.4). These drugs cause transient disequilibrium that subsides with cessation of the medication.

**MÉNIÈRE'S SYNDROME**

Ménière's syndrome is characterized by attacks of severe vertigo, tinnitus, fluctuating hearing loss, and ill-described aural sensations of fullness, with spontaneous recovery in hours to days. Initially, the patient develops a sensation of fullness and pressure along with decreased hearing and tinnitus in a single ear. This is followed by severe vertigo, which reaches peak intensity within minutes and slowly subsides over hours. A sense of disequilibrium persists for days after an acute episode. Occasionally, sufferers from Ménière's syndrome experience such severe attacks that they suddenly fall to the ground. Consciousness is not lost in such episodes, although awareness of surroundings may be altered by the intensity of the accompanying sensation and nausea, which has been called tumarkin's crisis. The most consistent pathologic finding in Ménière's syndrome is an increase in the volume of the endolymphatic fluid and distention of the canals, hence the term endolymphatic hydrops. Although some specific causes such as bacterial, viral, and syphilitic infections may lead to the same pathologic changes and symptoms, most cases are idiopathic. Ménière's disease usually develops between the ages of 30 and 50 and is slightly more common in women than in men. The prognosis is for progressive reduction in hearing along with increasing frequency of attacks. Some patients stabilize without subsequent attacks of severe vertigo, but they are left with residual hearing loss. Fifty percent of Ménière's patients become bilateral. The hearing loss often progresses to a moderate degree of deficit and then stabilizes.

**OTHER PERIPHERAL VESTIBULAR CONDITIONS**

Many other disorders affect the peripheral labyrinth, including acute otitis media, chronic ear infection, hereditary degenerative disorders of the end-organ, and local
Central Causes of Vertigo

Central pathologic causes of vertigo result from dysfunction of the vestibular portion of the eighth cranial nerve, the vestibular nuclei within the brainstem, and their central connections (Table 7.5). Neural connections with the central vestibular nuclei include interaction with the vestibular portions of the cerebellum (primarily the cerebellar flocculus), the visual sensory system, and afferent connections from muscle, joint, and tactile receptors. Normal persons will experience physiologic vertiginous sensations when visual and vestibular inputs are in conflict or when they are initially exposed to heights. Central pathologic causes of vertigo are less common than either peripheral or systemic causes, the vertiginous symptoms are usually less prominent, and additional neurologic signs are usually present on examination.

Table 7.5. CENTRAL NEUROLOGICAL CAUSES OF VERTIGO

1. Brainstem ischemia and infarction
2. Demyelinating disease: multiple sclerosis, postinfection demyelination, remote effect of carcinoma
3. Cerebellopontine angle tumor, acoustic neuroma, meningioma, cholesteatoma, metastatic tumor, etc.
4. Cranial neuropathy: focal involvement of VIII nerve or in association with systemic disorders
5. Intracranial brainstem lesions (tumor, arteriovenous malformation, trauma—remote)
6. Other posterior fossa lesions (primarily other intrinsic or extrinsic masses of the posterior fossa such as hematomas, metastatic tumor, and cerebellar infarction)
7. Seizures (convulsions—remote)
8. Hereditary diseases such as spinocerebellar degeneration
9. Malformations of the peripheral vestibular apparatus

*A hearing loss is rare except in 8.

Brainstem Ischemia and Infarction

The posterior circulation supplies blood to the brainstem, cerebellum, and peripheral vestibular apparatus, in addition to other structures. It is not surprising that brainstem insufficiency may be accompanied by vertigo. In general, brainstem TIAs should be accompanied by neurologic symptoms or signs in addition to vertigo or dizziness before a clear-cut diagnosis is entertained. However, it is clear that isolated episodes of vertigo lasting many minutes may be due to posterior circulation dysfunction. Symptoms include transient clumsiness, weakness, loss of vision, diplopia, perioral numbness, ataxia, drop attack, and dysarthria. Common signs of vertebrobasilar ischemia include disorders of motor function such as weakness, clumsiness, or paralysis. A crossed defect (a motor or sensory deficit on one side of the face and the opposite side of the body) is good evidence of brainstem dysfunction. If the occipital lobes are the site of ischemia, transient visual loss in the form of complete or partial homonymous hemianopia will occur. Ataxia, imbalance, unsteadiness, or disequilibrium not necessarily associated with spinning vertigo may occur because of labyrinthine or cerebellar ischemia.

However, it is incorrect to believe that dizziness must be present before a TIA of the posterior circulation can be diagnosed. Isolated symptoms like those described may occur without dizziness. On the other hand, it has been overemphasized that such symptoms must always accompany dizziness when the vertiginous symptoms are due to brainstem TIA. In elderly patients with no laboratory evidence of peripheral vestibulopathy or systemic disease, episodic disequilibrium or dizziness may be due to vertebrobasilar disease.

Sudden hearing loss with moderate dizziness may be due to infarction in the distribution of the internal auditory artery. In isolation, this symptom complex is uncommon in elderly patients with atherosclerotic vertebrobasilar disease and is more suggestive of diseases...
diseases affecting small- and intermediate-
diameter arteries, such as syphilis, systemic
lupus erythematosus, or periarteritis nodosa.
In the atherosclerotic patient, such symp-
toms are usually accompanied by other signs
of brainstem or cerebellar dysfunction,
which allow a more certain diagnosis. If ac-
tual brainstem infarction occurs, neurologic
signs are often present on examination. Such
signs may not be obvious and should be
carefully sought. They include nystagmus of
the central type, hyperreflexia, internuclear
ophthalmoplegia, homonymous visual field
defects, dysarthria, vertebral bruises, and
ataxia. Symptoms of dizziness are also quite
common in proximal extracranial occlusion
of the vertebral arteries and in the subclavian
steal syndrome.

Up to this point, the emphasis has been on
the accompanying signs and symptoms
that almost always occur with vertebrobasil-
dar disease. However, acute severe vertigo,
immitting labyrinthine disease, is an early
symptom of acute cerebellar infarction in the
distal territory of the posterior inferior cere-
bellar artery. To differentiate this condition
from labyrinthine disease, particular atten-
tion is directed to the type of nystagmus that
is present. Acute peripheral vestibulopathy
usually causes unidirectional nystagmus,
with the fast phase in the opposite direction.
This is similar to the situation described by
the mnemonic COWS (Cold, Opposite,
Warm, Same) for remembering the direction
of the nystagmus fast phase during thermal
irrigation of the ear. The fast phase is away
from the side of the cold water irrigation.
Cold water mimics a peripheral destructive
lesion of the labyrinth, and almost all lesions
are destructive. Therefore, with a peripheral
labyrinthine disturbance, the nystagmus fast
phase is in the opposite direction, or away
from the involved ear. The nystagmus in-
creases during gaze in the direction of the
fast phase, or contralateral to the peripheral
vestibulopathy. Swaying or falling occurs to-
ward the side of the lesion (opposite the
nystagmus fast phase). The nystagmus direc-
tion is said to be fixed in that it tends to be
unidirectional, away from the side of the pe-
ripheral vestibulopathy, and tends to remain
horizontal on upward gaze.

In certain syndromes of the posterior cir-
culation, the initial presentation with acute
vertigo suggests peripheral vestibulopathy.
With incipient cerebellar infarction, the sway
or fall is toward the side of the lesion. The
accompanying nystagmus may be variable in
direction but is most prominent during gaze
toward the lesion. In other words, with cen-
tral lesions, the fast phase of the nystagmus
is in the direction of gaze (direction chang-
ing nystagmus) but becomes more promi-
nent when gaze is directed ipsilateral to the
lesion. Ocular motor findings are often pre-
sent in brainstem disease, such as limitation
of vertical gaze, upbeat or downbeat nystag-
us, or disconjugate nystagmus.

Multiple sclerosis should only be diag-
nosed following the documentation of dis-
seminated CNS lesions such as optic neuritis,
transverse myelitis, internuclear ophthalmo-
plegia or other brainstem signs, and mag-
netic resonance imaging (MRI) changes. Oc-
casionally, signs and symptoms suggesting
multiple sclerosis, including disequilibrium
and dizziness, may be mimicked by an in-
trinsic brainstem tumor in a young patient.

CEREBELLOPONTINE ANGLE
TUMORS

Tumors of the cerebellopontine angle
rarely present solely with episodic vertigo.
The most common tumor in this location re-
sults from a proliferation of the Schwann
cells, hence the name schwannoma. Most of
these tumors arise on the vestibular portion
of the eighth cranial nerve within the internal
auditory canal. They progressively enlarge,
deforming the internal auditory meatus and
compressing adjacent neural structures such
as the acoustic portion of the eighth nerve,
the facial nerve, the trigeminal nerve, the
brainstem, and the cerebellum. Other tumors
occurring in the cerebellopontine angle in-
clude meningiomas, epidermoids, and meta-
stases.

The most common symptoms associated
with eighth nerve tumors are progressive
hearing loss and tinnitus. Vertigo occurs in approximately 20%, but a symptom of imbalance or disequilibrium is more common. Rarely, a patient with a vestibular nerve tumor may present with subtle hearing loss, tinnitus, and episodic vertigo. All those with progressive unilateral hearing loss, and particularly those with any vestibular symptoms, should be carefully examined for additional neurologic signs such as a depressed corneal reflex.

CRANIAL NEUROPATHY

Multiple or isolated cranial neuropathies occur in focal or systemic disease, including vasculitis, granulomatous disease, and meningococcal carcinomatosis. The cause is often elusive. Evidence of systemic involvement is elicited by history, physical examination, and laboratory evaluation. Cogan’s syndrome may be considered with cranial neuropathies. The condition is characterized by nonsyphilitic keratitis associated with vertigo, tinnitus, ataxia, nystagmus, rapidly progressive deafness, and systemic involvement.

POSTERIOR FOSSA LESIONS

Posterior fossa lesions in a variety of locations are unusual causes of isolated vertigo. The symptoms are usually positional vertigo of the central type (Table 7.3). MRI with coronal and sagittal reconstructions permits identification of small tumors close to the tissue-bone interface, a region often blunted by bone artifact in computed tomography (CT) scans.

Acquired disease of the brainstem and cerebellum produces a variety of types of nystagmus, which sometimes present as a complaint of oscillopsia, an illusion of environmental movement characterized by bouncing or jiggling of objects. Although oscillopsia is a common complaint with bilaterally reduced vestibular function, as from ototoxicity, the presence of vertical oscillopsia should alert the physician to look for primary-position upbeat or downbeat nystagmus. These nystagmus types are reliable indicators of CNS abnormality due to structural intrinsic midline cerebellar disease or drugs.

SEIZURE DISORDERS

Seizure disorders, especially complex partial epilepsy, are rare causes of dizziness or vertigo. The history almost always reveals additional symptoms such as loss of awareness, automatic behavior, or generalized seizure activity following an aura of vertigo. However, rare seizure patients, documented by additional history and EEG, have isolated auras of the symptoms listed in Table 7.1.

**Systemic or Medical Causes of Vertigo**

Systemic causes have been given a separate category to include more widespread conditions that secondarily affect peripheral and/or central vestibular structures to produce vertigo or dizziness (Table 7.6).

**DRUGS**

Side effects of drug ingestion frequently cause dizziness in the broadest definition of the term. Vestibulotoxic drugs, as previously described, can produce true vertigo. The dizziness produced by other drugs is more a sense of weakness, disequilibrium, or "fuzzy headedness." The agents listed in

<table>
<thead>
<tr>
<th>Table 7.6. SYSTEMIC CAUSES OF VERTIGO AND DIZZINESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Drugs (including anticonvulsants, hypnotics, amithihypertensives, alcohol, anesthetics, tranquilizers)</td>
</tr>
<tr>
<td>2. Hypothyroidism, palsy (including primary cardiac causes and postural hypotension from a wide variety of causes)</td>
</tr>
<tr>
<td>3. Infections diseases (including syphilis, viral and other bacterial meningitis, and systemic infection)</td>
</tr>
<tr>
<td>4. Endocrine diseases (including diabetes and hypothyroidism)</td>
</tr>
<tr>
<td>5. Vasculitis (including collagen-vascular disease, giant cell arteritis, and drug-induced vasculitis)</td>
</tr>
<tr>
<td>6. Other systemic conditions (including the hematological disorders, polycythemia, anemia, and dysproteinemia, sarcoidosis, granulomatous disease, and systemic toxins)</td>
</tr>
</tbody>
</table>

**HYPOVENTILATION**

The acute or chronic ventilatory dysfunction is not a common cause of dizziness, but is very important because long-term hypoxic states can have a profound impact on the brain and the body.
Table 7.6 are among the most common offenders. Every attempt should be made to determine the type and quantity of medication being taken by the dizzy patient. Frequently, the elimination or reduction of medication such as a mild tranquilizer will produce improvement. The dizzy patient may have been treated with a variety of medications that themselves can add to dis-equilibration or dizziness.

**HYPOTENSION**

The multiple causes of *presyncope* or postural hypotension are often responsible for complaints of vertigo or dizziness. Again, careful historic review and documentation of physical findings such as postural hypotension or cardiac arrhythmia direct further investigation and therapy. Presyncope is described as lightheadedness, among other phrases, and is actually a common mechanism for dizziness or even vertiginous sensations. Postural hypotension is a common side effect of antihypertensive agents, diuretics, and dopaminergic agents. When the symptom is intermittent, a history of lightheadedness following change from recumbent or sitting posture to an erect position, but not the reverse, is more helpful than blood pressure measurements. In adolescents, a hyposensitive carotid sinus reflex during the growth spurt is not rare, and transient symptoms of postural dizziness might be explained by this mechanism.

**ENDOCRINE DISORDERS**

Among the endocrinopathies that cause disorders of equilibration are diabetes and hypothyroidism. The mechanism in diabetes is probably the autonomic neuropathy and orthostatic hypotension that may accompany the disease. Though much less common as a specific cause, hypothyroidism should be considered when the symptoms of vertigo remain undiagnosed. Indeed, dizziness is not an infrequent presenting complaint in patients with thyroid deficiency. The remaining systemic conditions rarely present with isolated vertigo but are included as additional primary or secondary causes.

**MULTIPLE AFFERENT SENSORY LOSS**

The vestibular system functions to provide (a) spatial orientation at rest or during acceleration, (b) visual fixation during head and/or body movement (the vestibulo-ocular reflex), and (c) feedback control of muscle tone to maintain posture. These functions and their control mechanisms are interconnected in a complex fashion. Thus, the symptoms of episodic vertigo reflect disturbances in more than one system. The combination of multiple sensory deficits can produce disorientation or dis-equilibration that is interpreted as dizziness or vertigo. This often occurs in the elderly, in whom vision (cataracts), hearing (presbycusis), and proprioception (peripheral neuropathy) may all be impaired. There is an entity known as presbylabyrinth, or imbalance resulting from aging, which may be due to a selective progressive deterioration of the peripheral vestibular apparatus or a combination of sensory deficits.

Even an intact person is easily confused by afferent sensory information, as exemplified by the sensation of spinning or true vertigo experienced during full-field optokinetic stimulation. Almost every individual while quietly seated will experience a compelling illusion of rotation while viewing a moving environment of optokinetic stripes (the circularvection illusion). Thus, it is not surprising that patients with subtle abnormalities of peripheral or central vestibular mechanisms experience definite momentary periods of disorientation while viewing a moving patterned environment. Some experience episodic vertigo during vehicular travel.

The age-related degeneration of vestibular receptors, presbylabyrinth, contributes to vertigo. Although most younger patients readily compensate for unilateral peripheral vestibular damage, older patients frequently cannot or have very gradual improvement, indicating either bilateral peripheral vestibular dysfunction or a separate central abnormality that decreases their ability to compensate.
DIZZINESS IN CHILDHOOD

The most common causes of vertigo and dizziness in childhood and infancy are similar to those in the adult—acute peripheral vestibulopathy, trauma, and infection. Vertigo following air travel is more common in children than in adults because of the frequency of accompanying middle ear infection and effusion. Migraine is a significant cause of episodic dizziness or vertigo in childhood and should be considered even when the symptoms of headache are minimal.

Benign paroxysmal vertigo in childhood is a variety of vestibular neuronitis. Although unaccompanied by loss of consciousness, children may fall during the course of an attack. The episodes may last minutes to hours or recur for many weeks or even months, gradually decreasing in severity. The preservation of consciousness during an attack distinguishes the condition from temporal lobe seizures with a vestibular component and from vestibulogenic epilepsy in which an attack is triggered by labyrinthine stimulation. Congenital anomalies of the inner ear and brainstem are rare causes as is vascular disease or tumor in childhood. Rarely, typical signs and symptoms of Ménière's disease occur in childhood, the youngest reported patient being age 3.

Laboratory Evaluation of Dizziness

The primary techniques for evaluating vestibular function are electronystagmography (including caloric, specific ocular motor, and rotational testing) and posturography. Various screening tests are required with undiagnosed vertigo, and neuroradiologic imaging is indicated when a central cause is suspected.

ELECTRONYSTAGMOGRAPHY (ENG)

ENG is the most readily available test for assessing the vestibular system. Eye movements are recorded by means of the corneal or retinal potential by surface electrodes, with the results printed on strip-chart recording paper or analyzed by a computer. A primary function of the ENG is to determine whether there is unilateral weakness or decreased caloric responses bilaterally. Each ear is irrigated separately with warm and cool stimulation, produced by either water or by air. The resulting nystagmus is analyzed manually or by computer to determine the slow phase velocity (SPV) of the induced nystagmus. Peak SPV resulting from the warm and cool stimulation of one ear is compared with that from the other ear. The most important finding during ENG is a significant reduction in the response on one side compared with the other. A difference of more than 20 to 25% in one ear, compared with the other, is a clear indication of hypofunction in one peripheral vestibular apparatus. The ear with the weaker response is said to have a reduced vestibular response or unilateral weakness. A bilateral weakness is defined as an SPV below 80% to 10% for both warm and cool stimulation. Typical ENG recordings are shown in Figure 7.5.

Equally important information gained from the use of the ENG includes (a) documentation of spontaneous and induced nystagmus, (b) quantitation of fast eye movements, (c) smooth pursuit tracking, (d) optokinetic responses, and (e) gaze testing. These are briefly discussed below.

a. Positional nystagmus induced by certain head movements may be documented by the ENG, including the latency to onset. There is usually a delay in onset of the nystagmus or latency with peripheral types of positional nystagmus. The ENG may document a primary position horizontal or vertical nystagmus. Vertical primary position nystagmus suggests central nervous system disease. One type of induced nystagmus is positional nystagmus provoked by certain head movements.

b. The average speed of the fast eye movement is recorded. Slow saccades indicate CNS disease, such as degeneration in the brainstem.
Electronystagmogram (ENG). Typical bitemporal electrode recording using AC coupling. A. Calibration. Upward sweep of trace indicates eye movement to right; decay in position of trace is due to AC drift. A DC-coupled recording, standard in some laboratories, would show maintenance of this position before the eye returns to midline. B. Smooth-pursuit tracking eye movement trace shows sinusoidal side-to-side movement interspersed with minor saccadic interruption. C. Right-ear cold caloric test demonstrating left-beating nystagmus. D. Left-ear cold caloric test demonstrating right-beating nystagmus. E. Right-ear warm caloric testing demonstrating right-beating nystagmus. F. Left-ear warm caloric testing demonstrating left-beating nystagmus. G. Optokinetic testing with tape moving to right demonstrating rightward-beating nystagmus. The electronystagmogram would be interpreted as showing minor reduction in right ear responses because of slightly reduced responses in right-ear warm caloric testing. The asymmetry would be less than 30% and therefore not of clinical significance.
c. When smooth pursuit tracking eye movements are interrupted by a series of small saccades (a nonspecific abnormality known as cogwheel, or saccadic, pursuit), it may be caused by drowsiness, drugs, or CNS disease.

d. A major asymmetry in the optokinetic response indicates unilateral parieto-occipital CNS dysfunction.

e. Nystagmus produced during ocular excursions, in any direction, is known as gaze-evoked nystagmus. Gaze-evoked nystagmus can result from drugs such as sedatives or anticonvulsants or from cerebellar and brain-stem abnormality.

ROTATIONAL TESTING

The patient is rotated in a chair controlled by a computer and eye movements are measured. Patients are rotated in the dark with eyes open while performing mental tasks assigned to distract them from mental imagery that might suppress eye movement. During a chair rotation to the right, the eyes move to the left and then recenter with a fast phase. Thus, the slow component (phase) is in the direction opposite the spin, and the fast component of the resultant nystagmus is in the direction of the rotation. The fast components are eliminated by computer, and a slow phase is reconstructed and compared with the speed of the chair rotation. In this way, a gain (slow eye movement speed ÷ chair rotation speed) at different frequencies is obtained. Measurement is made of symmetry, which compares the response to rotation in one direction with that in the opposite direction. Also measured during rotational testing is the time relationship between the slow eye movement and the slow movement of the chair. This difference is called the phase lag. Various phase lags are also plotted against the frequency of rotation of the chair. Thus, both gain and phase plots are produced during rotational testing. Rotational testing provides little information about the site of the lesion, as opposed to caloric testing in the ENG. However, it is quite beneficial in quantitating bilaterally reduced vestibular function such as occurs with ototoxicity. Rotational testing, therefore, is helpful in determining response patterns in patients with bilateral vestibular loss. A symmetric response of a person with a previous unilateral peripheral vestibular abnormality indicates vestibular compensation, and abnormal phase-lag is a nonspecific marker indicating some degree of prior peripheral vestibular abnormality.

POSTUROGRAPHY

Posturography is a means of quantifying the Romberg test. Changes in body sway during Romberg testing with feet directly together, both with eyes open and eyes closed, are measured by means of a computer. Most recently, a dynamic posture platform has been introduced. The patient is surrounded by a movable visual field and stands on a posture platform that is mobile. By manipulating the visual field, visual cues that help maintain posture may be eliminated. Similarly, by moving the posture platform in response to movement of the feet, attempts are made to remove proprioceptive cues. The test results in all conditions are reported, and an interpretation is made on the basis of which systems are defective. Posturography, a promising technology currently in use and under evaluation for assessment of balance disorders, may be useful in rehabilitation.

ADDITIONAL DIAGNOSTIC TESTS

Patients with undiagnosed vertigo should have metabolic screening tests including a blood count, electrolytes and glucose determinations, and thyroid function testing. Many physicians involved in the evaluation of dizzy patients also perform lipid screens for hypercholesterolemia or increased triglycerides. The laboratory investigation, like the physical examination, is directed particularly by the patient's history. If there is a history of presyncope or syncope, the patient must have a cardiac evaluation, including at least an electrocardiogram and rhythm strip. A more suggestive history would lead to a Holter 24-hour monitor or an event monitor, during which the patient wears a battery-powered
apparatus that can be activated at times of symptoms. This device then records the cardiac rhythm. The presence of auditory symptoms requires a complete audiologic evaluation as described below. Multiple or recurrent cranial neuropathy would lead to a variety of screening tests for collagen vascular disease or skull-based pathology or meningitic processes.

**Neuroradiologic Investigation**

In the past, the primary neuroradiologic techniques for determining CNS abnormality and, in particular, cerebellopontine angle tumors included tomography of the temporal bone, CT scanning, and posterior fossa myelography with air or other contrast material. Currently, the high resolution obtainable on CT scanning has largely eliminated the need for tomography of the temporal bone. MRI has largely supplanted CT scanning for cerebellopontine angle tumors. For general neurologic screening, a CT scan, with and without contrast, is appropriate in patients suspected of having a CNS disorder on the basis of history or physical examination. The workup must include an MRI (Figs. 7.6, 7.7, 7.8) when there are persistent symptoms suggesting a CNS disorder. The best available images of the cerebellopontine angle and brainstem are clearly afforded via MRI.

![Figure 7.6.](image)

Lateral MRI scan showing marked atrophy of cerebellum in a patient who had progressive unsteadiness.
Figure 7.7.
Typical MRI scan of patient with multiple sclerosis showing periventricular white matter abnormality (arrow). White matter lesions extending in a perpendicular fashion from the ventricle are virtually pathognomonic for multiple sclerosis.

Figure 7.8.
High-resolution T2 large cerebellar.

Therapy 1

Vestibular

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MEDICAL TREATMENT

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Therapy for Peripheral Vestibular Disorders

The emphasis in this section is on medical and, to a lesser extent, surgical treatment of peripheral vestibular dysfunction and vertigo.

MEDICAL TREATMENT:
Therapy is outlined in Table 7.7 for symptomatic treatment of dizziness presumed to be of peripheral origin. When a definitive diagnosis such as vestibular schwannoma, autoimmune disorder, perilymph fistula, or systemic vasculitis has been made, the therapy must be directed to the underlying disorder.

Although most of the drugs used for dizziness are loosely referred to as vestibular suppressants, their mechanism of action may not be defined, and it is often unclear which agents will be effective in a given patient. The primary vestibular afferent system could be suppressed directly or indirectly through the inhibitory portion of the vestibular efferent system. An important effect of some agents may be to act on other sensory systems such as proprioceptive or visual inputs to the vestibular nuclei of the brainstem.

Few controlled studies have investigated the response of patients with presumed peripheral vestibular dysfunction. Most of the drugs used are empirical, based on studies of
Table 7.7. Medical Therapy of Vertigo

<table>
<thead>
<tr>
<th>Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
</tr>
<tr>
<td>Meclazine</td>
<td>25-50 mg 3 times/day</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>50 mg 1-2 times/day</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>50 mg 1-2 times/day</td>
</tr>
<tr>
<td>Promethazine</td>
<td>25-50 mg/day</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
</tr>
<tr>
<td>Scopolamine*</td>
<td>1 three times/day</td>
</tr>
<tr>
<td>Scopolamine tablets</td>
<td>0.45-0.50 mg 1-2 times/day</td>
</tr>
<tr>
<td>Scopolamine transdermal</td>
<td>1/3 days</td>
</tr>
<tr>
<td><strong>Sympathomimetics</strong></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>25 mg/day</td>
</tr>
<tr>
<td><strong>Antiemetics</strong></td>
<td></td>
</tr>
<tr>
<td>Trimethobenzamide</td>
<td>250 mg 1-2 times/day orally</td>
</tr>
<tr>
<td></td>
<td>200 mg suppository</td>
</tr>
<tr>
<td></td>
<td>25-50 mg/day</td>
</tr>
<tr>
<td></td>
<td>5-10 mg 3-4 times/day orally</td>
</tr>
<tr>
<td></td>
<td>25 mg suppository</td>
</tr>
<tr>
<td><strong>Tranquilizers</strong></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>5-10 mg 1-3 times/day</td>
</tr>
<tr>
<td>Serax</td>
<td>10-60 mg/day</td>
</tr>
<tr>
<td>Haloperidol†</td>
<td>0.5-1 mg 1-2 times/day</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>80 mg 1-3 times/day</td>
</tr>
<tr>
<td><strong>Combination Preparations and Others</strong></td>
<td></td>
</tr>
<tr>
<td>Scopolamine with ephedrine</td>
<td></td>
</tr>
<tr>
<td>Scopolamine with promethazine</td>
<td></td>
</tr>
<tr>
<td>Ephedrine with promethazine</td>
<td></td>
</tr>
<tr>
<td>Barabazine</td>
<td></td>
</tr>
<tr>
<td>Cyclandelate</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
</tr>
</tbody>
</table>

*Normal starting dose, can be increased by factor of 2 to 3. The most common side effect is drowsiness.
†The combination preparations Dophen and Donnatal each contain a mixture of atropine and hyoscine with approximately 1/4 grain (15-16.2 mg) phenobarbital.
‡Antihistamines are among the most commonly employed agents in the treatment of dizziness. The initial drug usually employed is meclizine hydrochloride in doses up to 50 mg three times per day. Since the main side effect of antihistamines is drowsiness, the smallest dose should be used initially, even as low as 12.5 mg two to three times per day.

For dizziness, antihistamines in the H1 antagonist group are used. Possibly the H1 blockers, effective in motion sickness, act by central antagonism of acetylcholine (ACh), as does scopolamine. An excellent drug as a second choice is Promethazine, a phenothiazine with the strongest ACh-blocking action. The usual starting dose is 25 mg three times per day, but if this amount produces drowsiness and still has a positive effect, the drug dosage may be reduced to 12.5 mg three times a day. Anticholinergics that block the muscarinic effect of ACh have been widely used and studied for the prevention of motion sickness. Atropine acts centrally to stimulate the medulla and cerebrum, but the closely related alkaloid scopolamine is more widely used. Transdermal delivery of scopolamine may prevent or mitigate the nausea and vomiting associated with motion sickness, but not the dizziness. In general, transder-
nal scopolamine is not useful in patients with acquired vestibulopathy. Frequent side effects are blurred vision and dry mouth, in addition to occasional confusion. Some patients have significant difficulty when they try to discontinue scopolamine patches. A side effect of low-dose scopolamine or atropine is the transient bradycardia (4 to 8 beats fewer per minute) associated with the peak action of oral scopolamine at 90 minutes and diminishing thereafter.

**Sympathomimetics** have been used in the treatment of motion sickness, particularly in combination with anticholinergics. The sole agent in this class that may have an application in combination with other drugs is ephedrine. Tolerance may develop after a few weeks of treatment.

**Antiemetics** may be used when prominent nausea is an accompanying feature of the patient's complaint. Many of the antihistaminic and anticholinergic drugs listed here are also used for their antiemetic actions. Prochlorperazine (Compazine) should be used with caution, particularly by the intramuscular route, because of the high incidence of dystonic reactions. Because promethazine (Phenergan) has a significant antiemetic effect, this drug is particularly useful when there is prominent nausea.

**Tranquilizers** is the general name for drugs from different classes with central and probably peripheral effects. They include benzodiazepines, butyrophenones, and phenothiazines. Diazepam is one of the most widely prescribed drugs for the treatment of dizziness. Many believe it should not be the first choice, primarily because of the significant potential for habituation and depression and because it can be the actual cause of dizziness. Nonetheless, it does remain the first choice of many otorhinolaryngologists. Other longer-acting benzodiazepines may be helpful in certain patients, but no study has substantiated their effectiveness. Haloperidol in small oral doses (0.5 mg three times a day) is effective in many patients with peripheral vestibular dysfunction who are not helped by other antidizziness medications.

**Combination preparations and other agents** include those listed in Table 7.6 and are frequently useful, particularly the combination of ephedrine and promethazine. Some other agents and regimens used primarily in the medical management of Ménière's disease are listed. Low-sodium diets and diuretics have been helpful with some patients. In the belief that in some cases an effect on blood supply to the peripheral end-organ might be a factor, agents such as cyclandelate have been used. The general approach to the patient with an acute or chronic vestibulopathy is to first use an antihistamine such as meclizine hydrochloride. If this is not helpful, the next step is to use promethazine (Phenergan), and if this is ineffective, low doses of haloperidol or low-dose Valium, always keeping in mind the potential for habituation with benzodiazepines.

**Exercise Therapy**

It is important to recognize that BPPV is responsible for at least 50% of all causes of vertigo, and exercise therapy may be curative in up to 90% of patients. The primary therapeutic option is one form or other of exercise therapy. The severity of the individual attacks and accompanying nausea may be lessened by medical therapy; however, this does not prevent future attacks.

Exercise therapy is indicated for all patients with BPPV. There are two general approaches to therapy: (a) a single treatment session in an outpatient office setting and (b) a series of exercises performed by the patient at home. Each is briefly described below.

**Office Single-Treatment Approach.** Among the single-treatment approaches are the canal repositioning maneuver (CRP) and its modifications (Fig. 7.9). One standard protocol is described below. This technique works best for patients in whom a specific head position produces attacks of vertigo, such as with the left ear down. Often, the examiner notices a characteristic rotary vertical nystagmus accompanying the vertigo when the head is placed in the offending position (Figs. 7.3 and 7.4).
Treatment Protocol for the Left Ear

1. The patient is moved quickly from a seated position back over the end of the examination table, with the head extended and turned approximately 45° with the left ear down. In each position, there may be nystagmus induced as a result of change from the prior head position. The patient is kept in the position until the nystagmus or symptoms subside, typically 10 to 15 seconds.

2. The head is slowly rotated so that the right ear is now turned 45° down, keeping the head extended.

3. The head and body are rotated to the right until the patient is facing downward.

This position is maintained for approximately 15 seconds.

4. The patient is then brought gradually up to a seated position with the head turned to the right.

5. The head is turned forward with the chin slightly depressed.

Over the next 24 to 48 hours, some recommend that the patient remain upright as much as possible. Another variation is to apply a hand-held mechanical oscillator to the head in each position. The overall success of this single treatment is reported to be 50 to 75%.
HOME EXERCISE THERAPY. The patient is first instructed carefully about the type of exercise to be performed (Fig. 7.10).

Treatment Protocol for Either Ear
1. In a seated position, on the edge of a couch or bed, the patient is asked to quickly lie on one side, placing the worst ear (if one can be discovered) down first (Fig. 7.9). The patient then moves rapidly from the sitting position and rests the head on a pillow or other support, without moving forcefully enough to produce a neck injury.

2. The patient then returns rapidly to an upright seated position and remains there for 30 seconds or until symptoms subside.

3. The patient rapidly lies down on the other side and remains there for approximately 30 seconds or until the symptoms subside.

4. The patient then returns to the upright seated position. This constitutes a single repetition.

Twenty repetitions should be performed two times per day. Each session lasts approximately 30 minutes. Some patients have intense symptoms at the onset of the BPPV, including vomiting. It is clear that patients who experience extreme discomfort during the maneuvers are not likely to pursue them on their own outside of an office or hospital setting. These patients may need hospital admission or hydration in an outpatient setting, with the concurrent administration of vestibular suppressant medications. Most patients are willing to perform exercises at home. This protocol is particularly useful for BPPV patients who have the following:

1. Bilateral BPPV
2. Uncertainty as to which ear is involved
3. Failure of single office treatment protocols

Recovery can be quite rapid occurring during the first few days of exercise therapy. Others progressively improve over weeks and months, suggesting that the vestibular system may adapt to whatever abnormal perturbation is causing the symptoms.

Approximately 50% of patients who have well-defined vertigo and nystagmus in cer-
tain head positions will have improvement following the single-treatment maneuver. Variations include the use of a hand-held oscillator or longer durations in each single position. The home set of maneuvers, known as the Brandt-Daroff maneuvers, may take days, weeks, or even months to produce a cure, but progressive improvement of symptoms should be noticed by the patient within the first few weeks. It is estimated that approximately 20% of patients have recurrences within the first year, and either of the maneuvers described above may be repeated with high expectation of further improvement. The overall success rate of exercise therapy approaches 90%, even with patients who have been symptomatic for years.

Surgical Therapy

Surgical therapy of chronic peripheral vestibular dysfunction includes exploration for fistulas, endolymphatic shunts, and destructive end-organ surgery. The details of these procedures may be found in standard otology texts. In patients with severe Ménière’s disease for whom no medical therapy such as that described earlier has been effective and who have severe recurrent disabling attacks, a labyrinthectomy may be performed. Unfortunately, Ménière’s disease may become bilateral, eventually resulting in the need for labyrinthectomy or vestibular nerve section on the contralateral side. A medical labyrinthectomy may be performed by the use of aminoglycoside drugs, those particularly destructive to the peripheral vestibular hair cells. Surgical or medical labyrinthectomy is usually a last resort in patients who have clearly defined severe attacks of peripheral vestibulopathy, presumably from Ménière’s disease.

Various shunting procedures have been used in the treatment of Ménière’s disease or endolymphatic hydrops. Although some patients can benefit, the long-term success with such shunting procedures, which include shunts to the mastoid region and to the subarachnoid space, has been only modest.

Some patients with benign paroxysmal positional vertigo do not have a benign course. Patients who experience classic but disabling symptoms persisting over 6 months are candidates for exercise therapy as described earlier. On rare occasions, the exercise therapy is unsuccessful; such patients are candidates for section of the nerve from the posterior semicircular canal.

Management of Central and Systemic Vestibular Disorders

Medical Treatment

Clearly the management of central vestibular disorders depends on the diagnosis. A simple separation into peripheral and central vestibular dysfunction is not always possible, as alluded to above. Some patients have inadequate central compensation for a peripheral vestibular abnormality and thus remain symptomatic. In such patients, medical therapy for peripheral vestibular dysfunction, as described above, may prove quite effective. When a specific diagnosis (e.g., postural hypotension secondary to diabetic peripheral neuropathy) is made, attention should be directed to treatment of the primary condition. Severe postural hypotension is notoriously difficult to manage. In general, the approach is to use agents that increase vasoconstriction, others that prevent vasodilation, or drugs that might increase cardiac output. Plasma volume may be increased by the use of mineralocorticoids such as fludrocortisone acetate, but they should be prescribed cautiously.

The patient who is diagnosed as having primary CNS disease, whether it be brainstem infarction or spinocerebellar degeneration, must be managed as a patient without the accompanying symptoms of disequilibration would be. Medical therapy of vertebrobasilar ischemia is directed at preventing new infarctions, primarily with antiplatelet agents and, on rare occasions, anticoagulation. Cerebellar dysfunction not caused by tumor may be treated with improvement or improvement of therapy of imbalance of meninestral symptom.

Therapy for vertigo also requires drug therapy. Of course, all drugs listed above may prove useful, but antineoplastic agents, antidepressants, or precipitatin

Surgical Therapy

Surgical wound repair of the peripherally.

Auditory Therapy

In the assessments of auditory therapy, the system may serve a pacemaker function. Therefore, performing a hearing test is critical. Auditory therapy also may be used to enhance the patient’s awareness of auditory stimuli.Auditory tests may include the audiologic examination, which may include tests such as pure tone audiometry, speech discrimination, and the use of a bone conduction aid. Auditory therapy may be used to improve the patient’s hearing acuity.

The patient who is diagnosed as having primary CNS disease, whether it be brainstem infarction or spinocerebellar degeneration, must be managed as a patient without the accompanying symptoms of disequilibration would be. Medical therapy of vertebrobasilar ischemia is directed at preventing new infarctions, primarily with antiplatelet agents and, on rare occasions, anticoagulation. Cerebellar dysfunction not caused by tumor may be treated with improvement or improvement of therapy of imbalance of meninestral symptom.

Therapy for vertigo also requires drug therapy. Of course, all drugs listed above may prove useful, but antineoplastic agents, antidepressants, or precipitatin...
Types of Hearing Loss

Hearing loss can result from a lesion anywhere within the auditory system. An abnormality within the outer or middle ear results in a conductive loss of hearing due to an inefficient transmission of sound to the inner ear system. When the loss of hearing is due to pathology in the cochlea or along the eighth cranial nerve from the inner ear to the brainstem, the loss is referred to as a sensorineural hearing loss. Patients may exhibit both conductive and sensorineural loss, which is referred to as a mixed hearing loss. Central hearing loss (or central auditory dysfunction) is present when a lesion exists in the central auditory pathway beyond the eighth cranial nerve; for instance, in the cochlear nucleus in the pons or in the primary or association auditory cortex of the temporal lobe. In addition to these organic types of hearing loss, one should also consider functional hearing loss. The diagnosis of functional hearing loss is made when an individual claims to have a hearing loss, but discrepancies in objective test measures suggest that the loss does not exist or is exaggerated.

Conductive hearing loss occurs with pathology in the outer or middle ear. The bone conduction thresholds are normal, but air conduction results suggest a decrease in hearing sensitivity. The patient with a conductive hearing loss typically demonstrates decreased sensitivity across all frequencies. Sometimes hearing is better for the higher frequencies than for the lower ones (Fig. 7.11). Another finding of conductive loss is that speech discrimination is relatively unimpaired. A patient with a conductive loss has good discrimination ability if the speech signal is of sufficient intensity.

Frequently, the patient with a conductive loss of hearing complains of tinnitus, which may be localized in one ear or in both ears, or unlocalized in the head. In the case of a conductive impairment, the tinnitus tends to be relatively low in pitch.

Sensorineural hearing loss occurs with pathology in the inner ear or along the nerve...
pathway from the inner ear to the brainstem. Hearing loss from cochlear disorders alone is termed sensory loss. As mentioned, there exists some ambiguity among audiologists, neurologists, and otologists concerning what is a retrocochlear and what is a central problem. For the purposes of this discussion, we define retrocochlear as between the cochlea and the brainstem (see below).

The term sensorineural includes both cochlear and retrocochlear disorders. A pure sensorineural impairment exists when the sound-conducting mechanism (outer and middle ear) is normal in every respect, but a disorder is present in the cochlea or auditory nerve. Sensorineural impairment can be congenital or acquired. Congenital sensorineural hearing loss may result from hereditary factors, malformation of the cochlea, in utero viral infections, or birth trauma. The cause of most sensorineural hearing loss is unknown. Acquired sensorineural hearing loss may be caused by noise exposure, acoustic tumor, head injury, infection, toxic drug effects, vascular disease, or presbycusis.

The configuration of the audiogram demonstrating a sensorineural hearing loss may vary significantly and, in some instances, may suggest the cause of the loss. Many people with sensorineural losses experience a loss only in the high-frequency region. These individuals have no difficulty understanding speech at normal intensities in a quiet environment, since low-frequency hearing is unimpaired. However, they do experience difficulty in understanding speech in a noisy environment. Generally, the low frequencies are defined as the range from 250 Hz to 750 Hz, the middle frequencies as 1000 Hz to 3000 Hz, and the high frequencies as 4000 Hz to 8000 Hz on the standard audiogram.
Loudness recruitment is usually associated with sensory loss of cochlear origin, which constitutes the majority of sensorineural losses. Recruitment is an abnormally rapid growth of loudness with an increase in intensity. The recruiting patient with sensory loss will not hear low-intensity sounds at all and may just barely hear sounds of moderate intensity, but the recruitment of loudness may cause moderately loud sounds to be perceived as uncomfortably loud. This disruption of normal loudness function may be painful to the individual and require the use of variable compression circuitry should the patient pursue hearing aid use.

The patient with sensorineural hearing loss is usually subject to tinnitus of a somewhat different sort from that associated with conductive hearing loss. Generally, the patient with sensorineural loss reports a constant ringing or buzzing noise, which may be localized in either ear or may not be localized. In general, the pitch of tinnitus tends to be higher in sensorineural impairment than in conductive impairment. In addition, the patient may report that tinnitus is only present at night or when background noise is minimal, when in fact it is always present, but the patient perceives it only in quiet environments.

In sensorineural losses, the audiometric Weber test is expected to lateralize to the better hearing ear. Audiometrically, sensorineural loss is characterized by overlapping air and bone conduction thresholds. The tympanogram is typically normal, and acoustic reflexes may be present, elevated, or absent. The audiometric findings for a typical sensorineural hearing loss are displayed in Figure 7.12.

Contrary to a commonly held misconception, sensorineural hearing loss may be

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![Figure 7.12](image)

Pure-tone air and bone conduction findings for a sensorineural hearing loss.
helped by the use of hearing aids. Current technology uses full dynamic range compression to increase significantly the effectiveness of amplification.

Mixed hearing loss consists of a conductive and a sensorineural component in the same ear. The patient's behavior will reflect attributes of both a conductive and a sensorineural disorder. Causes of mixed hearing loss may be any combination of the conditions described above for conductive and sensorineural hearing loss. The conductive component of the mixed hearing loss may be corrected by successful medical or surgical treatment, but the sensorineural component is not reversible. The pure-tone audiometric pattern for a mixed hearing loss is displayed in Figure 7.13. With a mixed loss, both air and bone conduction thresholds are elevated, but bone conduction thresholds are better than air conduction thresholds. The difference between the two thresholds, referred to as the air-bone gap, represents the amount of the conductive component present.

Sensory versus Neural Lesions

The problems of differentiating cochlear dysfunction from eighth-nerve lesions have received major emphasis during the past several years. In fact, this area has been emphasized to the extent that some audiologists have limited their concept of differential audiology primarily to tests that assist in localizing the defect within the sensorineural mechanism. The neurologist's interest in sensorineural hearing loss is with regard to the possibility of a cerebellopontine angle tumor. Although many referrals for audiological evaluation are made for this reason, we must emphasize that auditory speech discrimination scores fall in the normal range for these patients with Ménière's disease. In eighth-nerve unilateral hearing loss in the high frequencies, one may expect to find decreases in word discrimination scores, such decreases would come from discrimination tasks that are used in the evaluation of the eighth nerve, e.g., pure-tone audiometric and pure-tone speech discrimination tests.

Central

As would be expected, the central nervous system dysfunction in individuals with auditory dysfunction may be manifested by pure-tone discrimination scores. For instance, pure-tone auditory discrimination scores are often decreased in patients with auditory dysfunction, especially if one has not received sensory training of any type. This training may include occupational, vocational, and educational training.

*Figure 7.13.*

Pure-tone air and bone conduction findings for a mixed hearing loss.
must emphasize that even the more sophisticated special auditory tests cannot determine the specific pathology underlying the disorder. An MRI may indicate the presence of an abnormality somewhere in the nervous system, but it does not necessarily define the nature of the pathology. The audiologic tests, however, highlight patterns of auditory behavior that are generally associated with cochlear or neural involvement.

Routine pure-tone and speech testing can yield valuable information on the site of lesion during the initial phase of the differential audiologic study. For example, a pure-tone configuration that is often seen in patients with a presumptive diagnosis of Ménière's disease is a unilateral hearing loss most pronounced in the low-frequency range. In sharp contrast, patients with eighth-nerve lesions frequently present a unilateral hearing impairment most evident in the high frequencies and poor speech discrimination. Although such generalizations may describe a substantial number of cases falling into these two categories, numerous exceptions are encountered with either cochlear or neural pathology. Measures, such as tone decay, acoustic reflex measures, acoustic reflex decay, and speech discrimination at high-intensity levels must be used to distinguish between eighth-nerve, extraaxial, and intraxial brainstem dysfunction.

**Central Auditory Disorders**

As would be anticipated, lesions within the central auditory system are difficult to detect or localize. In fact, many central auditory dysfunctions are not demonstrated by conventional audiologic measurements. Individuals with known lesions in the central auditory tracts may not manifest any significant hearing loss when tested by conventional pure-tone audiometry. Total removal of one hemisphere of the brain in humans has not resulted in any major change of auditory sensitivity in either ear. Central disorders of hearing are quite unusual. When accompanied by other neurologic signs and symptoms, a central diagnosis is suggested. Normal measures mentioned above, such as tone decay or acoustic reflex, strongly suggest an eighth-nerve lesion. One excludes eighth-nerve lesions as a separate category and concentrates on the central auditory brainstem and hemispheric pathways. Neuroimaging procedures such as MRI may help to localize the abnormality.

**Tinnitus**

_Ear and head noises, the most common complaints presented to the audiologist or otolaryngologist_, are frequently seen by the neurologist as well. Up to 52% of the adult population has tinnitus, with 20% of the population rating their condition as severe. Tinnitus may be considered a significant symptom when its intensity so overrides normal environmental sounds that it invades the consciousness. The patient experiencing tinnitus may describe the sound as ringing, roaring, hissing, whistling, chirping, rustling, clicking, or buzzing, or use other descriptors. Although most patients report the tinnitus to be constant, others report it to be intermittent, fluctuating, or pulsating. Tinnitus may be perceived as a high- or low-pitched tone, a band of noise, or some combination of such sounds.

The perceived loudness of tinnitus in any patient may be intense enough to be highly debilitating. Most patients with sensorineural hearing loss report tinnitus to be a high-frequency tone, but tinnitus associated with conductive hearing loss tends to be low in frequency. However, knowledge of the pitch of the tinnitus is of little diagnostic benefit other than allowing for the gross dichotomy of conductive versus neural pathology.

Most tinnitus sufferers have a concomitant loss of hearing, which may be either conductive or sensorineural. A minority of tinnitus patients have audiometrically hearing sensitivity. Tinnitus may precede or follow the onset of a loss in hearing, or the two may occur simultaneously.
Tinnitus is a symptom of an underlying disease or specific lesion when it is perceived above the intensity levels of environmental sounds. It may be the first symptom that brings the patient to a neurologist. The complaint may be an early symptom of a tumor in the internal auditory meatus or in the cerebellopontine angle, a glomus tumor, or a vascular abnormality in the temporal bone or skull. Because tinnitus may be a characteristic symptom of a number of disorders, a complete medical and audiologic evaluation is an important initial step in the management process.

**CLASSIFICATION**

*Subjective tinnitus* is an auditory sensation heard only by the patient. It may be present in one or both ears or localized within the head. For most patients, tinnitus is a subjective sensation. This type of tinnitus can result from a lesion involving the external ear canal, tympanic membrane, ossicles, cochlea, auditory nerve, brainstem, and cortex. The most common cause is cochlear disease. Tinnitus associated with Ménière's syndrome is often low pitched and continuous and is described as a hollow seashell sound or very loud roaring. Tinnitus with otosclerosis is also low pitched, is described as a buzzing or roaring sound, and may be continuous or intermittent. Continuous bilateral or unilateral high-pitched tinnitus often accompanies chronic noise-induced hearing loss, presbycusis, and hearing loss due to ototoxic drugs. A number of drugs such as aminoglycosides, quinidine, salicylates, indomethacin, carbamazepine, propranolol, levodopa, aminophylline, and caffeine, may produce tinnitus with or without associated hearing loss.

*Objective tinnitus* is far less frequent than subjective tinnitus. It is perceived not only by the patient, but by the examiner as well. Objective tinnitus may be vascular (via arteriovenous malformation or fistula) or mechanical in origin. Objective mechanical tinnitus is due to abnormal muscular contraction of the nasopharynx or middle ear, as may occur in pulsatile myoclonus. Objective tinnitus of vascular origin may also be a referred bruit from stenosis in the carotid or verteobasilar system.

Tinnitus may be classified as mild, moderate, or severe. *Mild* tinnitus is usually noticed only in quiet environments or at bedtime. It is usually not very disturbing, and the patient can be easily distracted from the tinnitus by other stimuli. *Moderate* tinnitus is more intense and is constantly present; the patient is conscious of the tinnitus when attempting to concentrate or when trying to sleep. *Severe* tinnitus may disable individuals to the extent that they are unable to concentrate on little other than the tinnitus itself.

**EXAMINATION**

*Basic Office Examination of Hearing.* Whether or not the patient's complaint is one of hearing loss, a basic assessment of auditory function should be part of the neurologic examination. The external ear should be inspected with an otoscope to determine the patency of the external ear canal and the integrity of the tympanic membrane. If the external canal is occluded by cerumen, simple tests of hearing may be invalidated. The cerumen should be removed, if possible, with warm water lavage using a syringe with a 5- to 8-cm piece of rubber tubing affixed to the end to avoid injury to the ear. If water lavage has not removed impacted cerumen, a neurologist should refer the patient to an otolaryngologist for removal.

Assuming there is no cerumen in the external ear canal, the tympanic membrane should be inspected. The neurologist should be able to recognize an inflamed, bulging, or scarred drum and should note whether there is perforation of the tympanic membrane, blood behind the eardrum, or a pulsating blue mass that may indicate a glomus jugulare tumor. Excellent descriptions of tympanic membrane findings may be found in modern texts of otology. At times it may be helpful to inspect the mobility of the eardrum by increasing pressure within the external canal, using a hand-held pneumatic bulb attached by tubing to an outlet in the otoscope. Little or no mobility of the tympanic membrane is considered the classic finding in Meniere's disease.

The otic conductive examination may include the Weber test, which involves the pricking of the pinna of the better-hearing ear, in which the Weber test may be conducted with a 250 or 125 Hz stimulus, as noted on the audiogram.

**WEBER REACTION**

The Weber reaction is an important test in the evaluation of hearing. It is performed by touching the softest end of the tuning fork to the midline of the head at the vertex and observing the direction in which the patient indicates the sound is heard. If the patient can hear the sound equally well in both ears, the Weber reaction is normal. If the patient hears the sound in only one ear, the Weber reaction is abnormal. The Weber reaction is abnormal in a patient with a conductive hearing loss, as it indicates that the sound is heard more clearly in the better-hearing ear. It is also abnormal in a patient with a hearing loss in the better-hearing ear, as it indicates that the sound is heard more clearly in the less-hearing ear. The Weber reaction is normal in a patient with a hearing loss in both ears, as it indicates that the sound is heard equally well in both ears.

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lymphatic membrane suggests fluid or a mass behind the drum, or a fixed ossicular chain.

The office examination of hearing loss may include tuning fork tests of air and bone conduction. Tuning forks at a frequency of 256 or 128 Hz should not be used because of the vibrations they produce by bone conduction, which the patient may mistake for sound; 512 Hz is the lowest useful frequency. Two standard tuning fork tests are the Weber and Rinne tests.

**Weber Test.** The Weber test is based on the principle that the sound, when transmitted by bone conduction, will be localized to the better-hearing ear or the ear with the greatest conductive deficit. The test can determine the type of hearing impairment when the two ears are affected to different degrees. The stem of a vibrating tuning fork is placed on the skull in the midline, and the patient is asked to indicate in which ear the sound is heard. The usual location described is the forehead, but better locations are the nasal bones or teeth when a stronger bone conduction stimulus is required. In unilateral hearing losses, lateralization to the poorer-hearing ear indicates an element of conductive impairment in that ear. Lateralization to the better-hearing ear suggests that the problem in the opposite ear is sensorineural.

**Rinne Test.** The Rinne test is probably the most commonly used tuning fork test, but the name is usually mispronounced: It is German, not French, and is accented on the first syllable (Rin'neh). The Rinne test is a comparison of the patient's hearing sensitivity by bone conduction and air conduction. A normal individual will perceive the air-conducted sound as louder than, or the same as, bone-conducted sound. Proper placement of the tuning fork in each situation is important. When testing by bone conduction, the stem fork should be placed firmly on the mastoid, as near to the posterior superior edge of the ear canal as possible. The stem should not touch the auricle of the external canal, which should be held to the side by the examiner's fingers. Touching the external ear itself could give false results because of vibration of the auricle.

When testing by air conduction, the fork is held about 2.5 cm lateral to the tragus. In the Rinne test, when the conduction mechanism is normal in an ear (i.e., in individuals with normal hearing and in those with sensorineural hearing impairment), air conduction will be heard better than bone conduction as it is a more efficient means of sound transmission. This finding is termed a positive Rinne. Bone conduction will be heard better than air conduction when there is a deficit in the conduction mechanism; this is referred to as a negative Rinne. A conductive deficit of more than 15 dB reverses the tuning fork responses (i.e., bone conduction is better than air conduction) at 512 Hz. When testing by bone conduction, the examiner should not forget to have the patient remove his or her eyeglasses: the earpiece can interfere with proper placement of the stem of the tuning fork or give inappropriate conduction or vibratory information. Although tuning fork tests allow the examiner to distinguish conductive and sensorineural loss and, in some cases, lateralize the symptomatic ear, it does not evaluate the degree of impairment or the effects of that impairment on speech understanding.

**Tests of Auditory Function**

An audiologic assessment comprises pure-tone air and bone conduction testing and speech threshold and word discrimination measures. *Threshold* is defined as the lowest intensity (measured in decibels) at which an individual can detect a pure tone or speech signal more than 50% of the time. Pure-tone air and bone thresholds are established for frequencies from 250 Hz to 8000 Hz. This frequency range is important to the detection and understanding of the speech signal. Hearing is considered normal when threshold sensitivity is between 0 and 25 dB for frequencies of 250 Hz to 8000 Hz (Fig. 7.14). Responses above 25 dB are classified by degree as mild, moderate, severe, moderately severe, and profound (Fig. 7.14). Responses
at 500 Hz, 1000 Hz, and 2000 Hz are averaged together to compute the pure-tone average (PTA).

In the measurement of bone conduction thresholds, pure tones are transmitted via a bone oscillator, usually placed on the mastoid. This signal directly stimulates the cochlea, bypassing the external and middle ear. The presence of decreased air conduction thresholds and normal sensitivity by bone conduction suggests abnormality in the external ear or middle ear system and is termed a conductive hearing loss.

A speech reception threshold is the lowest intensity at which an equally weighted two-syllable word is understood approximately 50% of the time. The PTA and speech reception threshold should be within 7 dB of each other. Comparison of the speech reception threshold and the pure tone average serves as a check on the validity of the pure-tone thresholds. Discrepancies between these measures may suggest a functional or nonorganic hearing loss.

Speech discrimination is a tool used to assess an individual's ability to understand a speech signal at normal or above normal conversational levels. Most commonly, a phonetically-balanced word list of 50 one-syllable words is presented to the patient at a suprathreshold level. The patient’s score is represented as a percentage of the number of words correct. Generally, discrimination ability decreases proportionately with an increase of hearing impairment. However, there is an exception in conductive hearing loss in which discrimination ability remains relatively good because the inner ear system is normal. Poor discrimination ability in the presence of relatively good hearing sensitivity may suggest retrocochlear pathology such as acoustic neuroma and should be aggressively pursued by the clinician.

**IMMITTANCE TEST BATTERY**

Tympanometry, static acoustic immittance, and acoustic reflex threshold measures make up the acoustic immittance test battery. Tympanometry is a measure of middle ear mobility when air pressure in the external canal is varied. Results are graphically represented, with pressure along the x axis and compliance along the y axis. Normal tympanograms have a peak pressure point of ±50 mm H₂O.

Static compliance refers to the ease of flow of acoustic energy through the middle ear. Immittance measures are obtained at +200 mm H₂O and again after the tympanic membrane is stimulated with 300 to 400 mL of saline. If the tympanic membrane is intact and the middle ear pressure is normal, then the patient responds normally. If these tests are abnormal, then further investigation is needed.
common cause of excessive tympanic membrane mobility. Examples are shown in Figure 7.15. Extremely high equivalent middle ear volume and low static compliance suggest tympanic membrane perforation.

The acoustic reflex threshold is the lowest intensity needed to elicit a contraction of the stapedius and tensor tympani muscles using a pure-tone stimulus. The introduction of an intense sound into the ear canal results in a temporary increase in middle ear impedance. This phenomenon occurs bilaterally; however, it is typically measured in one ear at a time. Contralateral reflexes are measured by stimulating one ear and measuring the reflex from the contralateral ear. Ipsilateral reflexes are measured by stimulating

![Type A](image)

![Type B](image)

![Type C](image)

![Type A](image)

![Type A](image)

*Figure 7.15.*

Representative impedance measured by tympanogram. The tympanogram types are as follows. Type A represents normal middle ear function. Type A curves have normal mobility and pressures and typify normal hearing and semineural hearing loss with normally functioning middle ear systems. Type B represents restricted tympanic membrane mobility. Type B curves have little or no point of maximum mobility and reduced compliance. This curve is very typical of a stiff middle ear system as is seen in serous media. Type C represents significant negative pressure in the middle ear cavity. Type C curves have normal mobility and negative pressure at the point of maximum mobility (negative pressure is considered significant for treatment when more negative than -200 mm Hg). Type As represents normal middle ear pressure but reduced mobility, suggesting limited mobility of the tympanic membrane and middle ear structures, commonly seen in fixation of the ossicular chain. Type Ao represents normal middle ear pressure but hypermobility. This pattern indicates a flaccid tympanic membrane due to disarticulation of the ossicular chain or partial atrophy of the eardrum.
and recording from the same ear. Reflexes occur between 70 and 100 dB SPL (sound pressure level) in normal ears. Middle ear abnormalities or significant sensorineural hearing losses may elevate or obliterate the acoustic reflexes. Retrocochlear pathology and facial nerve disorders may also affect contralateral and ipsilateral acoustic reflexes.

**BRAINSTEM AUDITORY EVOKED POTENTIALS**

Brainstem auditory evoked potentials (BAEPs) are also known as brainstem auditory evoked responses (BAERs) or auditory brainstem responses (ABRs). These physiologic measures can be used to evaluate the auditory pathways from the ear to the upper brainstem. In addition, ABR threshold testing may be used to determine behavioral threshold sensitivity in infants or uncooperative patients. The most consistent and reproducible potentials are a series of five submicrovolts that are seen within 10 msec of an auditory stimulus. These potentials are recorded by averaging 1000 to 2000 responses from click stimuli by use of a computer system and amplifying the response (Fig. 7.16). The anatomic correlates of the five reliable potentials have only been roughly approximated. Wave I of the BAEP is a manifestation of the action potentials of the eighth nerve and is generated in the distal portion of the nerve adjacent to the cochlea. Wave II may be generated by the eighth nerve or cochlear nuclei. Wave III is thought to be generated at the level of the superior olive, and waves IV and V are generated in the rostral pons or in the midbrain near the inferior colliculus. The complex anatomy of the central auditory pathway, with multiple crossing of fibers from the level of the cochlear nuclei to the inferior colliculus, makes interpretation of central disturbances in the evoked responses difficult. Excellent reviews of the generation of the potential and interpretation of abnormality are found in recent contributions.

The BAEP is a sensitive, noninvasive diagnostic test for the diagnosis of cerebellopontine angle tumors. This test is used to differentiate cochlear from eighth-nerve hearing defects and, on some occasions, demonstrates an auditory abnormality when behavioral audiometric testing is still normal. Most patients with acoustic tumors have abnormal responses.

![Figure 7.16](image-url)

*Figure 7.16.*

Brainstem auditory evoked potential (BAEP) in a normal adult. Responses were recorded between electrodes on the vertex and the ipsilateral mastoid. Waves I, III and V are labeled, *ms/div* milliseconds per division, *μV/div* microvolts per division.

The absence of waves 0–III or marked hearing loss of the potential abnormal wave intervals (0–III or normal wave intervals 0–III) or an abnormal wave pattern or abnormal click rate is a cochlear pathology or abnormal pattern of responses from normative data sets.
The absence of waves III and V has been
seen in some patients with vestibular
schwannoma and in cerebellopontine angle
tumors. Such patients often have
impaired hearing deficits with poor discrimi-
nation on behavioral testing, suggesting
retrocochlear disease. The absence of all
waves should not occur unless a severe
hearing loss exists. The most specific evoked
potential abnormality is an increase in inter-
wave intervals. Abnormal interwave laten-
ces (I-III or I-V) are the most specific and
discriminable abnormalities seen with cerebel-
opontine angle tumors. The abnormal prol-
ongation or absence of wave V at increased
click rates is also characteristic of retro-
cochlear pathology. Increased absolute la-
tencies of all waves, compared with re-
flections from the other ear or with clinical
normative data, may signify a conductive
deficit.

**ELECTROCOCHLEOGRAPHY**

Electrocochleography (ECoG) is a
method of recording the stimulus-related
electrical potentials associated with the in-
ter ear and auditory nerve, including the
cochlear microphonic summing potential
(SP) and the compound action potential
(AP) of the auditory nerve. This measure is
beneficial in the differential diagnosis of
certain types of sensory disorders, such as
Ménière's disease or cochlear hydrops. The
amplitudes of the SP and AP are measured
and are of primary interest in evaluating an
ear for increased endolymphatic pressure.

**Therapy for Auditory Disorders**

Therapy for auditory disorders is largely
the province of the otolaryngologist and the
audiologist. However, the neurologist inter-
ested in neuro-otology should have some
knowledge of therapy to promote appropri-
ate referrals. The nature of the treatment
program depends on the exact diagnosis
(i.e., the type of hearing loss) and the age of
the patient. Both medical and surgical ther-
apiess are appropriate, depending on the
ature of the disorder. Medical or surgical
therapy is used in conductive losses due to
otosclerosis. Surgery is the primary therapy
for hearing loss caused by otosclerosis, usu-
ally manifested as a conductive type of hear-
ing loss, as described above. However, al-
most every type of nonconductive hearing
loss may be helped by a variety of amplifi-
cation devices and/or counseling.

**Amplification**

Contrary to a commonly held misconcep-
tion, sensorineural hearing loss may be
helped by the use of a hearing aid. How-
ever, hearing aids only compensate for loss
of sensitivity, but the manner in which in-
creased loudness is achieved may reduce
distortion and significantly increase discrimi-
nation in certain situations. Modern hearing
aids use the latest microcircuitry and signal-
processing techniques, such as digital filter-
ing, to improve significantly the effective-
ness of amplification.

In addition to hearing aids, devices such as
telephone amplifiers, television/radio ac-
cess systems, personal listening systems, and
alerting devices are designed to improve
communication in difficult listening situa-
tions. There are many assistive devices on
the market, and new systems and modifica-
tions are appearing at an accelerating rate.

We note that the hearing aid is the most
important rehabilitative tool available for
the management of sensorineural hearing
loss; however, counseling should be a cen-
tral focus of any management strategy for
the hearing-impaired adult. In addition, the
hearing-impaired should receive counseling
both before and after the provision of am-
plification. Lastly, cochlear implants have
proven to be extremely beneficial for indi-
viduals with severe to profound hearing
loss who receive minimal benefit from am-
plification.
Management of Tinnitus

The complete evaluation of the tinnitus patient should be approached from a dual perspective. The patient with tinnitus, regardless of location, type, or severity, must first have a thorough otologic and audiologic examination. If there are accompanying symptoms, a complete neurologic examination may be appropriate. The patient with an isolated symptom of a persistent, yet unexplained, tinnitus should receive follow-up examinations at definite intervals when initial medical, otologic, and neurologic studies reveal no evidence of disease. Tinnitus may be the first symptom of a disorder, appearing long before any other symptom, including hearing loss. When medical and otologic examinations fail to disclose a remediable cause for the tinnitus, or when a diagnosis is ascertained for which no known medical therapy is presently available, the tinnitus patient should undergo further evaluation to determine the most appropriate nonmedical avenue for rehabilitation.

When a specific otologic cause for the tinnitus is identified, otologic management is indicated. When a lesion or disease process is not identifiable, then tinnitus management is more difficult. Given no underlying otologic disease, there is at present no effective surgery or medical therapy for the treatment of tinnitus.

Research on the effectiveness of pharmacologic therapy for tinnitus, although certainly encouraging, involves medications such as carbamazepine, lidocaine, and intravenous barbiturates, whose potentially serious side effects limit their usefulness. There is some suggestion that relatively low doses may prove effective in tinnitus management.

MASKING

The use of masking as a management tool in the treatment of the tinnitus patient has met with mixed success over the years. The audiologist should remain cognizant of factors such as the patient's perception of the pitch and loudness and the overall spectral intensity of the masking signal. The referring neurologist should be aware of these issues as well.

Tinnitus maskers are designed to provide relief to the tinnitus sufferer by introducing an external masking sound into the affected ear or ears, thereby minimizing or eliminating the perception of the tinnitus. Although the use of tinnitus maskers has not proved universally successful, masking is still a feasible technique that cannot be ignored. The actual efficacy of tinnitus maskers in the average tinnitus patient is probably less than 30%. The use of a hearing aid may be more beneficial by addressing the primary hearing problem.

BIOFEEDBACK

Experience with tinnitus patients reveals that many have relatively high levels of anxiety, tension, or other symptoms of chronic stress. There is a significant correlation between tinnitus and tension. Biofeedback as a treatment in the management of tinnitus was first reported in the literature in the mid-1970s. These early studies reported the use of biofeedback as effective in the relief of tinnitus or the associated annoyance produced by it. Biofeedback is quite effective for enhancing relaxation, as are traditional relaxation procedures. When used together, muscle tension and general life stresses are reported to be reduced.

COUNSELING

Effective counseling is one important aspect of tinnitus management regardless of the management approaches taken with a given patient. Many patients are frightened by tinnitus and need a careful and clear explanation of the disorder, coupled with firm reassurance from both the neurologist and the audiologist. In light of the various effects tinnitus may have on a given patient, counseling must be directed toward all of the patient's difficulties, not this specific problem in isolation.
**SUGGESTED READINGS**


Diagnostic imaging techniques are becoming increasingly valuable in the evaluation of ophthalmologic patients. Recent advances in technology have greatly improved resolution and now provide physiologic as well as anatomic information. Although plain film radiology, computed tomography, and, more recently, magnetic resonance imaging are important modalities, other noninvasive techniques have important new applications. In this chapter we examine ultrasound, positron emission tomography, and nuclear medicine as they are currently used in evaluation of the patient with neuro-ophthalmologic symptoms.

ULTRASOUND

Ultrasound has been used in evaluating diseases of the globe and orbit for nearly 40 years. Earliest applications used amplitude (A) mode devices in which echoes are displayed as spikes whose magnitude depends on the density of the reflecting tissue. Such a device was used in the late 1950s by Macht and Hughes to detect intraocular tumors and by Oksala who described findings in tumors, vitreous hemorrhage, retinal detachment, and foreign bodies. The first use of brightness (B) mode techniques in ophthalmology was reported by Baum and Greenwood. Early B scans were obtained by sweeping an ultrasound probe across the eye to obtain a continuous series of A scans that were then spatially summed to produce a two-dimensional image.

Both techniques have advanced over the years, and both continue to be used to image orbital disease or intraocular anatomy obscured by opaque media where direct vision of the posterior segment with an ophthalmoscope may be impossible. In addition to defining lesion size and location, ultrasound can characterize the tissue as cystic, solid, or complex; determine its vascularity; and identify areas of calcification. Ultrasound often complements ophthalmoscopy. For example, with retinal detachment, easily seen with an ophthalmoscope in patients with clear media, ultrasound can exclude underlying choroidal pathology. A-scan techniques also provide an accurate means of obtaining measurements, as echoes reflected from two separate locations will reach the probe at different times and this time difference can be used to determine the distance between them. The application of the Doppler phenomenon to diagnostic ultrasound has provided a
Way of studying vascular anatomy and function. Doppler imaging is based on the principle that when an emitting source and a receiving sensor move with respect to one another, a shift in the frequency of the emitted sound wave occurs. This frequency shift is measured, and the direction and velocity of movement can be determined. The introduction of color Doppler imaging now has provided simultaneous 2-D visualization of structure and blood flow by superimposing Doppler information in color over a standard gray-scale image. Spectral analysis of the Doppler waveform is used to quantify blood flow velocity and, if accurate vessel diameters can be measured, will allow calculation of flow volume. Along with gray-scale ultrasound, color and duplex Doppler imaging has been used to evaluate normal vascular structures, demonstrate flow in ocular tumors, assess traumatic injury, and diagnose vascular malformations and fistulae. Modern high-resolution equipment has improved image quality and resolution and made ultrasound an essential part of ophthalmologic evaluations.

**Equipment, Technique, and Safety Considerations**

Most ophthalmologic scanning is performed with dedicated ultrasound machines using frequencies in the range of 5 to 20 MHz. Nondedicated machines have been used and appear to be adaptable to eye studies if transducers of appropriate frequency are employed. Conventional clinical ultrasound studies are usually performed in the 3.5 to 10.0 MHz range. Axial and lateral resolution of less than 1 mm is available with some 7.5 MHz and 10.0 MHz transducers, making them appropriate for eye scanning. Recently, use of very high frequency transducers has been reported as a means of improving resolution. These B-scan instruments, which operate in the 50 to 100 MHz range, provide near-microscopic resolution but at the expense of very limited penetration and are useful only for the anterior segment and superficial adnexal structures. In addition, curvature of the eye may result in degradation of image quality. This technique appears to be useful for evaluating anterior segment tumors and scleral and corneal disease entities and for preoperative study of structures behind corneal opacities. Measurement of very small structures is also facilitated. Further refinement of this instrumentation may lead to extended clinical and research usefulness.

Patients are examined in the supine position. For transorbital studies, the ultrasound transducer is applied directly to the closed eye with use of a sterile coupling gel or eye cup. Minimal pressure should be applied to reduce artifacts, and images are obtained and recorded in the sagittal and transverse planes. Gaze is directed toward the ceiling for most scans, but other positions can be used to optimize visualization of the entire eye. Depending on the direction of flow with respect to the transducer, blood flow is displayed in either red or blue when color Doppler imaging is used. The assignment of color is arbitrary and can be changed by the examiner; however, since the ultrasound beam is essentially parallel to the orbital and ocular vessels, flow toward the transducer is typically depicted as red and that away from the transducer as blue. This provides ease of visualization, as arteries and veins will appear red and blue, respectively.

Flow settings are chosen that are appropriate for the velocity of the interrogated vessel. Thus, for the ophthalmic artery, medium-to-high settings should be used, while for smaller vessels such as the central retinal or ciliary arteries, low-flow settings are employed. Color gain and sensitivity are adjusted to minimize artifacts resulting from movement of the lid or globe. To obtain Doppler spectra, a sample volume is placed within the vessel. The use of color Doppler imaging helps in identifying vessels, facilitates correct placement of the sample volume, and allows estimation of the Doppler angle so that measured frequency shifts can be converted to velocity estimates. Measurements
should be taken only when several consecutive waveforms are obtained. In addition to peak systolic (PSV) and end diastolic velocities (EDV), ratios of these velocities are frequently calculated to allow comparisons that are independent of the Doppler angle used. The resistive index (RI = PSV − EDV/PSV) and the pulsatility index (PI = PSV − EDV/V) are two such indices that are frequently reported. For purposes of comparing flow in different vessels, these indices may increase accuracy. This is a result of the fact that although changing the Doppler angle alters the absolute systolic and diastolic velocities, it does not alter the relationship between them. Calculation of RI and PI also provides quantitative measures of flow patterns useful in assessing and comparing the resistance of the downstream vascular bed.

As with any diagnostic technique, the safety of ultrasound is of fundamental importance. Because of the real or theoretical possibility of detrimental biologic effects, limits on energy deposition have been established by the Food and Drug Administration, and guidelines proposed by the Bioeffects Committee of the American Institute of Ultrasound in Medicine (AIUM). Since no adverse effects of ultrasound have been reported in more than three decades of use, formulation of limits is difficult. However, as higher frequencies are used and exposure levels increase, safety considerations must be kept in mind, particularly in pulsed Doppler applications. The current limit suggested by the FDA for ophthalmic applications is 17 mW/cm², and some studies will exceed this limit. AIUM guidelines are somewhat less restrictive and state that no significant bioeffects have been reported at intensities below 100 mW/cm² for unfocused ultrasound and below 1 W/cm² for focused ultrasound, which is commonly employed in clinical studies. Reported intensities vary somewhat and depend on the equipment used but typically fall well below these guidelines. Nonetheless, Doppler power should be set at the lowest levels that provide an adequate study, and exposure to spectral Doppler should be kept to a minimum.

**Sonographic Anatomy and Perfusion Patterns**

The eye is an ideal organ for ultrasound. It is essentially an empty globe divided into two compartments and filled with acoustically clear liquids with sound transmission characteristics similar to those of normal saline (Fig. 8.1A). In the normal globe, internal structures are distinctly visible. However, with an opaque lens or optically opaque media, visualization of posterior structures is obscured, and sonography becomes important. For many applications, ultrasound has been supplanted by computed tomography (CT) and magnetic resonance imaging (MRI). CT allows visualization of the entire orbit and is ideal for evaluating bony structures. Contrast enhancement provides additional information about vascular lesions. MRI is capable of displaying subtle changes within soft tissue and provides tissue characterization not possible with other modalities. Nonetheless, ultrasound provides available real-time imaging free of ionizing radiation and, with the use of color and Doppler, information regarding vascular structures and flow patterns that is not otherwise obtainable.

Examination of the anterior segment requires high-frequency transducers and often the use of a standoff mechanism (Fig. 8.1B). Posterior structures are more easily seen with contact scans. The vitreous is normally echo free and appears as a black area between the posterior lens echo and the retinal interface. The retina is highly reflective and not easily separated from the choroid in the normal eye. Morphologic abnormalities and the presence of intracellular blood or foreign bodies provide tissue interfaces and altered acoustic impedance and are easily seen sonographically.

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**Figure 8.1.**
Normal globe. **A.** Sonogram of the normal globe showing the cornea, iris, lens, vitreous, and the echoicogenic retina/choroid layer posteriorly. **B.** Higher-frequency transducers provide improved resolution at the expense of penetration. Here the anterior chamber is clearly seen including eyelid, cornea, ciliary body, lens, and lateral angles. (Courtesy of Dr. Luiz Antonio Balliao, Brazil.)

If inflamed (Fig. 8.2). Progressive increase in size may indicate tumor, as described below. This has been described using both A-scan and B-scan methods. Accumulation of fluid adjacent to the sclera and within the optic nerve sheath is seen, along with thickening of the choroidal-scleral complex in inflammatory and infiltrative conditions. Inflammation may also produce thickening and elevation of the optic nerve head. These changes are seen sonographically as is associated retinal detachment, which occurs rarely. Color-flow Doppler may document increased vascularity as expected by clinical findings and as demonstrated in inflammatory processes elsewhere. Drusen, or hyaline bodies of the optic nerve, have been seen sonographically even in cases where the nerve head is normal and the highly reflective, calcified material lies deeper.

Color Doppler imaging allows simultaneous evaluation of structure and blood flow and provides rapid real-time assessment of normal and abnormal vascular structures. A

**Figure 8.2.**
Optic nerve. The retina and optic nerve are imaged in this magnified view of the posterior globe. (Courtesy of Dr. Luiz Antonio Balliao, Brazil.)
transverse scan through the globe at the level of the optic nerve allows depiction of the central retinal artery (CRA) and central retinal vein (CRV) within the anterior portion of the optic nerve shadow. The normal artery and vein are easily distinguished by their color-coded direction of flow and also by analysis of spectral Doppler waveforms. The CRA shows a pulsatile pattern with high systolic velocities, while the vein demonstrates continuous, relatively low-velocity forward flow.

Medial and lateral to the optic nerve, the posterior ciliary arteries can be identified. Although not always seen, the long and short posterior ciliary arteries may be visible in some patients. These vessels are responsible for the choroidal blush seen on angiography, and the color Doppler correlate is usually seen to some extent.

The ophthalmic artery enters the orbit via the optic foramen, lateral and slightly inferior to the optic nerve. After crossing the superior margin of the nerve, it typically proceeds anteriorly on the medial side of the orbit. Cadaver studies have shown that there is considerable variability in the course of the ophthalmic artery; however, the typical pattern was seen in 80% of cases. Portions of the ophthalmic artery are seen sonographically in virtually all normal patients. The superior ophthalmic vein is commonly seen in the medial superior portion of the orbit, the inferior division is not usually visible. The ophthalmic artery normally has a Doppler waveform similar to that of the internal carotid, with a steep systolic upstroke and continuous, low-velocity forward flow in diastole. The ophthalmic vein demonstrates a typical venous pattern of continuous, nonpulsatile flow. Small branches of the ophthalmic artery include the supratrochlear and supraorbital vessels. The course of these is such that they are not usually identified with certainty on orbital sonograms.

Color Doppler findings in the normal orbit have been reported in several series. Erickson et al. studied 26 normal orbits with a 7.5-MHz transducer and identified the ophthalmic artery, central retinal artery, and central retinal vein in all cases. The superior ophthalmic vein was seen in 22 of 26; the inferior division was not identified. Portions of the posterior ciliary arteries, usually the long branches, were seen in all studies. Other series have confirmed the ability of color Doppler to visualize these orbital vessels. Lieb et al. reported a 400-case experience in which they visualized the ophthalmic artery, central retinal artery, posterior ciliary artery, central retinal vein, and portions of the vortex veins draining into the superior ophthalmic.

The analysis of selectively obtained Doppler spectra provides noninvasive measurement of flow velocity and flow patterns in orbital vessels. This information provides insight into orbital hemodynamics and baseline information useful in the study of eye disease in which blood flow is altered. An early study documented changes in flow pattern with position, documenting higher diastolic flow with patients supine than when they were sitting or standing. However, these changes have not been confirmed in recent studies, which suggest that autoregulation within orbital vessels provides compensation. Color and duplex Doppler allows evaluation of blood flow under real-time physiologic conditions and has been shown useful in patients with gaze-induced amaurosis. Change in vascular resistance in the central retinal artery with eye movement has been demonstrated sonographically in a patient with an optic nerve mass and correlated with visual changes. Normal hemodynamics returned in the vessel following surgical excision. This lends support to the theory of a vascular mechanism for gaze-induced amaurosis, as postulated earlier on the basis of angiographic studies. It is likely that retinal and optic nerve ischemia occur secondary to decreased flow in the CRA as well as in smaller adjacent vessels. Increased resistance to flow in the perioptic nerve has also been shown in patients with increased intraocular pressure (IOP) due to acute glaucoma, compared with normal subjects and patients with normal-tension glaucoma. These data also suggest that decreased
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blood supply to the optic disc occurs because of elevated IOP and leads to deterioration of the visual field. Doppler ultrasound was used to study the effect of artificially increased IOP in relation to blood flow. A study of 72 normal subjects demonstrated that CRA velocity progressively diminished as IOP increased and that no Doppler shift was obtained at pressures greater than 80 mm Hg. This absence of the Doppler signal correlated clinically with sudden blackout of vision. Maximal velocity is also seen to decline progressively as a function of age in normal patients.

Variations in orbital blood flow can be induced pharmacologically and may be evaluated using Doppler ultrasound. The effects of topical timolol installation have been examined in animals and in human subjects, and although investigations are not conclusive, the studies illustrate another application of the technique. It appears that timolol decreases the resistive index in the central retinal artery, which may compensate for the vasoconstriction induced by beta blockade and maintain optic nerve perfusion. Further study in normal persons and in patients with ocular disease may improve understanding of these effects on vascular perfusion in the optic nerve.

The accuracy and clinical significance of absolute velocity measurements in orbital vessels has not been definitively established. As technique and equipment vary significantly, comparison of results is difficult. Using Duplex scanning, Lieb et al. reported a mean systolic flow velocity in the central retinal artery of 10.3 ± 2.1 cm/s. This is in agreement with the findings of Berger et al., who used duplex ultrasound, and with Feke, who measured a mean velocity of 10.9 ± 2.0 cm/s at a similar site by laser Doppler velocimetry. However, the values are higher than those obtained by Rena et al. in the branch retinal arteries by laser Doppler technique. Values obtained in the ophthalmic artery tend to be somewhat higher, with values of 31 to 55 cm/s reported, although as for the more distal branches, results are variable and may depend on the ultrasound system and transducer frequency employed. In addition, several studies have confirmed an age-related loss of arterial blood flow in these vessels, and patient age must therefore be considered in interpreting ophthalmic arterial flow values. Indices such as the RI may be more suitable than absolute velocities for comparison and in addition provide information about the proximal and distal vessels.

Inaccuracies in quantitative measurements may be related to technical difficulties in obtaining accurate measurements. Errors in measurement of the Doppler angle are difficult to exclude given anatomic variations and the necessity of measuring from a two-dimensional image. Because frequency shift and velocity calculations are a function of the cosine of the Doppler angle, this becomes an important factor, particularly if the angle approaches or exceeds 60°. Differences in measured velocity also reflect the depth from which values are obtained. This may be related to real differences in flow in different parts of the vessel or to lesser variability of the arterial course in the posterior part of the orbit. In fact, differences probably reflect a combination of factors. Any comparison between normal and disease states should be based on values obtained with the same equipment and measurement parameters. Nonetheless, the technique holds great promise, and if quantitative assessment of velocities and flow patterns in orbital vessels can be proven accurate and baseline normal values can be established, color Doppler imaging may provide a valuable diagnostic tool in vascular disorders of the eye and orbit.

Difficulty in penetrating the skull with ultrasound has limited its usefulness in the intracranial vessels. However, in 1982 Aslidi described a technique to record velocity measurements of the basal cerebral arteries by ultrasound. This technique of transtranular Doppler (TCD) has been extensively evaluated since, and the list of clinical applications continues to expand. Although imaging of the intracranial vessels is also accomplished noninvasively with magnetic resonance angiography and CT angiography as well as
with conventional contrast angiography, TCD is an important new technique that can provide both hemodynamic and morphologic information and is briefly reviewed below.

The TCD examination is performed using a 2-MHz focused-pulse Doppler transducer and usually follows evaluation of the cervical carotid arteries. Both a transtemporal and a suboccipital window are typically used. The transtemporal approach provides the most information but can be the most difficult, as the ultrasound beam must penetrate the temporal bone. This window is used to locate the internal carotid bifurcation, an important landmark identified by the bidirectional signal obtained. This bidirectional signal reflects the flow toward the transducer in the middle cerebral artery (MCA) and away from the transducer in the anterior cerebral artery (ACA). The transtemporal window is also used to visualize the posterior cerebral artery (PCA), which typically demonstrates flow toward the transducer. As the midline is approached, bidirectional flow may be seen in both the ACA and the PCA, indicating that both the ipsilateral and contralateral vessels are being interrogated (Fig. 8.3). The anterior and posterior communicating arteries are identified only when they are involved in a collateral pathway. When found, they have turbulent high-velocity flow.

The intracranial vertebral arteries and the basilar artery are best evaluated from a suboccipital approach with the transducer at the nape of the neck, angled toward the patient's eyes. The vertebral arteries are located on either side of the midline and can be followed to their confluence (Fig. 8.4). Blood flow is normally away from the transducer in these vessels. In addition to these standard windows, a transorbital approach can be used to evaluate the carotid siphon and a submandibular window for the retromandibular and proximal intracranial ICA. These are newer techniques and are less frequently used than the transtemporal and suboccipital windows.

Accurate identification of intracranial vessels is multifactorial, involving primarily depth of sample volume, spatial relationship of Doppler signals, and direction of flow. Although physiologic parameters play a role, ranges have been published for normal subjects that demonstrate good interobserver agreement. If flow direction is reversed from the expected, it can be assumed that there is an anatomic variation or that the vessel is functioning as a collateral channel. In general, the differences in arterial velocities are more important than absolute values, and alterations from the expected patterns suggest hypoplasia or stenosis.

Vascular beds include connective tissues, smooth muscle, and adventitial layer. The vessels have wall thickness. The innervation is provided by parasympathetic and sympathetic fibers.
hypoplasia, stenosis, or collateralization. Velocity tends to decrease with age and increase with anemia. Measures of vascular impedance may be useful, as with Doppler applications in other vascular systems. These measures are ratios of systolic and diastolic flow velocity as described above and suggest conditions in the proximal and distal vessels. Distal to an obstruction, flow is damped and pulsatility decreased, while proximal to a high resistance bed, pulsatility increases.

The clinical applications of TCD are multiple and likely to increase. The technique was initially introduced to monitor vasospasm following subarachnoid hemorrhage but is now used to diagnose intracranial vascular disease, assess collateral vascular pathways and the effects of extracranial occlusive disease, and evaluate vertebrobasilar symptoms, subdural steal, and, in patients with head trauma, vascular malformations or suspected brain death (Fig. 8.5). It is a safe, noninvasive, and easily repeatable examination but is limited by anatomic variations and physiologic variables. It remains a strongly operator-dependent technique with variable sensitivity, best used in conjunction with other modalities for evaluation of the intracranial and orbital vessels. Angiography, CT, and MRI provide superior anatomic images, while TCD yields information about flow by measuring velocity and pulsatility. Its contribution is likely to be a better understanding of intracranial hemodynamics as experience is gained by evaluation of larger groups of patients.

Vascular Lesions

A number of vascular lesions are amenable to investigation with Doppler ultrasound. One common example is the carotid-cavernous fistula. This lesion may occur spontaneously or following trauma and results in shunting of blood into the cavernous venous circulation from the internal carotid. The increased pressure causes marked distension of the veins within the orbit and arterialization of their blood flow pattern, well demonstrated with Doppler flow patterns. In addition, decrease in the size of venous structures and return to normal flow patterns can be documented following therapeutic embolization, thus allowing noninvasive monitoring in these patients. In a series of three cases, Flaherty reported visualization of a dilated, arterialized superior ophthalmic vein with high-velocity flow toward the transducer and thickening of the extracranial muscles. Following embolization in one case, return to normal flow direction and pattern was documented without need for repeat angiography. Kroller et al. reported similar venous dilatation and flow reversal in two patients and also studied effects on the extracranial carotid. As expected, a higher than normal diastolic component and lower resistive index were seen in the ipsilateral ICA, reflecting decreased impedance downstream. Although similar changes have been reported in the carotid and intracerebrovascular vessels in patients with arteriovenous malformations, flow increases were more moderate and retrograde; arterialized flow in the ophthalmic vein is not seen. Thus, although direct visualization of a carotid-cavernous fistula may not be possible with sonography, the diagnosis can be made when high-velocity, low-impedance flow is seen in the ICA in association with dilatation and retrograde arterialized flow in the ipsilateral ophthalmic veins. Although carotid angiography remains necessary prior to embolization, ultrasound can aid in diagnosis and provide a means of monitoring response to therapy.

Color Doppler ultrasound was also used to document an orbital varix in a report by Lief et al. and can directly demonstrate the blood flow. These lesions may be difficult to demonstrate on CT or MRI unless a Valsalva maneuver is performed during the examination. The authors report expansion of the lesion during Valsalva, with cessation of flow at maximal dilatation as indicated by lack of color information. Displacement of the optic nerve was also seen in real time as the varix expanded. On relaxation, the lesion decreased in size, and normal flow returned.
Figure 8.5.

Applications of TCD. A, B. TCD is valuable in identifying areas of vasospasm. This black and white reproduction of color (A) and duplex Doppler (B) images illustrate the typical findings of aliasing with a mosaic pattern and high-velocity, turbulent flow. C. Distal to the area of spasm, a normal non-turbulent flow pattern is seen. D, E, F. Since direction of flow is easily determined with color-flow imaging, TCD can also be used to identify areas of flow reversal indicating collateralization and to image vascular lesions such as this arteriovenous malformation. (Courtesy of Advanced Technology Laboratories, Bothell, WA.)
Because treatment is indicated only for complications of varices, more-invasive studies such as contrast-enhanced CT or orbital neuroradiography may be unnecessary in uncomplicated lesions and reserved for cases where surgery is indicated.

Because static-imaging techniques are limited in their assessment of vascular hemodynamics, Doppler ultrasound can provide valuable additional information. In a case of ophthalmic vein thrombosis reported by Matherly, Doppler imaging clearly demonstrated lack of flow in the SOV, indicating thrombosis, and in addition illustrated collateral shunting into the contralateral orbital veins. The real-time dynamic nature of color Doppler ultrasound allows documentation of subtle vascular changes such as these and can add to the morphologic changes seen with CT and MRI in orbital disease.

Vitreoretinal Abnormalities

Retinal elevation is typically diagnosed by direct visualization at ophthalmoscopic examination. However, when the vitreous compartment is blood filled or an opaque lens prevents visualization, ultrasound can be used to make the diagnosis. The diagnostic criteria are well established and include visualization of a curvilinear echogenic structure attached to the optic nerve head posteriorly and the ora serrata retinae anteriorly and restricted movement of the retinal detachment on movement of the eye (Fig. 8.6). Over time, the detachments may become organized and thickened. When vitreous hemorrhage occurs after trauma or surgery, membranes may develop, which are opaque and may attach to the retina. These membranes are usually less echogenic and more variable in thickness than retinal detachments and demonstrate more mobility with eye movement (Fig. 8.7). In unusual cases, where such membranes attach in the vicinity of the optic disc, they may be difficult to differentiate from a retinal detachment. Demonstration of vascularity within a detached retina and the lack of vessels in a vitreous membrane can enable differentiation in equivocal cases and may alter treatment in vitrectomy candidates. Sonographic evaluation was performed in 25 symptomatic eyes by Wong et al. Seven had areas of retinal detachment, and all of these showed blood flow in a portion of the detached retina by high-resolution color-flow imaging. Fifteen patients had vitreous membranes in which no flow was detected. False positives were seen in diabetic patients, reflecting the neovascularity that may develop.

*Figure 8.6.* Retinal detachment. A. Detached retina can be diagnosed when a curvilinear echogenic structure is seen attaching to the optic nerve head posteriorly. B. This can be seen sonographically even when an opaque lens or dense vitreous as in this patient with cataract. (Courtesy of Dr. Luiz Antonio Balbino, Brazil.)
to identify if the cells are insufficiently clotted to produce an echogenic surface. Organized clots are easily identified as echogenic material within the echo-free vitreous and will typically demonstrate mobility with eye movement. Infections or inflammatory debris within the vitreous mimics the appearance of hemorrhage.

### Ocular and Orbital Masses

Although CT and MR are more frequently used, ultrasonography has proven helpful in the evaluation of ocular and orbital masses and, when color Doppler imaging is added, can demonstrate presence and degree of vascularity.

The most common intraocular tumors in adults are malignant melanoma, metastatic tumors, and hemangioma, and in children, retinoblastoma. Ultrasound can detect mass lesions as small as a millimeter, and as other masses including subretinal hemorrhage and inflammatory foci may mimic tumors clinically, tissue characterization is critical. In addition, a tumor underlying a retinal detachment or in the presence of vitreous hemorrhage may be clinically undetectable. Serial studies can be used to follow lesions over time and differentiate neoplastic from fibroproliferative lesions.

- **Figure 8.7.**
  Vitreous membranes. Vitreous membranes may form following hemorrhage and can be difficult to differentiate from a detached retina. Thickness, point of attachment, and movement should be observed. (Courtesy of Dr. Luiz Antonio Baillio, Brazil.)

- **Figure 8.8.**
  Vitreous hemorrhage. Sonogram of the posterior chamber shows echogenic hemorrhage within the vitreous. This will demonstrate mobility on real-time imaging (A) with ultrasound; hemorrhage is easily seen even with an opaque lens (B). (Courtesy of Dr. Luiz Antonio Baillio, Brazil.)

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In addition, the evaluation using a has been shown to be helpful in identifying the presence of intraocular fluid. This is especially important in the growth of tumors and may lead to the detection of tumors in many cases. In cases of normal Doppler signal, the presence of malignant masses can be detected in various pediatric tumors.
Malignant melanomas typically appear as a mass along the inner globe contour (Fig. 8.9). Most have a smooth, convex contour, although central necrosis or a fungating pattern are occasionally seen. They expand primarily inward, although a concave indentation posterior to the tumor is characteristic. Metastatic tumors have a similar location (i.e., within the urethral tract) but tend to be flatter and are multiple, while melanomas are nearly always solitary. Hemangiomas consist of multiple small vascular channels and blood-filled spaces and therefore produce high-amplitude echoes. If these lesions are large enough, differentiation can be made sonographically.

In addition to gray-scale findings, examination using color and duplex Doppler has been shown useful in diagnosis and management of intraocular tumors. Adequate vascularity is essential for tumor growth, and rapid growth of tumor vessels has been shown to lead to the development of abnormal vessels lacking normal mural muscularity. Abnormal Doppler signals have been reported from tumors in many tissues, likely reflecting this histologic difference, and have been proposed as a means of differentiating benign from malignant masses. Guthoff et al. evaluated the vascularity in ocular melanomas in 42 patients by color and duplex Doppler. They obtained signals in 41 lesions and demonstrated serial alterations following radiation therapy. After an early posttreatment increase in peak flow, signals disappeared or were markedly diminished despite evidence of residual tumor, suggesting that the remaining mass is devitalized. They propose that presence of circulation in an irradiated melanoma may indicate viability and potential for regrowth. In addition, since tissue with better perfusion is more radiosensitive than less well oxygenated tissue, therapeutic decisions might be made based on Doppler findings. In another study of 41 intraocular mass lesions, Lieb et al. demonstrated abnormal Doppler shifts in 39 neoplastic lesions but were unable to detect Doppler shifts in 3 tumor-simulating lesions. They also found lower Doppler shifts in melanomas following radiation therapy, likely reflecting decreased vascular supply. While color Doppler imaging has some inherent limitations and pitfalls, these results are encouraging, since no other technique can yet provide noninvasive quantitative assessment of blood flow, which may be useful in monitoring tumors treated conservatively. The recent development of sonographic contrast agents may provide improved visualization of normal and tumor vessels in the eye, as has been demonstrated elsewhere.

Some orbital tumors, both benign and malignant, can be identified by ultrasound and classified by location, size, contour, and acoustic properties. Typical ultrasound findings can differentiate cystic, solid, angiomatosous, and infiltrative lesions. Although newer-generation CT scanners and MRI have replaced ultrasound in evaluation of many orbital lesions, it remains a useful adjunctive technique, particularly for cystic lesions and cavernous hemangiomas.

Intrinsic tumors of the optic nerve are relatively rare orbital lesions. Gliomas account for 65%; the remainder are noninfiltrating. Ultrasound offers evaluation of the orbital optic nerve complimentary to CT and MRI in assessment of these lesions, providing information concerning internal structure and precise serial measurement of optic nerve diameter (Fig. 8.10). Intraorbital gliomas
ultrasound can demonstrate diffuse or localized changes in the affected orbit and provide differentiation from true neoplasm. A wide range of diseases including infection, lymphoid or granulomatous processes, cellulitis, and pseudotumor produce such changes. Enlargement of the extraocular muscles in Graves' disease has also been an important application of diagnostic ultrasonography in the orbit (Fig. 8.11). Expansion of the retrobulbar fat volume and a slight enlargement of the optic nerve are often seen sonographically in addition to the enlarged muscles and are highly suggestive of Graves' disease, although the appearance is not pathognomonic.

**Ocular Manifestations of Carotid Artery Disease**

Cerebrovascular insufficiency from carotid occlusive disease is frequently associated with ocular symptoms and signs. Common ophthalmologic manifestations include amaurosis fugax, retinal emboli, and anterior- or posterior-segment ischemic syndrome. In addition, since sympathetic nerves to the eye travel with the carotid sheath, Horner's syndrome has been reported with severe carotid disease or dissection. Evaluation of the extracranial carotid arteries is part of the workup of patients with such clinical findings. Angiography permits complete assessment of the cerebrovascular circulation but does not provide accurate assessment of vessel cross-section and is limited in evaluation of plaque morphology. In addition, it is invasive and associated with both minor and major complications. MR angiography is a new technique that holds great promise, but its accuracy is not yet well documented, and it is expensive and less readily available than ultrasound. Duplex Doppler ultrasound is therefore widely accepted as the primary screening modality for extracranial carotid disease. The B-mode ultrasound provides anatomic images of the vessel, color flow imaging provides global Doppler sam-
pling, and pulse Doppler measures flow velocity and pattern (Fig. 8.12). The study can identify and quantify stenosis, demonstrate presence and morphology of plaque, and is available and noninvasive, so that serial studies are practical. Sensitivity and specificity of 85 to 90% have been reported. Periarterial directional ultrasound can also be used to measure direction of flow in vessels arising from the external carotid. In carotid occlusion, there may be reversal of flow in these vessels as collateral pathways form. A positive correlation of 75% with significant carotid disease has been reported, although there is a false-negative rate of approximately 30%. While these techniques are accurate and well accepted, there are limitations in cerebrovascular sonography. Technical skill and familiarity with Doppler principles are required to perform and interpret the study and still significantly affect diagnostic accuracy. In addition, only the cervical portions of the carotid and vertebral arteries are directly examined, although some Doppler analysis of intracrani vessels is obtained indirectly.

Duplex instruments with frequencies of 5 to 10 MHz are used to evaluate the carotids. The study includes evaluation of the common carotid, carotid bulb, internal and external carotid branches, and both vertebral arteries. The vessels must be followed

* Figure 8.12.

Carotid ultrasound. A. Color and duplex Doppler ultrasound show the normal bifurcation without evidence of stenosis or turbulence. The branch vessels are identified by their size, position, presence of branches from the external, and their spectral waveforms. Direction of flow in all vessels is indicated by red or blue color overlay on real-time images. B. The internal carotid demonstrates a low-impedance waveform with high diastolic flow reflecting the low resistance in the cerebral circulation. C. The external branch demonstrates relatively high impedance as it feeds the facial musculature. D. The vertebral artery is imaged as it passes through the transverse processes and is evaluated for patency and direction of flow. (Courtesy of Dr. Kathleen Lazzarini, New Haven, CT.)
methodically using gray-scale, color-flow, and spectral analysis. Although in some patients, longitudinal and axial images allow direct estimation of stenosis, plaque morphology or extensive calcification may preclude satisfactory imaging, and Doppler measurements are therefore used to complement image analysis and quantify the degree of narrowing. Changes in velocity and the identification of disturbed flow have allowed definition of criteria for classification of stenosis. Measurements obtained or calculated include peak systolic velocity, peak diastolic velocity, and systolic and diastolic velocity ratios comparing values obtained in the internal at the site of narrowing with those in the mid-common carotid. Spectral broadening should also be assessed at the area of maximal turbulence and is especially important if shadowing from calcified plaque prevents assessment at the site rather than frequency shifts to remove some sources of error related to technical factors.

Although studies have demonstrated sensitivity of 91 to 94% and specificity of 85 to 99% using sonography for evaluation of carotid stenosis exceeding 50%, differentiation of occlusion from high-grade stenosis is a source of occasional error, and angiography is suggested in patients who may be surgical candidates when there is any question about internal carotid occlusion on the basis of sonographic findings. Recently developed amplitude-based or power Doppler imaging has proven helpful in some cases but is not yet widely available.

In addition to assessment of stenosis, evaluation of plaque morphology for identification of calcification ulceration or hemorrhage is important, as 50 to 60% of patients with ischemic symptoms have stenosis less than 50% on angiography. Heterogeneous plaque with surface irregularity, ulceration, and cystic areas within suggests hemorrhage and is associated with an increased risk of stroke. Accuracy of over 90% has been reported for identification of intraplaque hemorrhage by ultrasound. When a complete color and duplex Doppler examination is performed, sonography provides reliably, low-cost screening and identifies those who need further evaluation. Multicenter clinical trials have shown that endarterectomy can reduce the risk of stroke in both symptomatic and asymptomatic patients with significant carotid disease, and in some groups, ultrasound alone may be adequate to select patients for endarterectomy. Accurate plaque characterization can also identify patients without high-grade stenosis who are nonetheless at increased risk of stroke.

**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomography (PET) is an emerging clinical technology that uses cyclotron-produced radionuclides to generate images of tissue biochemistry. The unique ability of PET to provide information about tissue function is based upon the availability of tracer compounds of physiologic importance that can be labeled with positron-emitting radioactivity. Following intravenous administration, the whole-body distribution of these radiopharmaceuticals is imaged to derive quantitative measurements of regional blood flow and metabolism. Unlike MRI or CT, PET does not provide finely resolved images of organ anatomy. PET is characterized by images of relatively poor resolution (4 to 7 mm in plane) that describes organ function and are often used in conjunction with CT or MRI to define tissue-specific metabolic activity.

The history of PET imaging dates to 1946, when public interest in potential medical applications of radioactivity was sparked by a report of the complete disappearance of thyroid cancer metastases after treatment with radioactive iodide. During the ensuing rush to produce greater amounts of radioactivity to treat cancer, many positron-emitting radionuclides were discovered. One of the first positron-imaging cameras was built at Brookhaven and its blood flow/SCA Institute distributed to late algorithmic imaging systems. PET clinical equipment is now readily available to our OP high comp undertaking due to clinical errors. None of the development of this imaging technique may vary with myocardic neoplastic cancers. PET whole-body imaging, has been done in the evaluation of studies (CMB) imaging the visual cortex.
PET Imaging of the Visual Cortex

Clinical PET imaging of the visual cortex is performed with either of two cyclotron-produced radiopharmaceuticals, $\text{H}_2\text{O}$ or $\text{H}_2\text{O}$, radiolabeled water, has a 2-minute half-life. This radiotracer is a nearly ideal marker for regional blood flow; it freely diffuses into brain tissue and is used to evaluate CBF patterns at rest or with the presentation of visual stimuli. $^{18}$FDG (2-fluoro-2-deoxyglucose) has an approximate 110-minute half-life and is used to assess regional metabolic activity. This glucose analog competes for hexokinase and tracks the transmembranous exchange and phosphorylation of glucose. FDG-6-phosphate does not enter the glycogenic pathway and is therefore trapped in tissue, reflecting regional glucose utilization.

Imaging requires that the patient's head first be positioned within the doughnut-shaped PET camera gantry. An external source of positron-emitting radioactivity is then used to transmit photons through the patient's head to create an attenuation map of the skull and soft tissues. This "poor man's CT scan" is used later to correct the reconstructed PET brain scan for soft tissue and bony attenuation of internally administered radioactivity. An intravenous injection of either $\text{H}_2\text{O}$ or $^{18}$FDG is then given. Images of regional CBF are acquired immediately after radiopharmaceutical injection for a duration of 3 minutes. Images of regional cerebral glucose utilization are obtained approximately 40 minutes after $^{18}$FDG injection for a duration of 20 minutes. Delayed acquisition of $^{18}$FDG images is necessary to optimize tissue extraction of radiopharmaceutical.

PET image acquisition is based upon the coincidence detection of two simultaneously emitted 511-keV photons that result from positron annihilation. Two directly opposed radiation detectors must register the arrival of the two photons within 5 to 20 nanoseconds of each other for a decay event to be recorded and for that information to contribute to the
subsequent PET image of radiopharmaceutical distribution. This original projection data is reconstructed into tomographic images of brain activity through the process of filtered back-projection.

PET images of regional CBF or metabolism in healthy volunteer subjects show a homogeneous distribution of radioactivity throughout cortical and subcortical gray matter (Fig. 8.13). Uptake of tracer within the visual cortex is normally intense, even when the eyes are closed during radiopharmaceutical injection. Cerebral white matter is poorly visualized, based on its proportionally lower blood flow allocation.

**Functional Organization of the Human Visual Cortex**

PET studies of cerebral activation have provided new insight into the functional organization of the human visual cortex. These studies use serial $^{15}$O scans of regional CBF with and without presentation of visual stimuli to identify brain regions that are responsible for specific visual functions. Images of regional CBF obtained at baseline are computer subtracted from images obtained with stimulation, to yield a difference image that identifies areas of activated brain cortex. A pixel by pixel statistical comparison of regional CBF during the “on” and “off” conditions is then made to identify those cortical activation areas with significant task-induced hyperemia. In this manner, function is mapped to regional anatomy.

For example, Fox et al. compared regional CBF patterns in healthy volunteer subjects before and during fixation on an alternating checkerboard pattern. The investigators found that changes in the stimulus location (macular, perimacular, peripheral, upper field, lower field) caused systematic, highly significant changes in activation location within the visual cortex. These studies confirmed the retinotopic organization of human visual cortex.

Subsequent studies have identified specific brain areas associated with face recognition, form discrimination, and color and motion perception. These studies, among many others, lend credence to the concept of functional specialization within the human visual system and permit the rough division of the visual area in man into four large sectors. The primary visual area (VI) lines the calcarine sulcus. It is activated by all types of visual stimuli and is retinotopically organized. The immediate visual association areas surround the striate cortex and include part of the cuneus, the posterior lingual gyrus, and the occipital gyri at the poles. A major function of the immediate visual association area may be the coordination of retinal stimuli to yield stereoscopic vision. The intermediate visual areas include the remainder of the occipital gyri, the lingual and fusiform gyri, and cortex lining the parieto-occipital sulcus. Activation studies suggest that this area is involved in the analysis of visual patterns with regard to spatial frequencies, orientation, and color. The fourth large sector includes remote visual areal activated by form and stimulus visual pattern visual cortex.

**Metabolic Brain Imaging**

PET imaging utilizes $^{15}$O for its high resolution, as it shows a significant increase in metabolic activity with focal attention of visual focus. PET imaging through 57-year-old FDG uptake is relatively sensitive to a partially blood flow.

**Figure 8.13.**
Axial tomograms from a healthy volunteer reveal a symmetric pattern of $^{15}$FDG uptake within cerebral cortex. The right side of the brain is on the reader’s left; tomograms run superior to inferior (frontoparietal to temporal).
Visual areas such as the precuneus and the superior parietal lobule. This sector is activated by tasks that require the analysis of form and patterns. Features of the analyzed stimulus may be integrated in this area. Visual patterns may be stored in the remote visual cortex for future retrieval in integrated form.

**Metabolic Imaging of the Brain in Focal Epilepsy**

PET images of regional cerebral glucose utilization may be helpful in identifying the seizure focus in patients with medically refractory epilepsy and associated visual disturbance. PET images of the brain normally show a symmetric pattern of radiopharmaceutical uptake when right and left hemispheres are compared. However, in patients with focal epilepsy, a regional asymmetry is often identified. Following interictal injection of radiopharmaceutical, the seizure focus is visualized as a region of hypometabolism; after ictal injection, focal hypermetabolism is sometimes identified.

Figure 8.14 shows an axial tomogram through the temporo-occipital cortex of a 57-year-old man following injection of FDG during ictus. A clear asymmetry in occipital lobe metabolism is identified, with relatively greater activity on the right. PET imaging was repeated 2 days later. There was no EEG evidence of seizure activity at that time, although the patient continued to complain of visual hallucinations. PET images again showed relatively increased metabolic activity within the right occipital lobe. One month later, when the patient was well controlled on antiepileptic medications, an interictal injection of PET radiopharmaceutical was performed. Images now showed relatively decreased activity within the right occipital cortex, compared with the left, consistent with seizure site localization to the right occipital lobe.

**Metabolic Imaging of Brain Tumor**

Numerous studies have documented the utility of FDG imaging for the evaluation of primary brain tumor and for the differentiation of recurrent tumor from radiation necrosis. FDG uptake is positively correlated with tumor grade and negatively correlated with patient prognosis. While areas of radiation necrosis show no uptake of FDG radiopharmaceutical, areas of aggressive tumor recurrence show focal hypermetabolism. Figure 8.15 shows axial and coronal PET tomograms acquired in a 33-year-old man with suspected recurrence of a left occipital lobe glioma. The patient presented with visual field cuts, and imaging was consistent with recurrence of tumor within the left occipital cortex.

![Figure 8.14](image)

**Figure 8.14.**

PET images of the temporo-occipital cortex show asymmetric occipital lobe metabolism. Right occipital hypermetabolism is identified during ictus and again 2 days later during persistent visual hallucinations. An interictal PET brain scan obtained 1 month later showed right occipital hypometabolism.
Axial and coronal PET tomograms show focal, intense hypermetabolic activity within an aggressive left occipital lobe tumor that was associated with visual disturbance.

**Comment**

Applications for clinical PET imaging of the eye and visual pathway are still evolving. PET has already been instrumental, however, in defining the functional anatomy and regional specialization of the human visual cortex.

**NUCLEAR MEDICINE TECHNIQUES IN NEURO-OPTHALMOLOGY**

Nuclear medicine is the application of radiotracer methods to imaging the normal and pathologic distribution of radiopharmaceuticals in the body. Labeled pharmaceuticals are specific in their biodistribution and activity, providing information about physiologic and pathophysiologic processes (Table 8.1). In neuro-ophthalmology, these techniques offer functional information that is complementary to other imaging modalities, as disturbances in normal physiologic processes may be appreciated in the absence of detectable structural alterations. Nuclear scintigraphy is distinguished from plane film radiography and computed tomography in that the latter utilize x-rays generated from an external source, transmitted through the patient, while nuclear studies are emission scans obtained by the detection of gamma photons released from the nucleus of atoms during a nuclear transformation.

**Principles and Technique**

Summarizing key principles, radiopharmaceuticals are intravenously injected at very low mass doses, generally several thousand-fold below the minimal threshold for pharmacologic effects. Radiotracers undergo radioactive decay with the production of a gamma photon at a characteristic energy, which is emitted from the patient and detected by a gamma camera. The most commonly used isotope in nuclear studies is technetium-99m ($^{99m}$Tc) in the oxidized form as pertechnetate. This isotope is a pure gamma emitter with a favorable radiation safety profile. Gamma photons are highly penetrating, with less local tissue deposition of energy than emissions. The $^{99m}$Tc is ideal for high enough spatial resolution and high uptake by tissues but not for high spatial resolution.

The gamma detector components: (i) which photons incident on the detector crystal to by photons, (ii) convert and an electron pulse, (iii) with analog-to-digital converters, (iv) produce a planar scan or a 3D image. Results that penetrate the patient's body penetrate a single scan or a series of scans with acceptable dose levels.

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
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<tr>
<td>$^{99m}$Tc-MDP, HDP</td>
<td>Deposits in bone matrix in area of high flow, osteoblastic activity</td>
<td>Viability of orbital reconstruction, evaluation of vascular integrity to region, assessment of osteomyelitis</td>
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<tr>
<td>$^{99m}$Tc</td>
<td>Assessment of osteomyelitis, best in chronic infection, provides signal-to-noise ratio better than other agents</td>
<td></td>
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<td>$^{111}$In-IMPAC leukocytes</td>
<td>Detection of activated lymphocytes in ophthalmopathy, identification of pituitary adenomas with possible prediction of treatment response</td>
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<td>$^{123}$I-iodoindium octreotide</td>
<td>Somatostatin receptor analog</td>
<td>Cerebral perfusion, integrity of blood-brain-barrier, onset of autoimmune processes</td>
</tr>
</tbody>
</table>

*Figure 8.15.*

*Figure 8.16.*

Diagram of gamma camera. Only photons emerging into a light covering and image...
of energy than with alpha or beta particulate emissions. The 140-keV photon released by \(^{99m}\)Tc is ideal for imaging, with an energy high enough for emission through biologic tissue but not so high as to produce loss of spatial resolution by penetrating through the sides of the gamma camera and collimator. The gamma detector consists of four major components: (a) a lead collimator through which photons may pass only at angles 90% incident to the collimator face, (b) a scintillation crystal that produces light when struck by photons, (c) photomultiplier tubes that convert and amplify the light signal into an electron pulse, and (d) position logic circuits with analog-to-digital converters that produce a planar image for display. Spatial resolution results from collimation of photons that penetrate to the scintillation crystal only at specified angles (90% for parallell hole collimators) (Fig. 8.16). The large majority of photons are either scattered in the body or unable to penetrate the collimator, requiring 5 to 10 minutes to generate an acceptable delayed-phase image, although dynamic studies of blood flow may be accomplished with acquisition times as short as 3 to 5 seconds.

Photons must travel through the body, which is an attenuating media of approximately water density, leading to degradation of the spatial resolution of the image. Planar data may be further enhanced by obtaining a series of multiple, short planar scans circumferentially around the patient and applying a mathematical reconstruction of the data obtained from these views to create a three-dimensional volume of data. This volume may be realigned at any angle. The method, referred to as single-photon-emission computed tomography (SPECT), improves the resolving ability of the instrument for detecting small focal of activity within deep structures. SPECT imaging is particularly suited to neuro-ophthalmology applications, where structures adjacent to the orbits and fossa at the base of the skull may be poorly visualized with standard planar scintigraphy.

Another tomographic method in nuclear medicine is positron-emission tomography (PET), which is also capable of rendering three-dimensional data volumes. PET differs from SPECT in the use of positron-emitting radiopharmaceuticals, which are released from the nuclei of atoms into the adjacent soft tissue and undergo combination with an

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**Components of the Gamma Camera**

*Figure 8.16.*

Diagram of gamma camera with major components; emitted photons strike the crystal face after passing through the collimator. Only photons 90% incident to the collimator will pass through. After striking the crystal, energy is converted into light which is converted by the photomultiplier tubes into an electron pulse for subsequent processing and image display.
electron (annihilation event) with the release of two high-energy photons (511 keV) exactly 180° apart from each other. In PET, the crystal detectors are arranged around the patient and connected via a series of coincident circuits linking crystals directly opposed to one another. This arrangement can distinguish the position of the emitted photons on the basis of the temporal characteristics of crystal stimulation. Hence, PET renders positional information in a very different fashion from SPECT. In general PET is more sensitive than SPECT and has better spatial resolution. The requirement of an on-site cyclotron for generation of the very short half-life PET isotopes limits the widespread availability of this method.

Indications and Applications

Nuclear medicine methods have been utilized in a variety of indications in neuro-ophthalmology, including evaluation of the bony orbital cavity for infection or bone graft integrity following reconstruction procedures, assessment of benign and malignant orbital masses, and in specialized applications using newer receptor-specific agents including the somatostatin-receptor analogs.

Evaluation of focal infection, including osteomyelitis of the bones composing the orbital cavity is possible by radionuclide methods. Three-phase bone scan imaging is performed during the angiographic, vascular blood pool, and delayed phase (after 2 hours) after administration of a ⁹⁹mTc-labeled diphosphonate compound. Diphosphonates are incorporated by chemisorption into bone matrix dependent on the local blood flow; the intensity of osteoblastic activity is an important determinant of metabolic activity and regional blood flow. Osteomyelitis presents as increased uptake on all phases of the bone scan, with increasingly focal accumulation on delayed images. Three-phase bone scintigraphy is highly sensitive, although nonspecific for the detection of osteomyelitis. Coupled with a radiolabeled leukocyte scan (Fig. 8.17) (commonly performed with ⁹⁹mTc-HMPAO leukocytes, less commonly with indium-111-labeled leukocytes), the specificity for the detection of osteomyelitis is 80 to 85%.

Orbital reconstruction using a substrate matrix with transplanted bony tissue can provide a physiologically viable and stable orbital cavity in patients with bone destruction. The reconstruction may be nonviable, secondary to impaired revascularization of the graft. Scintigraphic evaluation using ⁹⁹mTc-diphosphonate compounds is useful for assessing the vascular integrity and viability of the bone graft. For these studies, an immediate angiographic phase nuclear study is performed, followed by delayed views after full incorporation of tracer into bone. Regions of impaired viability are indicated by poor initial perfusion to the region and reduced uptake on the delayed images, compared with surrounding bone. SPECT imaging may be particularly helpful in evaluating deep bone structures.

- Figure 8.17.

Osteomyelitis demonstrated by ⁹⁹mTc-HMPAO-labeled leukocytes. SPECT imaging in the left sphenoid bone of a diabetic patient presenting with headache and fever.
Oncologic diagnosis in neuro-ophthalmology may be enhanced with nuclear methods. In patients with prior surgical procedures, anatomic imaging modalities may poorly distinguish between surgical changes and tumor recurrence. PET imaging with the labeled glucose analog $^{18}$F-FDG has been successfully utilized in this fashion, demonstrating intense accumulation of FDG indicating high metabolic rates of metastatic or recurrent tumors. Nuclear scintigraphy using gamma emitters may also be helpful for characterizing the nature of a lesion. The benzamide dopamine D$_2$ receptor agent 123-I-D-N-(di-ethylamino-2-ethyl)4 iodobenzamide, was evaluated by Rodot and colleagues for the detection of metastatic malignant melanoma. In a group of 48 patients divided into subgroups with and without known metastases, the sensitivity for detecting lesions of the eye and orbit was greater than 80%. Deol et al. reported the use of $^{99m}$Te-labeled autologous red cells to diagnose a benign vascular hamartoma in a patient presenting with unilateral proptosis and a lesion of the apex of the orbit. Increasing tracer accumulation in the vascular lesion over time is highly specific for hemangioma.

Newer radiotracers may be useful for evaluation of activated lymphocyte infiltration in endocrine ophthalmopathy. Using $^{111}$I-octreotide to evaluate somatostatin receptors expressed by lymphocytes in 40 patients with endocrine ophthalmopathy, Diaz and colleagues showed markedly increased orbital accumulation of the tracer in the orbits in patients with clinically active ophthalmopathy in Graves' disease or orbital myositis. Patients without clinically active disease evidence modest radiotracer uptake. The significance of this may lie in describing an objective marker for identification of patients who would benefit from treatment and the subsequent serial evaluation of therapeutic response.

This radiopharmaceutical has also been used for assessment of patients with visual disturbances related to chiasmal compression of pituitary tumors. The identification of somatostatin receptors in pituitary and parasellar tumors predicts a good suppressive effect of therapeutic levels of octreotide on hormone release by these tumors. Data also suggest as many as 75% of nonfunctioning pituitary adenomas are visualized with $^{111}$I-DTPA-octreotide, although the treatment implications in this category are unclear.

Periphereal retinopathy (PR) is a condition seen in multiple sclerosis (MS) patients, characterized by transitory infiltrates around the retinal veins. Infiltration of veins within the central nervous system also occurs and may be the process that precludes white matter plaque formation. Engell and colleagues demonstrated a correlation between abnormalities in brain SPECT perfusion imaging in MS patients with active PR but not inactive disease. They suggest that disruption of the blood-brain barrier may account for these differences.

SUGGESTED READINGS

Ultrasound


Berger RW, Guthoff R, Helmke K, et al. Doppler sonographische be funde der arteia und vena


Positron Emission Tomography


Corbetta M. Positron emission tomography as a tool to study human vision and attention. Proc Natl Acad Sci USA 1993;90:10901–10903.


Fox PT, Minton MA, Raichle ME, Mieszt FM, Allman JM, Van Essen DC. Mapping human visual cortex with positron 1946;523:806.

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Nuclear Medicine


Diniz M, Kahaly J, Stain receptor site, a potent inotropic action of norepinephrine. RC
Noninvasive Imaging Techniques


Imaging of the Orbit and of the Visual Pathways

Larissa T. Bilaniuk

The introduction of modern imaging modalities, computed tomography (CT), and magnetic resonance imaging (MRI), has had a major impact in the fields of ophthalmology and neuro-opthamology. These imaging techniques not only can confirm the clinical diagnosis and precisely localize and characterize an abnormality, but they often also play a major role in the making of the diagnosis when the constellations of symptoms and signs are nonspecific, atypical, or confusing. Familiarity with the advantages and limitations of each technique in evaluation of the orbit and of the visual pathways is essential to arrive at the diagnosis most promptly and cost-effectively.

CT is a very rapid technique and provides excellent bony detail; thus it is the procedure of choice in cases of acute trauma (Fig. 9.1) and in evaluation of bony lesions or bony abnormalities. Patients who are unstable and require close monitoring can be much more easily evaluated with CT than MRI. Patients who are claustrophobic can tolerate a CT examination much better than MRI. Finally, there is a group of patients in whom MRI is contraindicated, in which case the choice has to be CT. Included among the contraindications are pacemakers, cochlear implants, certain vascular clips, and presence, or question of presence, of ferromagnetic foreign bodies. It is important to consult a publication that lists which implants, clips, etc. are safe and which are not. If the presence of a metallic foreign body is suspected, a screening test may be necessary.

In case of acute trauma, thin-section high-resolution CT (performed both with soft-tissue and bone algorithms) will demonstrate fractures, displaced fragments, foreign bodies (Fig. 9.1), air in soft tissues, blood, and edema. If the patient’s cervical spine has not been cleared from trauma, then direct coronals cannot be performed, and reconstructions have to be made from data collected in the axial plane. In such a case, it is important to obtain thin, contiguous, axial sections. Utilization of rapid spiral CT technique is also helpful. Spiral CT technique is particularly useful for this purpose, because it not only is very fast and involves less radiation, but it also permits relatively artifact-free planar and three-dimensional reconstructions. Spiral CT, which is one of the newer developments in CT technology, is based on acquisition of a volumetric data set, by continuously scanning while the table with the patient moves through the scanning gantry. The data acqui-
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Penetrating injury of the right orbit. Axial CT scan shows a pencil in the medial aspect of the right orbit, with the eraser (arrow) projecting through the superior orbital fissure.

Contrast generally takes from 24 to 30 seconds and allows a choice of various slice thicknesses ranging from 1 to 30 mm. Three-dimensional (3D) CT is of value when there is a major disruption of the orbit and facial structures. 3D CT is also useful in the evaluation of bony expansile lesions, such as fibrous dysplasia, and the demonstration of orbital and facial asymmetries due to developmental abnormalities, hypoplasia, or orbital expansion by an intraorbital lesion.

CT is usually utilized as the primary technique for evaluation of acute orbital infections that often arise from the adjacent paranasal sinuses. CT demonstrates bony demineralization, displacement, or breakthrough, as well as the degree and type of orbital inflammation. The important questions that need to be answered are whether there is an orbital abscess, where it is, how large, and whether there is intracranial extent of the infection. Contrast enhanced (CE) CT needs to be performed to provide this information. Contrast enhancement, either with CT or MRI (Fig. 9.2), permits differentiation of a diffuse inflammatory process from a localized collection of pus, an abscess. Another circumstance in which CT is preferentially performed is when patients with Graves’ ophthalmopathy (Fig. 9.3) require decompression. CT provides information about the bony orbit as well as its contents. The surgeon needs to have anatomic detail about the adjacent paranasal sinuses, including the thickness of cortical walls, and this may not be discernable on MRI if the sinuses

Right orbital cellulitis with subperiosteal abscess. A. Axial T1 weighted image with gadollinium enhancement and fat suppression shows increased abnormal enhancement in the medial aspect of the right orbit adjacent to the lamina papryacea. There is extensive enhancement throughout both ethmoid sinuses, but it is greater on the right, indicating sinusitis. The scan at this plane indicates right orbital cellulitis without a specific collection of purulent material. B. Axial MRI after gadollinium enhancement and fat suppression performed through the floors of the orbits reveals a subperiosteal abscess (arrow) in the intermedial aspect of the right orbit. A component of the abscess projects into the nasal cavity (open arrow). This abscess originated from the maxillary sinus, which was also filled with purulent material. There was poor response to antibiotic therapy, with progression of the subperiosteal abscess, which required drainage.
are aerated, because both air and cortical bone fail to give signal and appear markedly hypointense (black). However, demonstration of the optic nerve, as it is compressed by the thick muscles at the orbital apex, is better with MRI. Also, the optic nerve can be better demonstrated with MRI in cases of compression by a meningioma or by fibrous dysplasia (Fig. 9.28B).

The forte of MRI is its ability to characterize soft tissues and demonstrate normal and abnormal anatomy in multiple planes without subjecting the patient to uncomfortable positions (such as is the case with coronal CT imaging). Therefore, even though in trauma CT is the primary procedure, MRI can provide valuable information (Fig. 9.4).

MRI demod of lesions: lenticularity, and it is difficult component, plex, this is rapid sequence Turbo-seconds penion of the MRI can dil anteriorly trace, intracranially, often preclude. This advantage of optic canal, an extraorb to CT in the process. With cortical bone imaging bone, infections. MRI with compression is intracranial lesions, thereof MR imaging than CT.

- Figure 9.3.
Bilateral endocrine ophthalmopathy. Axial CT reveals prominent enlargement of the bellies and the posterior portion of the rectus muscles (arrows), causing marked crowding at the orbital apexes.

- Figure 9.4.
Inflammatory mass with retained foreign body caused by penetrating injury of the left orbit. A. Coronal T1-weighted MR image reveals a large mass (arrows) occupying the upper half of the left orbit and obscuring the normal anatomic landmarks. The optic nerve sheath complex surrounded by high-intensity fat can be identified in the lower one-half of the left orbit. B. Axial T1-weighted MR after gadolinium enhancement reveals a poorly defined mass that extends to the orbital apex, where a lower-intensity foreign body (solid white arrow) can be identified. The foreign body crossed from the orbital apex into the anterior aspect of the cavernous sinus. Open arrows indicate the optic nerves as they exit from the intracranial opening of the optic canals. C. Coronal T2-weighted MR reveals the foreign body, which is hypointense, surrounded by a halo of increased intensity caused by inflammatory reaction (black arrow), wedged at the left orbital apex and markedly compressing and displacing the optic nerve (curved arrow). The straight white arrow indicates the normal right optic nerve sheath complex on the right side. The patient had fallen onto firm dried-out stalks. Because the foreign body is vegetable material, it has produced recurrent and increased inflammatory reaction.

- Figure 9.
HASTE image well demonstrates sheath complex.
MRI demonstrates the internal architecture of lesions: lobulations, septations, cysts, vascularity, and hemorrhage, thus leading to a more precise diagnosis. While in many cases it is difficult on CT to separate the various components of the optic-nerve-sheath complex, this is easily achieved with MRI. A very rapid sequence, HASTE (Half-fourier Single-shot Turbo-spin Echo), which takes just 1.2 seconds per image, provides good visualization of the globes and optic nerves (Fig. 9.5). MRI can differentiate an optic process from a periocular one. Also, the optic nerve can be easily traced through the optic canal intracranially, while with CT, beam hardening often precludes adequate visualization of the intracanalicular portions of the optic nerve. This advantage of MRI is not limited to the optic canal. Once an orbital abnormality has an extrabulbar component, MRI is superior to CT in identification and delineation of this process. While CT is superior in showing the cortical bone, MRI is more sensitive in showing bone marrow abnormalities. In cases of infectious and/or inflammatory processes, MRI with contrast enhancement and fat suppression is superb in showing the soft-tissue abnormalities, as well as the facial and intracranial extent and complications (empyemas, thrombosis, infection).

MR imaging of the orbit is more complex than CT because there are numerous sequences to choose from, and the appearance of tissues may change considerably with different sequences. The two aims are (a) to get good contrast between the lesion and surrounding tissues in order to identify and delineate it and (b) to bring out the internal architecture of the lesion and to characterize its content. The first aim is achieved with T1-weighted image (T1WI) where the fat is bright (of increased intensity) and the other tissues of various shades of gray or black. Such a sequence usually does not take long, 1 to 2 minutes, but it can be longer, depending on the degree of resolution and detail required. The second aim is achieved with contrast-enhanced T1 and also with a T2-weighted sequence (T2WI), but the T2 technique must include fat suppression. A newer, faster T2WI technique referred to as fast spin echo (FSE) results in T2WI with bright fat—that is why the fat needs to be suppressed. The fat must also be suppressed for the T1WI scans after injection of a contrast medium in order to see contrast enhancement against the background of darkened fat.

There are numerous other sequences that can provide additional or specific information. Their utilization depends on the clinical question(s) and on results obtained with standard sequences that are performed first. For example, if there is a question of a vascular malformation, then MR angiography should be used; if the question is of a small optic nerve plaque, then an inversion recovery sequence can prove useful.

**ORBITAL MASSES**

To achieve differential diagnosis of orbital masses the following points should be considered: the age of the patient, the duration of the symptoms, the location of the lesion, the morphology of the mass (is it well defined, lobulated, or ill-defined?); the internal structure of the mass (are there septations? prominent vessels?); possible evidence of associated bone changes, and if there are such
changes, whether they are due to pressure erosion, infiltration, or destruction.

**Inflammatory Lesions**

**INFECTION**

Bacterial orbital infection is most often due to parasinusitis. Other causes of orbital infection include foreign bodies, skin infections, infected insect bites, and bacteremia. Once infection extends into the orbit, it can produce a diffuse inflammatory reaction that in some cases can evolve into an abscess. Management of a patient depends on the extent of infection and on the size of the abscess, if such is present. Clinical assessment may be very difficult because of the marked swelling and inflammation of the eyelids. Imaging is an excellent method to look inside the orbit. Following intravenous injection of a contrast material, both CT and MRI (Fig. 9.2) can demonstrate location, extent, and size of the inflammatory process and of the abscess. CT additionally provides information regarding the integrity of adjacent bone, if there is dehiscence or osteomyelitis. If there is diffuse orbital inflammation, with or without a small subperiosteal abscess, then treatment with antibiotics alone usually suffices. A large subperiosteal abscess almost always requires drainage. Young children most frequently develop infections in the medial aspect of the orbit secondary to ethmoid sinus disease. Adolescents and adults can develop subperiosteal abscesses in the superior portion of the orbit in connection with frontal sinusitis. On scans after contrast enhancement, the abscesses appear as elliptical, ovoid, or rounded regions of low density on CT and low intensity on T1WI MRI (Fig. 9.2), surrounded by enhancing tissues. Muscles adjacent to the abscess are swollen and displaced and show contrast enhancement. Rarely, there can be diffuse infection and inflammation of fat (Fig. 9.6). Extracranial fat, and at times intracranial fat, shows evidence of edema and inflammation and has the so-called dirty fat appearance. The connective tissue septa within the fat are accentuated, and their density is increased on CT; in an MR study, the intensity is decreased on T1WI and increased on T2WI. Both CT and MRI show the intracranial complications, such as epidural and subdural empyemas, but MRI is superior to CT. Thrombosis of venous sinuses or arteries is best demonstrated by MRI that includes MR venography and MR angiography.

IDIOPATHIC INFLAMMATORY SYNDROMES

Idiopathic inflammatory syndromes (Figs. 9.7-9.8) are a diverse group of disorders that may present with signs and symptoms of inflammation. Idiopathic inflammatory syndromes are a rare group of disorders that may present with signs and symptoms of inflammation.

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*Figure 9.6.*

Excessive infection and inflammation of the fatty tissues of the orbits and cheeks in a patient with rejection of a transplanted liver. A. Coronal T1-weighted MRI image shows irregular infiltrative process throughout the fat of both of the orbits, obscuring the anatomic detail of structures within the orbits. B. Coronal MRI after gadolinium injection and fat suppression shows slight-to-moderate enhancement of the involved fatty tissues (arrows) of both orbits and cheeks. This results in a grayish smeared appearance to the fat.
angiography. Fungal infections, such as aspergillosis or mucormycosis, which tend to occur in immunocompromised or diabetic patients, can progress rapidly with osteomyelitis, thrombosis, and infarction.

IDIOPATHIC ORBITAL INFLAMMATION

Idiopathic orbital inflammation, also commonly referred to as pseudotumor, is the most common cause of an intraorbital mass in patients aged 10 to 40 years. It often is unilateral, but it can also be bilateral. The idiopathic inflammation can be acute, subacute, or chronic. In the acute form, there is diffuse infiltration of tissues by lymphocytes, plasma cells, macrophages, and, at times, eosinophils. In the subacute and chronic forms, there is a variable degree of fibrosis, with some cases being primarily sclerotic, manifested by fixation and immobility of structures. On imaging, idiopathic inflammation shows a wide spectrum of changes, ranging from single muscle involvement (Fig. 9.7) to diffuse infiltration of the orbit (Figs. 9.8, 9.9, and 9.12).

One of the more typical imaging findings of idiopathic inflammation is that of contrast-enhancing uveal-scleral thickening. However, any structure can be involved, with the lacrimal gland being most commonly affected. Often there are multiple sites and structures involved (i.e., lacrimal glands, muscles, fat) (Figs. 9.8, 9.9, and 9.12). Infrequently, the idiopathic inflammation may mimic a well-defined mass. When the process extends into the cavernous sinus (Figs. 9.10 and 9.12) or is primarily in the cavernous sinus (Fig. 9.11), then the constella-

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**Figure 9.8.**
Idiopathic orbital inflammation. Irregular infiltrative process present around the globe and the optic nerve sheath complex (open arrow) is demonstrated on an axial contrast-enhanced CT scan. There is enlargement of rectus muscles, particularly the lateral rectus and especially at the insertion of the muscles on the globe (black arrows). There is also involvement of the extraconic fat lateral to the lateral rectus muscle.

**Figure 9.9.**
Bilateral idiopathic orbital inflammation (pseudotumor), much more extensive on the left. Coronal MR image after gadolinium enhancement and fat suppression reveals diffuse enhancement of the left orbital fat and enlargement of the rectus muscles. In addition, there is a periocular lobulated mass (black arrow). There is slight enhancement of the extraconic fat (open arrow) and some fullness and irregularity of the lacrimal gland (solid arrow) on the right side.
Idiopathic orbital inflammation on the right, with extension beyond the orbit. A. Axial T1-weighted MR image reveals markedly thickened right lateral rectus (straight arrow), and infiltrative process that envelops the posterior half of the optic nerve sheath complex and extends posteriorly (curved arrow) through the superior orbital fissure. B. Coronal T1-weighted image shows an expanded superior orbital fissure (open arrows) by the inflammatory mass. In addition, there is evidence of extension of the inflammatory process through the inferior orbital fissure into the pterygopalatine fossa (curved arrows). Compare with the normal high intensity of fat, in both the inferior orbital fissure and the pterygopalatine fossa. C. Axial image after gadolinium enhancement and fat suppression reveals fairly diffuse enhancement throughout the right orbit and of that portion that extends through the superior orbital fissure (arrow). D. Inversion recovery image shows the mass (white arrow) in the apex of the orbit as well as enlargement of the anterior portion of the cavernous sinus (black arrow). E. Axial T2-weighted image shows that the idiopathic inflammation is hypointense and therefore difficult to delineate from the also hypointense orbital fat.
A Figure 9.11.
Sphenoid sinusitis and right cavernous sinus inflammatory mass. A. Coronal T1-weighted image through the cavernous sinuses reveals diffusely opacified sphenoid sinus (thick vertical black arrow) and diffuse enlargement of the right cavernous sinus by a mass that encircles and constricts the intracavernous internal carotid artery (thin horizontal arrow). Compare with the normal size of the cavernous sinus and normal size of the internal carotid artery on the left side. B. Coronal T1-weighted MR image after gadolinium enhancement and fat suppression reveals marked enhancement of the inflammatory process in the sphenoid sinus and moderate enhancement of the inflammatory mass involving the right cavernous sinus. The straight arrow indicates the encased internal carotid artery, and the curved arrow points to the involved enlarged mandibular portion of the fifth cranial nerve. C. Axial T2-weighted MRI shows increased signal in the ethmoid and sphenoid sinuses involved by inflammation. There is decreased signal in the involved enlarged right cavernous sinus (open arrows).

ation of findings represent Tolosa-Hunt syndrome.

On CT, the density of the idiopathic inflammation is nonspecific, and enhancement varies with the type of process, being most prominent in acute forms (Fig. 9.7) and much less so in sclerotic types. On MRI, the idiopathic inflammation most typically is of low signal intensity, both on T1WI and on T2WI (Figs. 10E and 11C). The acute myositis form shows low intensity on T1 but increased intensity on T2WI. As on CT, the degree of enhancement on MRI varies with the type of idiopathic inflammation.

The imaging findings of idiopathic orbital inflammation, although typical, are not specific and therefore need to be correlated with the clinical picture and response to steroid therapy. The differential diagnoses of idiopathic orbital inflammation include lymphoproliferative diseases, bacterial and fungal infections, sarcoidosis, connective tissue disorders, vasculitis, Wegener's granulomatosis, and metastatic tumors.
Neoplasms

Lymphoproliferative tumours range from benign to malignant among them is - Imaging. On imaging, a spectrum of patterns to be extensive and infiltrative (Fig. 9.13) of tumours that have intracranial components are disease can and can involve various glands, conjunctiva and periocular or globe often are not deformed by the CT and MRI demonstrated extent of the lesions. The rapidity of development in elderly patients can develop the lymphoproliferative process is at the extracranial extent into the uncomfortable areas and difficulty coping with the encephalonic environment. The elderly patient may not show the discomfort. On MRI, masses are low and show variable signals. In what increased intracranial pressure, prominent enhancement with use of fat suppression results in imaging with the clinical findings with slowly developing mass, often lead to lymphoproliferative
Neoplasms

LYMPHOPROLIFERATIVE DISORDERS

Lymphoproliferative disorders in the orbit range from benign to malignant, and distinction among them is difficult clinically and by imaging. On imaging, they show a wide spectrum of patterns, and typically they tend to be extensive and lobulated as well as infiltrative (Fig. 9.13). There can be lobules of tumor that have both an extraconic and intraconic component. The lymphoproliferative disease can be unilateral or bilateral and can involve various structures: lacrimal glands, conjunctiva and eyelids, muscles, and periorbital or periglobal regions. The globes often are encircled and displaced but not deformed by the lobulated masses. Both CT and MRI demonstrate the morphology and extent of the lymphoproliferative lesions. The rapidity of CT scanning is an advantage in elderly patients, who tend to develop the lymphoproliferative disorders. These patients often have difficulty lying flat and difficulty cooperating in the more claustrophobic environment of MRI. However, the elderly patients have difficulty getting into the uncomfortable position required for coronal scanning, so in this regard, the multiplanar capability of MRI is an advantage. This becomes even more important when the process is at the apex of the orbit or has extracranial extent through superior or inferior orbital fissures (Fig. 9.13). On CT, the lymphoproliferative masses are homogeneous, are similar in density to muscle, and do not show significant contrast enhancement. On MRI, the lymphoproliferative masses are of low signal intensity on T1WI and show variable signal intensity on T2-weighted images, ranging from low to somewhat increased intensity. After injection of contrast material, there is usually fairly prominent enhancement noted, particularly with use of fat suppression (Fig. 9.13). The results of imaging, CT or MRI, combined with the clinical information in the older patient with slow development of proptosis or mass, often lead to the correct diagnosis of lymphoproliferative disorder.

**NEUROGENIC TUMORS**

**Meningioma.** Meningioma can originate in the orbit or can secondarily involve the orbit by extending from its primary intracranial location. Those meningiomas that secondarily involve the orbit, either by growing through bone or extending perivascularly (Fig. 9.14), or through superior orbital fissure are more common than those that originate within the orbit. When the meningiomas originate in the orbit, they most commonly arise from the periorbital dural sheath and only rarely from ectopic rests elsewhere in the orbit. Meningiomas are well-delineated but lobulated tumors that show great propensity to grow through dura, along dura, and through bone. On CT, the meningiomas have a density similar to or greater than brain, produce bone sclerosis and bone expansion (Fig. 9.15, A and B), and contrast enhance markedly. On MRI, on T1-weighted images, meningiomas have similar intensity to that of brain; on proton density or on T2WI, they show variable intensity, ranging from low to high intensity (Fig. 9.15C). The contrast-enhanced MRI with fat suppression is most valuable in detection and delineation of orbital menin-
**Figure 9.14.**
Periorbital extent of meningioma. A. Axial MRI after gadolinium enhancement and fat suppression shows prominent enhancement of the meningioma including the periosteal components (open arrows). B. Coronal MRI after gadolinium enhancement and fat suppression demonstrates the encasing meningioma (arrow) around each optic nerve sheath complex.

**Figure 9.15.**
Meningioma of the right orbit, right nasal cavity, and right anterior intracranial fossa. A. Coronal CT shows a mass (open short white arrows) in the superficial aspect of the orbit, which has expanded that portion of the bony orbit. In addition, there is a faint calcification (white solid arrow) noted intracranially. An elongated mass (curved arrow) fills the right nasal cavity. B. A bone-window image of the same scan shown in A better reveals the expanded sphenoid right orbit and also expanded right nasal cavity. In addition, there is bony sclerosis (arrows) involving the right ethmoid sinus and the osseous gill. C. Coronal proton-density MRI shows a hypointense mass (white arrows) in the right orbit and a hyperintense mass (black arrows) intracranially. D. Coronal MRI after gadolinium injection and fat suppression shows slight enhancement of the intracranial mass component of the meningioma (curved arrow) and marked enhancement of the intracranial component (straight arrow).
gliomas (Figs. 9.14 and 9.15D). When there is early involvement of the orbital apex by a meningioma, unless contrast material is used with thin contiguous sections, a meningioma may be missed. To demonstrate bony changes due to meningioma, it is necessary to use wide-window photography with CT (Fig. 9.15D). MRI can effectively demonstrate bony irregularity, sclerosis, bone marrow replacement, and bone scalloping produced by a meningioma.

Peripheral Nerve Sheath Tumors

Plexiform Neurofibroma. Plexiform neurofibroma is the most frequent orbital manifestation of neurofibromatosis. This tumor represents an overgrowth of the components of a peripheral nerve, is not encapsulated, and grows centrifugally along the nerve from the periphery toward the center. Plexiform neurofibromas are highly vascular and diffusely infiltrating, producing irregularity and enlargement of muscles, lacrimal gland, and optic nerve sheath complex as well as expanding the bony orbit and its fissures. The infiltrating pattern is well demonstrated on CT and MRI; however, more definition and more precise delineation is provided by MRI (Figs. 9.16 and 9.17). While on CT the optic nerve sheath complex may be demonstrated to be enlarged and irregular, MRI shows separately the optic nerve and the surrounding plexiform neurofibroma (Fig. 9.16, B and C). Often the plexiform neurofibroma extends into the cavernous sinus and into the pterygopalatine fissure (Figs. 9.16 and 9.17). These tumors show low density on CT, low intensity on T1WI (Fig. 9.16A), and variable intensity on T2WI, ranging from low to moderately increased (Fig. 9.17A). They show prominent contrast enhancement both on CT and MRI (Figs. 16, B and C, and 17, B and C). Differ-

**Figure 9.16.**
Plexiform neurofibroma of the right orbit and face. A. Coronal T1-weighted MRI shows a mass with infiltrative reticular pattern throughout the right orbit, causing obliteration and distortion of the normal tissue planes. The optic nerve sheath complex is enlarged and irregular. B. Following contrast enhancement and fat suppression, there is enhancement of the extensive plexiform neurofibroma, which is noted to encircle the optic nerve sheath complex (solid arrow). The plexiform neurofibroma also extends through the inferior orbital fissure and infiltrates muscles and fat (open arrows) below the orbit. C. Axial MRI after gadolinium enhancement and fat suppression shows well the optic nerve (open arrow), which itself is normal but is surrounded by the extensive contrast-enhancing plexiform neurofibroma which also extends posteriorly into the cavernous sinus (solid arrow).
ential diagnosis includes extensive capillary lymphangiomas, which show a similar infiltrative pattern on imaging. The lymphangiomas generally show greater signal intensity on T2WI.

Schwannoma. Schwannomas are encapsulated tumors that grow eccentrically from peripheral nerves and occur infrequently in the orbital and periorbital regions. However, when there is a well-defined mass or elongated mass encountered in the orbit, the diagnosis of schwannoma should be considered. If the muscles supplied by the oculomotor nerve are atrophic, then the cause may be an intracavernous schwannoma of the oculomotor nerve (Fig. 9.16). Because schwannomas grow slowly and may be in an extraconic location, they can produce bone scalloping, or widening of fissures. If the tumors are round and homogenous, they may be difficult to distinguish from such lesions as isolated neurofibromas or cavernous hemangiomas. But if they show internal heterogeneity due to cystic or fatty regions, such a finding favors schwannoma. On CT, they are of low density and show contrast enhancement. On MRI, they are hypointense on T1WI (Fig. 9.18B) and hyperintense on T2WI and show prominent contrast enhancement.

VASCULAR TUMORS

Capillary Hemangioma. Capillary hemangiomas that consist of abnormal blood vessels with varying degrees of endothelial proliferation are considered by some to represent hamartomas. These tumors often present at birth or during the first few weeks of life, show exuberant growth during the first 6 months, regress during the second year, or regress during the preferential lesion within those lesion structures. The extent of the lesion results in bone erosion or remodeling and leads to the adoption of the term “skeletal abnormality” (Fig. 9.19). The lesions are of slight to moderate in contrast.
6 months, reach a stationary phase by the first or second year of life, and finally slowly regress during the next 3 to 4 years. MRI is the preferable procedure for evaluation of these lesions because it shows their internal structure much better than CT does and thus leads to the correct diagnosis and differentiation from such lesions as lymphangiomas or rhabdomyosarcomas. On MRI, these lesions are poorly margined and heterogeneous because of internal lobulations and vascularity (Fig. 9.19). On T1WI images, these lesions are of slightly higher signal intensity than extracocular muscles; on T2WI, they are hyperintense and show prominent enhancement (Fig. 9.19, B and C) after injection of contrast material. Rhabdomyosarcomas (Fig. 9.20) do not have internal lobulations and such vascularity as the capillary hemangiomas. Also, in contrast to the hemangiomas, the rhabdomyosarcomas often are hypointense on T2WI (Fig. 9.20C).

**Cavernous Hemangioma.** Cavernous hemangiomas are the most frequent orbital tumors of young adults. These lesions are encapsulated and therefore are well defined. They typically are located intraconically and are generally round or oval (Figs. 9.21 and 9.22). Again MRI has an advantage over CT by showing delicate septation within them (Fig. 9.22), indicating their internal lobular structure; also, scanning during or immediately after injection of contrast material shows heterogeneity caused by the opacification of the large vascular channels within the tumor. If there is an interval between injection of contrast material and scanning, then the lesion will appear homogeneous (Fig. 9.20). On CT, the cavernous hemangiomas appear as well-defined homogeneous masses that contrast
• Figure 9.19.
Capillary hemangioma. A. Coronal T1 MRI shows a poorly defined mass (short arrows) in the superior aspect of the right orbit that displaces the globe inferiorly. Within the mass, there are linear and dotlike signal voids (long arrow) that represent vessels. B. Coronal MRI after gadolinium enhancement and fat suppression shows prominent enhancement of the mass (short arrows) with signal voids (long arrow) due to vessels within it. C. Axial MRI after gadolinium enhancement and fat suppression from another patient with a capillary hemangioma shows a large enhancing mass (arrows) in the right orbit. The mass contains curvilinear signal voids representing vessels.

• Figure 9.20.
Rhabdomyosarcoma. A. Axial T1-weighted MRI shows a large infiltrative mass that slightly expands the orbit and causes marked proptosis. The mass also infiltrates and widens the orbital apex (short arrows) and extends into the anterior aspect of the cavernous sinus (long arrow). The mass is fairly homogeneous. B. Axial inversion-recovery MRI shows that most of the mass has an intensity similar to that of brain tissue, and again, the posterior extension into the cavernous sinus (arrows) is demonstrated. C. Axial T2-weighted MRI reveals that the mass is primarily of decreased signal. Only the anterolateral portion of the mass shows slightly increased intensity.

• Figure 9.21
Cavernous hemangioma. B, well-defined right globe anterior hemangioma. Enhance. On to fat and is breaks hyp Lymphatic In the orbit su. They a malig nerve-directed lymphangio lating of
**Figure 9.21.**
Cavernous hemangioma. A. Axial MRI after gadolinium enhancement and fat suppression shows a markedly enhancing orbit mass (arrow) in the medial intracranial space of the left orbit. B. Coronal MRI after gadolinium enhancement and fat suppression localizes the mass (arrow) to the inferior medial aspect of the left orbit.

**Figure 9.22.**
Cavernous hemangioma. Axial T2-weighted MRI shows a well-defined intracranial mass (arrow) displacing the left globe anteriorly. A septum can be seen within the hemangioma.

Enhance. On T1WI MRI, they are hypointense to fat and isointense to muscle; on T2WI, they become hyperintense (Fig. 9.22).

**Lymphangiomas.** Lymphangiomas occur in the orbit, even though the normal postseptal orbit does not contain lymphatic tissue. They are considered benign tumors of congenital origin that probably arise from misdirected vascular precursors. Most of the lymphangiomas present during childhood. They are histologically heterogeneous, consisting of dilated lymphatic vessels, dysplastic blood vessels, blood products in various stages of evolution, lymphocytic aggregates, bundles of smooth muscle fibers, and loose connective tissue septa. The lesions lack a capsule and often insinuate themselves around structures or infiltrate tissues, thus crossing anatomic compartments. The lymphangiomas show great propensity for hemorrhage; therefore, they can present with sudden proptosis, which can be recurrent because of rebleeding or change in osmotic pressure within a resolving hematoma in the lymphangioma. The heterogeneity of the lymphangiomas is well demonstrated on CT and MRI images, but particularly with MRI because of its greater sensitivity to various tissues and blood products (Fig. 9.23). The infiltrating serpiginous and cystic character of the lesions is shown on CT, and if there is acute hemorrhage, it is specifically identified. However, when blood products break down, CT becomes less specific because the blood no longer appears as high density and mimics other fluids and tissues. On MRI, the lymphangiomas show a heterogeneous intensity pattern both on T1 and T2WI (Fig. 9.23). Because of the frequent presence of blood products within lymphangiomas, it is important to perform a T2 sequence in which fat is suppressed as well as to perform contrast enhancement with fat suppression to differentiate the cystic-hemorrhagic components from interspersed...
**Figure 9.23.**
Eraconic lymphangioma. A. Axial TI-weighted MR scan shows an elongated hyperintense mass (arrows) in the medial extraconic space of the left orbit. The increased intensity of the mass is consistent with hemorrhage. B. T2-weighted axial MRI shows marked decrease in the portion of the mass that was hyperintense on the TI-weighted image, indicating intracellular methemoglobin. Anterior and posterior to this hemorrhagic component are other cystic components (curved arrows) of the lymphangioma.

**Figure 9.24.**
Lymphoma metastatic to the anterior chamber of the left eye. A. Axial TI-weighted MRI shows increased intensity in the anterior chamber (arrows). Compare with the normal lower intensity of the anterior chamber of the right eye. B. Axial TI-weighted MRI following gadolinium injection reveals enhancement of the lymphoma in the anterior chamber.

Fat lobules and contrast-enhancing venous channels. The structure of the lymphangioma depends on which components predominate: capillary, cavernous, or cystic. When the lymphangioma is primarily of the capillary type and has not hemorrhaged, it may be difficult to differentiate from other diffusely infiltrating lesions such as plexiform neurofibroma.

**METASTATIC LESIONS**
Orbital metastases are reported to be relatively infrequent; however, they are increasing because of longer survival of cancer patients. In adults, carcinoma of the breast is the most frequent orbital metastatic tumor, followed by carcinoma of the lung, prostate, gastrointestinal tract, kidney, and thyroid. In adults, 70% of metastases are related to the globe (Fig. 9.24); only 30% are orbital. In contrast, in children, the orbit is more involved than the globe. The pediatric orbital metastases are often due to embryonal tumors, neuroblastoma, Ewing's sarcoma, and leukemia. On imaging, most of the metastatic tumors are poorly defined and infiltrative.
Metastatic breast carcinoma can mimic idiopathic orbital inflammation by infiltrating the uveoscleral junction, around the optic nerve sheath complex and the rectus muscles. On CT, these are of low density and show contrast enhancement. On MRI, such metastases are hypointense on T1WI but become hyperintense on T2WI, unlike most orbital idiopathic inflammations, which become hypointense. Metastatic scirrhus carcinoma produces enophthalmos and will not show hyperintensity on T2WI because of its fibrous content. Metastases to the bony walls of the orbit can produce a lytic or sclerotic pattern (Figs. 9.25 and 9.26). Carcinoma of the breast typically produces a lytic permeative pattern (Fig. 9.25), while carcinoma of the prostate or neuroblastoma produces

**Figure 9.25.**
Metastatic breast carcinoma to the walls of the left orbit. A. Coronal CT after contrast enhancement reveals enhancing soft tissue mass extending from the involved bones (black arrowheads and white arrows). The mass has actually broken through the roof of the orbit (long black arrow). B. Axial CT after contrast enhancement reveals the abnormal, irregularly thickened bone, with tumor extending beyond the margin of the bone (open arrows). C. Axial CT photographed with a wide window to bring out bone detail shows extensive bony destruction (arrows) by the metastatic tumor.

**Figure 9.26.**
Metastatic retinoblastoma to the left maxillary sinus and orbit. Coronal CT reveals a very large mass involving the left maxillary sinus, destroying its walls and extending into the adjacent structures, including the inferior portion of the left orbit.
bony thickening, sclerosis, and soft-tissue mass. On images, metastatic prostate carcinoma, neuroblastoma, and meningioma may have a very similar appearance.

ORBITAL WALL AND PARanasal SINUS LESIONS

**Langerhans Cell Histiocytosis.** Disease entities formerly referred to as eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease are now all designated as Langerhans cell histiocytosis, because all these disorders have the same histopathology. However, Langerhans cell histiocytosis represents a spectrum in terms of sites, extent of involvement, aggressiveness, and prognosis. The etiology is unknown but is thought to be related to an abnormality of the immune system. Orbital involvement may be focal and lytic or diffusely infiltrative (Fig. 9.27). When it is diffuse, the bony lesions can mimic metastatic neuroblastoma or leukemic infiltration.

**Fibrous Dysplasia.** Fibrous dysplasia, which probably represents a developmental mesodermal disorder, typically presents during the first two decades of life. Normal bone is replaced by immature bone within a fibrous stroma, which causes expansion of bone and encroachment on or upon adjacent structures. The monostotic facial form can occur in the orbit, resulting in proptosis and visual loss if there is involvement of the optic canal. While CT is better in characterizing and delineating the bony changes of fibrous dysplasia (Fig. 9.28A), MRI provides better information about the soft tissues affected by the expansile bone (Fig. 9.28B). On MRI, regions of fibrous dysplasia may be so hypointense (Fig. 9.28B) that they appear similar to air and, therefore, may be difficult to delineate within the paranasal sinus and if small may not be detected. In addition to fibrous dysplasia, other fibro-osseous lesions, such as osteomas, ossifying fibromas, and osteoblastomas may involve the facial bones and paranasal sinuses and thus encroach on the orbits (Fig. 9.29). On CT, they are of increased density; on MRI, they are hypointense on both T1- and T2-weighted images (Fig. 9.29).

**Paranasal Sinus Diseases.** The orbit and paranasal sinuses have many walls in common; therefore, it is not unusual to see intraorbital extension of various paranasal diseases. Infections of paranasal sinuses, particularly, have a tendency to involve the

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- **Figure 9.27.**
  Extensive Langerhans cell histiocytosis of both orbits and facial structures. A. Coronal T1-weighted MRI shows irregularity of the walls of the orbits, with prominent soft tissue, which is minimally hyperintense, encroaching on and widening the extraconal space of both orbits (open arrows). B. Axial MRI after gadolinium enhancement and fat suppression reveals a moderately enhancing soft-tissue mass that has extended beyond the confines of the involved irregular bones of the orbit. The open arrows indicate the soft-tissue components of the histiocytosis.
Figure 9.28.

Fibrous dysplasia. A. Axial CT reveals diffuse expansion and increased density (solid arrows) involving the right floor of the anterior cranial fossa and extending slightly to the left. The roof of the right orbit, the planum sphenoidale, and the right anterior clinoid process are extensively involved. Open arrows indicate narrowed optic canals. B. Coronal MRI on another patient with fibrous dysplasia reveals, on a T1-weighted image, expansion and a prominent decrease in signal in the involved portions of the sphenoid bone (black arrows). There is marked narrowing of the left optic canal (open arrow), constricting the left optic nerve. Another open arrow points to the normal right optic nerve.

Figure 9.29.

Expansile fibro-osseous lesion of the right maxillary sinus. A. Coronal T1-weighted MRI shows a large, expansile, fairly homogeneous mass that has encroached on the nasal cavity and right ethmoid sinuses as well as the inferior aspect of the right orbit, elevating the inferior rectus (arrow). B. Following gadolinium enhancement and fat suppression, there is faint and modest enhancement of the mass, which is more prominent on the lateral aspect of the mass. The mass remains mostly hypointense. C. Axial T2-weighted image through the floors of the orbits reveals heterogeneous, primarily hypointense mass. Open arrows indicate the expansion of the mass into the adjacent structures. Note that the mass is almost as hypointense as the normal sequested maxillary sinus on the left.
orbits. Both acute (Fig. 9.2) and chronic (Fig. 9.30) infections can affect the orbits. MRI can be especially helpful in longstanding cases when the content of the sinuses has become viscous and desiccated or even calcified, and when the sinuses are expanded and their walls demineralized. On CT, such processes can mimic tumors such as chondrosarcoma. MRI leads to the correct diagnosis by showing that the internal architecture of the sinuses is preserved, although the individual air cells are expanded. Most importantly, MRI reveals that there is such a low-intensity zone on prostatic inspissa. In many cases it is chronic bone and cortical and of the sinus concentration. The amount of fluid contents is not itself, b

**VISUAL PATHWAY**

MRI is the evaluation of from the globe visual cortex. 

**Globe**

Congenital 
Inflammatory,

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> Figure 9.30.
Allergic esopagitis of the paranasal sinuses. A, T1-weighted axial MRI reveals a markedly expansile process involving the ethmoid and sphenoid sinuses. Due to the marked expansion of the paranasal sinuses, there is encroachment onto the orbits and displacement of the medial rectus muscles. Portions of the mass are similar to soft tissues, and other portions are markedly hypointense (arrows). B, Coronal T1-weighted MRI shows the heterogeneous expansile mass, which causes elevation and thickening of the roof of the left ethmoid (open arrows). A portion of the mass is marked hypointense (straight highlighted arrows). Note that the hypointense component of the mass is almost as dark as the air in the maxillary sinus (curved arrows). C, Coronal MRI after gadolinium enhancement and fat suppression reveals that the mass contains lobules of hypointensity that enhance on the periphery. Because of the expansion and its effect on the bone of the anterior cranial fossa, there is enhancement of the dura (open arrows) adjacent to the affected bone. D, Coronal T2-weighted MRI through the sphenoid sinus reveals it to be expanded by the hypointense mass, and the planum sphenoidale is lifted and thickened (open arrows). There is narrowing of the left optic canal, resulting in a smaller left optic nerve (curved arrow), compared with the normal right optic nerve (curved arrow). The straight arrow indicates the high intensity of fluid trapped in the left maxillary sinus.
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MRI reveals that the contents of the sinuses have such a low signal (on T1WI, but particularly on proton density and T2WI) that it represents inspired material rather than tumor. In many such cases, the underlying cause is chronic fungal infection. However, both and coworkers have shown that the signal of the sinus contents depends on the concentration of macromolecular protein, the amount of free water, and the viscosity of contents and is not due to the fungal infection itself, blood, or paramagnetic ions.

**VISUAL PATHWAYS**

MRI is the procedure of choice for the evaluation of the optic pathways, starting from the eye to the visual cortex. The exception is the presence of ferromagnetic foreign bodies or clips and implanted electronic devices (e.g., pacemakers).

**Globe**

Congenital (Figs. 9.31 to 9.34), traumatic, inflammatory, and neoplastic lesions that

*Figure 9.31.*

Cryptophthalmus, Axial CT scan shows continuity of skin over the globes (short arrows), which are markedly abnormal, particularly in their anterior aspects. Each anterior chamber is very large, and there are foci of calcifications (long arrows) indicating abnormally formed tissues.

*Figure 9.32.*

Left microphthalmia with cyst. Axial proton-density MRI reveals a very small globe (open arrows) with an abnormal lens. Lateral to the abnormal small globe, there is an associated cyst (long arrow).

*Figure 9.33.*

Bilateral optic nerve head colobomas. A. Axial T2-weighted HASTE MRI shows focal increased intensity (curved arrows) at each optic nerve head, indicating small colobomas. This image also shows very small optic canals (open arrows). B. Coronal T2-weighted HASTE MRI obtained through the posterior aspects of the globes reveals the colobomas (arrows).
can involve the globe are well demonstrated with CT and MRI, but mass lesions with retinal detachment can be better differentiated from the subretinal fluid with MRI.

In adults, malignant melanoma is the most common intraocular malignancy and occurs predominantly in Caucasians. While CT can demonstrate the intraocular contrast-enhancing mass, MRI is often more specific and precise. The melanotic melanomas have a distinctive signal pattern because of the paramagnetic properties of melanin. They are hyperintense to vitreous on T1WI (Fig. 9.35), and become hypointense on T2WI.

Retinoblastoma is the most common intraocular malignancy of childhood. These tumors are characterized by multicentric origin and propensity to form calcifications. On CT, the calcified globular masses are easily recognized, and so it is the modality of choice for the evaluation of patients suspected of having a retinoblastoma. However, MRI is more specific than CT in delineation of subretinal fluid (Fig. 9.36), in detection of extraglucular extent and of optic nerve involvement (Fig. 9.37), and in distinction of the various causes of leukokoria. On MRI, the noncalcified retinoblastomas are slightly hyperintense to vitreous on T1WI (Figs. 9.36A and 9.37A) and are hypointense on T2WI (Figs. 9.36B and 37C); the calcified components are hypointense on both T1WI and T2WI. Because of CT’s sensitivy for calcification, the pineal region should be evaluated with CT, because a small calcification may not be detected by MRI. The presence of a calcified pineal in a patient under 6 years indicates the existence of a tumor. Once there is a pineal mass, then MRI becomes the better procedure (Fig. 9.38).

**Optic Nerve Sheath Complex Lesions**

The optic nerve sheath complex is actually a long extension of the brain and its coverings, and the optic nerve is not a true
Figure 9.36.
Bilateral retinoblastomas with retinal detachment on the right. A. T1-weighted axial MRI of the orbits reveals masses (arrows) in the globes. There are two components in the right globe. The medial component has hypointensity within it that is due to calcification, as can be seen in retinoblastomas. B. T2-weighted MRI shows the bilateral retinoblastomas and on the right clearly delineates the retinoblastoma, which is hypointense from subretinal fluid (arrows) that is of increased intensity.

Figure 9.37.
Bilateral retinoblastomas with extension through the wall of the globe on the left. A. Coronal T1-weighted MRI shows bilateral ocular masses (white arrows). The left, larger mass extends through the wall of the globe (black arrow). B. Following enhancement with gadolinium, the bilateral retinoblastomas (arrows) enhance. The left retinoblastoma extends to the optic nerve head (arrow). C. Coronal T2-weighted MRI reveals the retinoblastomas to be of decreased signal. The right one is volume averaged and can be seen only faintly (black arrow). Extension through the wall of the globe is demonstrated on the left side (white arrows).
nerve. Therefore, the types of lesions that can involve the optic nerve sheath complex are the same as those that occur in the brain and its coverings, i.e., glioma, meningioma, and multiple sclerosis. MRI shows the optic nerve and the surrounding subarachnoid space very well. In cases of increased intracranial pressure and papilledema, the enlarged subarachnoid space and bulging optic nerve heads can be demonstrated (Fig. 9.39).

**Optic Nerve and Visual Pathway Gliomas.** Glioma, which is the most common tumor of the anterior visual pathway, has been the subject of much controversy because of its unpredictable behavior. There are various views on how these tumors should be managed. Visual pathway gliomas present soon after birth or during early childhood and have a high association with neurofibromatosis type 1. The growth pattern of these tumors may be extremely erratic, and MRI plays a major role in management and follow-up of patients with visual pathway gliomas. MRI has shown that the pattern of involvement of the anterior visual pathway is variable. The tumor may grow within the optic nerves or chiasm, or it may grow within them as well as extraneurally encircling the abnormally enlarged nerve within the optic nerves or chiasm, or it may grow within them as well as extraneurally.
(Fig. 9.40C) and chiasm. In addition, there may be peripheral arachnoidal hyperplasia and/or trapping of cerebrospinal fluid. The tumors may be homogeneous or heterogeneous, both on T1WI and on T2WI, and show variable contrast enhancement (Figs. 9.41, A and B, and 9.42). The optic nerve may be markedly enlarged, and there may be no intracranial extent (Fig. 9.40), or there may be a large intracranial component (Figs. 9.41 and 9.42).

**Perioptic Meningiomas.** Perioptic meningiomas, as the name implies, arise in the meninges of the optic nerve sheath complex. They occur most often in middle-aged or older individuals and more often in women. The meningiomas may be flat and encircle the nerve, or they may grow as a large mass symmetrically or asymmetrically around the nerve. In contrast to the optic glioma that is contained by the dura, the meningioma shows a propensity for invading and growing through the dura. In the orbit, it can invade the intracranial fat and extend to the rectus muscles and beyond. Perioptic meningiomas are best demonstrated and delineated on post-contrast enhancement fat-saturated MRI images utilizing multiple planes (Fig. 9.14). Such a technique can demonstrate even very small intracanalicular meningiomas.

**Enlarged Optic Nerve Sheath Complex.** Differential diagnosis of a large, or large and enhancing, optic nerve sheath complex is a long one. It includes optic neuritis, sarcoidosis, and glioblastoma multiforme of the optic nerve. At times, all three conditions may have similar appearance on imaging, and the differential diagnosis has to be supported by clinical information, particularly the age of the patient and the mode of presentation.

![Image](image_url)

**Figure 9.40.**

Right optic nerve glioma. A, Axial T2-weighted MRI shows marked enhancement of the right optic nerve (white arrows); the intracranial component (black arrow) appears normal and similar to the left intracanalicular optic nerve (black arrow). B, Following gadolinium enhancement and fat suppression, sagittal MRI shows marked enhancement of the optic nerve glioma (white solid arrows) including the optic nerve head (open arrows). C, Coronal MRI after gadolinium enhancement and fat suppression reveals enhancement on the periphery (white arrows) and not in the center of the glioneuronal (black arrow). This pattern indicates that the tumor grew out of the optic nerve and surrounded it in addition to involving the optic nerve.
- **Figure 9.41.**
Bilateral optic nerve gliomas. A. Sagittal T1-weighted MRI after gadolinium enhancement shows a markedly enlarged chiasm (arrow) without significant enhancement. The chiasmatic mass displaces the enhancing infundibulum of the pituitary. This patient has neurofibromatosis 1 and also has a neurofibroma (arrow) compressing the cervical cord. B. Axial MRI after gadolinium enhancement and fat suppression reveals markedly enlarged non-enhancing intracranial optic nerves (arrows) as they join to form the chiasm. C. T1-weighted axial MRI reveals that the optic nerves (arrows) and chiasm involved by the gliomas are of decreased intensity.

- **Figure 9.42.**
Extensive visual pathway glioma. A. Axial T1-weighted MRI image after injection of gadolinium and fat suppression reveals a glioma in the right orbit (open arrow) as well as a large glioma (thin white arrows) in the optic tract region. Thick white arrow shows a lobule of the tumor invading itself into the midbrain. B. Sagittal MRI through the chiasmatic and optic tract region of the mass reveals areas that enhance (short arrows) and a cystic component (long arrow), which is not unusual to see associated with the chiasmatic gliomas.
may involve a part (Fig. 9.43) or the entire optic nerve (Figs. 9.44 to 9.46) and may be unilateral (Figs. 9.43 to 9.45) or bilateral (Fig. 9.46). When the inflammation involves the optic nerve head, it results in papillitis, which is well demonstrated on MRI (Figs. 9.45A, 9.46 and 9.47). Because of the frequent association of optic neuritis with multiple sclerosis (MS) (Fig. 9.46), it is important to examine the brain in addition to the optic nerves. Optic neuritis may be the first manifestation of MS or may develop during the course of MS. Optic neuritis is best demonstrated by fat-suppressed chemical-shift MRI or fat-suppressed contrast-enhanced MRI (Figs. 9.43 to 9.47). Inactive optic nerve MS plaques are better appreciated with inversion-recovery sequences.

**Optic Chiasm**

Thin-section high-resolution multiplanar MRI is ideal for demonstration of the chiasmal abnormalities, whether they are developmental (Fig. 9.48), traumatic (Fig. 9.49), or neoplastic. The tumors that commonly involve the chiasm—pituitary tumors (Figs. 9.50 to 9.53), visual pathway gliomas (Figs.

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**Figure 9.42. (continued)**

C. Axial MRI after gadolinium injection shows an enhancing glioma (arrows) that extends posteriorly from the chiasm into the region of the optic tracts.

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**Figure 9.43.**

Left optic neuritis. A. Axial T1-weighted image after gadolinium injection and fat suppression shows abnormally increased enhancement in the intracranial portion of the left optic nerve (arrows). B. Coronal MRI after gadolinium enhancement shows the enlarged and enhancing left optic nerve (solid arrow). Compare with the right optic nerve (open arrow).
**Figure 9.44.**
Right optic neuritis. A. Axial T2-weighted MRI shows increased intensity in the right optic nerve (arrow). B. Coronal MRI after gadolinium injection and fat suppression shows abnormally increased enhancement and enlargement of the right optic nerve sheath complex (arrow).

**Figure 9.45.**
Optic neuritis and papillitis. A. Axial T1 MRI after gadolinium injection and fat suppression reveals an enhancing thickened optic nerve sheath complex (open arrow) as well as prominence and enhancement of the optic papilla (curved arrow). B. Coronal T1-weighted MRI after gadolinium injection and fat suppression shows the enlarged enhancing left optic nerve sheath complex (arrow).

**Figure 9.46.**
Multiple sclerosis with optic neuritis. Axial MRI after gadolinium injection and fat suppression shows swelling and marked enhancement of the entire left optic nerve (black arrows), including swelling and enhancement of the optic papilla (open arrow). Also shown at this level is an enhancing plaque (white solid arrow) in the right cerebellum.
**Figure 9.47.**
Bilateral optic neuritis and papillitis. Axial MRI after gadolinium enhancement and fat suppression shows enlarged swollen optic nerve sheath complexes and enhancement of each papilla (open arrows).

**Figure 9.48.**
Septo-optic dysplasia. A. Axial T1-weighted MRI through the suprasellar cistern reveals a very small chiasm (arrow). B. Coronal T1-weighted MRI reveals absence of septum pellucidum (black arrow points to the region where the septum should be located) and lack of definition of chiasm (white arrow) because it is so small. Normally this section should reveal the chiasm.

**Figure 9.49.**
Chiasmal trauma. Coronal T1-weighted MRI image reveals transection (arrow) of the chiasm.

**Figure 9.50.**
Familial adenoma. Coronal T1-weighted image reveals a large pituitary adenoma (white arrow) that extends upward, lifting the chiasm. There is loss of demarcation between the mass and the chiasm on the right (black arrow), indicating involvement of the chiasm by the mass.
Figure 9.51.
Pituitary adenoma. Coronal T1-weighted MRI shows a moderately large pituitary mass that extends into the right cavernous sinus (solid arrow) as well as upward toward the chiasm (open arrow).

Figure 9.52.
Hemorrhagic pituitary adenoma. Sagittal T1-weighted MRI reveals a large heterogeneous mass in the pituitary fossa and in the suprasellar location. The high-intensity regions (arrows) within the mass represent hemorrhage in the methemoglobin state.

Figure 9.53.
Metastatic carcinoma of the breast. A, Coronal T1-weighted MRI shows a slightly hypointense mass that produces irregular destruction of the sphenoid bone (black arrows) and displaces the chiasm (open arrow) upward. Thin short solid arrows indicate the displaced internal carotid arteries. B, T2-weighted MRI shows moderately increased intensity in the mass (arrows). (This image is slightly degraded by motion because the patient was elderly and had difficulty lying flat.)

9.41 and 9.42), craniopharyngiomas (Fig. 9.54), and parasellar meningiomas (Figs. 9.55 and 9.56)—are usually easily differentiated by MRI. However, in addition to the appearance on images, the patient's age and clinical history must also be considered because an abnormally enlarged and enhancing chiasm may have a similar appearance in pediatric visual pathway glioma, adult glioblastoma multiforme (Fig. 9.57), and chiasmal neuritis.
- Figure 9.54.
Craniopharyngioma. A. Axial T1-weighted MRI shows two lobes of the hyperintense portion of the craniopharyngioma projecting into the suprasellar region and into the interpeduncular area (solid arrows). Note the proximity of the mass to the optic tracts (open arrows). B. Sagittal T1-weighted MRI without injection of contrast material shows a large craniopharyngioma that contains cysts (solid arrows) with material of increased intensity. Open arrows indicate solid portions of the tumor. C. Sagittal T1-weighted MRI after gadolinium enhancement. Note enhancement of the lower portion of the craniopharyngioma, which shows slight hypointensity on the nonenhanced image shown in B.

- Figure 9.55.
Pituitary meningioma. A. T1-weighted sagittal MRI shows a mass in the suprasellar, sellar, and intrasphenoid sinus location. The mass (arrows) has only slightly diminished intensity compared with brain. B. Following gadolinium enhancement, there is prominent enhancement of the meningioma as well as the characteristic tails of meningioma (white arrows), which are well shown. Note that the structure of the planum sphenoidale and sella turcica (black arrow) remain. This is typical of meningiomas, which tend to grow through structures without destroying them.
- Figure 9.55. (continued)

C. T2-weighted axial image shows markedly decreased signal intensity in the meningioma (lateral margins indicated by open arrows and anterior margins by long white arrows). Short white arrows point to the region of the intracranial opening of the optic canal.

- Figure 9.56.

Parsellar meningioma. A. Sagittal T1-weighted MRI after gadolinium enhancement shows a meningioma along the tuberculum sellae and along the clivus (curved white arrows). A long solid arrow indicates the upper part of the chiasm before it is engulfed by the meningioma. The large component of the meningioma (curved white arrows) along the clivus displaces and compresses the body of the pons of the brainstem (black open arrows). B. T2-weighted MRI image shows marked hypointensity in the multilobulated meningioma outlined by the solid arrows. Open arrows indicate the displaced pons.

- Figure 9.57.

Glioblastoma multiforme of the optic nerves and chiasm. A. Coronal T2-weighted MRI (HASTE sequence that takes 1.2 seconds per scan) reveals asymmetrical enlarged chiasm (arrows) with increased intensity on the right (arrowhead).
Also, on occasion, a hypothalamic glioma (Fig. 9.58) may mimic, by its morphology and heterogeneity, a craniopharyngioma. Because management of the two tumors is vastly different, it is important to differentiate them. For this, it may be necessary to perform MR spectroscopy. MR spectroscopy can differentiate a lesion that arises in brain tissue from one that originates outside of it.

Other lesions that may occur in the chiasmatic region and may produce symptoms similar to those of the sellar and parasellar neoplasms can be identified and characterized by MRI. These include aneurysms (Figs. 9.59 to 9.61), sarcoidosis, meningitis (Fig. 9.62), suprasellar cysts (Fig. 9.63), and involvement of chiasm by MS.

In pituitary apoplexy due to a large acute intraselenal hemorrhage, the presence of hemorrhage can be confirmed (Fig. 9.52); however, detection of asymptomatic hemorrhages within pituitary adenomas is not unusual.

**Optic Tracts**

Optic tracts are frequently affected by the posterior extent of sellar and parasellar tumor and other nonneoplastic lesions that usually involve the chiasm. In addition, lesions of the temporal lobe (Fig. 9.64) and of the midbrain can involve the optic tracts because of their anatomic proximity. The tracts course posterolaterally from the chiasm, medial to the temporal lobes, and along the cerebral peduncles to reach the lateral geniculate nuclei. When the temporal lobe is enlarged by a tumor or hematoma or when there is transuncisural herniation of the temporal lobe, compression and displacement of the optic tract results (Fig. 9.64).
- **Figure 9.58.**
Hypothalamic glioma that mimics craniopharyngioma in appearance. A. Sagittal TI-weighted MRI shows a heterogenous mass in the suprasellar and hypothalamic region (arrow). B. Following enhancement with gadolinium contrast medium, there is heterogeneous enhancement of the mass. This proved to be a hypothalamic glioma that mimics craniopharyngioma in appearance.

- **Figure 9.59.**
Suprasellar aneurysm. Sagittal TI-weighted MRI scan reveals a round, prominently hypointense mass (solid arrow) in the suprasellar location. Curved open arrow indicates a pituitary gland compressed by the aneurysm.

- **Figure 9.60.**
Suprasellar aneurysms. Coronal TI-weighted MRI image shows bilateral aneurysms of the supraclinoid internal carotid arteries (black arrows), producing marked displacement and distortion of the chiasm (open arrow).
Giant bilobed aneurysm. A. Axial T1 MRI shows a partially thrombosed bilobed giant aneurysm (black arrows) distorting and displacing the optic nerves. White arrow points to the right oculomotor nerve as it courses from the interpeduncular fossa toward the cavernous sinus that is occupied by this large aneurysm. B. T2-weighted axial MRI shows the multilaminated pattern of the giant aneurysm. It also shows that the aneurysm has scalloped out the posterior part of the orbit (arrow). C. Coronal T1-weighted MRI shows the bilobed aneurysm. Short arrows indicate the displaced intracranial portion of the right optic nerve. Long arrow indicates the left optic nerve. D. Coronal T1-weighted image slightly more posterior to that shown in C shows the medial smaller lobe of the giant aneurysm tilting the chiasm (arrow).
**Figure 9.62.**
TB meningitis with involvement of the chiasm and basal cisterns. Coronal T1-weighted MRI after gadolinium enhancement shows irregular focal regions of enhancement (arrows). Long arrows point to the region of the chiasm.

**Figure 9.63.**
Very large cyst of the third ventricle. A. Axial T1-weighted MRI shows an anechoic-shaped low-intensity cyst (solid arrows) displacing the chiasm (open arrow) anteriorly. B. A slightly higher axial section shows the large cyst and the left optic tract (arrow) being stretched by it.

**Figure 9.64.**
Herniation with optic tract displacement and compression. Axial T1-weighted MRI shows a large, partially hemorrhagic (short arrows) mass (long arrows) located in the left frontotemporal region. Due to the mass effect, there is medial herniation, with compression and displacement of the left optic tract (open arrow).
Lateral Geniculate Nuclei and Optic Radiations

The lateral geniculate nuclei are small triangular structures located on the inferolateral aspects of the thalami. Because of the smallness of the nuclei, it is unusual for a lesion to involve just the nucleus; most frequently, the lesion involves a larger region that encompasses both the lateral geniculate nucleus and the adjacent brain (Fig. 9.65). When fibers emerge from the lateral geniculate nucleus, they travel in various directions; some course through the temporal lobe and some through the parietal lobe before they terminate in the occipital visual cortex. While visual field defects that are quadratic will indicate the site of the lesion (temporal or parietal), imaging provides the best localization, and MRI has the highest sensitivity for detection, delineation, and characterization of lesions that involve the visual pathways. These consist of infarctions, tumors, hemorrhages, infections, demyelination, and vascular malformations. Recently developed new sequences and techniques have further increased MRI's sensitivity and specificity. Among them is diffusion imaging, which permits detection of infarction and/or ischemia within a few hours of the event.

Visual Cortex

Multiplanar MRI provides excellent detail of gyral and fissural anatomy; the calcarine fissure and the visual cortex enveloping it are shown in detail on sagittal and coronal planes. The most common lesion to involve the occipital region is infarction (Fig. 9.66). MRI sequences that are sensitive to increased

*Figure 9.66.*
Occipital infarction. Axial proton-density MRI shows increased intensity (arrows), indicating infarction in the left occipital lobe.

*Figure 9.65.*
Metastatic tumor in the lateral geniculate nucleus. Axial CT after injection of contrast material reveals a round contrast-enhancing lesion (arrow) at the site of the right lateral geniculate nucleus.
Water in tissue (T2WI, FLAIR, diffusion imaging) permits early detection of even small infarcts. The infarcts can be characterized in terms of the presence of blood. Thrombosed venous structures are shown in cases of venous thrombosis. Imaging is particularly helpful when clinical presentation is atypical. Imaging permits differentiation of infarcts (Fig. 9.66), tumors (Fig. 9.67), and inflammatory or vascular lesions (Fig. 9.68). If surgery is contemplated, then functional MRI of the visual cortex provides a road map to the mass.

SUGGESTED READINGS


Facial Nerve Disorders

Kenneth L. Marek and Peter D. Williamson

Disorders of the seventh cranial (facial) nerve are frequently associated with ophthalmologic findings. Facial nerve function can be altered by lesions anywhere in the central controlling pathways or in the peripheral distribution of the nerve. Pathologic conditions of the motor component of the facial nerve may result in either facial motor paresis or paralysis or facial motor hypokinetic syndromes.

ANATOMY

A fundamental understanding of the functional anatomy of the facial nerve is essential in evaluating seventh-nerve disorders. The signs and symptoms of facial nerve dysfunction vary, depending on the site of the lesion. Associated neurologic findings are often helpful in evaluating the nature and location of the facial nerve lesion.

The seventh cranial nerve has four important anatomic characteristics:

1. It is composed of two different anatomic and functional components. The branchial motor fibers, which control voluntary facial movements, form the largest component of the facial nerve. The second component, the intermediate nerve (nervus intermedius of Wrisberg) courses lateral to the motor fibers in a separate fascial sheath and contains visceral motor and general and special sensory afferents.

2. The motor nucleus receives contralateral and ipsilateral input from the corticobulbar tracts. These characteristics have clinical implications.

3. The course of the nerve from the facial motor nucleus to its exit from the brainstem follows an unusually circuitous pathway.

4. It is encased in bone for a considerable distance, rendering it vulnerable to compression injury.

The nucleus of the facial nerve proper, the motor nerve for the muscles of facial expression, is located in the dorsolateral caudal pons (Fig. 10.1). This nucleus receives its major input from the contralateral corticobulbar fibers. The contralateral input supplies the entire facial nucleus, whereas the ipsilateral fibers are concentrated on the cells that innervate the upper facial muscles. The nucleus also receives input from various sensory nuclei associated with reflex mechanisms, for example, the fifth-nerve nucleus for the corneal reflex.

Motor fibers leaving the seventh-nerve nucleus travel medially, dorsally, and slightly
Figure 10.1
Cross-section through the lower pons demonstrates the relationship of the seventh cranial nerve nucleus and cerebellum with other brainstem structures. Note particularly the relationship with the sixth cranial nerve nucleus.
rostrally to a position just beneath the floor of the fourth ventricle in the vicinity of the sixth (abducens) nucleus. At this point, the motor fibers sweep over the sixth-nerve nucleus, forming the facial colliculus in the floor of the fourth ventricle. The facial nerve fibers then travel in a ventrolateral direction, exiting from the brainstem at the caudal border of the pons, just medial to the eighth cranial (acoustic) nerve. The facial nerve leaves the cranial cavity with the eighth nerve through the internal auditory meatus to begin its long bony course (Fig. 10.2). At the lateral end of the internal auditory meatus, the facial and acoustic nerves part, and the facial nerve enters the smaller facial canal. In this bony canal, the facial nerve continues laterally to the medial wall of the tympanic cavity, then turns abruptly backward and downward, forming the genu, or bend, of the facial nerve. The nerve passes downward to the posterior wall of the tympanic cavity and exits at the base of the skull through the stylomastoid foramen. After exiting from the skull, the facial nerve enters the parotid gland and divides into many branches, which in turn innervate the various muscles of facial expression.

The intermediate nerve, or sensory portion of the facial nerve, is a combined visceral efferent and sensory afferent nerve. The visceral efferent components are parasympathetic fibers that regulate secretory functions in the salivary and lacrimal glands. The cells of origin of these nerves are in the superior salivatory nucleus of the brainstem. The sensory components of the intermediate nerve subserve primarily taste sensation for the anterior two-thirds of the tongue, but a small somatosensory component also conveys sensory impulses from the external auditory meatus and a variable area of the external ear. The geniculate ganglion, which is located at the genu of the facial canal, is the sensory nucleus for taste and somatic sensation. The central connections for taste fibers are to the solitary nucleus; those for somatosensory fibers are to the fifth-nerve nucleus. The intermediate nerve lies adjacent to the facial nerve at its point of exit from the brainstem and travels with this nerve as a separate entity for a variable distance before the two nerves fuse.

A number of branches exit from the facial nerve during its course in the facial canal (Fig. 10.2). Only those with clinical significance are described. The greater superficial petrosal nerve leaves the facial nerve in the region of the geniculate ganglion. This visceral efferent nerve subserves secretory function for the lacrimal gland and for the nasal and palatine glands. The stapedial nerve is a small motor twig that leaves the facial nerve in the posterior tympanic cavity and innervates the stapedius muscle. The function of this muscle is to dampen low-frequency sounds. The chorda tympani is a large branch of the facial nerve that leaves the parent trunk just prior to its exit from the skull at the stylomastoid foramen. The chorda tympani traverses the tympanic cavity, after which it emerges from the skull to join the lingual branch of the fifth nerve. It carries taste sensation from the anterior two-thirds or one-half of the tongue and provides visceral motor fibers for the sublingual and submaxillary glands.

**CLINICAL FINDINGS**

**Central Lesions**

Lesions within the central nervous system can be divided into those that affect the corticobulbar fibers above the level of the seventh-nerve nucleus and those that affect the nucleus and emerging fibers. The former, referred to as supranuclear lesions, can occur from the motor cortex to the midpons. The latter, referred to as nuclear lesions, are confined to the region of the seventh-nerve nucleus in the lower pons.

**SUPRANUCLEAR LESIONS**

In general, supranuclear facial paralysis can be easily differentiated from a nuclear or peripheral lesion. Since the portion of the nucleus that receives both ipsilateral and contralateral innervation is strongly biased in favor of the upper facial muscles, volitional
Figure 10.2.

Diagram showing the anatomic relationships and functional components of the central and peripheral facial nerve (seventh cranial nerve).
control of the frontalis and, to a lesser extent, the orbicularis oculi muscles is preserved following contralateral supranuclear lesions. The eyes can be closed, the eyebrows raised, and the forehead wrinkled. Minimal weakness in these muscles can be detected only by testing their strength against forced contraction. Weakness in the lower facial muscles following supranuclear lesions is much more pronounced, but some volitional control is often maintained. The involved side of the face droops slightly, the palpebral fissure is slightly widened owing to sagging of the lower lid, and the nasolabial fold is flattened. Attempts to move the mouth, as in smiling or grimacing, accentuate the weakness of the lower facial muscles. Often, a dissociation exists between volitional and emotional motor control. Asking a patient to show his or her teeth or grimace reveals a definite motor asymmetry, whereas spontaneous emotional responses such as laughing or crying produce a more symmetric motor response. The reverse pattern can be seen but is much less common. Taste, lacrimation, and salivation are not altered by supranuclear lesions. Supranuclear facial weakness generally occurs as a component of a more widespread neurologic deficit, which may include hemiparesis, hemisensory loss, language disturbance, or visual field defects.

The differential diagnosis of supranuclear lesions capable of producing a contralateral lower facial paresis is extensive and beyond the scope of this book. The most common causes are vascular accidents, cerebral trauma, brain tumors, and infection or inflammatory processes. If the lesion is a space-occupying process, increased intracranial pressure can occur, resulting in papilledema and, on occasion, unilateral or bilateral sixth-nerve palsies. The sixth-nerve palsy is an indirect effect of the increased intracranial pressure and are not caused directly by the space-occupying lesion.

NUCLEAR LESIONS

Lesions that involve the facial motor nucleus or its exiting fibers usually produce a complete facial paralysis on the same side as the lesion. This paralysis is identical to complete peripheral facial paralysis, which is described in detail in the section dealing with peripheral facial paralysis. Both the upper and lower facial muscles are paralyzed, in contrast with the predominant paralysis of lower facial muscles associated with supranuclear lesions. Taste and secretory functions are rarely affected. When the paralysis is not complete, the usual pattern is weakness in both upper and lower facial muscles. Occasionally, in partial nuclear lesions, lower facial muscles may be affected to a lesser or greater degree than the upper facial muscles. When the latter condition occurs, the weakness resembles that seen with supranuclear lesions. Because of the relatively small size of the brainstem and the compactness of structures, however, nuclear facial paralysis rarely occurs in isolation. Associated findings such as involvement of other cranial nerves, particularly the fifth, sixth, and eighth, serve to differentiate the occasional nuclear facial palsy with lower facial weakness from that which occurs with supranuclear lesions. Associated brainstem findings also prevent confusion between nuclear and peripheral nerve lesions.

Most lesions affecting the motor nucleus of the facial nerve and adjacent regions are due to brainstem vascular disease. An understanding of the blood supply to the brainstem is necessary for accurate interpretation of clinical findings. Each half of the brainstem receives an independent blood supply. The innermost, or medial, aspect of the brainstem is supplied on both sides by multiple, short, paramedian branches from the vertebral and basilar arteries. The paramedian arteries vary considerably in distribution and number. The lateral regions are supplied by a limited number of short and long circumferential arteries that also provide the blood supply for the cerebellum. The compactness of the structures of the brainstem combined with its multiple blood supply results in numerous possible clinical combinations following vascular occlusion. Previous authors have combined various
findings, attributed them to occlusion of specific arteries or to lesions in specific areas of the brainstem, and have applied their names to these syndromes. Considerable variation, however, exists in the number of brainstem vessels, their exact distribution, and their degree of overlap of blood supply. In addition, the vascular occlusive disease may be either partial or complete, also influencing the extent of the lesion. As a result, specific syndromes are rarely seen. Therefore, it is easier to understand the findings associated with brainstem lesions with respect to areas or zones involved. Only those conditions associated with alteration of facial nerve function are described here.

In the medial region of the lower pons, paramedian vessels from the vertebral and basilar arteries supply the corticospinal tract prior to pyramidal decussation, the abducens and paraabducens region, the seventh-nerve fibers as they arch over the abducens nucleus, part of the olivodentorubral tracts, and part of the medial lemniscus (Fig. 10.1). Clinical findings depend on the extent of the lesion in this area. A hallmark of brainstem disease is the appearance of motor or sensory findings differentially affecting both sides of the body (crossed findings), which reflect the location of the decussation of the relevant neural pathways in the brainstem. Typically, the facial paralysis involves the upper and lower face equally. Taste and secretory functions are not altered. The sixth nerve on the side of the lesion is involved. A variable hemiparesis of the arm and leg occurs on the opposite side of the body. If the paraabducens area is involved, a paresis of conjugate gaze occurs on the side of the lesion. This paresis can be seen in the absence of sixth-nerve palsy or in combination with it. Involvement of the olivodentorubral tracts can result in rhythmic contractions of the palate (palatal myoclonus). If the medial lemniscus is involved, position and vibratory sense on the contralateral side are altered.

The lateral area of the mid and lower pons is supplied by short and long circumferential branches from the basilar artery. The structures in this region include the eighth-nerve nucleus, the seventh-nerve nucleus, the sensory nuclei of the fifth nerve, descending sympathetic fibers, the spinothalamic tract, vestibular nucleus, and part of the cerebellar hemisphere (Fig. 10.1). Extensive lesions in this territory produce ipsilateral complete facial paralysis, hearing loss, loss of sensation over the face, Horner syndrome, nystagmus, cerebellar signs, and contralateral loss of pain and temperature sensation over the extremities and trunk. In practice, as with other brainstem syndromes, this one is seldom complete but occurs with a variable combination of the preceding findings.

Many conditions other than vascular occlusion can produce brainstem and seventh-nerve findings. These disorders include infection, hemorrhage, trauma, congenital abnormalities, and neoplasms. The most common primary neoplasm of the brainstem, the pontine glioma, is of particular interest to the ophthalmologist because the patient often has visual symptoms. Pontine gliomas are seen most commonly, but not exclusively, in children and young adults. They are usually slow-growing, infiltrative lesions and frequently present with unilateral sixth-nerve palsies. Facial weakness involving both the upper and lower half of the face often accompanies sixth-nerve palsy. As the tumor continues to infiltrate the brainstem, other nuclear and long-tract structures are compromised, resulting in predictable clinical dysfunction. Facial myokymia, although more often associated with multiple sclerosis, is occasionally seen in patients with pontine gliomas. When myokymia is persistent, often over months or years, and associated with a paretic facial contracture, it may indicate pontine glioma. This combination is occasionally seen with other brainstem lesions.

**Peripheral Nerve Lesions**

Lesions can occur in any location along the course of the facial nerve, from the exit from the brainstem at the lower border of the pons to the terminal motor branches.
Clinical manifestations depend on the extent and the site of the lesion. Lesions involving terminal branches produce regional paralysis of the muscles supplied by those branches. Severe damage to the facial nerve at any point along its course prior to branching into terminal motor nerves produces complete facial paralysis. At rest, the involved side of the face sags, and wrinkles are flat. The nasolabial fold is absent or greatly diminished. The lower lid sags, producing a wider palpebral fissure. Since loss of all voluntary and associated movements occurs, attempts at smiling or laughing result in the mouth being pulled to the opposite side. Eye closure is not possible, and attempts to do so result in upward rotation of the eye (Bell’s phenomenon). Testing the corneal reflex on either side causes a blink only on the uninvoluted side. The inability to close the eye results in corneal abrasions if the eye is left unprotected. Since the upper facial muscles are paralyzed, attempts to raise the eyebrows or wrinkle the forehead are successful only over the uninvolutioned side. Complete lesions in the region of the stylomastoid foramen produce total facial paralysis as described, while incomplete lesions produce less severe, but usually uniform, weakness (Fig 10.3).

The loss of peripheral sensory fibers produces no clinical findings, probably because of overlap with sensory fields from adjacent nerves. If the lesion is above the chorda tympani but below the nerve to the stapedius muscle, taste sensation is lost in the anterior two-thirds of the tongue on the affected side in addition to the complete facial paralysis. The patient may also notice decreased salivation, but this symptom is variable. Lesions at or above the site of the stapedius nerve are said to produce increased sensitivity to the low tones in addition to the foregoing findings. This hearing change is variable and is often difficult to demonstrate clinically without the aid of special audiometry techniques. Lesions from the geniculate ganglion to the brainstem produce all of the previously described findings plus decreased lacrimation on the affected side. In addition, hearing loss and vestibular symptoms can be associated with facial lesions in the internal auditory meatus.

Central nervous system findings are not seen with uncomplicated peripheral facial palsy. Peripheral and central findings can occur in certain conditions, such as tumors between the brainstem and the skull, in which both the brainstem and the facial nerve are invaded or compressed, or systemic illnesses affecting the facial nerve, such as sarcoidosis or Guillain-Barré syndrome.

Peripheral seventh-nerve disorders can be seen in association with general disease processes or with relatively specific syndromes or disease entities. Some of the more common causes of facial nerve paresis or paralysis are described below.

**BELL’S PALSY**

Bell’s palsy, or idiopathic acquired facial mononeuritis, is by far the most common disorder producing isolated peripheral seventh-nerve dysfunction. It accounts for most patients with facial palsy, while other identifiable causes of facial paresis, including trauma, infection, inflammatory disease, and neoplasm account for approximately 25%. The incidence of Bell's palsy is approximately 25/100,000 in young adults, increasing to 30 to 35/100,000 in individuals over age 60. The etiology of this condition remains unknown but may be related to local compression of the nerve in the facial canal, possibly related to epineural edema occurring after a nonspecific, possibly vascular, immune, or viral neuronal insult. Viral infection or exposure to cold are common antecedent events. Pregnancy, diabetes, and hypothyroidism are predisposing factors for Bell’s palsy. Several families have been identified with recurrent Bell’s palsy sometimes associated with oculomotor nerve palsies.

The patient may present with either a partial or complete facial paralysis. Signs and symptoms develop over hours to days, often initially with mild pain behind the ear or a tingling or numb sensation on the affected side of the face. Facial weakness may affect chewing or swallowing or may be initially
noted by others. Decreased blink and weakness of eye closure causes tearing, although alternatively, lacrimation be diminished. Any of the previously mentioned findings affecting taste, hearing, or salivation may be present, depending on the site and extent of the lesion. Progression occurs for a few days to up to 1 to 2 weeks.

Clinical evaluation should include a thorough neurologic examination to assess whether there is any central nervous system involvement. If cranial nerve or cortical involvement is suspected, then magnetic resonance imaging should be obtained. Establishing a diagnosis of Bell’s palsy also requires eliminating identifiable peripheral nerve abnormalities. Examination should include evaluation of taste sensation and inspection of the tympanic membrane for possible herpetic lesions. In those rare patients with apparent bilateral facial weakness, an illness such as Guillain-Barré syndrome, sarcoidosis, Lyme disease, or carcinomatous meningitis is much more likely to be found.

Recovery in Bell’s palsy is spontaneous and complete in up to 90% of patients. Indicators of potentially poor recovery include severity at onset, slow recovery, and older age group. Electrophysiologic evidence of facial nerve denervation may correlate with prognosis. Partial or incomplete recovery can be associated with the development of contractures in the involved facial muscles. In addition, seventh-nerve aberrant reinnervation can occur following recovery, resulting in abnormal muscle activity, such as eye blinking when the mouth is moved or contraction of multiple facial muscles when one movement is attempted. If aberrant reinnervation involves parasympathetic fibers that control glandular function, stimulation of salivary glands can result in excessive tearing (crocodile tears). Rarely, asynchronous spasms of the facial muscles occur following recovery, resulting in hemifacial spasm.

Treatment of Bell’s palsy is generally conservative, since the prognosis is very favorable. Some advocate a short course of steroids in an attempt to reduce neural edema and shorten the course of the facial paresis. Prednisone has been associated with a shortened course of Bell’s palsy--associated pain, more complete recovery, and less complication with aberrant reinnervation. It should be administered as soon after onset as possible, certainly within the first week of symptoms, and then tapered after 5 to 7 days. More recently, acyclovir has been suggested as an alternative to prednisone. Poor eye closure and reduced lacrimation may result in corneal irritation in patients with Bell’s palsy and should be treated with appropriate lubrication and/or a protective eye shield. Surgery may be considered for patients with severe persistent facial paresis to improve eye closure or lower facial motor function (Fig. 10.3).

TRIUMA

After leaving the bony facial canal, the seventh cranial nerve and its branches are distributed superficially and are therefore vulnerable to injuries. These injuries are usually of penetrating varieties such as stab wounds. Occasionally, blunt trauma or prolonged compression can produce functional impairment. Trauma of the nerve within the facial canal is not uncommonly associated with basal skull fractures. In addition, surgery of the middle ear, mastoids, and fifth nerve can be complicated by seventh-nerve damage.

INFECTION AND INFLAMMATORY DISEASE

Bacterial infections of the middle ear and mastoids can produce第七-nerve palsy. When this process spreads to involve the petrous portions of the temporal bone, a sixth-nerve palsy can also be seen (Gradengio syndrome). Suppurative or granulomatous meningitis can result in multiple cranial nerve palsy, including the seventh. Several viral infections have a predilection for peripheral nerve involvement. In the past, diphtheria and polio were often associated with bilateral or unilateral facial paralysis. Modern inoculation programs have reduced these diseases to rarities.

Herpes zoster involves the (Ramsay Hunt syndrome) and a pain occurs at the eruption of the tympanic membrane, as well as with movement of the tympanic membrane.

Lyme disease is a cranial neuralgic condition that resembles the dermatologic findings of Lyme disease.

Paralysis associated with Guillain-Barré syndrome is commonly a condition, being finding isolation, unlike loss of peripherality.

Sarcoidosis disease of the nervous system involves the peripheral nervous system. It is characterized by the development of tumors, commonly alone or in combination with other systemic processes.

NEOPLASMS

Various types of peripheral neuralgias develop directly or posterior to injury, due to the presence of a cranial nerve lesion or meningial involvement.
Herpes zoster (shingles) can frequently involve the seventh nerve. This condition (Ramsay Hunt syndrome) produces complete facial paralysis with loss of taste sensation and secretory functions. In addition, pain occurs, followed by the typical vesicular eruptions of herpes zoster in the peripheral sensory distribution of the seventh nerve (i.e., the external auditory meatus, the tympanic membrane, and the posterior aspect of the external ear). Tinnitus, decreased hearing, and vertigo are occasionally associated with this condition, owing to involvement of the adjacent eighth nerve.

Lyme disease may present with multiple cranial neuropathies including unilateral or bilateral facial nerve palsy. The neurologic syndrome may occur in the absence of clear dermatologic or rheumatologic manifestations of Lyme disease.

Paralysis of cranial nerves can be seen in association with postinfectious polyneuropathy (Guillain-Barré syndrome). Bilateral facial palsy is commonly seen, whereas extracranial movements are only rarely involved. In this condition, facial diplegia can be the presenting finding and can, on occasion, occur in isolation. Usually, an associated widespread loss of peripheral nerve function occurs.

Sarcoidosis is a systemic granulomatous disease of unknown cause. When sarcoidosis involves the parotid gland and the eye, it is referred to as uveoparotid fever. Approximately one-third of patients with this disease develop unilateral or bilateral facial palsy. More recently, it has been noted that uveitis, parotitis, or facial nerve palsies can exist alone or in combination. Isolated facial nerve paralysis is one of the common neurologic presentations of sarcoidosis.

NEOPLASM

Various types of malignancies can produce peripheral seventh-nerve palsies. These malignancies include primary bone tumors that directly compress the nerve; tumors of the posterior nasopharynx, which have a tendency to infiltrate the meninges and pick off cranial nerves in a sequential fashion; and meningeal leukemic infiltrations, which often produce multiple cranial and peripheral nerve palsies.

Acoustic neuromas may cause facial nerve paresis as the tumor enlarges and compresses the seventh nerve in the cerebellopontine angle. Initial symptoms usually relate to the eighth nerve and consist of decreased hearing and tinnitus. Initially, hearing loss may be mild. Progression can be so slow that it escapes detection by the patient, even to the point of a complete unilateral deafness. Tinnitus can be intermittent or constant. Vestibular symptoms are rare. Initially and, when they do occur, are more often a vague sense of giddiness than true vertigo. The seventh nerve, owing to its anatomic relationship with the eighth nerve, can also be involved early. It can present as a complete facial palsy, but more often the weakness is subtle, and only careful examination will reveal mild facial weakness. Early detection of acoustic neuroma is critical to successful treatment.

MELKERSSON-ROSENTHAL SYNDROME

Melkersson-Rosenthal syndrome, a rare condition, is characterized by recurrent episodes of facial paralysis and facial swelling. The facial swelling may precede, accompany, or follow facial paralysis. The condition is associated with a deeply furrowed tongue (lingua plicata) in approximately 30% of patients and migrainous headaches in approximately 10% of patients. The cause of this syndrome is unknown; however, some cases may be associated with sarcoidosis. The course is usually benign, although repeated episodes of facial paralysis and facial swelling may lead to permanent disfigurement.

MÖBIUS SYNDROME

Möbius syndrome, a rare congenital disorder, is apparent at birth. A bilateral facial palsy affects the upper part of the face more severely than the lower. Paralysis of abduction of the eyes and ptosis are common. Sagging and contracture of the facial muscles are not seen. Neither spontaneous nor induced
nystagmus are present. The patient does not complain of diplopia. Pupillary reactions are normal, as are conjugate vertical-gaze movements. A number of other findings suggesting cranial nerve involvement can also be seen, such as atrophy of the tongue, the muscles of mastication, and the sternocleidomastoid muscles. Other occasional findings include dysautonomia, foot deformities, and mental retardation. Postmortem examinations have revealed apparent aplasia of the involved cranial nerve nuclei, but multiple causes have been suggested.

HYPERKINETIC FACIAL NERVE DISORDERS—ABNORMAL EYELID AND FACIAL MOVEMENTS

Hyperkinetic disorders of eyelid and/or facial muscles include blepharospasm, lid-opening and ocular motor apraxia, hemifacial spasm, synkinesis following Bell’s palsy, and myokymia. The pathology underlying these disorders may range from a degenerative central nervous system process (blepharospasm) to a peripheral nerve lesion (post-facial paresis synkinesis). The use of botulinum toxin to reduce these abnormal involuntary movements has dramatically improved treatment of these disorders (Fig. 10.1).

BLEPHAROSPASM

Toxic involuntary spasm of the orbicularis oculi muscle producing eyelid closure is called blepharospasm. Blepharospasm may occur from local ocular irritants and diseases that produce photophobia such as iritis, uveitis, keratitis, corneal foreign bodies, and noxious fumes or, infrequently, occur after stroke or other mesencephalic or basal ganglia lesions.

Chronic or essential blepharospasm is a focal dystonia of the orbicularis muscles. It usually begins with increased blinking and progresses to involve sustained eyelid closure. Initially, blinking may occur only when precipitated by bright light, and initially one eye may be affected. Blepharospasm occurs most frequently in individuals over 50 years of age and is three times more common in females. In general, it is unassociated with other neurologic disease. However, blepharospasm is sometimes associated with other cranial or cervical dystonic syndromes and is then called Meige syndrome.

Initially, the blepharospasm may be only irritating or socially embarrassing, but it frequently progresses to the point that the patient cannot work, read, or drive a car and becomes quite dependent. The underlying pathology or anatomic lesion in essential blepharospasm is unknown. Many have suggested that blepharospasm like other dystonic processes may be associated with an abnormality of the basal ganglia. However, therapeutic trials of drugs that alter these neural systems, including dopaminergic and cholinergic pharmacologic agents, have not been successful.

Botulinum toxin type A (BTX-A) has provided an extraordinarily effective therapy for many focal dystonias, including blepharospasm and other hyperkinetic movements. It is injected locally to reduce muscle spasm and abnormal activity. Botulinum toxin acts on the presynaptic cholinergic nerve terminal to inhibit the release of acetylcholine. The exact mechanism of action is still not clearly understood but involves reduction in calcium-mediated quantal release of acetylcholine. The duration of action is from 3 to 6 months. Botox is usually measured in units of biologic activity, with 1 unit being the mouse LD50 by intraperitoneal administration. The doses used for injection in humans are well below the threshold for systemic effects of the toxin. Botulinum toxin is freeze-dried and diluted with normal saline (without preservative to reduce local irritation) immediately prior to injection. About 1 to 3 days after injection, muscles atrophy and become weak; maximal weakness usually occurs 4 to 14 days after injection. Local botulinum toxin injection is, in general, very well tolerated, without significant systemic effects. Adverse effects result from transient muscular weakness at the site of the injection.
Blepharospasm was the first focal dystonia to be treated with BTX-A. Investigators have differed in the concentration of BTX-A, exact injection location, number of injection sites, and the volume of injection per site. Injections range from 12.5 to 70 units of BTX-A per eye in five to seven sites around each eye, with a concentration of 2.5 to 5 units/0.1 mL (0.1 to 0.2 mL per site). A typical initial injection series would be 2.5 units in each of five to six sites in the orbicularis oculi of each eye; one to two intramuscular sites above the brow, one subcutaneous site each at the lateral canthus and in the lower lid, and two subcutaneous sites in the upper lid, for a total of 12.5 to 15 units per eye. Some patients who continue to have spasms at this dose will improve at a dose of 25 to 50 units.

Several open-label studies completed at numerous institutions demonstrate improvements in approximately 70 to 90% of patients with blepharospasm after BTX-A injections. The degree of improvement was variable. In a double-blind placebo-controlled study, all 11 patients injected with BTX-A showed improvement ranging from 40 to 70%. The most common reason for lack of response was inadequate dose. Ptosis crutches may be of benefit for patients with persistent symptoms or a short duration of benefit.

Ptosis, the most common side effect of injections for blepharospasm, occurs in about 10% of patients. The injection procedure is designed to reduce the risk of ptosis by injecting the upper lid as far from the midline as possible, limiting spread to the levator palpebrae at its insertion into the tarsal plate in the midportion of the upper lid. In addition, some investigators inject subcutaneously over the pretarsal component of the orbicularis oculi, just above the eyelashes. Eschymoses occasionally occur. Mild dermatomal (baggy skin) is common. Excessive tearing may occur but generally is prevented by avoiding injections in the medial lower lid. Conversely some patients will complain of dry eyes, possibly from a decreased blink rate. Patients may develop corneal irritation as a result of incomplete eye closure, which usually is controlled by artificial tears or nighttime ointment. Occasionally, patients develop diplopia, presumably because of the spread of BTX-A to the extrinsic muscles.

In individuals who do not choose or do not benefit from BTX-A, medical and surgical treatment alternatives should be considered. Medical treatment includes benzodiazepines such as clonazepam and lorazepam or other agents used to treat dystonia, including Lioresal, and anticholinergics such as trihexyphenidyl. Pharmacologic treatment of blepharospasm is generally unsuccessful, with improvement only in about 25% of patients. Several surgical procedures have been used to treat blepharospasm, either by reducing innervation of the facial nerve or by excising the orbicularis oculi and/or other facial muscles. Extensive resection of the orbicularis and adjacent muscles is required to successfully relieve blepharospasm. Myectomy may be combined with other lid procedures such as repair of brow ptosis, levator aponeurosis detachment, and lateral canthal tendon laxity to treat associated eyelid abnormalities (Fig. 10A).

APRAxia OF EYELID OPENING

Apraxia of lid opening is an inability to open the eyes voluntarily without blepharospasm or oculomotor nerve dysfunction. The condition is most commonly seen in severe neurodegenerative processes affecting the basal ganglia, such as progressive supranuclear palsy (PSP), multiple-system atrophy, cortical basal ganglionic degeneration, Huntington's disease, and more rarely in idiopathic Parkinson's disease. Some patients with PSP and apraxia of eyelid opening will improve with BTX-A injections, usually requiring higher doses than are used for blepharospasm. The injection technique is identical to that used for blepharospasm.

A related condition is the syndrome of ocular motor apraxia, in which the patient has difficulty producing voluntary ocular movements in the absence of ocular muscle paralysis. Often a patient with ocular motor apraxia will require a head movement or blink to initiate a voluntary eye movement.
HEMIFACIAL SPASM

Hemifacial spasm is a syndrome in which repetitive muscle contractions occur involving one side of the face. Muscle contractions, generally perceived as twitching, usually begin in the periorbital region and gradually extend to involve the entire facial nerve distribution. Contractions are initially intermittent and gradually become more prolonged and sustained. Despite these very annoying symptoms, a neurologic examination is usually normal.

Experience obtained from neurosurgery suggests that hemifacial spasm is frequently associated with compression of the facial nerve by a loop of blood vessels. However, physiologic studies suggest a possible central mechanism for this disorder. Rarely, hemifacial spasm may occur as a sequela to Bell's palsy. It is essential to distinguish hemifacial spasm from traumatic compressive lesions in the cerebellopontine angle, and these patients should be evaluated with magnetic resonance imaging to assess this brain region.

BTX-A is the most successful treatment for hemifacial spasm and improves symptoms in approximately 90 to 95% of patients for 4 to 6 months. Injections are performed around the eye using a technique as described above for blepharospasm. Injection may also be required in the affected facial muscles. In general, the total dose in the periorbital region is 7.5 to 12.5 units, and in the face, 2.5 to 7.5 units. Side effects are similar to those described for blepharospasm, including piosis and corneal irritation. Transient facial weakness may occur as a result of facial BTX-A injections.

For those who choose not to receive or do not benefit from BTX-A, alternative therapy with drugs like clonazepam, carbamazepine, or valproate may be helpful in about 25% of patients. Jannetta has popularized surgical

![Unilateral Facial Weakness diagram]

**Figure 10.3.**
Flow diagram for diagnosis and treatment of unilateral facial weakness.
decompression of the facial nerve for treatment of this condition. Success has been long-lasting in most cases. In a large series by Loeser and Chen, the hemifacial spasm was improved in about 88% of patients, but this procedure may have significant permanent complications such as facial weakness and decreased hearing (Fig. 10.4).

**MYOKYMA**

Myokymia of the eyelids is a rapid, fine, undulating movement that may occur in the orbicularis oculi muscle. When intermittent, this is a benign condition and frequently occurs at times of fatigue or stress. Persistent myokymia involving the facial muscles more widely may indicate central nervous system disease such as multiple sclerosis or posterior fossa neoplasm. Idiopathic facial myokymia may be treated with BTX-A using the technique described for hemifacial spasm.

**BLINKING AND MOTOR FACIAL TICS**

Motor tics including eye blinking or twitching are commonly seen in children.
and generally disappear spontaneously. A tic that is associated with more involved motor activity or with vocalizations may suggest Gilles de la Tourette syndrome and should be further evaluated.

SUGGESTED READINGS


Atmospheric measurement of electrical changes throughout the body have been going on for the past 100 years or more, and developments in electronics have allowed the appearance of highly sophisticated measuring devices. These devices have permitted measurement of ever smaller changes, sometimes at a marked distance from the organ of origin. The visual pathway has been an important center for investigation in this respect, and minute electrical impulses can now be recorded from the eye and visual cortex in a manner that would have astonished our Victorian forebears.

The basis of all these electrical changes is the bioelectrical potential, which can be defined as the electrical pressure difference between the inside and the outside of a cell—that is, the potential difference across a cell wall. All cells show this resting potential; a marked change in the potential may occur when a cell is stimulated, causing an electrical current to flow in the surrounding region. Bioelectrical potentials are often very small, in the region of a millivolt (mV) or very much less, they must be amplified before they can be detected by a suitable recording instrument, such as a pen-writer or oscilloscope.

One reason the recorded potential is so small is that often it must be picked up from a site remote from its source. If, during the course of clinical investigation, we were able to insert microelectrodes into individual cells in the body, we would be able to obtain some exact information about the function of that particular cell or group of cells. Such techniques have, so far, been limited to the laboratory, and in the clinic we must rely on placing electrodes at some point as near as possible to the organ under investigation.

The eye itself provides the clinician with a view of tissues that are normally covered by opaque skin. With the ophthalmoscope, one can examine blood vessels and nerves directly. It is also possible to place electrodes on and around the eye and record electrical changes that occur when diffuse light is flashed on the retina or when the retina is exposed to different forms of light stimulus. So far, at least, the electrical changes in the optic nerve have not been recorded directly, and changes in the optic tracts, lateral geniculate bodies, and optic radiations still remain beyond the reach of the clinician; however, electrical changes over the visual cortex in response to visual stimuli can now be measured.

Electrical changes over the visual cortex, especially in combination with the changes recordable from the eye, are becoming increasingly useful in clinical practice, and there would seem to be enormous scope for the development of this means of measuring body function in the future. It is important to understand that these measures are indicators of function rather than structure. They should never be regarded as an alternative to ultrasound, computed tomography, or other ways of detecting structural changes in the body. Instead, they complement the subjective tests of visual function that are carried out.
Electroretinogram (ERG) or visually evoked response (VER) is nearly useless, and the clinical reporting of these electrical changes needs to be backed up by a full history and the results of all the other relevant tests in a particular case. Electrodiagnosis usually provides one small piece of extra evidence that sometimes may be conclusive in reaching a firm diagnosis.

In this chapter, two types of electrical changes related to seeing are discussed: those recorded around the eye and those recorded from the surface of the scalp over the occipital cortex. Following this discussion, the clinical application of electrodiagnostic tests is considered.

**ELECTRICAL CHANGES RECORDABLE FROM THE EYE**

The Electroretinogram

The record of the changes in the electrical potential of the retina following stimulation by a flash of light is called an electroretinogram. In this section, the historic development of electroretinography, the origin of the response to light, and the components and types of normal ERGs are described.

**HISTORIC DEVELOPMENT OF ELECTRORETINOGRAPHY**

The first work in this field was concerned with the corneoretinal potential, the resting potential, which is defined as the difference in potential between the cornea and the posterior pole of the eye. This potential was first described by Emile Dubois-Reymond, who showed in 1849 that the cornea is electrically positive with respect to the posterior pole. In 1865, Holmgren reported that the resting potential can be modified by the action of light shining on the retina. Shortly after this, Dewar and McKendrick independently discovered this light response. They were able to show that the changes in potential on impact of light amounted to 3 to 10% of the normal resting potential and were independent of the anterior portion of the eye. Initially, their measurements were made by placing electrodes on the cornea and the posterior pole of the eye, but they subsequently showed that the response to light could also be recorded between the exposed brain and the cornea, allowing the eye to be left in situ. They then found that the same electrical changes could be recorded by placing electrodes on the cornea and an adjacent area of skin. Having made this discovery, they were able to attempt to produce a human ERG; this was achieved by using a clay trough filled with saline as the corneal electrode.

These early attempts at human electroretinography were far from satisfactory, and it was not until the turn of the century that advances in recording techniques allowed more accurate records to be made. At this point, the stage had been reached when a waveform could be accurately recorded and measured (Fig. 11.1), and it was known beyond doubt that this waveform was produced by the retina, even though it was recorded through electrodes placed at some distance from the eye. By the early 1930s, attempts were being made to record a human ERG using the valve amplifier.

At the same time, an important milestone was reached in the study of responses from animals in the classic work of Gersnt. He developed the idea, put forward by previous workers, that the ERG represents the sum of...
three waveforms, which he termed "processes." These he enumerated as P1, P11, and P11. He showed that if the ERG is recorded from a cat subjected to deepening levels of ether anesthesia, the waveform changes in a characteristic manner. This change in the waveform was thought to be caused by the selective inhibition of each of the three processes—P1, P11, and P11—in turn. Although they have been elaborated to some extent, these original ideas about the nature of the ERG are still held to be true today. As soon as the knowledge of the basic components of the ERG had become well established, much interest was centered on the relative contribution of photopic and scotopic mechanisms to the response. For example, in 1940 it was noted that the flicker fusion frequency was not the same under photopic and scotopic conditions. This difference is now being used in many electrodiagnostic clinics to assess cone function.

These various advances in our understanding of the electrical responses from the eye were based on work in animals. Meanwhile, investigations on human subjects were hampered by the technical problem of fixing the electrodes. A great step forward was made in 1941 when Riggs introduced the contact lens electrode. Until that time, clinical electrophysiology did not really exist, and little was known about alterations in disease. Use of the contact lens electrode was limited until the pioneering work of Karpe began to be published from Stockholm in 1945. It soon became apparent that the contact lens electrode eliminated much of the interference caused by background noise. The late 1970s saw a further development in this respect: the introduction of a flexible electrode that hangs over the lower lid and allows good recordings to be made but at the same time enables the subject to view the stimulus directly rather than through a contact lens. This electrode has certain advantages when a formed stimulus is required rather than a simple flash.

Using the method described by Karpe, the human ERG appeared as a biphasic response. However, it had previously been shown in other animals that a series of small wavelets could sometimes be seen on the 'b' wave. In 1954, Cobb and Morton described the same phenomenon in man and named it the oscillatory potential. They counted four to six wavelets using a brief flash stimulus; since then it has been shown that these wavelets may be selectively abolished by disease. The early receptor potential (ERP)—another component of the human ERG—can be seen at the very beginning of the response, immediately before the 'a' wave. Brown and Murakami first described it in 1964 and showed that it could be elicited only by an intense light stimulus. The latency period of the ERP is very short, less than 60 msec, and this response appears as a small positive peak followed by a larger negative one. The ERP is thought to be an electrical manifestation of the bleaching of the photopigment in the retina. These newer components of the human ERG can usually be seen if a photoflash stimulus is used; a typical ERG is shown in Figure 11.2.

ORIGIN OF THE ELECTRORETINOGRAM

If the clinical value of the ERG is to be fully realized in the future, a full understanding of the mode of production of the waveform will be essential. A superficial inspection of the problem might lead us to search for an origin of the 'a' wave in one layer of the retina, the 'b' wave in another; and so on. However, the research carried out so far indicates that the source of the recorded response must be considered in two stages. First, we must find out what component waves are added together to produce the final response; then, having isolated these components, we must determine their anatomic site of origin.

A further question arises when we consider that the ERG elicited by a diffuse flash of light is a mass response. Is this response the sum of different kinds of response from different parts of the retinal sphere? Local responses from different parts of the retina can now be obtained, and it is perhaps surprising that the response from a small area of
ERG is produced by a photo-flash stimulus showing the early receptor potential (ERP) and oscillatory potential.

**Figure 11.2.**

ERG produced by a photo-flash stimulus showing the early receptor potential (ERP) and oscillatory potential.

- In the electrodiagnostic clinic, the human ERG is seen as a biphasic response, a negative 'a' wave followed by a positive 'b' wave. The 'b' wave is modified by the oscillatory wavelets in its ascending part. The other components of the ERG can be elicited only by using special recording techniques. It is now widely accepted that the 'a' wave represents the leading edge of P111, which is a negative wave derived from the inner segments of the receptors. P111 has a faster cut-off from cones than it does from rods, and this difference can explain differences between ERGs from vertebrates with rod-dominated or cone-dominated retinas (Fig. 11.3).

Although the negative P111 continues for the duration of the ERG, its leading edge is all that is seen because P11 appears, and this positive wave is superimposed upon it. P11 is thought to arise from the middle layer of the retina, either from one type of bipolar cell or from the Müller cells. The rate of depolarization of the Müller cell is a little slow compared with that of the 'b' wave. P11 is sensitive to ischemia in the retinal circulation.

The 'c' wave, which is a positive wave following the familiar biphasic 'a'/b' wave pattern, is not usually seen in the clinic because recording conditions do not allow it. The 'c' wave is thought to arise from the pigment epithelium. Figure 11.4 shows how P1, P11, and P111 summate to produce an ERG.

**THE OSCILLATORY POTENTIAL** As mentioned, under suitable stimulus conditions, a number of small wavelets are seen on the 'b' wave. In the monkey, these wavelets are abolished in a striking manner by clamping the retinal circulation; they are also abolished in the human eye after central retinal
artery occlusion wavelets on injection suggest that part of the mechanism from the retinal ganglion cells is susceptible to the wave. Intraretinal wavelets are used to reconstruct outer nuclear layer responses, which are related to the response of retinal wavelets.

The response of the wavelets is produced by the wavelet itself, and this property arises from the wavelet response. It has been described that the amplitudes of the wavelets are related to the amplitude of the wavelet itself, and they are related to the retinal ganglion cell response. The wavelet amplitude is measured with the maximum of the wavelet response. The spectrum of the wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response.

The more well-known requirement is that wavelets must be marked with a maximum of the wavelet response. The spectrum of the wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response. The wavelet response is observed in the wavelet response.

- **Figure 11.3.**
  Comparison of ERGs from the rod-dominated eye of a cat (i) and the cone-dominated eye of a frog (ii). Note the absence of the c wave and the presence of the d wave in the cone-dominated retina.

- **Figure 11.4.**
  Diagram to show how PI, PII, and PIII summate to produce the ERG. Changes in the shape of PIII can account for the difference between rod- and cone-dominated retinas.
artery occlusion. The dependence of these wavelets on the integrity of the retinal circulation suggests that they may arise in the inner part of the retina, which receives its nourishment from this source. It is interesting, however, that the wavelets seem to be more susceptible to ischemic change than is the 'b' wave. Intraretinal microelectrodes have been used to record oscillatory responses from the inner nuclear layer of the frog’s retina, and the response can be produced only if a wide area of retina is stimulated. There is also some evidence that the wavelets are produced by tangentially oriented structures, and they are particularly well seen in vertebrates, whose retinas have a thick and well-developed inner nuclear layer.

It has been suggested that the wavelets are related to observed cyclical changes in the amplitude of the spike discharges in the optic nerve, thus explaining their origin from the ganglion cells. However, they are still present in optic atrophy, and antidromic stimulation of optic nerve fibers does not reset the rhythm of the wavelets. The wavelets can best be produced by exposing the eye to double flashes spaced about 15 seconds apart. The second flash tends to produce a more well-defined response, and this requirement for preadaptation becomes more marked when the eye is dark adapted. The maximum chromatic sensitivity of the wavelets has been shown to be at the red end of the spectrum, and it has been claimed that the wavelets are abolished in patients with congenital achromatopsia. Their exact site of origin is therefore still in doubt, although the evidence at present seems to point to the inner nuclear layer. In view of the fact that the wavelets show certain features in common with a response recordable from the amacrine cells, it has been suggested that they could represent a feedback mechanism from the amacrines to the bipolars.

More recently, it has been found that the list of the oscillatory potentials appears to behave differently from the others. Its timing alters with increase in stimulus frequency in a different manner. In fact, the last wavelet appears to be time locked to the stimulus offset, whereas the others are not. The suggestion is that the last wavelet is part of the off response, being generated by the retinal off elements described in single-cell recordings.

**THE EARLY RECEPTOR POTENTIAL (ERP).** Although the latent period of the 'a' wave becomes much shorter with stronger stimuli, it is never less than about 2 msec. For some years before 1964, it was suspected that a response might exist that bridged the gap between the moment of excitation and the onset of P111. In 1964, Brown and Murakami found that an electrical response of no detectable latency could be recorded from a microelectrode inserted into the inner segment of the receptors. It was then shown that this rapid biphasic response—termed the early receptor potential—could be recorded with large electrodes outside the retina. The ERP can now be recorded as a clinical procedure in the human.

The action spectrum of this response agrees with that for bleaching of visual pigment. The ERP was elusive in the past because it is easily obscured by artifacts and a strong flash is required to elicit it. The ERP comprises a small positive component, known as R₁, followed by a larger component, known as R₂, which leads directly into the 'a' wave. Because the latency is virtually zero, both R₁ and R₂ are thought to arise from the outer segments of the receptors, and it has been suggested that they are caused by movements of charge in visual pigment molecules.

The ERP is more resistant to disease than are the other components of the ERG. When recorded from the isolated retina, it is not much altered by formaldehyde or metal-chelating agents. When the retina is heated, the ERP disappears at the same temperature at which the regular orientation of the pigment molecules is lost.

**VARIATIONS IN THE NORMAL ERG.** The clinician who interprets ERG traces should fully understand all the different factors that
may influence a normal ERG. Without such knowledge, the reporting may be extremely misleading, and conclusions based on it unjustified. The factors that may influence a normal response can be summarized as follows:

1. Physiologic factors
   - State of dark adaptation
   - Pupil size
   - Diurnal rhythm
   - Refractive error
   - Age and sex
2. Type or adjustment of equipment
   - Amplifier (setting of gain and time constant)
   - Type of recorder
   - Electrode position
   - Stimulus color, duration, and intensity
3. Artifacts
   - Blinking
   - Tears
   - Bubbles in contact lens
   - Eye movements
   - Photoelectric and electric artifacts

**TYPES OF NORMAL ELECTRORETINOGRAPHY**

**PHOTOTIC AND SCOTOTIC ERG.** The electrical response of the dark-adapted retina to a white flash reflects both rod and cone activity, but in the clinic, it is often useful to be able to separate these. This separation may be achieved in the following way:

1. If a flickering light is used with a frequency of 30 cycles per second, then a pure cone response results because the rod system cannot respond at this rate.
2. A pure cone ERG can also be produced if the stimulus is superimposed on a steady background illumination. The background illumination serves to saturate the rods so that they cannot respond to brief flashes.
3. A rod response can be produced by stimulating the dark-adapted retina with a dim blue light, which is below the cone threshold.

**FLASH ERG.** When an intense photoflash is used to produce an ERG, certain special features appear in the response. First, the ERG can be seen immediately before the 'a' wave. The 'a' wave is abnormally large and the 'b' wave is small when measured from the resting potential. However, the potential difference from the peak of the 'a' wave to the peak of the 'b' wave is not very different from that obtained using the more classic technique of electroretinography described by Karpe. A further feature of this type of response is the prominence of the oscillatory potential. Finally, there is a pronounced refractory period after each response. If the stimulus is repeated half a minute after the first one, then the resulting response is half the size of the first; a repeat flash within 2 or 3 seconds of the first one produces no response whatsoever. Subjectively, a flash of this sort produces a dense afterimage, which changes color over a period of one-half to three-quarters of a minute and then disappears.

**RESPONSE TO FLICKER.** One method of obtaining a photopic ERG is to present the eye with a rapid series of flashes. If a stimulus flash is repeated every few seconds, using a weak stimulus, then the second response resembles a normal ERG. If the flash rate is increased to two per second, then the second response and successive responses have a photopic character and are reduced in amplitude. As the frequency is increased, the amplitudes of 'a' and 'b' waves approach one another. Beyond a certain frequency, the trace becomes sinusoidal, and finally it flattens altogether when the critical fusion frequency is reached. The critical fusion frequency varies with the intensity of the stimulus. If a graph is made by plotting intensity against critical fusion frequency, the resulting curve has a kink in it at about 20 per second. This kink corresponds with the rod/cone break in the dark-adaptation curve, and it suggests that the rods do not respond above the level of about 20 per second. With high intensities, a fusion frequency of 70 per second can be reached.
"OFF EFFECT." As a rule, the clinical ERG is recorded using a brief stimulus flash whose duration is limited to less than 20 msec. If a more prolonged stimulus is used, however, a change in electrical activity is evident when the stimulus is discontinued. In animal experiments, this has been termed the "off effect," or 'd' wave. The human "off effect" is a negative-going wave with a weak stimulus, but it becomes a positive wave as the stimulus is increased in intensity.

The clinical applications of the "off effect" have been limited. It has been shown that the negative-going wave elicited by a dim stimulus is absent in congenital stationary night blindness but present in rod monochromatopsia. It has also been shown that a series of wavelets may be found on the "off effect" that bear a resemblance to the oscillatory potential.

Nilsson has developed a DC registration technique that has allowed more detailed study of the "off effect." After a very fast positive 'd' wave, there occurs a fast negative change (the 'f' wave), a slower positive wave with a maximum at 0.9 to 1.5 seconds after "off" (the 'g' wave), and a slow negative change with a maximum of 4 to 6 seconds (the 'h' wave). The 'h' wave seems to be the "off" equivalent of the 'f' wave.

PATTERN ERG. Until recently it was assumed that the ERG produced by a pattern stimulus was similar to that produced by a flash stimulus if matched for luminance. Considerable interest has been aroused by reports that the pattern ERG, unlike the flash ERG, is reduced after section of the optic nerve. The response to a diffuse flash is normal after optic nerve section because it arises from the unaffected distal components of the retina. Furthermore, during an attack of acute optic neuritis, both flash and pattern ERGs may be normal at first, but over the ensuing weeks the pattern ERG may decrease in amplitude, whereas the flash ERG, as expected, remains normal. Such findings have stimulated considerable research interest, and it now looks as though routine measurement of the pattern ERG in the clinic can be useful.

The pattern ERG is now recognized to have two major components: P1 (or P-50, indicating the latency in milliseconds) and N1 (or N-95, a negative wave following P-50 at about 95 msec). Evidence is accumulating that the early P1 component may be generated in the bipolar region, whereas the N1 component is generated in the ganglion cell layer. The pattern ERG has been shown to be a sensitive indicator of diabetic retinopathy and particularly of early glaucomatous damage to the retina.

FOCAL ERG AND MULTIFOCAL ERG. In theory, it is possible to obtain an ERG from a small area of retina if a suitable background stimulus is used to preadapt the surrounding area and prevent spurious responses from stray light. However, the development of a reliable and widely accepted means of producing a focal ERG from a localized region of abnormal retina has proved difficult. One promising technique has involved the use of a stimulator optophthalmoscope with which the examiner can place the stimulus on the desired region of retina under direct observation. Such techniques are capable of detecting quite small focal lesions. The response obtained from local stimulation is very small and can only be identified by repeating the stimulus many times and averaging the results. This is done electronically so that the patient views a flickering light for a few minutes and a readout is obtained at the end. The size of such a response is in the region of 1 or 2 μV.

Recently this approach has been developed in a very interesting manner; a multi-input stimulus has been developed. The patient views a TV screen on which numerous illuminated squares or hexagons are presented, each being illuminated at independent moments or simultaneously with a probability of 1/2. The response from each consecutive moment of this pseudorandom sequence is recorded and analyzed. The analysis assumes that the local flash ERG shows spatial summation in a linear manner.

The end result of this technique is a map of the responses that resembles a plot of the
visual field obtained by standard clinical means. The method has the advantage of being objective, and it can be performed on both eyes simultaneously (Fig. 11.5).

STANDARDIZATION OF THE ELECTRORETINOGRAM

The present standardized ERG protocol was developed by a committee of the International Society for the Clinical Electrophysiology of Vision (ISCEV) and published in 1989. It was updated in 1994. This standard is now widely used. An example of responses obtained using this protocol is shown in Figure 11.6. In principle, the standardized technique involves:

1. Initial dark adaptation after dilating the pupil, followed by measurement of the rod response to a dim white flash of known intensity.

2. After this, a bright flash stimulus is applied to elicit a maximal response and the oscillatory potential. The latter can be portrayed separately by filtering the response.

3. A single-flash cone response is then measured by suppressing the rods with a constant background luminance.

4. The flicker response from the cones is measured.

SUMMARY

The important features of the normal ERG can be summarized as follows:

1. Although the ERG can be recorded through electrodes placed outside and even at a distance from the eye, there is no doubt that it is produced by the retina; other structures in and around the eye probably make no contribution to it.

*Figure 11.5.*

The type of graphical recording obtained by the multifocal ERG.
2. The ERG is made up of the following components: the ERP, the 'a' wave, the 'b' wave, and the 'c' wave. There is also an "off effect," whose position depends on the timing of the stimulus flash.

3. The ERP is thought to arise from the outer segments of the receptors. The 'a' wave is part of Granit's P11 component and is thought to arise from the inner segments of the receptors. The 'b' wave corresponds to Granit's P11 component and is thought to arise from the inner nuclear layer. The 'c' wave, which corresponds to P1, probably arises from the pigment epithelium.
Under suitable stimulus conditions, the 'b' wave is modified by the appearance of three or four small wavelets, which probably arise in the inner nuclear layer but not from the same source as the 'b' wave itself. These wavelets are particularly sensitive to pathologic changes in the retina.

4. Repetitive focal stimuli to different parts of the retina produce responses that can now be analyzed, giving a form of objective visual field measurement.

The Electro-Oculogram

So far we have been considering electrical responses that are produced by exposing the eye to a brief flash of light. Although a variety of light stimuli are used in electroretinography, they are all relatively short flashes, lasting for milliseconds rather than seconds. In electro-oculography, a slightly different technique, the electrical responses of the eye to a prolonged light stimulus lasting several minutes are measured.

The difference in potential between the cornea and the posterior pole of the eye, known as the corneoretinal potential (the resting potential) normally amounts to several millivolts. When the eye is exposed to a brief flash of light, the corneoretinal potential changes; the tracings of these changes constitute the ERG. Unfortunately, it is not easy to measure the corneoretinal potential over long periods of time because in practice the response is obscured by blinks, random eye movements, and other artifacts, which make the baseline potential unsteady. This problem can be alleviated during electroretinography by the use of an AC-coupled amplifier; this type of amplifier only responds to relatively rapid changes in potential, and in this way, a steady baseline is more easily maintained. When the eye is exposed to a continuous light stimulus, a slow change in the corneoretinal potential occurs. This change would not normally be seen using an AC-coupled amplifier, and the baseline would be too unsteady to obtain accurate measurements if a directly coupled amplifier were used.

Electro-oculography is a recording technique that allows an AC amplifier to be used to record these slow changes in the corneoretinal potential; rapid changes of potential are produced by moving the eyes to and fro and are fed through an AC amplifier to a pen recorder. These changes in potential have been shown to be related to the size of the corneoretinal potential if the size of the eye movements is kept constant.

To perform the test, the electrodes are placed on the skin on either side of the eye at the medial and the lateral canthi, and one indifferent electrode is usually placed on the forehead. The subject is seated, facing a screen that can be illuminated. In addition, two small red fixation lights are mounted on either side of the screen. The subject is then asked to look briskly from one fixation light to the other, thus making horizontal eye movements of a constant size.

The eye can be regarded as an electrical dipole, the cornea being positive with respect to the posterior pole. Figure 11.7 illustrates how eye movements in a horizontal direction can produce a modified square wave and how the vertical limbs of this waveform can increase and decrease in amplitude, depending on the size of the corneoretinal potential. The same method can, of course, be used to measure eye movements, but here we are concerned with changes in the corneoretinal potential, and the eye movements are kept at a constant value.

As long ago as 1929, it was shown that eye movements produce electrical changes that can be measured by skin electrodes, but at that time it was assumed that these electrical changes were related to muscle action potentials. It was later conclusively proved that the changes in potential were due solely to the existence of the standing potential.

Electro-oculography thus provides a means of monitoring long-term changes in the corneoretinal potential and, in particular, a means of assessing the changes induced by light. It is performed in the nurse's room, the cornea being negative with respect to the posterior pole. A vertical line is calculated for each horizontal movement of the eye, and the values are recorded.

In its most simple form, involves the eye being fixed at a particular point. If the light is then turned off and on again, the changes in potential can be observed. The corneoretinal potential falls to a new level, and the eye movements are kept at a constant value.

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by light. In the clinic, the tests can be performed in an automated fashion, so that a nurse is needed only to fix on the electrodes. A value known as the Arden index is calculated from the raw data. This value should be above 180 in a normal subject, although some myopes have slightly lower values.

In its most commonly used form, the test involves searing the subject in the dark; during this time, the corneoretinal potential tends to fall. In continued darkness, the potential remains at a low level but tends to wander up and down slightly. After 12 minutes, the light stimulus is applied. There is an initial electroretinographic response, and then the potential falls for about 2 minutes, after which it begins to rise steadily over a period of about 7 minutes. The initial fall is termed the fast oscillation, or transient, and the rise is known as the light rise. After about 7 minutes, the corneoretinal potential reaches a peak value and then begins to fall in spite of the fact that the light stimulus is still being applied. This fall in potential is followed by a further rise, and it becomes apparent that the response is a form of damped oscillation.

For clinical purposes, a Standard for Clinical Electro-oculography has now been developed, and as is the case for electroretinography, it is recommended that the standards be carefully followed.

**ORIGIN OF THE ELECTROOCULOGRAM AND ITS RELATION TO THE ELECTRORETINOGRAM**

The electro-oculogram (BOG) recorded with skin electrodes is probably the resultant of several potentials. Potentials in the skin or other parts do not change as the eye rotates and therefore do not affect the results. Nonretinal potentials arising out of the eye itself, on the other hand, could be more important. For example, the cornea is thought to be polarized so that its anterior surface is negative; that is, it acts against the resting potential. If the corneal potential were to be abolished, then one might expect a corresponding increase in the resting potential. Both the standing potential and the dark trough of the BOG are markedly reduced by the administration of atioide, which produces selective damage to the
pigment epithelium. Hence, this may be the anatomic origin of at least part of the EOG response. Laboratory studies have shown that a delayed hyperpolarization of the basal membrane of the retinal pigment epithelium correlates with the fast oscillation of the EOG. Longer exposure to light produces a gradual depolarization of the basal membrane, which accounts for the light rise of the standing potential. These electrical changes in the retinal pigment epithelium presumably depend on the integrity of the receptors, and the EOG could not therefore be expected to be a specific indicator of retinal pigment epithelial function. In certain diseases the ERG may be normal when the EOG is grossly abnormal or vice versa, and this may be of diagnostic value. Patients with vitelliform macular degeneration, for example, may have a diminished light rise and a normal ERG (see case 11.5 at the end of the chapter). In congenital retinal dysgenesis, the ERG is normal but the EOG is abnormal, whereas in a congenital retinal atrophy,' both the ERG and the EOG are affected. Despite a few examples in which changes in the EOG do not reflect changes in the ERG, our knowledge of the meaning of these differences is still inadequate.

In practice, the important differences between electroretinography and electro-oculography can be summarized as follows:

1. Electroretinography measures rapid changes in the resting potential in response to light, whereas electro-oculography measures slow changes.
2. A contact lens is not required for electro-oculography.
3. Less skill is required for electro-oculography, and the equipment is more portable.
4. Electro-oculography cannot easily be performed on patients who cannot fixate, and it is not suitable for testing retinal function in blind patients.
5. Children under the age of 5 or 6 years cannot usually cooperate sufficiently to allow accurate electro-oculography.

**ELECTRICAL CHANGES RECORDABLE FROM THE BRAIN: THE VISUALLY EVOKED POTENTIAL**

Recording the spontaneous electrical activity of the brain from electrodes placed on the scalp has been a clinical practice for many years. It has also been known that this spontaneous activity can be modified by the action of light on the eye. The visually evoked potential (VEP) is one of several evoked potentials that can be recorded from scalp electrodes. Such electrical changes can be produced by sound, smell, and taste, as well as by sensory stimulation.

The changes evoked by visual stimuli were first recorded in animals directly from the surface of the pia mater in the 1930s. At that time, it was well recognized that the alpha rhythm seen on normal electroencephalographic (EEG) traces could be accentuated by exposing the eyes to a light flashing at a similar frequency. When the eyes were exposed to repeated flashes at varying frequencies, the electrical changes recorded from scalp electrodes became small and more or less lost against the background of the normal spontaneous activity of the brain. The problem of detecting these small electrical signals was largely solved by the introduction of the technique of averaging. Before the development of modern electronics, this simply entailed superimposing the repeated responses after each flash stimulus. Examining the trace after a single flash revealed little or no sign of any waveform that one might relate to the flash, but when a sufficient number of traces had been superimposed, a response could be discerned that was not visible on the single record. This method of mechanical averaging has been supplanted by electronic averaging. The response following each consecutive stimulus is stored in the memory of a computer, and the average can be automatically displayed as a single trace on the face of an oscilloscope at the end of the opera-
Figure 11.8 shows the effect of averaging on a raw EEG tracing obtained when the eyes were exposed to repeated light flashes. If the responses to a large number of similar visual stimuli are averaged, the discrimination from irrelevant cortical activity can be improved greatly. From the clinical viewpoint, the introduction of signal averaging was an important breakthrough, because we can now record VEPs as small as 2 or 3 µV. Furthermore, the nature of the response and its amplitude and waveform can be related to the type of visual stimulus in a way never before possible. As is seen below, use of the VEP offers the possibility of a true objective measurement of visual acuity.

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**EEG recorded with Scalp Electrodes during Repeated Light Flashes of 1 ms duration at approx. 2 s Intervals**

Responses to light flashes are buried by EEG and noise

The above Waveform after Analysis by a Signal Averaging Instrument triggered from Light Flash

25 microvolt response clearly detected after averaging with 256 sweeps

---

*Figure 11.8.*

Diagram showing how signal averaging can bring out hidden information from raw traces.
METHODS OF RECORDING THE VEP

Many electrodiagnostic clinics throughout the world now measure the VEP routinely. A standardized VEP has now been developed under the auspices of the International Society for the Clinical Electrophysiology of Vision (ISCEV) and was approved in 1995. An abbreviated version of this is available in the guide to procedures published by the society. To record the VEP, four types of equipment are needed: a repeated stimulus, a suitable system of amplifiers, an averaging computer, and a readout system to display the information.

STIMULUS

The stimulus can be a diffuse flash of light or a pattern displayed on a screen. The diffuse flash, or unstructured stimulus, may vary in frequency, intensity, size, or color. The most popular patterned stimulus is a checkerboard of black and white squares, although for some purposes, lines, gratings, or other patterns are used.

It is important to distinguish between pattern reversal and pattern appearance, because each produces a different response from the scalp. In pattern reversal, the luminosity of the black and white squares is reversed alternately, the black becoming white and the white becoming black. In pattern appearance, a black-and-white checkerboard is presented in an on-off sequence. It is also important to distinguish between a rapidly repeated stimulus and a slowly repeated stimulus. The rapidly repeated stimulus produces a sinusoidal type of response, referred to as the steady-state response. Stimuli repeated fewer than two or three times a second produce a characteristic waveform known as the transient response.

ELECTRODES. Ideally, the skin electrodes must make good contact, be electrically inert, and have a low electrical resistance. The most popular ones are made of silver coated with silver chloride. A layer of electrode jelly is placed between the scalp and the electrode, which may be held in place by collodion or a head strap. Fitting the scalp electrode takes time and patience and should be performed by an experienced technician for best results. The exact positioning of the electrode is critical. The standard "10-20" system of electroencephalographers provides a useful variety of positions as direct measurements from the inion. In practice, the choice of electrode position depends on the particular aspect of the VEP being investigated.

SYSTEM OF AMPLIFIERS. Usually two amplifiers are used, a preamplifier and a main amplifier. The system must amplify the minute electrical signals from the scalp to a level acceptable for the computer and readout display without causing undue distortion of the signal and without danger to the patient.

AVERAGING COMPUTER AND READOUT SYSTEM. The design and function of electronic equipment are continually being improved. Until recently, a small computer designed only for signal averaging was used, but it is now more common to find larger and more versatile computers in use. These allow the waveform of the response to be processed mathematically in a short time and provide a convenient way of storing records.

NORMAL VEP

The character of the normal VEP depends on the type of stimulus used and the position on the scalp from which it is recorded. It also varies greatly from one individual to another. In spite of these difficulties, reliable features, particularly of the transient response to a checkerboard stimulus, are beginning to be identified. Figure 11.9 shows the features of the response to a flash stimulus recorded from the midline electrodes above the inion. The response to a pattern-appearence stimulus is shown alongside it for comparison.

In general, the VEP to flash stimulation consists of a complex series of negative and positive waves. The most common components are the N2 and P2 components at around 90 msec and 120 msec, respectively. An early positive wave 50 msec is also seen. This is more frequent in older subjects. The pattern-reversal VEP consists of N75, P100,
and N135 components. The nomenclature indicates their sign and latency. When a pattern-onset stimulus is used, the components are described as C1 (positive at about 75 msec), C2 (negative at about 125 msec), and C3 (positive at about 150 msec). The response to a plain flash stimulus is smaller and less well defined and cannot easily be compared with the patterned response; as the check size of a patterned stimulus becomes very large or very small, the electrical response more closely resembles that produced by an unstructured flash stimulus.

The normal VEP has been studied under a wide variety of stimulus conditions. Investigations of the effect of altering the size of the stimulus indicate that most of the response is derived from the central macular area of the retina. The VEP shows a progressive increase in size with dark adaptation, and it is abolished by pressure blinding the exposed eye, recovering after about 90 seconds.

Many other types of stimulus have been used, and studies have been made on the effect of altering contours and the size of the pattern elements, the effect of eccentricity of retinal stimulation, and the effect of retinal disparity in binocular stimulation.

VEP AND THE VISUAL FIELD

If different parts of the visual field are stimulated by a small patterned stimulus and the VEP is measured from the midline electrodes, the amount of information obtained is disappointing. This is not only because the response becomes very small when the stimulus is only a few degrees from fixation, but also because the method is not capable of detecting extensive defects in the visual field. Responses from the upper part of the field are always smaller than those from the lower part, in normal subjects, using midline electrodes. Furthermore, all three components of the transient response show a polarity reversal when the stimulus is changed from the upper to the lower half of the visual field. The information obtainable from a single midline electrode when different parts of the visual field are stimulated is therefore limited, and numerous workers are now investigating the detailed scalp topography of the VEP.

A more fruitful approach to studying the effect of stimulating different parts of the retina on the cortical evoked response has been gained from hemifield stimulation. By stimulating corresponding right or left half-fields of vision, thereby presumably...
stimulating contralateral hemispheres, significant electrical changes can be measured from electrodes placed away from the midline on either side.

At first sight, the results of various investigators appear to conflict with one another: some claim clear-cut contralateral responses with half-field stimulation; others claim, surprisingly, a large response over the ipsilateral hemisphere. The apparent difference in these results is probably related to the different type of stimulus used, whether pattern reversal or pattern onset, and also to the fact that different peaks on the transient response were measured. Thus, an early peak, measured 90 msec after the stimulus, is found contralaterally and well away from the midline with pattern-onset stimulation, whereas a well-developed peak at 25 msec is found over the ipsilateral hemisphere with a pattern-reversal stimulus. The positive peak at 125 msec is largely ipsilateral, as is the negative peak at 165 msec, with pattern reversal. The peak at 225 msec is largest in the midline in both pattern-onset and pattern-reversal stimulation, but the peak at 125 msec is contralateral with pattern-onset stimulation.

The steady-state VEP (i.e., the VEP recorded using a rapidly repeated pattern stimulus) has also been used to assess the visual field, and some recent evidence suggests that this might be a better approach.

**VEP AND THE MEASUREMENT OF VISUAL ACUITY**

The fact that blurring the outline of a checkerboard stimulus or altering its size can greatly influence the latency and the amplitude of the VEP has led to attempts to use it as a measure of visual acuity. The results of such attempts are not likely to have much meaning when they are compared with the results of standard Snellen test types because a different aspect of visual acuity is being measured in each case. Psychophysical measurements of the ability to detect changes in contrast can also be made and compared with the VEP, using contrast gratings. Here, the results of psychophysical testing can be more closely related to electrophysiologic findings.

The VEP has also been used in attempts to develop an objective assessment of refractive error. Regan has shown that by rotating a stenoptic slit in front of the cornea of a subject viewing a checkerboard stimulus, the axes of astigmatism can be determined. Once these axes have been ascertained, the necessary lens power in each axis can be determined by a variable-power lens system. A graph of VEP amplitude versus slit angle and another of VEP amplitude versus lens power can be produced electronically within a few seconds of starting the tests.

The investigation of the electrical changes over the scalp has attracted the interest of research workers from many disciplines all over the world, because such electrical changes might give some indication of the working of the brain itself. A rudimentary knowledge of the pattern of changes over the scalp in response to certain repeated stimuli is beginning to emerge. As the results in normal subjects are beginning to be understood more clearly, investigations into the changes in disease are also taking place. It is shown below that the VEP has an important place in the detection of healed retrobulbar neuritis; it also can be used for assessing visual acuity and field defects in young children.

**FACTORS INFLUENCING THE NORMAL VEP**

The method of recording the VEP varies considerably from center to center. A major point of confusion arises from the fact that there is no agreement about which way up the trace should be recorded. In clinics that have been concerned largely with clinical electrophysiology, the convention is to have negative upward, and in clinics with a background of pure science or ocular electrophysiology, the convention is to have positive upward. Some of the factors that must be taken into account when reporting a VEP are the stimulus, age and sex, electrode position, and anatomic variations.

**STIMULUS**

Increases in stimulus intensity have been demonstrated. A possible VEP was recorded only in the macular region. This appears to be related to the retinal sensitivity within the macular region.

Even though a stimulus is applied to the retina, a blink reflex or other response is not observed. This is probably related to the retinal sensitivity within the macula.

**AGE AT ONSET**

VEP has been observed in neonates, even in those as young as a few days old. The method is sensitive to the presence of an optic nerve lesion, and the results are different in infants, children, and adults. The VEP is sensitive to the presence of an optic nerve lesion, and the results are different in infants, children, and adults. The VEP is sensitive to the absence of an optic nerve lesion, and the results are different in infants, children, and adults.
**STIMULUS.** The VEP with a flash stimulus increases in amplitude with an increase in stimulus intensity, but a saturation point is reached. The latency is reduced with an increase in intensity. Dark adaptation can be demonstrated with a VEP, as it can with the ERG, and a rod/cone break has been shown. A possibly useful clinical application of the VEP was realized when it became known that the response to a flash was relatively large with a small centrally located stimulus. This appeared to reflect the wide area of macular representation on the occipital cortex. The VEP can therefore be used as a test of macular function.

Even though the response to an unstructured stimulus has been proved to be of some clinical value, pattern stimuli are now widely preferred because the response to a pattern is much larger and bears a closer relationship to the act of seeing. Thus, it has been shown that small patterns give a relatively large response when viewed by the macula area, whereas progressively larger patterns give a maximal response as the more peripheral parts of the retina are stimulated.

A completely different stimulus approach has been made by recording the transscleral VER. This is elicited by light delivered through an optical probe on the lower lid. The method has some promise for investigating retinal function in the presence of opaque media.

**AGE AND SEX.** The effect of age on the VEP has been extensively studied, and its possible value as a measure of visual function in young children and infants has been the focus of many studies. The pattern-reversal VEP at the age of 6 months appears to resemble that of the adult. In premature infants, the VEP is limited to the occipital region and gradually spreads with increasing age; the waveform also changes. It has been claimed that the diffuse-flash VEP of the premature infant can be distinguished from that of the full-term infant. During maturation, the occipital VEP shows a rapid increase in amplitude of most components. This is seen in early childhood and reaches a maximum in 6- to 8-year-old children. At this age, the VEP may be more than twice as large as that in older age groups. After this peak, there appears to be a decline in amplitude associated with increasing age until 13 to 14 years of age, when a further abrupt increase is seen, especially in the earlier components occurring in the first 200 msec. The amplitude of the VEP seems to stabilize about the age of 16, showing a subsequent gradual reduction throughout life and then a more rapid decline in old age.

The difference between male and female responses is not great, although female responses appear to be larger during adolescence and in adults, whereas male responses are larger in children.

**ELECTRODE POSITION.** Recording the VEP from a single electrode placed above the union reveals only a small facet of the total response. For clinical purposes, it is preferable to use an array of electrodes across the back of the scalp. The electrical changes from each electrode vary from millisecond to millisecond in a different manner at each electrode. This means that the response over a period of 500 msec following the stimulus flickers across the scalp like light from moving water. Methods have now been worked out to represent this graphically or as spatiotemporal maps. Again, it must be remembered that these results depend on the type of stimulus presented and may vary greatly depending on whether the stimulus is a flashed pattern, pattern onset, or pattern reversal.

**ANATOMIC VARIATIONS.** The amplitude of the VEP differs markedly from subject to subject. Although not yet clearly proven, much of this variation probably is caused by anatomic differences such as the thickness of the skull or the orientation of the occipital cortex in relation to the scalp. This hypothesis is supported by studies on identical twins, who show similar responses, and by the fact that in a given individual, the response is repeatable from day to day and hour to hour.

**OTHER FACTORS.** Unfortunately, accurate recording of the VEP depends on subject
cooperation and may be influenced by attention, fixation, and focusing. A malingering subject could produce misleading results by deliberately defocusing the eyes from the pattern or by fixing on a point elsewhere in the room. The problem of fixation in children can be overcome by presenting a television image in the center of the screen to attract the child's attention. It is, of course, essential that the patient's correct spectacle prescription be worn at the time of the test.

**SUMMARY**

The VEP is defined as the electrical changes that can be recorded from the scalp in response to a repetitive light stimulus presented to the eyes. The important features of the VEP can be summarized as follows:

1. The characteristics of the VEP depend critically on the type of stimulus presented.
2. The VEP appears to be largely derived from the macular area of the retina—that is, the central 5 to 10° of visual field on each side.
3. Specific changes in the VEP can be seen when a checkerboard pattern of differing check sizes is presented.
4. It is possible to make accurate measurements of the latency—that is, the time taken from stimulus presentation to appearance of electrical response on the scalp; such measurements have proven clinically useful.

**CLINICAL APPLICATION OF ELECTRODIAGNOSTIC TESTS OF THE VISUAL SYSTEM**

**Inherited Retinal Diseases**

Characteristic changes in the ERG, EOG, and/or VEP occur in some inherited diseases and may be useful in diagnosing or evaluating these conditions.

**RETINITIS PIGMENTOSA**

Since the late 1940s, it has been known that the ERG shows marked changes in patients suffering from retinitis pigmentosa. Even at an early stage of the development of this type of retinal degeneration, the ERG is more or less completely abolished; the light rise of the EOG is similarly affected.

Most patients who show the typical fundus changes of retinitis pigmentosa have an extinguished ERG (Fig. 11.10). Patients in the early stages of this disorder clearly have some response; in fact, a close relationship probably exists between ERG sensitivity and the functioning area of the retina. Patients with a relatively well-preserved ERG often have a history of late onset of a mild form of the disease. In some series in which early cases have been examined, the ERG has been almost normal. The early changes are usually seen in the scotopic ERG, particularly if this is recorded with a red-light stimulus.

The ERG has been used to distinguish types of retinitis pigmentosa presenting with predominant damage to the rods from those showing early damage to the cones (rod/cone or cone/rod degenerations). Now that a number of mutations and deletions in the rhodopsin gene have been discovered in patients with these conditions, attempts are being made to link phenotype and genotype more closely. Carriers may also show a reduced amplitude of the ERG and the EOG, and this may be important confirmatory evidence for a mother-to-be. Often, of course, a firm diagnosis of retinitis pigmentosa can be achieved with the ophthalmoscopes alone. In spite of this, one cannot claim that such a case has been properly documented until a record has been made of the visual field and ERG. If the ERG is totally abolished, there is little point in repeating the test subsequently, unless some new form of treatment is being tried and it is necessary to monitor the disease objectively.

Patients with retinitis pigmentosa have a normal VER unless the disease is advanced or unless there is early macular involvement.
SYSTEMIC DISEASE ASSOCIATED WITH RETINITIS PIGMENTOSA

A wide variety of diseases have been associated with retinitis pigmentosa and some of the other progressive degenerations related to it. Although electrodiagnostic investigations cannot now distinguish between classic retinitis pigmentosa and that associated with systemic disorders, they have a particular value when applied to the latter. Sometimes, the fundus changes are minimal in these patients, and they may be referred from the neurologist or the physician with the question “Are the eyes normal?” The ERG and the EOG can provide an immediate answer. Apart from this, the vision may be affected by other pathologic processes.

Figure 11.11 shows the ERG report for a patient with ill-defined peripheral constriction of the visual fields and enlargement of the pituitary fossa. She also had polydactyly, having had the extra finger removed in infancy. The fundi showed one or two irregular flecks of pigment in the periphery. The problem was deciding whether the field defect was caused by chiasmal compression or early retinitis pigmentosa in association with polydactyly, the Laurence-Moon-Biedl syndrome being suspected.
The electroretinogram was barely recordable from either eye even when a bright stimulus flash was used. The findings are consistent with retinitis pigmentosa.

**EVOKE POTENTIALS REPORT**

---

**Figure 11.11.**

The ERG report for a patient with ill-defined peripheral constriction of the visual fields, enlargement of the papillary fossa, and polydactyly. The absence of an ERG response, consistent with retinitis pigmentosa, and the other signs point to a diagnosis of Laurence-Moon-Biedl syndrome.

The systemic disorders associated with progressive retinal degeneration include the following conditions:

1. **Metabolic disorders**  
   a. Lipid abnormalities  
      i. α,β-lipoproteinemia  
      ii. Refsum's disease  
      iii. Familial amaurotic idiocy

2. **Neurologic disorders**  
   a. Laurence-Moon-Biedl syndrome  
   b. Hereditary ataxias  
   c. Ocular myopathy  
   d. Syndromes involving mental retardation

3. **Occasional associations**  
   a. Dermatologic disorders  
   b. Megacolon  
   c. Marfan syndrome  
   d. Familial nephropathies

Familial amaurotic idiocy, although characterized by progressive degeneration of the retina, is probably a completely separate entity. The ERG in the infantile form has been reported as normal by several workers. This finding is consistent with the pathologic changes, which are restricted at first to the ganglion cell layer and spare the outer part of the retina whence the ERG arises. In late infantile and juvenile amaurotic idiocy, however, the ERG may be reduced or absent.

All the other conditions listed above are associated with retinitis pigmentosa, and the ERG and the EOG are affected accordingly. Several of these conditions show specific biochemical abnormalities, which may throw some light on the cause of the pigmentary degeneration. For example, the association of α,β-lipoproteinemia, retinitis pigmentosa, ataxia, and acanthocytosis of the red cells also involves a lowering of the blood level of the fat-soluble vitamins, including vitamin A. It has been claimed that vitamin A supplements in sufficient dosage to raise the vitamin A level to normal also restore the dark-adaptation curve and the ERG to normal. In the mucopolysaccharidoses, vision may be impaired by infiltration of the cornea, and the fundus may not be visible. Electrodiagnostic tests may thus be the only way of detecting associated retinitis pigmentosa. It should be apparent that because retinitis pigmentosa may sometimes present...
with minimal changes in the fundi, an ERG is essential if any of the above conditions are suspected.

Figure 11.12 shows the serial ERGs in a patient with Refsum's disease. Here the ERG was recorded annually because the patient was maintained on a special diet. No improvement in the response is visible.

The ERG and the EOG have been investigated in a wide variety of conditions related to retinitis pigmentosa. For more details, the reader is referred to the more specialized textbooks listed in Suggested Readings.

LEBER’S AMAUROSIS

Leber's amaurosis was first described by Leber in 1869. He classed the condition with pigmentary degenerations of the retina, even though the pigmentation was minimal or appeared at a late stage. The condition is usually congenital, with the affected child being blind from birth, but some become blind during the first year of life. The fundi may appear normal, but a variety of minor changes have been described from fine pigment stippling to choroidal sclerosis. On occasion, the classical appearance of retinitis pigmentosa may be observed.

The advent of electroretinography has made it possible to distinguish children with Leber’s amaurosis from those with optic nerve atrophy and Tay-Sachs disease. Since it is usually necessary to examine the fundi under a general anesthetic, it is important to

\[ \text{Figure 11.12.} \]

Periodic ERGs recorded from each eye in a patient with proven Refsum's disease. In this patient, the ERG was used to monitor the effectiveness of treatment; the ERG has started to decline between 1984 and 1992.
take the opportunity to perform electro-retinography at the same time. If a general
anesthetic is contraindicated, it is often sur-
prisingly easy to insert a contact lens with-
out an anesthetic in a child up to 3 or 4
months old. The ERG is abolished or very
small in Leber's amaurosis but normal in op-
tic nerve atrophy and Tay-Sachs disease.

Sometimes, these children present as hav-
ing congenital nystagmus. In such cases, the
ERG under general anesthesia may be cru-
cial in making the diagnosis. The diagnosis
must be made as soon as possible, so that
the parents can be properly advised about
the future education of the affected child.

HEREDOMACULAR DYSTROPHIES

The heredomacular dystrophies are a
group of diseases characterized by bilateral
macular degeneration, a hereditary ten-
dency, and the absence of associated dis-
case in the central nervous system. These
diseases have been classified and named ac-
cording to the age of the onset, but they may
all be one and the same condition. They
may be listed as follows:

Infantile heredomacular dystrophy (Best's
disease or "vitelline dystrophy")
Juvenile heredomacular dystrophy (Starg-
gardt's disease)
Adult heredomacular dystrophy (Behr's dis-
ease)
Presenile and senile heredomacular dys-
thropies

As a general rule, these patients present
with a gradual deterioration of their central
vision. Children may have difficulty in read-
ning or seeing the blackboard at school,
which is not corrected by wearing glasses.
The fundus appearance varies considerably
from case to case. In Best's disease, a round
or oval lesion is seen at the macula, which
has a yellowish color and has been likened
to the yolk of an egg—hence, the term
"vitelline dystrophy." The vitelline lesion
evolves into a pigmented scar. Rather sur-
prisingly, the vision of these patients may re-
main normal in spite of the fundus appear-
ance. In Stargardt's disease, which usually
appears between the ages of 8 and 11 years,
the vision may be impaired when the fundus
is normal. The earliest change is disapper-
ance of the normal foveal reflex; gray, yel-
low, or brown spots may appear at the mac-
ula. Eventually, an oval circle of pigment
stippling is seen; occasionally, this may
spread to involve the entire posterior pole.
Senile macular degeneration is associated
with degenerative changes in the underlying
choroid and Bruch's membrane. Although it
may bear some resemblance to the types
that occur at an earlier age, it may be com-
licated by the presence of hemorrhages and
subretinal exudates. Sometimes, senile
macula degenerations are divided into dry
and wet types, referred to as degeneration of
Haab and disciform degeneration, respec-
tively.

It has been shown that if the macular area
in the monkey is photoanagulated, the ERG
obtained from this damaged eye is normal.
Furthermore, a normal ERG has been de-
scribed in cases of solar retinopathy. It is not
surprising, therefore, that early reports re-
valed normal ERGs in patients with hered-
omacular dystrophy. However, when ex-
amination is carried out using a red-light
stimulus, a high percentage of patients show
a reduced amplitude of the 'b' wave. The
photopic ERG is normal, but its spectral sen-
sitivity curve may be displaced toward
shorter wavelengths. The foveal ERG is sub-
normal in all these patients, including those
whose visual acuity is still fairly good. The
VER has also been shown to be abnormal.
This might be expected considering the rel-
atively large macular representation on the
occipital cortex.

Some slightly unexpected changes have
been described in the EOG in cases of mac-
ula degeneration. Several different sources
report that the EOG may be markedly ab-
normal in patients with vitelline dystrophy;
the ERG in these patients is usually normal.
In Stargardt's disease, the EOG is usually
normal unless the retinal periphery is in-
volved.
Therefore, in contrast to early reports, the ERG and the EOG may be abnormal in patients with macular degeneration, but the difficulty still remains that a physically minute lesion can cause a serious disturbance of vision in macular disease. Thus one sometimes finds relatively minor changes in the electrical responses even with severe impairment of visual acuity. The foveal ERG is a promising technique, but its value is limited when opacities in the media scatter the stimulus light.

The VEP may be of some help in monitoring the progressive nature of these conditions. Figure 11.13 shows the VEP obtained from a child with a lesion on one macula, with a doubtful history of contusion injury. In this particular patient, the history of injury was probably irrelevant because there was a family history of macular disease, the child's brother being affected. The VEP shows specific changes that were repeatable from month to month.

ALBINISM

Hereditary albinism became of great interest to the electrophysiologist following the work of Guillery, who showed that the normal crossover of nerve fibers at the chiasm is greatly altered in many albino mammals. VEP studies have subsequently shown that the same abnormality exists in human albino. The normally uncrossed fibers from the temporal retina undergo decussation to a greater or lesser degree in albino; this abnormality is seen as asymmetry in the amplitude of the VEP as recorded from each side of the scalp. Although these findings have not so far been backed up by equivalent psychophysical research, the VEP studies have been extensive.

Acquired Retinal Diseases

DIABETIC RETINOPATHY

It has been known for many years that the classic ERG waves are not affected until a late stage in diabetic retinopathy, and even then, the reduction in amplitude does not show any features that might be specific for diabetes. However, a renewed interest in the subject was created by Yonemura and Kawasaki, and others, who described the selective disappearance of the oscillatory potential. Similar changes were also described in some other circulatory disturbances of the retina. A recent report involving a large series of eyes has shown beyond doubt that this component of the ERG may be absent; furthermore, there is no doubt that ERG changes also occur early in diabetic retinopathy. The exact point in the development of the retinopathy at which the oscillatory potential is affected differs markedly in different series, but this is probably due to differences in the type of stimulus used.

Therefore, selective loss of the oscillatory potential appears to be a consistent sign of diabetic retinopathy (Fig. 11.14). This change is often accompanied by a reduction in the size of the 'b' wave and the 'a' wave; in advanced diabetic retinopathy, a small 'b' wave alone may persist. Now that vitreous surgery has become better developed, it is often important to assess the retinal function in advanced cases. The ERG must be interpreted with great care under such circumstances because sometimes a small island of healthy retina may remain at the posterior pole and yet the ERG may be poor. A very small 'b' wave is therefore not a contraindication to vitreous surgery, but a well-developed response would suggest a good prognosis.

Changes in the VEP in diabetic cerebrovascular disease so far have not been accurately assessed.

OCCLUSIVE VASCULAR DISEASE

From the early days of clinical electroretinography an interest has been shown in the effect of retinal vascular disease on the electrical response of the eye. As described above, striking changes can occur in patients with diabetic retinopathy. In this section, the electroretinographic changes that may be seen in other types of vascular disease of the retina are described.

OCLUSION OF THE CENTRAL RETINAL ARTERY. The retina may be regarded
The VEP from a patient with a right-sided macular hole in response to large-check (boxes) and small-check (dots) stimuli. Note the impaired response to small checks in the affected eye.

**Figure 11.12.**

- **R** 100 V/cm.
- **L** 100 V/cm.

The POG from effects diffuse may be weak.

*Note: The text is not fully legible in the image.*
**Figure 11.14.**
The ERG from a patient with advanced diabetic retinopathy. Note the absence of the oscillatory potential. The ERG reflects diffuse retinal function, not macular function; thus, even when small areas of healthy retina remain, the ERG may be weak or absent.

As having a double blood supply: the inner half being supplied by the central retinal artery and the outer half being nourished from the choroidal circulation. Obstruction of the circulation in the central retinal artery might, therefore, be expected to affect that part of the ERG response derived from the inner half of the retina and spare those components that originate from the receptors and pigmented epithelium.

Two characteristic features of the ERG usually present in central artery occlusion are (a) loss of the oscillatory potential and (b) a "negative" type of ERG with enlargement of the 'a' wave and no change or slight diminution of the 'b' wave. However, the more severe types of occlusive episode, those with a poor prognosis, generally show a marked reduction in the size of the 'b' wave, whereas the milder types of occlusion may show a "negative" response.

In branch artery occlusions, the ERG may be normal or minimally affected. The oscillatory potential may be reduced in amplitude or even absent in branch artery occlusions. It has been claimed that the wavelets give a good indication of the prognosis in any given case.

**OCLUSION OF THE CENTRAL RETINAL VEIN.** The findings in venous occlusion are similar to those in central retinal artery occlusion, the most common change being a subnormal negative response and diminution of the oscillatory potential. The changes, however, are milder than in arterial occlusion.

Sometimes, patients are referred to the electrodiagnostic clinic with unexplained field defects and systemic hypertension. The ERG can help to decide whether these defects are caused by retinal ischemia or proximal changes in the optic nerve.
Diseases of the Optic Nerve Head

ERG IN OPTIC NERVE ATROPHY

For many years, it has been generally accepted and confirmed that damage to the optic nerve does not affect the electrical response from the retina as measured by routine methods. Histologic evidence also indicates that the part of the retina that is thought to give rise to the ERG response is not damaged with optic atrophy. This fact creates a serious pitfall in the interpretation of ERG traces; an eye may be completely blind from glaucoma and yet show a normal ERG. In fact, minor changes in the photopic components of the ERG have been described in chronic glaucoma, but these are slight.

In traumatic optic atrophy, the VER shows changes in proportion to the amount of visual loss, whereas the ERG remains normal. The ERG has also been reported as normal in patients with congenital unilateral hypoplasia of the optic nerve. The observation that some patients with optic nerve atrophy seem to have a supernormal response has excited some interest, and there are several authentic reports of this phenomenon. It has been suggested that the decrease in amplitude of the ERG may be caused by the division of centrifugal fibers in the optic nerve; these fibers may normally have an inhibitory influence on the size of the response.

In general, any changes that are seen in the ERG as evoked by an unstructured flash of light appear to be minimal in optic nerve atrophy. As explained above, the use of a patterned stimulus gives a very different result in patients with optic atrophy. It appears that this type of stimulus produces a response that may arise partly in the ganglion cells.

VEP IN RETROBULBAR NEURITIS

A high incidence of abnormal-pattern VEPs in patients suffering from retrobulbar neuritis was described by Halliday, McDonald, and Mushin. This finding in itself would not have been of clinical interest except that more subtle changes in the VEP persisted long after the clinical signs of optic neuritis had subsided. A test of previously healed optic neuritis is of more value to the clinician than a test of active disease, which is already detectable by routine clinical methods. Therefore, it was of special interest when Halliday and several others showed that the latency of the major peaks in the transient VEP with a pattern-reversal stimulus is increased and may remain increased for several years following an acute attack. This delay in the response is best shown by comparing the response from the two eyes.

During an acute attack of retrobulbar neuritis, when the visual acuity is severely impaired, the VEP is severely affected. In some cases, the response from the affected eye is abolished altogether. As the vision recovers, the amplitude of the VEP returns toward its normal value, but a characteristic slight delay in the response remains.

The VEP recorded from a patient with acute retrobulbar neuritis is shown in Figure 11.15. It can be seen that the response from the right side is greatly impaired. The VEP recorded from the same patient 4 months later is also shown; although the response from the right eye has apparently recovered, careful inspection shows a delay in the latency of all the major components. It is this slight change that enables the electrodiagnostican to say that a patient has suffered from retrobulbar neuritis in the past, and the change may persist after other clinical evidence of the attack has disappeared.

A surprisingly large number of patients with multiple sclerosis who have supposedly normal eyes give abnormal results when the VEP is checked. This abnormal response is not, of course, specifically seen in demyelinating disease; other possible causes of altered response such as amblyopia or macular disease must be excluded. Other evoked responses have also been investigated in multiple sclerosis, and measurement of a variety of evoked responses can provide diagnostic evidence in suspected cases.
The VEP in acute and healed retrobulbar neuritis. a. Acute phase, showing a greatly diminished response in the affected right eye. b. Healed phase, 4 months after previous trace. Although the amplitude of the response in the right eye has recovered, the latency of all the main components is slightly greater than in the unaffected left eye.

VEP IN TOBACCO AMBLYOPIA

The amplitude of the VEP is sensitive to changes in visual acuity during an acute attack of optic neuritis, in which the response may be abolished altogether. Similar findings have been recorded in patients with tobacco amblyopia, in whom it is possible to monitor recovery by measuring the VEP at intervals when the patient has abstained from tobacco. In some of these patients, the normal positive peak at about 100 msec may be inverted.

VEP IN CHRONIC GLAUCOMA

Attempts to relate VEP changes to visual field defects have been described above. A purely objective test for field changes in glaucoma could prove useful because election of glaucoma surgery may depend on an increase in field loss. Clear-cut alterations in phase and amplitude have been demonstrated in the VEBs of patients with glaucomatous field defects. This was achieved by examining steady-state VERs to pattern-reversal stimulation of retinal areas corresponding to discrete field quadrants.

One of the problems in using the VEP to monitor chronic simple glaucoma or to detect early disease is that the VEP only measures a small central area of the visual field. For this reason, patients with advanced chronic glaucoma may have a normal VEP.
In fact, the VEP is likely to be more useful in monitoring cases over a period of months rather than in detecting early cases. This is because the changes in the VEP are rather unpredictable: Sometimes a severe case of glaucoma exhibits few changes, and sometimes a fairly mild case may show more marked changes that do not always seem to be consistent with the field defect. The VEP tracings, however, should remain the same over a period of a few months, as long as the glaucoma has not advanced (Fig. 11.16).

Following the discovery that the pattern ERG arises in part from the ganglion cell layer, there has been considerable research interest in the early detection of glaucoma. Clinicians specializing in glaucoma wish to know which patients with ocular hypertension are likely to go on to develop optic nerve damage. Some progress has been made in this respect. It appears that the pattern ERG can be useful if combined with other psychophysical tests.

**VEP IN OTHER DISEASES OF THE OPTIC NERVE**

In Tay-Sachs disease, the VEP usually is absent, whereas the ERG is normal. One

**Figure 11.16.**

The VEPs from a patient with chronic simple glaucoma recorded on two separate occasions. Note the consistency in these tracings, which were obtained about 8 months apart; the visual field also remained unchanged. These findings indicate the disease had not progressed noticeably.
might expect these findings from a lesion at the level of the retinal ganglion cells, which involves central vision.

The function of the optic nerve can be monitored by means of the VEP, and this technique has been practiced in orbital surgery. Permanent loss of vision following surgery is a recognized risk, particularly when hypotensive anesthesia is being used. Wright, Arden, and Jones have described monitoring the function of the optic nerve by continuously stimulating the retina with an unstructured stimulus and recording the VEP throughout the operation.

Knowledge of the electrodagnostic changes in diseases of the optic nerve is essential when interpreting these responses in general. A surgeon who is encouraged to remove a cataract on the grounds of a normal ERG alone may be unpleasantly surprised at the poor visual result if he or she has been led astray by an inadequate report.

**Drug-Induced Retinopathy**

A considerable amount of information is now available about the effect of various drugs on the electrical responses from the eye. These data have come from animal experiments and from cases of overdose or accidental ingestion in humans. Electrodagnostic tests have been applied in such circumstances to find out more about the nature and origin of the response and, in some cases, to help make a diagnosis. These techniques are also being used in an attempt to localize the site of action of drugs in the eye. Undoubtedly, the nature of these electrical changes is such that they can give useful objective clinical information, but our knowledge is still limited. Much of the work so far has concerned the ERG rather than the VEP.

For many years, much interest has been centered on drugs used to produce selective damage to different layers of the retina. Sodium iodate, for example, causes selective damage to the pigment epithelium and abolishes the 'c' wave in rabbits. Another substance that has been used in localization studies is sodium glutamate, which causes loss of vision in mice and selective loss of the inner layers of the retina, with destruction of the bipolar and ganglion cells. Several drugs have been used to assess the site of origin of the ERG. Table 11.1 shows the effect of some drugs on the ERG.

**QUININE**

Although the toxic effects of quinine have been well recognized for many years, the exact mode of action of this poison is still controversial; electrodagnostic tests help to throw some light on the problem. An overdose of quinine is usually taken in an attempt to procure an abortion, but cases have been reported in which an overdose was ingested as a prophylactic for malaria.

Symptoms may follow after taking as little as 1 g of quinine in sensitive individuals, but the usual dose to cause blindness is 1.5 to 4 g. The affected patient experiences deafness, tinnitus, and visual failure; larger doses produce coma. Although the fundus may appear

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**Table 11.1.** EFFECT OF SOME DRUGS ON THE ELECTRORETINOGRAM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Electroretinogram</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl alcohol</td>
<td>Increase in 'b' wave</td>
<td>Manfredini and Trimarchi</td>
</tr>
<tr>
<td>Amyl acetate</td>
<td>Progressive reduction of 'a' and 'b' waves but return to normal after 45 days</td>
<td>Gargallo et al. (1970)</td>
</tr>
<tr>
<td>Dichlorphenamide</td>
<td>Increase in 'b' wave by 55%</td>
<td>Tota and Cavallucci (1970)</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>Rapid and irreversible extinction of 'a' and 'b' waves</td>
<td>Milliano et al. (1972)</td>
</tr>
<tr>
<td>Tritetramine</td>
<td>Increase in 'b' wave by 40% in rabbits</td>
<td>Tota and Cavallucci (1971)</td>
</tr>
<tr>
<td>Strychnine</td>
<td>Increase in 'b' wave at low concentration and reduction in 'b' wave at high concentrations in rabbit</td>
<td>Yerkel and Hanitzsch (1971)</td>
</tr>
</tbody>
</table>
normal at first, in some cases, there is retinal edema with a cherry red spot at the macula. The visual fields become grossly constricted. The symptoms and signs often improve over a period of weeks; however, the fundus then begins to show optic atrophy and narrowing of the retinal arteries.

For many years, arguments have been put forward to decide whether the toxic effect of quinine is primarily on the retinal vessels or whether it acts directly on the retina. The role of vascular spasm is not easy to assess because almost any condition that causes optic atrophy also causes constriction of the retinal vessels.

Investigation of the effect of acute quinine poisoning in animals has shown that the ERG is initially depressed but recovers in a matter of hours; after this, a further slow deterioration in the response occurs. The relatively slight degree of these changes compared with the severe visual loss indicates primary damage to the ganglion cells and the nerve fiber layer. In humans, the ERG may show a gradual decline between 10 days and 10 months after quinine intoxication; paradoxically, the vision may gradually improve during this period.

The EOG has shown an absent light rise during the first few days after intoxication; this has then recovered in parallel with the subjective improvements. The absence of a light rise on the EOG is not easy to explain in terms of a ganglion cell poison, and more cases will have to be investigated in detail to resolve this conflicting evidence.

The clinical picture of quinine intoxication may mimic that of the bilateral optic neuritis that sometimes is the presenting sign of multiple sclerosis, especially in young females. That is, in both conditions, the fundus may be completely normal, and the gradual recovery of vision is followed by optic nerve atrophy and narrowing of the retinal arterial vessels.

CHLOROQUINE (RESOCHIN)

Chloroquine was used extensively but in small doses in World War II as a prophylactic treatment for malaria. Corneal changes resulting from this drug were described at the end of the war, but the more serious retinotoxic effects were not observed until large doses were employed in the treatment of disseminated lupus erythematosus and rheumatoid arthritis. Its value in the treatment of disseminated lupus erythematosus was described in 1954, and the first case of chloroquine retinopathy was described in 1957.

Since then, reports from many different centers have confirmed that when the total annual dose of chloroquine exceeds 200 g per year, there is a risk of permanent visual disturbance with associated changes in the fundus. The earliest sign of a perimacular pigmentary disturbance is described as a "bull's eye appearance." In more advanced cases, the arteries become attenuated, and peripheral pigmentation may appear. By this time fundus changes appear, irreversible field defects can be detected, and in some cases, a progressive deterioration of vision occurs in spite of cessation of treatment. Histopathologic investigation of human eyes and animal experiments have shown that chloroquine accumulates in and damages the receptor layer and the pigment epithelium, thus confirming the cumulative nature of the toxicity.

In some electoretinographic studies of patients treated with chloroquine for more than a year, the amplitude of the 'b' wave was depressed; in other studies, however, the ERG was normal in the presence of fundus changes. One long-term follow-up study of 15 patients with chloroquine poisoning suggests that electoretinography may be of some prognostic value in such cases.

The effects of chloroquine on the EOG were first described by Arden and Kelsey in 1962. In a detailed study, Kolb showed that depression of the light rise of the EOG is often an early sign of toxicity and may sometimes precede the fundus changes; however, in a series of 47 cases, there was considerable overlap between treated and control groups. Furthermore, in a group of patients
who had not received treatment but who suffered from collagen disease, the mean value of the Arden index was below normal, although not as low as in the group that had been treated with chloroquine. A study of patients in whom chloroquine therapy had been stopped revealed a return to normal in the Arden index in many cases (Fig. 11.17).

Both chloroquine and hydroxychloroquine (Plaquenil) produce similar toxic effects, but the toxic and the normal dosage of hydroxychloroquine is much larger. The evidence now indicates clearly that these drugs should be used with caution and that patients should be carefully monitored. Ocular toxicity is very unlikely with doses of less than 4 mg per kg lean body weight per day of chloroquine phosphate. It is important to realize that the dosage of chloroquine varies depending upon which salt is prescribed. If the EOG is depressed, the drug should be stopped, even if there are no subjective signs of toxicity. Unfortunately there is no doubt that some patients may develop severe toxicity although retaining a normal EOG.

In spite of its obvious hazards, chloroquine is still being prescribed; ocular damage can be avoided if the toxic dose is not exceeded. Recently, it has been found useful in short courses for the treatment of pulmonary sarcoidosis. Ophthalmologists must be continually on their guard for the appearance of side effects.

Opacities in the Media

The electrical response of the eye to a patterned stimulus is, of course, severely affected by the presence of even slight opacities in the media, depending on how greatly they affect the visual acuity. However, in response to a flash, both the VEP and the ERG can be obtained, even when dense opacities are present. Indeed, providing the stimulus is bright enough and the retina is normal, there is virtually no opacity that can prevent a response from occurring. Thus the ERG and the flash VEP can be used to assess retinal and cortical function when the fundus of the eye is not visible with the ophthalmoscope. For example, a normal ERG may be obtained using a bright flash stimulus through a dense vitreous hemorrhage. This can be of help when assessing retinal function in patients with diabetic retinopathy.

Similarly, the ERG and flash VEP can be helpful in assessing general retinal function in patients with dense cataracts who are being evaluated for surgery. However, because the ERG is a measure of diffuse retinal function, small areas of the retina can be damaged (e.g., in macular degeneration) with no effects on the ERG. For this reason, the ERG alone cannot predict the outcome of cataract surgery. The flash VEP has been shown to be a more accurate predictor of visual outcome in cataract surgery. As a general rule, both the VEP and the ERG should be obtained when assessing opacities in the media: the ERG to indicate whether widespread retinal disease or severe retinal ischemia is present, and the VEP to indicate something about the function of the macular area.

There are special instances in which electrodiagnostic tests can be of value in the presence of opaque media: in particular, vitreous hemorrhage following subarachnoid hemorrhage and head injury and also vitreous hemorrhage in which a retinal detachment is suspected. It is also extremely useful to determine whether the wavelets are present in a diabetic patient with dense cataracts.

Poor Vision with a Normal Optic Fundus

Several conditions in the eye or visual pathway may present to the ophthalmologist as poor vision with a normal fundus. Some of these have been mentioned above. In retinitis pigmentosa in its early stages and the related condition Leber's amaurosis, electroretinography may be diagnostic. Likewise, in patients with suspected healed retrobulbar
**Figure 11.17.**

A. The electro-retinogram from a patient who had taken chloroquine for 2 years and who complained of blurred vision but had no ophthalmoscopic or slit-lamp evidence of toxicity. B. The EOG from the same patient taken several months after chloroquine was stopped. The Arden index is now within the normal range.
neuritis, measurement of the VEP is an effective means of confirming or denying the underlying diagnosis.

**AMBLYOPIA OF DISUSE**

A patient with reduced visual acuity associated with squint or anisometropia, but with no visible abnormality in the retina, would seem to be an ideal subject for VEP studies, especially if we assume that the VEP arises in the primary visual cortex. VEP studies might be expected to tell us something about the site of the defect in amblyopia. In general, the pattern VEP recorded by stimulating the affected eye shows a reduction in amplitude; this is in contrast to the ERG as routinely recorded and the flash VEP, which are usually normal.

At present it is not possible to distinguish between the different types of amblyopia of disuse based on the VEP, but some interesting facts are emerging. For example, a "binocular negative" effect has been described in which the binocular VEP is smaller than the VEP recorded from each eye individually. In normal subjects, the binocular VEP is usually larger than the response from the individual eyes and can be seen to represent the sum of the waveform of the two. This binocular negative effect, which appears to represent some form of suppression, is found most frequently in strabismic amblyopia.

Attempts to correlate the VEP with some of the psychophysical findings in amblyopia seem to indicate defects both peripheral to and "above" the primary visual cortex. In the normal eye, the VEP shows a maximum amplitude with 15-minute checks; the response is smaller when the stimulus is composed of either larger or smaller checks. In one careful study of an adult amblyope, the affected eye showed a maximum amplitude for the amblyopic eye with the 60-minute check stimulus, and there was a significantly larger signal for the 60-minute check from the amblyopic eye than from the normal eye. Furthermore, when a small-field stimulus was used, there was no difference in amplitude between the normal and amblyopic eyes. It has been suggested that in the amblyope, the normal central area is unable to exert sufficient lateral inhibitory effect on the surrounding retina and that the well-recognized increase in visual acuity with separate-letter testing that is found with some amblyopes may be due to the fact that they are looking at each letter in a manner equivalent to a small-field pattern stimulus.

A different light has been thrown on this type of amblyopia by examination of subjects with high degrees of astigmatism. It is known that the resolving power of the human visual system is better in the vertical and horizontal orientation than in the two oblique orientations. The same effect can be seen in the VEP. When astigmatic subjects are examined, a high proportion show a reduction in the amplitude of the VEP when a grating stimulus is oriented in the meridian with the lower refractive error. This impairment of the VEP occurs with full spectacle correction.

When a child with amblyopia is treated by occluding the sound eye, interesting changes can be observed in the VEP as the vision of the weaker eye improves. These changes differ according to the check size of the patterned stimulus that is being applied. Figure 11.18 shows the improvement that occurs in the response. The VEP provides the only objective way of measuring the results of treatment of amblyopia; for this reason, it is likely to have considerable importance in the future. It is well recognized that visual acuity measurements by themselves can occasionally be misleading.

**HEMIANOPIA**

Sometimes, the ophthalmic surgeon may be puzzled by an apparent reduction in visual acuity and subsequently finds it is caused by a homonymous hemianopia. In the very young and the very old, these defects may not be easy to pick up, and so it is of special interest to consider some of the relevant VEP findings.

The use of an unstructured flash stimulus together with laterally placed electrodes can
give aspirin
large doses.
The use seems to
shown that
prolonged
the electrode
hemisphere
tends to
two half-
Full-he
tients w
hemianopia
this tech
this as

- Figure 11.18.
A. Serial recordings of the VEP produced by stimulating the right amblyopic eye during a period of left-eye occlusion. Note the increase in the amplitude of the VEP with the passage of time. B. The corresponding VEPs from the left (occluded) eye in the same amblyopic child. Little change is seen other than a possible fall in the amplitude of the response after 4 weeks.
give asymmetric responses from the two sides in hemianopic patients, but by and large such results have not proved reliable. The use of a patterned hemifield stimulus seems to be more promising. It has been shown that a hemifield pattern-reversal stimulus produces a larger response when the electrodes are placed over the ipsilateral hemisphere than when over the contralateral hemisphere. A full-field pattern stimulus tends to produce the summed effect of the two half-field responses.

Full-field and hemifield stimulations of patients with homonymous and bitemporal hemianopias give predictable results, using this technique. The exact position of the electrodes and the specifications of the stimulus appear to be important.

The rather surprising finding that a larger response is found over the intact hemisphere has been confirmed in a patient who had undergone an occipital lobectomy, which suggests that the electrical changes must be projected from the active side directly to the scalp rather than through the corpus callosum (Fig. 11.19). This paradoxical response occurs only if the stimulus is flashed at a fairly high speed. If low-frequency, pattern-onset stimulation is used and the so-called transient response is examined, the response behaves predictably; that is, it is larger over the intact hemisphere and smaller over the diseased side. In other words, with a low-frequency pattern-onset stimulus, there is a reduced response over the right occiput in a patient with a left homonymous hemianopia.

![Figure 11.19.](image)

The VEPs to a pattern-reversal stimulus from a patient with a right subtotal occipital lobectomy. Note the larger responses from the damaged side. (After Blumhardt LD, Burtet G, Halliday AM. The asymmetrical visual evoked potential to pattern reversal in one half field and its significance for the analysis of visual field defects. Br J Ophthalmol 1977;61:454.)
Check size

10'

15'

20'

30'

45'

60'

120'

V.E.R.

5μV

100 ms

- Figure 11.20.
The effect of changing the stimulus check size on the VEP in a normal subject. Note especially the increase in the amplitude of the later positive peak with smaller checks.

CORTICAL B
Since unilaterally stimulated visual cortex can cause the VEP, one would expect blindness with the absence of the results for a test of visual field. Cases of blindness have been reported, apparently as a result of such stimulations. Cortical blindness should have an abnormal blink reflex and itself be a test for such cases. The blink reflex is abnormal in a number of cases, and the results can be expected in other patients. It is difficult to determine what the response can be with such a test, thus the need to review a large number of cases. A test of visual field becomes an important test of cortical blindness when small areas are involved. Behavior about this can be expected to be abnormal, being unable to see, unless some signals are present. The test chart is surprisingly effective in such tests and no doubt have clinical significance. It is known that the visual fields of the cases are often small, especially with HYSTERICAL.

Although it is possible to be a victim of hysteria, such patients have clinical significance.
CORTICAL BLINDNESS

Since unilateral damage to the occipital cortex can cause unilateral impairment of the VEP, one might logically conclude that total loss of the occipital cortex and occipital blindness would always be associated with the absence of any VEP. Unfortunately, the results from the limited number of published cases have been conflicting. VEPs have been recorded from some patients with apparently complete cortical blindness, but in other patients, the VEP has been abolished. Cortical blindness must be carefully defined in this kind of study. The patient should have no perception of light and no blink reflex to a flashing light. The eyes themselves must be normal as well as the ERG, and the pupils also should react normally both directly and consensually.

It is difficult to imagine how an electrical response can arise in a defunct part of the brain. However, before revising our idea about the origin of the VEP, we might be wise to review a larger store of clinical data when it becomes available. Some patients with extensive cortical damage can be left with a very small area of central field. Such patients are behaviorally blind, being unable to walk about without knocking into furniture and being unable to read the Snellen test chart unless some time is spent locating it. Once the test chart has been found, they may have a surprisingly high level of visual acuity. The VEP in such patients should be measured, and no doubt the result of such tests will have clinical relevance in the future. We know that the stimulation of relatively small areas of the central field can produce a VEP, especially when a patterned stimulus is used.

HYSTERICAL BLINDNESS

Although in theory the VEP and the ERG seem to be ideal objective tests for the diagnosis of hysteria or malingering, in practice, such patients often refuse to cooperate during the tests, perhaps because they suspect that the results of the tests will lose them the sympathy they so much require. Of course, one would expect the ERG and the VEP to be entirely normal. One must remember, however, that some patients have very small responses and yet are still within the normal range; this particularly applies to the VEP. In these cases, the VEP should be measured with different sizes of pattern stimulus so that a clear-cut change can be noted, especially the increase in size of the second positive peak with smaller checks. Figure 11.20 shows the effect of altering the check size that one might expect to see in a normal subject.

SUMMARY

The reader should now be aware that electrodiagnosis has something to offer the neuro-ophthalmologist. The main advantage of this type of test is that it is purely objective, and no one can argue about the result, providing that it is accurately recorded. Better and more accurate recording devices are now available, and perhaps more important, they are becoming portable.

Both the VEP and the ERG tend to show considerable intersubject variation, but in a given subject they are highly consistent when determined from month to month. For this reason, these measures are particularly useful for monitoring disease and for deciding whether treatment is effective. Because the ERG is particularly sensitive in detecting diffuse retinal disease, it is used to help achieve a diagnosis in patients with early retinitis pigmentosa and especially in children with Leber's amaurosis. The VEP has special value in detecting healed optic neuritis when the diagnosis of disseminated sclerosis is suspected. It can also be used when an objective measure of visual acuity is needed and in monitoring the treatment of amblyopia of disuse.
INDICATIONS FOR ELECTROPHYSIOLOGIC TESTS ON THE EYE

The following is a list of eye conditions in which the diagnosis or follow-up may be facilitated by electrodagnostic tests. The column on the right shows the preferred test or tests to be used.

| Inherited retinal degenerations | Standardized ERG |
| Vascular disease of the eye including diabetes | Standardized EOG | Pattern VEP |
| Opaque media | Pattern ERG |
| Retrobulbar neuritis (remission stage) | Standardized ERG | Bright flash ERG | Flash VEP |
| Unexplained visual loss | Pattern VEP | Pattern ERG |
| Albinism | Standardized ERG | Pattern ERG |
| Toxic and nutritional eye disease | Multichannel VEP | Full-field stimulation ERG |
| Glaucoma | Standardized EOG | Pattern ERG |
| Suspected intracranial visual pathway lesion | VEP | Pattern ERG | Standardized VEP | Pattern ERG |

CASE STUDIES

Case 11.2

A 21-year-old male presented with left-side weakness and blurred vision. One year previously, he had suffered a right pontal intracerebral hemorrhage with no vascular abnormality. After a nearly complete recovery, he had a grand mal seizure about 3 months later. At that time, he was started on phenytoin, 300 mg at night and in the morning. After returning to his job in Zanzibar, he had contracted cerebral malaria and had been treated with “large doses” of quinine intravenously. He recovered gradually, but presented with his current symptoms after several months.

The eye examination revealed RV 6/18 and LV 6/5, both with glasses. The fundi appeared as pale discs with arteriolar attenuation. The intraocular pressure was 15 mm Hg in both eyes, and the visual fields showed generalized constriction. The EOG and ERG for this patient are presented in Figure 11.22.

Discussion

The ERG shows a reduced ‘b’-wave amplitude, and the EOG shows an abnormal Arden index. These findings are more consistent with quinine poisoning than with optic atrophy following anemia or compression of the visual pathway.

Case 11.3

A 70-year-old male presented with the complaint that for more than 9 years straight lines had looked bent to him. When he was seen 9 years earlier, a yellow cyst at the right macula and scar at the left macula had been noted. The patient’s deceased father had been unable to read in later years. The eye examination showed RV 6/9 unassisted and LV 6/24 with glasses. The results of electro...
Figure 11.21.
Clinical findings (A) and electroretinogram (B) from case 11.1.

Discussion

The EOG shows a reduced light rise on the left side, whereas the ERG was within the normal range for both eyes. These findings together with the fundus appearance confirm a diagnosis of Best's disease.

Case 11.4

A 12-year-old boy, who had been using a hammer and chisel the previous day, was admitted with eye pain and irritation. An intraocular metallic foreign body was removed from the left eye with a magnet the same day. Postoperatively, the injured eye became painful with hypopyon. After treatment with systemic and local antibiotics, the eye initially improved, but the patient's vision remained poor. The ERG was normal on the right but absent on the left (Fig. 11.24). A left lensectomy and vitrectomy with silicone oil exchange was performed 12 days later. Massive preretinal exudate and total retinal detachment were observed during surgery.
**Figure 11.22.**
The electroretinogram (A) and electro-oculogram (B) from case 11.2.

**Electrodiagnosis**

**Figure 11.23.**
The electroretinogram (A) and electro-oculogram (B) from case 11.3.
Suggested Readings

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Solot S. Visual evoked potentials to checkerboard pattern stimuli in strabismic amblyopia. In: Dismedt JE, ed. Visual Evoked Potentials in
Electrodiagnosis  •  357


Unexplained Vision Loss: Macula or Media?

John T. Thompson

Unexplained vision loss presents a diagnostic dilemma for the ophthalmologist. Many causes of vision loss can be determined by a general ophthalmologic examination, but eyes with unexplained vision loss might require more extensive evaluation. The three basic causes of unexplained vision loss are opacities/irregularities of the ocular media, macular disease, and optic nerve disease. In this chapter, I discuss the diagnostic evaluation and causes of the most common types of unexplained vision loss resulting from media opacities and macular disease, which may not be apparent on a routine ophthalmologic examination. Unexplained vision loss from optic nerve disease is discussed in depth in Chapter 13, Blurred Vision.

UNEXPLAINED VISION LOSS FROM OCULAR MEDIA ABNORMALITIES

General Diagnostic Evaluation

Many of the causes of unexplained vision loss resulting from media opacities or irregularities can be detected by a careful anterior segment examination. Slit lamp biomicroscopy allows detection of most anterior media opacities or irregularities in the optical interface between structures of the anterior segment. Special attention must be paid to the contour, as well as the clarity, of the anterior segment structures. Keratometry may be helpful in detecting irregularities in the anterior surface of the cornea. The placido disc and computerized corneal topography are also useful in evaluating the shape of the cornea. Retinoscopy may also allow identification of refractive irregularities in the cornea and lens. Posterior media opacities, such as vitreous hemorrhage, are easily detected by indirect ophthalmoscopy. The direct ophthalmoscope is a very useful tool for a semiquantitative estimate of the extent of vision loss from media opacities. The view of the optic nerve or macula using a direct ophthalmoscope is generally proportional to the sum of all opacities of the ocular media.

MACULAR TESTING THROUGH MEDIA OPACITIES

The presence of an opacity in the ocular media (e.g., a corneal opacity, cataract, or vitreous opacities) can often be assessed with the aid of indirect ophthalmoscopy. The indirect ophthalmoscope allows visualization of the macula and nerve head. When the media is sufficiently clear, the retinal vessels are visible, and the examiner can evaluate the macula and optic nerve for abnormalities.

Other diagnostic tests may be necessary to further evaluate the macula and optic nerve when they are not sufficiently visible through the media. Fluorescein angiography, optical coherence tomography (OCT), and magnetic resonance imaging (MRI) can be used to assess macular and optic nerve function and structure. These tests can provide valuable information about macular and optic nerve health and can help differentiate between macular and optic nerve disease.

The blue-tinted direct ophthalmoscope can be used to identify microdots or macular spots that are not visible through the clear media. These spots may be indicative of underlying pathology.

In summary, the evaluation of unexplained vision loss should include a thorough examination of the anterior segment, posterior media, and macula and optic nerve. Diagnostic tests such as fluorescein angiography, OCT, and MRI can provide additional information about the underlying cause of vision loss.
Vitreous opacity may prevent a thorough evaluation of the macula. Several ancillary tests are useful for evaluating macula function prior to corneal surgery, cataract extraction, or vitrectomy, when the macula is poorly seen by ophthalmoscopy alone.

Fluorescein angiography gives a general assessment of macular anatomy and may uncover macular dysfunction obscured by a media opacity. The optics of fundus cameras are similar to the indirect ophthalmoscope, and fluorescein angiography may show macular disease that is not readily apparent by ophthalmoscopy alone.

Other diagnostic tests are more useful when there is a dense media opacity. The entoptic phenomenon can be tested by placing a fiberoptic transilluminator over the closed lower or upper eyelid and moving the transilluminator slowly in a circular motion. The patient should be able to see readily the shadow of the perimacular retinal vessels, which resemble branches of a tree. This test is very useful and should be considered before resorting to other special diagnostic tests. Some patients with normal macular function, however, have difficulty understanding this test and may respond negatively despite normal macular function. The blue-field entoptic test is performed by directing a 530-nm blue light into the eye. The patient often visualizes the perimacular vessels more easily in this test than in the transilluminator test and may also see small dots traversing the perimacular capillaries. These dots have a surrounding light halo and are believed to be white blood cells within a column of red blood cells in the perimacular capillaries.

The entoptic tests have the advantage that they can be performed through very dense media opacities. The laser interferometer may allow a more quantitative measure of macular function through mild-to-moderate media opacities. The Potential Acuity Meter also may be used to quantify visual acuity through focal media opacities but generally cannot be used with media opacities severe enough to obscure the retina under indirect ophthalmoscopy.

REFRACTIVE ERRORS

The evaluation of unexplained vision loss must always include a careful refraction. Retinoscopy may be helpful as a screening tool because some patients give conflicting responses during subjective refraction. Retinoscopy may also uncover occult corneal or lenticular abnormalities that are potentially amenable to refractive correction with spectacles or contact lenses. Patients with nuclear sclerotic cataracts may develop progression of myopia and present with unexplained vision loss. Keratometry and computerized corneal topography may be useful to guide the retinoscopy and subjective refraction in some persons with high astigmatic errors or diseases that alter the normal spherical shape of the cornea (e.g., keratoconus and Terrien's marginal degeneration).

Corneal Opacities and Irregularities

Keratoconjunctivitis sicca and other corneal-surface diseases may lead to disruption of the precorneal tear film, thus altering the smooth air-cornea interface, causing optical irregularities and decreased visual acuity. The precorneal tear film and corneal surface should be evaluated by slit lamp biomicroscopy. Damage to the corneal epithelium from recurrent corneal erosions may also cause irregularity in the anterior surface of the cornea, leading to visual loss. Corneal erosions are easily identified by slit lamp examination after the instillation of fluorescein dye into the eye. A plano contact lens may be used to neutralize an irregular anterior corneal surface, with improvement in the visual acuity.

Abnormalities in the shape of the cornea may also lead to unexplained vision loss. Anterior keratoconus may not be evident on slit lamp biomicroscopy unless the central cornea is thinned, the anterior chamber is unusually deep, a Fleischer iron ring is present at the base of the cone, or the lid is distorted.
by the cornea on down-gaze (Munson's sign) (Fig. 12.1). Keratometry will reveal an unusually steep corneal contour, often with irregular astigmatism, in patients with this condition. Corneal topography will confirm the steep contour of the cornea. Retinoscopy of eyes with keratoconus will show a central area of irregular astigmatism with a more myopic refraction centrally than peripherally. Posterior keratoconus, a concave indentation of the posterior corneal surface is usually only present in the central 2 to 3 mm of the cornea. Posterior keratoconus is rare but may decrease visual acuity, owing to the abnormal interface between the posterior corneal surface and aqueous humor. The central cone in posterior keratoconus may also become opacified, leading to decreased acuity.

The increasing popularity of keratorefractive surgery has created new potential sources of corneal irregularity. Radial keratotomy may create irregular astigmatism by changing the normally spherical surface of the cornea. The shape of the cornea changes during the day and may exhibit changes over months or years, which may not be initially recognized as a changing refractive error. These patients typically complain of fluctuating or decreased acuity. Phototherapeutic keratectomy by the excimer laser also alters the spherical contour of the cornea and may create changes in the corneal contour. Excimer laser photokeratectomy may also result in opacification of Bowman's membrane with superficial corneal haze, but this is usually not visually significant. Irregular astigmatism may be unintentionally created by the excimer laser, which is difficult to correct during routine refraction with spectacle lenses. Computerized corneal topography is very helpful in uncovering abnormalities in the spherical contour of the cornea, which may be difficult to detect by other means, and it should be performed in those with unexplained visual loss and a previous history of keratorefractive surgery.

Opacities in Bowman's membrane and the corneal stroma are usually easily seen and only occasionally result in unexplained vision loss. More commonly, it may be necessary to determine if the corneal opacity explains all of the vision loss. Discrete corneal opacities outside the center of the visual axis do not cause vision loss unless associated with irregular astigmatism, as may be found with a traumatic corneal scar. Discrete opacities or diffuse corneal opacification within the central visual axis usually results in vision loss. The severity of the loss is generally predictable by the size and density of the corneal opacity in the visual axis. Central corneal opacities may also result from corneal dystrophies, such as macular or lattice dystrophy. Central corneal edema from corneal endothelial dysfunction may lead to mild or severe vision loss, depending on the severity of the corneal edema. The visual acuity may be restated in eyes with corneal edema after instillation of a topical anaesthetic and topical glycerin, which transiently decreases the corneal edema. Deposits on the surface of the corneal endothelium (e.g., keratic precipitates in eyes with anterior uveitis or extensive pigment deposition on the corneal endothelium) rarely cause decreased acuity.

Slit lamp biomicroscopy is the best means to assess decreased acuity resulting from corneal disease. Direct ophthalmoscopy is another useful technique for determining the extent of vision loss from corneal opacities. The view of the disc and retinal vessels in an eye with a well-dilated pupil is proportional to the extent of vision loss from the media opacity.
Anterior-Chamber Opacities

Circulating hyphema, or anterior-chamber inflammation, may result in decreased visual acuity. This condition is easily detected by slit lamp biomicroscopy. Intracocular inflammation may also result in a translucent pupillary membrane covering the anterior surface of the lens. Posterior synechiae between the iris and lens may be associated with pigment deposition on the anterior surface of the lens. The posterior synechiae may occasionally prevent pupillary dilation and obscure the central pupillary opening with pigment or fibrous tissue, leading to vision loss.

Lenticular Opacities and Irregularities

Cataracts are the most common cause of decreased acuity due to a media opacity. The severity of the central lenticular opacity is usually proportional to the severity of vision loss. In general, peripheral cortical lens opacities and small punctate cortical opacities cause minimal vision loss. Posterior subcapsular cataracts located in the visual axis tend to cause more significant vision loss from cataract. Cortical lens opacities and posterior subcapsular cataracts are easily seen by slit lamp biomicroscopy. Nuclear sclerosis is a much more common cause of unexplained vision loss from cataracts because this condition may induce increased myopia and interfere with the uniformity of the lens refractive power. Nuclear sclerosis may cause the lens to become a stronger plus lens centrally than peripherally. This causes the eye to become more myopic and may cause distortion in the image reflected by the lens onto the retina because of disparity between the central and peripheral lens power. Retinoscopy is useful for evaluating the optical uniformity of the lens in eyes with nuclear sclerosis. Direct ophthalmoscopy may also reveal the optical distortion induced by nuclear sclerosis when the examiner views the retina.

Subluxation of the lens may lead to unexplained vision loss if the center of the lens is displaced away from the visual axis. The subluxed lens may also be tilted, causing an astigmatic error due to induced astigmatism of oblique incidence. Subluxation of the lens may not be apparent if the lens is not examined in a well-dilated pupil.

Irregularities in the surface of the lens are an uncommon cause of decreased acuity but may easily be missed if the contour of the lens is not examined carefully. Microspheroaphakia in persons with Weil-Marchesani syndrome and lentiglobus or lenticonus may result in myopia and irregularity in the optics of the lens. Anterior and posterior lenticonus are characterized by a central circular protrusion on the anterior and posterior surfaces of the lens, respectively. This may lead to an irregular astigmatism with progressive vision loss. Lenticonus may be associated with Alport syndrome, which is characterized by progressive renal failure and nerve deafness, with some patients also exhibiting vestibular dysfunction (Fig. 12.2).

Vitreous Opacities

Vitreous opacities may be associated with unexplained vision loss, but these are usually easily detected by slit lamp biomicroscopy of the vitreous and indirect ophthalmoscopy.
Although often considered a cause of decreased acuity, vitreous inflammation must be very dense in the visual axis to explain a significant decrease in acuity. Vitreous inflammation may result from an endogenous vitritis, such as pars planitis, or may be secondary to inflammation in the anterior segment or retina/choroid. Associated macular disease (e.g., cystoid macular edema or age-related macular degeneration) may be obscured by vitreous inflammation. Such associated macular disease is the more likely cause of vision loss rather than the vitritis, which often is erroneously considered the cause of vision loss. Large cell lymphoma (reticulum cell sarcoma) may cause vision loss if the vitreous cellular debris is severe or if there is a choroidal tumor within the macula. Rarely, neoplasms such as breast carcinoma, bronchogenic carcinoma, or cutaneous melanoma may metastasize to the vitreous, causing vitreous opacification. Seeding of a retinoblastoma into the vitreous over the macula or macular involvement by the retinoblastoma may cause decreased visual acuity in a child.

Vitreous hemorrhage may cause decreased acuity in a variety of vitreoretinal disorders. Vitreous hemorrhage may occur secondary to retinal vascular disease (e.g., proliferative diabetic retinopathy, sickle cell retinopathy, and venous occlusion). A second common cause of vitreous hemorrhage is a posterior vitreous detachment with or without an associated retinal tear or detachment. Vitreous hemorrhage may develop after ocular trauma due to bleeding from anterior segment structures (e.g., the root of the iris or ciliary body) or from bleeding in the posterior segment (e.g., a retinal tear or a choroidal rupture with a breakthrough vitreous hemorrhage). The density of the vitreous hemorrhage in the visual axis is the best predictor of visual acuity. In general, a diffuse vitreous hemorrhage causes less vision loss than a more focal vitreous hemorrhage located posteriorly over the macula. Focal vitreous hemorrhages often disperse in the first several weeks after onset, with an associated improvement in acuity if the hemorrhage is the primary cause of the decreased acuity.

Asteroid hyalosis results from deposition of calcium- and phosphate-containing lipids on vitreous fibrils (Fig. 12.3). This condition may make examination of the retina by indirect ophthalmoscopy, direct ophthalmoscopy, and contact lens biomicroscopy difficult, but it rarely causes substantial vision loss. Persons with asteroid hyalosis generally have much better visual acuity than would be predicted by the examiner. Fluorescein angiography may be useful in evaluating the macula of a patient with asteroid hyalosis and decreased acuity, since the angiographic image of the retina is often better than the view by indirect ophthalmoscopy.

Posterior vitreous detachment may also be associated with focal opacities on the detached posterior hyaloid. The focal opacities on the posterior hyaloid usually occur at the site of previous attachment of the vitreous to the optic nerve. These opacities may be very troublesome to the patient but virtually never cause significant vision loss.

Preretinal Opacities

Preretinal hemorrhages can result from the same causes as vitreous hemorrhage. If
the preretinal hemorrhage is trapped between the posterior hyaloid and the retina, it results in a more focal, dense opacity (Fig. 12.4). If the preretinal hemorrhage lies directly over the fovea, the visual acuity is usually decreased to the level of 20/400 or worse. Preretinal hemorrhages generally take longer to clear than intravitreal hemorrhages. Preretinal hemorrhages associated with trauma often obscure macular damage such as choroidal rupture or commotio retinae.

Fluorescein angiography is the most useful ancillary test in the evaluation of occult macular disease. Fluorescein angiography should be performed in eyes with unexplained vision loss if no other explanation is found for the vision loss. Color vision testing is an important tool to uncover cone dystrophies and unexplained vision loss in children due to achromatopsia. The Ishihara color plates and Farnsworth D-15 test are useful screening tools primarily to detect red-green color defects, but the Farnsworth Munsell 100 hue test should be performed if a more precise assessment of color vision is needed.

Visual field testing with automated perimetry, Goldmann perimetry, or a tangent screen is primarily useful to define diseases of the optic nerve, chiasm, optic tract, lateral geniculate, and occipital cortex. Visual field testing is rarely helpful in uncovering retinal diseases because other examination techniques are more specific for determining the retinal diseases such as a rhegmatogenous retinal detachment or retinoschisis, which produce visual field defects. The Amsler grid is useful for detecting subtle macular disease causing elevation or distortion of the fovea. Because the Amsler grid is not very specific, a fluorescein angiogram is usually needed when the Amsler grid shows distortion or a scotoma.

Electroretinography and electro-oculography may be very useful in eyes with suspected retinal degenerations or dystrophies such as retinitis pigmentosa or Best's disease. B-scan ultrasonography is used in eyes with opaque media. The resolution of ultrasonography is not sufficient to detect many types of macular pathology, but it may be useful in detecting elevation of the macula from hemorrhage or serous fluid. Computed tomography (CT) and magnetic resonance imaging (MRI) are primarily used to define optic nerve, orbital, and other central nervous system disease. However, some retinal diseases such as posterior scleritis and choroidal osteoma show characteristic changes on CT scans.

**UNEXPLAINED VISION LOSS FROM MACULAR DISEASE**

**General Diagnostic Evaluation**

Evaluation for macular disease causing vision loss must include a thorough evaluation of the anterior segment, as described in the section on general diagnostic evaluation for media opacities. Most macular pathology causing unexplained vision loss can be detected by a combination of indirect ophthalmoscopy and contact lens biomicroscopy. Additional tests may be used to confirm or uncover the diagnosis in certain causes of occult macular disease.

Figure 12.4.
Preretinal hemorrhage between the posterior hyaloid and retina in an eye with proliferative diabetic retinopathy.
Disorders of the Vitreoretinal Interface

MACULAR HOLE

Full-thickness macular holes are visible as small defects in the neurosensory retina. Some eyes develop changes in the fovea called an impending or stage 1 macular hole prior to the development of a full-thickness macular hole. The evolution of macular holes has been subdivided by Gass into four stages. A stage 1 macular hole usually results in mild metamorphopsia with minimal reduction in visual acuity. The fovea shows loss of the normal foveal depression because of traction on the fovea from attached cortical vitreous (Fig. 12.5). The visual acuity is often minimally reduced to the 20/25 to 20/30 range. This may be followed by development of a small break in the edge of the fovea, which may progress to a round full-thickness hole (Fig. 12.6). The visual acuity may remain relatively good (20/30 to 20/60) in eyes with a stage 2 or early stage 3 macular hole. The macular hole is very small at this point and only detectable by slit lamp biomicroscopy with a contact lens. The visual acuity will generally decrease to the level of 20/80 to 20/200 over the course of 6 months as the macular hole and cuff of subretinal fluid around the macular hole gradually enlarge. The vast majority of eyes with macular holes have no other ocular disease. The fellow eye in patients who present with unilateral macular holes has an increased risk of developing a macular hole in the future. Eyes with macular holes often present as unexplained vision loss, since they are often not detected in the early stages and are not readily apparent unless slit lamp biomicroscopy is done.

Fluorescein angiography shows a central window defect in most macular holes and can be a useful diagnostic tool to confirm the diagnosis in eyes with stage 2 or early stage 3 macular holes. Pars plana vitrectomy with use of an intraocular gas bubble closes most macular holes, with improvement in the visual acuity. It is uncertain whether adjunctive agents such as transforming growth factor β1, serum, or autologous platelet growth factor may improve the visual and anatomic results of macular hole surgery.

Vitreous surgery for impending macular holes (stage 1 macular holes) is not recommended, since it does not improve the visual prognosis in these eyes.

**Figure 12.5.**
Stage 1 impending macular hole. There is loss of the normal foveal reflex, and the foveal umbo is elevated by biomicroscopy.

**Figure 12.6.**
Full-thickness macular hole with a small rim of subretinal fluid. This is the fellow eye of the patient in Figure 12.5.

**EPIRETINAL MEMBRANE**

Epiretinal membranes, which result from cellular proliferation on the surface of the retina, may produce vision loss by distorting the normal macular architecture or by producing cystoid macular edema from traction on the macula (Fig. 12.7). The vision loss associated with epiretinal membranes is usually of gradual onset. Some patients complain of metamorphopsia, although most present with macular dysfunction.

**VITREORETINAL SYNDROMES**

Vitreoretinal syndromes are disorders that may lead to macular abnormality or exudates. Vitreoretinal syndromes are often associated with age-related macular degeneration and ocular anomalies associated with child abuse.
with decreased acuity. Epiretinal membranes may develop following retinal tears, intracocular inflammation, retinal detachment repair, or trauma; however, most epiretinal membranes are idiopathic. Idiopathic epiretinal membranes usually develop after a posterior vitreous detachment, so this history may be elicited in patients who have visual loss secondary to an epiretinal membrane.

Contact lens biomicroscopy is helpful in making the diagnosis of epiretinal membrane and in assessing the amount of foveal distortion by this lesion. Fluorescein angiography is also important in highlighting the distortion of retinal vessels by the epiretinal membrane and determining whether the epiretinal membrane is causing cystoid macular edema. Many epiretinal membranes show little progression and cause only mild vision loss. Surgical removal of the epiretinal membrane by pars plana vitrectomy is indicated in most eyes if the visual acuity is decreased to the level of 20/70 or worse.

VITREOMACULAR TRACTION SYNDROME

Vitreomacular traction syndrome is a disorder that has some similarities to epiretinal membranes but which represents a distinct abnormality of the vitreoretinal interface that is often missed as a cause of visual loss. The posterior hyaloid is attached to the macula and causes traction on the macula in eyes with vitreomacular traction syndrome. The posterior vitreous is usually detached in the midperiphery, with an area of persisting posterior hyaloid attachment around the optic nerve and macula. Patients with vitreomacular traction syndrome typically complain of metamorphopsia and reduced vision. Eyes with vitreomacular traction syndrome typically have distortion of the perimacular vessels but lack a fibrotic-appearing membrane typical in eyes with an epiretinal membrane (Fig. 12.8). Contact lens biomicroscopy is usually necessary to make the diagnosis and visualize the hyaloid traction on the macular area. The visual acuity is typically reduced to the level of 20/40 to 20/100, depending on the severity of macular traction. Fluorescein angiography is a very useful diagnosis test, since these eyes show distortion of the macular vessels, often with macular edema in areas of retinal traction. Vitrectomy is indicated for the treatment of vitreomacular traction syndrome if the visual acuity is reduced to 20/60 or worse.

RHEGMATOUS STANGLINE RETINAL DETACHMENT

Unexplained vision loss may result from shallow macular detachment caused by an
unrecognized peripheral rhegmatogenous retinal detachment. Often these retinal detachments are due to small inferior retinal breaks or dialyses, which produce a shallow rhegmatogenous retinal detachment that progresses slowly toward the macula (Fig. 12.9). Patients may relate a history of photopsias, floaters, or peripheral visual field loss. The patients may note metamorphopsia or a shadow over part of the central vision when the macula starts to detach. Persons with posterior vitreous detachment, high myopia, cataract extraction, and ocular trauma are at increased risk for retinal detachment. Cytomegalovirus (CMV) retinitis has become an increasingly frequent cause of retinal detachment in patients with AIDS or immunosuppression after organ transplantation (Fig. 12.10).

Examination of the retina with scleral depression is the most useful technique to identify the retinal detachment. Ultrasound may be useful for detecting the retinal detachment in eyes where the peripheral retina cannot be adequately visualized because of media opacities. Rhegmatogenous retinal detachments should be repaired by use of a scleral buckle, pars plana vitrectomy with fluid-gas exchange, or pneumatic retinopexy, depending on the clinical circumstances.

Retinal Vascular Diseases

CENTRAL SEROUS RETINOPATHY

Central serous retinopathy is characterized by the accumulation of serous fluid in the macula beneath the neurosensory retina. The serous detachment has the appearance of a blister in the fovea and is best detected on clinical examination by contact lens biomicroscopy. There may be small, punctate yellow dots within the detached retina (Fig. 12.11). There are often subtle pigmentary changes at the level of the retinal pigment epithelium (RPE) near the center of the serous detachment. The size of the serous detachment may vary from several hundred microns to several millimeters. The center of the serous detachment is often slightly eccentric to the center of the fovea but usually involves the center of the fovea before the patient displays clinical symptoms.

Patients with this condition usually complain of blurred vision or metamorphopsia. The visual acuity may vary from 20/20 to 20/200, depending on the degree of elevation of the macula, the duration of the serous detachment, and the extent of foveal RPE changes, although most eyes have a visual acuity between 20/20 and 20/60. Males are about 10 times more likely than females to develop central serous retinopathy, which
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CENTRAL TELANGIECTASIA

Serous retinopathy is characterized by the presence of serous fluid in the sensory retina. This condition usually appears as an acute onset, with a vitreous hemorrhage, and is most often detected using a fluorescein angiogram, a contraction of the retinal pigment epithelium, and an increase in the leakage of the retinal artery. The serous retinopathy is usually associated with a yellow spot in the center of the macula. Many patients with this condition will have a type A personality.

Fluorescein angiography is very helpful in confirming the diagnosis. The fluorescein angiogram shows a central hyperfluorescent spot at the level of the RPE (Fig. 12.11). Frames of the fluorescein angiogram taken 10 to 30 minutes after dye injection often show progressive filling of the serous detachment because of diffusion of fluorescein dye from the foveal area. The serous detachment must then be detected by contact lens biomicroscopy.

The serous detachment usually resolves spontaneously within several months but may recur in about one-third of patients. Laser photocoagulation to extrafoveal leakage sites may be performed in eyes with persistent or recurrent episodes of serous detachment.

Figure 12.11. Central serous retinopathy. A. Contact lens biomicroscopy reveals punctate yellow spots in the retina, which is elevated by the serous detachment. B. Fluorescein angiogram shows a focal hyperfluorescence at the site of leakage into the serous detachment.

SEROUS DETACHMENT FROM OPTIC PIT

Serous detachment of the macula from optic pits may present as occult vision loss from a low-lying serous detachment of the macula. Serous detachments of the macula resulting from optic pits usually occur in eyes with larger pits located on the temporal side of the optic disc. The serous detachment is contiguous with the temporal border of the optic disc, has a tear-drop configuration, and may be associated with small yellow spots in the inner retina similar to those seen in some eyes with central serous retinopathy (Fig. 12.12, A and B). Fluorescein angiography may show leakage from the optic pit into the serous detachment (Fig. 12.12 C).

Some ophthalmologists have suggested that the fluid in the serous retinal detachment arises from the vitreous, whereas others have suggested that the fluid arises from the cerebrospinal fluid or is a result of retinoschisis. Serous detachments in eyes with optic pits usually occur in adults between 20 and 35 years of age. Patients may complain of metamorphopsia or vision loss when the serous detachment involves the fovea.

The serous detachment may fluctuate in size but usually does not resolve completely. Argon laser photocoagulation can be used to create a barrier between the optic disc and the serous detachment. Laser photocoagulation may hasten resolution of the serous detachment but does not seem to improve the overall visual prognosis. Vitreous surgery...
with drainage of the serous detachment, laser photocoagulation, and injection of an intraocular gas bubble may be considered in eyes with persistent leakage from the optic pit.

**DIABETIC MACULAR EDEMA**

Eyes with diabetic retinopathy may develop vision loss from macular edema characterized by thickening of the fovea and lipid deposition (Fig. 12.13). Some eyes with macular edema have minimal diabetic retinopathy and hard exudates to suggest the presence of macular thickening. Contact lens biomicroscopy with identification of foveal thickening is essential in establishing the diagnosis of diabetic macular edema. Patients with diabetic macular edema usually complain of blurred vision, although some complain of metamorphopsia or increased glare, which is due to light scattering in the thickened macula rather than decreased acuity.

Diabetic macular edema is almost always associated with visible diabetic maculopathy such as microaneurysms or intraretinal hemorrages. Other possible causes of vision loss, such as vascular occlusion or anterior ischemic optic neuropathy, should be considered in persons with diabetes who have vision loss but minimal visible retinopathy. The prevalence of diabetic macular edema increases with the duration and severity of the diabetic retinopathy. Diabetic macular
edema results from damage to the blood-retinal barrier with leakage of serum into the macula.

Fluorescein angiography is helpful in assessing the extent of diabetic microangiopathy, as the microaneurysms may be difficult to visualize by ophthalmoscopy alone. Fluorescein angiography also allows localization of the foci of greatest leakage, which assists in planning the location and density of focal laser burns. Focal or grid laser photocoagulation should be considered in persons with clinically significant diabetic macular edema as defined by the Early Treatment Diabetic Retinopathy Study Research Group. Focal treatment usually decreases the macular thickening and lipid deposition in eyes with mild-to-moderate macular edema. Laser photocoagulation usually does not improve visual acuity but does help to slow further vision loss from progression of the macular edema.

**FOVEAL NONPERFUSION FROM DIABETIC MACULOPATHY**

Foveal nonperfusion, which usually is observed in more advanced diabetic retinopathy, results from occlusion of capillaries supplying the macula. The macula is often diffusely thickened and may have a pale translucent appearance. It is usually difficult to distinguish between foveal nonperfusion and diffuse macular edema by contact lens biomicroscopy, although the presence of occluded retinal vessels or retinal neovascularization near the fovea suggests foveal nonperfusion (Fig. 12.14A). It is important to distinguish foveal nonperfusion from diabetic macular edema because the former does not appear to benefit from focal laser photocoagulation.

Patients with foveal nonperfusion usually have some preexisting vision loss from diabetic macular edema; however, their vision loss accelerates out of proportion to the extent of macular edema, with the acuity often decreasing to 20/400 or worse. Patients with foveal nonperfusion often have significant systemic microvascular disease (e.g., renal failure or cardiac ischemic disease). Eyes with macular edema and foveal nonperfusion may benefit from focal laser, but usually a light focal treatment should be placed in areas of leakage to avoid exacerbating the macular edema, which may increase as a result of the laser.

Foveal nonperfusion is best demonstrated on a fluorescein angiogram that shows irregularity or enlargement of the foveal avascular zone, which is normally about 500 μm in diameter. Eyes with foveal nonperfusion may have an enlarged circular foveal avascular zone, or sectors of the foveal avascular...

![Figure 12.14.](image)

Foveal nonperfusion may cause decreased acuity in patients with diabetic retinopathy or other vaso-occlusive retinopathies. A. This patient shows evidence of occlusion of retinal vessels and adjacent retinal neovascularization, which may be a clue to the presence of severe ischemia. B. The fluorescein angiogram demonstrates extensive capillary dropout in the macula, which accounts for the poor visual acuity of 2/200.
zone may be enlarged, corresponding to occlusion of segmental branches of the capillaries supplying the fovea (Fig. 12.14B). There is no specific treatment for foveal nonperfusion secondary to diabetic retinopathy; however, good control of blood pressure, blood lipids, and renal function may minimize the macular edema often associated with foveal nonperfusion.

BRANCH RETINAL VEIN OCCLUSION AND CENTRAL RETINAL VEIN OCCLUSION

Branch retinal vein occlusion is a common cause of unexplained vision loss, especially if the eye is not examined soon after the vein occlusion. Branch retinal vein occlusion occurs at the site of an arteriovenous crossing where the artery compresses the vein. The location and size of the retina damaged by the vein occlusion depend on the extent of the capillary bed drained by the occluded venous segment. Eyes with recent branch retinal vein occlusions have superficial intraretinal hemorrhages and macular edema in the distribution of the involved retinal vein (Fig. 12.15A). The involved retinal vein may appear to be nonperfused distal to the occlusion.

Branch retinal vein occlusion most commonly involves the superotemporal or inferotemporal retinal veins, so macular involvement and vision loss are common. The intraretinal hemorrhages usually resolve gradually within 3 to 9 months after the vein occlusion. The macular edema may improve but is more likely to persist than the intraretinal hemorrhages. This cause of vision loss may be difficult to diagnose by ophthalmoscopy alone once the intraretinal hemorrhages have resolved; however, shunt vessels crossing the midline raphe in the portion of retina drained by the occluded branch retinal vein may suggest the diagnosis (Fig. 12.15B).

Patients usually present with the sudden onset of blurred vision at the time the occlusion occurs, but some patients may only recognize the visual deficit when the other eye is covered months or years following the vein occlusion. Most persons with a branch retinal vein occlusion are elderly, many have a history of hypertension, but most are otherwise healthy. Fluorescein angiography is very helpful in establishing the diagnosis of branch retinal vein occlusion if the diagnosis is not apparent from ophthalmoscopic examination, since the macular edema will be visible for years in the quadrant of the vein occlusion. The angiogram will show macular edema that is greater in the quadrant of the venous occlusion. Argon laser photocoagulation is helpful in treatment of the macular edema and improves the visual prognosis in eyes that meet the criteria of the Branch Vein Occlusion Study Group.

![Figure 12.15](image)

*Figure 12.15.*

Inferotemporal branch retinal vein occlusion. A. Acute stage with intraretinal hemorrhages and edema. B. One year later the only sign of the previous vein occlusion was shunt vessels nasal to the fovea.
Previous central retinal vein occlusion may present as unexplained visual loss if the patient does not recognize the decreased vision within 1 year of the venous occlusion. The flame-shaped intraretinal hemorrhages typical of central retinal vein occlusion usually resorb within 1 year. These patients typically present when they accidentally cover the eye with better acuity or following a routine eye examination. One clue to a previous central vein occlusion is the presence of shunt vessels on the optic disc (Fig. 12.16). These patients virtually always have residual disc edema, but this may be only detected by contact lens biomicroscopy or fluorescein angiography, since the edema is typically diffuse with minimal lipid.

- **Figure 12.16.**
  Shunt vessels may develop on the optic disc after previous central retinal vein occlusion. The intraretinal hemorrhages typical of acute central retinal vein occlusion had completely resolved when this patient presented with a visual acuity of 20/80.

Oclusion of the Central Retinal Artery, Branch Retinal Artery, and Choroidal Artery

Occlusions of the central retinal artery (Fig. 12.17A), branch retinal artery (Fig. 12.18), and ciliary retinal artery present acutely as sudden vision loss associated with retinal whitening and edema in the distribution of the central retinal artery, branch retinal artery, and ciliary retinal artery, respectively. Most eyes with central retinal artery occlusion have poor vision, which does not improve substantially when the retinal edema subsides. Visual acuity after branch retinal artery occlusion is variable, depending on whether the occluded artery supplies most of the fovea. Eyes with ciliary retinal artery obstruction have a much better prognosis, with 90% of such eyes attaining a visual acuity of 20/40 or better. Some eyes with ciliary retinal artery occlusion have an associated ischemic optic neuropathy or central retinal vein occlusion; the visual outcome in such cases is much poorer than when these associated conditions are absent. Eyes with an arterial occlusion may present subsequently with unexplained vision loss if the loss is not detected shortly after the arterial occlusion, since the retinal whitening only lasts several weeks after the arterial occlusion (Fig. 12.17B). Often, the only ophthalmoscopic

- **Figure 12.17.**
  Central retinal artery occlusion. A. Acute stage showing perifoveal edema. B. Two years later the retina appeared normal except for mild attenuation of the retinal arteries. The visual acuity remained 1/200.
clues of an arteriole occlusion older than 1 month is mild narrowing of the involved arterioles. Occasionally, visible arteriolar emboli may also provide a clue to previous arteriolar occlusion.

Patients with carotid occlusive disease, cardiac valvular disease, and hypertension are at greatest risk for developing retinal arteriolar occlusion. A general medical evaluation should be performed in persons with retinal arteriolar obstruction, looking specifically for causes of embolic disease. An erythrocyte sedimentation rate should be obtained in elderly persons with arterial occlusion to rule out giant cell arteritis. Digital massage, paracentesis, or carbogen administration may be considered in selected eyes that present within hours of a central retinal artery occlusion, but these therapies are not of proven benefit. Systematic evaluation to include carotid duplex ultrasonography and transesophageal echocardiography should be performed to try to identify the source of the emboli. Treatment of any underlying systemic disorders is important to minimize the risk of additional arteriolar occlusions in the eye or brain.

**JUXTAFOVEOLAR TELANGIECTASIS**

Juxtafoveal (paravascular) telangiectasis is characterized by telangiectatic capillaries in the paravascular region (Fig. 12.19). Small, yellow, intraretinal crystalline deposits may develop near the telangiectatic vessels. Persons with juxtafoveal telangiectasis are often asymptomatic unless the capillaries cause macular edema with metamorphopsia or visual loss. Some eyes with apparent juxtafoveal telangiectasis probably had previous occlusion of the macular branch retinal vein.

The telangiectatic vessels are best seen by contact lens biomicroscopy, although they may be defined well by fluorescein angiography. Some eyes with juxtafoveal telangiectasis and macular edema respond to focal laser photocoagulation to the area of telangiectasis. Many of these eyes have good visual acuity and do not require any treatment. Some eyes with juxtafoveal telangiectasis develop choroidal neovascularization, which can be considered for treatment by laser photocoagulation or if the choroidal neovascularization does not involve the center of the fovea.

**IRVINE-GASS SYNDROME**

Aphakic or pseudophakic cystoid macular edema developing after cataract extraction may lead to vision loss. The cystoid macular edema typically starts several weeks to months after the cataract extraction. Patients often complain of worsening vision after initially improved vision following the cataract extraction. The decrease in acuity may be associated with photophobia and metamorphopsia.
phosphenes in some eyes. Biomicroscopy of the macula shows macular edema with cystoid changes, which is best seen by retroilluminating the adjacent retina with a narrow slit-lamp beam.

Most eyes with Irvine-Gass syndrome have a history of an uncomplicated cataract extraction with no visible ocular inflammation. Vitreous strands to the cataract wound, recent YAG capsulotomy, anterior-chamber intraocular lens placement, or vitreous loss, and other possible causes of ocular inflammation predispose an eye to developing cystoid macular edema. Cystoid macular edema is most easily diagnosed by fluorescein angiography, which is more sensitive than clinical biomicroscopic examination (Fig. 12.20).

Cystoid macular edema is often self-limited and may resolve within weeks to months without any specific clinical intervention. Although a number of therapies for cystoid macular edema are available, many eyes do not respond to any therapy. Some eyes respond to intensive topical steroids, sub-Tenon’s steroids, or systemic steroids. Other eyes may respond to nonsteroidal antiinflammatory agents (e.g., topical ketorolac, diclofenac, flurbiprofen, or systemic indomethacin). If a specific cause for the cystoid macular edema, such as vitreous to the cataract wound, is identified, then surgical intervention should be directed at the cause if the eye does not respond to medical therapy. Vitrectomy may lead to resolution of cystoid macular edema in eyes with vitreous to the cataract wound. Vitrectomy may also have a therapeutic role in eyes with cystoid macular edema, even in the absence of visible vitreous adhesions in the anterior segment. Cystoid macular edema is also more prevalent in eyes with rigid haptic anterior-chamber intraocular lenses. Removal of an anterior chamber intraocular lens and suturing of a posterior chamber intraocular lens may be performed in eyes in which the lens implant appears to be the source of the macular edema.

**INFLAMMATORY DISEASES OF RETINA OR VITREOUS CAUSING MACULAR DISEASE—PARS PLANITIS**

Pars planitis is characterized by vitritis and accumulation of white debris in the pars plana (often called “snowbank”). It may also be associated with vitreous opacities, periphlebitis, cystoid macular edema, and mild anterior-segment inflammation (Fig. 12.21). Cystoid macular edema usually is the cause of decreased acuity, although some patients complain primarily of floaters rather than blurred vision. Patients with pars planitis may present with unexplained vision loss, because the vitreous inflammation and pars plana exudates are not detected unless a careful examination of the vitreous base is performed.

Pars planitis may be limited to one episode lasting several months or may have a chronic course of intermittent exacerbations and remissions. Pars planitis is most common in young adults who are otherwise entirely healthy. There are no known precipitating factors for pars planitis, but it precedes the development of multiple sclerosis in a small number of patients. Pars planitis is diagnosed by careful examination of the vitreous and scleral depression of the pars plana. Contact lens biomicroscopy of the
macula, looking for cystoid macular edema, is helpful; however, fluorescein angiography is more sensitive for detecting subtle macular edema.

Pars planitis often responds to topical, periocular, or systemic steroids. Periocular or systemic steroids are usually reserved for eyes with 20/40 visual acuity or worse from cystoid macular edema. Cryotherapy to the pars plana snowbanks, pars plana vitrectomy, or systemic antimetabolites (e.g., cyclophosphamide, cyclosporin, and chlorambucil) may be used in refractory cases.

**Diseases of the Photoreceptors or Retinal Pigment Epithelium**

**DRUG-INDUCED MACULAR DAMAGE**

Drugs that have an affinity for the retina or RPE (e.g., chloroquine, hydroxychloroquine, tamoxifen, and thioridazine) may cause macular changes with decreased acuity. Chloroquine and hydroxychloroquine toxicity result in a bull's eye maculopathy with a ring of atrophy surrounding the central fovea, with some pigment dispersion. A careful drug history and the nature of the macular changes are most helpful in suggesting the possibility of drug-induced macular damage.

Chloroquine retinopathy usually occurs in persons treated with more than 2 mg/kg/day of chloroquine or 3 mg/kg/day of hydroxychloroquine for at least several years, resulting in a total dose of more than 100 to 300 g. Cessation of the drug may lead to limited improvement in some eyes. However, vision may continue to deteriorate following cessation of the chloroquine because of the slow drug excretion. High-dose tamoxifen may produce white refractile deposits in the superficial retina associated with visual loss. Thioridazine toxicity may produce progressive vision loss with punctate areas of RPE atrophy, which coalesce to form areas of geographic foveal atrophy (Fig. 12.22). Rifabutin, a drug used for treatment of *Mycobacterium avium* infection in patients with AIDS, causes anterior segment with hypopyon, fibrin, and vitreous inflammation in some eyes. This inflammation may resemble infectious endophthalmitis but the inflammation resolves with cessation of rifabutin therapy. Intensive topical steroids may be used to control the inflammation in patients who require continued rifabutin therapy.

**PHOTOTOXIC RETINAL DAMAGE**

Foveal damage may result from exposure to the operating microscope. Such damage occurs in traction, if procedure is usually p at the le rum, whi to 2 disc about 1 changes develop fiberotic may also l held i ng macu brane or 12.23).

Photomicroscope lesion in patients typ surgery, scotoma, determined by foveal d helpful in weeks or eudre, it after the
of systemic steroids may be used to try to minimize edema and damage to the RPE.

COMMOTIO RETINAE (BERLIN'S EDEMA)

Blunt trauma to the eye may produce retinal edema and damage to the RPE, termed commotio retinae (Fig. 12.24). The retina may develop geographic areas of pale white-gray edema, depending on the biomechanics of the blunt injury. The edema may be associated with intraretinal hemorrhages and leads to vision loss if the macula is involved. Immediately following an acute injury, commotio retinae is readily diagnosed,

occurs most commonly during cataract extraction, although it can occur in any ocular procedure in which an operating microscope is used. The operating microscope usually produces a yellow-white oval lesion at the level of the retinal pigment epithelium, which is about 1/2 disc diameter by 1 to 2 disc diameters. The lesion fades after about 1 week, and punctate pigmentary changes within an area of RPE atrophy often develop at the site of the lesion. The fiberoptic light pipe used in vitreous surgery may also cause phototoxicity if the light pipe is held near the fovea for too long. This problem most commonly develops following macular surgery for an epiretinal membrane or treatment of a macular hole (Fig. 12.23).

Phototoxic damage from the operating microscope is usually only detected when the lesion involves the center of the fovea. Patients typically present days to weeks after surgery, complaining of blurred vision or a scotoma. The final visual acuity is determined by the location and severity of the foveal damage. Fluorescein angiography is helpful in detecting the ovoid RPE atrophy weeks or months following the surgical procedure. If a foveal burn is noted immediately after the intraocular surgery, a short course
but it may present as unexplained vision loss weeks or months following an injury if the patient does not detect the decreased acuity. The visual acuity is often 20/200 or worse if the macular involvement is extensive.

The retinal edema and intraretinal hemorrhages typically fade after several weeks and may leave minimal clumps of pigment, with RPE atrophy in the distribution of the edema. The visual acuity often remains poor despite the minimal residual macular changes. Fluorescein angiography is very helpful, since the geographic RPE atrophy following trauma is more prominent on the fluorescein angiogram. Patients must be specifically questioned about ocular trauma, since they often don't volunteer this information because of the circumstances surrounding the trauma. There is no specific treatment of commotio retinae, although systemic steroids may be considered immediately following the injury to try to minimize the retinal edema.

HEREDITARY RETINAL DYSTROPHIES OR DEGENERATIONS

There are many retinal dystrophies or degenerations that may present with vision loss. Most of these conditions have characteristic fundus, angiographic, and/or electrophysiologic abnormalities, which assist in their diagnosis. Some of these dystrophies may have minimal macular changes in the early stages of the disorder, leading to their presentation as unexplained vision loss. These disorders include fundus flavimaculatus (Stargardt's disease, Fig. 12.25), pattern dystrophies of the RPE, cone dystrophies, X-linked juvenile retinoschisis (Fig. 12.26) and lysosomal storage diseases (e.g., Tay-Sachs disease, Niemann-Pick disease, and metachromatic leukodystrophy).

Fluorescein angiography, electroretinography, electro-oculography, perimetry, and appropriate biochemical tests should be performed when a hereditary retinal degeneration or dystrophy is suspected. Examination of genetically related family members can also be very helpful, since other family members, especially older siblings or parents, may show more typical changes of a particular retinal degeneration or dystrophy.

Diseases of the Retinal Pigment Epithelium, Bruch's Membrane, Choroid, and Sclera

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration is a very common cause of vision loss in the elderly. The severity of the retinal changes from macular degeneration usually parallels the visual acuity, but some eyes with macular degeneration present as unexplained visual loss.

Age-related macular degeneration may also be classified into wet (exudative) and dry (non-exudative) forms. Dry age-related macular degeneration is characterized by the presence of drusen. These are subpigment epithelial deposits that are usually seen in normal aging eyes, but when they reach a critical size, the macula may become involved. Wet age-related macular degeneration is characterized by the presence of subretinal neovascularization. This can be caused by either choroidal neovascularization or subretinal neovascularization. Subretinal neovascularization can be caused by choroidal neovascularization or subretinal neovascularization.

AGE-RELATED MACULAR DEGENERATION (continued)

In wet age-related macular degeneration, subretinal neovascularization can be caused by choroidal neovascularization or subretinal neovascularization. Subretinal neovascularization can be caused by choroidal neovascularization or subretinal neovascularization. Subretinal neovascularization can be caused by choroidal neovascularization or subretinal neovascularization.

Figure 12.25

Stargardt's disease with white flecks primarily in the macula. The visual acuity in this patient was mildly reduced to 20/25.

Figure 12.26

Juvenile X-linked retinoschisis. There is retinoschisis visible in the intertemporal retina and macular schisis.
There are two basic subtypes of age-related macular degeneration: atrophic and exudative.

Aphotic macular degeneration is characterized by drusen and atrophic changes in the RPE beneath the macula. Patients usually complain of decreased acuity but may complain of metamorphopsia, even in the absence of exudative changes. The visual acuity in eyes with aphotic macular degeneration may vary from 20/20 to less than 20/200, depending on the severity of the macular changes. The drusen are readily visible by ophthalmoscopy, but the RPE atrophy, which is a better predictor of visual acuity, is best seen by fluorescein angiography (Fig. 12.27). There is no specific treatment for aphotic macular degeneration.

Exudative macular degeneration can be subdivided into two subtypes: pigment epithelial detachment and choroidal neovascularization. Eyes with either type of exudative macular degeneration may present with unexplained vision loss because the serous detachment in the macula may not be detected on routine ophthalmoscopy. Contact lens biomicroscopy allows detection of the serous detachment.

Eyes with pigment epithelial detachment alone have a translucent blister in the fovea (Fig. 12.28). The pigment epithelial detachment may be solitary, or there may be clusters of multiple pigment epithelial detachments. Patients usually complain of decreased acuity or metamorphopsia. Fluorescein angiography of the pigment epithelial detachment shows a uniformly fluorescent lesion with an increase in fluorescein intensity but not size in the late frames of the angiogram.

**Figure 12.27.**
Atrophic age-related macular degeneration. A: Drusen and pigment are visible by ophthalmoscopy. B: Extensive RPE changes are seen most clearly by fluorescein angiography.

**Figure 12.28.**
A: Pigment epithelial detachment without visible choroidal neovascularization in an eye with age-related macular degeneration. B: The pigment epithelial detachment fills uniformly in the late frames of the angiogram.
Pigment epithelial detachments without angiographically identifiable choroidal neovascularization have a more favorable prognosis than eyes with choroidal neovascularization. These pigment epithelial detachments may remain stable for years or even show spontaneous regression, although most eyes with this lesion do eventually show progressive visual loss. No treatment is currently recommended for pigment epithelial detachment without choroidal neovascularization. Indocyanine green videoangiography is a useful diagnostic tool, since it may identify extrafoveal hyperfluorescent foci within the pigment epithelial detachment which can be treated with laser photocoagulation, resulting in resolution of the detachment in some eyes.

The presence of subretinal hemorrhage in an eye with macular degeneration is highly suggestive of choroidal neovascularization. Choroidal neovascular membranes may develop in eyes with atrophic macular degeneration or in association with pigment epithelial detachments. The choroidal neovascular membrane may have the appearance of a gray or green discoloration in the macula, with overlying serous detachment of the macula (Fig. 12.29). Patients usually complain of the sudden onset of metamorphopsia or decreased acuity in the involved eye. Fluorescein angiography is crucial in establishing the diagnosis and determining the distance of the neovascular membrane from the fovea. Indocyanine green videoangiography is also helpful in defining the location and extent of choroidal neovascularization in some eyes with poorly defined choroidal neovascularization by fluorescein angiography. Unfortunately, most patients with exudative macular degeneration have poorly defined choroidal neovascularization that cannot be treated with laser photocoagulation using current techniques. Laser photocoagulation should be considered in patients with well-defined extrafoveal, juxtapfoveal, and subfoveal choroidal neovascular membranes on the basis of the recommendations of the Macular Photocoagulation Study.

**ANGIOID STREAKS**

Angioid streaks are linear gray, brown, or red-brown lines that extend radially from the optic disc and are located at the level of Bruch's membrane. These streaks usually are associated with peripapillary atrophy and RPE changes surrounding the optic disc (Fig. 12.30). Angioid streaks may not be readily visible or may be more extensive than apparent by ophthalmoscopic examination alone. Patients may present with vision loss when a streak extends into the fovea or when choroidal neovascularization develops in the macula, most commonly at the distal tip of an angioid streak. Angioid streaks may be idiopathic or may be associated with systemic disorders such as pseudoxanthoma elasticum, Paget's disease, or inflammatory conditions such as sarcoidosis, or secondary to hypercholesterolemia.

**MYOPIA CHOROIDAL DYSTROPHY**

Myopic choroidal dystrophy is an idiopathic disorder characterized by thickening of the choroid. Patients may have decreased visual acuity and metamorphopsia. The angiod streaks are not visible with ophthalmoscopy. Laser photocoagulation is not effective in treating angioid streaks.

*Figure 12.29.*

A. Gray choroidal neovascular membrane in a 78-year-old patient without visible macular degeneration. B. The new vascular membrane fills during the choroidal phase with leakage in the later frames of the angiogram.
An eye with myopic choroidal degeneration may have a previous history of subnormal vision due to anisometropic amblyopia. The fundus usually shows signs of high myopia with round or ovoid areas of peripapillary RPE atrophy, and the macula often has focal RPE atrophy with pigmentary changes (Fig. 12.31). Linear breaks in Bruch's membrane, called lacquer cracks, may be present. The posterior pole may have staphyloma with marked attenuation of the RPE. It is often difficult to predict the visual acuity from the macular changes, and previous records of best-corrected acuity may be helpful in determining whether the severity of visual loss can be explained by the macular changes alone. The higher the degree of myopia, the more likely the development of progressive vision loss from macular changes. Elderly patients with high myopia are also at greater risk of developing substantial vision loss with relatively mild age-related macular degeneration. Myopic choroidal degeneration and age-related macular degeneration may coexist to produce vision loss. Some patients with myopic degeneration develop choroidal neovascularization at the third to fourth decade of life. The choroidal neovascular membranes are often small and are usually located within the foveal avascular zone. The large disciform scars found in many eyes with exudative macular degeneration are unusual in eyes with choroidal neovascularization related to myopia. The choroidal neovascularization.
membranes related to myopia typically undergo involution to a small flat fibrotic scar (Poeuster-Fuchs' spot). Laser photocoagulation may be considered if the choroidal neovascularization is outside the center of the foveal avascular zone but should be avoided for choroidal neovascularization within the foveal avascular zone. Choroidal neovascularization within the fovea may regress spontaneously, and visual acuity may improve spontaneously in some eyes.

MULTIPLE EVANESCENT WHITE DOT SYNDROME

Multiple evanescent white dot syndrome (MEWDS) is an uncommon disorder that may present as unexplained mild unilateral vision loss, most commonly in young adult females. The characteristic features include small white or gray dots in the outer retina, primarily posterior to the equator (Fig. 12.32A). These dots may be associated with vitreous cells and may appear following flu or other viral illness. Patients may complain of mild blurring of vision or para-central scotoma. MEWDS appears to have some similarities to acute multifocal posterior placoid epitheliopathy, which is also believed to be related to a viral etiology.

Fluorescein angiography shows mild hyperfluorescence at the site of the white spots, which stain in the late frames of the angiogram (Fig. 12.32B). The disc may also show late staining in some eyes with MEWDS. The electroretinogram may show a decrease in the amplitude of the "a" wave. The visual acuity, fundus changes, and fluorescein angiographic and electroretinographic abnormalities usually return to normal within 2 to 3 months.

CHOROIDAL HEMANGIOMA

Choroidal hemangiomas are minimally elevated red-orange tumors of the choroid, which can present with unexplained vision loss. The choroidal hemangioma is usually under 10 disc diameters in size and is often missed on routine ophthalmoscopy. Patients present with metamorphopsia or vision loss, which results most frequently from serous detachment of the retina if the choroidal hemangioma is near the macula and, less frequently, from serous detachment of the macula. Most can be treated uneventfully, but the occasional large choroidal hemangioma may require surgical resection.

Fluorescein angiography usually shows hyperfluorescence of the choroidal hemangioma in the early frames, while late leakage of dye may accumulate in the retina in the late frames. Ultrasound may help to confirm the diagnosis.

Treatment of choroidal hemangiomas is controversial. Arguments are that choroidal hemangiomas are frequently bilateral and may regress spontaneously.

CHOROIDAL HEMANGIOMA

Choroidal hemangiomas can cause severe vision loss or serous retinal detachment loss. Choroidal hemangiomas may be difficult to visualize with fluorescein angiography.

- Figure 12.32.
  A. Multiple evanescent white dot syndrome in a 39-year-old female with white spots in the deep retina. B. There is punctate staining of the white dots in the late frames of the angiogram.

- Figure 12.33.
  Diffuse choroidal hemangioma in a patient with Sturge-Weber syndrome. A choroidal detachment visible in the periphery, developed after minor trauma to the eye.
frequently, from cystoid retinal changes if the choroidal hemangioma is beneath the macula. Most choroidal hemangiomas are idiopathic, but some are associated with Sturge-Weber syndrome (Fig. 12.33).

Fluorescein angiography of a choroidal hemangioma shows prominent large choroidal vessels, which fill with the choroidal circulation. There is usually diffuse leakage of fluorescein dye from a choroidal hemangioma in the late frames of the angiogram. Some eyes with choroidal hemangiomas, however, show only mild hyperfluorescence during choroidal circulation, with minimal late leakage of fluorescein dye. Fluorescein dye may accumulate in cystic spaces within the retina in the late frames of the angiogram.

Ultrasoundography of a choroidal hemangioma usually shows high internal reflectivity because of the vascularity of this lesion.

Treatment is usually not required for most choroidal hemangiomas unless the hemangioma is causing serous detachment of the macula. Argon laser photocoagulation on the surface of a choroidal hemangioma outside of the macula may be used when a serous detachment involves the macula.

**COROIDAL FOLDS**

Choroidal folds may cause mild-to-moderate vision loss in eyes with unexplained vision loss. Choroidal folds are best seen by fluorescein angiography, which reveals the folds as alternating dark and light lines (Fig. 12.34). Patients with choroidal folds may complain of blurred vision or metamorphopsia, depending on the cause of the choroidal folds.

Choroidal folds are most commonly idiopathic but may be caused by a number of disorders such as orbital tumors, posterior scleritis, choroidal tumors (e.g., choroidal melanoma), choroidal neovascularization, and hypotony. A shift in the previous refractive error toward increasing hyperopia is common. The evaluation and treatment of choroidal folds should be directed to their cause, whenever possible. Eyes with idiopathic choroidal folds generally have good visual acuity and do not require any treatment.

**PRIMARY AND METASTATIC CHOROIDAL TUMORS**

Tumors of the choroid may result in visual loss that is not detected on routine examination. The first mechanism of visual loss occurs when the choroidal tumor grows directly beneath the macula or when there is a serous detachment from a nearby choroidal tumor. The most common primary tumor in adults is a malignant melanoma, and the most common secondary tumor is a metastatic tumor from primary sources such as bronchogenic or breast carcinoma. Choroidal melanomas may be amelanotic and may not be seen on

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**Figure 12.34.**

A. Idiopathic choroidal folds presenting as unexplained vision loss. B. The choroidal folds appear as alternating dark and white lines on a fluorescein angiogram.
routine fundus examination (Fig. 12.35). Metastatic tumors are typically amelanotic and often present as small, multifocal choroidal masses (Fig. 12.36). Indirect ophthalmoscopy is the best method to detect the choroidal tumor by elevation of the choroid or subtle changes in the coloration of the fundus over the tumor. Large cell lymphoma may present with multiple small choroidal tumors and malignant cells in the vitreous causing visual loss. Another common presentation occurs when the choroidal tumor causes secondary exudative retinal detachment that extends into the macula. These exudative retinal detachments are usually associated with shifting subretinal fluid. When the patient is examined in a sitting position, the subretinal fluid may shift inferiorly and not be readily apparent on ophthalmoscopy.

POSTERIOR SCLERITIS

Posterior scleritis is characterized by one or more cream-colored subretinal masses often associated with an overlying pigment epithelial or exudative retinal detachment (Fig. 12.37). Choroidal folds may be observed in association with subretinal nodules from posterior scleritis. Ultrasonography usually shows thickening of the choroid, and computed tomography with contrast dye may reveal enhancement of the sclera.

- **Figure 12.35.**
  This 56-year-old female presented with visual loss (20/200) secondary to a serous detachment from a small choroidal melanoma above the macula. She was treated with an iodine plaque but the choroidal melanoma showed continued growth requiring enucleation.

- **Figure 12.36.**
  This patient presented with decreased acuity (20/400) secondary to a metastatic choroidal tumor. She had a known history of metastatic breast carcinoma and was treated with radiotherapy to the eye. The choroidal tumor decreased in size and developed nontubular pigmen
tary changes demonstrated in this photograph.

- **Figure 12.37.**
  A. Pigment epithelial detachment in an eye with posterior scleritis. B. The pigment epithelial detachment fluoresces uniformly as it fills with fluorescin dye.
Patients complain of the rapid onset of decreased acuity associated with ocular pain, especially with eye movements. If the posterior scleritis is associated with anterior scleritis, the patient may have more severe ocular pain with injection of the scleral and episcleral vessels. Most eyes have signs of intraocular inflammation such as vitritis or anterior uveitis. Patients who present with posterior scleritis, often have a history of rheumatoid arthritis, Wegener's granulomatosis, systemic vasculitis, or other collagen vascular disease. Treatment of posterior scleritis is directed toward the underlying cause of the inflammation. Most patients respond to systemic steroids or nonsteroidal antiinflammatory medications such as indomethacin. Some patients must be treated with immunosuppressive agents such as cyclophosphamide or cyclosporin if they do not respond adequately to oral steroids.

TOXOPLASMOsis ChoriOREtINITIS

Toxoplasmosis causes an intense focal chorioretinitis usually associated with vitritis. The chorioretinitis usually starts at the edge of an older chorioretinal scar. Toxoplasmosis is usually easily diagnosed by fundus examination but may present as unexplained vision loss when an extrafoveal focus of retinitis is associated with serous detachment of the macula (Fig. 12.38) or with branch arterial occlusion. Patients often complain of floaters and mild decreases in vision when the chorioretinitis is outside of the fovea. More profound vision loss occurs when the chorioretinitis extends into the fovea or optic nerve or when subfoveal choroidal neovascularization develops at the edge of a chorioretinal scar. Toxoplasmic chorioretinitis usually occurs in otherwise healthy persons but may present with atypical features such as minimal retinal inflammation in immunocompromised patients following transplantation or in patients with AIDS.

Ophthalmoscopy usually suffices to determine whether a serous detachment of the fovea is the cause of vision loss, although fluorescein angiography may assist with this diagnosis. A serum toxoplasmosis titor is useful in establishing toxoplasmosis as the cause of the chorioretinitis in atypical presentations of chorioretinitis. Most eyes with toxoplasmosis respond to therapy with a combination of oral clindamycin, pyrimethamine, sulfadiazine, and prednisone. Some eyes with toxoplasmosis have resolution of the chorioretinitis without therapy. Drug therapy does seem to hasten resolution of the chorioretinitis. Some advocate treatment with the combination of clindamycin and prednisone, while others favor use of pyrimethamine, sulfadiazine, and prednisone. Quadruple therapy with pyrimethamine, sulfadiazine, prednisone, and clindamycin should be considered in eyes with chorioretinitis extending into the fovea or optic nerve. Patients treated with pyrimethamine must be given supplemental folic acid to prevent folate deficiency.

PRESUMED OCULAR HISTOPLASMOSIS

The presumed ocular histoplasmosis syndrome is characterized by multiple small, atrophic, white chorioretinal scars around the posterior pole or peripheral retina with minimal surrounding pigment. The fundus may also show peripapillary atrophic changes and choroidal neovascular membranes, which are usually located around or beneath the fovea. Fluorescein angiography

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*Figure 12.38.* Serous detachment of the retina associated with toxoplasmosis chorioretinitis at the temporal border of the optic disc.
should be considered in any patient with histoplasmosis and unexplained visual loss, since the neovascular membranes are often small and may be the source of unexplained vision loss. Patients usually complain of metamorphopsia or blurred vision when choroidal neovascularization extends beneath the fovea (Fig. 12.39). Most persons with the presumed ocular histoplasmosis syndrome have lived or traveled in an endemic area for histoplasmosis in the central and eastern United States, although some persons have no known travel to areas endemic to histoplasmosis.

Fluorescein angiography is helpful in diagnosing choroidal neovascularization causing vision loss, even in the absence of visible adjacent histoplasmosis spots. Laser photocoagulation should be considered in eyes with well-defined extrafoveal choroidal neovascular membranes, and vitrectomy with removal of subfoveal choroidal neovascularization is the treatment of choice in eyes with well-defined subfoveal choroidal neovascular membranes. Angiography may also help to establish the diagnosis of histoplasmosis syndrome in eyes with subretinal neovascularization without visible histoplasmosis spots, because the atrophic spots may be more easily detected by angiography than by ophthalmoscopy.

**CONCLUSION**

Careful evaluation of the ocular media and macula with appropriate diagnostic tests can determine the cause of unexplained visual loss in most eyes. The most common cause of unexplained visual loss referred to a retina practice following cataract surgery are cystoid macular edema and age-related macular degeneration. The most common causes of unexplained visual loss in phakic eyes include age-related macular degeneration, previous vein occlusion, and epiretinal membranes. As a general rule, the visual acuity is equal to the sum of the ocular media opacities and severity of retinal disease. For example, a 20/30 cataract and a 20/70 macula from macular degeneration may result in an approximate visual acuity of 20/100. Many eyes with unexplained visual loss have more than one potential source of unexplained visual loss. A crucial aspect of the ophthalmologic examination is to determine whether the severity of the ocular abnormalities explains the extent of the vision loss. Experienced ophthalmologists can estimate the degree of vision loss expected from abnormalities of the media or retina. Further diagnostic evaluation must be considered if the degree of vision loss is much greater than that explained by the known pathology.

If the cause of vision loss is not discovered by a careful ophthalmologic examination, then optic nerve disease should be suspected. Some eyes with unexplained vision loss have amblyopia that has not been detected previously by the patient. Examination for small strabismic deviations, anisometropia, and high astigmatism error or a history of unilateral sensory deprivation should alert the ophthalmologist to the possibility of amblyopia. The presence of an apparent pupillary defect, optic disc pallor, a large cup/disk ratio, or visual field loss in the absence of corresponding retinal pathology should suggest the possibility of optic nerve disease or central nervous system disease. If the cause of the vision loss cannot be uncovered by extensive diagnostic evaluation,
Unexplained Vision Loss: Macula or Media?


Blurred vision (and distorted vision) is a common complaint that has an extremely broad differential diagnosis. The complaint as expressed by the patient usually does not suggest any one particular diagnosis. This chapter outlines some of the tests and techniques employed in evaluating blurred vision and also reviews the more common causes of the condition to help the physician come to a rapid and correct diagnosis.

Evaluation of blurred vision requires more than the Snellen chart examination. It involves also examination of color vision, testing of the visual fields and pupillary function, and detailed examination of the retina.

**EVALUATION OF THE SYMPTOM**

**Testing of Visual Acuity**

Visual acuity is evaluated primarily by the Snellen chart at 20 feet and by a standard near card at 14 inches. It is assumed that the patient is wearing the full distance correction and appropriate add if needed for near vision.

Up to the present, the rule by which we have judged normal acuity has been the Snellen chart; however, even some patients with 20/20 acuity will say there is a difference. It appears that patients are more sensitive to small defects in vision than our standard tests can detect. Recent studies in many laboratories have shown that these patients have abnormal contrast sensitivity tests despite normal visual acuity and fields. Microelectrode studies have demonstrated that certain groups of cells in the visual system respond to different spatial frequencies, just as Zeki showed that some cells were color coded. Tests to measure the sensitivity gradient have been designed but are not in widespread clinical use outside of experimental laboratories.

In those situations in which an immediate refraction is not possible, a careful check of the pinhole vision may provide a valuable diagnostic clue. Improvement of vision by several lines on the Snellen chart (even if vision is not fully corrected to 20/20) by a single or multiple pinhole test suggests that the decreased acuity is the result of a refractive error. The vision of patients with retinal or optic nerve disease usually remains the same or is made worse by pinhole vision. The refractive error, however, may represent disease of the cornea, such as a keratoconus with increased astigmatism, or disease of the lens with increased myopia.

A patient who has hemianopsia may read only half the line of Snellen letters. Repetition of this error in many lines strongly suggests a hemianopic field defect.

Sometimes, visual defects can be inferred in patients who cannot read a Snellen chart. For example, if the eyes of an infant are covered once at a time, the infant may show extreme resistance to the cover over one eye but not to the cover over the other eye. Lack
of resistance to the cover may suggest poor vision in that eye.

A visual complaint in which the near acuity and the distance acuity are vastly different suggests a functional, rather than an organic, problem. The near and distance acuities should be within one or two Snellen lines of each other, when corrected.

Complaints of decreased acuity after strenuous exercise (such as several games of tennis) or after warm baths suggests Uthoff's sign, a phenomenon that occurs in nerves that have a conduction defect, which may be caused by a demyelinating process.

The use of a neutral density filter may help to differentiate childhood amblyopia from organic optic nerve disease. The Kodak filter 96 ND #2 is recommended. Place the filter in front of the normal eye; the decrease in acuity should not be more than two Snellen lines. If the decrease in acuity is caused by organic optic nerve disease, a marked decrease in vision occurs.

Researchers are always trying to find a more refined method of testing acuity than the Snellen system. Testing of visual performance by luminance differences has been a popular area of investigation. Waterman and his associates, however, found color was affected more than luminance defects. Luminance tests are more difficult to perform than the color plates, particularly in new patients unaccustomed to such subtle visual testing. I always use the HRR plates and find them more sensitive for optic nerve function.

Testing of Color Vision

Retinal disease, even of a significant degree, usually does not cause a severe loss of color vision as shown on the HRR plates. Most people with macular degeneration with a visual acuity of 20/200 can see most of the color plates. A slight decrease in acuity (even 20/30) owing to optic nerve disease causes a severe loss in recognizing the HRR plates. Thus, when a decrease in vision is minimal and when identification of a central scotoma with small white test objects is difficult, use of the HRR plates may point out the difference between retinal and optic nerve disease. This approach is valid also for patients who report having had a color defect all their lives. It is the comparison of one eye with the other that is important. Women, particularly, are sensitive to subtle differences in color appreciation, and they may complain that colors now seem faded to them or that they have trouble working out the color scheme of their wardrobe.

It is not unusual for the loss of color vision to be greater than the loss of acuity. A decrease in acuity or a subtle involvement of small-caliber myelinated fibers decreases cone function, causing color loss particularly in the red-green spectrum; however, some patients have loss in the yellow-blue spectrum. Since most optic nerve disease affects acuity, it seems reasonable to test for red-green defects initially. Plotting subtle central scotomas with a red test object can save time and be easier than using very small white test objects. Some patients may not notice an absolute color defect, but on comparing a red test object in one eye with one in the other, they may notice that one is bright and that the other is faded. A popular clinical method of testing this is to use the red top of a mydriatic bottle as the test object.

Patients with optic nerve disease frequently comment about dimness of vision, even when fully recovered to 20/20 Snellen figures. They say they see clearly with the affected eye, but objects are not as bright as with the other unaffected eye. Patients with subtle macular disease do not mention this phenomenon, only that their vision is blurred. Inquiry about this phenomenon of dimness of vision is not necessary with more severe optic nerve or macular disease. It is most valuable in directing our investigation to optic nerve dysfunction or macular dysfunction in very subtle disease.

Chronic progressive decrease of acuity associated with color changes may also be caused by brunescence cataract formation. (The changes in Gauguin's color style during his later years have been attributed to just such a cause.)
Afferent Pupillary Defect

The Marcus Gunn pupillary escape phenomenon, or afferent pupillary defect (APD), is a particularly valuable sign when only one optic nerve is involved. Occasionally, it is of value in bilateral, but extremely asymmetric, optic nerve involvement. The RAPD is primarily a sign of optic nerve disease. It can also be seen if there is severe unilateral retinal disease such as diabetic retinopathy. In disease of this degree, optic nerve involvement cannot be ruled out. However, the RAPD is not particularly useful in this setting. A casual look at the fundus reveals the obvious reason for the loss of vision. The RAPD is useful in patients with visual complaints and no physical findings. The combination of a very dense cataract and the use of a subdued light can produce an RAPD. This is an error in testing, and a bright light makes it disappear. The usual reason given for cataracts not producing an RAPD is that the scattering effect offsets the amount of light absorbed by the cataract. Sadun advances a different explanation. The gradual diminution of light by a progressively dense cataract allows time for a compensatory retinal response to occur. This results in no difference in the retinal response, which should normally produce an RAPD in this clinical setting. (Directions for eliciting this sign are given in Chapter 3.) A subtle method of eliciting the sign may become apparent during the initial testing of acuity. When the involved eye is covered for the acuity test, the size of the pupil should show no significant change. When the uninvolved eye is covered, both pupils dilate because of decreased conduction of the involved optic nerve in the exposed eye. Acuity is usually tested in dim illumination, which helps bring out the APD. Grading the RAPD response may be of value in following a patient if other signs of improvement are not forthcoming. Fineberg and Thompson used neutral density filters to evaluate the pupillary response. The density of the filters is progressively increased in front of the nonaffected eye until the swinging flashlight test is canceled out.

The degree of the direct pupillary response is usually not an accurate guide to visual acuity. Severe visual loss secondary to retinal disease does not substantially affect the pupillary response. This is also true of mild decreases in acuity owing to optic nerve disease; however, a marked difference in the direct pupillary response to light can usually be considered to result from a decrease in acuity. The exception to this rule occurs when the pupillary response itself has been altered, as in cases of tonic pupil, Argyll Robertson syndrome, trauma, or the use of topical drugs.

The Pflügref phenomenon is related to the APD. In a patient with normal conduction time in both eyes, an object swinging in a frontal plane before both eyes appears to move in a straight line. However, in a patient with decreased acuity in one eye from optic nerve disease, the optic nerve conduction defect makes the swinging object appear to move in an elliptical fashion. Patients who recover from optic nerve disease such as optic neuritis may notice this phenomenon as unusual movement of objects crossing their frontal plane. Another pupil test reported by Miller and Thompson is the pupil cycle time. A thin beam of light from the slit lamp is projected on the edge of the pupil. The cycling of the pupil response is compared between the normal and the abnormal eye. The difference is considerable.

Head Position

The position of the head is usually related more to ophthalmoplegia than to visual acuity. In congenital nystagmus, the visual acuity is at its best when patients are allowed to turn their heads so that their eyes are at the null point (point of least nystagmus). Frequently, patients are forced to read the acuity chart with their eyes straight ahead, which is not where the null point is usually located. The nystagmus is worse in the straight-ahead position, and acuity decreases markedly. As a rule, the null point is 10 to 15° lateral to the straight-ahead position.
Another feature of congenital nystagmus is brought out when one eye is covered, no matter whether the eyes are turned to the null point or not. When one eye is covered to check the acuity of each eye individually, an increase in the nystagmus drops the acuity even lower. In some instances at least, a slight blurring of one eye by a plus lens allows enough vision to suppress the latent nystagmus component, thus permitting the acuity to be measured in the other eye.

The position of the head may also be important if nystagmus is present in only one field of gaze. I have had several patients with vertical nystagmus only in down-gaze. Their complaints regarding problems in reading had previously been called presbyopia, and they had been given many different prescriptions to correct their apparent problem. They all said that the strength of the glasses was adequate but that they had to either depress their heads or raise their reading material to see. Obviously they had not been examined carefully with their eyes in down-gaze.

Photo Stress Testing

Visual function depends on the breakdown and regeneration of visual pigments at a steady rate, which ensures a smooth, continuous visual process. In retinal disease, this rate is disturbed. Bleaching the visual pigments with a steady bright light may further distort this process and prolong the recovery phase. This possibility can be demonstrated clinically by shining a bright light into the affected eye for a specified time (such as 2 minutes) and then determining the time it takes for acuity to return to the pretesting level. If a big difference exists between the pretesting and the posttesting recovery times of the two eyes, retinal disease, not optic nerve disease, is suggested. If the patient has only one eye, the response of the patient's eye can be compared with that of the physician's own eye tested similarly. Unless the physician and the patient are the same age, this technique is not as accurate, since the time of recovery varies for different ages; however, if the difference in recovery time between the patient's eye and the physician's eye is great, retinal disease is certainly suggested.

BRIGHTNESS TESTING

Snellen and visual field testing is sometimes not enough to evaluate a visual complaint. Patients may say that seeing is not the problem but the image is less bright or chiller in one eye. Sadun used polarizing lenses to quantify their responses. He placed polarizing lenses in a trial frame. Another set of polarizing lenses are placed on the rotating part of the trial frame. If both lenses are set at 0°, then they are parallel, and there is a maximum appreciation of light and brightness. If one lens is set at 90°, then only 1% of light is transmitted. These lenses are rotated in front of the nonaffected eye until the brightness is equal to that of the fellow eye. This comparison test is similar to the progressive neutral density filter response in evaluating the RAPD. This difference in brightness is not appreciated in patients with unilateral cataracts and, to a lesser degree, macular degeneration.

Prolonged retinal stimulation in patients with optic nerve disease shows fatigue-like effects. A conclusion that can be drawn from this response is that there are different response channels served by different cells or impulse patterns. Work done by King-Smith on the luminance channel and by Weber and Fechner on response and threshold, support the different response channel theory. Examination of human retina demonstrates three different types of axons, which travel to different parts of the lateral geniculate body. Different injuries or even degree of injury may affect these axons to a different extent and give a varied response. One of our group in the Neurology Department, Dr. Waxman, examined patients with demyelinating disease and demonstrated this different response time. He found a difference between low- and high-frequency impulses. The low-frequency impulses conduct, whereas the high-frequency impulses do not.
Testing of the Visual Fields

The patient frequently has a difficult time distinguishing blurring in a particular field from an overall blurring. The complaint often is that the patient does not see well—as if the central acuity were blurred. A hemianopic defect is suspected when a patient reading the Snellen chart consistently misses half of a line of letters.

In informal testing of the fields, use color comparisons between nasal and central fields in the same eye. Present two bright red objects (such as the caps of two mydriatic bottles) simultaneously to the nasal and temporal fields as the patient fixates centrally, and ask the patient to compare the colors. If a hemianopic defect is present, the patient reports that one cap has a faded or washed-out color and the other cap is bright red. If no hemianopic color difference exists, compare the color appreciation in one eye with that in the other eye. If one eye has an optic nerve defect, that eye will see the red object as faded and the other eye will see it as bright red. As a rule, moderate macular lesions do not distort color perception.

Testing with the Amsler Grid

The Amsler grid charts can be helpful in detecting subtle macular lesions in patients complaining of both blurred vision and distorted vision. Small changes in retinal topography, such as those caused by central serous retinopathy, can distort the perfect appearance of the grid to patients. The lines may appear to be distorted in the same way the symmetry of a chain link fence is altered by someone leaning against it. (Figs. 13.1 and 13.2).

![Vision Flowchart](image-url)

- **Figure 13.1.**
  Clinical approach to blurred vision, part 1.
**VISION**

- Refraction
  - Dilated Pin Hole
    - No Better
      - Normal Fundus
        - Normal Media
          - Normal Pupil
            - Normal Nerve
            - Do Malingering Tests
            - Functional Visual Loss
    - Fundus does not explain it
      - Fields Normal
        - ERG positive
          - ROD - Cone Disease
    - Decreased vision equal to both eyes
      - Media and fundus does not explain it
      - Cortical Blindness
      - Paracentral or Hemianoptic defect
      - Normal Vision, Complaint persists
        - Field Exam Positive
          - Complaint poorly expressed

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**HEREDITARY CAUSES**

Optic atrophy and blurred vision from hereditary causes are rare. Kjer groups them into Leber's disease, recessive congenital optic atrophy, and two forms of dominant optic atrophy—congenital and infantile.

**Leber's Optic Atrophy**

Leber's optic atrophy is the best known of the hereditary optic atrophies. It begins usually in a person in the teens or twenties, and it is predominantly a disease of males. It begins in one eye, frequently as a papillitis. Shortly after the first eye is involved, invariably the second eye becomes similarly involved. The atrophy of the disc appears weeks later.

In genetic classifications, the disease is usually described as sex linked, with recessive inheritance; however, pedigrees of Leber's optic atrophy do not strictly follow the Mendelian rules for this type of genetic transmission. Although the male is predominantly affected, he does not transmit the disease to his children. The woman who is heterozygous for the gene can transmit the disease to both her male and female offspring. Since the gene is recessive, 50% of her sons will have the clinical disease. All her daughters will be carriers, but only...
about 10% will have the clinical disease. Recent work suggests that true maternal inheritance is the most likely mode of inheritance of Leber's optic neuropathy, as 100% of male offspring of a heterozygous mother either have the disease or the ophthalmologic findings of peripapillary microangiopathy.

Mitochondria are the cellular driving force. They contain 90% of the total adenosine triphosphate needed by the cells. Mitochondrial DNA is inherited only from the mother. Dna molecules are in the cellular cytoplasm. The most common mitochondrial replacement mutation is at position 11778, which changes an arginine to a histidine. The next most common location is at position 3460. Other sites have also been identified. Not all individuals with these mutations develop optic neuropathy. One explanation is that different tissues may have different numbers of abnormal mitochondria. An additional explanation, particularly with the secondary mutations, is that they may require an outside environmental stimulus to activate the disease.

Leber’s original description of this disorder mentioned cardiac palpitations; however, cardiac abnormalities have been mentioned infrequently by other authors. Nikoskelainen and Savontaus reported cardiac abnormalities in 51% of females and only 5% of males; these abnormalities were usually the Wolff-Parkinson-White or the Lown-Ganong-Levine syndromes. Fortunately, most of the patients in this series were asymptomatic.

The patient typically has large central scotomas, which may enlarge to the point that they break out into the periphery and (most commonly) in the upper nasal quadrant. Some patients report improvement after the initial episode, but the improvement may represent an increased ability to use the remaining field rather than real improvement.

Smith, Hoyt, and Susac have reported that in the early phase of optic neuritis, there is circumpapillary telangiectatic microangiopathy. This is associated with swelling of the nerve fiber layer around the disc and an absence of staining on fluorescein angiography. Tortuosity of the peripheral retinal vessels was also noted.

Optic neuritis is the only constant symptom of Leber’s atrophy. Periodic headaches, ataxic paraplegia, spasticity, and various degrees of mental defects and seizures have been recorded. A review of the cases shows that a significant number of patients have had recurrent convulsions and cramping of the calf muscles.

In advanced cases of Leber’s optic neuritis, there is no visually evoked potential (VEP). In less severe cases, the VEP is reduced in size, delayed, and desynchronized. As the time increases from the initial clinical episode, the VEP in Leber’s optic neuritis progressively deteriorates, which is not the case in optic neuritis caused by demyelinating disease unless episodes are recurrent. VEP abnormalities have been seen in the fellow asymptomatic eyes of patients with Leber’s optic neuritis, just as they have been seen in the fellow asymptomatic eyes of patients with demyelinating disease. If the fellow eye is asymptomatic, greater abnormality is usually found in patients with demyelinating disease than in those with Leber’s optic neuritis. The VEP cannot differentiate Leber’s optic neuritis from demyelination caused by multiple sclerosis. The VEP only attests to a conduction defect in the optic nerve.

Recessive Congenital Optic Atrophy

As described by Waardenburg, recessive congenital optic atrophy begins with the onset of optic atrophy, either at birth or during the first few years of life. The patients have poor vision and severe defects in color vision. Since the poor vision develops before the patients are 4 years of age, nystagmus also develops. (This situation is not true in Leber’s optic atrophy, which begins later in life.) Bilateral poor vision developing before
Dominant Juvenile Optic Atrophy

Dominant juvenile optic atrophy comes on early in the first decade of life, but it is usually not severe and frequently is not discovered until the child goes to school. The decrease in acuity is frequently mild to moderate, with most children maintaining an acuity of 20/200 or better. A defect to blue is particularly evident. Nystagmus is rare and is probably related to an onset late in the first decade of life. Kjer's report mentions that 25% of sufferers had some abnormalities of mentation or personality but rarely other neurologic symptoms. The pallor of the disc is predominantly temporal, not circumferential.

Dominant Congenital Optic Atrophy

Dominant congenital optic atrophy exhibits nystagmus, which places the onset of the disease earlier than that of the juvenile form described above, perhaps before 4 years of age. Besides the decrease in visual acuity, constriction of the peripheral field varies from slight to severe, depending on the family pedigree.

Krabbe's Disease (Familial Infantile Diffuse Brain Sclerosis)

Optic atrophy and blindness are prominent features of Krabbe's disease. It results from an autosomal recessive inherited defect in sphingolipid metabolism. Children with Krabbe's disease are usually normal at birth but rapidly deteriorate, beginning to experience symptoms somewhere between 6 weeks and 6 months of age. They develop progressive rigidity, convulsions, deafness, and blindness, and death occurs usually by the age of 2 years.

Leigh's Disease (Subacute Necrotizing Encephalomyelopathy)

Patients with Leigh's disease develop blindness owing to optic atrophy. This is a progressive disease with a course ranging from weeks to years. The diagnosis is rarely made before death unless there is a family history, which is present in about one-half of the infantile cases. The juvenile and adult forms occur sporadically, and the diagnosis is not confirmed until autopsy. In addition to blindness, patients develop somnolence, deafness, and spasticity of the limbs. At autopsy, there are bilateral, focal, subacute, necrotic lesions from the thalamus to the pons. The course prior to death varies from weeks to months.

Optic Atrophy Associated with Hereditary Ataxias

Optic atrophy is also associated with certain forms of spinocerebellar atrophy that are more generally referred to as the hereditary ataxias.

Friedreich's disease exhibits ataxia, loss of tendon reflexes, and pes cavus. The patients do not have optic atrophy, but they do have nystagmus. The disease begins in persons between the ages of 6 and 15; clumsiness of the arms and legs is the earliest sign. The clumsiness progresses to incomplete incoordination until the patient is bedridden.

Optic atrophy is an early sign in the spastic types of hereditary cerebellar ataxia (such as Sanger-Brown's ataxia and Marie's ataxia). Since Sanger-Brown's ataxia comes on between the ages of 16 and 35, nystagmus does not accompany the development of optic atrophy. The symptoms are those of lack of coordination of the arms and hands, but the incoordination is caused by spasticity. This fact, a common, and types of optoforms are the in the optic ataxia from Francis. Demyelinating CAUSES

Optic Nerve

The retrobulbar common, and types of optic ataxia from Francis. Demyelinating ophthalmodynia usually the affecting the affected or sinus blurred vision occur of the pain. for several but steadily months. The or near-nonfirst cases are not often an obvious optic nerve ataxia. In the optic neuritis years past, cases of oph repeated sclerosis figure close even if the time, and repeated with optic ataxia, such as are extraocularly an af
DEMYELINATING DISEASE

CAUSES

Optic Neuritis

The retrobulbar form, which is the more common, and the papillitis form are the two types of optic neuritis. The causes of both forms are the same; it is the site of the lesion in the optic nerve that is different. The patient usually reports pain on movement of the affected eye, either immediately preceding or simultaneously with the onset of blurred vision. Then a precipitous drop in vision occurs, with a lessening or cessation of the pain. The vision stays at a low level for several days or weeks and then slowly but steadily improves over several weeks or months. The prognosis for return to normal or near-normal vision is excellent with the first attack. The prognosis in subsequent attacks is not as good.

Even when full recovery of vision occurs, an obvious temporal or even a generalized optic nerve atrophy is not unusual. This disparity between recovery of acuity and atrophy of the disc is particularly common in optic neuritis owing to multiple sclerosis. In years past, it was said that about 50% of cases of optic neuritis were caused by multiple sclerosis; more recent studies put the figure closer to 78%. Bilateral optic neuritis, even if the two episodes are separate in time, and recurrent optic neuritis are associated with a much higher incidence of multiple sclerosis. The usual field defect is a central scotoma; however, other field defects, such as arcuate scotomas and quadrantic defects, are seen. Some cases of optic neuritis even occur with normal visual acuity but an extrafoveal field defect. In such cases, usually an afferent pupillary defect and a color vision defect exist, as demonstrated by the HRR plates. On rare occasions, the lesion of optic neuritis is located in the nerve just as it enters the chiasm; therefore, it also affects the lower nasal fibers crossing over from the other optic nerve. The result is a junction scotoma, which is an ipsilateral central defect in the affected eye and an upper temporal field cut in the other eye. This type of defect more commonly occurs with chiasmal masses and must therefore be differentiated from optic neuritis.

Occasionally, patients complain of a fluctuation in vision when they take a hot bath or indulge in prolonged and strenuous exercise. The increase in body temperature that results from both types of activity causes a change in the conduction ability of nerves already compromised by the demyelinating process. Such a fluctuation in vision is called Uhthoff’s sign.

The usual report of the examination in retrobulbar neuritis is that the patient sees nothing and the physician sees nothing. At the onset of the disease, patients say they see nothing or what they see is blurred. In the retrobulbar form, no fundus or disc changes occur; therefore, the physician sees nothing abnormal. The atrophy comes on later; at this stage, the pupillary signs, the field defect, and the rapid visual loss suggest the diagnosis.

The patient who has a slow and steady visual loss should be regarded as possibly having a condition other than optic neuritis. A mass lesion should be seriously considered in any case of chronic progressive visual loss. In cases of papillitis, the disc is swollen, and hemorrhages may be present around the disc. Swelling of the disc in papillitis cannot be differentiated from papilledema owing to increased intracranial pressure solely from the appearance of the disc. The appearance of the disc in papillitis and papilledema is also similar with fluorescein staining, so fluorescein studies are not useful in differentiating the conditions.

Optic neuritis usually begins in young people, but rarely in those under 10 years of age. If a child has visual loss in one eye, be
suspicious of any report that the onset was sudden. Sudden recognition of a visual loss (e.g., in a school vision-screening test) does not always indicate a sudden onset. In a child under 10 years of age, the condition may be a slow-growing optic nerve glioma that is followed only weeks or months later by clinically obvious optic atrophy.

Evaluation of optic neuritis includes a carefully taken history—the signs and symptoms must fit the diagnosis. The history taking should also include questions about poor eating habits as possible causes of a nutritional amblyopia, particularly if the patient is a fast dieter.

Ask the patient particularly about possible exposure to toxins at work or at home (e.g., lead or mercury). Today, it is especially important to ask about the use of drugs, even the legitimate ones (e.g., ethchlorvynol, Placidyl, birth control pills, ethambutol, and isoniazid). Ask too about the use of tobacco and alcohol; they are more commonly associated with nutritional amblyopia than with true optic neuritis, but still they may contribute to optic neuritis.

Magnetic resonance imaging (MRI) and computed tomography (CT) should be done of the optic canal and sphenoid ridge, and bone changes suggesting tumor should be looked for. Ultrasonography and CT of the retro-orbital space are important in excluding an orbital mass lesion that may be affecting only the optic nerve and not causing ophthalmoplegia or exophthalmos. The two techniques can show the optic nerve to be swollen in optic neuritis, which helps somewhat to confirm the diagnosis. The enlarged optic nerve may also represent an intrinsic tumor such as glioma or meningioma.

The usual treatment of optic neuritis is either no treatment or removal of the offending agent (such as a drug or toxin). Steroid treatment is discussed below.

**Multiple Sclerosis**

Optic neuritis is frequently the presenting sign of multiple sclerosis (MS), particularly in young patients. In a large series of patients in England, McDonald found optic neuritis as a presenting sign in 25% of MS patients. Lessell predicted that 74% of females and 34% of males with optic neuritis would eventually become affected with MS. Some investigators believe that a patient who presents with optic neuritis is likely to have a mild form of MS. This impression is difficult to substantiate statistically from the longer longitudinal studies that are now in the literature. Bilateral optic neuritis in the adult has a worse prognosis for the development of MS than does either the unilateral or recurrent form. This is not true in children, in whom the incidence of MS following optic neuritis is not related to the optic neuritis. Children also have a better prognosis for recovery from optic neuritis than do adults.

A central scotoma is the commonest presenting defect in optic neuritis. It is not unusual with minimal decreases in vision to be unable to plot a central scotoma. Gunn, in 1897, first noted that the densest part of the central scotoma is surrounded by an area of a color deficit. I have observed over years of experience that using a red test object rather than a very small white test object or subtle computerized test object allows identification of the scotoma more easily. Kollmer was the first to suggest that red was the preferential color deficit. Muller's studies seemed to indicate that blue-yellow colors are equally effective. I have performed central scotoma measurements with blue and with red test objects, and the latter are much easier. The defect to blue is frequently difficult to distinguish. The patients frequently can't tell blue from lack of blue or call it "dark," which is impossible to distinguish from a color defect. If red is not a more definitive test, at least it is easier and more accurate for the patient to perform.

Many MS patients who present with another symptom eventually develop optic neuritis. In some studies, between 27 and 37% of such patients have developed optic neuritis. Obviously, the length of follow-up influences this percentage. Hutchinson in Ireland, in a 15-year study, found that 78%
of his MS patients exhibited optic nerve involvement at some time in the course of the disease. McDonald also found that optic neuritis occurred in a large proportion (73%) of all MS patients. Similar long-term studies in the United States, however, have reported much lower percentages. Physicians dealing with patients presenting with optic neuritis would like to be able to predict their chances not only of contracting clinically symptomatic MS but also of contracting any significant disability. Many patients with optic neuritis are asymptomatic for the clinical disease of MS but do have other abnormalities, such as abnormal evoked potentials or silent plaques in the brain on MRI, particularly in the periventricular area (Fig. 13.3). Peripherebitis has been previously described as an associated clinical sign of MS. It is extremely rare in my experience. Graham found ocular inflammation in the form of venous sheathing in 18% of 50 cases. Autopsy of 93 eyes with known MS found periphlebitis in only 8.5%. What would be most helpful to optic neuritis patients for projecting their future, particularly if they are young and planning families, is some assessment of the potential degree of their functional disability 10, 20, or 30 years in the future. Available studies of the degree of future disability in patients presenting with optic neuritis and developing MS do not extend far enough to compare their disability with that of MS patients who present with other signs.

The optic neuritis treatment trial group has tried to determine whether steroids are beneficial in this disease. Their initial conclusion and recommendation was that intravenous methylprednisolone was better than oral steroids or a placebo. They did comment that the final visual result was minimally different at 6 months, and no difference was noted at 1 year. After 1 year in the trial, 20/40 vision or better was obtained in 95% of the placebo group, 94% of the intravenous group, and 91% of the oral steroid group. They felt, however, that intravenous steroids did shorten the course of the disease. The choice of using or not using steroids was governed by the depth of the visual loss and the degree of worsening vision. They also commented on the number of cases developing MS at 2 years. MS occurred in 16.7% of the placebo group and 14.7% of the oral group, but in only 7.5% of the intravenous group. The inference is that oral steroids alone are not as efficacious as

![Figure 13.3.](image_url)

A. CT image of the brain of a patient with multiple sclerosis shows no lesions. B. MR image of the same patient reveals multiple lesions, especially in periventricular area.
intravenous steroids. It is hard to understand why such a short course of immunosuppressive therapy should give that difference far out as 2 years. Although the statistics are interesting, they don’t go out far enough for a valid conclusion. Rizzo and Lessell’s study at 15 years revealed an incidence of MS of 34% in men and 74% in women. However, after 5 years later, it rose to 44.8% in men and to 91.3% in women after one mononeuropathy of optic neuritis. The optic neuritis treatment study group reviewed their statistics at 4 years and found that the incidence of MS in the intravenous group was 24.7%, in the placebo group, 26.9%, and in the oral group, 29.8%. The difference is narrowing. Some studies, such as the one by Herishanu, suggest that intravenous steroids increase the chances of MS. The definitive study on this subject is obviously not yet available.

One of the study group’s initial conclusions was that there was no testing required as part of the initial event of optic neuritis. It is a clinical diagnosis. A later review has modified their report. If MRI is performed initially and periventricular lesions are found, their number and size may be of significant predictable value for the onset of clinical MS. If the lesions are less than 3 mm and not periventricular, the incidence for developing MS is only 9.3%. If the lesions are 3 mm or larger and there are more than three, the incidence increases to 43.1%. Their interesting findings bear directly on the workup of optic neuritis and its resultant costs. So far their numbers are too small and the time span too short for a definitive conclusion. However, several of the studies on the significance of MRI findings agree with theirs.

The identification of monoclonal cells in the cerebral spinal fluid has led to the increasing realization that MS has an immunopathologic mechanism. This has led to the suggestion that other immunosuppressive therapies should be used. No definite conclusion has been forthcoming on this form of therapy either.

The correlation between silent MRI lesions and cognitive deficits due to MS has been examined by RAO and Associates. This is additional evidence that confirms the meaning of the silent lesions on MRI. Studies comparing VEPs and MRI seem to prefer the VEP as more sensitive.

In one large study, Weinshenker et al. tried to evaluate disability in all of their MS patients, no matter what clinical signs they presented with. About 17% of all patients presented with optic neuritis. The lower the age at presentation, the higher the percentage of those presenting with optic neuritis. In this study of 1099 patients from Ontario, Canada, the researchers tried to evaluate the overall disability of patients over a prolonged period of time; the median follow-up period was 14 years. This study was conducted at an MS referral center that had all the neurologists in the province either on its staff or associated with it. The researchers were thus able to obtain nearly complete referral of all MS patients in the area. In contrast, many series have been conducted at MS centers to which only the severe cases get referred; this referral pattern may bias the results, shifting the incidence and degree of disability to higher values than they might be with a more representative sample of MS patients.

In their study, Weinshenker et al. used the disability scale status (DSS) to assess their patients. A DSS rating of 0 corresponds to a state in which the patient can still walk but only with an aid; although somewhat impaired, these patients can move around without another person’s help. A DSS rating of 8 corresponds to a bedridden status with retention of the use of arms. The median time of onset to progression was 5.8 years in this group of patients. Of those patients who progressed, 33% reached the DSS 6 level within 10 years; one-half of those reaching this level did so within 5 years. At 30 years of age, 33% of the patients who followed had reached DSS 6, and 54% were rated DSS 8.

Although these studies all differ in one respect or another and are difficult to compare, one fact seems obvious. If patients with optic neuritis are followed long enough, many more of them will develop other signs of MS.
than we had previously thought. The degree of incapacity that is reached 10 to 20 years after onset of optic neuritis is still an unknown quantity. The hypothesis mentioned above, that patients who present with optic neuritis may manifest a milder form of MS than those who present with some other sign has not been systematically investigated, and more longitudinal studies designed to test this concept are needed.

Most patients with optic neuritis can get used to blurred vision in one eye or even some difficulty with their gait as long as they can remain useful, independent persons. I do not routinely tell such patients (unless they ask me) that they may develop MS. It is difficult to tell young patients, particularly those who recover their vision, that they may have a significant disease later on that may affect their entire lives. I would not like to alter a patient’s entire life with statistics that may not apply to him or her or that might alter a very productive life. I believe this approach is particularly appropriate with such patients because at this time, we cannot alter the onset of MS or its final course. The use of different immunosuppressive agents in the treatment of MS is constantly under investigation, but their efficacy is not proven. Their ability to change the ultimate course of the disease is even more in question.

As mentioned above in this chapter, color testing is important in evaluating optic nerve function. Even with visual acuity of 20/40 or better, defects can still be found using the Parnsworth-Munsell 100 HUE test. It is also important, with a history of optic neuritis, to look at these patients in red-free light for the optic nerve dropout that one sees.

In cases of MS, Charcot’s triad of nystagmus, intension tremor, and scanning speech is rarely seen at the onset of optic neuritis. The diagnosis of MS is usually made after both white and gray matter have multiple lesions that are separated in time and location and that are characterized by remissions and exacerbations.

The nystagmus in Charcot’s triad is usually nonspecific, and it can take any form, including horizontal, vertical, or ocular dysmetria. The nystagmus of internuclear ophthalmoplegia is more specific. The nystagmus occurs in the abducted eye when the eyes are directed into horizontal gaze. When the internuclear ophthalmoplegia is bilateral, the nystagmus occurs in the abducted eye in both directions, and the diagnosis of MS is almost certain. In about 10% of cases of optic neuritis owing to MS, sheathing of the peripheral veins occurs. The sheathing probably represents some degree of periphlebitis, but it is usually so mild that the patient does not have symptoms.

Internuclear ophthalmoplegia, cerebellar ataxia, intention tremor, urinary sphincter problems, sensory changes, motor disturbances, and emotional aberrations are all part of the symptom complex that suggests MS. Electric shock-like waves moving down the spinal cord, particularly with neck flexion (Hermite’s sign), suggest MS, but they can also be seen with spinal cord tumors (Fig. 13.4, A-B).

The diagnosis of MS is usually made on the basis of the occurrence of remissions and exacerbations and the presence of widely separated lesions in the central nervous system (CNS). Occasionally, laboratory studies can help in making the diagnosis. In 50% of cases, there is a slight increase in the spinal fluid cell count (the count should not exceed 50 cells/mm³).

Oligoclonal bands may not be present during quiescent periods of demyelinating disease, since they represent activity. Because the onset of optic neuritis is evidence of activity, we would expect oligoclonal bands also to be present, but in fact they cannot always be demonstrated. Newer laboratory techniques have decreased the negative responses in clinically evident cases of MS to about 10%. I know of no study that correlates optic neuritis with oligoclonal bands and predicts with longitudinal findings who will and will not get MS.

T-lymphocyte subpopulations have also been studied in acute optic neuritis as a possible diagnostic test to confirm MS as the probable cause. In MS patients, the
Figure 13.4.
Bilateral internuclear ophthalmoplegia. A. Poor adduction of right eye in left gaze. B. Poor adduction of left eye in right gaze. C. Straight in the primary position. D. Discrete lesion in the MLF on MRI.
- Figure 13.4. (continued)

C, D. Discrete lesion in the MLF on MRI. E. Anatomy of internuclear ophthalmoplegia. (Courtesy of Dr. Caleb Gonzalez.)
appearance of new lesions on MRI has been associated with reduced suppressive cell activity. Investigation of this phenomenon in patients with acute optic neuritis has been disappointing so far.

Trying to predict which patients with unilateral optic neuritis will develop MS is impossible at this state of our knowledge. Examining the spinal fluid of these patients for pleocytosis, IgG, or oligoclonal band distribution is a poor prognosticator for the development of MS.

Immersing a patient suspected of having MS in a hot bath is a test that has been used for many decades. Worsening of the patient's symptoms and signs or the development of new symptoms or signs is positive evidence that a conduction defect exists in the affected nerves. Rasminsky demonstrated that increases in temperature of as little as 0.5°C could induce symptoms. This worsening of nerve function is probably related to a change in sodium and potassium flux in and around the myelin sheath. This test should not be undertaken lightly because permanent defects have been reported. Since the hot-bath test is clumsy and may be detrimental, an alternative approach may be preferable. By appropriate questioning, you may discover that patients do not take hot baths because they feel very weak or their vision dims if they do. Similarly, patients may report that they do not play tennis or jog for the same reasons. Any activity that heats up the core body temperature can cause a worsening of whatever part of the nervous system is affected. This phenomenon is called Uhthoff's sign. The part of the nervous system that is affected may, under normal circumstances, produce no or subclinical symptoms until challenged. Patients usually do not relate such symptoms to their present problem and may not volunteer the information unless properly asked about it.

In looking for widely separated signs in the CNS, the VEP has been a useful tool. The VEP may demonstrate a conduction defect in one optic nerve, suggesting its involvement when the patient has no present symptoms or past history of that nerve being involved. This would then fix the criteria for separation in time and space in a person who will have unexplained paresthesias. In the interpretation of the VEP, not only the absolute latency but also the intraocular differences in latency and the waveform are all diagnostic. In recent years, a constant, reversing checkerboard pattern has produced a more consistent response than the old flash technique. Demyelinating disease is not the only disease that can produce these abnormal changes in the VEP. Similar abnormalities can be seen in glaucoma or in the sector optic atrophy of ischemic optic neuritis. Both of these latter diseases may spare fixation, suggesting that these VEP changes are not specific for the papillo-macular bundle but reflect only axonal damage. It is, therefore, not a specific test for MS. However, as an adjunct test in establishing the diagnosis of MS, Halliday, McDonald, and Mustin found conduction delays in one or both optic nerves in many patients who had no history of optic nerve involvement in the disease process.

The latency of the human occipital potential induced by a light flash depends on the intensity of the light stimulus. The dimmer the flash of light, the longer the latency. The same difference occurs with equal light flashes to both eyes, but with slower conduction of information to the occipital pole in the damaged nerve. The Pufriich effect occurs when the CNS cannot correct for the temporal discrepancy in the arrival of information from the two eyes. This lack of CNS correction for temporal discrepancy of sensory stimuli has also been shown clinically by Halliday and McDonald. They conducted experiments in which the toe and index finger of a patient were simultaneously stimulated. Because the finger was closer to the brain than was the toe, the patient perceived that the finger was stimulated first. If the brain corrected for any visual time lag, stereopsis could not occur.

A test for evaluating the conduction velocity of one optic nerve versus the other employs the Pufriich phenomenon. If an ob-
but moves from a normal patient’s right field to the left and back again in a straight line. It will be perceived as moving in a straight line. If one eye has a conduction time delay owing to an optic nerve disease such as optic neuritis, the retinal images of the involved eye will arrive later at the visual cortex than those of the normal eye. The object, therefore, will be perceived as moving in an elliptical fashion rather than in a straight line. This is an example of the temporal discrepancy mentioned before. The background objects may influence the response to this test, and it is best done against a blank background. The experiment should not be performed with a luminous object in a dark room as a technique to decrease visual clues. It should be done in a lighted room so that the retina can be light adapted.

The Pulfrich phenomenon is not meant to replace the VEP, but rather to be another tool for the clinician trying to evaluate subtle decreases in vision. It can help in differentiating subtle macular disease from optic nerve disease, since macular disease does not cause a time delay to the visual cortex. Even patients who apparently have recovered fully from an episode of optic neuritis and who have 20/20 vision, a full visual field, and apparently normal color vision with the pseudo-isochromatic plates, may still complain about their vision. Frequently, they will say that the vision in the affected eye is dull or different. If there is still a conduction defect in that nerve, they may have symptoms as a variation of the Pulfrich phenomenon. Frisen, Hoyt, Bird, and Weale reported patients who had difficulties knowing at what station on the subway to get off because of the induced Pulfrich phenomenon caused by the moving train.

Hoyt, and Van Dellen and Greve believe that the earliest defects in MS are isolated defects in the Bjerrum area, but off center between 15 and 25°. These defects were found in visually asymptomatic patients; however, a central scotoma is the most common field defect in those patients with visual complaints and MS. Hoyt found narrow arcuate defects in the Bjerrum area and correlated them with nerve fiber bundle defects found by the red-free light technique. Patterson and Heron reported a similar experience in patients with MS and no visual symptoms or history of visual system disease.

Vitreous fluorophotometry is one of the new tests for evaluating retrobulbar neuritis. The increased concentration of fluorescein in the posterior vitreous compartment is not specific for retrobulbar neuritis caused by MS. It indicates a disturbance in the vascular-vitreous barrier, which is altered in optic neuritis from any cause. Since most cases of retrobulbar optic neuritis have normal-appearing nerve heads initially, this test may be of help in cases in which the diagnosis is in doubt.

**Neuromyelitis Optica**

Neuromyelitis optica is extremely rare today. The sufferer develops bilateral optic neuritis (but both optic nerves are usually not affected simultaneously), which is followed some weeks later by a transverse myelitis at any level of the spinal cord. The transverse myelitis can come first, but it rarely does so. The optic neuritis usually disappears but generally not as fully as in the cases of optic neuritis discussed above. The disc may appear normal, or more typically, a low-grade edema of the nerve head exists. Nystagmus, which is so prominent in MS, is rare in neuromyelitis optica. Usually, some residual paralysis results from the transverse myelitis, but a significant degree of recovery is the rule.

The cause and treatment of neuromyelitis are not known, and its relationship to MS is questionable at best. Despite some of the obvious similarities (noted above), marked differences exist between this disease and MS. Bilateral optic neuritis is rare in MS but the rule in neuromyelitis optica. Significant differences also occur in the pathologic findings.
Schilder's Disease
(Encephalitis Periaxialis Diffusa)

Schilder's disease, although rare, should be considered because of its relationship to vision. Its onset is late in the first decade of life. It is one of the few causes of acquired cortical blindness in children of this age group. Apparent blindness, along with personality changes (unusual crying, irritability, apathy) in a previously healthy child, suggest this disease. Visual problems are not always an early sign, which adds to the difficulty of making the diagnosis. As the disease spreads anteriorly into the internal capsule, spastic paralysis develops. When the frontal lobes become enlarged, intellect and personality further deteriorate.

The fundus may be normal, or it may show papilledema (in about 20% of cases) owing to slightly increased intracranial pressure.

The cause and treatment are unknown, and death usually occurs within a year. Some cases may have a hereditary component, and this possibility should be particularly evaluated in every instance.

ISCHEMIC CAUSES

Nonarteritic Ischemic Optic Neuritis (AION)

AION is a major cause of loss of vision in persons over 45 years of age. Typically, the patient is younger than one with temporal arteritis. The loss may first be related to a central scotoma, but altitudinal defects are more common. The optic disc usually shows a low-grade pale edema with a few splinter hemorrhages. No filling of disc vessels occurs as in papilledema owing to increased intracranial pressure. More than 50% of patients have other vascular disease, such as hypertension.

The initial episode of AION is usually acute. If it stabilizes, it only rarely recurs in the affected eye. Although recurrence in the same eye was once thought to never occur, several authors have now reported a few such cases. About 75% of patients with only a central scotoma show some improvement. Those with altitudinal field losses usually show improvement and atrophy follows (Pl. 13.1.4). Unlike the cases of optic neuritis that demonstrate a profound loss of color vision relative to a small loss of acuity, nonarteritic AION color loss is proportional to the loss of vision. Involvement of the second eye within 2 years ranges from 25 to 65% in different series. When the second eye is involved, the patient has optic atrophy with visual loss in the previously affected eye and pale edema in the acutely affected eye. This condition can be mistaken for the Foster Kennedy syndrome, which generally is considered to be caused by a frontal lobe tumor and which, as described, is rare. Hayreh stated that the basic problem lies in the posterior ciliary arteries located in the disc and the retrolaminar area. In about 30% of cases, patchy atrophied areas appear in the more peripheral parts of the choroid. The atrophy is caused by involvement of other posterior ciliary arteries (Fig. 13.5, A–D). The nerve edema is thought to be due to infarction from involvement of the posterior ciliary arteries. Hayreh has demonstrated in monkeys that occluding the posterior ciliary arteries affects the retrolaminar and laminar portions of the optic nerve. This produces an infarction of those areas with a reduction in axoplasmic flow and disc edema. Postmortem studies of the optic nerve by Ellenberger and Netsky demonstrated minimal layer thickening of the posterior ciliary arteries. They concluded that these arteries can be obstructed by the same atherosclerotic process that affects other arteries.

Heyt first described the characteristics of discs that are predisposed to ischemic optic neuropathy. He referred to these discs as a disc at risk. The features of such a disc are abnormal branching of the central vessels, full nerve fiber bundles obscuring the disc margin, and a small nerve head with no physiologic cup. This is the type of disc that is seen
- **Figure A**
  Akutal disc atrophy after resolution of ischemic optic neuropathy.

- **Figure B**
  An eye with sarcoidosis involving the disc.

- **Figure C**
  The same eye as in Figure B after resolution of the sarcoidosis. Note change in the appearance of the disc.

- **Figure D**
  Lymphoma: Involvement of the optic nerve with compromise of the disc circulation and severe loss of vision.

- **Figure E**
  Optic disc shunt vessels secondary to optic nerve meningioma.
*Figure 13.5.*
Case of AION with secondary cavernous atrophy in right eye. A. Right eye. B. Left eye.
Figure 13.5. (continued)
C. Similar cupping due to pituitary adenoma. C. Right eye. D. Left eye.
in AION, AION of the young, Leber's optic neuropathy, and the papillopathy of juvenile diabetes. Burde described the AION of the young, and it is unlike the nonarteritic AION of those seen later in life. The cases of the young occur in episodes and eventually lead to atrophy and blindness. This is different in the older age group, who have one episode and frequently preserve fair vision. Burde feels that in the young, a hypercoagulable state contributes to impairment of disc microcirculation.

The sedimentation rate (unlike that in temporal arteritis) is normal. According to Hayreh, fluorescein angiography may be of some help in diagnosis, although early in the course of the disease, no optic disc fluorescence is present. About a week after the onset of the first episode, some fluorescein staining of the disc appears, but only late in the fluorescein sequence. Choroidal filling is delayed, particularly in the peripapillary area.

Differential Diagnosis of Nonarteritic AION

Systemic lupus erythematosus (SLE) can cause decreased vision. Retinopathy is more common than optic nerve involvement, but the latter occasionally is the presenting feature of this disease. When the optic nerve is involved early in SLE, optic neuritis from demyelinating disease is the major differential diagnosis. The usual form of AION is different. The age group affected by AION and temporal arteritis is much older as a rule than that affected by SLE. AION usually produces altitudinal defects and spares central vision proportionally to the rest of the visual field; this is not true in SLE or temporal arteritis.

Clinical reports are not encouraging for a return of vision in SLE, even with the use of steroids. Although cupping of the optic disc is usually associated with glaucoma, it is also seen in AION, particularly in the arteritic variety. The most consistent disc feature for separating the two forms of excavation is pallor of the temporal rim in the ischemic cases. Other signs such as bearing of circumlinear vessels and backward bowing of the lamina cribrosa are reported in both forms of disc cupping. They are not reliable signs for differential diagnosis. An aberrent pupillary defect is more common in ischemic cases but can be seen in asymmetric glaucoma. Not only do glaucoma and ischemic disease cause cupping, but it has also been reported in cases of anterior visual pathway compression by mass lesions. In a series of 250 patients with compression of the anterior visual pathway reported by Kuppersmith and Krohn, 16 had cavernous atrophy. These cases included chiasmal glioma, meningioma, aneurysms, and pituitary adenoma.

In comparison to the standard differentiation of the arteritic and the nonarteritic variety of AION, posterior ischemic optic neuropathy (PION) is not as easily identified. Cases of PION do not show the papillitis type of presentation. The diagnosis of PION includes not only the usual differential diagnosis of AION but also embolic disease with obstruction of the ophthalmic artery and silent carotic occlusive disease. Research by Hayreh has shown that the lamina and prelamina areas of the optic nerve head are supplied by the posterior ciliary arteries. When there is a drop in perfusion pressure, these arteries are particularly vulnerable and affect nerve head tissue both functionally and physically with ischemic papillitis. These same findings of AION with papillitis have also been reported in cases of cardiopulmonary bypass surgery, cardiac arrest, and acute severe blood loss.

Ischemic optic neuritis has also been seen in several forms of sickle cell disease including sickle cell anemia and trait, hemoglobin C, and thalassemia disease. Although AION due to sickle cell disease is extremely rare in my experience, involvement may be more common than we clinically suspect. This type of optic nerve involvement and sub cortical infarctions have been shown to occur more frequently than clinically suspected. The diagnostic features of sickle cell disease are usually enough to firmly establish the diagnosis.

Most likely of such diabetes or were blood.

The use of such as VE of AION from specificity.
Identify the region of normal and normal WP is not highly sensitive in central retinal venous occlusion. A test visual acuity and central retinal hemody.

Clinical test venous occlusion help the clinician focus on other cerebral blood flow.

AION also years of age and as long as patients report have vaso hypertensive vascular disease.

Not unlike the age group: loss of visual field and relaxed field loss. I involvement years. The young age occurred in it whereas in
lish the diagnosis. AION can occur in the normal course of sickle cell disease but is most likely to occur with precipitating features such as arteriosclerosis, acidosis from diabetes or infection, cardiac failure, or severe blood loss.

The use of newer diagnostic techniques, such as VEPs, in the differential diagnosis of AION from any cause has not added much specificity to the diagnosis. Most studies identify a reduction in amplitude but retention of normal latencies. Although a variety of abnormalities have been reported, the VEP is not disease specific.

Venous stasis retinopathy, another form of ischemic disease, can be misdiagnosed as central vein occlusion or even as diabetic retinopathy. This retinopathy is secondary to internal carotid occlusive disease. The fundus appears with retinal hemorrhages, microaneurysms, capillary dilatation, and enlarged, irregular veins. In these cases, however, the ophthalmodynamometry is very much different on the side of the retinopathy and suggests carotid disease rather than central retinal vein obstructive disease. Ophthalmodynamometry is therefore an essential clinical test in the workup of central retinal vein occlusion. It is not perfect, but it will help the clinician do the appropriate workup for carotid disease and lead to the corrective therapy to protect the eye and the cerebral hemisphere.

AION also occurs in those younger than 40 years of age. For example, the younger patients reported by Dutton and Burde did not have vascular disease (e.g., arteriosclerosis, hypertension, diabetes, or systemic collagen vascular disease), and their presentation was not unlike the AION of the nonarteritic older age group: that is, they presented with rapid loss of vision over hours to days and pale edema of the optic nerve head and altitudinal field loss. These younger patients also had involvement of the second eye over several years. The main difference was that in this young age group, the disease commonly recurred in the same area with further damage, whereas in AION of the elderly, recurrence has been reported in the same eye very rarely. The recurrent swelling in the young age group, as expected, is confined to the nonarteritic areas. Steroids in the usual oral dosage did not appear to change the course of the disease.

Other causes of nerve head ischemia include migraine, severe anemia or blood loss, trauma, severe preeclampsia, chronic papilledema, postoperative severe increased intraocular pressure, and collagen vascular disease.

Cupping of the disc (particularly, asymmetry) is highly suggestive of glaucoma and is far and away the most common cause. However, cupping can occur in the arteritic form of AION. Another difference is equally important in distinguishing glaucomatous from nonglaucomatous cupping. In the cupping due to glaucoma there is loss of the neuroretinal rim. The nonglaucomatous variety reveals a rim that is pale and atrophic. Cupping has also been reported by Kupersmith in compressive lesions of the anterior visual pathway. Most of his cases could be identified by loss of vision out of proportion to the cupping. These patients also had field defects such as bitemporal hemianopia, which is inappropriate for a glaucomatous field loss.

A second form of optic neuritis seen in the young patient is the autoimmune variety summarized by Kupersmith and coworkers. Visual loss is rarely the presenting sign but does occur and should be considered an occult collagen vascular disease in which the patient is otherwise asymptomatic. Although the commonest cause of optic neuritis in young patients is MS, the prognosis and treatment is quite different for these two etiologic types of optic neuritis. Collagen vascular disease frequently affects the retina more than the optic nerve. Optic neuritis has been reported to occur in collagen vascular disease and can occur as a presenting sign before other signs of the disease appear. A battery of tests for collagen vascular disease should be performed; the ANA seems to be the most likely to turn positive according to Kupersmith. However, he found no
definite ANA pattern in his group of patients. The ANA elevation can occur in MS patients but is much lower than that found in patients with acute immunologic optic neuritis, which can be picked up with routine ANA screening techniques. Other tests helpful in the diagnosis of autoimmune optic neuritis include the anti-DSDNA, anti-RNA, and anticardiolipin angi-o-antibody.

The patients reported by Kupersmith did not respond favorably to the usual dose of steroids but did to a megadose, with retention of vision in many cases and improvement in others. This group appears to differ from the patients reported by Dutton and Burde, who did not respond to the usual oral dosage steroid and had no laboratory findings of collagen vascular disease. The steroid factor may be misleading, since megadose steroids were not used in Dutton and Burde’s cases. In demyelinating cases, optic neuritis usually improves without therapy.

**Temporal Arteritis**
(Arteritic ION)

Hutchinson first described the disease now called temporal arteritis in the modern literature in 1889. He referred to it as a peculiar form of thrombotic arteritis caused by the agent that sometimes produced gangrene. The same condition had been reported much earlier by the 10th-century oculist Ali Ibn Isa (940–1008 AD). He noted that cautery of arteries treats not only migraine headache but also active sharp catarhal affections including those showing heat in, inflammation of, the temporal muscles, which may terminate in loss of eyesight.

Temporal arthritis presents as a sudden unilateral loss of vision. Most patients, if they review their history, can tell of other signs and symptoms of temporal arthritis that they had either ignored or misinterpreted. Sometimes, however, the patient has no premonitory symptoms.

Classic temporal arthritis develops as a headache with temporal scalp tenderness. This tenderness is sometimes so pronounced that patients cannot comb their hair or put on a hat. Erythema and swelling may appear in the area of the temporal arteries. If erythema and swelling are not present, the temporal arteries feel like pipettes, and they are not compressible. Other symptoms, such as stiffness (usually starting in the neck and the shoulder girdle), polymyalgia, jaw pain, weight loss, low-grade fever, anemia, and an elevated sedimentation rate are also found. The disease affects persons 55 years of age or older; most patients are in their 70s and 80s—about 10 years older than persons with anterior ischemic neuritis.

Persons with central visual loss owing to temporal arteritis do not recover their vision, whereas most people with AION recover some of their vision. In untreated temporal arteritis, the second eye is frequently involved. Involvement of the second eye can occur at any time, but rarely after 8 weeks. The optic disc does not show the edema seen in nonarteritic AION. Despite the severe loss of central vision, the fundus picture of occlusion of the central retinal artery is not present.

The diagnosis of temporal arteritis should be suggested by the history and the elevated sedimentation rate. A temporal artery biopsy is indicated to establish the diagnosis. Steroid therapy should be started as soon as the sedimentation rate is reported to be elevated. It is unwise to wait for confirmation by biopsy, because the other eye may become involved during the delay. Moreover, even if steroid therapy has been started, the biopsy can be done within the next 48 hours without its validity being affected by the steroid therapy.

**Carotid Cavernous Sinus Fistula**

Carotid cavernous sinus fistulas are uncommon medical occurrence. If they are low grade, they frequently are missed or treated as chronic conjunctivitis because of a persistent red conjunctiva without chemo- thalytic, the intervening not clear.

There is a list of the direct-fl carotid arteri- nihabit high and type in arteries into minimal sig- threness, threaten- causes ischa- form of glau- lem, previc to preserve vation and, neurologic Newer tech- ed tender obstr. fewer neu-}

**Transient Attacks**

The fear that has been with the patient since apoplexy—the consensus by vascular neither pre was the first relationship to the next. The were pres. heart disease. Intensive 1960s into
persistent red eye. The red eye in these patients shows dilated vessels with clear conjunctiva between the vessels, with or without chemosis. In true infectious conjunctivitis, the vessels are prominent but the intervening conjunctiva is pink or red and not clear.

There are basically two major types of carotid cavernous sinus fistula. The first is the direct-flow type from the intercavernous carotid artery into the cavernous sinus; it exhibits high flow and marked signs. The second type involves a flow from smaller dural arteries into the cavernous sinus; it exhibits minimal signs. Neither type is usually life threatening, but the high-flow type may threaten vision. Prolonged ocular profusion by poorly oxygenated arterial-venous blood causes ischemic optic neuritis or an ischemic form of glaucoma. In addition to these problems, previous modes of treatment designed to preserve the vision tend to worsen the situation and, not infrequently, add significant neurologic defects to the patient’s problem. Newer techniques that are radiologically oriented tend to be safer and to cause less arterial obstruction; these techniques have fewer neurologic and visual sequelae than previous treatments.

**Transient Ischemic Attacks (Adults)**

The fear of finality or helplessness associated with the word stroke has been prevalent since the Greeks coined the word apoplexia—to strike down. For many years, the consensus was that strokes were caused by vascular accidents to the brain that were neither preventable nor treatable. Gowers was the first to bring to our attention the relationship between retinal emboli and hemiplegia. The emboli that he saw and reported were presumably caused by the patient’s heart disease, not concomitant carotid artery disease.

Intensive research beginning in the mid-1960s into the cause of stroke and its prevention has revealed that lesions of the intracranial arteries may cause strokes and may be treated surgically. Frequently, the stroke itself may be preceded by focal attacks of cerebral or retinal ischemia that we arbitrarily refer to as transient ischemic attacks (TIAs) if they last less than 24 hours and leave no residual neurologic deficit. Many investigators have used the eye as a monitor of carotid blood flow when these lesions are below the branching off of the ophthalmic artery as it comes off the internal carotid artery. The significance and prognostic value of different types of TIAs are not as clear-cut as we would like in terms of who is more likely to develop a stroke or, specifically, where or what the lesion is. We rely, therefore, on techniques such as ophthalmodynamometry, carotid ultrasound, and, finally, arteriography.

Arteriography helps to identify the surgical candidates. Even certain types of intracranial ischemic symptoms, particularly along the distribution of the middle cerebral artery, have been treated surgically by the superficial temporal artery-anastomosis technique described by Yasargil and his coworkers.

Some studies have tried to review the patients suspected of having TIAs and, based on the types and frequency of the episodes, to develop guidelines for predicting strokes. A second TIA increases the likelihood of a stroke 17-fold in the year after the first TIA. The TIA signals the risk of a stroke occurring within 5 years. The risk overall is 40%; half of these strokes will occur in the first month after the initial TIA. The most vulnerable period is the first 18 months after the initial TIA. Angiographic data indicate that 75% of patients with ischemic strokes have at least one responsible lesion, and in 40% of cases, the lesions are limited to the extracranial vasculature. These are operable lesions, and hypothetically, most of these strokes might be avoided by timely endarterectomy, if the lesion can be demonstrated before the stroke.

How good an indicator are some of the signs of a TIA? Consider carotid bruit as one sign of arteriosclerotic disease. A well-local-
ized bruit that extends throughout systole indicates a stenosis of at least 50%. It usually is considered hemodynamically significant because it reduces the cross-sectional area of the artery by 75%, substantially diminishing the blood flow.

Jarett and McHugh studied the natural history of carotid bifurcation plaques by performing serial arteriograms during a period of 1 to 9 years. Notable increases in the size of the plaques were found in 62% of the atheroma and in one-third of the lesions; the plaques increased in size by more than 25% per year. In a long-term follow-up study by Thompson and Tallback, almost one-half of the 102 patients studied with asymptomatic bruits became symptomatic, one-fourth had TIAs and underwent endarterectomy, and another 19% suffered strokes without any prodromal symptoms. Nowadays, complications of arteriography are few, but they can, and do, occur; thus, it is not a procedure to be taken lightly.

Futty et al. evaluated the visual symptoms of TIAs and their significance. They found that the most common transient symptoms of carotid system disease were monocular loss of vision and contralateral sensory or motor symptoms. A third common symptom was dysarthria. Dysarthria occurred as often in vertebral basilar system disease and, therefore, was not a reliable sign of carotid artery disease alone. Since today’s vascular surgery is designed primarily for carotid artery disease, it is important to identify carotid artery disease. In the Futty study, the only combinations of symptoms that were more predictive of significant carotid system disease than a single symptom, such as transient loss of vision, were (a) contralateral sensory or motor symptoms for the left carotid artery system and language disturbance and (b) right arm and leg motor or sensory symptoms and facial weakness; these symptoms were in addition to the visual loss. In most cases, the patient had more than one symptom; however, visual loss was the most common single symptom. It seems reasonable to assume that most patients with potentially treatable carotid system disease will be seen by, or present to, an ophthalmologist. It behooves the ophthalmologist to be alert to these patients and to try to develop easy, quick, reliable, and nontraumatic tests to identify the patient who require further evaluation.

Classically, carotid artery insufficiency of occlusion is supposed to cause ipsilateral loss of vision and contralateral hemiplegia, but such a syndrome rarely occurs. When the carotid artery is gradually occluded, collateral circulation frequently develops to protect the cerebral hemisphere. Ipsilateral loss of vision does occur, however, and carotid disease must be included in the differential diagnosis of monocular sudden loss of vision. After occlusion of the artery and loss of vision, the fundus may initially appear normal. Clinically obvious optic atrophy usually occurs weeks later, although it may occur sooner if the infarction of the optic nerve occurs just behind the lamina cribrosa.

As part of the workup in acute visual loss, ophthalmodynamometry (ODM) should be performed. If the reading shows a significant decrease in ophthalmic artery pressure, carotid artery occlusive disease with probable ischemia is suggested. Although, by today’s standards, ODM seems crude, it is readily available in the office of any doctor interested in cerebral vascular disease. However, only high-grade obstruction in the carotid artery causes a significant enough decrease in blood flow to the eye to be reflected in a drop in ODM pressure. ODM will not detect moderate or low-grade obstruction or irregularity of the arterial lumen from arteriosclerotic plaques. All of these can cause similar transient visual symptoms, just as if there were high-grade obstruction of the artery. Ischemia of the optic nerve can also give transient, partial, or complete loss of vision to one eye, but with a normal ODM reading. Decreased pulsations of the ipsilateral carotid artery and the presence of a carotid artery bruit are good evidence of a decreased blood flow to the ipsilateral eye. Since collateral circulation may supply enough blood to give a normal ODM reading, a negative response does not rule out...
the possibility of carotid artery insufficiency. The acute loss of vision can be caused by a combination of a drop in pressure and an already decompensated small-vessel circulation in the optic nerve that is caused by hypertension and atherosclerosis. Significant long-term obstruction to a carotid artery may be inferred in patients with significant diabetes or hypertension, in whom the eye ipsilateral with the carotid artery insufficiency shows none of the fundus changes of these diseases.

Since carotid artery occlusion is caused by atheromatous disease, embolization from an ulcerated atheromatous plaque may also cause acute vision loss. As described by Hollenhorst, these plaques lodge at bifurcations or narrowings of vessels (as when they pass through the lamina cribrosa) (Figs. 13.6 and 13.7). The retina should be carefully inspected for the yellow, crystalline plaques, particularly at the bifurcation of vessels. If the plaques occlude a branch, central vision is spared, sector defects occur, and whitish edema of the retina in that sector is easily seen during the acute stage. If the embolization occurs in the central artery, the entire retina is cloudy white, and a cherry-red spot appears in the macula. When the embolization occurs some distance behind the lamina cribrosa, the retina may appear normal. Hollenhorst plaques can lodge in vessels without causing an obstruction. Even when the entire vision of the eye is lost, it is worthwhile examining the retina in detail for evidence of these plaques, because they may give a clue as to what is causing the loss of vision. Light pressure on the globe as the fundus is viewed causes the vessels to pulsate and the plaques in an artery to move, which may make them more readily visible.

The treatment of carotid occlusive disease ranges from aspirin to endarterectomy. The later treatment has been controversial. The national endarterectomy study interim conclusion was that it is a worthwhile treatment in selected patients. The carotid obstruction should be 60% or greater. The patient

- Figure 13.6.
A Hollenhorst plaque (white area) is seen lodged at a bifurcation of a vessel, the typical location for these plaques.
selected should have the contributing risk factors controlled. Poor candidates are those with uncontrolled hypertension, bilateral carotid stenosis, symptomatic vertebral basilar disease or severe distal obstructive disease in the carotid system, and also chronic obstructive pulmonary disease. Candidates who are selected should have cerebral, not retinal, TIA symptoms and other risk factors controlled. Since endarterectomy is designed to prevent stroke and preserve life, other statistics need to be considered in evaluating their treatment. The patients with carotid TIAs, whether retinal or cerebral, have a 30% chance of myocardial infarction, and 18% will die. The endarterectomy study also emphasizes the importance of doing the procedure in an institution where the surgeons have less than a 3% rate of morbidity and mortality. If you consider only visual TIA, then the stroke rate of those treated medically was 2% annually in a small study done at Duke University. In patients with carotid stenosis and cerebral TIAs, the stroke incidence averaged 8% per year. The assumption is often made that the carotid stenosis and subsequent stroke have a direct cause-and-effect relationship. Several studies refute this conclusion. The endarterectomy study reported a stroke rate of 2.3% in the perioperative period and an overall rate in 5 years of 4.8%. In the medically treated group, the rate was 10.6%. However, remember the 30% myocardial infarction rate within 5 years.

The key to all these studies, particularly emphasized by the national study, was the selection of patients and the surgical center for performing the procedure with acceptable results of less than 3% mortality and morbidity.

The other embolic phenomenon causing transient symptoms is called white plugs. These result from increased adhesiveness of the platelets, causing a rouleaux effect. Such platelets become stacked on one another to form platelet plugs, which temporarily lodge in retinal vessels, causing ischemia and transient loss of vision before passing on into the peripheral circulation. Carotid atherosclerotic plaques can contribute to increased platelet adhesiveness owing to changes in laminar flow over these irregular areas. Larger white emboli are considered to originate in the heart.

Venous stasis retinopathy, another sign of vascular insufficiency, represents a more chronic cause of decreased blood flow to the eye. The fundus picture is one of microaneurysm, particularly near retinal veins, hemorrhages, and dilated and tortuous veins. This type of retinopathy is usually unilateral, and the findings are more prominent in the midperiphery than at the posterior pole. Diabetic retinopathy, with which it has been confused, is not usually unilateral and
is more concentrated in the posterior pole. Patients who have venous stasis retinopathy on the basis of carotid ischemia can also have ischemic facial pain. Improving blood flow by endarterectomy or by superficial temporal-middle cerebral artery bypass surgery can reverse the fundus changes and facial pain and cerebral symptoms.

Until recently, noninvasive techniques were never quite adequate for the diagnosis of carotid obstructive disease. In the past, if significant treatable carotid disease was suspected, hospital admission was required and arteriography was performed. This was not only expensive and time-consuming for all involved, but the test carried some serious risks to the patient. Ultrasound examination has achieved results equal to those with digital subtraction angiography and is preferred. In view of the natural history of TIA, it is now more important than ever to identify the patients who can be helped by surgery.

The differential diagnosis in the older age group for transient visual ischemia after arteriosclerotic disease is not great. Diseases that affect platelet adhesiveness are rare in this age group and are discussed in the section on TIA in children and young adults. Cardiac arrhythmia should always be high on the list of differential diagnoses. Patients going in and out of atrial fibrillation can have valvular vegetations break off, producing embolic symptoms. Postural hypotension causing transient symptoms usually can be suspected from the history. A carotid sinus syndrome may also be suspected from a careful history. A recurrence of migraine is always in the differential diagnosis, but it is much more common in females than in males. The usual migraine presentation is for a female to have had several episodes of classic migraine in her teenage years and then go into a state of remission for 20 years. As she approaches the menopause, the visual symptoms return without the headache and are interpreted as TIA, secondary to vascular disease, rather than as true migraine. The patient is a little young for significant arteriosclerotic disease, since she is usually in her 50s. This should alert the wary physician that this constellation of symptoms represents something other than carotid vascular insufficiency.

**Transient Ischemic Attacks (Children and Young Adults)**

It is a general perception in medicine that there is little therapeutic advantage in searching for the cause of a nonhemorrhagic stroke unless the diagnosis of remediable extracranial arterial disease can be made. This is generally true in patients 60 years of age or older, described in the previous section, but it does not apply to children and young adults. Although only 5% of all strokes occur in those under the age of 45, many of these are caused by treatable diseases, not by arteriosclerotic disease. Since many of these diseases are not found by routine neurodiagnostic procedures, better history taking is required to uncover the clues that will lead to the proper diagnostic tests and diagnosis.

One of the easiest tests to perform is to take the blood pressure in both arms and legs. It is important to have a proper size cuff, rather than one cuff for all ages. Although hypertension in young people is rare, compared with its incidence in the older population, it is not that uncommon in young patients with transient ischemic symptoms. Because of the rarity of hypertension in young people, blood pressure is infrequently taken in this age group. The ophthalmologist has an opportunity to make a quick and simple diagnosis of hypertensive vascular disease. A list of the causes of hypertensive vascular disease in this age group would fill several pages. It is not the province of the ophthalmologist to do a workup on the patient for hypertensive vascular disease and to identify the specific cause; rather, he or she should be alert enough to identify hypertension as a problem and bring it to the attention of the family physician.
Pure ocular TIAs and retinal artery obstructions in young people are even more rare than strokes, if one excludes migraine. This is because the collateral ocular circulation in this nonatheromatous age group is adequate to prevent this symptom. The following list—though by no means complete—includes those causes of TIAs and strokes in children and young adults (both with and without visual symptoms) that we have seen in our practice: atrial myxoma, mitral valve prolapse syndrome, oral contraceptives, consumption coagulopathies, Waldenström's macroglobulinemia, Trousseau syndrome, sickle cell disease, subarachnoid hemorrhage, moyamoya disease, neurofibromatosis, carotid sinus syndrome, Takayasu syndrome, talc, congenital heart disease, fibromuscular dysplasia, Todd's paralysis, porphyria, dysautonomia (Sies-Holm syndrome and Riley-Day syndrome), and periarteritis nodosa and migraine. Field loss from the migraine syndrome is rare. Recent studies would suggest that it may not be as benign a disease as previously thought. Lewis studied 60 patients with migraine for at least 2 years. They found 21 patients or 35% had some visual field abnormality. To see these findings in a proper perspective, experience teaches us the rarity of clinically noticeable defects. The migraine syndrome rarely causes persistent positive visual phenomena. These phenomena may last from months to years after the insult. They may be hemianopic or bilateral and demonstrate nothing on the MRI. West theorized that previously recorded perceptions can break through. Normally, the multiple and constant external impulses we are receiving keep these previous perceptions from coming to consciousness until a defect is produced in the system that processes input information. Each of these conditions is briefly reviewed below.

**Atrial Myxoma.** Cardiac tumors occur in about 0.05% of routine autopsies; 50% of these are atrial myxomas, and the vast majority of them are found in the fossa ovalis of the left atrium (Fig. 13.8). These tumors occur about three times more often in women than in men and can be symptomatic at any age.

When patients are symptomatic, it is usually between the third and sixth decade of life. They may present with an embolic phenomenon or progressive obstruction of cardiac outflow with progressive failure, or they may have constitutional symptoms suggesting cardiovascular disease or endocarditis. The murmur these patients develop may mimic that of mitral stenosis or mitral insufficiency and will vary with their position. Patients with atrial myxoma also show a decrease in weight, increases in their sedimentation rate and in their gamma globulin, fatigue, mild anemia, and an embolization phenomenon. An embolic phenomenon may cause an initial infarction. It may also cause weakening of the arterial walls, so that aneurysm formation may occur years later, after the atrial myxoma has been surgically resected. This aneurysm may then present as a subarachnoid hemorrhage or as a primary intraparenchymal hemorrhage.

Three features of atrial myxoma should be noted: (a) it is a preventable cause of cerebrovascular disease if found in time; (b) it is a disease that should be considered even in young patients without cardiac symptoms; and (c) aneurysms can occur late in the disease, even after definitive treatment has been undertaken.

**Mitral Valve Prolapse Syndrome (Barlow Syndrome).** The mitral valve prolapse syndrome is also referred to as the midystolic click-murmur syndrome. It also occurs more frequently in women than in men and is present in approximately 10% of adult females. Most patients are asymptomatic, but 30 to 40% may have nonspecific symptoms. Not infrequently, there is a positive family history to help in the diagnosis.

The symptoms and signs include fatigue and exertional dyspnea, so that one may consider other forms of cardiac or pulmonary disease. Palpitation and occasional detectable arrhythmias are also part of the picture. Some patients suffer from syncpe, frequently with light-headedness, particu-
They have an abnormal bifid cardiac pulse, particularly when in the left lateral position.

The ECG shows inverted T waves, particularly in lead II. Supraventricular arrhythmias such as atrial fibrillation are seen in about 60% of these patients. They also have conduction disturbances such as the Wolff-Parkinson-White syndrome. M mode echocardiography reveals a pansystolic prolapse posteriorly of the mitral valve leaflets, which is seen best in the posterior leaflet (Fig. 13.9). A late systolic diplopping posteriorly of the leaflets may also be seen. In two-dimensional echocardiography, one or both leaflets go posteriorly beyond the mitral ring (Fig. 13.10).

Complications of this syndrome are progressive mitral regurgitation with failure, infective endocarditis, spontaneous rupture of the chordae tendinae secondary to endocarditis, and myxomatous degeneration of the valve with sudden failure and, rarely, sudden death.
Figure 13.9.
A. Echocardiogram of a patient with normal movement of both the anterior and posterior mitral leaflets. B. Echocardiogram of a patient with mitral valve prolapse syndrome. The arrow indicates the hammocking of the posterior mitral leaflet that is characteristic of this syndrome.
**Figure 13.10.** Diagrammatic representation of prolapsing mitral valves into atrium. (Courtesy of Lewis E. Calver.)

**ORAL CONTRACEPTIVES.** Oral contraception medication, or “the pill,” has been with us since the mid-1960s. Despite the controversies, it is generally agreed that there is an increased risk of deep-vein thrombosis and pulmonary embolism in patients taking the pill. An increased incidence of the migraine syndrome has been observed in those women taking oral contraceptives who already have a propensity for migraine. Therefore, it has been recommended that women with signs and symptoms consistent with congenital heart disease or other vascular abnormalities are probably poor candidates for this method of contraception. The relationship between use of oral contraceptives and the occurrence of stroke in young women is still somewhat controversial. There has not been as significant an increase in stroke since the introduction of the pill as there has been of deep-vein thrombosis. In those women developing a strokelike syndrome, the findings are unusual. About one-fourth of these patients develop a stroke along the distribution of the vertebral basilar arterial system. Just as experimental animals on exogenous steroids develop intimal hyperplasia and secondary thrombosis, the women on oral contraceptives developed these changes, demonstrated at postmortem. Until we can
identify which patients are at risk for stroke as well as for deep-vein thrombosis, we should consider the pill as the potential cause of any cerebral vascular accident in young women.

**CONSUMPTION COAGULOPATHIES.** Consumption coagulopathies represent an abnormal state of the blood coagulation mechanism. This abnormality results from an increase in intravascular coagulation factors, often associated with diseases that have a hemorrhagic diathesis. These diseases include abruptio placenta, fat embolism, endotoxin shock, Waterhouse-Friderichsen syndrome, thrombocytopenia purpura, cirrhosis, acute pancreatitis, hemorrhagic shock, extensive surgery, acute leukemia, and carcinomatosis. The common denominator of all of these conditions is a release of thromboplastin or a thromboplastin-like substance into the vascular system. Because these diseases do not present to the ophthalmologist as a patient's initial complaint, they are not high on the list of differential diagnoses considered by the ophthalmologist.

**WALDENSTRÖM’S MACROGLOBULINEMIA.** Waldenström’s macroglobulinemia occurs in mid-to late life, rather than in childhood or very young adulthood, but it generally appears earlier than symptomatic cerebral arteriosclerosis. It occurs mostly in males. It usually has an insidious onset, with the patient experiencing increasing weakness, lassitude, weight loss, pallor, and hemorrhagic diathesis (epistaxis, gingival, retinal, and cutaneous hemorrhages). These patients can also demonstrate a painless increase in the size of their lymph nodes and will have hepatosplenomegaly, anemia, relative lymphocytosis, thrombocytopenia, and an increased sedimentation rate. About 25% of these patients have neurologic signs, with retinal changes seen in about 30%. Convulsions are uncommon. Strokes or focal brain syndromes, encephalopathies, neuropathies, and subarachnoid hemorrhages are some of the neurologic presentations.

The Sia test is the appropriate one to perform. If a drop of the patient’s serum is added to a test tube of distilled water, a white flocculus is formed.

**TROUSSEAU SYNDROME.** The well-known Trousseau syndrome is characterized by thrombophlebitis associated with nephrosis. The most common neoplastic process is that of cancer of the tail of the pancreas. Cancer of the head of the pancreas presents with other signs and symptoms at a much earlier stage of the development of the cancer. Other abdominal malignancies can also cause thrombophlebitis, but the pancreas is still the outstanding example.

**SICKLE CELL DISEASE.** Sickle cell trait occurs in about 8% of black Americans, whereas sickle cell anemia occurs in 0.15% of black Americans, and most of these are children. The reason this disease is found mostly in children is that the life expectancy of these patients is shortened, and therefore the incidence drops in the adult age group. Persons who have sickle traits usually have minimal symptoms. The precipitating factor for their becoming symptomatic is a reaction to toxic agents, infections, or severe stress. The most frequent target organ is the renal medulla, which develops small infarcts. As a result, patients have difficulty concentrating their urine and develop painless hematuria, which causes hypertonicity of the intravascular fluid. Any situation that pulls water out of the red blood cells increases the chances of their sickling.

The involvement of the renal medullae with sickling usually does not start until after 6 months of life when HbF is replaced by HbS. Patients who have sickle cell disease usually show an impairment of growth and a failure to thrive during their first few years. They also have difficulty in fighting infection because of recurrent splenic infarcts, which decrease their ability to clear circulating bacteria. The morbidity and mortality of this disease usually are caused by recurrent vaso-occlusive episodes. Other, more common, symptoms include abdominal pain suggestive of an acute abdomen, chest pain with a differential diagnosis of infection versus infarction, and joint involvement. All of these
symptoms may be precipitated and preceded by upper respiratory infections. They may also occur more frequently in cold weather when there is vasoconstriction of vessels. These patients can also have signs and symptoms of CNS involvement, including seizures, strokes, and coma.

Patients with sickle cell disease can also have central retinal artery occlusions, although this is not common. The conjunctival sickling sign is well known, and one can see it with the magnification of the slit lamp (Fig. 13.11). If one places topical phenylephrine HCl on the conjunctiva, the vasoconstriction it causes may increase the sickling sign. On the other hand, the increased heat of a prolonged observation with the slit lamp may decrease the amount of sickling that one usually sees.

**SUBARACHNOID HEMORRHAGE.** Anurysms frequently present as a subarachnoid hemorrhage. The differential diagnosis of subarachnoid hemorrhage in children includes syndromes that have a hemorrhage diathesis such as leukemia, idiopathic purpura, and hemophilia. These diseases usually show bleeding in other areas as well, which helps in the differential diagnosis. If bleeding occurs only into the CNS, then one should consider rupture of an arteriovenous malformation, aneurysm, vascular hamartoma, bleeding associated with a tumor, extension of an intercerebral hemorrhage into the subarachnoid space, and spinal cord tumor. If a tumor bleeds into the subarachnoid space directly, it is usually an epidermoidoma or a tumor of the choroid plexus. Under the age of 30, bleeding from an arteriovenous malformation is much more common than an aneurysm. Most of these patients bleed intracerebrally, rather than into the subarachnoid space. Bruits can be heard in about 20% of these patients and are heard best over an eye or in the temporal fossa.

**MOYAMOYA DISEASE.** Moyamoya disease presents either as motor paresis in the young or as apoplectic stroke in the middle aged. The anatomic findings are occlusion of the carotid arteries in the area of the carotid siphon, which usually occurs bilaterally. Besides this obstruction, there is a bilateral hemangiomaticous vascular network that extends across the base of the brain and is easily seen on cerebral angiography. Before the development of sophisticated subtraction techniques, these vessels were not easily seen, and only the dye was seen as a milky diffuse pattern in the area of this network. This appearance was the reason for the name of the disease. This fine network of vessels is more easily seen as individual vessels with today's techniques of subtraction and magnification (Fig. 13.12). The cause of this vascular abnormality is not well known but is thought to be of a congenital nature. Anatomic examination of the vascular development in fetus specimens reveals a similar network prior to the full development of the carotid system. Many investigators feel that this is an example of the lack of development of that carotid system.

Moyamoya disease was originally described by the Japanese but has now been seen in all other races and parts of the world. Most of these patients do well, but some of them show progressive changes in their carotid artery on repeat arteriography, and some of them die. In a series of 111 patients reported in Japan, 73 were under the age of 16. Six of these children had progressive neurologic deficit and 4 died. The other
drome. Patients show gradual development of narrow carotid arteries, leading to occlusion in the supraclinoid portion. This obstruction is caused by proliferation of Schwann cells, with intimal thickening. If the obstruction is unilateral, then no changes may occur, owing to the gradual development of collateral circulation through the circle of Willis. If the obstruction is bilateral, then the hemangiomatous vascular network develops in the region of the basal ganglia and on the surface of the corpus callosum. This involvement of the cerebrovascular network is not common but has been reported and should be kept in mind when dealing with patients with neurofibromatosis, rather than ascribing all of their cerebral symptoms to a recurrence of their tumors or to the development of new tumors. Review of the recent studies indicates that gliomas associated with neurofibromatosis have a more benign prognosis. Since patients with neurofibromatosis have a propensity for vascular occlusion, radiation vasculopathy may be a severe extra risk factor. Radiation therapy should therefore be viewed with caution.

CAROTID SINUS SYNDROME. Stimulation of a hypertirritable carotid sinus can result in a profound fall in arterial pressure, associated with a marked bradycardia. Carotid sinus syndrome tends to be more common in males in the sixth decade of life than in young adults, but it can occur in this age group and should be given some consideration. These patients may experience light-headedness and syncope and may have an associated decrease in blood flow to the eyes, with a decrease in vision.

The most common causes of this syndrome are arteriosclerosis and hypertensive vascular disease, which is not a disease of the young as a rule. Other causes can be local disease such as lymphadenopathy, scarring, and carotid artery tumors. Carotid sinus-like syndrome can also be caused by anatomic changes, such as extreme turning of the head with compression of one of the vertebral arteries when the other one is incompetent, perhaps congenitally. The condition can also be seen with hyperextension of the neck, constipation, heavy weight, depression, or other secondary causes. The carotid sinus syndrome should not be confused with the carotid body tumor, which is uncommon.

TAKAYASU disease was first described in Japanese patients suffering from narrowing and occlusion of the aorta and its major branches. It is a systemic disease with involvement of the aorta, its major branches, and the renal arteries. There is a familial form that is more common in women, and a sporadic form that is more common in men. The aorta is involved in more than 90% of patients, and the carotid arteries are involved in about 50% of patients. The disease is characterized by the presence of aneurysms and dissection, with obstruction of the affected vessels.

The ocular manifestations of Takayasu disease include optic atrophy, retinal arterial narrowing, and retinal arteriovenous malformations. The disease is characterized by symptoms such as headache, fatigue, and loss of vision. The disease is usually treated with immunosuppressive agents, such as corticosteroids and cyclophosphamide. The goal of treatment is to reduce the inflammation and halt the progression of the disease.
TAKAYASU SYNDROME. Takayasu syndrome was originally described in young Japanese females but has been seen in other races throughout the world. It is produced by a slowly progressive obliteration of the major vessels arising from the aortic arch, with a decrease in blood flow to the head and upper extremities. It is primarily a disease of the aorta but can extend down to the renal arteries, with the development of secondary hypertension. The pathologic studies reveal a panarteritis with intimal thickening, fibrosis, and vascularization of the media and fragmentation of elastic tissue. There is also some mild lymphocytic infiltration and thickening of the walls of the vasa vasorum in the adventitia.

The ocular symptoms of Takayasu syndrome include amaurosis fugax, which is made worse with standing or with exercise. ODM usually shows a decrease in readings, particularly when taken immediately after changing from the lying or sitting to the standing position. The fundus is typically pale, with dilated retinal vessels. This dilation of vessels is particularly obvious around the disc and forms a caput medusae type of arteriovenous anastomosis around the nerve head. There is also some peripheral retinal artery obliteration; occasionally, a central retinal artery occlusion may develop with secondary retinitis proliferans and vitreous hemorrhages.

TALC. Blurred vision may occur when foreign substances injected into the bloodstream become lodged in the eye. Today, one of the more common substances in this category is talc, which is used to dilute narcotics. Small pieces of talc that enter the system by use of intravenous drugs can act as emboli in the retinal vessels. This cause of blurred vision has been reported infrequently, but the condition has been documented photographically.

CONGENITAL HEART DISEASE. The patient with congenital heart disease is usually discovered at an early age and does not normally present initially with an ophthalmologic problem. The congenital heart defects that cause a right-to-left shunt allow embolism from the peripheral veins to bypass the lungs and enter the arterial circulation. It is from this point that they become lodged in arterial vessels, causing the signs and symptoms of thrombosis in the tissue fed by that vessel. Arterial thrombosis is uncommon in young people, but children under 1 year of age with cyanotic congenital heart disease are predisposed to venous thrombosis. This condition can result in focal neurologic signs such as decreased vision, increased intracranial pressure, seizures, and coma. Most of these children have polycythemia, but they may also have microcytic hypochromic anemia.

FIBROMUSCULAR DYSPLASIA. Fibromuscular dysplasia is a disease caused by irregularly spaced areas of fibrous and muscular hyperplasia of the media, with disruption of the elastic lamina. At these areas of rupture, there is an aneurysm-like appearance. The most common area for this to develop is the middle third of the extracranial carotid artery. Patients with this disorder may also have hypertension; many of them are young women with involvement of the renal arteries and development of secondary hypertension.

Arteriograms from patients with fibromuscular dysplasia have a characteristic corrugated appearance—the so-called string-of-pears sign—in the areas where there is spaced fibrous and muscular hyperplasia (Fig. 13.13). In women who have this disease, it is more common to find additional aneurysms throughout the vascular system than it is with the population in general. Because these patients are young, with good collateral circulation, decreased vision, and defects of the optic nerve or field defects
*Figure 13.13.*

Arteriogram of a patient with fibromuscular disease shows the characteristic corrugation or "string-of-pears" sign (arrow).

have been recorded only five times in the literature. This collateral circulation, however, does not protect their renal arteries from the disease; therefore, secondary hypertension is a frequent problem, with its associated ocular findings.

**TODD'S PARALYSIS.** The hemiparesis and aphasias that may follow a generalized seizure and that clears within 24 hours has been referred to as Todd's paralysis. This decrease in neuronal function can be seen in the visual system as well. Three possible mechanisms have been proposed: neuronal exhaustion, vasoconstriction and vasodilation phases of the vascular response, causing ischemia and metabolic exhaustion of the neurons, and an active inhibitory state of the cells after a seizure. Cells around the active seizure site may discharge increased amounts of inhibitory substance to the cells that are involved in the active seizure pattern. The symptoms and signs of this post-seizure neuronal depression should clear within 24 hours.

**PORPHYRIA.** The two major forms of porphyria are erythropoietic and hepatic. The usual onset is between the third and the fifth decade of life. It can be precipitated by fasting, starvation, and drugs such as barbiturates, hormones, and steroids.

Hepatic porphyria is an acute, intermittent disorder that is inherited as a mendelian dominant trait. It usually presents with recurrent gastrointestinal, psychiatric, and neurologic symptoms. Paresthesias of the extremities are common initial symptoms. Weakness of the muscles, of the trunk and extremities may rapidly advance to complete paralysis. Weakness is usually generated in the distal parts, but occasionally proximal muscles may be more severely involved. Also, any cranial nerve, including those of the visual system, can be involved. The erythropoietic form of porphyria is rare and is recessively inherited.

**DYSAUTONOMIAS.** One of the more common dysoautonomias—an unusual group of diseases—is the Shy-Drager syndrome. Patients with this disorder present with postural hypotension without a change in pulse rate. This sign represents adrenergic system failure owing to intermediolateral column cell disease. There are also cases with cholinergic dysfunction involving lacrimal and salivary glands and gastrointestinal, urinary, bladder, and sweat gland signs and symptoms. These patients do not show pupillary dilatation to topical hydroxyamphetamine; there is an absence of the ciliospinal response, and no tachycardia is seen with the postural hypotension. The tests for parasympathetic dysfunction include using dilute pilocarpine to induce pupillary miosis. Also, no change occurs in the heart rate with the Valsalva maneuver. These patients show minimal tachycardia in response to a pharmacologic dose of atropine, suggesting vagal hypoactivity.

The more common childhood form of dysautonomia is the Riley-Day syndrome, which usually shows an autosomal recessive type of inheritance. Riley-Day patients usually start showing symptoms during the first 5 years of life; these include emotional irritability, insensitivity to pain, absence of taste discrimination, and attacks of severe vomiting. They also have hyperpyrexia, hypotensive episodes, and episodes of skin blanching.

Laboratory findings include decreased serum epinephrine levels with negative metanephrine reactivity. The hyponatremia may be related to a low renin.

**PERIODIC PENDULAR MUSCLE SPASM.**

This periodic pendular muscle spasm syndrome is characterized by episodic muscle spasms of the neck and face. These spasms can be associated with headache and seizures. The spasms may be triggered by stress, fatigue, or a variety of medications. Treatment options include anticonvulsants, muscle relaxants, and sometimes surgery.

**HYPERPYREXIA.**

No specific treatment is available for hyperpyrexia. Management includes supportive care such as hydration, cooling measures, and managing any underlying cause. Close monitoring of vital signs is essential to prevent complications such as seizures or organ failure.
blotching alternating with pallor. They may have seizures, absent deep-tendon reflexes, and dysphasia. They frequently have recurrent upper respiratory infections and pneumonias and may die from pneumonia, hyperpyrexia, or severe dehydration. The physical examination shows absence of fungiform and circumvallate papillae of the tongue. These patients also have impairment of normal lacrimation.

Laboratory studies reveal an increased ratio in urinary excretion of homovanilliac acid to vanillylmandelic acid. There is low serum dopamine β-hydroxylase activity and impaired norepinephrine release. Dysautonomic patients, after standing for a while, do not have a normal increase in levels of norepinephrine, which supports the view that the hypo- and hypertension in these patients are related to abnormal rates of norepinephrine release.

**PERIARTERITIS NODOSA.** Periarteritis nodosa is caused by focal disseminated inflammatory lesions involving the medium and small arteries. The average age of onset of periarteritis nodosa is 47, but it may range from 9 to 77 years. Those who have the severe form, which ends in death, have an active period of signs and symptoms averaging about 12 months. They commonly have neurologic signs, particularly peripheral neuropathy. Laboratory examinations reveal anemia, increased sedimentation rate, reversal of the AG ratio, abnormal urinary findings, leukocytosis, and increased BUN. Roentgenograms may show pulmonary infiltrates suggesting this type of disease.

**Hypotension**

No matter what the cause, hypotension can result in acute loss of vision in one or both eyes. Loss of vision related to acute hypotension usually has other signs and symptoms, so the diagnosis is not obscure. One cause of hypotension that is usually not obvious is a too-rapid and too-ambitious control of hypertensive vascular disease. The following descriptions of three hypothetic patients illustrate this iatrogenic cause of hypotension.

1. Patient 1, who has no symptoms of a visual disorder, has had known hypertension for years, so his eye is accustomed to a high head of pressure. His well-meaning physician aggressively lowers the patient's blood pressure, so he has no systemic symptoms of hypertension. In the course of his hypertensive therapy, he loses vision. The eye that has had a high head of pressure and that has arteriosclerotic changes now experiences ischemia, and the optic nerve is infarcted. The ophthalmologist should consider such infarction in a patient who has pronounced hypertensive retinopathy, relatively normal blood pressure, and visual loss.

2. Patient 2 has a hypertensive fundus and normal blood pressure but has had no recent changes in the medication he is taking for hypertension. His blood pressure may not have been under good control, and now it has dropped because of a silent myocardial infarction. An electrocardiogram is indicated for this patient as well as for Patient 1.

3. Patient 3 has hypertension and glaucoma. The glaucoma has been well controlled for years but not the arterial hypertension. The glaucomatous eye, which has perhaps marginal perfusion, is accustomed to a certain head of pressure. When the arterial pressure is dropped for any reason, the glaucomatous eye may suddenly begin to lose field, even though the intracranial pressure seems to be at the same level as it was on previous examinations. The drop in this patient's arterial pressure should be evaluated as a possible cause of the change in his glaucoma.

It is well recognized that patients with advanced glaucoma who have small residual central islands of vision can have that remnant snuffed out, even when surgery goes smoothly. This vision loss probably has to do with a sudden change in the vascular
dynamics of the eye, perhaps from the pressure being lowered too fast (e.g., by too much filtration). A similar visual loss has also been reported in similar cases of laser iridotomy for acute-angle-closure glaucoma with sudden lowering of intraocular pressure. The central island of vision can also be lost through a secondary but transient rise in intraocular pressure, such as may occur after laser trabeculoplasty. Both extremes of a tenous status of ocular vascular dynamics can produce loss of this small remaining island of vision.

HEMATOLOGIC AND VASCULAR CAUSES

Blood Loss

Acute or chronic blood loss may also cause loss of vision or field in one or both eyes. Acute blood loss rarely causes these symptoms unless chronic compromise of the ocular circulation already exists or the blood loss is severe (as in postpartum hemorrhage and massive gastrointestinal hemorrhage). A day or two after the hemorrhage, the patient may complain of loss of vision and show a decrease in vision or an altitudinal field loss, particularly in the lower field. The optic disc shows an ischemic edema.

Chronic Anemia in Pregnancy

Chronic anemia in pregnancy occurred in the past but is rarely seen today.

Vascular Hypotension

Vascular or any other kind of surgical procedure in which cardiac arrest or prolonged hypotension occurs can leave the patient with unilateral loss of vision or even cortical blindness. The degree and duration of hypotension and the status of the vessels in the affected area are factors that contribute to the degree of visual loss.

Blood Dyscrasias

Blood dyscrasias are of several varieties. Optic neuritis with a centrocecal field defect is well known in pernicious anemia. This disease usually occurs in persons over the age of 30, and it should be suspected in patients who have optic neuritis with evidence of glossitis and gastrointestinal symptoms. It is a macrocyclic anemia with a defect in the gastrointestinal absorption of vitamin B₁₂. The Schilling test, the accepted confirmatory test, measures the body's ability to absorb radioactive vitamin B₁₂ over a 24-hour period. Another frequently used test involves the injection of histamine and the measurement of hydrochloric acid secretion in the stomach. (This secretion is severely impaired in pernicious anemia.) The treatment of pernicious anemia is administration of hydroxycobalamin rather than the standard form of vitamin B₁₂, thus bypassing the enzymatic defect that prevents proper absorption.

Another form of blood abnormality—and an all too common one—is central retinal vein occlusion. Patients with this abnormality complain initially of blurred vision; their visual acuity is usually 20/200 or better. The fundus shows hemorrhage, particularly along the veins, which are fat and sausage-like, with sludging of the blood column. Sometimes, such veins are seen with no hemorrhage, a condition referred to as impending venous occlusion. Patients with impending venous occlusion usually have no symptoms. Some have transient blurring of vision, which leads them to seek an evaluation.

Central retinal vein occlusion is caused by sludging of the blood column, which may be caused by an elevated pressure in the eye (glaucoma), slowing of the blood column, or a decrease in blood flow into the eye with normal intraocular pressure. It may also occur in known diabetes or as a premonitory symptom of early unsuspected diabetes. Central retinal vein occlusion is caused by a

change in blood flow seen in the rare such as Waller. These hyperviscous blood proteins, manifestations of which may occur occasionally, may occasionally lead to retinopathy.

The diagnostic clue is the appearance of the optic disc.

Transient Cilioretinal Artery Occlusion

Blurred vision is occasionally a manifestation of arterial occlusion. Blood flow may be slowed for 5 to 15 seconds a day, the patient may go about his activities with no symptoms. With or without hypertension, the patient may experience occasional transient visual changes of such severity that the patient seeks medical attention.

The obturator syndrome is the term used for a condition in which a patient has transient visual obscurations, which last a few seconds and then disappear. This condition is usually bilateral, or increased intracocular pressure occurring in a single eye of a patient with ocular hypertension or previously normal tension.

Cortical Blindsight

The most common cause of loss of vision in patients with bilateral or unilateral blindness is a lesion in the occipital lobe. Lesions in the occipital lobe may be caused by disease, trauma, or stroke. Lesions in the occipital lobe may be caused by disease, trauma, or stroke. Lesions in the occipital lobe may be caused by disease, trauma, or stroke. Lesions in the occipital lobe may be caused by disease, trauma, or stroke.
change in blood viscosity, and it can also be seen in the rarer hyperviscosity syndromes, such as Waldenström's macroglobulinemia. These hyperviscosity syndromes, which can be identified by paper electrophoresis of the blood proteins, can also occur as secondary manifestations of carcinoma. Polycythemia vera can also cause sludging of the blood; it may occasionally be secondary to a hemangioblastoma of the cerebellum.

The diagnosis of central retinal vein occlusion usually presents no problem, since the appearance of the retina is dramatic and specific.

**Transient Obscurations**

Blurred vision from transient obscurations is occasionally seen with increased intracranial pressure. Because the episodes last only 5 to 15 seconds and occur only a few times a day, the patient usually thinks they are insignificant and does not complain of them. I happen to have treated several patients who experienced transient obscurations frequently during the day and so did complain of them.

The obscurations differ from the amaurosis fugax of carotid artery insufficiency, which lasts anywhere from 5 to 25 minutes and which the patient notices and does complain about. Transient obscurations are usually bilateral, and they are always related to increased intracranial pressure. Other causes of disc edema do not cause transient obscurations; thus they are quite specific.

**Cortical Blindness**

The most common cause of cortical blindness is arteriosclerosis, and it obviously occurs in the older age group. In the young patient, the causes are more protean. They include trauma, poisoning from carbon monoxide and nitrous oxide, neoplasms, and infections (e.g., meningococcal, mumps, rubella, and syphilitic meningitis). Cortical blindness also occurs after seizures and represents a form of Todd's paralysis.

In the days of ventriculography, it would occur occasionally with that procedure. The cause of the loss owing to ventriculography is only speculative. It was felt that it occurred more commonly with multiple passes of the ventriculography needle or was due to some shift of the brain when the ventricular fluid was withdrawn. Cardiac surgery with cardiac arrest or severe decreased blood pressure during the procedure is also implicated in cortical blindness.

Rare cases of cortical blindness have been reported with acute intermittent porphyria, blood transfusions, and temporal arteritis. Cortical blindness also occurs, although rarely, as the result of infectious disease of the CNS. *Hemophilus influenzae* is the usually reported agent, although the mechanism is not entirely clear. Pathologic descriptions have included occlusion, necrosis, and thrombophlebitis on the venous side of the circulation. There have also been findings of arteritis and subarachnoid exudate. Toxie factors have also been considered to play a role in these cases. Schilder's disease, which is quite rare, is also a cause of cortical blindness in infants.

The final visual results from cerebral infarcts that cause cortical blindness is difficult to predict, particularly in infants and the newborn. Severe cerebral ischemia tends to affect different areas in different age groups. In infants who have rubric cerebral palsy, the parasagittal area is a common target area. This is the watershed zone between major cerebral arteries. In a study by Volpe et al. of asphyxiated infants, recorded blood flow in the parasagittal area was significantly lower than in other areas. PET studies demonstrated a 25 to 50% decrease in flow rate compared with that to the sylvian fissure; normally there is no more than a 10% difference. Cortical blindness is less common in premature infants because of meningeal anastomosis between the cerebral arteries. Premature infants develop infarcts in the periventricular area, which is seen on scans as prominent cortical sulci.
decreased periventricular white matter, and later, enlargement of the ventricles. Some of these children recover useful vision because of a rewiring of neurons and neurochemical adaptations not available to older patients with mature brain tissue and arteriosclerosis. Infantile brains may also have collateral axonal sprouting and replacement by supernumerary neurons, which are known to exist during early neural development.

The more severe the infarct appears on CT scan, the worse is the prognosis for vision. For example, Lambert et al. found that in more than 30 cortically blind infants, the more widespread the infarction on CT scan, the worse the visual results were. However, if the hypodense areas were scattered, the visual results were better, and these areas were interpreted as representing incomplete myelination rather than infarcts. This feature is not found in adult cases of cortical blindness (Fig. 13.14).

In adult patients with cortical blindness, measurement of the VEP is not very reliable. Vision is so poor, if present at all, that only flash VEP can be done because of the inability to fixate on a pattern-reversal stimulus. The variability in the latency and amplitude of the VEP makes it difficult to tell where the lesion is along the visual pathway. Sometimes it is even difficult to determine whether the patient can or cannot perceive light. However, opening and closing of eyes will affect the posterior dominant alpha rhythm if there is not complete cortical blindness. A few cases have been reported in which there was no light perception documented over a significant period of time and multiple examinations and yet normal VEPs were present. It is postulated that the responses in such cases are mediated by extrageniculo-laminar pathways from the association areas of 18 and 19.

**Intracranial Aneurysm**

Rupture of an intracranial aneurysm is either a lethal or, at the least, a devastating disease. Ninety-five percent of aneurysms occur in the anterior circle of Willis. One-third of these occur on the anterior communicating artery and from its junction with the anterior cerebral artery. Signs of impending rupture are not always easy to detect. Headache, although a common symptom, is infrequently of a severity or type that would suggest an aneurysm and the workup that it demands. Most aneurysms do not cause visual loss. There are spontaneous fluctuations in vision that are not entirely understood. The mechanism may be related to variation in the size of the aneurysm or associated arteriospasm from subarachnoid hemorrhage. Visual deficits can range from total blindness in one eye to field defects, which are variable from one examiner to another. The presence of this variability should alert an astute clinician to the possibility of an aneurysm rather than attributing it to the variable quality of the examiners.

In one retrospective survey of aneurysm patients, the highest incidence of warning signs was for those aneurysms located at the junction of the internal carotid and posterior communicating arteries, with those at the bifurcation of the carotid and the middle cerebral arteries running a close second. The older the patient the fewer warrant three mechanisms: and red blood cells, which are called cause symptom subarachnoid with compression as in the cerebral artery. Ninety percent of children fusions if cuts place. If they are accurate as to suspicion of a

Aneurysms are usually seen, and 65% of all fatal deaths. Eighty-four percent of aneurysms have a small aneurysm that occur in the anterior circle of Willis. The symptoms mild to the extensive in confusion or painful stimuli demonstrating Brudzinski's sign, and sharp hyperesthesia or irritation, or a mild, throbbing dural headache suggest.
older the patient who ruptures an aneurysm, the fewer warning signs usually occur. The three mechanisms for these premonitory symptoms and signs are (a) vascular disturbances, (b) minor leakage of blood, and (c) ischemic lesions.

Ninety percent of intracranial aneurysms are congenital and average between 0.5 and 1.5 cm in diameter. Those that enlarge to 3 cm are called giant aneurysms. Aneurysms cause symptoms either by rupture into the subarachnoid space or by slow expansion with compression of nearby structures such as the cavernous sinus. Those that are less than 5 mm in diameter rarely bleed. This is fortunate, since aneurysms 5 mm or more can be seen on today's high-quality MR machines if cuts are made in the appropriate place. If they are not seen, MRA is not so accurate as to preclude arteriography if the suspicion of aneurysm is high enough.

Aneurysms appear in 4% of adult autopsies and are multiple in 20% of cases. They usually become symptomatic between 40 and 65 years of age. They account for 30% of all fatal cerebral vascular accidents and for 50% of all fatal cerebral vascular accidents occurring in patients under 45 years of age. Eighty-five percent of aneurysms occur on the anterior circle of Willis. In the 15% that occur in the posterior circulation, most occur at the bifurcation of the basilar artery and posterior cerebral artery.

The symptoms of aneurysm can vary from mild to the most severe of headaches. Alterations in consciousness can vary from mild confusion to unresponsiveness even to painful stimuli. Meningeal irritation can be demonstrated by positive Kernig and Brudzinski signs. These patients may also demonstrate photophobia, hyperacusis and hyperesthesia, mild fever from meningeal irritation, or high fever secondary to hypothalamic disturbances. There may be other hypothalamic dysfunctions, such as vomiting, sweating, chills, and irregular heart rate. Focal damage may give a clue as to which artery is affected. Weakness in one or both legs suggests hemorrhage from the anterior communicating artery. Weakness in an arm and the face suggests a middle cerebral artery location. If a dense hemiplegia occurs, its location is usually in the internal carotid or in a middle cerebral artery. Since any intracranial aneurysm can cause a significant and sudden rise in cerebral spinal fluid pressure, a preretinal hemorrhage may be seen. If the preretinal hemorrhage is in front of the optic nerve, then no visual symptoms occur; however, if the hemorrhage occurs in a subhyaloid location in front of the macula, there may be a severe decrease in acuity. If the patient survives and the hemorrhage does not break out into the vitreous, the hemorrhage will absorb and good vision be restored.

Not all intracranial aneurysms present with the same signs and symptoms. The posterior cerebral artery passes around the cerebral peduncle medial to the temporal lobe, superior to the third nerve, and inferior to the optic tract. Aneurysms of this artery cause hemiplegia with involvement of the corticospinal tract in the cerebral peduncle, homonymous field defects, temporal lobe seizures, and third cranial nerve paresis.

The anterior communicating and anterior cerebral arteries are located above the optic nerve and chiasm and below the olfactory nerve. A giant aneurysm of the anterior cerebral artery causes unilateral loss of vision and smell; that of the anterior communicating artery may give a bitemporal field defect.

Carotid ophthalmic aneurysms account for about 5% of the total number. They occur on the superior or medial surface of the internal carotid artery above the cavernous sinus. As they enlarge, they can erode the optic canal or anterior clinoid bone, which can be seen even on routine tomograms, and cause associated visual loss. Supraclinoid aneurysms can also cause visual loss. They also develop from the internal carotid artery but distal to the origin of the ophthalmic artery.

Aneurysms located along the middle cerebral artery occur in the sylvian fissure and
cause hemiplegia, focal seizures, homonymous field defects, and speech problems.

Aneurysms of the posterior communicating artery occur near the junction of the internal carotid artery, usually between the anterior choroidal and posterior communicating arteries, and rarely, at the junction of the two. These aneurysms present with classic third cranial nerve palsy with pupillary involvement. These aneurysms and those of the cavernous sinus are more fully described in the section on third cranial nerve paralysis in Chapter 6, Diplopia.

Aneurysms occurring on the basilar artery, particularly in the interpeduncular fossa, produce third cranial nerve paresis and headaches that are not necessarily caused by rupture of the aneurysm but by the obstruction of the sylvian aqueduct that then causes increased intracranial pressure and autonomic disturbances with hypothalamic pressure. Pressure on the fifth nerve can cause tic like syndrome, and pressure on the facial nerve in particular can cause hemifacial spasm. Aneurysms located on the vertebral artery and posterior inferior cerebellar artery cause apraxia and bulbar involvement. If they occur on the anterior inferior cerebellar artery, they may cause hemifacial spasm and can mimic a cerebellopontine angle tumor or Ménière’s disease.

INFLAMMATORY CAUSES

Intraocular Inflammations

Intraocular inflammations that cause blurred vision are numerous enough to constitute a division of ophthalmology. Only some of them are alluded to here. Endophthalmitis is usually a complication of intraocular surgical procedures, so the diagnosis is not usually missed. Blood-borne endophthalmitis is a rarer inflammation, however, and initially the physician may not consider it as a cause of blurred vision. Meningococcal meningitis is a rare disease. Ocular involvement is prominent in some epidemics and rare in others. Its most common ocular involvement is endophthalmitis. In meningococcal meningitis, ocular pain and a cloudy-yellow pupillary reflex suggest meningococcus as the causative organism. Decreased vision and hazy media always suggest either intraocular infection or uveitis. Retinobulbar optic neuritis and visual cortex involvement occur much more rarely in meningococcal encephalitis, but the prognosis in regard to vision is good when the condition is treated promptly.

Uveitis is usually caused by one of the granulomatous diseases. The chorioretinitis that these diseases cause may sometimes be identified from the appearance of the fundus. Histoplasmosis should be considered when macular hemorrhages and peripheral yellow drusenlike choroidal lesions occur without surrounding reactive pigmented changes. In toxoplasmosis, large punched out chorioretinal lesions with pigmented chumping occur, particularly in the macular area. Toxoplasmosis in an adult probably is a recurrent condition, since most cases first occur during the intrauterine period. With each recurrence, new daughter lesions develop that frequently can be followed along one vessel into the periphery. Serologic confirmatory tests for both histoplasmosis and toxoplasmosis can be done conveniently (i.e., without recourse to state laboratories).

Sarcoïd uveitis is less common than the forms of uveitis described above, but it shows the typical fundus, with the individual white exudates extending from the vessels into the vitreous humor, particularly in the peripheral retina. These exudates are referred to as candle wax drippings, “en taches de bougie.” The optic disc may also be involved by a localized granuloma (Pl. 14.1, B and C). Sarcoïdosis has protein manifestations beyond ocular involvement. These may be unilateral or bilateral painless swelling of the lacrimal gland, with or without involvement of the parotid gland. The symptoms may be minimal, with only decreased tearing and mild symptoms of keratitis sicca, or they may progress to the more severe form of Sjögren syndrome. Since lacrimal gland involvement is so common and is often asymptomatic, a gallium scan may be useful in establishing the diagnosis.

Sarcoïdosis, direct infiltra
tion and C. There is increased intraocular fluid with second shunt vessel as well as in the anterior chamber. Shunt vessels may cause uveitis. The drainage foci reported in the orbit of the pseudoaneurysms of the lacrimal gland, and C. Pseudotumor
may be useful in identifying it. Infiltration of the angle can cause obstruction of the trabecular meshwork, with the development of secondary glaucoma. Gonioscopy will easily demonstrate the deposits on the meshwork and confirm the diagnosis. This inflammatory form of glaucoma should be a serious consideration in the differential diagnosis of unilateral glaucoma. Conjunctival biopsies are useful in establishing a tissue diagnosis even when symptoms of sarcoidosis occur in other tissues. Nichols et al. reported up to 55% positive biopsies in random conjunctival biopsy specimens.

Sarcoidosis can involve the visual pathway from the intracranial structures to the optic nerve, orbit, and intracranial structures such as the chiasm. It has been estimated that one-third of patients with sarcoidosis will develop some ocular involvement, predominantly uveitis. About 5% of patients with sarcoidosis will develop CNS symptoms, usually in the form of basilar meningeal with involvement of the hypothalamus and pituitary. The cerebral spinal fluid does not always show the increase in protein, lymphocytic pleocytosis, and slight decrease in glucose level that generally is associated with CNS involvement. The cranial nerves also can be involved, most commonly the seventh cranial nerve, followed by the optic nerve. It is interesting to note that in another infectious disease, Lyme disease, the seventh nerve is also the cranial nerve most commonly involved.

Sarcoidosis can involve the optic nerve by direct infiltration as shown in Plate 14.1, B and C. There may be papilledema due to increased intracranial pressure or papillitis with secondary optic atrophy. Opticociliary shunt vessels can occur in this disease as well as in optic nerve meningiomas. Opticociliary shunts are thought to occur with any cause that can slow down the venous drainage from the eye; they have also been reported in cases of arachnoid cysts, gliomas of the optic nerve, orbital vascular malformations, central retinal vein occlusions, and chronic papilledema, particularly pseudotumor cerebri. In at least one case of pseudotumor cerebri, the shunt vessels disappeared when the pseudotumor cerebri resolved.

Recently, there has been interest in the angiotensin-converting enzyme test as a means of identifying sarcoidosis in the laboratory. This enzyme is usually produced by the endothelial cells of most capillaries and some arteries, as well as by the cells of the proximal convoluted tubules of the kidney. It is elevated in sarcoidosis and other diseases such as lupus, Sjogren's, and Crohn's disease. It is postulated that this enzyme is produced by monocytes that have been transformed from phagocytic cells into storage or secreteory cells.

Since a chest roentgenogram may show signs of pulmonary involvement, one should be done in all cases of suspected sarcoid uveitis. A careful physical examination may also reveal a lymph node (particularly in the suprascapular area), so a biopsy should be performed. If the patient has signs of diabetes insipidus or a facial paralysis, sarcoid uveitis should be considered first as the cause of the blurred vision. About 12% of cases of sarcoid uveitis have CNS involvement, with diabetes insipidus and facial paralysis being the two most common manifestations. Tuberculosis, usually miliary tuberculosis, is a much less common cause of uveitis, but it does not present a diagnostic problem. Coccidioidomycosis and blastomycosis are even rarer causes of uveitis. The chest roentgenogram and the skin tests (and, in the case of coccidioidomycosis, knowing that the patient has lived in the San Joaquin Valley) help to confirm the diagnosis.

Intraretinal cell sarcoma may present as a nonspecific uveitis (PL 14.1D). If a patient with this presentation also develops a cranial nerve paresis, particularly a seventh cranial nerve paresis, consider retinum cell sarcoma as well as sarcoidosis in the differential diagnosis. When the diagnosis remains obscure, a vitreous biopsy may show the presence of a monoclonal immunoglobulin and light chains in the B lymphocytes present in the vitreous inflammatory tissue.
Acquired Immune Deficiency Syndrome (AIDS)

Reports of new forms of ophthalmologic involvement in patients with AIDS are appearing in the literature daily. Ocular involvement is very common and has been estimated clinically as occurring in up to 70% of patients with AIDS. The incidence is even higher in postmortem studies, ranging up to 95%. One of the most common forms is retinal cotton-wool spots and hemorrhages (Fig. 13.15, A and B). This sign may be a prognosticator for the severity of the disease to come. In a study involving 127 patients, Freeman et al. did not see any cotton-wool spots in seronegative homosexual males or in patients who were seropositive for the HIV virus but still asymptomatic. However, this sign was seen in 43.3% of symptomatic AIDS patients. This last group of patients also had a decrease in the ratio of T-helper cells to suppressor cells, confirming their immunodeficiency. Cotton-wool spots and hemorrhages can be seen in other diseases, such as hypertension, vascular disease, and collagen vascular disease, but these should not cause confusion in this clinical setting. The hemorrhages are in the nerve fiber layer and take the appropriate shape. Stasis of axoplasmic flow creates the cotton-wool spot appearance. An occlusion of a precapillary arteriole causes an infarct in the nerve fiber layer. Occasionally, there are hemorrhages with white spots that are somewhat similar in appearance to Roth spots. This type of retinal hemorrhage suggests other diagnoses such as subacute bacterial endocarditis, leukaemia, lupus, anorexia, carbon monoxide poisoning, and candidiasis. Again, however, the clinical picture usually is clear enough to lead the physician away from these other diagnoses and to suggest AIDS as the most likely diagnosis.

Infection in the retina is another common ocular presentation in AIDS patients. The most common pathogen is cytomegalovirus (CMV), although it is not the only pathogen found. CMV be family. It is containing virus as retinitis, encephalitis, hepatitis and adrenalitis, to involve first and then the en- nals invariably le: The retinitis is blindness in AI can also present uveitis, vitritis, and retinal ne even though AI CMV infection, the retinitis als varicella-zoster nerosis syndro: nodal opacification scolloped borders abnormal retina dcribed as “no appear as minin
found. CMV belongs to the Herpetoviridae family. It is a deoxyribonucleic acid—
containing virus. CMV infection can present as retinitis, encephalitis, esophagitis, pneu-
monitis, hepatitis, colitis, polyradiculopathy, and adrenalitis. The CMV retinitis can spread
to involve first one part of the optic nerve and then the entire nerve. Disc CMV papilti-
itis invariably leads to severe loss of vision. The retinitis is the most common cause of
blindness in AIDS patients. CMV infection can also present as episcleritis, anterior
uveitis, vitritis, obliterative retinal arteritis, and retinal necrosis syndrome. However,
even though AIDS patients are candidates for CMV infection, the differential diagnosis of
the retinitis also includes herpes simplex, varicella-zoster retinitis, and acute retinal
necrosis syndrome. In AIDS patients, the reti-
nal opacification is usually peripheral, with scalded borders between the normal and
abnormal retina; a later appearance is de-
scribed as “moth-eaten.” The early lesions
appear as minimal graying of the retina with-
out hemorrhage. The hemorrhagic phase
progresses to new necrotic retinitis and total
retinal destruction. CMV infection can pre-
sent as a retinal detachment. Indirect opht-
almoscopy of the retinal periphery may re-
veal retinitis and be the clue to the diagnosis
of CMV infection in patients receiving treat-
ment for nonocular CMV disease. Atrophic
areas with indistinct borders develop and
progress to total retinal destruction before
more obvious signs of retinitis develop.
There is now some promising treatment for
these patients in the form of intensive ganci-
clovir for 2 to 3 weeks, with a maintenance
dose after that. The problem with this treat-
ment is the development of neutropenia,
which can be reversed when the medication
is discontinued. This CMV retinitis may mimic
the acute retinal necrosis syndrome, but the
latter has more-marked vitritis.

More and more reports of AIDS patients
with multiple infections are appearing in the
literature. Because those at high risk for
AIDS are also at risk for such diseases as

**Figure 13.15. (continued)**

A and B. Fundus of AIDS patient with diffuse hemorrhage, cotton-wool spots, and arterial changes. (Courtesy of Dr.
Kathleen Stoessel.)
syphilis, they should be screened for syphilis, particularly if there are neurologic symptoms. The usual condition of the immune system in these patients may make the usual serologic screening for syphilis abnormal. Vitreous biopsies can be done, but cultures from such biopsies are notoriously unproductive. Retinal biopsy has potentially more serious problems than vitreous biopsy but may be considered if one eye is gone and the other is threatened. The widest possible culture media should be explored so as not to miss any bacterial, viral, or fungal diseases, all of which have been reported.

Neurologic symptoms in AIDS patients are not unusual. About 40% of these patients will have neurologic symptoms, and 10 to 20% of these will have them as the initial presenting symptom of the disease. Syphilis should always be considered in AIDS patients with neurologic symptoms. Brainstem syndromes are not an uncommon presentation; these include gaze palsies with or without sixth- or seventh-nerve palsies and internuclear ophthalmoplegias. The differential diagnosis of such a presentation in young people includes demyelinating disease, hemorrhage, paraneoplasms, neoplasms, and a congenital malformation with enlargement and/or hemorrhage.

There are also external disease manifestations with AIDS patients. These include molluscum contagiosum, ulcerative keratitis (herpes simplex, herpes zoster), Kaposi's sarcoma, and keratitis sicca. The patients with AIDS and molluscum contagiosum differ from the usual presentation of those diseases. These lesions are more numerous and more frequently present on mucous membranes, and they coalesce. The keratitis of herpes simplex and herpes zoster appear similar and yet demonstrate some differences. The dendritic figures of herpes zoster are peripheral and not central in location. They do not have the multiple arborizations and end knobs seen in herpes simplex. They stain poorly and are generally flatter and broader.

Kaposi's sarcoma is the most common neoplasm and is seen in up to 50% of AIDS patients. In patients with Kaposi's sarcoma, the most common site of presentation is nonocular. It presents on the eyelid or conjunctiva in only 20% of patients.

Non-Hodgkin's lymphoma and toxoplasmosis are the two leading causes of a mass lesion in the brain of AIDS patients. MRI cannot always differentiate these lesions. Brain biopsy is not without its morbidity, and a spinal tap with a cell count is frequently negative. The alternative site for identification may be the eye. The lymphoma may be primary in the eye or secondary in its disseminated form. If it is primary in the eye, then it affects the retina and spares the choroid. If it is metastatic, then the uveal tract is the primary site of involvement. The ocular presentation is of a rapidly progressive loss of vision and floaters. A vitreous biopsy may be diagnostic. The cells are described as having prominent nuclei and scant cytoplasm. These large atypical cells are characteristic of a large-cell lymphoma.

Other types of ocular involvement found in AIDS include papilledema, papillitis, optic atrophy, cortical blindness, retrobulbar neuritis, field defects, visual asthesia, pupill abnormalities, and ocular motor palsies.

**Leber's Stellate Neuroretinitis**

Leber's stellate neuritis is a disease of unproven etiology. Both eyes often are involved at the same time, suggesting a blood-borne infectious disease, and there is frequently a history of a recent viral-type illness. Infections such as cat scratch fever and syphilis have been seen in the differential diagnosis of these patients.

The symptoms of Leber's stellate neuritis include decreased visual acuity, vitreous cells, disc swelling, peripapillary retinal detachment, and macular stars. The latter are an expression of juxtapapillary retinal detachment and lipid exudation, which can be demonstrated on fluorescein angiography. The differential diagnosis of macular...
Lyme Disease

Lyme disease was first recognized in Lyme, Connecticut, in 1975 when a group of children developed a mono- or multijoint inflammatory arthropathy. One-fourth of them had an associated expanding skin lesion, named erythema chronicum migrans (ECM), which preceded the arthropathy. The lesion was a red macular papule that expanded to form a large red ring with partial central clearing (Fig. 13.17). This lesion was similar to the one seen in a European disease transmitted through the bite of the *Ixodes ricinus* tick. However, the European version of the disease had more neurologic symptoms and rare joint involvement. The European disease was referred to as tick-borne meningogepoly neuritis as early as 1922 by Garin and Bujadoux; it was described more extensively by Horstap and Ackermann in 1973. At that time, the specific causative agent had not been identified in either disease. The geographic distribution of Lyme disease has steadily increased. By the late 1980s, 92% of cases had been reported from New York, New Jersey, Pennsylvania, Connecticut, Massachusetts, Rhode Island, Wisconsin, and Minnesota. In 1987 to 1988, New York reported 57% of the cases. The location of the skin lesions, which are found mostly on the thigh, axilla, and groin, suggests a crawling arthropod vector rather than a flying vector. However, it was not until 1982 that

![Image of an eye with a red macular papule and edema of the disc.](image-url)
Burgdorfer et al. were able to isolate and identify the Lyme spirochete. The organism was first extracted from the *Ixodes dammini* tick and then from humans with clinical Lyme disease; this organism is now called *Borrelia burgdorferi*. Shortly thereafter, a similar organism was identified as the causative agent of the European version of the disease.

Lyme disease, like other spirochetal diseases such as syphilis, has remissions and exacerbations, with different manifestations at each stage. The first-stage symptoms occur within several days to a month after the bite and infection by the tick. The typical skin lesion starts at the location of the bite, with an expanding area of erythema; it expands to an average diameter of 15 cm. This is followed by some clearing of the central area of erythema, resulting in a ringlike appearance.Transient skin eruptions occur rarely but are not as diagnostic as the erythema chronica migrans. During this early phase, the patient has a flu-like syndrome with fever, headache, neuroarthralgia, myalgia, malaise, and lymphadenopathy. Arthralgia of the temporomandibular joint may be seen; this symptom is typical in Lyme disease but is not seen in rheumatoid disease.

Conjunctivitis is the most common ophthalmologic involvement during the first stage of Lyme disease. Chorioiditis, exudative retinal detachment, keratitis, iridocyclitis, and retinal vasculitis have also been reported at this stage or early in stage 2. I have seen one patient with recurrent iritis who finally cleared when diagnosed as having Lyme disease and treated with intravenous antibiotics. The usual presentation of stage 2 is neurologic or cardiac symptoms. The neurologic symptoms are three times more common, with facial nerve palsy the leading sign. The sixth and optic nerves are much less frequently involved. These manifestations are much rarer than conjunctivitis. Neurologic involvement includes the form of meningitis with headache and stiff neck. Spinal fluid examination reveals a lymphocytic pleocytosis with 15 to 700 white blood cells per milliliter. There is also a slight elevation of the protein and a normal glucose level. These findings may falsely suggest septic meningitis rather than Lyme meningitis. Other neurologic signs and symptoms are peripheral neuropathy and cranial-nerve palsies, particularly of the seventh cranial nerve. The latter occurs in up to 10% of patients in the course of Lyme disease and not uncommonly is bilateral. Papilledema has been reported in five patients with some decrease in vision, but only one had increased intracranial pressure and a pseudotumor-like syndrome. One case of Lyme disease with disc edema, decreased vision, and an atypical defect has been reported.

Second-stage Lyme disease is characterized by cardiac involvement and additional CNS involvement. The incidence of Bell's palsy increases, and some cases with sixth-nerve and third-nerve palsies have been reported. Lyme carditis, which occurs in 8% of patients within 2 to 6 weeks of the initial infection, is manifested by varying degrees of
atrioventricular block. In some patients, the block has been severe enough to require a temporary pacemaker, but rarely have there been long-term conduction difficulties requiring a permanent pacemaker. If there is ventricular dysfunction and arthritis, then rheumatic fever may confuse the differential diagnosis.

Stage 3 can occur within a few weeks up to 2 years after the initial infection and is manifested by arthritis and more chronic sequelae. About 15% of patients eventually show neurologic complications. The usual clinical picture is fluctuating meningoencephalitis associated with variable cranial and peripheral radiculoneuropathies. The most common neurologic symptoms are cognitive impairment, behavioral changes, chronic fatigue, chorea, cerebellar ataxia, and rarely seizures. MRI can show demyelinating-type lesions, cerebral atrophy, or ischemic infarcts. That these lesions on MRI are reversible, that they occur in patients with CNS symptoms, and that specific antibodies are present in the cerebral spinal fluid all suggest the hypothesis of CNS infection with *B. burgdorferi*. An elevated level of cryoglobulins in stage 1 is a good predictor for which patients will develop arthritis in later stages; the cryoglobulin level rises again in stage 3 in patients who later develop neurologic symptoms. As a patient develops attacks of neurologic or arthritic symptoms, the cryoglobulin level rises with each attack. Elevated cryoglobulins are also seen in immune-complex diseases such as serum sickness, lupus erythematosus, and infectious mononucleosis, suggesting that a similar immune response mediates the more chronic neurologic symptoms in Lyme disease.

Although the fetus can be affected by maternal infection with the Lyme spirochete, most pregnancies of such women have been normal. No uniform congenital malformation pattern has been observed in the offspring of women with Lyme disease. If the mother contracts the disease during the first trimester of pregnancy, the abnormalities are predominately cardiac, such as coarctation of the aorta, septal defects, and lesions of the heart and great vessels. Lyme disease may be a cause of fetal death in women who do not know they have the disease but have a positive titer.

Laboratory testing to determine markers of Lyme disease has steadily improved but is still not perfect. The enzyme-linked immunosorbent assay (ELISA) is preferred to immunofluorescence assay (IFA), which is not practical for large-scale testing. Immunoblotting techniques are also used and can identify major surface proteins, but these are not in general clinical use. A disease-specific protein with a molecular mass of 41 kilodaltons (kDa) has been identified in early Lyme disease when the typical erythema chronicum migrans is present. In the later stages, a 31-kDa surface protein that is specific for *B. burgdorferi* can be found. The first-stage protein may be useful in difficult early cases when the diagnosis is not clear or the skin lesion is atypical. During this early phase, the IgM level may not have risen enough to be diagnostic.

Starting 3 to 4 weeks after the onset of erythema chronicum migrans, serum IgG increases for about 1 month and then decreases. At this point in the disease, serum IgG begins to rise and will do so with each exacerbation of the disease, such as repeated attacks of arthritis. False-positive IFA and ELISA assays can occur as the result of cross-reactivity with other spirochetes such as *Borrelia hermsii*, *Treponema pallidum* (the syphilis agent), and the common mouth contaminant *Treponema denticola*. Biopsy of the skin lesion has produced evidence of organisms but has a low potential yield.

As noted above, cryoglobulin levels tend to be elevated during the first stage of Lyme disease in those who go on to arthritis. The cryoglobulin level rises again later if neurologic complications occur, a phenomenon observed by Reik et al. in a review of their patients with neurologic complications. The exact origin of these cryoglobulins is unknown, but they are considered to be derived from antigen-antibody complexes. However, the cryoglobulin response is not specific, as cryoglobulins are seen in serum
sickness, systemic lupus erythematosus, infectious mononucleosis, CMV infection, hepatitis B, essential mixed cryoglobulinemia, and a host of other diverse diseases. Most of these viral and rickettsial diseases can be ruled out by other serologic tests. Serum sickness, a known immunocomplex disease, has a multifocal mononeuropathy similar to that seen in Lyme disease. Serum sickness is characterized by a widespread vasculopathy, and the diffuse symptoms of Lyme disease suggest that the same mechanism is operating. However, it is not known whether immune complexes are primary in Lyme disease or result from the vascular injury.

Several diseases besides Lyme disease are in the major differential diagnosis. Serum sickness, as mentioned above, has a similar neurologic picture; however, unlike Lyme disease, it does not recur without repeat exposure to the antigen. Other diseases that cause similar neurologic, ophthalmologic, and arthritic symptoms include MS, sarcoidosis, Behcet syndrome, and Vogt-Koyanagi-Harada syndrome. Both MS and Lyme disease can have widespread multifocal symptoms, exhibit remissions and exacerbations, and show increased cerebral spinal fluid IgG when neurologic symptoms present. Lyme disease shows lymphocytosis, peripheral neuropathies, and encephalitis, which are not seen with MS. Sarcoidosis has neurologic symptoms such as seventh-nerve palsy and recurrent aseptic meningitis. Usually, sarcoidosis has pulmonary symptoms, which help in the differential diagnosis, but these are not always present. Behcet syndrome has meningoencephalitis, arthritis, and uveitis, but not cryoglobulins; it also has oral and genital ulcerations. Vogt-Koyanagi-Harada syndrome (uveomeningoencephalitis syndrome) has ocular and neurologic symptoms that recur and remit. However, the skin signs are different from those in Lyme disease. The secondary skin changes in this syndrome include poliosis, vitiligo, and alopecia; they may occur any time during the course of the disease but usually occur weeks to months after the ocular and meningoencephalitic symptoms present.

Lyme disease is usually treated with tetracycline or doxycycline in all patients except children and pregnant women. For the latter two groups, phenoxymethyl penicillin is the drug of choice. For the more severe neurologic complications, intravenous penicillin for 10 to 14 days or ceftriaxone for 14 days is recommended. Unfortunately, neurologic cases refractory to treatment do occur and must run their course.

**Orbital Inflammations**

Orbital inflammations usually show sufficient signs to suggest the diagnosis. The relationship of sinus disease to optic neuritis has been vastly overemphasized. If sinus infections affect the optic nerve, they usually do so when they break through the medial wall and the peristome into the orbit and create an orbital abscess with marked edema, struma, pain, and systemic signs of infection. In children, sinus infection generally comes from the ethmoid sinuses, since these sinuses are formed in early life, and only a thin wall (the lamina papyracea) separates them from the orbital contents. FrONTAL sinus disease is not seen until the teenage years, since the frontal sinuses do not form until a person is about 12 years of age. Orbital infection in infants, which occurs rarely, is caused by an infected tooth bud.

The usual presentation of orbital involvement from extension of bacterial sinusitis often is dramatic. There is proptosis, swelling, pain, ophthalmoplegia, and visual loss. The decrease in vision may present as either papillitis, neuroretinitis, or retrobulbar optic neuritis. If improperly diagnosed and treated, the infection spreads into the cavernous sinus, with thrombosis and even death. The more posterior the infection, the more subtle these signs may be, and visual loss may be the most prominent of all the signs. This is particularly likely to occur when the sphenoid sinus is the site of the infection. The optic nerve is an particularly the sphenoid (incomplete by only the leptin from the spine). Optic neuritis occurs about initial symptom picture of bills nerve head; it accumulation. There is optic vision. Varicab those assoc. In the case of gestin vari. changes in th. Herpes zoster frequent clinical comes on wh. well into the 1st is unilateral. The visits the childhood vascular ba. Optic neuritis infectious mo. Optic nerve herpes zoster over the first is rare. If it is quently leads Thyroid dis the thyrotoxi...or an ent. the orbital ap...ion (Fig. 1). Treated consi...sionally orb... (infect...
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... cc nerve is attached to the optic canal and is particularly vulnerable as it runs adjacent to the sphenoid sinus. In some people, there is incomplete bony protection in the canal, and only the leptomeninges separate the nerve from the sphenoid sinus.

Optic neuritis associated with septic infections other than sinusitis has been well reported, but infrequently. It has been seen particularly in childhood rubeola when other signs of encephalitis are present. Optic neuritis has also been reported in rubella and mumps. The clinical course is very similar in all of these diseases. The optic neuritis occurs about 1 week after the onset of the initial symptoms. The optic nerve presents a picture of bilateral papillitis with a swollen nerve head; this swelling may be axoplasmic accumulation. When the infection clears, there is optic nerve pallor and usually good vision. Varicella infections do better than those associated with the other exanthems. In the case of measles, particularly the congenital variety, there may be additional changes in the retina.

Herpes zoster optic neuropathy has a different clinical profile. Optic neuritis usually occurs when the skin manifestations are well into the healing phase. The optic neuritis is unilateral to the side of the skin infection. The visual result is not as good as in the childhood exanthems and is probably on a vascular basis rather than demyelination. Optic neuritis occurs, although rarely, with infectious mononucleosis.

Optic nerve involvement related to typical herpes zoster ophthalmicus with vesicles over the first division of the trigeminal nerve is rare. If it is of the ischemic variety, it frequently leads to blindness.

Thyroid disease, either the thyrotoxic or the thyrotropic form, can cause optic neuritis, probably as a result of orbital inflammation or an enlarged confluence of muscles at the orbital apex, causing vascular compression (Fig. 13.18). Most patients can be treated conservatively with steroids, but occasionally orbital decompression may be required (infrequently, I find). Optic neuritis has also been related to diabetes, but the relationship is on less solid ground.

Sarcoid uveitis has been discussed. Orbital sarcoid involvement as a mass lesion can also occur. It requires the same type of evaluation as that for sarcoid uveitis, as well as the evaluation outlined for an orbital mass.

Syphilis causes many types of ocular involvement. When the disease involves the optic nerve, it affects the peripheral part of that nerve more than the axial part. The opposite happens in other forms of optic neuritis, such as that owing to MS. Although the central visual acuity is not totally spared, the peripheral field loss is greater in syphilis. The serologic tests and other clinical signs should establish the diagnosis. Optic neuritis is usually a form of secondary syphilis. Syphilis has been in the medical literature since time immemorial. Since the introduction of penicillin, the incidence has dropped dramatically. However, in the late 1970s, the incidence began rising. By 1988 there were over 40,000 new cases of primary and secondary syphilis reported in the United States. Uveitis has been the most common presentation in a recent series.

Figure 13.18.
An enlarged muscle encroaching on the optic nerve (arrow) caused decreased vision with minimal proptosis in this patient. This optic neuritis can be seen in patients with thyroid disease.
Gass has reported six patients with secondary syphilis who developed large placid yellowish lesions at the level of the pigment epithelium, with faded centers. They were located in the macula and juxtapapillary area. The fluorescein test showed early hypofluorescence and late staining. They were treated with antibiotics and improved.

A rare form of ocular involvement is periostitis of the orbit. There is severe pain when the periosteum is palpated. The appropriate serologic tests will confirm the diagnosis.

**Pars Planitis**

Pars planitis—a chronic exudative inflammation of the pars plana area of the retinal occurs with gross involvement of the anterior vitreous humor. It causes blurred vision because of cellular debris in the vitreous humor and, eventually, macular edema. Pars planitis usually occurs in persons between the ages of 20 and 35. It is bilateral in 75% of cases. Anterior uveal involvement usually occurs, as exhibited by a slight anterior chamber flare and fine keratic precipitates. The most specific sign is the collection of white exudates (referred to as “snow-banking”) on the peripheral retina, particularly inferiorly. The cause is not known. Systemic steroids appear to be of little help.

**Radiation Retinopathy**

Delayed radiation effects can occur 18 to 36 months after the radiation therapy. This optic neuropathy may present as progressive bitemporal field loss after radiation for pituitary adenoma, confusing the issue of recurrent tumor versus radiation effect. This condition can occur even when proper amounts of radiation have been administered. If the brain radiation is anterior, radiation retinopathy may occur even when the eye was properly shielded.

The retinal findings are those of small-vessel telangiectasis with capillary microaneurysms, hemorrhages, and cotton-wool spots. The resulting exudate frequently takes a circinate pattern. Additional signs of vasculitis include sheathing of vessels. There is a particular predilection for the macular and perimacular areas. Secondary to this ischemic process, papillitis and subsequent optic atrophy may occur. All of these findings, plus areas of nonprofusion on fluorescein angiography, suggest that radiation retinopathy is secondary to vascular injury.

Delayed radiation effects on cerebral tissue peak 12 to 18 months after the radiation exposure. The daily dose seems to be more related to delayed effects than is the total dose. Patients treated for chiasmal gliomas are particularly susceptible, probably because the carotid arteries are included in the radiation field. This finding lends credence to the vascular theory. Delayed radiation effects seem to occur more readily in those with other forms of vascular disease, such as diabetes and arteriosclerosis. Chemotherapy may also potentiate the effects of radiation. Delayed radiation effects in cerebral tissue may involve several mechanisms, just as in the retina, radiation may cause direct vascular damage and secondary necrosis of cerebral tissue. There may also be an altered antigen response, with secondary vasculitis or direct injury to neural tissue itself. After radiation of a pituitary tumor, there sometimes is a further decrease in vision after a period of stable vision. The question is whether this is progression of the tumor or a radiation effect. In some cases, radiation has caused secondary tumors (e.g., sarcomas, meningiomas, and gliomas) to occur. Radiation may also cause a prolapse of the chiasm into an empty sellar, arachnoiditis, or pituitary apoplexy. The treatment for each of these is different. High-resolution CT with metrizamide can demonstrate areas of decreased attenuation in the white matter, representing cerebral radionecrosis. The effectiveness of treatment for radiation effects, even large doses of steroids, has been dismal. If the necrotic area caused by the radiation creates a mass effect, an excision of it should be considered. Some preliminary work has been reported as beneficial, but caution is necessary for any intervention.

**Intracranial**

Herpes simplex virus infection is often acute, usually localized. The fever and headache occur with or without a rash, followed by blurring of vision and photopsia. The corneal reflex is absent. Corticosteroids reduce inflammation, cell damage, and photopsia. The entire eye is inflamed, and cells are seen in the aqueous. There is a rapid reaction to antiviral medication. The disease usually recovers completely within 2 weeks, even with treatment. However, after a latent period, reactivation may occur. HSV1 reactivation is less common than HSV2 reactivation. HSV1 reactivation usually occurs 3 to 5 weeks after the initial infection. HSV1 reactivation is typically a more severe condition than HSV2 reactivation.

**TUMOROSITY**

**Ocular Tumor**

Ocular tumors are rare and can be benign or malignant. Benign tumors are more common than malignant tumors. Benign tumors include choroidal nevi, papilloma, and hemangioma. Malignant tumors include primary ocular melanoma, metastatic melanoma, and melanoma of the choroid. Melanomas can be either malignant or benign. Metastatic tumors include breast cancer, prostate cancer, and lung cancer. Metastatic tumors are more common than primary tumors.

**Metastatic**

Metastatic tumors are more common than primary tumors. Metastatic tumors include breast cancer, prostate cancer, and lung cancer. Metastatic tumors are more common than primary tumors.
work with hyperbaric oxygen may prove beneficial, but the research is too preliminary for any final assessment.

**Intracranial Inflammations**

Herpes simplex encephalitis is uncommon but not as rare as was once thought. This is because the diagnosis was only made postmortem. The condition begins abruptly with fever and headache. Convulsions and delirium also occur, which progress to coma and death within 1 week on the average. Frequently, there is cranial nerve involvement, signs of pyramidal tract damage, and an unusual increase in intracranial pressure. The initial and most vital treatment is directed toward equalizing the increased intracranial pressure by steroids or surgical decompression. The cerebral spinal fluid usually shows a lymphocytosis of 175 to 1000 cells/cm³. Viral cultures are rarely positive, but a rising antibody titer against herpes simplex can help make the diagnosis. A brain biopsy with a demonstration of inflammatory changes consistent with acute encephalitis in association with a Cowdry-type intranuclear inclusion body is helpful in establishing the diagnosis. The disease usually results in death; spontaneous recovery is rare. Type 1 herpes simplex is the usual type in the adult form. Type 2, which is associated with genital herpes, is seen in infants who are infected with the virus as they pass through the vaginal canal. Herpes simplex encephalitis occurs so frequently that it is hard to associate it with any contributing factors; however, it is slightly more prevalent in patients who have Hodgkin's disease, most likely because these patients have a reduced or impaired host immune response.

**TUMOROUS CAUSES**

**Ocular Tumors**

Ocular tumors are primarily melanomas or metastatic tumors from the breast or lung. They affect central vision either primarily by way of a solid retinal detachment involving the macula or by the edema around the mass that extends into the macula. A careful fundus examination easily identifies this cause of blurred vision as a mass lesion.

**Leukemia**

When leukemia occurs with increased blood viscosity because of an increase in leukemic cells or the presence of abnormal proteins (such as macroglobulins or cryoglobulins), vascular occlusive disease may result. The acute variety of leukemia shows more retinal changes, with mild disc edema and retinal hemorrhages, particularly Roth spots (PL 21, C). A loss of vision may also occur owing to choroidal infiltrates with overlying serous detachment of the retina. The chronic form of leukemia can produce a retrobulbar optic neuritis whose relationship to chronic lymphatic leukemia may go unnoticed because of the time lapse between the onset of leukemia and the appearance of the optic neuritis. Steroids are particularly beneficial in this type of optic neuritis, which is the reason for identifying the cause.

Direct invasion of the optic nerve and uveal tract, once thought rare, is becoming more frequent as a result of increasing therapeutic efficacy. However, these chemotherapeutic drugs create other problems, which are hematologic. The anemia and hyperviscosity that develops causes capillary closure, microaneurysms, and retinal neovascularization. Intrathecal therapy is not as effective on optic nerve lesions as it is on the rest of the brain. Radiation is effective, since leukemic cells are more radiosensitive than the optic nerve tissue. Combined therapy may be more effective. The radiation can cause a reduction in leukemic cells, and then the intrathecal therapy has a better pathway to reach the remainder of the leukemic cells. The combined therapy is not without problems and increases the risk of leukencephalopathy.
Optic neuropathy related to carcinoma is becoming more widely understood. Carcinoma can cause optic neuropathy without direct involvement, probably because of the vitamin and other nutritional deficiencies that are caused by the malignancy. If meningeal involvement and secondary involvement of the optic nerve are present, a cerebral spinal fluid examination should be performed. The spinal fluid can be spun down for a cell block examination. The spinal fluid sugar level can be decreased as well, suggesting a malignancy is likely.

In some types of carcinoma, particularly carcinoma of the stomach, an increase of the macroglobulins and cryoglobulins causes intravascular coagulability. Vision can also be affected by the hypercoagulability and sludging of the formed elements of the blood in the polycythemia that is secondary to hemangioblastoma of the cerebellum.

**Extraocular Tumors**

The entire range of orbital and intracranial tumors makes up the extraocular tumors affecting vision. Chronic increased intracranial pressure from whatever cause—tumor or pseudotumor—eventually causes progressive loss of vision and, if not treated, blindness. The discussion below is limited to two of the more common orbital tumors—glioma and meningioma.

Glioma of the optic nerve usually has an insidious onset. The diagnosis of poor visual acuity generally is made at a school vision-screening test, or a strabismus is noted. The patient usually does not come to the physician with a specific complaint of loss of vision. Eighty to 90% of optic nerve gliomas occur in persons under 20 years of age, and most of these occur in persons under 10 years of age. The central visual acuity is decreased, and occasionally, exophthalmos has already begun.

In a person under 10 years of age who has loss of vision in one eye, optic nerve glioma, rather than optic neuritis, should be ruled out first. Since optic nerve gliomas usually start in the intraorbital part of the optic nerve, vision loss and exophthalmos are the early observable signs. Roentgenography of the optic canal may already show erosion of the canal, a finding that not only confirms that a tumor is present but also indicates its intracranial extension. Observation of the patient for any of the signs of neurofibromatosis is also important, they are present in about 25% of cases of optic nerve glioma. An MRI with corona view of the orbit should show enlargement of the optic nerve. If possible, a careful field examination of the uninvolved eye should be done. Pay particular attention to the presence of a temporal field defect in the upper quadrant of the uninvolved eye, which indicates that the intracranial involvement has reached the chiasm.

The treatment of gliomas is somewhat controversial. Glaser, Hoyt, and Corbett, in their review of chiasmal gliomas, and Hoyt and Baghdassarian, in their review of cases of optic nerve gliomas, concluded that these tumors represent a hamartoma. They felt that most patients maintain stable vision and do not require radical surgery except for the relief of proptosis in a blind eye. Optic nerve gliomas appear to act differently from gliomas in other parts of the CNS. This may be the result of their high association with neurofibromatosis. In a review of cases in the British literature, the authors concluded that optic nerve gliomas associated with neurofibromatosis are less aggressive than gliomas of the CNS in general. All of these cases, however, must be followed closely for any signs of continued growth into the intracranial cavity.

Meningioma is the most common intracranial tumor and the second most common intracranial tumor that produces neuroophthalmologic signs (pituitary tumor is first). Loss of vision is the most common of these signs. The tumor can occur in persons of any age, but it is most common in persons in their 40s and 50s. It is more common in women than in men. The dictum of progressive loss of vision, female, and 40 years of age has not always held true.
you add ophthalmic shunt vessels, then the diagnosis is almost ensured. The usual MRI picture of an optic nerve meningioma is tubular thickening of all or part of the optic nerve, with a central linear lucency. Meningiomas are isomorphic to the brain and not as easily identified except with gadolinium. The latter technique is important to identify intracranial extension. Childhood meningiomas are rarer, associated with neurofibromatosis, and usually more invasive. One of the early signs is transient visual loss, frequently seen with optic nerve edema. These transient obscurations may be related to ocular ductions, which may cause vascular compression and decreased blood flow to the retina. Although slow, progressive, insidious, visual loss is the usual scenario, some meningiomas can cause rapid loss of vision. The latter can be seen in pregnancy, when a previously slow-growing meningioma changes its growth characteristics and rapidly expands, causing vision loss. The change in growth is probably related to some hormonal receptor in the tumor that stimulates it beyond its usual growth pattern. Meningiomas in children are rare and account for 1.5% of all meningiomas. In adults, meningiomas occur predominantly in the anterior fossa. In children, they occur in all the fossae. The prognosis for meningioma in children is somewhat worse than that in adults, because they undergo sarcomatous changes. The presence of shunt vessels on the disc is an excellent sign that one is dealing with a meningioma of the optic nerve (PI. 14.1E). Although a few cases have been reported in which the tumor was surgically removed from the eye leaving good vision, this is not the usual experience of most physicians treating this disease. It is felt that in removing the tumor from the nerve, the fine vessels from the perineural to the nerve are also destroyed, causing more ischemia to an already compromised nerve.

Sphenoid ridge meningiomas commonly affect vision before they cause exophthalmos or extraocular muscle paralysis. Roentgenograms of the sphenoid ridge usually show changes; for example, diffuse decalcification that has left only a shadowy bony area where the sphenoid bone, with all its landmarks, should be. Hyperostosis of the superior orbital fissure and optic canal is another possible change, and one that is far more suggestive of the diagnosis. If hyperostosis is present, the patient needs to be evaluated by a neurosurgeon and with contrast studies that outline the extent of the lesion. The tumor may spread to surrounding structures to such an extent that removal may be impractical because of the neurologic deficit that an operation would cause.

The use of CT and MRI has immeasurably improved the diagnosis of optic nerve tumors short of a biopsy and pathologic confirmation. The CT image of an abnormally small optic nerve reveals either a hypoplastic or an atrophic nerve. The fundus appearance of the nerve helps differentiate these two diagnoses. Optic nerve enlargement, on the other hand, has a larger differential diagnosis. The commonest cause of enlargement is increased intracranial pressure with papilledema. Inflammations of the optic nerve are also a common cause, but an enlarged nerve is not always seen on CT and MRI. Tumor is the least common cause of enlargement and includes gliomas, meningiomas, and carcinomatosis with leptomeningeal infiltrates. Coronal sections give the best chance of delineating the features of the optic nerve enlargement that help in the differential diagnosis. Coronal sections not only show the enlargement, but also the cross-sectional view of the nerve, perineural space, and optic nerve sheath. In meningiomas that arise from the optic nerve sheath, the enlargement is perineural or tubular in configuration. The density of the tumor differs from that of the nerve, which appears as a central radiolucent area (Fig. 13.19). Some meningiomas are more aggressive and break through the dural coat, forming an excrecent configuration. This configuration can also be seen in infections such as sarcoidosis and some viral infections that cause a periostic neuritis.

The absence of a difference in density between the nerve and surrounding sheaths in
a CT image of an enlarged optic nerve with a tubular configuration is consistent with an optic nerve glioma. However, leukemia and lymphoma also affect both the nerve and sheath, giving a uniform density.

Opticiliary shunt vessels on the optic nerve may be seen with optic nerve meningiomas and may help with the diagnosis. Opticiliary shunt vessels have also been reported, with hydrocele of the optic disc, drusen, pseudotumor cerebri, arachnoid cysts of the optic nerve head, and venous thrombosis of the optic disc. Shunt vessels have been reported with optic nerve glioma, but their incidence with this tumor is much lower than with meningioma.

MRI recently has added another dimension to the investigation of optic nerve tumors associated with neurofibromatosis. Optic nerve tumors not associated with neurofibromatosis involve the intraneural portion of the optic nerve and do not invade the pit; this gives the nerve a tubular configuration. Tumors associated with neurofibromatosis have a proliferation of astrocytes in the perineural space. Glial tissue has a higher water content than the tumor. A T2-weighted MR image can demonstrate this difference.

Fusiform enlargement of the optic nerve is more compatible with meningioma.

Two rare forms of optic nerve enlargement are a perineural hemorrhage and cystic compression. Both are responsive to optic nerve sheath decompression.

Surgical removal of optic nerve meningiomas with preservation of vision has had a poor prognosis. The Mayo Clinic experience with 20 cases was reviewed by Hollenhorst and Young, who confirmed this assessment. Kuno, however, reported the microsurgical removal of an optic nerve meningioma with preservation of good vision in one patient. One reason given for the lack of good vision following surgery is the intimate relationship between the blood supply of the nerve and the tumor. Dissection of the tumor interferes with the blood supply of both and causes ischemia and infarction of the nerve. In reviewing their cases involving microsurgical removal of anterior visual system meningiomas, Rosenberg and Miller found that morbidity and postoperative results were no better than when removal was performed without microsurgical techniques. It seems that the longer a tumor is present, the poorer the visual result following surgical removal. This correlation is to be expected because of the more the optic nature of the tumor.

Many sur and ophthalmic cases of meningiomas of the optic nerve may be removed without complications, but there is always a risk of recurrence. Intraocular meningiomas are rare, and a similar degree of risk is expected. I have seen rare cases of meningiomas occurring in the optic nerve that do not involve the dura mater.

Somatic features of meningiomas include a long history and a rapid course. There is a higher incidence of meningiomas in men than in women. The highest incidence is in the fifth decade of life. Meningiomas are more common in men than in women. The highest incidence is in the fifth decade of life. Meningiomas are more common in men than in women.
the more intimate relationship between the optic nerve and tumor that develops with growth of the tumor. Microsurgical techniques have advanced the frontiers of many surgical operations in neurosurgery and ophthalmology. More extensive experiments and expansion of present techniques may yet conquer the problems of early diagnosis and early successful microsurgery in cases of optic nerve meningioma.

Cranopharyngioma is another tumor that may be missed because of its symptomatology. Instead of a slow, steady, progressive course, the symptoms are often intermittent and variable. Although these tumors are the result of a congenital variant, they can cause symptoms at any age. They may cause disturbances of growth and sexual development in children, both with and without increased intracranial pressure. Progressive loss of vision is common. In adults, dementia and visual loss are the most common signs and symptoms. In children, the roentgenogram shows calcification in the suprasellar region in over 90% of cases. This calcification is rarely seen in the adult form of the disease.

Sometimes it is difficult to differentiate infectious from neoplastic meningitis. Carcinomatous infiltration can take the form of a subacute meningoencephalitis, with headache, associated disturbances in mentation, and sixth cranial nerve paresis. Patients may also develop blindness and deafness from infiltration of those cranial nerves. In cases of carcinomatous meningitis, the deep-tendon reflexes are usually decreased or absent, whereas in the infectious form, the reflexes are usually intact or accentuated. There is no fever in the neoplastic form. In carcinomatous infiltration, the cerebral spinal fluid has an increase in intracranial pressure, usually with 100 white blood cells/mm³ or fewer, predominantly of the lymphocytic and, to a lesser degree, the polymorphocytic type. There is also an increase in protein and a decrease in the glucose level of the fluid. These laboratory findings can also be seen in cryptococcal, candidal, and sarcoid involvement of the meninges. The cerebral spinal fluid cytology, India-ink preparations, and culture of the spinal fluid should make the differential diagnosis. The spinal fluid cytologic examination of bacterial meningitis usually contains 1000 to 10,000 cells, with polymorphocytic cells predominating. One exception to this is that in about 20% of patients with meningococcal meningitis, the count is below 100 cells/mm³.

Paraneoplastic Syndromes

Ophthalmologic involvement by remote tumors usually results from metastatic invasion rather than remote systemic effects. The most common noninvasive effects of cancer are peripheral neuropathy, subacute cerebellar degeneration, and brainstem and limbic encephalitis. Cases have also been reported of a myasthenic syndrome similar to Eaton-Lambert syndrome but with no ocular involvement except for one with a sixth-nerve palsy. Pillay et al. reported a case of internuclear ophthalmoplegia and optic neuritis attributed to the paraneoplastic effects. Waterston and Gilligan reported a case of paraneoplastic bilateral papillitis with loss of vision and progressive external ophthalmoplegia, both of which improved on steroids.

The most common tumor to cause these neurologic complications is small cell carcinoma of the lung, perhaps because these tumor cells are closely related to amine precursor uptake and decarboxylation (APUD) cells, which may also be derived from neural crest tissue. This suggests some cross-immunologic relationship.

Reticulum cell sarcoma usually presents as a uveitis. In the absence of other systemic symptoms, an anterior-chamber or vitreous tap may be the best diagnostic test. Cranial nerve involvement also occurs. The combination of uveitis and cranial nerve palsy, particularly of the facial nerve, should suggest the diagnosis. When this tumor occurs with more widespread involvement of the CNS, the condition is called lymphomatous leptomeningitis. Optic nerve involvement in the absence of leptomeningitis has been
reported in other lymphoproliferative disorders, such as acute lymphoblastic leukemia, and less commonly in Hodgkin’s disease and lymphosarcoma.

Drusen

Although optic nerve drusen are a common ophthalmologic finding, they are an uncommon cause of visual loss or field defects. The commonest form of visual involvement is inferior nasal field defects, which are seen as individual but multiple excrescences in the prelaminar area of the nerve. They are more easily seen in adults because of the atrophy of overlying glial tissue. Discs with drusen also show an abnormal vascular pattern. The question is, Which comes first and which is cause and which is effect? The abnormal vascular pattern crowding the available space in the nerve head may cause an alteration in axoplasmic flow that, according to Sacks et al., acts as a nidus for the deposition of extracellular material to form the disc. Hemorrhages with drusen have been reported many times, usually without visual field loss. This association also suggests some vascular compromise of the disc.

Drusen, on the other hand, do not preclude a patient from having another, more remediable, reason for the loss of vision. The alternative reasons need to be ruled out before accepting the drusen as the sole cause of vision and/or field loss. Drusen certainly can make field testing difficult in terms of evaluating which disease process is causing any progression of vision loss. Although we are used to a full disc without coppering in cases of drusen, the presence of drusen does not preclude coppering in glaucoma. It may even add to the problem, because of the vascular abnormality and compromise associated with the drusen.

Drusen can even cause disc swelling associated with loss of vision, suggesting papillitis. Three such cases of drusen with swollen discs were reported by Karel, and other cases were reported by Kohn, Hoyt et al., Rosenberg et al., and Gittinger et al.

TOXIC CAUSES

Tobacco and Alcohol

Tobacco-alcohol amblyopia is misnamed, as the condition appears to be the result of a biochemical defect. The clinical syndrome can be seen in nutritionally deprived persons who do not use tobacco or alcohol as well as in persons who use excessive amounts of tobacco and alcohol and thus have poor appetites and poor nutrition. In tobacco-alcohol amblyopia—and in all the toxic amblyopias—the involvement is bilateral. Usually one eye is involved for several weeks or months before the other eye is affected. The typical field defect in tobacco-alcohol amblyopia is the cecocentral defect, which serves to quickly differentiate this condition from other causes of optic nerve or chiasmal disease. Although several authors have reported cases of a chiasmal tumor that caused the cecocentral field defect, such an occurrence is extremely rare. In the toxic amblyopias, the fundus appears normal for a long time before temporal disc atrophy develops.

In trying to differentiate tobacco-alcohol amblyopia from other optic nerve diseases, the VEP has been employed. Unfortunately, there is not always a delay in conduction time, which suggests a mechanism other than demyelination. The theory has been proposed that there is an abnormality in cyanide detoxification, related to an insufficiency of sulfur donors from sulfur-containing amino acids. Patients with tobacco-alcohol amblyopia usually have a poor quality of food intake and perhaps lack some coenzyme in the cysteine-homocysteine cycle.

The treatment, if any, is usually a proper diet with a multivitamin supplement. Foulis, Cant, and Chisholm believe that cyanide plays a role in tobacco-alcohol amblyopia, and they report success in treating the condition with hydroxocobalamin. My limited experience with hydroxocobalamin in treating the condition has been uniformly unsuccessful.

Cocaine

That cocaine is evident. Sherlock’s comment was spontaneous and not intended to mean that cocaine was the cause of the patient’s nasal obstruction, but rather that the patient had been using cocaine within the past several months. The intranasal cocaine was used to improve the symptoms of rhinitis. Its localization and the presence of granulation tissue and a chronic obstructing nasal polyp suggested that the patient might have been using cocaine for its subjective effects. The patient denied using cocaine for several years, but the history of recent use was consistent with the clinical findings. The patient was advised to discontinue the use of cocaine and to undergo further evaluation for the possible cause of the nasal obstruction.
Cocaine

That cocaine use is not a recent phenomenon is evidenced by the familiar phrase of Sherlock Holmes, “Quick, Watson, the needle.” The originator of Sherlock Holmes, Arthur Conan Doyle, was a cocaine addict himself, and in his stories, he made Holmes a cocaine user also.

The intranasal route commonly used by cocaine users today causes irritation of the nasal mucosa. Its toxicity to that type of nonkeratinized epithelium should be familiar to any ophthalmologist who has seen its effect on corneal epithelium. Chronic intranasal use causes nasal septum perforation, proceeds to chronic osteolytic sinusitis, and finally affects the neighboring optic nerve. Involvement of the optic nerve may occur either by extension of the inflammatory process or by compression from an inflammatory mass. Since chronic use of cocaine causes local nasal discomfort and symptoms, over-the-counter nasal sprays with vasoconstriction are self-prescribed by the patient. This type of drug makes the local inflammatory and erosive process worse by adding a certain amount of local ischemia. The destructive process can be so extensive as to initially suggest Wegener’s granulomatosis or lethal midline granuloma. It is important to differentiate these two conditions from intranasal cocaine use because the treatment of all three is different. Wegener’s granulomatosis is treated with cytotoxic agents, and lethal midline granulomas with high-dose radiation. The treatment for chronic cocaine use is uncertain, but steroids have an effect in some cases.

Since patients do not usually volunteer a cocaine history, even when asked if they use drugs, it is important to suspect it in cases that are not straightforward. Using a nasal speculum to look into the nose is certainly within the expertise of any physician. By the time optic nerve damage occurs and the patient consults an ophthalmologist, there has been long and heavy intranasal use of cocaine, so that the nasal changes are likely to be obvious.

Lead

Lead intoxication is more rare today than previously because of the decreased use of lead-based paints. Children, especially children with a pacifier, typically develop lead poisoning after eating lead-based paint chips from walls, toys, and other objects. But lead can be absorbed through the skin and respiratory tract as well, so it is important to question adult patients carefully about their job and hobbies. It has been reported that toll takers at bridges and tunnels have had increased blood lead levels because of their exposure to the exhaust fumes from automobiles, but I am not aware of any cases of associated optic nerve disease.

In acute lead intoxication, particularly in children, convulsions may be the presenting sign. In the chronic form, colic, constipation, headache, and muscle weakness are more common. Since lead is stored primarily in the bones and liver, a ready store may be present after the initial period of absorption. During infections that cause some degree of acidosis, lead is released from the bone storage depots, and the signs and symptoms of lead poisoning occur.

Vision is commonly affected; the more severe the lead poisoning, the worse the optic nerve involvement and the prognosis in regard to vision. Extraocular muscle involvement in association with the visual deficits indicates a poor prognosis in regard to vision.

The laboratory findings in lead intoxication include anemia with punctate basophilia and stippled red blood cells. A blood lead level above 0.1% is required for a diagnosis of lead poisoning.

Roentgenograms of the lower end of the femur and upper end of the humerus show a lead line. In lead encephalitis, the spinal fluid has an increase in globulin that is disproportionately high for the increase in cells, which rarely exceed 100/mm³.

Prompt use of a chelating agent is the treatment of choice.
Methy1 Alcohol

Even in small amounts, methyl alcohol is particularly harmful to the retinal ganglion cells. The history and associated symptoms usually suggest methyl alcohol poisoning. Blindness is a common result. No treatment exists.

Digitalis

Digitalis poisoning may be acute, or it may represent a chronic buildup over months, caused by inadequate utilization and excretion. In toxic conditions, serious cardiac problems (such as heart block) occur, and these problems take precedence over the visual complaints. The usual visual complaint is of a change in color vision; for example, the patient may say that everything looks yellow. Regulation of the digitalis dosage reverses the visual symptoms.

Isoniazid

Isoniazid in small doses rarely causes ocular symptoms. Larger doses, particularly when the drug is given in combination with a salicylate or alcohol, leads to ocular symptoms including optic neuritis, optic atrophy, vertigo, paresthesias, and convulsions. These symptoms are similar to those of pyridoxine deficiency, so the treatment is administration of pyridoxine as well as reduction of isoniazid.

Ethambutol

Visual toxicity from ethambutol is usually an early sign of drug intoxication. Loss of color vision is the first sign of this toxicity, and all patients taking the drug should be screened periodically with the HRR plates. After developing a color defect, the patient develops a cecocentral field defect. Even these defects should be reversible if they have not progressed to an advanced stage.

Favism

For years favism was thought to occur only among people living in Mediterranean areas and eating fava beans. It is now known to occur also in the United States. In susceptible persons, ingestion of fava beans causes hemolytic anemia. The retinal signs of favism are those of hemorrhage secondary to increased coagulation. The increased hemolysis of the red blood cells causes a thromboplastin-like activity in the blood that leads to increased coagulation.

Iodochlorhydroxyquin
(Enterio-Vioform)

Iodochlorhydroxyquin is commonly used outside the United States for treatment of diarrhea. In recent years, frequent reports have detailed the toxic effects of this drug, including optic neuritis. A carefully taken history of patients who have traveled outside the United States may reveal exposure to this medication.

Antimetabolic Agents

Antimetabolic agents have many undesirable side effects, which are all too common. Ocular side effects are rare except for the secondary cataracts and secondary glaucoma associated with steroid therapy. Vincristine not uncommonly causes peripheral neuropathies with paresthesias of the extremities and a decrease of the deep-tendon reflexes. It also causes abdominal pain and convulsions. Eye signs are rare, but optic neuritis has been reported with this drug in particular.

Keto-

The ketogenic diet is an im-

adequate mechanism of produc-
ting ketosis. This diet decreases the ability of the substra-
tum to provide energy to the

abdominal muscles, and vitamin deficiencies. It has

been known for a long time that

Wernicke-Korsakoff syndrome

can be improved with thiamine.

The treatment of the

other

cause of the disorder is

Trauma

Trauma to the eye can cause hyphema, angle recession, and detachment of the retina. Signs and symptoms seen are pain, redness, and decreased vision. The treatment of the disorder is difficult.
Ketogenic Diets

The ketogenic diet has become a popular adjunctive form of therapy in children with inadequate control of epilepsy. The mechanism of this diet is thought to be through the production of ketone bodies, which help to decrease the excitability of cerebral tissues. This diet is much more effective in children, since their cerebral cortex has a greater ability to oxidize ketone bodies as a metabolic substrate than does the adult cortex. The systemic reactions are usually minimal and limited to occasional vomiting, diarrhea, and abdominal pain. Ketone diets are deficient in vitamin B. As the carbohydrate intake decreases, there is a concomitant decrease in thiamine requirement. Therefore, we do not see the usual thiamine deficiency syndrome of Wernicke's encephalopathy in these children. Infrequent cases of optic neuritis have been reported; however, optic neuritis and Wernicke syndrome can be seen in any prolonged diet regimen without vitamin supplements, particularly in adults, who do not handle ketones as well as do children.

OTHER MISCELLANEOUS CAUSES

Trauma

Trauma to the eye, which usually is easily diagnosed, varies from a ruptured globe to hyphema, cataract, dislocation of the lens, angle recession, vitreous hemorrhage, retinal detachment, commotio retinae, and choroidal ruptures. All of these conditions can be seen and easily identified by the ophthalmologist. Trauma to the head or eye can also cause loss of vision or field without any of the above-mentioned defects. The diagnosis and management of these cases is more difficult.

The trauma that causes optic nerve disease most commonly is a frontal blow in which the force is concentrated in the area of the optic canal. This has been demonstrated by using holographic interferometry to demonstrate the surface perturbations caused by a frontal bone blow. The cause is obvious when optic canal fractures are seen on the CT image. However, most patients do not show fractures, and another mechanism of visual loss must be postulated. One theory is a vascular one. In the area of the optic canal, there are small penetrating arteries from the ophthalmic artery that enter the nerve at a right angle. The nerve does not lie loosely in the canal but has septal attachments, particularly superiorly. This fixation of the nerve, arteries that enter at right angles, and concentration of frontal traumas to the canal area probably combine to cause the optic nerve damage. These penetrating arteries may rupture, causing ischemia, or they may hemorrhage, causing compression in the limited space of the canal. A greater hemorrhage in the orbit, as we occasionally see after retrobulbar anesthesia, rarely causes any loss of vision, perhaps because the nerve is coiled somewhat, is more mobile, and can be displaced rather than compressed against the bony optic canal.

There is a controversy about how to handle patients with trauma-induced visual loss. Most ophthalmologists treat them conservatively with cautious observation, with or without steroids to reduce the swelling, which may compress the nerve in the canal. Others, like Fukada, believe a more aggressive surgical approach, particularly by the transsphenoidal route, is the best mode of treatment. Fukada's series of 750 cases of decompression of the optic nerve head is larger than any other and includes a large number of canal fractures. None of his patients with immediate blindness improved with conservative treatment; 28 of these were then surgically treated, and 7 improved. His successful visual results with this operation have not been shared by others with equal surgical experience. Another frequent consideration in these cases is the general neurologic condition of the patient and the associated trauma. Many of these cases involve vehicular accidents or severe blows on the head from a fall or falling
objects. These patients may be in an intensive care unit with multiple services looking after multiple problems, ranging from possible ruptured viscus, unconsciousness, and other fractures. Although a transsphenoidal surgical approach is less traumatic than an intracranial approach, these are not the best patients for general anesthesia. This is particularly true when the visual results of surgery are still open to question. I prefer to observe and treat such patients with large doses of steroids, which will also help with any other intracranial swelling.

Some trauma patients appear to have full vision initially and then lose it sometime afterward. Admittedly, assessing the degree of vision is not easily done during the initial management of a patient with life-threatening problems. Nonetheless, some trauma patients experience a loss of vision that appeared to be present at the initial examination, a few hours or days after their injury. At this point, one thinks of compression by swelling or hemorrhage, which could be relieved by unroofing the canal and decompressing the nerve. This scenario suggests that the nerve was not irretrievably damaged at the initial injury and can be retrieved by prompt surgical intervention. This conclusion is still an open question, and all the diagnostic skills at hand are required to decide which patients have the greatest chance of a surgical success.

Another form of trauma that we have seen is chiropractic manipulation. Fruhnk described four cases of Wallenberg syndrome from chiropractic neck manipulation. We have seen several Horner syndromes and one case of a carotid dissection with subsequent embolic infarction of the ipsilateral optic nerve.

Recent studies by Spoor suggest that megadose use of steroids makes a significant difference in the recovery. This is based on the work of Braughler, who postulated different mechanisms for megadose steroids and regular-dose steroids. The results are also better the sooner the steroids are instituted after the traumatic incident. This makes sense, since prolonged compression of the nerve by edema and associated vascular compression in ischemia will only increase nerve damage. Spoor’s series showed improvement in 70% of 21 patients; an impressive number, even if some increase has been improved without therapy. Most series have a very dismal outlook for any improvement in untreated cases. Lessell’s review in 1989 can attest to that fact. Of 25 patients, only 3 spontaneously improved, and 2 of 6 patients with no light perception had minimal improvement; 4 were treated with a routine dose of steroids, and 1 improved; 4 were treated with steroids and optic canal decompression, and 3 improved. In a more recent study by Joseph, 11 of 14 patients treated with dexamethasone and a transethmoid-sphenoid decompression of the optic canal improved, with no operative morbidity or mortality.

**Shunt Malfunction**

Chronic increased intracranial pressure is a well-known cause of optic atrophy and vision loss. This sequela can occur with chronic pressure resulting from pseudotumor cerebri more frequently than was previously suspected. It also can occur with a failed shunt put in place for that problem or others, such as hydrocephalus. Although the loss of field and vision often is slow, it can also be abrupt, so cautious observation of chronic increased intracranial pressure is not always safe. Rapid loss may be due to interference of blood flow to the optic nerve and the occipital lobe or to herniation of the parahippocampal gyrus through the tentorial notch with damage to the lateral geniculate body.

If the involvement of the visual system is anterior (e.g., in the optic nerve), then there may be no changes in the sensorium to guide clinical judgment. If the involvement is posterior with compression of the posterior cerebral artery and ischemia to the occipital cortex, it may cause a decrease in vision and/or fields. The same area of compression may also extend caudally, affecting the reticular sulting in ch

Central sc detachment retina. A causal findings case. The d the indirect contact lens then confirm VEP latency usually association. However, demonstrate a serious retincrease in VI relative afferent appearance dence to d and central resolved case as to the oc vision and both ente APD is a m nerve dise 

**Paget’s**

Paget’s disease of the skull genograms have a cott irregular lay resorption usually there is
the reticular formation and midbrain and resulting in changes in the sensorium.

Constant and cautious observation is required in managing patients with chronic increased intracranial pressure and shunts. No examination of these patients is the final one.

**Central Serous Retinopathy**

Central serous retinopathy is an idiopathic detachment of the sensory layer of the retina. A casual observer may miss the retinal findings and diagnose optic nerve disease. The diagnosis is best made with use of the indirect ophthalmoscope and fundus contact lens. A fluorescein angiogram can then confirm the diagnosis. An increase in VEP latency and the presence of an APD are usually associated with optic nerve dysfunction. However, Folk and his coworkers have demonstrated that patients with central serous retinopathy may also have an increase in VEP latency, color defects, and a relative afferent pupillary defect. The fundus appearance should serve as adequate evidence to differentiate optic nerve disease and central serous retinopathy. However, a resolved case of each may leave some doubt as to the correct diagnosis. Defects of color vision and VEP latency may remain after both entities resolve. The presence of an APD is a much more likely residual of optic nerve disease than of central serous retinopathy. The relationship between final visual acuity and the VEP latency is much more significant for optic nerve disease than central serous retinopathy.

**Paget's Disease**

Paget's disease is a progressive disease of the skeletal system in adults. Roentgenograms of affected individuals typically have a cotton-wool appearance because of irregular laying down of abnormal bone and resorption of normal bone. The more activity there is in this disease, the more positive is the scan, because of increased uptake in the hyperactive bone. The usual cause of decreased vision in Paget's disease is optic nerve compression in the canal. Another cause that has been postulated is a steal phenomenon of the nearby neural structures such as the optic nerve or eighth nerve from the hypervascular bone. Other ocular signs with this disease are exophthalmus, angioid streaks, glaucoma, corneal opacities, and extracocular muscle palsies.

The medical treatment of Paget's disease is administration of calcitonin, which decreases the vascularity and is aimed at decreasing the steal phenomenon. Surgical treatment is directed toward relieving direct pressure on the optic nerve.

**Opacities of the Media**

Most opacities of the media involve the lens, with cataract leading the list. It is amazing that most people with nuclear sclerosis cataract and a decrease in acuity rarely notice their loss unless it is severe, whereas persons with a small degree of posterior subcapsular cataract complain bitterly of it.

Dislocation of the lens can result from trauma. It also occurs in congenital syphilis, homocystinuria, and Marfan syndrome.

Vitrous degeneration is almost as common a problem as cataract. The degeneration causes parts of the vitreous humor to become visible to the patient, and if the degeneration is extensive, the patient's vision is slightly blurred. The prime cause of vitreous degeneration is age. Myopia and chronic inflammations are the next most common causes.

Hemorrhages into the vitreous humor may herald the onset of retinal tears and detachment and posterior vitreous detachment. If diabetes or angiosmas are present, the hemorrhages come from abnormal vessels. A detailed look at the retina will readily identify the cause. Frequently, the hemorrhages are so severe that the retina is obscured. Continued observation of the patient as the hemorrhages clear eventually affords an
adequate view of the fundus. If an earlier decision is desired as to whether a retinal detachment is present, ultrasonography can be employed. Examination of the fellow eye may reveal signs of diabetes or peripheral retinal degeneration that is most likely caused by retinal detachment.

Corneal opacities may be caused by corneal dystrophy, bullous keratopathy, and band keratopathy. Band keratopathy may be seen in defects of calcium metabolism, chronic uveitis with secondary corneal decompensation, and juvenile rheumatoid arthritis.

Numerous retinal causes of blurred vision also exist. Unsuspected diabetes or hypertension, conditions that the ophthalmologist may be the first to diagnose, are among them.

**REFRACTIVE ERRORS**

Persons who experience normal changes in refractive errors usually do not complain to the ophthalmologist about acute loss of vision. In some diseases associated with a slow change in visual acuity, however, they interpret the problem as a sign that they need a change in their prescription. The following paragraphs describe the diseases that cause hyperopic, myopic, and astigmatic changes.

In my experience, hyperopic changes caused by disease are the least common ones, usually because the retinal rods and cones are moved into a more anterior plane, without their ability to function being materially affected. This situation occurs in posterior scleritis or with retrobulbar masses that indent the posterior part of the globe. A refraction of both eyes shows a difference in refractive error, which indicates the reasons for the blurred vision (although it is not absolute proof). Horizontal striae at the posterior pole are more commonly seen in tumors of the muscle cone but may also occur with the edema of posterior scleritis.

Retinal edema is not always easily observed. Central serous retinopathy with some degree of hyperopia can be one of the more difficult forms of retinal edema to identify. Patients with this condition usually have only modest decreases in vision. Because of the slight retinal elevation, they may complain of distortion, which may be evaluated by means of the Amsler grid. The retinal edema in central serous retinopathy is not as easily seen with the ophthalmoscope as it is in branch artery occlusion. The slit lamp and the fundus contact lens must be used. With the ophthalmoscope, it is difficult to differentiate central serous retinopathy from detachment of the pigment epithelium. I often use fluorescein angiography in making the differential diagnosis.

Myopic changes occur more commonly. Spasm of accommodation is frequently a cause in young women. A comparison of the manifest refraction and the cycloplegic refraction establishes the diagnosis. Diabetes also causes myopia owing to the lens changes characteristic of this disease. Cataracts from whatever cause, particularly nuclear sclerosis, cataracts, cause myopia. Chronic use of sulfonamides can cause myopia by a mechanism that is not understood. The mechanism is not ciliary muscle spasm because atropine does not relieve the condition. Diamox and the thiazide compounds, closely related to the sulfonamides, may also cause myopia. As mentioned, patients with Marfan syndrome have increased curvature of the lens, which causes myopia. A partially anteriorly subluxated lens, as in Marfan syndrome or homocystinuria, shows a myopic shift. Trauma to the globe can also cause shallowning of the anterior chamber, with anterior displacement of the lens-iris diaphragm and a myopic change.

Astigmatism is associated with corneal diseases, such as keratoconus and peripheral corneal dystrophy (e.g., furrow dystrophy), which place unequal stresses on the cornea. Keratometer readings, Placido’s disc testing, and careful slit lamp evaluations will identify the cause. Cataract formation, as well as the healing of incisions for cataract operations, can result in astigmatism. Lid tumors and, occasionally, chalazions can press on the eye and create astigmatism. Increase in accommodative reading difficulty by 10 degrees may cause astigmatism to pull on the lens.
accommodation from the rest position to the reading distance at near increases astigmatism by 10%. Ciliary muscle spasm can also cause astigmatism because of the unequal pull on the ciliary muscles in the lens.

SUGGESTED READINGS


Blurred Vision • 455


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Diseases cause eye, eye pain and a painless opthalmic nerve base neurosis base and eye p
line some aspect of the physiology, other complications of common causes of the headache and ambiator.

The new subset of the tension headache, Tolosal, op drome, op drome of sinususes, at I do not source of best cover ache syndromes. Table 14.1 nosed head. Further some of this have been
Diseases that cause headache frequently cause eye pain. In evaluating the patient with eye pain and upon determining that there is no primary ophthalmologic problem, the ophthalmologist can form a differential diagnosis based on a clear understanding of the neuroanatomy and neurophysiology of head and eye pain. This chapter attempts to outline some of the theoretical and anatomic aspects of head pain and reviews the pathophysiology of migraine as a model for understanding headache. Rather than attempting to provide an exhaustive list of causes of head pain, this chapter instead focuses on the evaluation and management of the headache patient in the emergency and ambulatory settings.

The neurologic causes of eye pain are a subset of those causing headache in general, including migraine and cluster headaches, tension-type headaches, trigeminal neuralgia, Tolosa-Hunt syndrome, Rasmussen syndrome, optic neuritis, and referred pain syndromes from lesions of cerebral arteries, sinuses, and dental sources. In this chapter, I do not discuss primary ocular or dental sources of eye pain, since these would be best covered by others, but focus on headache syndromes that also cause eye pain. Table 14.1 lists many of the commonly diagnosed headache disorders according to the International Headache Society and also lists some of the newer types of headache that have been described in the recent literature.

**ANATOMY AND PHYSIOLOGY OF HEAD PAIN**

Pain-sensitive structures in the head and neck include the skin, subcutaneous tissue, muscles, arteries, and periosteum of the skull. Pain fibers also innervate delicate structures of the eye, ear, nasal cavity and sinuses, intracranial venous sinuses and their tributaries, parts of the dura at the base of the brain, and the arteries within the meningeal spaces. Structures above the tentorium, including the anterior and middle cranial fossa, are supplied by the trigeminal nerve. The face, to the middle of the head (coronally), is also innervated by the trigeminal nerve. The back of the head and the posterior fossa are served by a plexus of nerves that includes branches from cranial nerves VII, IX, and X and the first three cervical spinal roots.

Headache pain is a type of referred pain. When a deep structure and skin are supplied by the same nerve, a painful pathologic process of the deep structure can be perceived as a pain on the skin. For example, the carotid artery is innervated by the ophthalmic division of the trigeminal nerve, so pain originating there can be referred to the ipsilateral forehead.

The structural lesions that cause the referred pain in most headache syndromes are not known. In some cases, a fixed structural
### Table 14.1. CLASSIFICATION OF HEADACHE DISORDERS

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine without aura</td>
<td></td>
</tr>
<tr>
<td>Migraine with aura</td>
<td></td>
</tr>
<tr>
<td>Tension headache</td>
<td></td>
</tr>
<tr>
<td>Cluster headache and chronic paroxysmal hemicrania</td>
<td></td>
</tr>
<tr>
<td>Other vascular headaches</td>
<td>such as benign exertional headache or headache associated with sexual activity</td>
</tr>
<tr>
<td>Chronic daily headache</td>
<td>such as transformed migraine, tension type, or new persistent headache</td>
</tr>
<tr>
<td>Chronic rebound headache</td>
<td></td>
</tr>
<tr>
<td>Hormonally mediated headache</td>
<td></td>
</tr>
<tr>
<td>Headache associated with head trauma</td>
<td></td>
</tr>
<tr>
<td>Postconcussion syndrome headache</td>
<td></td>
</tr>
<tr>
<td>Postoperative headache</td>
<td></td>
</tr>
<tr>
<td>Headache associated with vascular disorders</td>
<td>such as that seen in stroke, intracranial hematoma, subarachnoid hemorrhage, cranial arteritis, carotid dissection, venous thrombosis, or arterial hypertension</td>
</tr>
<tr>
<td>Benign Intracranial Hypertension</td>
<td></td>
</tr>
<tr>
<td>Low CSF pressure headaches</td>
<td></td>
</tr>
<tr>
<td>Intracranial inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Intracranial neoplasm</td>
<td></td>
</tr>
<tr>
<td>Headache associated with substances or their withdrawal</td>
<td></td>
</tr>
<tr>
<td>Headache associated with systemic infection</td>
<td></td>
</tr>
<tr>
<td>Headache associated with metabolic disorder</td>
<td>such as hypoxia, hypercapnia, hypoglycemia, etc.</td>
</tr>
<tr>
<td>Headache or facial pain</td>
<td>associated with disorders of the bony cranial, neck, eyes, ears, nose, sinuses, teeth, mouth, etc.</td>
</tr>
<tr>
<td>Cranial neuralgias</td>
<td>such as trigeminal neuralgia</td>
</tr>
</tbody>
</table>

Lesion can be identified, such as in the headaches caused by brain tumors or bleeding aneurysms, but in many cases the structural cause can only be inferred. Not all headache syndromes definitely have structural etiologies. Some, such as migraine or tension headache, may be caused by disruption of function of the nervous and/or vascular systems in the head and neck, without any structural correlate. The pathophysiologic causes of most of these headache syndromes are not well understood. Most investigators have focused on migraine as a model type of headache because the clinical manifestations of migraine can be clearly defined, but much of the knowledge gained from these investigations has been and may continue to be applied to the study of other headache syndromes.

Migraine headaches occur episodically, causing a severe, disabling, throbbing pain on one side of the head that can last more than 24 hours. The headache pain of migraine is accompanied by nausea, vomiting, and photophobia. Some 10% of migraine attacks are preceded by an aura, which is defined as a neurologic event such as visual loss or hemiplegia. The auras clearly represent brain or retinal ischemic changes that are usually transient. These changes and the throbbing nature of the headache pain in migraine led to the use of the term “vascular” to describe migraine and similar headache types. Although migraines are usually unilateral in location in any given episode, the pain can switch sides during subsequent episodes, indicating that a fixed lesion is unlikely to be the cause of the syndrome.

Over the course of this century, the work of several prominent investigators has led to a synthesis of previously disparate theories on the causes of migraine. It now seems likely, for example, that migraines have, at least in part, a neurogenic origin. This concept strongly resembles the original theory for the cause of migraine put forth by Lewis in 1944. According to this theory, a slow-moving wave of suppression of electrical activity begins occipitally and then spreads across the brain during, or just preceding, a migraine attack. This neurologic event can then lead to the migraine syndrome by acutely and transiently affecting brain function and causing cerebrovascular changes.
Neurogenic changes can either precede or follow cerebrovascular changes. A vascular etiology for migrainelike headaches was popularized by Wolff. In this theory, changes in the external or internal cerebrovasculature lead to a phase of vasoconstriction that is followed by a phase of vasodilation. The vasoconstrictive phase is associated with the aura of the migraine attack. The subsequent phase of dilation presumably occurs as a response to the constriction and seems to appear during the period of head pain. Recent evidence obtained using transcranial Doppler to measure cerebral blood flow, supports the theory that changes in cerebrovasculature figure prominently in the onset of a migraine attack but does not rule out a preceding, causative neurologic event. In particular, it has been found that direct pharmacologic constriction of cerebrovasculature in migraine patients during an episode can relieve the headache pain.

Another well-studied feature of the pathology of migraine headaches is the onset of an inflammatory response in the walls of blood vessels where the nerve fibers supplying those vessels are located. These findings point out the role of the trigeminal nerve in head pain. The trigeminal nerve and the plexus of nerves that supply the back of the head are stimulated to release neurotransmitters and neuropeptides such as substance P during a migraine attack. These agents lead to inflammation in the blood vessel wall, cause release of locally acting vasoactive peptides, and increase blood flow to the brain.

The trigeminovascular system interacts with the central pain pathways. The central pain pathways include the periaqueductal gray (PAG) matter of the midbrain, which contains cells that respond to opiates. At least one theory of migraine pathogenesis involves disruption of function of this system. When the central pain pathways are activated, the serotoninergic PAG neurons activate cells in the nucleus raphe magnus (NRM) of the medulla. These cells in turn inhibit pain afferents at the level of the spinal cord and the medullary nucleus of the trigeminal nerve, possibly by excitation of intermediary neurons that release opiates. The function of these pathways can be explained by the hypothesis of pain inhibition. This hypothesis states that when a sufficient number of pain fibers (spinthalamic tract neurons or spinotrigeminal tract neurons) are excited and provide their input to the central pain system, the system is activated to inhibit pain via a negative feedback loop. It therefore seems likely that pain itself causes activation of the suppression system.

Opiate analgesics can enhance the responsiveness of the central pain suppression system and can also work at the level of the spinal or trigeminal afferents. Serotonin agonists may also activate the suppression system. One theory of migraine pathogenesis takes into account the finding that migraine sufferers have low levels of serotonin during a migraine and even between attacks. Depletion of this transmitter may occur because of excessive secretion just before an episode of migraine. Low levels of serotonin in the central pain pathways would result in decreased pain suppression. Although other investigators have found high levels of serotonin during acute migraine, the hypothesis can still explain the dysfunction of the suppression system if one takes into account some latency to onset of activity of the suppression system. The latter is predicted by the finding that a prolonged painful stimulus is much more effective at activating the system than a short one.

Thus, in migraine sufferers and possibly in other headache patients, pain may result from dysfunction of the central pain system during times of excessive stimulation of the system. The inputs to the system include the cerebral cortex, the thalamus, the hypothalamus, and the internal and external carotid vasculature. The trigeminal system contacts the pain system through other brainstem nuclei and possibly through a thalamic feedback loop. If the central pain system is dysfunctional, excessive stimuli from any of the above-mentioned inputs will not be properly suppressed. These stimuli may include emotional stress such as that experienced during
an argument or during a prolonged period of personal difficulties at work or at home, loud noises, strong smells, internal clocks that cause diurnal or episodic variation in hormone levels, and vascular phenomena such as constriction of a cerebral blood vessel. When these stimuli are not suppressed by the central pain system, a migraine headache may occur.

**DIFFERENTIAL DIAGNOSIS OF HEAD PAIN**

Although most headaches have a benign etiology, it behooves the practitioner to recognize serious conditions in the headache patient so that they can be treated promptly. The first or worst headache or a change in pattern of a chronic headache condition may signify a serious or emergent condition. The history is very important because it yields clues about the etiology of the pain. The physician should question the patient about the location of the pain on the head, the character of the pain, the severity of the pain, and the time and mode of onset of the pain (e.g., sudden or gradual, morning or night). For chronic or subacute conditions, additional information about frequency and duration of episodes is needed. Prodromes and auras signify migraine or other types of vascular headache. Associated symptoms such as nausea, vomiting, tearing of eyes, nasal congestion, neck stiffness, tenderness of scalp or forehead, and depression all contribute to the accuracy of the diagnosis. Information about precipitating factors and family history is also helpful.

The physical examination is also important. In benign headache conditions, the examination can be normal, but subtle clues may be important. These include trigger points on the scalp or over sinuses, circum-ocular erythema, and conjunctival or nasal mucosal infection. To rule out potentially more serious causes of headache, one must be aware of the patient’s vital signs. For example, systemic and central nervous system illness can cause headache in association with fever. Acute hypertension can also cause headaches. The physician should also look for signs of head trauma, meninges, or tender, indurated temporal arteries that one might find in vasculitis and perform a careful funduscopic examination looking for papilledema or hemorrhages. The neurologic examination is also important in detecting a focal lesion of the brain. The mental status examination can also be very useful by signifying cerebral dysfunction, even without signs of locality. A summary of the workup of the headache patient encountered in the emergency room is found in Table 14.2.

<table>
<thead>
<tr>
<th>Table 14.2. WORKUP OF HEADACHES IN THE EMERGENCY ROOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain careful history, including time of onset, location and type of pain, duration and frequency of attacks, aggravating factors, relieving factors, and associated symptoms.</td>
</tr>
<tr>
<td>Maintain a high index of suspicion of serious condition if headache is “first,” “worst,” different from previous headache, or associated with constitutional or neurologic symptoms or signs.</td>
</tr>
<tr>
<td>Perform general physical examination—check vital signs carefully; look for signs of trauma on scalp, listen for bruits, examine head for edema, erythema, skin infections, and nasal or ear discharge.</td>
</tr>
<tr>
<td>Perform neurologic examination including careful funduscopic examination looking for papilledema.</td>
</tr>
<tr>
<td>Order and read brain imaging study.</td>
</tr>
<tr>
<td>Order and check appropriate blood tests such as chemistries, kidney and liver function tests, complete blood count, erythrocyte sedimentation rate, arterial blood gas, and thyroid function tests.</td>
</tr>
<tr>
<td>Perform lumbar puncture looking for hemorrhage, inflammation, increased intracranial pressure, and infection.</td>
</tr>
<tr>
<td>Order other tests designed to evaluate specific possibilities more fully, such as dental or sinus disease.</td>
</tr>
<tr>
<td>Call appropriate consultants if further medical or surgical intervention is needed.</td>
</tr>
</tbody>
</table>

**HEADACHES PRESENTING AS EMERGENCIES**

**Subarachnoid Hemorrhage**

Headache caused by SAH or subarachnoid hemorrhage (SAH) may be very sudden or may present insidiously. Sometimes by a global decrement to coma. Subarachnoid hemorrhage is preceded by some weeks. These headaches are severe and persistent. Patients may have severe headaches and severe vomiting. Although these headaches are often referred to as “migraine” by patients, they are likely to be due to SAH. Therefore, it is important to consider SAH when evaluating patients with headaches. Serum chemistry tests such as electrolytes, blood glucose, and complete blood count may be necessary to rule out other causes of headache. Computed tomography (CT) or magnetic resonance imaging (MRI) is needed to confirm the diagnosis of SAH.

**Cerebrovascular Dissection**

Stroke can be a result of cerebrovascular dissection. This condition occurs when there is an abnormal tearing of the artery walls, leading to a decrease in blood flow to the brain. Symptoms may include sudden onset of headache, visual changes, weakness or numbness in the face, arms, or legs, and difficulty speaking. In cases of cerebrovascular dissection, imaging studies such as CT or MRI scans may be performed to confirm the diagnosis and determine the appropriate treatment plan.

**Cerebral Aneurysm**

Aneurysms are abnormal dilations of blood vessels in the brain. They can occur anywhere in the brain and are caused by a congenital abnormality or acquired factors such as hypertension. Symptoms of cerebral aneurysms can include headache, seizure, changes in mental status, or focal neurologic deficits. In cases of cerebral aneurysms, imaging studies such as CT or MRI scans may be performed to confirm the diagnosis and determine the appropriate treatment plan.

**Cerebral Venous Sinus Thrombosis**

Cerebral venous sinus thrombosis is a condition in which blood clotting occurs in the veins draining blood from the brain. Symptoms can include sudden onset of headache, visual changes, changes in mental status, or focal neurologic deficits. Imaging studies such as CT or MRI scans may be performed to confirm the diagnosis and determine the appropriate treatment plan.
HEADACHE DISORDERS PRESENTING IN THE EMERGENCY ROOM

Subarachnoid Hemorrhage

Headache caused by a subarachnoid hemorrhage (SAH) is usually characterized by a very sudden onset of a severe head pain that can be at the vertex or referred from the site of the lesion. The pain is often accompanied by nausea, vomiting, and meningismus and sometimes by focal neurologic signs and/or a global decrease in mentation progressing to coma. Subarachnoid bleeding can also be preceded by a sentinel headache occurring some weeks before the actual bleeding. These headaches can be so acute in onset and so severe as to resemble a clap of thunder, hence the name thunderclap headache. Although these headaches may be related to a leak of blood in some patients, other investigators have shown perfectly clear lumbar puncture (LP) fluid during these pains and have postulated that the severe pain is from dissection or distension of the aneurysm wall. The actual bleeding itself occurs later and is usually caused by a ruptured cerebral aneurysm or AVM. A workup is always indicated for any patient with the first or worst headache. If the aneurysm can be detected before the bleeding, during or just after the sentinel headache, the prognosis for recovery from the aneurysm is higher. It is always prudent to err on the side of unnecessary testing if there is any doubt. Most intracranial bleeding can be detected with computed tomography (CT) or magnetic resonance imaging (MRI), but LP is indicated in the appropriate clinical setting, even after normal imaging studies have been obtained.

Cerebrovascular Disease

Stroke can be associated with headache in cases of bland or hemorrhagic stroke, cerebrovascular dissection, or transient ischemic attack. Headaches occur in 29% of cases of bland stroke, 57% of patients with parenchymal hemorrhage, 36% of transient ischemic attacks, and 17% of lacunar infarcts. Patients with a history of migraine are significantly more likely to develop headache during stroke, as are women. The location of a headache precipitated by stroke is not necessarily correlated with the site of the lesion. The headache of cervical internal carotid dissection is usually located in the ipsilateral forehead, orbit, or temple and can be accompanied by ipsilateral neck pain and Horner syndrome. The pain can be the warning sign of an impending stroke. In cases of intracranial hemorrhage, headache can be caused by distension of the meninges adjacent to the hemorrhage or by increasing intracranial pressure. Another type of stroke commonly associated with severe headache is central venous thrombosis (CVT). Cerebral thrombosis is most common in the sagittal sinus with secondary extension into the cortical veins. The thrombus may occur spontaneously or as a combination of a hypercoagulable state and a decrease in cerebral blood flow, such as is seen in pregnant patients during labor and delivery. Thrombus in the sagittal sinus obstructs the arachnoid villi, blocks reuptake of cerebral spinal fluid (CSF), and produces intracranial hypertension. Cortical vein occlusion produces focal cerebral ischemia and edema, followed in severe cases by bland or hemorrhagic infarction. The clinical syndrome consists of increased intracranial pressure including progressive headache resistant to medications, followed by nausea, vomiting, visual blurring, and changes in mentation. Seizures and lateralizing neurologic signs can also result from cortical venous infarction. The diagnosis of CVT is usually made by CT or MRI, but angiography may be necessary. Treatment for this disorder includes intravenous fluids, anticoagulation, and, depending on the clinical setting, antibiotics.

A headache disorder that presents in an emergency setting is temporal arteritis or large vessel cranial arteritis. This is a disease...
of the cranial arteries that affects women more frequently than men and is associated with polymyalgia rheumatica in about 25% of cases. The disease gets its name from the procedure used to make the diagnosis, temporal artery biopsy. Patients present with severe burning pain along the side of the head and often have fever and constitutional symptoms. The temporal artery can be indurated and tender to the touch. The fact that the temporal artery is not the only vessel involved means that the patients can also present with retinal artery ischemia or stroke. They must be treated promptly with high-dose corticosteroids. An erythrocyte sedimentation rate is helpful in determining the diagnosis, but it can be normal in some patients. In the correct clinical setting, the patient should be treated before the diagnosis is confirmed by biopsy. The technique of temporal artery biopsy will yield the diagnosis in a large percentage of patients, but in some cases, the artery is not involved along its entire length, and false negative results can be obtained.

Central Nervous System Infections

Infections are a frequent cause of headache. Systemic infections causing fever can cause a frontal or diffuse pounding headache. Meningitis causes a diffuse, constant, dull headache accompanied by meningismus, nausea, and changes in mental status. When the brain parenchyma also becomes inflamed, the patient is said to have meningoencephalitis. Encephalitis can cause an alteration of mental status, focal neurologic findings, and seizures. Meningitis and meningoencephalitis can be caused by bacteria, viruses such as herpes, mycobacteria, and fungi. Inflammatory disorders, autoimmun diseases, some medications, and carcinomas can also cause meningeval inflammation. The symptoms and signs of meningitis require a workup with neuroimaging and LP, and treatment will depend on the specific cause of the meningeval inflammation. Acute purulent sinusitis also causes headache but is associated with localized pain and tenderness over the involved sinus and a purulent discharge from that sinus. An exception is sphenoid sinusitis. The sphenoid sinus rarely can become infected but does not drain externally and is not accessible to direct clinical examination.

Head Trauma

Trauma usually presents in the emergency room, and the diagnosis can usually be made easily. Two types of disorders causing headache that can present diagnostic dilemmas should be considered, however: subdural hematoma and epidural hematoma. The latter presents after a blow to the head that is usually of sufficient force to cause loss of consciousness. After the loss of consciousness, the patient awakens, and there can be a short lucid interval during which the patient may complain of a focal headache at the site of the scalp lesion. This awake period is followed rapidly by another episode of decline in level of consciousness that comes on only slightly more gradually than the first. This second episode occurs during the period of accumulation of blood in the epidural space, resulting from tearing of a meningeval artery. The blood accumulates quickly because the bleeding is arterial, and if the patient is not treated promptly by surgical evacuation of the clot, the rapid increase in intracranial pressure will cause the brain to herniate through the foramen magnum. One should be aware that, rarely, the diagnosis of epidural bleeding can be missed by axial CT scanning but can be made by obtaining a CT scan with coronal images. The second type of hematoma is called subdural and usually involves bleeding of the veins bridging the top of the cerebral hemispheres that drain the brain parenchyma into the large venous sinuses. This kind of bleeding can occur more slowly and can be precipitated by more minor trauma. The patient may not even be able to recall the traumatic event and can present weeks after the confusion, or without signs of an issue can be made and can be evacuated.

HEADACHES: THE EMERGENCY AMBULATORY

Several types of headaches can occur, ranging in severity from days to weeks or even months. A headache in the ambulatory setting is one that appears in the clinic setting, and the patient presents with symptoms that are more chronic or recurrent.

Benign Intracranial Hypertension

One kind of headache that is frequently present is benign intracranial hypertension. The patient may present with headaches and increased intracranial pressure due to swelling of the head, and the disorder is unknown. Increased intracranial pressure can be due to a number of causes, including tumors, headaches, and other conditions. The patient may present with symptoms of headache, nausea, vomiting, and blurred vision. The diagnosis is made by measuring the intracranial pressure and performing imaging studies, such as MRI or CT scans.
weeks after the episode with headache, confusion, or focal neurologic deficits but without signs of external injury. The diagnosis can be made by CT scan, and the blood can be evacuated surgically.

HEADACHES PRESENTING IN THE EMERGENCY OR AMBULATORY SETTING

Several types of headache present in a subacute manner, worsening over some days, weeks, or months. The patients experiencing these headaches may at first present in the ambulatory setting but, if the diagnosis eludes the practitioner, may eventually appear in the emergency room. In these cases, it is most important to differentiate between the headaches that have been steadily worsening over time and those that are chronic or recurrent.

Benign Intracranial Hypertension

One kind of headache disorder that frequently presents in the emergency room is pseudotumor cerebri. In this syndrome, headache is accompanied by papilledema and increased intracranial pressure without focal neurologic abnormality. The disorder is much more common in obese women of child-bearing age. The etiology of the disorder is unknown but is thought to involve decreased reabsorption of cerebrospinal fluid.

Headache, the most common symptom of the disorder, is characterized by a generalized, episodic pain that is throbbing and worse in the morning. Staining, coughing, and performing other activities that cause an increase in intracranial pressure will aggravate the condition.

In many cases, diagnosis can be delayed for several weeks to months, especially before papilledema becomes marked. Pseudotumor without papilledema has also been well reported. It has been suggested that aside from needing to treat the patient for symptomatic relief, it is also necessary to take steps to prevent loss of visual acuity from chronic optic nerve ischemia. It is not clear, however, that treatment can successfully prevent the eventual visual defect that occurs in a small number of patients. Evaluation includes performing a history and physical examination, excluding space-occupying lesions with neuroimaging, and documenting an initial CSF pressure of over 200 mm H2O. Routine chemistries, a complete blood count, and an erythrocyte sedimentation rate can help exclude causes such as infection, inflammatory conditions, and endocrine abnormalities. Many medications, most notably some of the antibiotics, have been implicated in causing the syndrome, so the physician may consider the possibility that any medicine the patient is taking may cause elevated pressure. Funduscopic examination cannot always rule out the possibility of the diagnosis of pseudotumor, because patients with abnormally elevated intracranial pressure and normal funduscopic examination have been described. Treatment of the disorder is controversial. Recommended therapies have included diuretics (especially the carbonic anhydrase inhibitors, which seem to decrease the production of CSF) and steroids, but the author and others have found the most effective therapy to be repeated LP on a symptomatic basis combined with regular funduscopic evaluations. The effects of one LP can last several days, possibly because of the creation of a CSF leak that takes time to seal. Surgical treatments for this disorder have included optic nerve sheath fenestration and subtemporal craniectomies, but the most useful surgical treatment for refractory cases has been shown to be lumbar-peritoneal shunt. The risks of this procedure include infection and shunt failure, as well as development of low-pressure headaches.

Intracranial Neoplasm

Headache is a prominent although nonspecific symptom in patients with brain tumors.
In most patients, headaches arising from tumors are similar to tension headaches, but in a smaller percentage of patients, they can resemble migraines. Only a small proportion of patients have the classic brain tumor headache that is severe, worse in the morning, and associated with nausea and vomiting. Most of the headaches are dull, pressurelike pains that are usually bifrontal and can be worse on the ipsilateral side. Other features of brain tumor include signs of increased intracranial pressure (nausea, vomiting, papilledema, and visual disturbances). Brain tumors also manifest themselves as localizing neurologic signs and can cause focal and secondarily generalized seizures. The diagnosis is usually made by neuroimaging, such as MRI, which yields the most specific information.

**Elevated Systemic Pressure**

The headache that is associated with increased systemic blood pressure is important for diagnosis of preeclampsia and eclampsia and also for the diagnosis of pheochromocytoma. The headache associated with these disorders is usually intermittent and correlated with peaks in mean arterial pressure. It is throbbing, bifrontal, and severe and usually cannot be relieved with medications.

**Intracranial Hypotension**

The syndrome of low-pressure headaches has recently been more clearly defined. These headaches can be debilitating, although they are not usually life threatening. The pain is caused by low CSF pressure that can be precipitated by LP, placement of a ventricular or lumbar shunt, or previous meningitis. The headache is characterized by positional pain of the occiput, worsened by sitting up or sudden movements. Gadolinium-enhanced MRI will occasionally show meningeal enhancement that is presumably caused by compensatory dilatation of meningeal blood vessels, with accompanying subdural fluid collections. The diagnosis must be made by documentation of low pressure of the CSF (usually less than 10 mm H2O or undetectable) measured during LP. The treatment presents difficulties, because the patient usually improves only when the low pressure resolves or, in the case of a shunt, is remedied surgically. Anti-inflammatory agents, tricyclic antidepressants, and antihypertensives can be useful in attempts to alleviate the associated inflammatory and vascular changes.

**Metabolic Imbalance**

When evaluating a patient in the emergency setting or in the ambulatory setting who has no obvious cause for head pain and whose pain is diffuse and without clinically classifiable features, the examiner should consider metabolic causes of headache. Chief among these is anemia, a frequently overlooked cause of headache in young women who become iron deficient from heavy menstrual bleeding. Acute anemia, such as that seen in gastrointestinal hemorrhaging, can rarely present with headache. The pain of anemia is usually throbbing and is probably associated with vascular changes. The headaches of hypoxia and hypercarbia have similar clinical features. Patients with pneumonia and exacerbations of chronic obstructive pulmonary disease or asthma can present with headache, often secondary to hypoxia or hypercapnia. Patients who experience nocturnal hypercarbia such as that described with sleep apnea often present with headache and fatigue. Thyroid disease, especially hyperthyroidism, is also a cause of a throbbing headache, although the mechanism that leads to these pains has not been clearly defined. Other metabolic causes include acute or chronic liver or kidney disease and hypoglycemia. Headaches have been described after renal dialysis. No specific treatment exists for these metabolically related headaches. The treating physician will usually try...
to restore the patient to a normal metabolic state in an attempt to alleviate the symptoms.

**HEADACHES PRESENTING IN THE AMBULATORY SETTING**

Several of the benign headache disorders can be diagnosed by strictly clinical criteria, but a brief workup including MRI, blood work to rule out metabolic disarray and inflammatory disorders, and an LP if indicated can help to eliminate other, more serious diagnostic possibilities.

The International Headache Society developed a classification system that provides more precise definitions of headache types than were previously available; the practitioner should try to use these criteria whenever possible to diagnose the common headache syndromes.

**Migraine**

Migraine without aura was previously known as common migraine and is defined as at least five attacks of a headache lasting 4 to 72 hours with at least two of the following: (a) unilateral location, (b) pulsating quality, (c) moderate or severe intensity, and (d) aggravation by walking up stairs or similar routine physical activity. Migraine headaches can be prostrating and, according to the criteria, are associated with either nausea and/or vomiting or phonophobia and photophobia. When the diagnosis is made, the practitioner must be sure to rule out an organic cause with a careful examination and pertinent imaging studies. Migraine with aura, previously known in the literature as classic migraine, fulfills all of the criteria for migraine without aura and, in addition, is associated with an aura symptom, defined as at least two attacks with three of the four following characteristics: (a) a reversible aura symptom indicating focal cerebral cortical and/or brainstem dysfunction, (b) at least one aura symptom developing gradually over more than 4 minutes, (c) no single aura symptom lasting more than 60 minutes, and (d) the headache following the aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura).

Other important characteristics of migraine that are not as clearly outlined in the diagnostic criteria are nevertheless extremely helpful in its diagnosis. For example, migraine is an intermittent headache disorder with headache-free intervals between episodes. Attacks can vary in frequency, usually occurring approximately once every month or several months. If the patient reports a headache frequency of more than twice a month, the examiner may begin to entertain other diagnoses or suspect that the patient may have more than one type of headache disorder. Another aspect of migraine that is helpful in diagnosis is the time of day of its occurrence. Unlike tension headache and some other syndromes, migraine headaches occur in the morning when arising from bed or can awaken the patient from sleep. The headaches also seem to come on when the patient is relaxing, such as on the weekend or on vacation, hence the term "weekend migraineur." The entire migraine episode typically lasts 1 to 3 days. Sleeping late or missing sleep or meals can also bring on a headache. Certain foods may be correlated with the onset of these headaches in certain patients. Common foods that seem to increase abnormal vascular responsiveness include red wine, aged cheeses, chocolate, and certain food additives such as monosodium glutamate. Caffeine can also cause a headache in some migraine patients but can clearly relieve headache in others. Because the sensitivity to certain foods is individually determined, the practitioner must be circumspect in any recommendations to limit intake of these socially and personally pleasing items. Finally, migraine, unlike some other vascular headache types such as cluster headache, occur more frequently in women (3:1) and have a peak age incidence of 45 years.
Tension Headache

Tension headache is defined quite differently from migraine. The headaches last from 30 minutes to 7 days and have two of the following: (a) a pressing, tightening, nonpulsating quality, (b) mild or moderate intensity, (c) bilateral location, and (d) no aggravation by walking stairs or similar physical routine. It also must be characterized by both of the following: no nausea or vomiting and absence of both photophobia and phonophobia (but one or the other may be present). Episodic tension headache must be present fewer than 180 days/year and fewer than 15 days/month, but chronic tension headache may occur for more than 15 days/month. Again, an organic cause must be ruled out. Unlike migraine, tension headaches are less severe and they are more often correlated with work and busy times in a patient's day, such as the late afternoon and early evening. As a general rule, these headaches are milder than migraine or cluster headaches and do not require the patients to leave work but may predispose them to limit social activities. Tension headaches also appear to occur more frequently in women.

Cluster Headaches

Cluster headaches are not as common as the above headache syndromes but are a group of headache disorders that are quite striking in their clinical presentation because of the severity of the pain and the unusual constellation of symptoms accompanying the pain. Cluster headaches affect men more than women (7:1) and occur most frequently between the ages of 20 and 50 years. The pain of cluster headache is unilateral and does not switch sides as a rule. It is excruciating and has a boring or knife-like quality. The attacks are frightening to the patient and cause feelings of impending doom. Unlike the pain of migraine attacks, which makes patients want to lie very still, the pain of cluster headaches makes patients pace around the room holding their heads. The attacks occur in clusters but, during a cluster, can occur once per day or more than once per day. The attacks begin gradually, with the pain intensity increasing with time until a peak of pain occurs, after which the pain wanes slowly. Each episode lasts 45 minutes to 3 hours. Associated with the headache are autonomic signs that affect the face, including facial pallor, pupillary changes, unilateral facial sweating, and rhinorrhea. In the typical cluster headache patient, the headaches occur once a day like clockwork, often awakening the patient from REM sleep at the same time each night. The clusters last a few weeks to several months then disappear for months to years, only to recur with the same characteristic pattern and location during subsequent clusters. During a cluster, alcohol can bring on an attack, whereas between clusters it is unable to do so.

Chronic Cluster Headaches

Chronic cluster headaches are defined as cluster-like headaches that do not undergo remission. Another variant seems to be a syndrome manifesting some of the symptoms of both cluster headaches and migraine. These patients have headaches that last slightly longer than cluster headaches, but which have similar severe autonomic characteristics and occur in discrete clusters. The headaches, like those of cluster patients, are not associated with vomiting or prostration. However, the pain of this type of headache can switch sides during a cluster or even during an attack, and the patients also experience a sensation that a headache will recur during the entire cluster, even during headache-free intervals, similar to the sensation reported by the migraine patient who is said to be in "status migrainosus."

Paroxysmal Hemicrania

Another variant of cluster headaches is paroxysmal hemicrania. The pain of this disorder is similar to that of cluster, but the episodes last 30 minutes, a 30 times per day usually occur. The headache is the office while the headache is the office while the
episodes are brief, lasting from seconds to minutes, and frequent, occurring up to 20 to 30 times per day. The headaches also do not usually occur in clusters. This type of headache can often be easily diagnosed in the office because an attack will often occur while the patient is present for a visit. The headache pain of these attacks can be controlled by indomethacin.

**Chronic Daily Headache**

A fairly recent category of headache that is gaining more widespread understanding is chronic daily headache. It appears that approximately 40% of patients in the major headache clinics fall into this category. Various terms have been used to describe this disorder in the literature and in common clinical parlance, including chronic tension headache, tension/vascular headache, and mixed headache syndrome, but the epidemiologic and clinical characterization of the syndrome are still unclear. The headache syndromes in this diagnostic grouping fall into several different types.

One of these types is transformed migraine. In this type, the patient usually begins to have an increase in the frequency of episodic migraine headaches that began in their twenties. The headaches become increasingly frequent and severe until they eventually occur daily, with varying severity. Some of the headaches experienced by the patient resemble migraines, whereas others are more similar to tension in type, but the episodic nature of the more severe, migrainelike exacerbations usually remains, and these events are perceived by the patient as needing more acute and dramatic attention than the chronic low-grade, daily headaches.

The second type of headache in this group is the tension type. These headaches can be quite severe, but they usually cause bilateral pain and have other features of tension headache. They tend not to be as prostrating as migrainelike events.

The most surprising of these headache types is the one termed new daily persistent headache. This headache evolves fairly rapidly. Often the patient can recall the exact day or time that the headache began, although workup of the patient never reveals any identifiable cause for the pain, including any history of previous headache disorder, trauma, or surgery.

All the headaches in the category of chronic daily headache are associated with feelings of depression as well as with other psychiatric ailments, and it is the opinion of the author that there may be an abnormality in common in the two concomitant disorders, such as an abnormal level of a neurotransmitter necessary for both normal mood and pain suppression. The headaches usually cause significant disability at work and in social life.

**Chronic Rebound Headache**

A closely related headache disorder has been termed chronic rebound headache. Often on presentation of the patient for evaluation, the differential diagnosis between chronic daily headache and chronic rebound headache is unclear, because the patient may not recall the time of onset of the daily headache syndrome in relation to the rapid escalation of medication use. Rebound headaches are defined as headaches that respond to analgesic or abortive medication taken in a scheduled, ritualistic way. These headaches tend to affect patients upon arising in the morning, when they will take the first dose of one or several medications. The pain usually responds to some degree to the medication, but upon a decrease in serum level of the medicine, the headache returns, only to require another dose. Patients usually require large doses of medication to control their pain but will not escalate the use of a particular medicine for pleasurable purposes. These headache patients appear to differ from other pain patients. For example, patients who require large doses of
analgesic agents to treat the pain of an arthritic condition do not develop the rebound headache syndrome unless they had previously experienced chronic recurrent headaches of some type. Associated features of the syndrome include psychiatric symptoms, sleep disturbances, and disturbances of memory and intellectual functioning. The headaches usually have mixed features, without any clearly identifiable symptom complex. When the medication is withdrawn, the patients usually undergo a period of 6 to 12 weeks of severe headaches accompanied by restlessness and disturbances of mood and sleep, after which there can be dramatic improvement in the rebound headaches and unmasking of the original headache type that precipitated use of the medication. Rebound headaches are therefore treated by withdrawal of the offending agent, but failure to achieve this goal on the part of both patient and physician is frequent. The most effective methods of medication withdrawal combine starting a preventative medicine with either an outpatient tapering schedule or a brief inpatient stay, during which the patient is treated with an abortive medication that does not cause the rebound phenomenon, such as dihydroergotamine-45 or sumatriptan.

Postconcussion Syndrome

The source of headaches that occur for an extended period of time after a concussion or minor head injury can be more difficult to localize, because usually there is no apparent external lesion. Undoubtedly there exists a site of injury in these cases, and the pain is most likely referred from that location. The headaches are usually poorly defined and can be persistent or recur daily. They can be difficult to treat and may not resolve over time, indicating that the injury is permanent, having caused either scar tissue formation or disruption of the central pain-inhibition mechanism. The headaches associated with trauma also include those seen in patients with “whiplash.” This injury results from the response to the sudden deceleration experienced with an automobile collision. The resulting neck pain and occipital headache may be caused by a referred pain syndrome whose source is irritation of the cervical roots.

Hormonally Mediated Headaches

The headaches related to sex hormones have been widely studied. Evidence has suggested a link between headache and sex hormones. The headache type most widely studied in relation to changes in hormone levels is migraine, but changes in the brain and in cerebral vessels during pregnancy, menstruation, and menopause may also influence other types of headache. Epstein carried out a clinical survey of the relationship between the menstrual cycle and migraine in a large group of otherwise healthy women. He found that 17% of them had onset of migraine within a year of the onset of menarche, although most had the onset of migraines during their teens and early twenties. True menstrual migraine (MM), defined as that occurring at or during the period of blood loss, was rare (1.4% of the women questioned).
Nevertheless, a relationship between menstruation and migraine exists, and several investigators have attempted to determine which hormones play a role in the phenomenon. Evidence obtained by Somerville suggests that a drop in estrogen levels after a prolonged exposure to this hormone, not the absolute level of estrogen, determines the onset of hormone-related migraine. He carried out a careful study of the effects of estrogen withdrawal on migraine by injecting women with exogenous estrogen and determined that the onset of their headaches was correlated with rapidly decreasing levels of measured serum estrogen. Exogenous estrogen given before the onset of a naturally occurring menstruation clearly delayed onset of the headaches with no effect on the time of onset of menstruation. In another study, however, progesterone given premenstrually did not delay the onset of the headache, even as it delayed the onset of menstruation. Subsequent clinical studies have also shown efficacy in treating with estrogen during menstruation to prevent migraine.

Given the above findings, one would expect that migraine should improve during pregnancy because of the elevated estrogen levels, which continue to increase throughout gestation. In fact, in most studies, migraines do improve during pregnancy in 50 to 77% of women, but some prominent studies have reported the opposite result. These studies found that the prevalence and, in some cases, the incidence of migraine during pregnancy exceed that prior to pregnancy. It seems plausible, based on the two groups of studies, that there are at least two types of pregnant headache patients, one whose headaches improve and one whose headaches begin or worsen during pregnancy. The degree of fluctuation of estrogen in pregnancy may differ in these two groups, although the underlying pathophysiologic mechanisms to explain these differences have not been elucidated.

There may be a link between the findings that migraine patterns change in response to estrogen and the known vascular and neurogenic changes seen in migraine. Many studies have reported that estrogen has acute and chronic effects on cerebrovascular and coronary vasculature. Moreover, women with severe angina and normal coronary arteries by cardiac catheterization have been found to have abnormally responsive arteries. The symptoms of this disorder can be treated with estrogen replacement therapy.

Recent investigations have begun to probe the cellular mechanisms underlying the observed changes in vasculature in response to estrogen. Estrogen has acute effects on ion channels in smooth and cardiac muscle and on neuronal ion channels. The importance of the effects of estrogen on ion channels in smooth muscle has obvious implications for vascular responsiveness. Estrogen increases cardiac output and decreases vascular resistance and systolic and diastolic blood pressure. Doppler ultrasound studies of the carotid artery show that transdermal estradiol benefits postmenopausal women by decreasing the pulsatility index. These findings have relevance to migraine patients who may be susceptible to increased vascular reactivity.

**Trigeminal Neuralgia**

Disorders of the cranial nerves can lead to pain in the distribution of these nerves. These pains are not called headaches by the patients who experience them, so they have been lumped under the term “facial pain syndromes.” The most frequent example of these is the pain syndrome of the trigeminal nerve, although neuralgias of other cranial nerves are also seen. The trigeminal nerve, as described above, contains three divisions that supply the face with somatic sensation, the ophthalmic, maxillary, and mandibular. Each of these nerves can be affected by other disorders, both systemic and local, such as trauma, vascular diseases, demyelinating disorders, infections, and neoplasms. When the function of the nerve is disturbed by these diseases, the symptoms are sharp,
aching pain and often sensory loss or dysesthesia in the relevant portion of the face. Occasionally, involvement of the motor division of the trigeminal nerve or other cranial nerves adjacent to the area involved can occur. Examples of this type of symptomatic trigeminal nerve include the Tolosa-Hunt syndrome, which is defined as a granulomatous or neoplastic disorder of the cavernous sinus or superior orbital fissure. The syndrome is manifested as sharp, aching retro-orbital pain and sensory loss over the forehead accompanied by ophthalmoplegias, but not accompanied by pupillary involvement. Herpes zoster can also affect the trigeminal nerve in any of its divisions, resulting in symptoms similar to those described above, usually accompanied by a typical eruption on the skin of the face in the appropriate region of sensory innervation. Another symptomatic disorder is Raeder's paratrigeminal neuralgia, which is a syndrome of intense pain in the trigeminal distribution accompanied by ocular sympathetic paresis. Raeder syndrome must be differentiated from acute carotid disease such as dissection, aneurysm, or arteriovenous malformation within the cavernous sinus.

The trigeminal nerve can also be involved at its root near the cerebellopontine angle to tumors such as acoustic neuromas or meningiomas. Tumors of the sphenoid bone may compress branches of the nerve as it exits through its foramina.

Idiopathic trigeminal neuralgia, otherwise known as tic douloureux, is diagnosed clinically and consists of paroxysms of intense, stabbing, facial pain in the second or third trigeminal division. The pain lasts seconds to minutes and can be very intense. The episodes occur frequently and can be disabling. Stimulation such as water or wind hitting the face or light touch or movement of the face, such as chewing, yawning, or brushing the teeth, can bring on an episode. The syndrome can be diagnosed by clinical history and examination. Rarely is there any sensory loss on the face. If the examination reveals sensory loss, a symptomatic cause must be ruled out by further testing with MRI, lumbar puncture, and appropriate laboratory work. The treatment for tic douloureux is usually an anticonvulsant, neurotransmitter reuptake inhibitor, or GABA-ergic agent, but ablation of the nerve can be performed surgically in severe cases. The cause of the disorder is unknown, but some surgical investigators have suspected that compression of the nerve by a tortuous blood vessel may produce the symptoms.

TREATMENT OF HEADACHES

Treatment of the patient with a chronic benign headache syndrome is an intricate, time-consuming process that should be undertaken only with the understanding that headache patients are chronic pain patients who may require lifelong, or at least long-term, attention. The practitioner must evaluate each patient carefully and attempt to establish a working diagnosis before initiating treatment but must be able to be flexible enough to change the diagnosis if necessary and modify the treatment accordingly. The patient and physician must be willing to establish a long-term doctor/patient relationship that will lead to the exertion of mutual effort toward improvement of the condition of the patient. A good working relationship can also lead to a growing sense of understanding of, and control over, the disease process on the part of both.

Medications are an important part of the management of chronic headache syndromes. Treatment with these agents should be initiated when the patient has failed management by other measures. When a new treatment is initiated, the physician should give the new medicine a full therapeutic trial of at least 3 months before deciding that it is not efficacious. The goal with chronic headache patients is to try to limit the intensity and frequency of events, rather than to try and eliminate the pain entirely. With this in mind, it is often useful to have patients keep a diary of the painful events and their response to medication or other interventions. If, at the end of 3 months, there is a decrease in pain, the medication is continued. Another is another medication will not prove effective. Features of these will usually the emerge manage patients from work.

When dealing with patients, constraints, age, and the problems that are associated with chronic pain: prophylactic and treatment medication are the two major categories of medication that are used.

Prophy
decrease in an agreed-upon parameter of pain, the drug may be considered effective. Another issue to consider when prescribing medications is patient preference. Patients will not use a drug if they do not tolerate its common side effects. Some other important features of treatment are that the practitioner will usually wish to attempt to keep visits to the emergency room to a minimum, maximize patient comfort, and minimize time lost from work because of pain.

When designing a treatment plan for an individual, one must consider therapeutic constraints such as kidney or liver disease, age, and allergy, to give a few examples. Pregnant patients cannot use certain medications that affect fetal development. Risk factors to the fetus have been defined, and each drug has been assigned a level of risk. Drugs in categories A to C pose increasing fetal risk, based on animal studies. Category D drugs have been shown to pose human fetal risk but may be allowable in emergent or life-threatening situations. The final category, category X, includes drugs that are absolutely contraindicated in pregnancy.

There are three main categories of agents that are used for the treatment of headache pain: prophylactic, abortive, and analgesic. The most widely used agents differ for the different headache syndromes, but the separate groups overlap.

**Prophylactic Medications**

Treatment can be most effectively designed for each patient if the examiner can identify a model that describes the pathophysiology of the syndrome. The best example is migraine. In this case, we can develop a model based on clinical and scientific evidence that states that the pain and symptom complex of migraine stems from, for example, an abnormal cerebral discharge that sets off abnormal neurotransmitter release. That release eventually causes constriction, followed by dilation of cerebral blood vessels, stretching of the blood vessel wall, firing of trigeminal pain fibers, and release of locally acting vasoactive and inflammatory substances. The model can take into account an abnormal response of the central pain-suppression system in reacting to the onset of the painful stimulus and can implicate serotonin as the neurotransmitter involved in the evolution of the migraine episode.

One can now observe how a treatment program can be designed. One way to prevent the attacks would be to use an agent that works by inhibiting the abnormal cerebral discharge, such as an anticonvulsant (e.g., phenytoin, sodium valproate) or a benzodiazepine (e.g., diazepam, baclofen). These agents can also work prophylactically by blocking nervous impulses conducted along pain fibers of the trigeminal nerve. Another way would be to give an interictal serotonin-releasing agent such as amitriptyline or fluoxetine. These agents may work by increasing interictal levels of serotonin and preventing the upgrading of receptors that may occur in migraine patients. Another prophylactic strategy would use serotonin receptor-blocking agents. These medications (e.g., cyproheptadine, methysergide) inhibit the effects of serotonin, preventing the actions of that neurotransmitter on constriction of blood vessels and on receptor sites on presynaptic neurons. Constriction of blood vessels can also be inhibited by use of antihypertensive agents as prophylactic medications. Examples of commonly used classes of antihypertensives include the calcium channel blockers and the beta-blockers. The latter agents also work by blocking adrenergic receptors in the central nervous system as well as on blood vessels. A summary of the types of agents used to treat migraine headache is found in Table 14.3. Examples of agents used in other types of headache disorders can be found in Table 14.4.

**Abortive Medications**

The second category of treatment is the abortive. In theory, abortive agents act after
Table 14.3. TREATMENT OF MIGRAINE HEADACHE

<table>
<thead>
<tr>
<th>Prophylactic</th>
<th>Abortive</th>
<th>Analgesic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressant (amitriptyline, 10-150 mg p.o./day)</td>
<td>Serotonin agonists (sumatriptan, 6-12 mg s.q./day or 25-50 mg p.o./day, dicyclomamine 1.5-3.0 mg i.v. or I.M./day—q6h dosing)</td>
<td>Nonsteroidal anti-inflammatory agents (naproxen, 550-750 mg p.o./day—not for daily use)</td>
</tr>
<tr>
<td>Serotonin-reuptake inhibitors (fluoxetine, 20-60 mg p.o./day)</td>
<td></td>
<td>Mixed barbiturate analogues (butalbital with aspirin or acetaminophen, some with caffeine, 6 tablets p.o./day—q6h dosing, not for daily use)</td>
</tr>
<tr>
<td>Calcium channel blockers (verapamil, 180-360 mg p.o./day)</td>
<td>a-Adrenergic agents (ergotamine and caffeine, 2-4 tablets p.o./day)</td>
<td>Opiate analogues (codeine, propoxyphene, oxycodone, meperidine)</td>
</tr>
<tr>
<td>&amp;beta-blockers (propranolol, 60-160 mg p.o./day)</td>
<td></td>
<td>Opiate agonist/antagonist (butorphanol-1 spray in nostril, twice/day)</td>
</tr>
<tr>
<td>Anticonvulsants (carbamazepine, 200-800 mg p.o./day; valproic acid, 250-1000 mg p.o./day)</td>
<td></td>
<td>Antiemetics (chlorpromazine 10 mg p.o. or 25 mg p.o. q6h)</td>
</tr>
<tr>
<td>GABA-ergic agents (baclofen, 5-60 mg p.o./day—three doses; clonazepam, 1-3 mg p.o./day—three times/day dosing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonergic blockers (cyproheptadine 4-8 mg p.o./day; methysergide 4-8 mg p.o./day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone therapy (estradiol)</td>
<td>a-Adrenergic agonist (clonidine 0.2 mg p.o./day—twice-a-day dosing)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: p.o., by mouth; I.M., intramuscular; I.V., intravenous; p.r., by rectum; s.q., subcutaneous.*

the period of vasoconstriction has occurred. They work to keep cerebral blood vessels constricted to prevent the period of vasodilation that brings on excitation of the trigeminal pain-receptor fibers and subsequent inflammatory events. These medications include the ergots, ergot derivatives such as dicyclomamine (DHE), caffeine, isometheptene, and the new serotonin agonist sumatriptan.

Serotonin has long been implicated in causing migraine headache. It causes vascular constriction and can cause pain when applied to nerve terminals. Reserpine, which causes presynaptic release of serotonin and catecholamines, will induce migraine in susceptible individuals but not in controls. Several studies, however, have shown that intravenous injection of serotonin relieves migraine headache, so it seems likely that different subtypes of serotonin receptors may be responsible for inducing and relieving migraine. Sumatriptan works on a subtype known as the 5-HT1B receptor and also probably interacts with the 5-HT1D receptor subtype. The actions of sumatriptan include constriction of isolated intracranial arteries in vitro and a type of regional blood-flow variation in anesthetized animals that suggests vasoconstriction in the carotid system of those animals. Using Doppler ultrasound, it has been shown that dilation of the middle cerebral arteries during a migraine attack can be reversed by intravenous sumatriptan, with subsequent relief of headache. Also, sumatriptan can attenuate neurogenic inflammation in dura mater. The central actions of sumatriptan are not well understood. Although studies have suggested that sumatriptan does not cross the blood-brain barrier.
### Table 14.4: Headache Management

<table>
<thead>
<tr>
<th>Headache Type</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension headache</td>
<td>Neurotransmitter-reuptake inhibitor, calcium channel blocker, valproic acid, analgesic agent</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>Calcium channel blocker, beta-blocker, oxygen, lithium, neurotransmitter-reuptake inhibitor, antiemetic, sumatriptan, ergotamine and caffeine, analgesic agent</td>
</tr>
<tr>
<td>Paroxysmal hemiconvulsia</td>
<td>Indomethacin, calcium channel blocker</td>
</tr>
<tr>
<td>Chronic daily headache (Migraine or Tension type)</td>
<td>Appropriate agents for those disorders</td>
</tr>
<tr>
<td>Chronic rebound headache</td>
<td>Dihydroergotamine, antiemetic, stop all analgesic agents</td>
</tr>
<tr>
<td>Catamenial or menstrual migraine</td>
<td>Estrogen patch or tabs during menstruation</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>Anticonvulstatic, GABA-ergic agent, neurotransmitter-reuptake inhibitor</td>
</tr>
</tbody>
</table>

The other abortive agents, such as ergotamine and dihydroergotamine, are less specific than sumatriptan and tend to affect adrenergic receptors as well as serotoninergic receptors, thereby causing side effects of peripheral vascular constriction, hypertension, and nausea (ergotamine) or just nausea (dihydroergotamine). Nevertheless, these agents may work on central serotonergic receptors, stabilizing serotoninergic neurotransmission. These effects are similar to those thought possibly to occur as a result of the actions of sumatriptan, as well as the neurotransmitter reuptake inhibitors and other preventive antimigraine drugs. DHE has been found to be especially useful in the treatment of chronic rebound headache. In conjunction with an antiemetic, parenteral administration of DHE can relieve the headache associated with chronic analgesic use.

### Analgesic Medications

The final treatment category in the treatment algorithm is the analgesic. The analgesic agents include the nonsteroidal anti-inflammatory drugs, acetaminophen, opiates, the newer combination opiate agonist/antagonists such as butorphanol, and the combination analgesics such as butalbital/caffeine/aspirin. Some analgesics act in the central nervous system by stimulating the pain-suppression pathway or by binding to central opiate receptors. Others act by blocking the inflammation that may develop in vascular walls or trigeminal nerve endings. Often, inflammation and pain may be quite severe by the time an analgesic is used, so the effectiveness of these agents may be increased if they are used at the earliest possible moment during a headache attack.

In general, the physician should first attempt to treat the headache patient nonpharmacologically by urging stress reduction and elimination of precipitating environmental factors such as foods or smells that bring on headaches in that particular individual. The patient may also try to decrease physical...
stress by, for example, arranging a work station to optimize his or her comfort. The physician should also encourage regular sleep and meals. Reassurance to the patient that a serious or life-threatening condition does not exist is very important. Headaches can be severe and debilitating, however, and intervention with medications is often necessary; for example, if the patient becomes disabled by the head pain.

**CONCLUSION**

Much still needs to be learned about the treatment and causes of many different types of headache. The field is rapidly growing as knowledge gained from research and the use of new techniques is applied to the clinical management of headache. Learning about the actions of new (as well as traditional) pharmacologic interventions also plays a part in increasing our understanding of the mechanisms underlying the pathophysiology of headache syndromes.

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Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. JAMA 1992;267:64–69.
Since man depends on his visual sense more than on his other senses, the ability to direct the eyes accurately toward an object of interest is very important. To accomplish this task, volitional, reflex, and vestibular commands all converge on gaze centers in the brainstem. Processing and integration of these commands results in stimulation of the appropriate ocular motor nuclei and inhibition of the nuclei of the opposing muscles. In addition, the speed and amplitude of the movement in both eyes must match each other and the target position. The final task is to hold the eyes in an eccentric position, resisting the elastic forces in the orbit, to maintain fixation.

A sophisticated system exists to accomplish these movements. The advent of eye-movement recording and computer analysis have given us a better understanding of the anatomic and physiologic mechanisms of gaze. Most clinicians, however, do not have easy access to an eye-movement laboratory for help in diagnosing gaze disorders. Therefore, in this chapter I emphasize the correlation of clinical gaze abnormalities with anatomic lesions. Gaze palsies do not have specific causes. Indeed, any category of disease that can affect the nervous system can potentially cause a gaze palsy.

NORMAL GAZE: TERMINOLOGY, STRUCTURES, AND PATHWAYS

Gaze involves the movement of the eyes to bring an object of interest before the fovea. If the object is moving horizontally, vertically, or obliquely in a frontal plane, the eyes move together, or conjugately; this is called a version movement. If the object is moving away or toward the person in a sagittal plane, the eyes move in opposite directions to maintain binocular fixation; this is called a vergence movement. Divergence is an abduction movement of both eyes to move the eyes from fixation on a closer target to a more distant target; convergence is the opposite.

Versional eye movements are divided into fast eye movements called saccades and slow eye movements call pursuits. Saccades occur when the eyes must move quickly to fix on a target or to follow a rapidly moving target. The initiating stimulus in the environment can be (a) auditory (e.g., a command or hearing a sound) or (b) visual (e.g., a peripheral target that causes involuntary or reflex saccades). Random eye movements and eye movements during REM sleep are
also saccades. The velocity of the saccadic eye movement varies between 30° and 800°/sec, with a duration of 20 to 160 msec.

Saccadic commands originate from a portion of the premotor cortex just anterior to the motor strip, called the frontal eye fields (FEFs) (Fig. 15.1). The command for right horizontal gaze begins in the left hemisphere and travels down fibers in the anterior limb of the internal capsule, reaching the medial cerebral peduncle. At the level of the trochlear nucleus, the fibers decussate and synapse in the horizontal-gaze center of the pons called the parapontine reticular formation (PPRF). This gaze center is an ill-defined structure extending from the level of the trochlear nucleus to the abducens nucleus lying ventral to the nuclei within the reticular formation. Neurons within the PPRF send messages to the adjacent abducens nucleus and interneurons in the region of the abducens nucleus called the paraabducens nucleus. Interneuron fibers decussate immediately to the opposite medial longitudinal fasciculus (MLF) and travel up the brainstem to the medial rectus subnucleus. Therefore, excitation of the left PEF results in a right horizontal saccade. For the right lateral rectus and left medial rectus to move, the antagonist muscles must be inhibited (right medial rectus and left lateral rectus). An inhibitory system for this purpose is located in the PPRF.

Within the PPRF, three important cells are present: the burst cell, pause cell, and tonic cell. The burst cell is the cell that sends the “pulse-step” signal to move the eyes. The pause cell, which continuously inhibits firing of the burst cell, turns off with the supranuclear command for a saccade, thus allowing the burst cell to initiate a saccade (Fig. 15.2). The pause cell turns back on when the saccade is complete. Once the eyes have successfully fixated on the target, they must be held in place eccentrically by an active process. The tonic cells in the reticular formation along with help from a neural integrator, located either in the nucleus prepositus hypoglossi or possibly a portion of the vestibular or cerebellar system, maintain the eyes’ position (Fig. 15.3). Malfunction in any of these subsystems can result in gaze abnormalities, nystagmus, or other abnormal eye movements. The latter two subjects are discussed in Chapter 16, Nystagmus and Related Ocular Oscillations.

A parallel control pathway for saccades originates in the superior colliculus (SC). Visual information from the retina and visual cortex feeds into this area. Afferents go to the vertical and horizontal gaze centers. The superior collicular system, according to experimental data, generates saccades toward new visual stimuli in a reflex manner. A lesion in either the PEF or the SC only leads to transient contralateral gaze dysfunction, whereas simultaneous lesions in both systems lead to more severe and permanent gaze palsies.

Pursuit is a slow smooth movement used to maintain fixation on an object that is moving slowly in space. Although slow eye movements have a maximum velocity of 90°/sec, their accuracy declines when the...
• Figure 15.2.

Proposed model of the saccade system in the primate. Supranuclear commands produce inhibition of the pause cells (P), thus relieving the inhibition of the burst cells (B), which then send commands necessary for fast eye movement (FEM). When feedback from the visual system, via the neural integrator (NI), indicates that the intended target and fovea are matched, the pause cells are turned back on and the burst cells are turned off. PPRF, parapontine reticular formation.

1. RESTING STATE

2. INITIATION SACCade

3. MAINTAIN ECCENTRIC GAZE

velocity is greater than 40°/sec. The pursuit gaze center presumably resides in the deep parieto-occipital junction next to the occipital trigone of the lateral ventricle (Fig. 15.4). It receives its driving commands from the primary visual cortex. The pursuit gaze center drives pursuit movements to the ipsilateral side; for example, left hemisphere stimulation results in left pursuit. The details of the pursuit system are not well delineated but appear to involve extrastriate visual areas in the temporal and parietal lobes, dorsolateral pontine nuclei, and the vestibulocerebellar system. The observation that experimental lesions in the PPRF primarily affect saccades indicates that this region is not included in the pursuit system.

• Figure 15.3.

Mechanisms for establishing and maintaining horizontal gaze. (1) Resting state: The pause cells (P) continuously inhibit the burst cells (B). (2) Initiation saccade: After the supranuclear command arrives in the ponte, the excitatory burst cells stimulate the ipsilateral abducens and contralateral oculomotor nuclei (Fig. 15.2). An inhibitory system inhibits the contralateral abducens and ipsilateral oculomotor nuclei. (3) Maintenance of eccentric gaze: Once the eyes have successfully fixated on the target, the neural integrator (NI) holds fixation by inhibiting the burst cells and stimulating the pause cells. Modulation of eccentric fixation is performed by the cerebellar flocculus (FLOC).
Vertical eye movements do not have a known gaze center in the cerebral hemispheres. Experimental stimulation of both hemispheres produces vertical eye movements and sends commands to the brainstem bilaterally. The brainstem nucleus that primarily controls vertical gaze is the rostral interstitial nucleus of the MLF (riMLF) (Fig. 15.5). It is just superior to the oculomotor nucleus in the midbrain. Messages for down gaze and up gaze pass directly from the riMLF down to the oculomotor and trochlear nuclei. A portion of the up-gaze fibers goes up into the posterior commissure and crosses to the opposite side. This separation of the pathways for down and up gazes explains the selective up-gaze paralysis seen with pressure on the dorsal midbrain (Parinaud syndrome). The caudal PPRF also has fiber connections to the vertical-gaze centers in the midbrain. Experimental and clinical lesions of the caudal PPRF have led to loss of vertical gaze.

Another important input to the gaze system is the vestibulocerebellar system. Information from both the semicircular canals and the otoliths (utricle and sacculus) can initiate and modulate eye movements. The ability to stabilize the eyes against gravitational and accelerational forces is important for avoiding the sensation of environmental movement and for maintaining clear vision. The vestibular nuclei send afferents to the ipsilateral cerebellar hemisphere, primarily the flocculonodular lobe. Messages from this system travel to both sides of the brainstem to the ocular motor nuclei (III, IV, and VI) via the MLF (Fig. 15.5). The primary connection for the vertical vestibular fibers is to the contralateral oculomotor and trochlear nuclei. The horizontal vestibular fibers cross and synapse in both the abducens and paraabducens nuclei. The paraabducens interneurons stimulate the oculomotor nucleus ipsilateral to the original vestibular nucleus via decussating MLF fibers. Therefore, stimulation or increased tone from one horizontal semicircular canal causes contralateral eye movement.

The cerebellum has several roles in ocular movements primarily concerned with eye movement and fixation accuracy. The cerebellum helps suppress the vestibulo-ocular reflex (VOR). 

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**Figure 15.4.**
Lateral and axial views of the brain. Shaded areas represent the proposed location of the pursuit gaze centers.

**Figure 15.5.**
Location of the midline structures in the brainstem involved in vertical and horizontal gaze. The vertical-gaze center in the midbrain consists of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), posterior commissure (PC) containing the interconnecting up-gaze fibers, oculomotor nucleus (III), and trochlear nucleus (IV). The horizontal-gaze center in the pons consists of the paramedian reticular formation (PPRF) and abducens nucleus (VI). Counting through the entire length of the brainstem is the medial longitudinal fasciculus (MLF), which carries messages between the oculomotor nuclei (III, IV, and VI) and the vestibular nuclei.
reflex (VOR), so that each time the head moves, the eyes do not move passively in the opposite direction. The cerebellum also controls the smoothness of pursuit movements and the accuracy of saccades. Breakdown of the cerebellar control system leads to cogwheel pursuit, hypometric saccades, and ocular dysmetria. Last of all, maintenance of eccentric gaze requires input from the cerebellum; disruption of this function causes gaze-evoked nystagmus.

The ocular motor system is further divided according to anatomic location into supranuclear, infranuclear, internuclear, and nuclear components. Supranuclear refers to structures and pathways that descend into the brainstem and are placed proximal to the ocular motor nuclei (III, IV, and VI); an example is the FEF. Infranuclear refers to structures and pathways ascending in the brainstem to the ocular motor nuclei; the vestibular nuclei are the prime example of infranuclear structures. Internuclear refers to connections between the ocular motor nuclei; the MLF is the structure most often implied by this term. Nuclear refers to the ocular motor nuclei themselves. Differentiation of a supranuclear gaze palsy from a nuclear palsy by the clinical examination techniques presented below is helpful in the differential diagnosis of gaze abnormalities.

**CLINICAL EXAMINATION**

The patient may be asymptomatic for the gaze palsy or complain of blurry vision. Diplopia is present in deficiencies of vergence movements and disconjugate gaze abnormalities such as skew deviation and internuclear ophthalmoplegia. If the vestibular system is involved, the patient may have vertigo or complain of environmental movement or tilting. Very commonly the patient will have other neurologic complaints referable to dysfunction of structures contiguous to the gaze pathways and nuclei.

The clinician should observe the position of the eyes in primary gaze first to see if the patient has a conjugate deviation of the eyes or a tropia or phoria. The patient is then asked to pursue a slow-moving target with each eye separately (ductions) and together (versions and vergence movements). The moving target must be moved slowly enough that pursuit movements are elicited and not saccades, which will occur if the movement is too rapid. The clinician should note any gaze movements that are not full.

If the pursuit system is intact, the patient should be asked to perform saccades by looking quickly from primary position to eccentric gaze. The patient should be instructed to look from the examiner's nose to the examiner's finger and then back to the nose, with the finger held to the right, left, up, and down. A blind person also can perform saccades with directions such as "Look to your right" and so forth. If the patient has difficulty looking in a certain gaze position, oculocephalic maneuvers (doll's head maneuvers) should be done to check the integrity of the infranuclear structures, ocular motor nuclei, the nerves, and extraocular muscles. Oculocephalic maneuvers are performed by having an alert patient fix on a straight-ahead target while the physician moves the patient's head to see if the eyes can be driven in the opposite direction. If this maneuver moves the eyes appropriately into the weak field of gaze, then the gaze palsy is supranuclear. If oculocephalic maneuvers do not move the eyes appropriately, then lesions in the following structures must be considered: vestibular connections from the medulla and pons, cranial nerve nuclei or nerves, extraocular muscles, and MLF in internuclear ophthalmoplegia.

In a progressive central gaze palsy, the order in which the subsystems are affected is saccades first, pursuit second, and vestibular last. A patient may have difficulty with saccades in a certain direction but still have the ability to move the eyes normally with pursuit or vestibular movements. Further progression of the disease can result in loss of all functions. Diseases outside the nervous system that can cause gaze palsy include myasthenia gravis, Lambert-Eaton syndrome, progressive external ophthalmoplegia, thyroid
ABNORMAL VERTICAL GAZE: CLINICAL CORRELATIONS

As discussed above, vertical gaze occurs after stimulation of both cerebral hemispheres and later activation of midbrain nuclei and pathways. Therefore, abnormalities of vertical gaze should raise the question of a midbrain lesion or bilateral cerebral hemisphere dysfunction. Unilateral or bilateral lesions in the midbrain may result in abnormal vertical gaze. Elderly people may have difficulty with up gaze in a nonspecific manner; if this symptom occurs in isolation, without other neurologic signs or symptoms, it does not require further evaluation.

In general, lesions of the dorsal midbrain can result in up-gaze paresis, and lesions in the ventral midbrain preferentially affect down gaze. Examples of bilateral cerebral dysfunction that result in vertical-gaze palsies include Parkinson's disease, progressive supranuclear palsy, and certain lipodisosis.

Dorsal Midbrain Syndrome (Parinaud Syndrome)

The dorsal midbrain contains pathways for both up gaze and pupillary constriction to light. The dorsal midbrain syndrome consists of (a) poor-to-absent up gaze, (b) midposition pupils with light-near dissociation, and (c) convergence-retraction nystagmus. The most common cause of this syndrome by compression, occurring either from mass lesions in the pineal region (Fig. 15.6) or dilation of the third ventricle from hydrocephalus. Increased intracranial pressure is usually present, causing papilledema. Other causes of this syndrome include midbrain infarction, multiple sclerosis, arteriovenous malformation, and infections.

Convergence-retraction nystagmus, an unique part of Parinaud syndrome, is seen best when the patient attempts to saccade up. On attempted fast up-gaze, the eyes pull in and the globes retract. Electromyography of the eye muscles in patients with this disorder has shown cocontraction of the oculomotor innervated muscles, resulting in retraction of the globes. Rarely, divergence-retraction nystagmus

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stagnus is seen instead of convergence-retraction nystagmus. The easiest way to bring out convergence-retraction nystagmus is to ask the patient to follow down-going stripes on an optokinetic drum; this maneuver will elicit convergence-retraction nystagmus in place of up-going saccades.

Other signs of dorsal midbrain dysfunction are lid retraction (Collier's sign) and conjugate down-gaze in the primary position ("setting-sun sign"). Neurosurgeons see these signs most commonly in patients with failed ventriculoperitoneal shunts with rapid reappearance of hydrocephalus.

Any patient with the dorsal midbrain syndrome should have a neuroimaging scan to look for an anatomic lesion. If a lesion is present, surgical treatment may result in resolution of the ocular findings.

**Progressive Supranuclear Palsy**

Progressive supranuclear palsy (PSP) is a disorder of the basal ganglia resembling Parkinson's disease, with bradykinesia and rigidity. PSP patients differ in that they have marked rigidity of the trunk and neck, very little tremor, and a lack of response to parkinsonian drugs. They initially have difficulty with vertical eye movements, down more than up; the disorder progresses to involve horizontal gaze. The end-stage of PSP is a global ophthalmoplegia. Oculocephalic maneuvers or caloricics can drive the eye movements, confirming the supranuclear origin of this gaze palsy.

**Parkinson’s Disease**

Vertical-gaze abnormality is common in patients with Parkinson’s disease. This is usually an up-gaze palsy affecting saccades first and pursuit later. Saccades in other gazing can be slow, and the smoothness of pursuit disrupted, causing “cogwheel pur-

**Lipidosis**

Vertical supranuclear ophthalmoplegia has been observed in patients with a lipid-storage disease that is a variant of Niemann-Pick disease. The patients present with a history of a progressive dementia beginning in late childhood, choreathetosis, and hepato
tosplenomegaly. Ocular motility testing reveals inability to move the eyes vertically using saccades. Pursuit may remain until later. Intact vertical oculocephalic maneuvers confirm the supranuclear location.

**Whipple’s Disease**

Involvement of the central nervous system by Whipple’s disease can lead to supranuclear gaze paralysis that is initially vertical. The patients develop a progressive dementia, hypersonnia, and ataxia. Uveitis has been seen in some patients. A history of malabsorption and diarrhea may or may not be present. Patients with acquired immuno
deficiency syndrome (AIDS) have an increased incidence of Whipple’s disease.

Magnetic resonance imaging (MRI) reveals areas of increased signal on T2-weighted images in the diencephalic-midbrain region. Occasionally, the spinal fluid will contain PAS-positive macrophages. If Whipple’s disease is suspected, a small-bowel biopsy should be done. Recommended treatment of Whipple’s disease is either chloramphenicol or trimethoprim-sulfamethoxazole.

**Monocular Elevation Paresis**

In monocular elevation paresis, the patient has no ocular deviation in primary gaze but has an inability to elevate one eye. The
lesion, in the pretectum, involves the connection of the rMLF to the oculomotor nuclei. The oculocephalic maneuver is normal; forced ductions and Tensilon tests are negative, confirming the supranuclear origin. This condition may be congenital or acquired and may be mimicked by muscle diseases such as thyroid ophthalmopathy, myasthenia gravis, and chronic progressive external ophthalmoplegia.

**Skew Deviation**

The patient with a skew deviation has a vertical deviation of the eyes in primary gaze and notices vertical diplopia. The vertical tropia may be comitant or noncomitant, but unlike acute cranial nerve palsies, no primary or secondary deviations are present. Skew deviation denotes posterior fossa disease and is nonspecific for etiology and location. If an internuclear ophthalmoplegia (INO) is also present, the lesion causing the skew is usually ipsilateral to the INO, with the ipsilateral eye being hypertropic. In cases without an INO, the hypotropia eye usually is ipsilateral to the lesion (64% in one study). Isolated skew deviation in neonates may be a harbinger of horizontal strabismus.

**Ocular Tilt Reaction**

In ocular tilt reaction—a rare disorder related to skew deviation—the patient has a skew deviation, torsion of the eyes in the direction of the hypertropic eye, and a head tilt in the same direction. This condition may occur episodically or persist. Reported causes include lesions in the subthalamus, midbrain, and medulla, and, less commonly, peripheral vestibular disease. The otolith pathways appear to be involved, producing this unique triad of findings. Baclofen has been used in some patients with benefit.

**Down-Gaze Palsy**

An isolated inability to look down can occur in patients with infarcts in the pretectum affecting the rMLF. Some patients with basal ganglia disorders, such as progressive supranuclear palsy, initially have down-gaze palsy. In progressive supranuclear palsy, the extrapyramidal findings are the clue that bilateral hemispheric dysfunction is responsible.

**Conjugate Downward Deviation of the Eyes**

The patient who presents with acute onset of conjugate downward deviation of the eyes has dysfunction in the pretectum. The level of consciousness is often impaired as the result of involvement of the reticular activating system. Transient downward gaze can occur as a benign condition in neonates. A careful neurologic evaluation of these babies should be done to eliminate more serious conditions.

**ABNORMAL HORIZONTAL GAZE: CLINICAL CORRELATIONS**

Horizontal-gaze abnormalities are more common than vertical ones. Because the horizontal-gaze system depends on unilateral gaze centers and pathways, it is more vulnerable than the vertical-gaze system, which has bilateral input. Horizontal-gaze paresis can vary from (a) gaze-evoked nystagmus to (b) slowing or dysmetria of the movement to (c) a total inability to move the eyes in the involved direction of gaze. Severe gaze paralysis results in conjugate deviation of the eyes in the opposite direction at rest.

The most common abnormalities in this group are gaze palsy resulting from a cerebrovascular accident (CVA). Localization of the lesion depends on concurrent neurologic function, field loss, lowering deficits first.
logic findings such as hemiparesis, visual field loss, and cranial nerve palsy. The following discussion covers saccade abnormalities first and then pursuit abnormalities.

**Horizontal-Gaze Paresis**

An isolated horizontal-gaze paresis is rare. The lesion can be located anywhere in the horizontal-gaze pathways and cannot be localized more specifically without other neurologic signs and symptoms.

**Horizontal-Gaze Paresis with Hemiparesis**

The FEF lies immediately anterior to the motor strip in each hemisphere, both areas receiving branches of the middle cerebral artery. These regions initiate commands for movement contralaterally; horizontal saccades in the FEF and voluntary movement of the face, body, and limbs in the motor strip. When a CVA involving the middle cerebral artery occurs, the patient can present with a contralateral hemiparesis and gaze palsy. In extensive strokes, the patient has conjugate deviation of the eyes "toward the lesion." Theoretically, the combination of hemiparesis and gaze palsy toward the same side as the hemiparesis can occur in a lesion of the corticobulbar and corticospinal tracts down to the level of the trochlear nucleus. In clinical settings, however, the lesion is almost always in the cortical distribution of the middle cerebral artery.

As the patient recovers, the eyes come back to the midline, and the speed and accuracy of the horizontal saccades gradually improve. Improvement may not occur if a previous stroke has affected the opposite FEF, which assumes the function of the damaged gaze center through the ipsilateral system.

If the patient presents with a saccadic horizontal-gaze palsy to one side and a hemiparesis on the opposite side, then the lesion must be in the pons. The PPRF or the abducens nucleus could be the site of the lesion, since all fibers from the PPRF go to the abducens nucleus, as discussed above. Oculoccephalic maneuvers or caloric, which bypasses the PPRF, can differentiate between the two sites. If the abducens nucleus is affected, the infranuclear input will not generate a response. Dysfunction of the pontine gaze system does not recover well, often leaving the patient with a persistent deficit.

**Internuclear Ophthalmoplegia**

INO occurs when a lesion is present in the medial longitudinal fasciculus, which connects the abducens nucleus with the medial rectus subnucleus of the oculomotor complex. Therefore, when the PPRF burst cells fire, the lateral rectus responds, but the opposite medial rectus responds poorly. The lesion is ipsilateral to the eye with the adduction weakness. The patient exhibits decreased abduction and adduction nystagmus. The affected eye can be either orthotropic in primary position or abducted. The severity of the adduction abnormality varies from total inability to adduct the eye during a saccade to a mild abnormality consisting of an adduction lag. In the latter case, the clinician will see the abducting eye arrive at the final gaze position earlier than the adducting eye. Characteristically, the abducting eye displays jerk nystagmus in the direction of gaze with an INO. The cause of the nystagmus is debated. The well-known maxim is that a young patient with INO has multiple sclerosis and an elderly patient has a CVA. For the most part, this generalization is useful. However, other causes such as tumor, infection, trauma, and drug intoxications have to be considered. INO is specific for the anatomic site of the lesion but not for the cause. A young patient with bilateral INO most often does have demyelinating disease (Fig. 15.7).
One-and-One-Half Syndrome

A lesion involving the PPRF, the abducens nucleus, or both and the ipsilateral medial longitudinal fasciculus causes the one-and-one-half syndrome (Fig. 15.8). The patient has a horizontal-gaze palsy ipsilateral to the lesion and an INO in the ipsilateral eye. Motility testing shows paralysis of all horizontal eye movements except abduction of the contralateral eye. The lesion is on the side of the immobile eye. The genu of the facial nerve may be affected as it arches over the abducens nucleus, causing a peripheral seventh-nerve palsy. This syndrome is specific for a midline pontine lesion. The causes are similar to those in INO.

Conjugate Horizontal Gaze and Seizures

During a seizure, the eyes may deviate to one side. In contrast to a destructive lesion, stimulation, or "irritation," of the PPRF in seizure patients causes contralateral deviation of the eyes. Therefore, a patient with an irritative focus have deviation of the eyes, while a patient with a lesion is true to have deviation of the eyes.

Congenital Apraxic

Cogan separated INO into two separate groups on the basis of involvement or sparing of adduction with the near reflex. The near-reflex pathways do not go below the oculomotor complex, therefore, if convergence is normal, then the lesion is below the oculomotor nuclei, and if not, the lesion is in the medial longitudinal fasciculus at the level of the nuclei. Cogan named these posterior INO and anterior INO, respectively.

Lutz also proposed a posterior INO and anterior INO, but his criteria differ from those of Cogan. The anterior INO of Lutz has the same criteria as the posterior INO of Cogan. The posterior INO of Lutz is a disconnection of the fibers from the PPRF to the abducens nucleus that causes an abduction abnormality and spares adduction. The posterior INO of Lutz is extremely rare and depends on proof of preserved function of the sixth nerve during pursuit or vestibular eye movements.

*Figure 15.8.* Location within the pons of the lesions responsible for the one-and-one-half syndrome (dotted area) and internuclear ophthalmoplegia (diagonal lines). VI, abducens nucleus; MLF, medial longitudinal fasciculus; PPRF, paramedian reticular formation.
imitative focus in the left frontal region may have deviation of the eyes to the right as part of the seizure. This generalization usually is true, but studies of seizure patients have revealed that in some cases, the deviation is ipsilateral to the focus.

**Congenital Ocular Motor Apraxia**

Cogan initially described a unique gaze disturbance in infants and children that he named ocular motor apraxia (OMA). An affected child has difficulty performing horizontal saccades to commands. To move the eyes, the child uses a head thrust in the direction of desired gaze, resulting in passive movement of the eyes in the opposite direction. Once the eyes reach the desired position or target, they maintain fixation. The head, which overshoots the target position, is then slowly brought back so the eyes are in primary gaze position. Spontaneous and reflex saccades are more easily performed than command saccades. With maturation, the patient’s eye movements usually improve with less need for head thrusts to generate saccades. Eye-movement recordings have shown abnormalities in saccadic latency and amplitude but not velocity, suggesting that the PPRF burst neurons are intact. Pursuit eye-movement recordings may show hypometric abnormalities.

The exact anatomic site of abnormality in congenital OMA is unknown. Recent reports of patients with OMA, however, document diffuse neurologic involvement resulting in slow motor and speech development. In addition, agenesis of the corpus callosum and hypoplasia of the cerebellum have been seen on scans. A brainstem tumors have been reported in one patient with the clinical findings of OMA. Patients with OMA should be followed and scanned if the condition worsens. The clinical findings of OMA also have been seen in Pelizaeus-Merzbacher disease and spinocerebellar degeneration.

**Unilateral Pursuit Paresis**

A patient with a lesion of the parieto-occipital junction may have decreased ability to pursue a target in the ipsilateral direction and, instead of normal pursuit movements, will use small saccades to follow a target (saccadic pursuit or cogwheel pursuit). A contralateral homonymous field loss is often present in these patients because of the proximity of the optic radiations to the pursuit gaze center. Optokinetic nystagmus (OKN) is absent or decreased ipsilateral to the lesion. Before the development of scanners, patients with homonymous field loss underwent OKN testing to differentiate tumors from posterior cerebral artery infarcts. The pursuit gaze area receives blood from the middle cerebral artery whereas the occipital cortex is supplied by the posterior cerebral artery. Therefore, normal pursuit function on OKN testing favors a posterior cerebral infarct, and dysfunction favors a tumor that extends beyond arterial supply zones.

Unilateral pursuit paresis also can be seen in patients with unilateral cerebellar lesions. These patients will usually have other signs and symptoms of ataxia.

**Bilateral Pursuit Paresis**

A patient with bilateral pursuit paresis is unable to pursue a target smoothly. Saccadic pursuit, also called cogwheel pursuit, is the clinical finding. This abnormality is not anatomically specific and can be seen with diffuse disease of the hemispheres, cerebellum, or stem. Impaired attention or sedative drugs also can cause bilateral pursuit paresis.

**VERGENCE ABNORMALITIES: CLINICAL CORRELATIONS**

Although the anatomic pathways for vergence movements are not well delineated, it
is known that the brainstem pathways for convergence are in the midbrain anterior to the oculomotor complex.

Convergence Paralysis

A patient with convergence paralysis will complain of horizontal diplopia at near. Examination will reveal normal medial rectus function during ductions and versions but little or no convergence to a near target. This disorder is caused by lesions of the rostral midbrain resulting from infection, infarction, trauma, or demyelination. A lack of effort on the patient's part can simulate a convergence paralysis. If the pupils constrict on near effort but no convergence occurs, then the examiner can assume the patient is cooperative.

Spasm of the Near Reflex

In spasm of the near reflex, the patient presents with episodic adduction of one or both eyes and complains of diplopia, eye fatigue, blurred vision, or pulling of the eyes. Poor abduction of the eye is evident when these episodes occur, raising the possibility of sixth-nerve palsy or palsies. The clue to the diagnosis is miosis of the pupil that appears with attempted abduction, denoting the stimulation onset of near-reflex pathways. Normal function of the lateral rectus can be assured using reflex maneuvers such as OKN testing, oculocephalic maneuvers, or caloric. Usually the patient is in a stressful situation or using the eyes to read a lot when a spasm occurs. Rarely, this condition is organic in nature, presenting with associated signs and symptoms of brainstem disease.

Divergence Paralysis

A patient with divergence paralysis complains of horizontal diplopia at distance only. Measurements reveal an esotropia at distance but not near. The lateral rectus has normal function with version testing. When this condition exists in isolation, no further evaluation is necessary. Treatment of isolated divergence paralysis consists of prisms and extraocular muscle surgery. If a question of lateral rectus weakness is present or other neurologic signs are evident, the clinician needs to look for evidence of tumor, multiple sclerosis, or infection. Other causes include CVA, increased intracranial pressure, and following lumbar puncture.

Thalamic Esotropia

Patients with a lesion of the midbrain diencephalic junction can present with a contralateral esotropia and inability to abduct that eye. Often, the patient has an associated hemiparesis on the same side as the esotropia. This abnormality has been termed thalamic esotropia, or "pseudo-sixth," by Fisher. Computed tomography (CT) or MRI will show the lesion, which is usually a basal ganglia infarction. Oculocephalic maneuvers or caloric may not overcome the abduction weakness. Abnormalities of supranuclear vergence pathways to the third- or maybe the sixth-nerve nuclei are felt to be responsible, resulting in a "hyper-convergence" of the contralateral eye.

MISCELLANEOUS GAZE DISORDERS

Wernicke's Encephalopathy

Wernicke's encephalopathy is a common disorder in patients with poor nutrition resulting in a thiamine deficiency. The hemorrhagic lesions characteristic of this disorder are found in the hypothalamus, mammillary bodies, and periventricular and periaqueductal regions of the brainstem (Fig. 15.9). The cardinal symptoms and signs are ophthalmoplegia, confusion, and gait ataxia. The ophthalmoplegia initially begins as gaze-evoked horizontal nystagmus and may progress to gaze paralysis. The patient may become disoriented, and in the later stages of the disease, premature death may occur.
evoked nystagmus and then progresses to gaze palsies. The nystagmus is most often horizontal, less commonly vertical, and rarely rotary. If not treated with parenteral thiamine, the patient develops total ophthalmoplegia, coma, and eventual death. The mortality rate is 10 to 20%.

Those most at risk for Wernicke's encephalopathy are alcoholics, chronically ill patients with poor nutrition, and patients with anorexia or bulimia. The physician can precipitate Wernicke's encephalopathy by giving intravenous fluids containing glucose but not thiamine. The ocular motility findings begin improving quickly with the administration of intravenous thiamine.

**Functional Gaze Palsies**

Although functional gaze palsies are rare, the physician needs to know how to differentiate them from organic lesions. If a horizontal-gaze palsy is seen, the physician should look closely for evidence of miosis during attempted gaze. This finding would suggest the use of the near reflex to suppress gaze. To evaluate the integrity of the infranuclear structures, nuclei, nerves, and muscles, the VOR should be stimulated with either oculocephalic maneuvers, caloric, or chair rotation. OKN testing can be done with the initial targets being gradually moved into the paretic field of gaze on repeated testing. Testing of refixation saccades by gradually moving the targets into the paretic field of gaze can be informative also. Pursuit can be evaluated by putting a large mirror in front of the patient. The mirror is then turned either to the right or left for horizontal-gaze palsies or up and down for vertical-gaze palsies. The physician watches for movement of the eyes as they follow the moving facial image. Documentation of intact movements of the eyes with these maneuvers proves the functional character of the complaint.


**CASE STUDIES**

**Case 15.1**

A 20-year-old college student collapsed and lost consciousness at a rugby practice soon after hitting another player with his head. Upon arrival at the emergency room, the patient was unconscious with a dilated right pupil, decerebrate posturing, and a left hemiparesis. After a complicated course requiring barbiturate coma, he woke up and had a residual quadriparesis, left greater than right. The oculomotility examination revealed a left esotropia with moderately reduced abduction of the left eye. In addition, he had a right hypertropia. Pursuit movements were cogwheel on gaze to the right and left.

Based on these clinical findings, what is the differential diagnosis? What investigations would be appropriate?

**Discussion**

The loss of consciousness and quadriparesis obviously indicate that the head trauma affected the brainstem. The initial dilated pupil and left hemiparesis would be consistent with Weber syndrome, which is caused by a lesion of the midbrain involving the third nerve and cerebral peduncle. Although poor abduction of the left eye usually indicates sixth-nerve palsy, a lesion causing sixth-nerve palsy is associated with contralateral hemiparesis, not ipsilateral hemiparesis as in this patient. A lesion involving the midbrain-diencephalic junction on the right could cause a thalamic esotropia with poor adduction to the left and a left hemiparesis. The hypertropia could be skew deviation or a fourth-nerve palsy. The patient had an emergency CT scan that was normal. Later MRI scans revealed an infarction of the right posterior thalamus, midbrain, and upper pons (Fig. 15.10). Arteriography revealed occlusion of the distal basilar artery (Fig. 15.11). The diagnosis of thalamic esotropia is most likely in this case.

**Case 15.2**

A 46-year-old woman was brought to the emergency room because of the abrupt onset of a severe headache and coma. An emergency CT scan revealed a left inferior frontal hematoma and subarachnoid hemorrhage. Arteriography showed a left proximal internal carotid artery aneurysm. After the aneurysm was clipped, the patient did well until 9 days postoperatively when she became lethargic and developed a right hemiplegia and left-gaze preference with inability to look to the right.

What is the most likely cause of the patient’s postoperative deterioration? How could this be demonstrated?

**Discussion**

The patient’s postoperative symptoms are most consistent with a lesion involving the left hemisphere, resulting in a right hemiplegia and loss of voluntary right gaze. In addition, the patient was probably “looking toward the lesion” in a fixed conjugate left gaze. Involvement of the FEFs would be likely. Often when a patient has a conjugate gaze opposite to a hemiparesis from cerebral infarction, the infarct is large. The depressed sensorium suggests the possibility of pressure on the reticular activating system from increased intracranial pressure. Additional CT scans revealed a large middle cerebral artery infarction with mass effect (Fig. 15.12). Involvement of the FEFs resulted in loss of right voluntary gaze. The infarction was believed to be vasospastic in origin.

**Case 15.3**

A 59-year-old man with presumed multiple sclerosis presented for evaluation 26 years after his initial diagnosis. He required an automated wheelchair to get around and had labile affect, decreasing memory, and incontinence. Ocular motility testing revealed an absent up gaze, mildly reduced down gaze, and poor adduction of the eyes bilaterally. His pupils demonstrated light-near dissociation. At multiple patient history of diplopia, a pneumoencephalogram analysis revealed a sequelae lesion at What subsequent patient's
tion. At the time of his initial diagnosis of multiple sclerosis, at the age of 33 years, the patient had presented with a complaint of diplopia. His evaluation at that time included a pneumoencephalogram and spinal fluid analysis, both of which were unremarkable.

Are the patient's current symptoms likely sequelae of multiple sclerosis? What type of lesion and what location are most likely? What surgical treatment might improve the patient's condition?

**Discussion**

The patient's progressive history is unusual for multiple sclerosis. The vertical-gaze palsy and pupillary light-near dissociation suggest an abnormality of the midbrain. The symptoms of difficulty walking, dementia, and incontinence raise the possibility of hydrocephalus.

CT scans revealed a calcified lesion in the midbrain (Fig. 15.13), and severe obstructive hydrocephalus was evident above the
**Figure 15.11.**
Vertebral arteriograms from case 15.1. Lateral (A) and anterior-posterior (B) views reveal that the tip of the basilar artery is occluded and that the posterior cerebral arteries do not fill as they should.

**Figure 15.12.**
CT scans from case 15.2 demonstrate a large left middle cerebral artery infarction with mass effect. The frontal eye fields are involved.

MRT scans demonstrated old blood in the midbrain lesion consistent with a previous hemorrhage into an arteriovenous malformation (Fig. 15.14). Apparently, the arteriovenous malformation had enlarged, calcified, and blocked the cerebral aqueduct. The patient's mental status, sphincter control, and leg strength all improved after a ventriculoperitoneal shunt. The eye abnormalities persisted, however.
Figure 15.13.
CT scan from case 15.3 shows a calcified lesion in the midbrain causing obstructive hydrocephalus.

Figure 15.14.
MRI scans from case 15.3. A. Axial view reveals a heterogeneous lesion in the midbrain, which suggests a previous hemorrhage. B. Sagittal view shows total obliteration of the cerebral aqueduct and massive hydrocephalus.

SUGGESTED READINGS


Nystagmus and Related Ocular Oscillations

Lenore A. Breen

Nystagmus is one of the most difficult subjects in neuro-ophthalmology for three reasons: first, the most common type of nystagmus is nonspecific for anatomic location and cause; second, lesions at specific sites in the posterior fossa can lead to more than one type of nystagmus; and third, specific types of nystagmus can result from lesions at various sites and have multiple possible causes. This chapter concentrates on basic principles of nystagmus, the common nonspecific types of nystagmus, and the more anatomically specific types of nystagmus. Related ocular oscillations that do not satisfy the requirements for nystagmus are discussed also.

DEFINITION OF TERMS AND MECHANISMS

There are two general categories of nystagmus: pendular in which the to-and-fro movements are of equal velocity and jerk in which the movements are slow in one phase and fast in the alternate phase. Jerk nystagmus is defined by the fast movement. For example, if the fast component of the nystagmus is moving to the left, the patient has left-beating nystagmus. In actuality, the pathologic movement generated by the brain is usually the slow phase; the fast phase is a corrective refixation saccade.

Nystagmus is further defined by the axis of movement as horizontal, vertical, torsional, circular, or combinations of more than one directional movement. Torsional nystagmus, also called rotary nystagmus, is a rhythmic rotation of the eyes in which the 12 o’clock meridian of the limbus rotates, causing either intortion or extortion. The nystagmus is described as being either clockwise or counterclockwise. Circular nystagmus is movement in which the 12 o’clock meridian remains stationary. The eye moves in both vertical and horizontal axes subtending a circular path. If the movement in one axis is larger, the eye displays elliptical nystagmus. Diagonal (also called oblique) nystagmus is also a subcategory of circular nystagmus.

Nystagmus occurs from a breakdown of fixation mechanisms or, less commonly, gaze mechanisms. During primary gaze, the major factors maintaining fixation are visual input, cerebellar input, balanced vestibular tone, and functioning pause cells in the mesen-
Cephalic and pontine gaze centers. Disruption of any of these systems can cause nystagmus when the eyes are looking straight ahead. Examples of nystagmus resulting from dysfunction of these systems include (a) congenital nystagmus from visual deprivation, (b) horizontal-rotary nystagmus from acute labyrinthitis, and (c) ocular flutter and opsoclonus from poorly functioning pause cells and cerebellar input.

Fixation in eccentric gaze requires an additional system, called the neural integrator, to hold the eyes against elastic forces of the orbit. The neural integrator is thought to reside in the nucleus prepositus hypoglossi or possibly the vestibular nuclei and cerebellum. Dysfunction of the neural integrator is felt to cause gaze-evoked nystagmus, which is discussed in more detail below.

Nystagmus resulting from malfunctions in the saccade and pursuit gaze systems is much less common than that due to fixation malfunction. One example is gaze-paretic nystagmus, which is a transitional finding during recovery from gaze palsy. When the patient looks in the previously affected field of gaze, jerk nystagmus occurs in the direction of gaze. Another example is internuclear ophthalmoplegia (INO), in which abducting nystagmus is seen.

Physiologic nystagmus is seen when the patient looks in extreme lateral gaze. Usually the movement occurs when the eye moves beyond 30°. The jerk component has a small amplitude, is horizontal, and fatigues quickly. If the patient brings the eyes back a few degrees, the nystagmus will stop. If the nystagmus occurs in both lateral gazes, it is of equal amplitude and speed. It is important to differentiate this normal form of gaze-evoked nystagmus from pathologic gaze-evoked nystagmus.

**METHODS FOR INDUCING NYSTAGMUS**

Clinical maneuvers can be used to induce nystagmus for diagnostic purposes. Optokinetic nystagmus, caloric nystagmus, and positional nystagmus fit into this category. The physician needs to know the physiology and anatomy involved in producing the nystagmus and the way to perform the tests.

**CLINICAL EVALUATION**

Nystagmus may be asymptomatic or cause oscillopsia and visual blur. Sophisticated electrophysiologic eye-movement recordings have helped separate the different types of nystagmus, which total at least 45 in all. Without the aid of recordings, the physician can observe only the general characteristics of the nystagmus pattern. Careful observation and documentation of the eye movements not only help categorize the movement but facilitate future examinations. In describing the nystagmus, the physician should note the movement's speed (slow to fast), amplitude (fine to coarse), and direction in each of the nine gaze positions. Maneuvers that accentuate the nystagmus should be documented also. An example is use of down-going optokinetic targets to bring out convergence-retraction nystagmus. Some gaze positions or maneuvers can bring out symptoms of vertigo or oscillopsia, and this should be recorded in the chart also. Sometimes, the nystagmus is seen better by using the slit lamp or ophthalmoscope.

Only a few types of nystagmus are specific enough in pattern to be diagnostic. Usually, the physician has to rely on a combination of the history and physical findings to interpret the diagnostic importance of nystagmus. If an eye-movement recording laboratory is available, more accurate categorization of the abnormal eye movement can be helpful in the patient's evaluation.

**Caloric Stimulation**

The semicircular canals in the inner ear can be inhibited or stimulated by cold or warm water, respectively. When this occurs, the vestibular tone is no longer balanced,
and the vestibular nuclei receiving the most excitation drive the eyes to the opposite side (Fig. 16.1). If the person is awake, a corrective refixation saccade will occur, which is seen by the physician as the fast phase of the nystagmus. Therefore, placement of cold water in the right ear leads to inhibition of the semicircular canals on the right. The unopposed messages from the left vestibular complex will move the eyes slowly to the right, and the fast phase of the nystagmus will be to the left. The mnemonic "COWS," cold—opposite and warm—same, describes the fast phase of the nystagmus. In this example, the nystagmus (fast phase) is to the left when the cold water is placed in the right ear. In a comatose patient, the fast phase does not occur because the patient is not alert enough to initiate a refixation saccade. When cold water is placed in the right ear, the eyes will slowly move toward the right ear, this is the normal response in a comatose patient. If no movement occurs, a lesion of the vestibular system, eighth nerve, infranuclear connections, or abducens nucleus is suspected. If the ipsilateral eye abducts normally but the contralateral eye fails to adduct, a lesion of the medial longitudinal fasciculus (MLF) or oculomotor nucleus is possible.

To perform horizontal caloric tests, the horizontal semicircular canal must be placed parallel to the floor. This is done by raising the patient's head 30° or lowering the head 60°. In addition, the physician should make sure the external canal is unobstructed and the tympanic membrane is not torn. If the tympanic membrane is not intact, the test should not be performed on that side. To inject the water, sharp-tipped objects that could injure the tympanic membrane (e.g., cutoff IV tubing) should not be inserted into the canal. I use a catheter-tipped 50-cc syringe, which just barely fits into the opening of the canal. Vertical caloric tests are done by introducing water into both ears simultaneously. The fast phase of the vertical caloric stimulations occur when the eyes move in the direction of gravity.

**Positional Stimulation**

Some patients with vertigo only suffer symptoms when they turn their head into a certain position. This condition, which can result from central vestibular or peripheral (labyrinthine) dysfunction, is termed benign positional vertigo. The inciting head position may be a head or body turn to the right or left, or extension of the head.

Using a technique called Dix-Hallpike maneuvers, the physician can determine whether the positional nystagmus results from a central or peripheral dysfunction (Table 16.1). The patient sits lengthwise on an examination table so the head will hang off the table when he or she is lowered. The physician quickly lowers the patient into two different positions: first, with the head turned to the right and then, with the head turned to the left. The physician supports the head and neck with one hand, allowing the head to extend 30 to 45° and watches the eyes closely for the onset and pattern of the nystagmus. The physician must observe whether the nystagmus begins immediately after repositioning or has a delay.

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**Figure 16.1.**

Diagram showing eye movements in vestibular nystagmus, which can be induced by caloric stimulation or be caused by central or peripheral vestibular disease. SOC, semicircular canal.
Table 16.1. CHARACTERISTICS DIFFERENTIATING CENTRAL AND PERIPHERAL POSITIONAL NYSTAGMUS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Central Dysfunction</th>
<th>Peripheral Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency of nystagmus</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Vertigo:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Fatigability</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Habituation</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

delay in onset, called latency. Central positional nystagmus does not have a latency, whereas the peripheral form does. The direction of the fast phase should be noted. Also, the patient is asked to tell the physician if the vertigo appears, in which direction the environment is moving, if he or she is nauseated, and when the vertigo stops. The patient is brought back up to sitting if no vertigo occurs within 1 minute. If vertigo is brought on by the maneuver, the patient must be brought back up and then lowered into the inducing position repeatedly to see if the vertigo habituates to the stimulus and disappears. Peripheral positional vertigo habituates with repeated tests, whereas central positional vertigo persists.

Patients with benign positional vertigo can benefit from specific physical therapy. The patient sits on the side of a bed or couch and then lies down on his or her side. If vertigo occurs, the patient stays in this position until it abates. The patient then sits up for 30 seconds, and then repeats the process to the other side. If possible, the therapy should be done every 3 hours while awake and continue until the patient experiences at least 2 symptom-free days.

Optokinetic Stimulation

Optokinetic nystagmus (OKN) is a reflex movement of the eyes when multiple targets are moved quickly past the eyes. The initial movement is a following movement of the first target seen. When the eyes reach the limits of eccentric gaze, a reflex saccade moves the eyes back to look at the next target. Therefore, the fast phase is away from the direction of target movement. Patients watching an optokinetic drum rotating to their right should have left-beating nystagmus.

The optokinetic drum uses targets that can be seen if the vision is 20/200 or better. If the patient shows the appropriate response, then vision is present. The primary usefulness of OKN testing is the ability to test vision in patients whose subjective responses are unreliable. Infants, patients with Anton syndrome (cortical blindness with denial of visual loss), and patients with either a conversion reaction or malingering are good examples. If a patient claims unilateral vision loss, OKN can be examined in a monocular fashion. The patient can voluntarily suppress the response by not looking at the targets. In this situation, the physician must use a stimulus that the patient cannot look beyond.

Optokinetic testing is also useful for evaluating gaze palsy. Patients with dorsal midbrain syndrome (Parinaud syndrome) characteristically have convergence-retraction nystagmus. An effective way of eliciting this sign is down-going OKN targets that stress the up-gaze system during the refixation saccades. Instead of seeing upbeating nystagmus, convergence-retraction nystagmus is elicited. A subtle INO may only be found with horizontal OKN targets, bringing out the adduction lag.

Prior to development of neuroimaging scanners, patients with homonymous field loss underwent OKN testing to differentiate tumors from posterior cerebral artery infarcts. The pursuit gaze area, located in the
ANATOMICALLY NONSPECIFIC NYSTAGMUS

Gaze-Evoked Nystagmus

Gaze-evoked nystagmus is the most common pathologic type of nystagmus. Nystagmus is not present in primary gaze, but when a person looks in the affected direction, jerk nystagmus occurs. Gaze-evoked nystagmus is nonspecific for both anatomic location and cause. Usually, it appears in diseases that affect the posterior fossa.

A "leaky" neural integrator is theorized to be the underlying pathophysiology causing gaze-evoked nystagmus (Fig. 16.2). When the neural integrator is unable to hold the eyes in eccentric gaze, they drift back slowly toward midline. The displacement of the target image off the fovea causes a saccadic corrective movement to regain fixation. The fast eye movement moves the eyes back toward the target in the direction of gaze. Repetition of this cycle leads to jerk nystagmus.

Drugs are one of the most common causes of gaze-evoked nystagmus. Sedatives, tranquilizers, ethanol, and "recreational drugs" can all cause nystagmus. Physicians even look for nystagmus in patients on anticonvulsants to measure compliance. Drug-induced nystagmus can be seen on lateral gaze and up gaze but rarely in down gaze. The fast component is in the direction of gaze. If no evidence of drug ingestion is present, then other causes must be considered, based on the history and examination. If a person has a unilateral cerebellar lesion, nystagmus is often seen when the person looks toward the lesion. A characteristic type of nystagmus seen with cerebellopontine angle tumors is called Bruns' nystagmus. This nystagmus is a combination of slow, large-amplitude nystagmus when looking toward the side of the lesion and fast, small-amplitude nystagmus when looking to the opposite side. The ipsilateral nystagmus is secondary to poor function of the neural integrator, as discussed above, and the contralateral nystagmus is secondary to vestibular nystagmus, which is discussed in the next section.

Gaze-evoked nystagmus can be seen with cranial nerve palsies, myasthenia gravis, and restrictive muscle disease in the orbit. In the first two disorders, a partially weak muscle is unable to hold the eyes in eccentric gaze, thus allowing the fovea to slip off the target; subsequent fast corrective saccades produce the nystagmus. In myasthenia gravis, the nystagmus can be corrected with Tensilon. The most common restrictive orbital muscle disease is thyroid ophthalmopathy. In this condition, the inability to maintain eccentric fixation is due to the pull of the restrictive muscle displacement.

Vestibular Nystagmus

Dizziness causes patients to examine the environment for clues. A recent diagnosis is that vertigo is present in primates, and the laterals are not. In the lateral category, Alex: jerk nystagmus move horizontally (Alex categories of degree nystagmus). Eyes move to compensate. Sudden nystagmus movement increases the fast component of nystagmus will move the eyes toward vestibular linkage.

Certain peripheral fibers from these include...
muscle displacing the eye and leading to nystagmus.

**Vestibular Nystagmus**

Dizziness is a common symptom that causes patients to seek medical care. When examining the dizzy patient, the physician often searches for nystagmus to help in the diagnosis. Vestibular nystagmus can be present in primary gaze and increase in eccentric gaze or can occur only with eccentric gaze. In the latter case, the nystagmus falls into the category of gaze-evoked nystagmus. In 1912, Alexander described the principle that jerk nystagmus increases when the eyes move into the direction of the fast component (Alexander's law). He described three degrees of nystagmus in his paper. First-degree nystagmus is present only when the eyes move into the direction of the fast component. Second-degree nystagmus has jerk nystagmus in primary gaze, but the movement increases with gaze in the direction of the fast component. Third-degree nystagmus has nystagmus in all gazes but maximal nystagmus with movement into the direction of the fast phase. Subsequent studies have linked this phenomenon most closely with vestibular dysfunction.

Certain findings can help differentiate peripheral from central vestibular disorders; these include (a) the presence or absence of tinnitus or deafness, (b) the severity of vertigo, (c) duration of symptoms, (d) the type of nystagmus, and (e) whether fixation suppresses the nystagmus (Table 16.2).

In peripheral vestibular nystagmus, the patient usually has severe vertigo with nausea and vomiting and may have symptoms or signs of auditory involvement. The vertiginous episode is usually limited in time, and the nystagmus is most often a combination of horizontal and rotary nystagmus. If it is present in primary gaze, gaze in the direction of the horizontal jerk component characteristically accentuates the nystagmus, thus obeying Alexander's law. When a labyrinth is dysfunctional, the other labyrinth drives the eyes slowly to the opposite side, or "toward the lesion," by stimulating the contralateral abducens nucleus and ipsilateral oculomotor nucleus via the medial longitudinal fasciculus (Fig. 16.1). The fast phase of the nystagmus is opposite the side of the lesion. Therefore, if the left inner ear has acute labyrinthitis producing horizontal nystagmus, one would expect right-beating nystagmus. The direction of the rotary component is not predictable on the basis of the laterality of the lesion.

The fast component of central vestibular nystagmus can move in any direction. If the nystagmus is pure rotary or pure vertical, it is central in origin, not peripheral. Symptoms of vertigo can become chronic with central lesions, and fixation does not inhibit the nystagmus. The vertigo is milder than in

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**Table 16.2. CHARACTERISTICS DIFFERENTIATING CENTRAL AND PERIPHERAL VESTIBULAR NYSTAGMUS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Central Dysfunction</th>
<th>Peripheral Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of vertigo</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Inhibition of nystagmus with fixation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>Chronic</td>
<td>Acute</td>
</tr>
<tr>
<td>Auditory symptoms</td>
<td>No</td>
<td>Can be present</td>
</tr>
<tr>
<td>Nystagmus direction</td>
<td>Fast phase away from lesion</td>
<td>Uni- or bidirectional</td>
</tr>
<tr>
<td>Direction of Romberg fall</td>
<td>Varies</td>
<td>Ipsilateral to slow phase</td>
</tr>
<tr>
<td>Direction of post-pointing</td>
<td>Varies</td>
<td>Ipsilateral to fast phase</td>
</tr>
<tr>
<td>Direction of environmental spin</td>
<td>Varies</td>
<td></td>
</tr>
</tbody>
</table>
Peripheral disorders, and auditory symptoms are rare. When the laterality of environmental movement, spinning sensation, post-pointing, and Romberg fall do not fit the pattern of a peripheral lesion, then a central disorder should be suspected.

A more detailed discussion of vestibular disorders is presented in Chapter 7, Neuro-Otology.

**Congenital Nystagmus**

Congenital nystagmus has unique characteristics that identify it clinically. This nystagmus begins at birth or during infancy. Most patients exhibit horizontal pendular nystagmus in primary gaze and jerk nystagmus on lateral gaze, although some patients have horizontal jerk or, rarely, rotary or vertical components in primary gaze. The continuation of horizontal nystagmus even in vertical gaze differentiates congenital nystagmus from gaze-evoked nystagmus, if the latter is present in vertical gaze, it beats in the direction of gaze. Congenital nystagmus decreases with convergence, and increases with fixation or anxiety. Because most patients have a gaze position, called the null region, in which the nystagmus dampens, they may adopt a head turn to place the eyes in this area to improve visual acuity by prolonging foveation time. If the head turn is significant, prisms or muscle surgery can help alleviate it. Inversion of the optokinetic response can be seen in 67% of patients with congenital nystagmus. In these patients, the fast phase of the OKN beats toward the side of the target movement. There is disagreement over the mechanism of this sign.

Two types of congenital nystagmus have been described: motor and sensory. Sensory congenital nystagmus is diagnosed when an underlying visual impairment is found on examination, whereas the motor type occurs in the absence of visual pathology. Previously, the literature stated that motor nystagmus was more common. However, recent evidence has shown that most patients with congenital nystagmus have a visual sensory disorder as the underlying cause. The patient evaluation should include a search for ocular albinism, optic nerve and retinal abnormalities, and electrophysiologic testing including VER and ERG.

The importance of recognizing congenital nystagmus cannot be overemphasized. Adults may present after trauma seeking compensation for abnormal eye movements that they believe are the result of an accident. If the physician documents the characteristic findings of congenital nystagmus, the issue is settled. Recently, I evaluated a child referred with the diagnosis of ocular flutter and possible occult neuroblastoma. Congenital nystagmus was found instead, and multiple expensive tests were avoided.

**Latent Nystagmus**

Latent nystagmus appears when one eye is covered, breaking binocular fixation, usually during visual acuity testing. The slow phase is toward the covered eye and the fast phase toward the uncovered eye. The direction changes depending on which eye is excluded. Obscuring the vision in one eye with high plus lenses or a neutral-density filter can bring out latent nystagmus also. The latent nystagmus reduces visual acuity due to the short foveation time. Visual testing with binocular fixation using devices such as polarized acuity charts and lenses will ablate the nystagmus and allow accurate testing. Another binocular testing technique uses a small dot of tape on one lens covering fixation, while testing the acuity in the other eye. Input from the peripheral field suppresses the nystagmus. Latent nystagmus is a benign condition and does not denote underlying neurologic disease.

Manifest latent nystagmus has been described in patients with horizontal strabismus and alternating fixation. The nystagmus will be toward the fixing eye. If one eye becomes blind, comes permanently.

**Nystagmus Deprivation**

Pendular or torsional nystagmus can develop bilaterally with the differentia
cus and acquis
tion of visual skills. When the onset of oscillation is sudden, removal of the stimulus for saccades will lead to a slow drift toward the side of the absent eye.

**Mononuclear and Similar Diseases**

**SPASMUS N**

Spasmus n of nystagmus. This is a child with a history of transient anoxic encephalopathy. The child will walk, sit, and play normally. However, an episode of severe hypoxia may lead to a temporary arrest of visual acuity and inability to track objects. The nystagmus will be low amplitude but may be seen with a head tilt.

Until the patient is able to walk, sit, and play normally, the patient may present with a head tilt and a slow drift toward the side of the absent eye. The nystagmus will be low amplitude and may be seen with a head tilt. Treatment is supportive, and the patient will recover fully.
comes blind, the latent nystagmus can become permanent and cause reduced vision.

**Nystagmus from Visual Deprivation**

Pendular or jerk primary-position nystagmus can develop in children who have acquired bilateral visual loss. In some patients, the differential between congenital nystagmus and acquired nystagmus cannot be determined without an accurate history regarding the onset of visual loss.

**Mononuclear Nystagmus and Similar Conditions**

**SPASMUS NUTANS**

Spasmus nutans is a unique combination of nystagmus, head nodding, and torticollis. This is a childhood disorder that begins between the ages of 4 and 14 months. It usually resolves in a few months (average 12 to 24) up to age 5 years. The nystagmus is often asymmetric, being monocular or, if binocular, showing varying direction and amplitude between the two eyes. Characteristically, the movement is very fine and fast, with the direction being either vertical or horizontal. The head and neck movement does not appear to compensate for the eye movements.

Until the past decade, physicians were taught that spasmus nutans was a benign, self-limited condition that did not require neurologic evaluation or scanning. However, multiple reports of parasellar and hypothalamic tumors in these patients have led to a change in this recommendation. Any child presenting with spasmus nutans should have a head scan, preferably a magnetic resonance imaging (MRI) scan. A history of growth retardation, delayed milestones, and poor appetite is additional evidence of a possible hypothalamic tumor. If the scan is normal, the patient should be followed with the expectation that the condition will remit without further treatment.

**DISSOCIATED NYSTAGMUS WITH INTRACRANIAL OPHTHALMOPLEGIA**

The most common type of dissociated nystagmus is associated with internuclear ophthalmoplegia. Strictly speaking, this is not true nystagmus but rather a gaze paresis. The lesion is in the medial longitudinal fasciculus and causes poor adduction of the ipsilateral eye on horizontal gaze. The abducting eye often has horizontal jerk nystagmus in the direction of gaze. Internuclear ophthalmoplegia is described in more detail in Chapter 15, Gaze Abnormalities.

**SUPERIOR OBlique MYOKYMIA**

Superior oblique myokymia (SOM) is a monocular rhythmic oscillation in which the superior oblique muscle intermittently contracts causing the eye to adduct and intort. The patient complains of blurred vision or environmental movement, especially when trying to read. Moving the eye into the field of action of the superior oblique can often bring out the myokymia. The physician can best observe the fine, torsional movements by using a slit lamp. Until recently, no reports of a compressive lesion causing SOM existed. In 1989, Morrow, Ranalli, and Sharpe reported a patient with SOM who had an astrocytoma in the region of the trochlear nerves. The underlying pathophysiology of SOM is debated. Treatment with carbamazepine (Tegretol) can be beneficial. If the condition persists despite medical therapy, surgical weakening of the superior oblique is recommended.

**VISUAL DEPRIVATION**

If one eye becomes blind, the eye can develop monocular nystagmus. Most often the nystagmus is vertical and may be confused with spasmus nutans in children. Documentation of the visual acuity helps classify the nystagmus correctly.
ANATOMICALLY SPECIFIC NYSTAGMUS AND RHYTHMIC OSCILLATIONS

The following discussion covers those types of nystagmus and rhythmic oscillations that, combined with other neurologic findings, are diagnostic of relatively specific anatomic lesions. The discussion is divided according to the predominant direction of movement for easy reference. Table 16.3 summarizing this material lists the name of the movement, whether it is spontaneous or primary gaze, important associated history and physical findings, maneuvers that bring out the movement, and the common anatomic location. Rhythmic oscillations that are not classified as nystagmus have the letter

<table>
<thead>
<tr>
<th>Name</th>
<th>Spontaneous</th>
<th>Associated Findings/History</th>
<th>Inducer</th>
<th>Anatomic Location of Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HORIZONTAL MOVEMENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convergence-excitation</td>
<td>+/-</td>
<td>Poor up gaze; light-near dissociation; lid retraction</td>
<td>Down OKN; attempted up gaze</td>
<td>Dorsal midbrain</td>
</tr>
<tr>
<td>nystagmus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebound nystagmus</td>
<td>-</td>
<td>Ataxia; ethanol abuse (type 1)</td>
<td>Type 1: Move eyes to eccentric gaze. Type 2: Move eyes to primary gaze</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Periodic alternating</td>
<td>+</td>
<td></td>
<td>None</td>
<td>Vestibular nuclei; convicomedullary junction; ocular media opacities</td>
</tr>
<tr>
<td>nystagmus (PAN)</td>
<td></td>
<td></td>
<td></td>
<td>Cerebellum; posterior columns</td>
</tr>
<tr>
<td>Macro square-wave</td>
<td>+</td>
<td>Ataxia</td>
<td>Fixation</td>
<td>Fixation</td>
</tr>
<tr>
<td>jolts (RO)</td>
<td></td>
<td></td>
<td></td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Ocular dysmetria (RO)</td>
<td>-</td>
<td>Ataxia</td>
<td>Move eyes to primary gaze</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Ocular flutter (RO)</td>
<td>+</td>
<td>Ataxia; paraneoplastic syndrome</td>
<td>Fixation</td>
<td>Fixation</td>
</tr>
<tr>
<td>VERTICAL MOVEMENTS</td>
<td></td>
<td></td>
<td></td>
<td>Cerebellum; posterior columns</td>
</tr>
<tr>
<td>See-saw nystagmus (acquired)</td>
<td>+</td>
<td>(a) Bitemporal field loss; growth failure; slow development</td>
<td>None</td>
<td>(a) Paramedian tegmentum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Trauma vertebrobasilar insufficiency</td>
<td></td>
<td>(b) Brainstem</td>
</tr>
<tr>
<td>Upbeat nystagmus</td>
<td>+</td>
<td>Ataxia</td>
<td>(a) Increases with up gaze</td>
<td>(a) Vermis</td>
</tr>
<tr>
<td>(a) Large amplitude</td>
<td></td>
<td></td>
<td>(b) Decreases with down gaze</td>
<td>(b) Medulla oblongata</td>
</tr>
<tr>
<td>(b) Small amplitude</td>
<td></td>
<td></td>
<td>Increases with down gaze</td>
<td>Cervicomedullary junction</td>
</tr>
<tr>
<td>Downbeat nystagmus</td>
<td>+</td>
<td></td>
<td>None</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Ocular holding (RO)</td>
<td>+</td>
<td>Loss of horizontal eye movements</td>
<td>None</td>
<td>Myoclonic triangle</td>
</tr>
<tr>
<td>Ocular myoclonus (RO)</td>
<td>+</td>
<td>Palatal myoclonus</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>RANDOM MOVEMENTS</td>
<td>+</td>
<td>Ataxia; occult neuroblastoma; post-infection; paraneoplastic effects of visceral carcinomas</td>
<td>None</td>
<td>Cerebellum</td>
</tr>
</tbody>
</table>

*Indicates whether movement occurs (+) or does not occur (-) spontaneously in primary gaze.

Other maneuvers that bring out the eye movement.
Horizontal Movements

CONVERGENCE-RETRACTION NYSTAGMUS

Convergence-retraction nystagmus is part of the dorsal midbrain syndrome. The eyes display a fast phase consisting of convergence of the eyes and apparent retraction of the globes. The nystagmus may occur spontaneously or be brought out by attempted up gaze or down-going optokinetic testing. Other associated findings are pupillary light-near dissociation, poor or absent up gaze, and lid retraction. The lesion occurs in the dorsal midbrain, in particular in the posterior commissure. A more thorough discussion of this disorder is in Chapter 15, Gaze Abnormalities.

PERIODIC ALTERNATING NYSTAGMUS

Periodic alternating nystagmus (PAN) is a unique nystagmus that occurs spontaneously in primary gaze. Unless the physician is meticulous in watching the eyes for an extended period, he or she may miss the recurrent cycle the eyes are going through. Horizontal jerk nystagmus begins first in one direction and continues for an average of 90 seconds. The amplitude of the nystagmus gradually increases and then decreases during this time. The eyes then remain still for approximately 10 seconds before switching to similar nystagmus in the opposite direction. This condition can be congenital or acquired and persists during sleep.

PAN can be secondary to an abnormality of the cervicomedullary junction. An MRI scan should be done to rule out a compressive lesion at the foramen magnum, such as an Arnold-Chiari type 1 malformation. Lesions in the vestibular nuclei are also believed to cause PAN. Other causes include stroke, tumors, multiple sclerosis, trauma, infections, drug intoxications, and degenerative diseases. PAN has been described in patients with severe opacification of the ocular media bilaterally. In these cases, PAN has disappeared after surgery for vitreous hemorrhage and also for cataract. Patients who do not have a surgically treatable lesion have responded to therapy with baclofen (Lioresal).

REBOUND NYSTAGMUS

Both types of rebound nystagmus that have been described are elicited by eye movement. Type 1 is seen when the patient looks eccentrically, causing gaze-evoked nystagmus; an eccentric gaze is sustained, the gaze-evoked nystagmus diminishes in amplitude and then "rebounds," reversing its direction. Type 2 is seen when the patient refixates to primary gaze, eliciting transient nystagmus in the direction opposite to the eye movement. Both types of rebound nystagmus are associated with ataxia and cerebellar disease. Type 1 is commonly associated with ethanol abuse.

MACRO SQUARE-WAVE JERKS (RO)

Macro square-wave jerks (MSWJs) are clinically visible back-to-back saccades that interrupt fixation. An MSWJ consists of a single saccade away from fixation followed by a brief pause and then a saccade back. The patient often has cerebellar disease.

OCULAR DYSMETRIA (RO)

Ocular dysmetria can be conceptualized as the ocular equivalent of a cerebellar intention tremor. Just as the extremities can past-point missing the target, so can the eyes. When this happens, corrective saccadic movements occur to place the eyes in the proper position. Therefore, this abnormal movement will be seen only when the eyes move eccentrically or back to primary gaze. Ocular dysmetria is easier to see when the eyes move back to primary gaze. The patient may have evidence of cerebellar disease on neurologic examination. Some authors feel that ocular dysmetria, ocular flutter, and opsoclonus represent a continuum of cerebellar dysfunction affecting the eyes.
OCULAR FLUTTER (RO)

Ocular flutter is a spontaneous oscillation of the eyes that is brief and intermittent. The eyes move quickly to the left and right for a few seconds, breaking the patient's fixation. The current theory is that dysfunction of the pause cells in the horizontal-gaze center causes ocular flutter. Other reports refute this theory on the basis of different computer model and lesion studies. The latter reports favor abnormal cerebellar input. Ataxia and paraneoplastic syndromes have been associated with ocular flutter.

VOLUNTARY NYSTAGMUS

Voluntary nystagmus is fast, small-amplitude horizontal nystagmus that cannot be sustained for more than 25 seconds. Often the nystagmus will be associated with lid fluttering or be terminated by closure of the lids. Most patients with this skill have a family history of voluntary nystagmus. Vertical voluntary nystagmus has been described in patients with underlying vertical deviations. A patient forced to keep the eyes open cannot continue producing the nystagmus. It is important to recognize this entity in cases of malingering for monetary gain.

Vertical Movements

SEE-SAW NYSTAGMUS

See-saw nystagmus is a unique spontaneous dissociated nystagmus in which one eye moves up as the other eye moves down. In the acquired variety, intortion occurs in the up-going eye and extorsion in the down-going eye. A congenital form displays reversals of the torsional movements.

Parasellar tumors can cause acquired see-saw nystagmus. Visual field examination should be performed looking for bitemporal field loss. Children with acquired see-saw nystagmus and parasellar tumors may have growth failure and developmental retardation. Other causes of see-saw nystagmus include trauma, especially injury to the mesencephalon, and vertebrobasilar insufficiency.

UPBEAT NYSTAGMUS

Upbeat nystagmus that is seen in primary gaze is always pathologic. Anatomic localization of the lesion is based on the amplitude of the nystagmus and changes with up gaze and down gaze. Large-amplitude upbeat nystagmus that increases in up gaze has been associated with vermal lesions and ataxia. Small-amplitude upbeat nystagmus that decreases in down gaze has been seen with medullary lesions. Upbeat nystagmus that is evident only in eccentric gaze is gaze-evoked nystagmus and is nonspecific.

DOWNBEAT NYSTAGMUS

Downbeat nystagmus in primary gaze characteristically increases in down gaze. The maximal increase in nystagmus usually is seen in down and left or down and right gaze rather than straight down. Classically, this type of nystagmus is associated with abnormalities of the cervicomedullary junction, such as Arnold-Chiari malformation. In some patients with cervicomedullary lesions, downbeat nystagmus and periodic alternating nystagmus have been seen simultaneously. An MRI scan should be done to look for a surgically correctable lesion in this area. The most common cause of downbeat nystagmus is spinocerebellar degenerations. Downbeat nystagmus also has been seen in other disorders including drug intoxication, vitamin B12 deficiency, magnesium deficiency, encephalitis, paraneoplastic syndromes, posterior fossa tumor, and multiple sclerosis. Several reports have been published of patients developing downbeat nystagmus while taking lithium carbonate. The downbeat nystagmus from lithium was permanent or temporary even after discontinuing the drug; valproic acid helped those patients whose nystagmus continued.

OCULAR MYOCLONUS (RO)

Ocular myoclonus is a spontaneous vertical pendular oscillation that is continuous even during sleep. The frequency varies between 1.5 and 5 Hz. It can be associated with rhythmic movements of the palate at the same frequency. The lesion may involve the medial geniculate body, thalamus, internalcapsule, brainstem, and/or cerebellum. A variety of conditions has been associated with ocular myoclonus, including damage to the internal capsule, thalamus, or cerebellum. The movements are often bilateral and conjugate, involving both eyes. The mechanism of ocular myoclonus is thought to be related to the generation of electrical discharges in the brainstem, which are transmitted to the oculomotor nuclei. The movements are often associated with other neurological symptoms, such as ataxia and dysarthria. The treatment of ocular myoclonus is symptomatic, and may include medications such as clonazepam, propranolol, or baclofen. Surgery may be considered in refractory cases.
same frequency (oculopalatal myoclonus). The lesion is located in the "myoclonic triangle," which consists of the red nucleus, inferior olive, and contralateral cerebellar dentate nucleus; the connecting pathways are, respectively, the central tegmental tract, inferior cerebellar peduncle, and superior cerebellar peduncle. Some authors classify ocular myoclonus as a true nystagmus. GABA agonists, such as valproic acid, have inhibited the movement in some cases.

**OCULAR BOBBING (RO)**

Ocular bobbing is a unique eye movement in which the eyes move quickly down from primary position and then slowly glide back up. Characteristically, the patient is comatose and has loss of all horizontal eye movements. A lesion of the pons is most often found.

Reverse ocular bobbing consists of a fast movement up with the slow phase down. It has been described in coma secondary to metabolic encephalopathy and pontine lesions. Inverse bobbing, also called ocular dipping, is a slow movement of the eyes down followed by a fast movement up. Dipping has been seen in coma and in an alert patient with a pinealoblastoma.

**Random Movements**

**OPSOCLONUS (RO)**

Opsoclonus is a striking clinical sign in which the eyes constantly or intermittently move in random directions. The chaotic movements are fast, thus classifying them as saccades. The patient usually has full extraocular movement and optokinetic responses. A total loss of pause-cell inhibition is thought to cause opsoclonus, although as discussed above, there is disagreement regarding the pathophysiology. Ocular flutter and opsoclonus are felt to represent a continuum of pause-cell dysfunction, and indeed some patients with opsoclonus have evolved to ocular flutter with clinical improvement.

Opsoclonus can be the presenting sign of occult neuroblastoma in children. It is often associated with ataxia and improves with adrenocorticotropic hormone (ACTH) and removal of the tumor. An idiopathic syndrome of limb myoclonus and opsoclonus in children is also treated with ACTH. Normal neonates have been reported with transient opsoclonus that resolved spontaneously. In all ages, opsoclonus most commonly occurs after viral encephalitis. Paraneoplastic effects of visceral carcinomas can cause opsoclonus in adults. Other causes include multiple sclerosis, head trauma, and poor vision.

**MISCELLANEOUS NYSTAGMUS**

**Acquired Pendular Nystagmus**

Pendular nystagmus can begin in adults and is often asymmetric in direction and amplitude. The pendular component can occur in any direction. Multiple sclerosis is the most common cause. Often the patients have tremors of the extremities, face, or palate. Other ocular findings include skew deviation and internuclear ophthalmoplegia. Acquired pendular nystagmus is usually permanent, causing significant visual impairment. Traccis et al. reported successful treatment of this condition with isoniazid and base-out prisms.

**Convergence-Evoked Nystagmus**

A rare type of nystagmus occurs when the patient attempts to converge the eyes. The induced nystagmus may be fast in either a vertical or horizontal plane. The disorder denotes posterior fossa disease and most commonly occurs with multiple sclerosis or infarcts.
EYE MOVEMENTS IN COMA

Comatose patients may display rhythmic movements of the eyes on examination. Entities such as ocular bobbing, reverse bobbing, and dipping are most commonly seen in such patients. Patients may have horizontal “roving” eye movements that are better classified under the terms periodic alternating gaze and periodic alternating ping-pong gaze. The eyes move first to the left and then right in a continuous fashion. The difference between the two entities is the period of time the eyes remain in eccentric gaze before reversing direction. In periodic alternating gaze, the eyes remain in eccentric gaze for approximately 2 minutes; in ping-pong gaze, the eyes remain still only briefly. The anatomic site of the causative lesion is unknown.

MEDICAL TREATMENT OF NYSTAGMUS

Medical treatment of nystagmus is a relatively new venture in neuro-ophthalmology. Theoretically, the goal is inhibition of the abnormal movement by manipulating neurotransmitters or their agonists. The primary inhibitory neurotransmitters in the ocular motor pathways are GABA and glycine. GABA agonists that have been used with some success include clonazepam, baclofen, valproic acid, and isoniazid. Anticholinergic agents also have been tried but do not appear to be as effective. A potentially useful tool in the future may be retro-orbital injections of botulinum toxin. The major drawback of this treatment is the need for repeated injections every 4 to 20 weeks.

CASE STUDIES

Case 16.1

A 69-year-old man presented with a 2-month history of diplopia and occipital headache. He was seen by an ophthalmologist who diagnosed a left fourth-nerve palsy. A CT scan at the time was read as normal. Shortly thereafter, the patient developed difficulty walking, falling to the left, nausea, and vomiting. Significant past medical history included surgery for adenocarcinoma of the lung 1 year prior to his presentation with diplopia.

Examination in the emergency room revealed a thin man who had vertical diplopia by red glass test. Further testing revealed right hypertropia believed to be most compatible with skew deviation. The patient had coarse nystagmus on gaze to the left. Early papilledema was seen bilaterally. He displayed poor accuracy on finger-nose-finger testing using the left arm. On tandem walking, he fell to the left repeatedly. His strength, sensation, and Babinski reflexes were normal.

Which of the findings in this case can be associated with lesions in a specific anatomic location? What additional workup would be helpful in reaching a diagnosis?

Discussion

The patient’s history of progressive neurologic dysfunction over 2 months and past history of adenocarcinoma of the lung strongly suggest a metastatic tumor to the brain. Surprisingly, the initial CT scan was reported as normal. Based on the findings of skew deviation, left-sided ataxia, and left-beating gaze-evoked nystagmus, one would suspect some lesion in the posterior fossa. A left cerebellar lesion would be a strong possibility, as gaze-evoked nystagmus from a cerebellar lesion is characteristically ipsilateral to the lesion. The papilledema is most likely the result of a mass lesion.

A repeat CT scan was done immediately. A large cystic mass was seen in the left cerebellar hemisphere, with associated left-to-right shift of the brainstem (Fig. 16.3). The edge of the mass enhanced with contrast. The patient improved symptomatically with dexamethasone (Decadron). The mass was removed, and pathologic examination confirmed metastatic adenocarcinoma.
Nystagmus and Related Ocular Oscillations

Case 16.2

A 28-year-old man presented with oscillopsia and visual blur. Nine years prior to the onset of these symptoms, he had been involved in an automobile accident in which he suffered a severe brainstem contusion. After a prolonged hospital stay and rehabilitation, he had returned to his college studies. His current visual impairment was hampering his ability to read.

Examination revealed a visual acuity of 20/40 in each eye. He had asymmetric continuous nystagmus. Closer examination at the slit lamp revealed that one eye was ascending and one descending. Along with these movements, the ascending eye was intorting and the descending eye was extorting. Intermittently, convergence nystagmus was also seen. The patient had decreased up gaze, mild left internuclear ophthalmoplegia, and pupillary light-near dissociation.

What type of continuous nystagmus does this patient have? What is the most likely cause of his visual symptoms? What type of neuroimaging would be useful?

Discussion

The characteristics of the patient's continuous nystagmus are consistent with acquired see-saw nystagmus, which can result from head trauma, especially trauma involving the mesencephalon. The poor up gaze, pupillary light-near dissociation, and convergence nystagmus also point toward a mesencephalic lesion.

MRI scans showed a midline abnormality in the midbrain, which was dark on T1-weighted imaging and bright on T2-weighted imaging (Fig. 16.4). These findings are consistent with a posttraumatic lesion. Sagittal views, not shown, also demonstrated the lesion in the midbrain. Valproic acid helped reduce the patient's oscillopsia and see-saw nystagmus.

Case 16.3

A 12-year-old boy was referred for ophthalmologic evaluation because of abnormal eye movements. He had had a shunt placed at the age of 2 years for hydrocephalus (Fig. 16.5). On examination, his visual acuity was 20/50 and 20/30. He had spontaneous intermittent convergence-retraction nystagmus and, on separate occasions, clockwise rotary nystagmus. He had cogwheel pursuit on both horizontal gazes. Saccades were difficult for him to perform in all directions. Oculocephalic maneuvers successfully moved the eyes in all directions. Pupil examination was normal.

What general types of disease are indicated by the patient's eye-movement abnormalities? What anatomic location is indicated by the nystagmus? What further investigations would be appropriate?

Discussion

The patient's global problems with supranuclear eye movements narrow the possible
Figure 16.4.
MR images from case 16.2. A. T1-weighted image reveals a decreased signal (dark area) in the midbrain. B. T2-weighted image shows an intense signal (bright area) in this region.

Figure 16.5.
Lateral skull roentgenogram from case 16.3 taken soon after a shunt was placed. Note enlargement of the head and shunt tubing in the occipital region.

causes to bilateral hemispheric disease or brainstem disease. The convergence-retraction nystagmus indicates midbrain dysfunction, and the rotary nystagmus indicates dysfunction of vestibulocerebellar input.

An air ventriculogram revealed enlarged lateral and third ventricles, suggesting an obstruction at the aqueduct (Fig. 16.6). CT scans demonstrated a large cyst in the posterior fossa with associated vermian hypoplasia, which is diagnostic of a Dandy-Walker cyst (Fig. 16.7). The motility findings are from either previous or continued compression, maldevelopment of supranuclear pathways, or both.
Figure 16.6.
Air ventriculogram from case 16.3. Note severe enlargement of the lateral ventricles and the third ventricle.

Figure 16.7.
CT scan from case 16.3. Note large cyst filled with spinal fluid (A), which appears to have a connection with the fourth ventricle as a result of vermian hypoplasia (B). These features are consistent with a Dandy-Walker cyst.

SUGGESTED READINGS

Lee JR. Surgical management of nystagmus. Eye 1988;2:44.
EXAMINATION TECHNIQUES

To get as much information as possible from a field examination, the physician must make some adjustments for the type of field defect he or she expects to see and for the ability of the patient to perform a particular test. Patients who have neurological problems may be difficult subjects for examination. They may be ill, slightly obtunded, afraid they have a terrible disease, or simply apprehensive about having their first field examination. Such factors tend to affect the test results.

In a patient who is slightly obtunded, a good confrontation field test may be more revealing than a formal Goldmann field test in which the patient performs poorly because of a lowered level of consciousness. The patient with headaches and skull roentgenograms that show a sella turcica at the upper limits of normal in size probably has a bitemporal defect. Thus the physician who spends an inordinate amount of time mapping a blind spot or looking in the Bjerrum area succeeds only in fatiguing such a patient. The physician does not find the subtle bitemporal field defect, which starts at the vertical meridian peripherally.

Recorded Fields

The tangent screen test is a sensitive one, and it can be relied on to identify any central field defect. I use it most of the time initially because it permits me to observe patients closely and to evaluate their degree of alertness and their speed of response. Later we obtain computerized fields. Many neuro-ophthalmologic patients are ill, and it is more satisfactory to have them seated in the examining chair than balanced on a stool with the head on a small stand in a fishbowl. The tangent field method also allows the physician more intimate contact with patients so that he or she can question them when needed. I find this contact lacking when I see the patient only through the observer tube of the Goldmann perimeter. I prefer to start with a 2-mm white object and then vary the size and color and technique as the situation demands.

When doing a peripheral field examination, I use the computerized perimeter for many of the same reasons that I select the tangent screen. The real value of this projection perimeter is that it helps keep the patient unaware of the direction from which the test object is coming. The computerized
perimeter is useful in following the progress of the patient if the patient is alert and cooperative. The large number of variables that can be used with the computerized perimeter makes it a valuable instrument for identifying the presence and extent of subtle defects and their progress or resolution.

Although there are published limits for an average person's field, they vary, and this variation must be considered in interpreting the perimetry results. The temporal field constricts with age after the sixth decade of life. This may be partially due to senile miosis but probably due to decreased oxygenation of the peripheral retina with age. This has been shown experimentally by reducing the O2 concentration in measuring the fields. Peripheral loss has also been reported in dive bomber pilots in World War II, who noticed peripheral loss as they went into power dives and increased the G-forces, reducing the oxygenation to the head.

There are many types of defects, and each has a specific anatomic localization. Some are peripheral, such as general contraction, quadrantanopia, hemianopia and altitudinal, to name a few. Those inside the peripheral limits of a normal field are central, para-central, cecocentral, and arcuate scotomas. Some defects are best seen at the vertical meridian, such as temporal lobe and pituitary lesions. Arcuate lesions may be seen along the horizontal meridian and are called nasal step defects. Not all defects of the central field cause loss of acuity. Therefore, good acuity does not rule out defects near the center that do not break out to the periphery. That is why it is important to examine the central field as well as the peripheral field.

Automated perimetry is a significant step forward in quantitating field testing. My experience is solely with the Humphrey and Octopus instruments, which display the almost 3000 points in a series of symbols and shades of gray to black, much like the gray scale of a CT scan (Figs. 17.1 and 17.2). Certain qualifications should be made, however. This display of almost 3000 points is mostly interpolation, as less than 3% of those points are actually tested. If you are looking for defects in a certain area, therefore, it is important to select the appropriate program. It is a useful instrument in long-term follow-up of patients who can be expected to show subtle and slow changes in their fields. As an initial testing technique for many neuroophthalmologic patients, I find it too protracted a test for the attention span of sick patients who may also have cerebral problems owing to their disease and who have never had any experience with field testing.

Non-Self-Recorded Fields

Several other types of field testing are important and should be considered for the patient who cannot perform when one of the more formal testing techniques is used. The techniques discussed in the following sections may help to identify a field defect that would be missed with more formal testing techniques if the patient is not alert or is uncooperative.

CONFRONTATION FIELD TESTS

Confrontation field-testing techniques are much maligned, but helpful if they are done properly and used when indicated. They are not a substitute for formal field tests, but they are useful as screening devices or in bedside examinations.

The confrontation method involves the following three steps.

**STEP 1.** The patient is asked to fixate with one eye on the physician's nose. The physician then uses the field of his or her right eye as a standard for measuring the field in the patient's left eye, and the field in his or her left eye for measuring the field in the patient's right eye. Instead of using the wriggling finger method, the physician asks the patient to count the number of fingers on the hand that the physician presents successively to each of the four quadrants of the patient's eye. The number of fingers may be
Visual Field Defects

**Figure 17.1.**

A. Typical printout for normal eye from Octopus field instrument. Note the different symbols for different densities of the field. The symbols are interpreted in scale at the bottom. B. Digital printout for a normal eye. (From the Hiron Corporation, Westminster Industrial Park, E. Providence, R.I.)
one, two, five, or none (Plate 17.1, A and B). Thus four choices are given rather than the two choices of the wiggling-finger method. If the patient fixates poorly, a variation on the finger-counting method may be substituted. The physician presents the finger(s) to the patient quickly—before the patient has a chance to shift fixation.

**STEP 2.** The physician uses both hands simultaneously, presenting stimuli to both the nasal and temporal fields of one eye. The combination of fingers presented are (a) one finger of one hand and one finger of the other hand, (b) one and two, (c) two and two, or (d) one and five. The patient is asked to tell how many fingers are seen. Besides evaluating the fields, this step tests both the patient’s ability to calculate, which is a parietal lobe function, and the existence of the extinction phenomenon. The patient with parietal lobe disease may miss one-half of the field because of the extinction phenomenon rather than because of a true field defect.

The physician should consider the extinction phenomenon in the patient who consistently misses seeing objects in one field with bilateral stimulation but who has no trouble counting fingers accurately when only one-half of the field is tested at a time. Therefore, when a patient who is reported to have a field defect turns out not to have one, the physician should test for the extinction phenomenon by bilateral field testing using confrontation. In this instance, a gross technique may pick up a defect that a more sophisticated method has missed using a single test object.

**STEP 3.** The physician presents fingers to the patient’s nasal and temporal fields as in step 2. This time, however, the patient is asked to compare the appearance of the fingers. Are pieces of a finger missing? Is one finger faded compared with the other? Although this test requires that the patient make a subjective judgment, it may be valuable, when the results are compared with those in the other eye, in detecting a bitemporal or homonymous defect.

After all three steps are completed with one eye, they are repeated for the other eye.

A more subtle confrontation test involves presenting identically colored test objects to the patient’s nasal and temporal fields. (The red tops of two plastic mydriatic bottles can be used.) If the defect is subtle, the patient may say that one cap is not colored or is a faded-red or pink color compared with the other cap. Such a response indicates the presence of a subtle hemianopic defect. In optic nerve disease, the patient’s response is usually uniform in that one eye sees the color the same in all four quadrants, and the caps may only look different when compared with the way the other eye sees them. A more subtle form of optic nerve disease may be suggested when the color of the cap is more faded when the patient looks at it directly than when the cap is held in a para-central position (Plate 17.1, C–F).

**PROJECTION LIGHT TEST**

The projection light test can be used with the bedridden patient who cannot be tested with more formal techniques, but who needs a more critical examination than the confrontation field test. The physician uses a battery-operated flashlight that has a small focused beam of light (of the type used as a pointer during lectures). The physician asks the bedridden patient to cover one eye and then to look at a fixation point on the wall or the ceiling. The physician, standing out of the patient’s view, shines the light on the wall or ceiling and looks for and identifies the patient’s blind spot. Using the field of his or her right eye as a point of reference, the physician explores the limits of the field of the patient’s right eye. The physician’s hand covers the light each time it is moved, so that the patient has no idea in what direction it will move next. The physician should shine the light frequently into the patient’s blind spot to determine whether the patient still sees the light. A patient who consistently does not see the light when it is in the blind spot must be fixating accurately; a patient who consistently sees the light must not be fixating accurately. To increase the sensitivity of the test, the physician can partially cover the light with his or her hand and thus make
**Plate 17.1**

Confrontation field testing.

- **Plate 17.1A**
Correct technique for presenting fingers. Note that the fingers are beside one another.

- **Plate 17.1B**
Incorrect method for presenting fingers. When fingers are presented one behind the other, the patient perceives them as one and gives an incorrect response.

- **Plate 17.1C**
When two identical test objects are presented to the nasal and temporal field and perceived equally, no defect is present.

- **Plate 17.1D**
When two identical objects are presented and patient perceives temporal one as paler than nasal one, a temporal defect is suggested.

- **Plate 17.1E**
When three identical test objects are presented to the temporal, central, and nasal field and perceived equally, no defect is present.

- **Plate 17.1F**
When three identical objects are present and patient perceives the central one as paler than the other two, a central scotoma is suggested.
the light less intense. The background illumination in the room also influences the test sensitivity.

**HRR PLATES**

Using the HRR plates can be more valuable than simply examining the patient for congenital defects in red-green color vision. Patients with optic nerve disease, even those with excellent visual acuity, frequently miss most of the HRR plates. On the other hand, a patient with severe macular degeneration usually does not miss any—at most one or two—of the more subtle plates. Distinguishing optic nerve disease and macular disease with the use of the HRR plates is easier than trying to plot a central scotoma in a patient with minimal decrease in acuity to the 20/30 level.

**AMSler GRID**

Testing with the Amsler grid can be valuable, but in my experience it is difficult for the patient to perform. The patient is asked to look at the center of a grid system and to say whether any of the lines are faded, distorted, or missing (Figs. 17.3 and 17.4). I find that most patients have a hard time fixing centrally and simultaneously appreciating the surrounding area. Most patients, regardless of instructions, tend to explore the surrounding area with their fovea, a maneuver that defeats the point of the test. Also, by the time I have explained to patients what I want them to see or not to see, I have almost suggested the defect to them. This test requires considerable understanding and patience from both physician and patient. If it is used correctly and if the patient is intelli-

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**Figure 17.3.**
A person with no central defect sees all the lines in the Amsler grid as straight and equally clear.
gent, the test can be valuable for detecting subtle defects. I have found a useful variation in the standard format. One of the standard test plates is made up of red lines on a black background. The red lines are so dark that frequently even the normally intelligent patient misses them. I have made up grids of the same size but with red lines on a white background. With such a grid, the patient can easily detect lines that are faded red, missing, or completely lacking in color.

A specific response to the Amsler grid is seen in patients with serous detachments of the macula. Even small amounts of serous macular disease result in symptomatic central defects that cause a patient to complain. These macular changes are often missed on routine ophthalmoscopy. The patient with serous macular disease sees the Amsler grid as distorted rather than as having pieces missing. The distortion is similar to that caused in a chain-link fence when somebody leans against it (Fig. 17,5). When the patient reports such a distortion in the Amsler grid, the physician should study the fundus carefully with a fundus contact lens to identify the cause of the complaint.

USE OF COLOR

The use of color has always been controversial. Even those that subscribe to the use of color don't agree about which technique to use. Some use color as an object of decreased sensitivity while others use it as a color recognition. I prefer to use color recognition. This experience agrees with Kollner's law, even if that law is not perfect. The decreased sensitivity technique gives varied results, even in the same patient from examination to examination. There is even
some argument about which color is preferable for central field defects. Red has been the most used and seems the most reliable. As mentioned above, if you use color recognition as the technique, then using the smallest red object defeats the purpose. Therefore, use a large test object. Certainly smaller and smaller white test objects can reveal the same scotoma, but the progressive decrease in the size of white test objects is governed more by the minimal visual threshold than any other feature. If rods are affected, blue test objects seem to be more sensitive. If the optic nerve is the location of the defect, then red has traditionally been more sensitive. It is difficult to say if this increased sensitivity is due to lower intensity than the same size white test object or if it is due to a different wavelength. The most important use of color is in the detection of subtle central scotomas. In optic nerve disease in the patient who has reasonably good visual acuity, identifying a central field defect with even small white test objects may be difficult. The defect that can be observed when a small red test object is used is generally so pronounced and easy to map that it is hard to believe how difficult it was to find with a small white test object. A common mistake of the beginner is to go from the smallest white test object to the smallest red test object. It is usually better to go from the 1-mm white test object to a 6- or 9-mm red test object. The patient is able to see the test object but not its color and describes it as either faded red or black. The physician then moves the test object out from the area where the color of the object is abnormal in all directions until it reaches the area in which the patient can perceive the proper color. This technique delineates the scotoma, and the information obtained can be used for comparison on subsequent field examinations.

Chamlin pointed out that homonymous bitemporal field defects, when the defect is subtle, result from hemiretinal suppression rather than from a defect involving just a few peripheral fibers. Chamlin’s testing technique is to compare the retinal sensitivity of the two halves of the field. The following paragraph describes a variation of Chamlin’s technique that uses small white test objects and colored test objects.

It is sometimes difficult to evaluate small peripheral contractions of a field. Do they represent early but definite intracranial pathology? A slow response from the patient? A big eyebrow? A peripheral retinal degeneration? The correct answer can be discovered in several ways. The first and
most common method is to take two identical white test objects, small enough to show up the peripheral contraction. The physician brings these two test objects down from above on either side of the vertical meridian (Figs. 17.6 and 17.7). If the patient sees the test object on the side of the peripheral contraction later than on the other side, the previous peripheral contraction may represent an intracranial hemianopic defect. There must be a 10° difference from one side to the other in recognizing the two test objects. Many patients show a consistent difference, but not one that is as much as 5 to 10°. In these patients, color again can be of use. Using two identical red test objects that are 6 or 9 mm in size, the physician asks the patient to report when he or she can recognize the color. (They will first be seen as white or colorless.) If a hemianopic defect is present, the patient will see color in the test object presented to the nonaffected side before seeing it in the test object presented to the abnormal side.

In patients who show an equivocal response to a small white test object, a big difference may be found when red test objects are used. It is not uncommon for a patient who shows a 7° difference in response to a small white test object to show an absence of color in an entire quadrant. Occasionally, even this technique may not be consistently reproduced. If it cannot be reproduced, the physician should move the red test objects horizontally rather than vertically. Then the red test object should be brought from the area where the color is lacking, across the vertical meridian into the area where the patient can appreciate the color normally. Each time the test object crosses the vertical meridian, the patient quickly perceives the color. The vertical meridian effect identifies the difference between the nasal and temporal fields and establishes the significance of the defect and its intracranial location.

**PUMPKIN TEST**

As mentioned, a central scotoma in a patient with reasonably good visual acuity is difficult to plot. I find that cecocentral defects are even more difficult to identify. It is essential to establish that a defect is cecocentral and not just central, because if the defect is cecocentral, there are three diagnostic possibilities, whereas a central sco-
Cecocentral defects are most commonly caused by nutritional amblyopia; occasionally, they are caused by pernicious anemia and, rarely, by Leber's disease.

To establish the cecocentral nature of the defect, I have used a variation on the color technique described for central scotomas. I have found that when small colored test objects are used, it is difficult to plot the cecocentral defect and to be sure that the defect is not just a central scotoma. These patients seem to fixate more poorly than the usual patient does, which obscures the validity of the test. There are also varying degrees and islands of different density in the area between fixation and the blind spot that keep varying the patient's response. Therefore, instead of pursuing the usual technique of moving a test object from a nonseeing to a seeing area of the field, I make the entire central field a colored test object. I then ask the patient to point out any color defects. The color field is created by using a standard-size orange poster board, which easily covers fixation and the blind spot. (Orange proved, by trial and error, to be the best color because red poster board is so dark a red that it is hard for the patient to differentiate an area of dark red from one that is simply dark or black.) A fixation object is attached about one-third of the way in from one edge of the cardboard. The fixation object so placed allows the cecocentral area to be more easily and completely covered by the cardboard than would a central spot on the cardboard. The patient is instructed to delineate with a long dowel rod the area(s) where the orange color is missing while he or she looks at the fixation target. If the patient does not fixate steadily, the area he or she is trying to delineate seems to move and cannot be outlined. This difficulty encourages the patient to fixate more steadily. With this method, the patient can tell the physician that the defect is worse between fixation and the blind spot and not in front. The patient can also show the physician that the defect is not equidistant around.

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A. 

**Figure 17.7.**

A. Champion step test performed with a test object presented just on either side of the vertical meridian reveals a significant step defect.
### Visual Field Defects

**Central 24 - 2 Threshold Test**

<table>
<thead>
<tr>
<th>Name</th>
<th>Birthdate</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>01-12-31</td>
<td>12-19-94</td>
</tr>
</tbody>
</table>

**Fixation:**
- **Central:** 30
- **TIME:** 2:30 PM

**Results:**
- **Age:** 63
- **Fixation Losses:** 0/20
- **False Pos Errors:** 0/10
- **False Neg Errors:** 0/10

**Questions Asked:** 277

**Test Time:** 01/11/94

**Exam:** 9/6/92 630-2358

**Probability Symbols:**
- 20% (P: 0.25)
- 50% (P: 0.5)

**Graytone Symbols**

<table>
<thead>
<tr>
<th>SYM</th>
<th>ASB</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>55</td>
</tr>
</tbody>
</table>

**Yale Eye Center**
- **Glaucoma Center**
- **Referring MD**
- **Remarks**

**Tested by:**
- **Humphrey Instruments**
- **A Carl Zeiss Company**

### Figure 17.7. (continued)

B. Humphrey representation.
PLATE 17.11

- **Plate 17.11A**
  In the pumpkin test, a piece of orange cardboard with an eccentric fixation object is used to cover central and temporal portions of a cecocentral defect.

- **Plate 17.11B**
  Patient performing the pumpkin test uses a pointer to outline the cecocentral defect.

- **Plate 17.11C**
  Right-tilted disc.

- **Plate 17.11D**
  Left-tilted disc.

**ESSENTIALS OF AUTOMATED PERIMETRY**

Accurate assessment of the visual field is of great importance in many neuro-ophthalmologic disorders. Historically, ophthalmologists have relied on manual techniques such as the tangent screen and Goldmann kinetic perimeter to map a patient's peripheral vision. Over the past two decades, automated perimetry has increased in popularity and is currently a frequently employed formal method to evaluate a patient's peripheral vision. Reasons for this change include a more reproducible, standardized test that is readily quantifiable and that provides the opportunity for data storage, statistical analysis, and comparability among patients and offices. In addition, because automated perimetry uses a computer-controlled test algorithm, the role of the physician or technician performing the test may be less demanding in terms of time and training required. The Humphrey perimeter is currently the most widely used automated perimeter in the United States, and examples...
In this chapter have been largely obtained with this instrument.

The hill of vision may be mapped by kinetic (moving stimulus) or static (stationary stimulus) methods. Kinetic perimetry uses a stimulus of a constant size and intensity, which is moved from nonseeing to seeing areas of the visual field (Fig. 17.8). Accurate detection of the boundary between nonseeing and seeing requires a sloping hill of vision in the tested area. Adjacent similar-sensitivity boundary points are connected to produce linear maps of transition zones, termed isopters. Kinetic techniques are not optimal for the examination of relatively flat areas of the visual field. Manual perimetry typically uses kinetic testing.

Static perimetry evaluates stationary locations with test objects of a constant size. It is the stimulus intensity that is varied, and the results are generally displayed in terms of threshold intensity at each location tested (Fig. 17.9). Automated techniques of stimulus presentation are particularly suited to making static measurements since the computer algorithms are relatively straightforward. Threshold is defined as the stimulus intensity that has a 50% probability of being seen at that particular location.

Suprathreshold static perimetry uses a stimulus intensity that should be seen everywhere in the visual field; i.e., it is slightly above the predicted threshold value for each location. The predicted threshold values can be based on age-matched normal data or on the results of an individual’s prior threshold testing. Stimulus intensity for suprathreshold tests may be constant over the entire field (Fig. 17.10) or may conform to the slope of the visual hill (threshold-related, Fig. 17.11). Static suprathreshold strategies were devised by Armaly for screening glaucoma defects. While this type of screening is rapid, it does not detect some early abnormalities such as shallow localized depressions or increased variability of responses in localized areas. Suprathreshold screening techniques may be used to make qualitative estimates of the

---

**Figure 17.8.**

Kinetic perimetry uses a stimulus of uniform size and intensity, which is varied in location from nonseeing areas of the field until the patient sees the stimulus. This technique is relatively insensitive to shallow depressions in the field.
**Figure 17.9.**
Static perimetry uses a uniformly sized stimulus that is presented at different stimulus intensities to determine threshold.

**Figure 17.10.**
Suprathreshold static perimetry uses a uniformly intense stimulus that should be seen in most of the field.
Figure 17.11.
Superthreshold static testing uses a stimulus that is slightly brighter than expected in that location. These stimuli may be based on normal patient data or on prior threshold results for that particular patient.

Visual field defects are required to obtain the quantitative data needed for the early diagnosis and careful follow-up of patients.

Manual perimeters, such as the Goldmann and the Tübingen, are capable of quantitative threshold measurements when operated by an experienced perimetrists. Such techniques are tedious and require highly trained personnel. The greatest advantage of computerized perimetry lies in its ability to make static threshold measurements in an acceptable length of time under standardized conditions. Static threshold measurements are relatively sensitive to shallow depressions of the visual field when the stimuli are sufficiently close together (Fig. 17.12). This sensitivity has led to a higher detection rate of early visual field defects than with manual techniques and has enhanced the ability to meaningfully compare successive visual field examinations.

The human visual system possesses an exceptional adaptive ability, and generally, our ability to estimate absolute magnitude of light intensity is poor. The human visual system has, however, a remarkable aptitude to perceive contrast. Thus, it is the differential light sensitivity of stimulus against a constant luminance background that is measured by static perimetry.

The measurement of light in units based on the response of the eye is termed photometry, with the apostilb (asb) as the unit of measure for the luminance of a perfectly diffusing surface. Most automated perimeters use neutral-density filters, graded in decibels (dB), over a maximally emitting bulb to vary stimulus intensity. Retinal locations of reduced sensitivity require brighter stimuli to reach threshold, represented by lower decibel values. Higher decibel threshold values represent more-sensitive retinal locations (Fig. 17.13). Each decibel 0.1 log unit. Thus, 10 dB equals 1 log unit or a 10-fold change in intensity, and 30 dB equals 3 log units or a 1000-fold change in intensity. The maximum bulb intensities vary; Goldmann and Octopus
- **Figure 17.12.**
Static perimetry is often more sensitive in detecting shallow depressions of the field than kinetic perimetry.

- **Figure 17.13.**
Graytone key to the Humphrey perimeter. Note that more sensitive areas of the visual field depicted as light symbols require higher neural-density filters graded in dB to produce dimmer threshold stimuli. Note that the maximum bulb intensity with the Humphrey perimeter (DB = 0) is 10,000 asb.

Perimetry is a subjective psychophysical test requiring the patient's cooperation, effort, and communication. As in any diagnostic test, the response to a specific question has an associated error. The frequency-of-seeing curve is a useful construction to emphasize the importance of probabilistic considerations in estimating a location's threshold (Fig. 17.14). In mathematical terms, threshold is the stimulus luminance that is seen on 50% of repeated presentations.

A frequency-of-seeing curve is generated by testing repeatedly at a single location. For example, a location in visual space might be tested 10 times each with stimuli of 39, 37, 35, 33, 31, 29, and 27 dB, for a total of 70 questions. For each stimulus intensity, the frequency of the positive responses is plotted. Figure 17.14 indicates that these proba-
**Figure 17.14.**

Sample of frequency of seeing curve. Note that as stimulus intensity increases, the frequency of seeing also increases. Threshold is defined as the stimulus intensity that is detected 50% of the time. Note that false-negative and false-positive responses will limit the maximal and minimal frequency of seeing values, respectively.

**Stimulus Intensity (dB)**

Sensitivities can never be 0 or 100% because of the influence of false-positive and false-negative responses, respectively.

Several recent studies have explored the characteristics of frequency-of-seeing curves in glaucoma. The slope of the curve, a measure of uncertainty in determining the threshold, is highly correlated to actual threshold or threshold deviation (threshold deviation is the deviation from age-appropriate normal values at a particular location). Thus, areas of high retinal sensitivity (normal central locations) tend to test with high reproducibility, while locations with reduced sensitivity (abnormal central locations or peripheral locations) have a more shallow slope of the frequency-of-seeing curve, which is associated with greater uncertainty (Fig. 17.15).

Numeric measurements of a physiologic parameter produce variation around the mean of a test result. Quantitative measurements are not usual with manual perimetric techniques; therefore, fluctuations in sensitivity that cause these variations are not easily recognized. In addition, there is a strong tendency for the perimetrist to make the current visual field test conform to the results of previous tests. Computerized threshold perimetry has no such built-in bias. Careful objective static measurements have uncovered fluctuations in visual field thresholds. Bebie et al. described several components of this fluctuation. These are short-term fluctuations (STFs) and the homogeneous and heterogeneous components of long-term fluctuation (LTF).

STF is the variation of responses that occurs over the performance of a single test. It is calculated by measuring the sensitivity at a location several times within the context of a single testing session. Some authors consider it important to examine both local and global STF values. While double threshold determinations accurately measure global
STF, it may be necessary to rethreshold a location as many as five times to accurately assess the local STF. In clinical practice, the Humphrey machine calculates global STF by thresholding 10 locations twice during the course of a given test and displays this number on the test printout.

STF is caused by a combination of the instability of the threshold being tested and the level of cooperation and attentiveness of the patient. Similar to the broadening of the frequency-of-seeing curve seen in locations with reduced sensitivity, patients with glaucomatous visual field loss have higher STF than normal subjects. These data are consistent with earlier clinical experience with manual techniques in which variable responses in localized areas were interpreted as early manifestations of glaucomatous damage.

LTF, the fluctuation between tests, occurs over days, months, or years. By definition, LTF excludes learning effect and STF. Homogeneous LTF refers to a unidirectional change in sensitivity throughout the entire visual field and is typically about 1 dB in normal eyes. Heterogeneous LTF refers to different directions and amounts of change in sensitivity at different visual field locations. Heterogeneous LTF varies according to location and presence of disease, with a typical normal value of 1.5 dB. The LTF at a single test location increases by approximately 0.2 dB for each 1 dB decrease in sensitivity. As a rough guideline, a location with a 10-dB defect may fluctuate by as much as 10 dB without reaching the 95% confidence interval for a change. The magnitude of LTF is usually greater than that of STF and is not routinely presented to the examiner numerically.

The causes of LTF are not yet fully established. In normal patients, LTF may increase with age and increases as the intertest time interval increases. In a group of clinically stable glaucoma patients, LTF was correlated with initial sensitivity (Fig. 17.16) and with distance from fixation. Although STF is weakly correlated with LTF, the relationship is not strong enough to accurately predict LTF from STF in an individual patient. Knowledge of the magnitude of LTF
in an individual is necessary for comparisons of visual fields for change over time. This represents a limitation in the current ability to detect subtle visual field changes.

A basic understanding of the test algorithm used by automated perimeters employing a full threshold strategy is essential to interpreting the results and troubleshooting problematic fields.

**Bracketing Strategy**

Since the visual threshold of a given point in the retina is the luminance at which 50% of the presented stimuli are perceived, a patient undergoing a threshold examination may see only half of the presented stimuli. This can be a source of frustration to patients, who may feel they have performed poorly. Understanding the phenomenon requires knowing the bracketing strategy used to make threshold measurements at each location of the visual field. Commonly used algorithms to estimate threshold employ a double crossing of the threshold (Fig. 17.17). For instance, if the initial stimulus is subthreshold (not seen), intensity is increased in 4-dB steps until the patient responds with a "yes" (seen). The stimulus intensity is then decreased in 2-dB steps until the patient does not respond (not seen). The visual threshold is thereby crossed twice.

If the initial stimulus is suprathreshold, stimulus intensity is decreased by 4-dB steps until the threshold is crossed, then increased in 2-dB steps (the threshold again is doubly crossed). With this strategy, accurate threshold estimates are achieved by presenting, on average, approximately five stimuli per test location. Stimulus presentations are not performed sequentially at a single location but are moved randomly throughout the entire visual field. This discourages "cheating," since the patient does not know where to expect the next stimulus presentation.
**Figure 17.17.**
Graphical depiction of the 4-2 double crossing test algorithm. O, a nonseen stimulus; x, a seen stimulus. Because question number 1 is subthreshold (not seen), the stimulus is increased in intensity by 4 dB. In this case, stimulus number 2 is also not seen, and with an additional 4 dB in intensity, stimulus 3 is seen. The algorithm then lowers stimulus number 4 by 2 dB which, in this case, is also seen. Stimulus number 5 is further reduced by 2 dB and is not seen. For the Humphrey perimeter, the last-seen stimulus (number 4) is taken as threshold.

**Figure 17.18.**
Seed and short-term fluctuation map superimposed on 24-2 grid. Early in the test strategy, the Humphrey perimeter tests 4 seed locations (circles), each located 9° from the horizontal and vertical meridians. These locations are each tested twice and used to determine starting values for surrounding locations. Throughout the remainder of the test, an additional 6 locations (squares) are intentionally tested twice, and these 10 locations are used to calculate the global short-term fluctuation. Throughout the remainder of the test, additional locations that deviate unexpectedly from normal values are also thresholded twice, with the results presented in parentheses.
Foveal Sensitivity

Measurement of the foveal sensitivity is an option that, if selected, occurs at the very beginning of the test. This option should generally be left on, as it takes very few stimulus presentations and provides information about the most valuable portion of the visual field. The patient is asked to maintain gaze on an illuminated diamond that is projected inferior to the standard central fixation target used throughout the remainder of the test. The initial stimulus intensity is 30 dB, and the regular 4-2 bracketing strategy is used to determine foveal sensitivity. Once this portion of the test is completed, the fixation diamond is removed, and the patient is asked to fixate on the central target.

Catch Trials

Throughout the performance of the test, patient fixation and level of alertness is periodically assessed. The Humphrey perimeter estimates fixation with the Heijl-Krakau technique of projecting a stimulus in the anticipated blind spot location. If the blind spot checks are not seen, fixation is assumed to be central, which is not necessarily the case. A high number of fixation losses may result from wandering fixation, but they may also result from a displaced blind spot or from many false-positive responses. High plus lenses tend to shift the blind spot toward fixation, while myopic correction moves the blind spot peripherally.

Another technique to reduce the percentage of fixation losses is to instruct the technician to set the machine to replot the blind spot if high fixation losses are detected early in the test and seem to have an optical cause. The machine then executes a short subprogram that presents densely packed stimuli in the region of the expected blind spot until the actual blind spot is mapped.

The technician's description of patient fixation is also extremely valuable in detecting pseudo-loss of fixation. The absence of a low patient reliability message should not fool the examiner into a false sense of security. Consider the patient who falls asleep at the machine. Clearly, that patient is unlikely to respond to stimuli presented in the blind spot, despite poor fixation.

False-positive errors are tested by periodically withholding a stimulus presentation, although the faint noise that usually accompanies a stimulus projection is created. False-positive responses tend to indicate anxious, "trigger-happy" patients. The rate of false-positive responses can often be improved if the perimetrists coach patients to respond only when they are certain that they have seen the stimulus.

False-negative errors are tested by projecting a 9-dB suprathreshold stimulus in a region already thresholded. Failing to respond to this markedly suprathreshold stimulus
indicates patient fatigue. False-negative errors are less influenced by coaching; however, the perimetrists should ensure that the patient is awake and consider giving the patient a short break. False-negative errors are produced both by patient inattention and by a diseased, easily fatigued visual system. If the threshold results are markedly reduced, the machine may not be able to generate suprathreshold stimuli. This may dull the inexperienced perimetrists into a false sense of patient responsiveness.

**Single Test Printout**

The single test printout from Programs 30-2 and 24-2 of the Humphrey perimeter contains a large amount of data, with various analyses presented in multiple ways (Fig. 17.19). The inexperienced examiner may find the printout overwhelming at first, but familiarity with the overall organization and the derivation of the plots and indices will greatly ease interpretation. The printout can be conveniently divided into six sections: (a) general information, located at the top; (b) reliability, located in the second row, at the left; (c) raw data, located in the second row, at the right; (d) total deviation, a plot located in the third row, at the left; (e) pattern deviation, a plot located in the third row, in the middle; and, (f) global indices, located in the third row, at the right. At the bottom of the printout is a general legend that explains the graytone and probability symbols.

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**Figure 17.19.**

A sample test printout of the Humphrey perimeter. The printout can conveniently be divided into six sections, (a) at the top, general information; (b) middle left, reliability data; (c) middle right, raw and graytone data; (d) lower left, total deviation plot with accompanying probability symbols; (e) middle bottom, pattern deviation plot with accompanying probability symbols; and (f) lower right, general indices. To create the pattern deviation value, the seventh-best total deviation value is used to adjust the entire total deviation plot. In this case, most locations are corrected by 2 dB, producing a slightly less significant pattern deviation plot. The general indices include mean deviation (MD), pattern standard deviation (PSD), short-term fluctuation (SF), and corrected pattern standard deviation (CPSD).
GENERAL INFORMATION
Positioned at the top of the printout, the
general information section displays impor-
tant data about the individual patient as well
as particular test variables. Included here is
the program name (e.g., Central 24-2), pa-
tient name, patient birth date, stimulus size,
background illumination, blind spot check
size, threshold strategy, fixation target type,
patient identification number, test time and
date, optical correction, pupil diameter, and
Snellen acuity. Many of these variables can
significantly affect the raw or calculated data,
and they can be invaluable in interpreting re-
sults. For example, a miotic pupil or incorrect
refraction can reduce threshold values, while
an incorrectly entered birth date will create
wrong age-compared deviations.

RELIABILITY INDICES
The reliability data, located below and to
the left of the general information section, in-
dicate which eye (left or right) was tested and
displays a calculated patient age. The num-
ber of questions asked typically averages five
per test location. The number of fixation
losses estimates how stably the patient main-
tained gaze at the fixation target. The number
of false-positive errors aims to identify the
"trigger-happy" patient, while the number of
false-negative errors indicates patient fatigue.
The final items of information displayed with
the reliability data are test duration and the
optional selection, fovea sensitivity.

RAW DATA
The two largest plots on the printout, lo-
cated to the right of the reliability indices,
are the raw data printouts. These display, in
numeric and graytone format, the actual
threshold values in decibels. The same 10
locations are always measured twice and are
used to calculate the STF of the test session
(Fig. 17.18). The duplicate values are dis-
played in parentheses in the numeric print-
out and are averaged for the graytone dis-
play. The testing algorithm also rethresholds
locations where the initially obtained values
deviated greatly from the age-matched nor-
mal data (these doubly determined values
are not included in the STF calculation). The
graytone plot is extrapolated from the nu-
meric plot, and although it implies uniform
sampling of the 50° field, in reality, less than
1% of this area is actually tested. The gray-
tone plot remains useful to alert the exam-
iner to problem areas and is an effective way
of showing visual field results to the patient.

TOTAL DEVIATION
Since the introduction of the Humphrey
perimeter, the manufacturer has upgraded
the machine with increasingly sophisticated
statistical analysis packages. The first of
these, Statpac, allows comparison of the raw
threshold data with age-matched normal val-
ues at each location: accompanying proba-
bility symbols indicate the significance of
any abnormality. This plot is termed the to-
tal deviation plot. These plots are displayed
in the lower left portion of the printout, both
numerically and with probability symbols.
The p values take into account the wider
range of normal values as the distance from
fixation increases. For example, a value re-
duced 14 dB in sensitivity, compared with
the age-matched normal value that is located
27° superior to fixation, may be only mar-
ginally significant (p < 0.5%), while the same
14-dB deviation located 10° inferotemporally
to fixation may be highly significant (p <
0.5%). The examiner should always keep in
mind that statistical significance does not al-
ways mean clinical significance.

PATTERN DEVIATION PLOTS
Patterns of visual field loss can be conve-
niently divided into generalized depression,
which uniformly affects the entire field by a
similar amount, and localized ("scotoma-
tous") loss, which is frequently more diag-
nostic. Generalized depression is most com-
monly caused by cataract and can hide
underlying scotomatous loss. Statpac modi-
fies the total deviation plots in an attempt to
display any superimposed patterns of local-
ized loss hidden under generalized depres-
sion. This is done by correcting the seventh-
best deviation value within the Program 24-2
test grid to zero deviation and "adjusting" the entire field by that value (Fig. 17.19). The resulting plot is termed the pattern deviation plot. The threshold value of this seventh most elevated location has been termed the general height value, although it is not routinely displayed on the printout. For example, if the entire visual field is diffusely reduced in sensitivity by 7 dB, with an underlying moderate superior arcuate defect of an additional 12 dB, the deviation plot will be reduced by 7 dB and displayed in the area labeled pattern deviation, and the 12-dB relative depression will become more apparent. A probability analysis is again displayed on these adjusted deviation values.

GLOBAL INDICES

In the lower right corner of the single field printout, Statpac displays the global indices, which describe the entire visual field in four numeric values: (a) MD, mean deviation, is a location-weighted mean of the values in the total deviation plot. It is essentially a distilled value that represents the average height of the entire hill of vision. Negative values represent depression. MD is relatively insensitive to localized defects and is strongly affected by generalized trends; (b) PSD, pattern standard deviation, represents the unevenness of the surface of the hill of vision. It is calculated by taking a location-weighted standard deviation of all the threshold values. PSD is insensitive to the overall average height and is strongly affected by localized defects; (c) STF, short-term fluctuation, is the standard deviation of the 10 doubly thresholded locations. STF increases in inconsistent patients. This increase may be due to poor patient cooperation or attention, but STF also tends to increase in scotomatous areas, particularly at their borders; (d) CPSD, corrected pattern standard deviation, calculated because STF influences PSD. This attempts to better represent the unevenness of the surface of the hill of vision by accounting for the influence of STF, Statpac provides probability values for each global index value, compared with age-matched normals. For example, if the MD value is accompanied by a p < .05 symbol, the MD of the field is depressed by an amount greater than that found in 95% of the same age normal population.

Glaucoma Hemifield Test

Statpac 2, Humphrey's more recent statistical upgrade of the single field analysis printout, introduced an additional statistical analysis titled the glaucoma hemifield test (GHT). The software produces the GHT result by dividing each of the upper and lower halves of the field into five mirror-imaged zones. Each zone is subsequently scored according to its pattern deviation values, and each upper zone is then compared with the corresponding lower zone. In addition, a general height of the field is determined by analyzing the most normal region of the field. The GHT has not been specifically validated in neuro-ophthalmic patients, but several of the responses may be useful. These include the result WNL, which is usually a reliable indicator of a normal field. Abnormally high sensitivity indicates a "trigger-happy" patient. General reduction in sensitivity indicates uniform field loss. The other two possible GHT descriptions, borderline or abnormal, may result from asymmetric loss across the horizontal meridian. While these descriptions more typically result from glaucomatous visual field defects, they can be seen with any nerve fiber bundle defects.

3-6 Alternative Tests

Increasing the number of test locations and the precision with which they are tested does not necessarily provide a more accurate picture of the visual field. Lengthy tests become fatiguing to the patient and may result in greater variability of responses. A number of strategies have been devised in an attempt to shorten the test and reduce the number of tested points while still providing an accurate representation of the visual field.
These strategies are described in the sections that follow. Multiple other tests available with the Humphrey perimeter (e.g., Temporal Crescent, Neurologic N0, Neurologic 50, Program 24-1, and Program 30/60-1) are rarely used.

**Grid Size**

The standard Humphrey Program 30-2, one of the more commonly used tests, samples 76 locations with a uniform 6° grid extending to 27° from fixation (Fig. 17.20). All Humphrey programs ending in -2 (e.g., 30-2, 24-2, 10-2) are offset from the horizontal and vertical meridians. Programs 30-2 and 24-2, which use 6° spacing, are thus offset by 3°.

To threshold every location, generate reliability indices, measure STT, and rethreshold unexpected values, approximately 550 questions are asked in a typical test, which takes about 15 minutes per eye. As the distance from fixation increases, the normal threshold values decrease, with a corresponding increase in the intratest and test-retest variabilities, providing diminishing returns. One approach to shortening the test is to delete the outer row of locations. Program 24-2 only tests out to 21°, except for preserving the important nasal extent of Program 30-2. The resulting test contains 54 locations, a 25% reduction compared with the Program 30-2 grid, and considerably shortens the test duration. This represents an attractive tradeoff in patients who fatigue with additional testing.

---

**Figure 17.20.**

Program 24-2 and 30-2 test grids. Program 24-2 deletes the outer row of the 30-2 test grid with the exception of the two nasal locations. This produces a 30% reduction in test time. Because the outer row of locations are typically least reliable, this is often an attractive tradeoff between test speed and the ability to detect disease.
Fast Threshold

A further decrease in time can be realized by choosing the fast threshold strategy (different from Fastpac), which performs the entire bracketing process only at locations that are not seen with a predicted 2-dB suprathreshold stimulus. The stimulus intensity can be calculated from age-matched normal data or preferably from the results of the patient's prior conventional-threshold tests. In this way only "abnormal" points are bracketed. Fast strategies can cause misinterpretation in the initial evaluation of patients whose visual field may be a bit supranormal.

Fastpac

The recently introduced Fastpac uses an entirely different testing strategy. Instead of the standard 4-2 full strategy with a double crossing of threshold, Fastpac adjusts the stimulus intensity by 3-dB increments until the threshold is crossed once. Fastpac saves up to 40% of test time in normal or near-normal fields and provides less advantage in patients with larger amounts of field abnormality. The time savings is accompanied by a small reduction in the estimate of scotoma extent and severity and higher STF. In comparisons of Fastpac and full threshold strategies, Fastpac shortens test time by 35 to 40%. Fastpac may be most suitable for following up reliable patients with previously near-normal results, although few longitudinal data are available on its use in these populations, and the effect on LTF is presently unknown. One potential advantage of Fastpac over the fast threshold program is the ability to use the Statpac 2's programs that analyze for change over time.

Programs 30-1 and 24-1

Programs 30-1 and 24-1 test a uniform 6° grid out to 30° and 24°, respectively, but are not offset from the horizontal and vertical meridians. Because scotomas centered on the meridians are difficult to classify (superior vs. inferior, nasal vs. temporal), these locations have less diagnostic, localizing value. Therefore, these programs are infrequently used.

Program 10-2 and Macula Test

Program 10-2 provides a high-resolution test of the central 10°, with a tight 2° grid, offset 1° from the meridians (Fig. 17.21A). A total of 68 locations are used. Central tests are useful in carefully defining central or paracentral scotomas and are more sensitive in detecting subtle progression within the central visual field. In patients with advanced damage and small remaining central islands of vision, Program 10-2 can be performed with stimulus size V. This strategy provides the advantage of testing more area with measurable threshold and seems to increase patient cooperation and reduce patient fatigue.

An even more localized test is the macula test, which thresholds 16 locations within the central 5°. Each location is thresholded three times to provide better estimates of local STF (Fig. 17.21B).

Program 30/60-2

Additional programs allow exploration of the peripheral visual field (beyond 30°). Program 30/60-2 extends the test out to 60°, with a uniform grid testing 68 additional locations.

Nasal Step Program

Patients with possible nasal steps can be further explored with the nasal step program, which tests 12 locations beyond 30° nasally. Two locations in the temporal visual field are also included to reduce the predictability of the questions to the patients.
Figure 17.21.

A. Program 10-2. This grid uses 2° spacing, offset 1° from the meridians and tests out to 9°. This test is useful to better define dense paracentral defects as well as small remaining central islands of vision. B. The macular threshold test thresholds the central 16 locations of the 10-2 test grid. Each location is tested 3 times to provide a better estimate of fluctuation. This test is useful in measuring small central and paracentral scotomas.
Stimulus Size Option

Most programs are performed with stimulus size III, which subtends a diameter of 0.43° in visual space. This size is derived from the 4 mm² size 3 used by the Goldmann perimeter. Testing with size III allows application of the Statpac 2 sophisticated statistical analysis. In fields where most test locations are markedly reduced, it is often preferable to increase the stimulus size to V (1.72° in diameter). This larger size is often preferred by the patient and may reduce fluctuation, although the option of using the glaucoma change analysis is lost.

Follow-up Printout

When evaluating a series of automated fields performed over time, the perimetrist may find the integration of the mass of amount of data overwhelming. The Humphrey instrument allows the creation of several serial printouts to ease confusion and allow statistical analysis of change over time.

Overview Printout

The overview printout (Fig. 17.22) simply presents a sequential listing of condensed single field printouts chronologically. For each test session, four plots are displayed (from left to right): grayscale threshold plot, numeric threshold plot, total deviation p value plot, and pattern deviation p value plot. Above these four plots are listed the glaucoma hemifield test results, reliability data, pupil size, and Snellen acuity. Below the plots are listed foveal sensitivity and global indices. The viewer familiar with the single field analysis printout will have no difficulty understanding terms used in the overview printout.

Change Analysis Printout

The change analysis printout represents each field as a box plot, depicted graphically over time (Fig. 17.23). To create this plot, deviation values at each location are ranked from least to most depressed. As can be seen from the legend at the left side of the printout, each box contains the 15th to 85th percentile deviation values from this ranking, with a central line representing the median value. In general, a small box with long tails suggests a clumping of values with a few outliers. If a small box is near 0 dB, most of the field is normal. If the box changes in location over time with a stable size, a generalized change is likely occurring. A change in box dimension usually indicates a more localized process.

The change analysis printout also plots the four global indices over time, with threshold levels for statistical significance. Probably most useful is the MD value over time. If this plot is not worsening, it is likely that most of the field is not worsening, although a stable MD with an increasing CPSD may indicate early progression of a localized scotoma. If the MD value is declining, the examiner must inspect the other indices and actual fields to discern confounding developments such as cataract formation. For the plot of MD over time, a linear regression analysis, titled MD slope, is performed, which describes the slope in decibels per year and assigns a significance level.

Glaucoma Change Probability Printout

Statpac 2 introduced the glaucoma change probability printout (Fig. 17.24A), which allows the examiner to average two initial fields into a baseline field and then perform a point-by-point statistical comparison of each subsequent field, looking for significant change (Fig. 17.24B). The "expected" fluctuation values have not been validated in nonglaucoma patients.
Figure 17.22.

Overview printout. In this case, three sequential 30-2 tests are presented. The plots from left to right include gray-tone, numeric dB, total deviation, probability, and pattern deviation probability plots. In this case, over the first three fields, a significant learning effect has occurred.
**Figure 17.23.**

Change analysis printout. In this printout, each field is depicted as a box plot at the top of the printout. The box plots are created by ranking total deviation values and displaying the 0, 15th, 50th, 85th, and 100th percentile graphically. In this case, notice the learning effect over the first four fields. A change in box plot location with a retention in dimension indicates a generalized trend, while lengthening of tails indicates more localized processes. At the bottom of the printout, the four general indices are graphed over time. A linear regression of the MD slope is performed with an accompanying significance of value.


Learning Effect

The results of many psychophysical tests improve as the subject gains more experience performing the test. The learning effect in automated perimetry seems to be small in most patients who have had experience with manual perimetry. Some patients, however, may demonstrate a dramatic improvement in the second test, compared with the first, despite previous experience with manual perimetry (Fig. 17.22). Occasionally, patients continue to improve over the initial three, four, or (rarely) five automated fields. The variability of test results decreases significantly with experience. Whenever possible, a patient new to perimetry should undergo several test sessions to establish a baseline for subsequent comparisons. The magnitude of the learning effect can be reduced by an attentive, thoughtful, operator who takes the requisite time to explain the examination thoroughly to the patient.

Interpreting a Single Test

Armed with a solid understanding of the test printout algorithm and derivation of catch trials, the examiner is better prepared to interpret a single test. Of great concern is the reliability of the particular patient. The patient with a tendency toward high false-positive errors can be thought of as trigger-happy, eager to perform well. These patients frequently respond to machine noise instead of perceived visual stimulus. The typical high false-positive printout will demonstrate

**Figure 17.24.**

Glucoma change probability. A. The glaucoma change probability averages the a and b first two fields into a baseline field.
**Figure 17.24. (continued)**

The field in each subsequent field then underwent a point-by-point comparison with baseline presented as a change in dB from baseline with accompanying probability symbols. These symbols were derived from the fluctuation of a population of glaucoma patients treated four times over a 1-month period. They have not been validated for other disorders.
physiologically supranormal sensitivity values, which will be depicted as "white scotomas" on the graytone printout. The general height adjustment of the total deviation plot to produce the pattern-deviation plot may artifactually depress most of the field, producing a highly significant pattern deviation plot. The mean deviation general index is often above +2 dB, and these patients typically have high pattern standard deviation and STF (Fig. 17.25).

The patient with a tendency toward high false-negative responses can be thought of as the easily fatigued patient who gradually becomes less responsive during the test. Because the outer edges of the test grid are tested last, the easily fatigued patient will tend to produce patchy reduction in sensitivity toward the periphery of the field. Although distinguishing such peripheral depression from true defects can prove difficult, the high false-negative patient will

---

**Figure 17.25.**

High false-positive patient. Note the thresholds in the 50s in peripheral areas of the field, which are nonphysiologic. The seventh-best total deviation value of +10 is used to define the general height of the field and correct it to 0. This produces a markedly abnormal appearing pattern deviation plot. The glaucoma hemifield test has correctly identified the field as containing abnormally high sensitivity values. The general index mean deviation is extremely positive, and the field contains high pattern standard deviations and short-term fluctuation.
often produce a result that does not respect anatomic boundaries and is not consistent with other aspects of the ophthalmologic examination. The reader is reminded that patients with diseased visual systems are also more easily fatigued. One suggestion for confirming or disproving the absence of true peripheral defects is to test the patient with a different-sized test grid to see if the defects are reproducible in location. The influence of high false-negative responses on the printout is, in many ways, the opposite of the high false-positive patient. If the seventh-best value on the total deviation plot is affected by fatigue, then the general height correction of the total deviation plot will create a false good-appearing pattern deviation plot. The mean deviation index will become more negative in a high false-negative patient (Fig. 17.26).

**General Reduction in Sensitivity**

One of the more common ocular conditions that can affect the visual field is cata-

![Diagram]

*Figure 17.26.*

High false-negative errors due to patient fatigue. Note the patchy reduction in sensitivity near the periphery as well as the high false-negative error ratio in the reliability section. The seventh-highest value in the total deviation plot if -3 has been corrected to 0, with a reduction in the abnormality of the pattern deviation plot. The MD value is very negative, and there are high PSD, SF, and CFSD.
Cataract formation characteristically reduces the field in a fairly uniform fashion. Moderate nuclear sclerosis, even with retention of 20/20 Snellen acuity, can reduce the visual field uniformly by several decibels. Several clues to diagnosing general reduction sensitivity include a reduced foveal sensitivity. The graytone plot is uniformly darkened, and the general height correction of the total deviation plot will produce a fairly normal-appearing pattern deviation plot. Although the mean deviation index may be statistically significant, the PSD, SF, and CPSD should be normal (Fig. 17.27).

**Localized Defect**

Table 17.1 lists graded minimal criteria for defining localized loss. This table emphasizes the importance of excluding far peripheral values as well as values around the physiologic blind spot because of high fluctuation.

---

**Figure 17.27.**

Generalized depression due to cataract. This patient with 20/40 acuity had 3+ nuclear sclerosis. This has reduced the foveal sensitivity as well as fairly uniformly reducing the total deviation plot. The general height correction does a good job of removing the generalized depression, leaving a clear-appearing pattern deviation plot indicating absence of localized scotomas. This is also correctly identified by the glaucoma hemifield test. The only general index abnormality is a negative mean deviation. The normal PSD, SF, and CPSD also indicate absence of localized scotomas.
Table 17.1. MINIMAL CRITERIA FOR GRADING ABNORMALITY (CENTRAL 30°)

<table>
<thead>
<tr>
<th>Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strict</strong></td>
<td>≥4 adjacent points of ≥5 dB loss each</td>
</tr>
<tr>
<td></td>
<td>≥2 adjacent points of ≥10 dB loss each</td>
</tr>
<tr>
<td></td>
<td>Difference of ≥10 dB across nasal horizontal meridian at ≥3 adjacent points</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> physiologic blind spot, superior and inferior rows</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>≥3 adjacent points of ≥5 dB loss each</td>
</tr>
<tr>
<td></td>
<td>≥2 adjacent points of ≥10 dB loss each</td>
</tr>
<tr>
<td></td>
<td>Difference of ≥10 dB across nasal horizontal meridian at ≥2 adjacent points</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> physiologic blind spot, superior and inferior rows</td>
<td></td>
</tr>
<tr>
<td><strong>Liberal</strong></td>
<td>≥2 adjacent points of ≥5 dB loss each</td>
</tr>
<tr>
<td></td>
<td>≥1 adjacent points of ≥10 dB loss each</td>
</tr>
<tr>
<td></td>
<td>Difference of ≥5 dB across nasal horizontal meridian at ≥2 adjacent points</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> physiologic blind spot, superior and inferior rows</td>
<td></td>
</tr>
</tbody>
</table>

*Loss is relative to normal values or to values of surrounding points. For probability maps that compare measure thresholds to normal values, substitute P < .05 for 5 dB loss, and P < .01 for 10 dB loss.

TOPICAL DIAGNOSIS

Retinal Lesions

DIFFERENTIATING OPTIC NERVE DEFECTS FROM RETINAL DEFECTS

The diagnosis of monocular field defects can be difficult. The appearance of the fundus frequently does not identify whether the defect arises from a retinal lesion or an optic nerve lesion. If a retinal defect is very recent, obvious changes shown on ophthalmoscopy may establish the site of the lesion, but days or weeks after the defect has occurred, the retina returns to normal, and the ophthalmoscopic sign is gone. One feature of field testing, however, usually does distinguish a retinal site of origin from an optic nerve one. Optic nerve quadratic or hemianopic field loss begins at fixation (Fig. 17.28). If the defect is caused by a retinal vascular lesion, the apex of the defect is at the blind spot (Fig. 17.28). The retina is separated into quadrants vascularity by the vessels coming off the disc, not off the fovea. Therefore, in defects that are less than a quadrant, smaller and smaller test objects should be used to enlarge the defect so that the location of the apex can be identified.

CECOCENTRAL VERSUS CENTRAL SCOTOMAS

Cecocentral scotomas involve not only the central part of vision but extend temporally to involve the blind spot. In testing fields, it is important to differentiate pure central scotomas from cecocentral ones, since cecocentral scotomas have a much more limited differential diagnosis. One additional feature of cecocentral versus central scotoma is that in the former the densest part may not be at the center of the defect, but located between fixation and the blind spot. Once the diagnosis of cecocentral scotoma is made, the differential diagnosis becomes more limited. Cecocentral scotomas most commonly present bilaterally, and the most common cause is tobacco-alcohol nutritional amblyopia. Cases of bilateral cecocentral scotoma that are congenital or caused by demyelinating disease have been reported, but these are much less common than the cases re-
Figure 17.28.
A. A field defect with the apex at fixation results from an optic nerve lesion. B. Humphrey representation.
Central 24 - 2 Threshold Test

Birthdate 01-10-31 Date 01-20-95

Visual Fields

- Optic Nerve Head
- Position
- Tension
- Color
- Pattern Blindness
- Size

Graystone Symbols

RYH

†00

50

45

40

35

30

25

20

15

10

5

0

Figure 17.29.
A. A field defect with the apex at the blind spot is caused by retinal vascular disease. B. Humphrey representation.
resulting from nutritional amblyopia. Unilateral cecocentral scotomas are much less commonly seen than bilateral ones. Shaw and Smith reviewed a large series of cases of cecocentral scotoma; they found 13 unilateral cases, which were attributed to inflammatory, idiopathic, and demyelinating causes.

These authors also mention one other cause of field defects—optic nerve pits. When this is the cause, the field defect usually is denser above the horizontal meridian, corresponding to the usual inferotemporal location of the pit on the optic nerve head. In my experience, one other cause of field defects can be confusing if one is not careful in performing the fields. I have seen four cases in which there was aqueduct stenosis with enlargement of the third ventricle, pressing down on the chiasm. This produced bitemporal defects, which were para-central and initially interpreted as cecocentral defects, since they extended more temporally than nasally. Careful observation of the patient's fixation and identification of the shape of the defect and the location of its densest part will usually clarify any confusion.

**GUN BARREL FIELDS**

Severe peripheral contraction of the fields—termed gun barrel fields or tunnel fields—is usually considered to indicate hysteria or malingering; however, organic causes of small central fields should also be considered. Glaucoma is probably the most common one. It is easily diagnosed at this stage by inspection of the disc. By the time the field is reduced to 5°, the cupping of the nerve head should be so extensive as to be obvious.

The next most common organic cause of gun barrel fields is retinitis pigmentosa. Patients with this condition, who have 5° fields, do not have the central acuity that persons with glaucoma have. Occasionally, the retinal pigmentary changes are minimal, and they may be missed when only the posterior pole of the retina is seen through a small pupil and if there is no family history to suggest the diagnosis. The atrophy of the disc is frequently interpreted as optic atrophy, the cause of which is unknown. Therefore, in persons with contracted fields, examination of the fundus when the pupils are dilated is mandatory. Particular attention should be paid to the equatorial region, where the pigmentation usually begins and is more likely to be seen.

Patients with cerebral vascular disease may develop bilateral hemianopia owing to occipital lobe infarction. Some of these patients have sparing of the macular projection in the occipital lobe and are thus left with 2 to 5° of field and good central acuity in both eyes. Such patients have a normal fundus and normal pupils.

This type of field defect may be seen in one eye if a central retinal artery occlusion occurs but the chorioretinal artery is spared. The chorioretinal artery supplies the fovea and preserves a small central field and good acuity. In such cases, optic atrophy is present. These cases differ from those involving occipital cortical infarction, in which the fundus has a normal appearance.

Severe contraction of the fields can also occur in extensive choroiditis. The condition is obvious on ophthalmoscopic examination.

**ARCUATE SCOTOMAS**

Arcuate scotomas are usually associated with glaucoma. Any patient with an arcuate scotoma should be investigated first and exhaustively for glaucoma. Other diseases and conditions occasionally cause an arcuate scotoma (Table 17.2).

**Optic Nerve Disease**

**PERIPHERAL AND CENTRAL FIELD LOSS**

The usual field defect in optic nerve disease is a central scotoma with or without peripheral field loss. Sometimes relative sparing of central acuity and pronounced loss of peripheral field are seen; for example, this
### Table 17.2. Some Causes of Arcuate Scotomas

<table>
<thead>
<tr>
<th>When Lesion Is at Disc</th>
<th>When Lesion Is of Anterior Nerve</th>
<th>When Lesion Is in Posterior Nerve and Chiasm</th>
<th>When Blind Spot Is Enlarged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juxtapapillary choroiditis</td>
<td>Ischemic infarct and segmental atrophy</td>
<td>Meningioma at optic foramen</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Colobomas and pits of optic nerve</td>
<td>Cerebral arteritis</td>
<td>Meningioma of dorsum sellae</td>
<td>Peripapillary atrophy</td>
</tr>
<tr>
<td>Drusen of optic nerve</td>
<td>Retrolubar neuritis</td>
<td>Pituitary adenoma</td>
<td>Drusen</td>
</tr>
<tr>
<td>Papillitis</td>
<td></td>
<td>Opticohiasmatic neuritis</td>
<td>Juxtapapillary choroiditis</td>
</tr>
<tr>
<td>Arteriosclerotic plaque in vessel on the disc</td>
<td></td>
<td>Myelination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tilted discs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colobomas</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slow patient response</td>
<td></td>
</tr>
</tbody>
</table>

occurs occasionally in syphilitic optic neuropathy (Fig. 17.30). The leading known cause of axial optic nerve disease with sparing of the peripheral field is demyelinating disease. (Other causes of axial—as opposed to periaxial—optic nerve disease are discussed elsewhere.)

**JUNCTION SCOTOMA**

Usually, if the lesion causing the loss of vision is located in the optic nerve, no features exist to identify what part of the nerve is affected; however, a lesion in one area of the optic nerve does have a sign that is of localizing value. This lesion occurs where the optic nerve joins the chiasm. The lower nasal fibers coming across the chiasm dip up into the opposite optic nerve for about 1 mm before they turn into the optic tract. A lesion so located causes not only a central scotoma in one eye but also an upper temporal field defect in the other eye (Figs. 17.31 and 17.32). The patient who has a central scotoma should have the upper temporal quadrant of the other eye examined carefully for an upper temporal field defect. The patient is usually unaware of such a field defect, since there is no central visual loss in that eye.

A lesion at the posterior aspect of the chiasm damages the posterior knee of Wilbrand. The expected defect is a lower temporal field defect in the ipsilateral eye, but it is rarely seen. An incongruous hemianopia is the most common defect. The location of the defect usually depends on whether the tract or the chiasm sustains more damage. Occasionally, there is encroachment on the macular crossing fibers, and a para-central homonymous defect occurs in the other eye, and a temporal defect occurs in the ipsilateral eye owing to involvement of the posterior knee of Wilbrand.

**Lesions Affecting the Chiasm**

**BITEMPORAL HEMIANOPIA**

The most common field defect caused by chiasmal disease is a bitemporal hemianopia that begins in the upper quadrants (Figs. 17.33 and 17.34) and occasionally in the lower quadrants (Fig. 17.35). Cushing tried to divide diseases that cause this type of field defect into two groups. Cushing's first group shows bitemporal hemianopia, optic atrophy, and roentgenographic changes, particularly enlargement of the sella turcica. This group is made up primarily of pituitary adenomas with an enlarged sella turcica, as shown on the roentgenogram. The second group shows bitemporal hemianopia, optic atrophy, and normal roentgenograms. This group is made up of meningiomas, craniopharyngiomas, and aneurysms. The second group does not have as negative an appearance on the roentgenogram as was once thought. Eighty-five percent of childhood
Figure 17.30.
Humphrey fields of patient with optic neuritis in the left eye secondary to syphilis. A. Disproportionate loss of the peripheral field in the left eye. B. Relative sparing of the central field and near-normal field in the right eye.
A lesion in the optic nerve where it joins the chiasm produces a junction scotoma consisting of a central scotoma in one eye (on the side of the lesion) and an upper temporal field defect in the other eye. In this example, the lesion was in the left optic nerve.

cranioopharyngiomas show suprasellar calcification. Occasionally, longstanding aneurysms have a curvilinear calcification that may be seen on routine roentgenograms. Suprasellar meningiomas are still difficult to visualize on plain roentgenograms, and the use of techniques that examine the suprasellar space, such as CT and MRI scans with contrast material, are required. Most J-shaped sellars are caused by gliomas of the chiasm; however, they can also be seen in patients with achondroplasia, osteogenesis imperfecta, Morquio syndrome, Hurler syndrome, Turner syndrome, hydrocephalus, and chondroectodermal dysplasia.

For years it was thought that the macular fibers crossed exclusively in the posterior chiasm and that a lesion in that area affected the macular fibers primarily. In the textbooks, such a lesion was described as causing a bitemporal paracentral defect. A common cause of such a field defect is enlargement of the third ventricle that causes the ventricle to press on the posterior chiasm from above and posteriorly when the chiasm is anteriorly placed. I have seen several such panmacular bitemporal field defects. My experience with lesions so located in the posterior chiasm is that they cause the usual bitemporal hemianopia or, occasionally, an optic tract defect with a hemianopia.

One of the more useful advances in chiasmal disease has been the finding of elevated prolactin levels in the blood of patients with diseases involving the pituitary-hypothalamic axis. This elevation of prolactin is not specific for these organs, but in combination with bitemporal visual field defects or an enlarged sella, it is certainly compatible with and highly suggestive of tumors affecting these organs. Other causes of elevated prolactin can be stress, pregnancy, breast feeding, intercourse, estrogen administration, some cases of primary hypothyroidism, occasionally secondary amenorrhea, renal failure, and some drugs such as thyrotropin-releasing hormone, phenothiazines, methyldopa (Aldomet), reserpine, and oral contraceptives. Elevated prolactin levels have also been reported in diseases of the hypothalamus such as sarcoidosis, Schüller-Christian disease, and craniopharyngioma. These diseases of the
- **Figure 17.32.**

  Humphrey fields demonstrating a junction scotoma. A. Central scotoma in the left eye. B. Upper temporal field defect in the right eye.
hypothalamus cause an elevated prolactin level by interfering with the pituitary-hypothalamic axis. The hypothalamus secretes a prolactin-inhibitory factor (PIF), which regulates the level of prolactin in the bloodstream. When this inhibitory factor is not secreted in sufficient amounts owing to some local disease, then the prolactin level can rise. It is important to note that lack of an elevated prolactin level does not rule out a pituitary tumor; however, in view of a patient's signs and symptoms, with or without field defects, an elevated prolactin level is certainly confirmatory evidence of such a tumor being present.

In the past, many surgical procedures involving the pituitary gland were difficult to do without encountering some further damage to the chiasma that was overlying it. The transsphenoidal approach using microsurgery has been a tremendous step forward in managing these tumors and reducing the morbidity to the patient and to his or her visual status. A review by Laws, Trautmann, and Hollenhorst of a fairly large series of tumors managed by this surgical approach shows that the visual result has been at least as good, if not better, and that the patients in general have been immeasurably better than by the subfrontal craniotomy approach. There are some limitations, however, as to the patients for whom this procedure is appropriate. This surgical approach is best selected for patients with an adenoma confined to the sella turcica, those with cerebrospinal fluid rhinorrhea, and those with tumors extending into the sphenoid sinus. It also is indicated for tumors with paracentral scotomas. This latter field defect indicates retrochiasmal extension, a prefixed optic chiasm, or a tumor that is difficult to remove by means of the standard subfrontal approach. Some tumors with suprasellar extension can also be removed by this technique, but this is more difficult and is related to the experience of the surgeon. Several groups of patients are not candidates for this approach. Those patients with a dumbbell type of adenoma, in which there is tumor not only in the fossa but also through the diaphragma sella, are not good candidates for this approach. Lateral suprasellar extension, massive suprasellar tumor, or an incompletely pneumatized sphenoid sinus all preclude this surgical approach. The greatest advantages of this procedure are that the op-
• Figure 17.34.
Humphrey fields of a patient with an asymmetric bitemporal hemianopia. A. Left field. B. Right field.
tlc nerves are directly visualized through the microscope, and therefore, less surgical damage can result during the extirpation of the tumor. This approach through the sphenoid sinus rather than through a craniotomy is much less stressful for patients, and many of them are up and around comfortably the next day.

The symptoms of lesions in the chiasmal area usually develop slowly. The field defect is often not noticed, nor does the patient complain about it. If the patient has any visual complaints, they are typically interpreted as a central acuity deficit. In children, it is unexpected by a patient's symptoms change in moplegia, which is considered a prompt nee.

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Figure 17.34. (continued)
C, D. MR images of the same patient show a lesion at the chiasm consistent with a craniopharyngioma.

Figure 17.35.
Bitemporal hemianopia that is asymmetric and begins in the lower quadrants suggests a lesion above the chiasm.
Visual Field Defects • 569

visual complaints, they are made when the central acuity fails; a defect that is interpreted as a need for different eyeglasses. In children, loss of vision that cannot be corrected by glasses may signify a glioma. When a bitemporal hemianopia is found in a patient who has had a sudden onset of symptoms (including severe headaches), change in level of consciousness, ophthalmoplegia, and pituitary apoplexy must be considered. Most of these patients require prompt neurosurgical intervention.

Recent work suggests that junction scotomas related to Wilbrand’s knee are an artifact. The evidence is not convincing. However, in practice we all have seen junction scotomas, and they are located where we expect them to be, regardless of the traditional anatomic explanation.

NASAL FIELD DEFECTS

Nasal field defects are usually intraocular in origin. However, giant internal carotid aneurysms commonly produce uniocular nasal field loss. They compress the lateral aspect of the optic nerve as it goes intracranially and before it enters the chiasm. As it enlarges, it can affect the crossing nasal fibers from the contralateral eye, causing an upper temporal defect in the contralateral eye. Patients with this type of aneurysm may present with just a central scotoma or junction scotoma. Other causes of compression in the anterior chiasm that may cause nasal field defects are meningioma, anterior communicating aneurysm, dolichoectatic artery, pituitary apoplexy, and chromophobe adenoma. Ischemic optic neuritis, drusen, glaucoma, optic nerve pits, and chronic papilledema also can lead to nasal field defects.

Binasal field defects are infrequently seen, but it is important that they be recognized (Fig. 17.36). The most common cause of binasal field defects is glaucoma, not a chiasmal lesion. Other causes of binasal defects are drusen and chronic increased intracranial pressure. The internal carotid arteries are located just lateral to the chiasm, and compression of the chiasm by arteriosclerotic carotid arteries allegedly causes compression of the crossing temporal fibers and thus produces a binasal field defect. A more plausible explanation of the binasal field defect is that the arteriosclerotic process that affects the internal carotid arteries also

![Figure 17.36.](image)

A binasal field defect, although uncommon, also suggests a chiasmal lesion.
affects the nutrient arteries to the lateral chiasm.

FALSE LOCALIZING HEMIANOPIA

Bitemporal hemianopia has always been associated with a chiasmal lesion; however, there are cases of falsely localizing bitemporal hemianopia. Third ventricle enlargement from any cause results in compression of the posterior chiasm. Sylvian aqueduct stenosis causes enlargement of the third ventricle and secondary compression of the chiasm. In such a case, the disease is somewhat remote from the chiasm proper. Associated signs of the sylvian aqueductal syndrome, such as paralysis of up-gaze, retraction nystagmus, and light-near dissociation of the pupils, should help establish the true location of the primary lesion.

Another cause of falsely localizing bitemporal field depression is tilted optic discs.

TILTED-DISC SYNDROME

Tilted-disc syndrome is a rare cause of bitemporal field depression. Characteristically there is a situs inversus of the disc, with a tilting of its vertical axis in an oblique direction (Plate 17.11, C and D). In about 80% of cases, the condition is bilateral. A temporal hemianopia also exists; if bilateral, it gives the impression of a bitemporal hemianopia owing to chiasmal disease (Fig. 17.37). The hemianopia is peripheral, and it is not progressive. The patient may have a large increase in myopic correction in the lower fundus, compared with the upper fundus. If such is the case, repeating the field examination with an increase in the myopic correction may cause the bitemporal defect to decrease or disappear. Besides tilting of the disc and myopia, thinning of the retinal pigment epithelium and of the choroid is also present in the tilted-disc syndrome.

Optic Tract Lesions

Lesions of the optic tract characteristically give rise to incongruous homonymous hemianopia (Figs. 17.38 and 17.39). If the defect is gross in both the patient's eyes, its homonymous and incongruous nature is easily identified. If the defect is subtle and highly incongruous, however, the homonymous nature of the defect may be missed. In a field defect that involves a hemianopia in one eye, a careful search should be made for a homonymous defect in the other eye. It is in just such a situation that the Chalmers step test, perhaps using color, is of great value.

Newman and Miller also demonstrated an afferent pupillary defect in some patients with optic tract lesions. Savino and coauthors had a similar experience. In general, the denser or more complete the optic tract lesion, the more likely was the presence of an afferent pupillary defect. Therefore, in cases of a complete homonymous hemianopia in which the anatomic location of the lesion is not immediately obvious, an afferent pupillary defect confirms the location in the optic tract.

Lesions of the Lateral Geniculate Body

Lesions of the lateral geniculate body (LGB) have usually been thought to give rise to incongruous field defects exclusively. However, evidence from a scattering of cases suggests that both congruous and incongruous defects can be produced by LGB lesions.

The blood supply through the anterior hilus and the anterior and lateral aspects of the nucleus of the LGB develops from the anterior choroidal branch of the internal carotid artery. Occlusion of that artery produces an upper- and lower-sector field defect (Fig. 17.40). The remainder of the nucleus receives its blood supply through the lateral choroidal artery, which is a branch of the posterior cerebral artery. Occlusion of that artery produces a homonymous horizontal sectoranopia (Fig. 17.41).

The LGB is structured in a six-layer stratum, with certain fibers allocated to each layer. Starting in a ventrodorsal direction,
**Figure 17.37.**
A bitemporal defect caused by tilted optic discs does not come to the vertical meridian as does the defect chiasma stemming from chiasmal disease (Fig. 17.35). This is an example of a false localizing hemianopia.

**Figure 17.38.**
An incongruous homonymous hemianopia suggests a lesion in the optic tract.
Figure 17.39.
Humphrey fields of a patient with a lesion in the right optic tract demonstrate an incongruous homonymous hemianopia. The defect is greater in the left eye (A) than in the right eye (B), indicating that the lesion is on the right side.
- Figure 17.40.

A. B. Goldmann fields demonstrate a defect involving the upper and lower sectors. This defect resulted from occlusion of the anterior choroidal artery, which supplies part of the lateral geniculate body. A. Left field. B. Right field.
• **Figure 17.40. (continued)**

C. Humphrey representation.
*Figure 17.41.*

A, B. Goldmann fields showing homonymous horizontal sectoranopia secondary to occlusion of the lateral choroidal artery, which supplies part of the nucleus of the lateral geniculate body. A. Left field. B. Right field.
layers 1, 4, and 6 have crossed fibers, and the ipsilateral fibers terminate in layers 2, 3, and 5. The macula accounts for most of the lateral geniculate nucleus, with corresponding points representing contralateral and ipsilateral points aligned along the vertical axis. The separation of the crossed and uncrossed retinal fibers into separate visual fiber columns and separate vascular compartments allows partial lesions of the lateral geniculate body and, therefore, incongruous field defects. This particular aspect of the vascular supply was demonstrated by Galloway and by Fujino. Gunderson and Hoyt reported two cases of an incomplete lateral geniculate lesion with incongruous...
field defects from a vascular lesion (arteriovenous malformation) in one instance and a tumor (astrocytoma) in the other. However, Fricsen, Holmgaard, and Rosencrantz have reported cases of vascular lesions producing congruous homonymous horizontal sectoranopias. Thus, there is evidence of both kinds of field defects when certain parts of the nucleus are differentially defective. Lesions of the LGB may produce field defects similar to those seen in optic tract lesions and with optic atrophy in the superior and inferior temporal poles of the optic disc ipsilateral to the lesion and a horizontal band-shaped pattern contralateral to the lesion. Sometimes the defect is more subtle and is seen only in a careful evaluation of the nerve fiber layer.

**Cerebral Lesions**

**TEMPORAL LOBE**

Field defects resulting from temporal lobe lesions are homonymous, and they always begin at the vertical meridian. Therefore, in a patient suspected of having a temporal lobe disease, the vertical meridian is the field area to concentrate on. Since a large area in the tip of the temporal lobe has no fibers of Meyer's loop, tumors in this area will not produce a field defect. If the tumor encroaches on these fibers and causes an early defect (which often is subtle), the mass may be large. Use of color can also be of value in detecting minimal temporal lobe field defects as well as chiasmal and optic nerve defects.

Presence of other neurologic symptoms, such as seizures and formed visual hallucinations, suggests possible temporal lobe disease and calls for prompt and careful inspection of the field. Since the fibers of Meyer's loop spread out, the field defect progresses through the upper quadrant of the field in a stepwise fashion. The fibers of the lower field, which are in a tight bundle, are affected as a group. Therefore, the field in the lower quadrant is lost as a unit, a phenomenon that differentiates the defect from one in the upper quadrant, in which the field is lost progressively from the vertical meridian down to the horizontal raphe (Figs. 17.42, 17.43, and 17.44). The rate of field

*Figure 17.42.*

Homonymous hemianopia that is congruous and densest at the vertical meridian suggesting an anterior temporal lobe lesion.
- Figure 17.43.
The field loss associated with a temporal lobe lesion occurs in stepwise progression in the upper sectors, resulting in a full quadrantanopia.

- Figure 17.44.
In a patient with a temporal lobe lesion, the field in the lower quadrants is lost as a unit, not in stepwise progression as occur in the upper quadrants. Thus, a full homonymous hemianopia appears after the quadrantanopia illustrated in Figure 17.23.
loss in the lower quadrant differs from that in the upper quadrant because of a difference in anatomy rather than a difference in the growth of the tumor.

The question of whether temporal lobe field defects are congruous or incongruous is still a matter of controversy. In my experience, most temporal lobe field defects are incongruous; however, some are definitely incongruous. This finding has also been the experience of others. The reason for the variation is not clear, but the presence of these two different types of field defects as the result of lesions in the same area is a clinical fact. One proposed explanation of the incongruous nature of some temporal lobe field defects is that the temporal lobe tumor exerts pressure medially and compresses the tract, as proposed by Anderson.

PARIETAL LOBE

Field defects caused by lesions in the parietal lobe are described as homonymous hemianopias that have the densest part of the defect in the lower field (Fig. 17.45, A and B). Patients with a parietal lobe field defect may also have a defect in the horizontal optokinetic response as well as right-left confusion, finger agnosia, dysgraphia, dyscalculia, or dyslexia. These signs, which can be easily tested by the perimetrist, help in the interpretation of any field defect that is found.

Two signs of parietal lobe disease are of particular interest and require further comment—the extinction phenomenon and the motor impersistence sign. If the ophthalmologist cannot find a field defect in a patient who has been referred for the evaluation of a field defect, the ophthalmologist should not assume that the referring physician made an error. The patient may have the extinction phenomenon, which can be detected only when the nasal and temporal fields are examined simultaneously. Such an examination can best be done with the confrontation field technique. Simultaneous stimulation of both fields is not routinely or

![Figure 17.45](A. Homonymous hemianopia with the densest defect in the lower quadrants results from a lesion in the parietal lobe.
easily done with most of the instruments used for performing field examinations, so the extinction phenomenon is usually missed.

The motor inperstience sign is also frequently missed. Patients with the motor inperstience sign cannot maintain a willed motor act, a condition that manifests itself by the patient's inability to maintain fixation. Because the patient cannot maintain fixation, it is almost impossible to do an accurate field examination. Such a patient seems intelligent enough to perform the test but also seems cantankerous, a combination that brings the physician close to frustration and even anger. The physician who has a right-handed patient should conscientiously identify the area of the field that is impaired by the patient’s inability to maintain fixation. A good check for this condition is done quick fixation—on a degree of peripheral vision. Other signs of inperstience should be recorded in the patient's case history.

**OCCIPITAL HEMIFIELD LOSS**

The field of the visual pathway passes through the occipital lobe and is responsible for color perception and form identification. A field loss in this area indicates that some component of the pathway is missing. The patient may perceive light that is not actually present.

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*Figure 17.45. (continued)*

B. Humphrey representation.
handed patient who fits this description should consider the possibility that the patient may have right-sided parietal disease and may thus be unable to maintain fixation. A good confrontation field examination done quickly—before the patient can shift fixation—may readily demonstrate a large degree of hemianopia, at which point the physician should examine the patient for the other signs of parietal lobe disease (described above).

**OCCIPITAL LOBE**

The field defects resulting from occipital lobe disease are varied; they include homonymous hemianopias, homonymous quadrantanopias, altitudinal defects, paracentral and midzone defects, as well as cases of splitting and sparing of fixation (Figs. 17.46 through 17.52).

The Riddoch phenomenon is an infrequent but valuable sign of occipital lobe disease. In occipital lobe infarction with hemianopia, perception of motion before perception of form indicates the Riddoch phenomenon and some recovery in the occipital lobe. The patient does not perceive a steady non-moving light that has been projected into the blind field until the light moves. The Riddoch phenomenon does not indicate full recovery from the field defect, but it is a sign of improvement. The phenomenon occurs in occipital lobe field defects, but others feel its value is only lateralizing to a hemisphere.

Some patients with occipital lobe disease complain about paracentral defects, which are located near the center of vision and thus interfere with reading. When such patients are examined, their vision and peripheral fields are found to be normal. Many physicians believe that when visual acuity is normal and no central defect exists, there is no need to examine the central field; however, the possibility of a paracentral field defect (Fig. 17.51) shows that this conclusion is unjustified.

Homonymous hemianopia suggesting a lesion in the calcarine cortex (Fig. 17.46) can, on rare occasions, be a false localizing sign. In such a case, the true disorder lies in the frontal lobe. Frontal lobe tumors can cause displacement of the brain, which compresses the posterior cerebral arteries as they cross over the tentorial edge, causing an occipital lobe field defect. Therefore, what initially was considered a vascular cause

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**Figure 17.46.**

Congruous homonymous field defect suggesting an occipital lobe lesion.
A. An altitudinal hemianopia results from lesions involving both sides of the calcarine cortex in the occipital lobe.

appears on a radioisotope brain scan to be two lesions and can be misinterpreted as metastatic disease because of the multiple defects. However, only one tumor (which is probably surgically accessible) exists in the frontal lobe. A brain scan repeated 6 weeks later will show some resolution of the occipital lobe lesion, which essentially rules out an occipital lobe tumor. The frontal lobe lesion would show no change on the scan—a finding that suggests the diagnosis to the physician. A CT or MRI scan will show a difference in tissue density on the initial scan, suggesting that one lesion is a tumor and that one is an infarction. This scan provides immediate evidence in contrast to the comparison scan, which requires a 6-week waiting period.

Sometimes, the time of onset of the homonymous hemianopia is inaccurately reported. Patients may say that the onset was acute (an acute onset suggests a vascular cause), but they may be referring to the time that they first noticed the condition, not to when the condition first occurred. Simons and Cogan have suggested the use of the optokinetic test for identifying tumors from a vascular source in cases of occipital lobe homonymous hemianopia. They have stated that if the horizontal optokinetic response is normal in a patient with an occipital lobe homonymous hemianopia, the cause of the field defect is most likely vascular. If the optokinetic response is abnormal, a tumor is more likely to be the cause. The rationale behind this distinction is that a tumor will readily localize to the occipital lobe, but it will encroach on the parietal lobe and the optokinetic pathway. Horizontal homonymous visual field defects have been seen in LGB lesions. It has also rarely been reported in lesions of the occipital cortex.

The occurrence of macular sparing versus macular splitting as a sign of occipital lobe lesions has raged for years. One form of this sparing occurs when the patient fixation eccentrically and moves the entire hemianopic field over. The patient does not spare just the 2 to 5° around fixation but all up and down the vertical meridian (Fig. 17.49). There are examples, however, of occipital lesions that do spare the central 2 to 5° even when there is a total homonymous hemianopic defect around this area (Fig. 17.50).

B. Humphrey rep
The concept that vision is cut down the middle evenly and exactly in every person is anatomically precise, but it probably is not true. Young, in his examination of visual field defects in the radiations, postulated that there is no sharp vertical line exactly at the vertical meridian but rather that it may be off by several degrees on either side. Morax proposed that the foveal area of the retina of each eye is composed of a mixture of both crossed and uncrossed fibers. This overlapping of crossed and uncrossed fibers, at least in the foveal area, has been shown to be present in cats and in the primate monkey.
**Figure 17.48.**
Homonymous hemianopia that splits right through fixation may result from an occipital lobe lesion, although a similar defect also occurs with temporal lobe lesions (Fig. 17.44).

**Figure 17.49.**
Spurious sparing. A. Not just 3° around fixation is spared, but the entire hemianopic line is moved over when the patient fixates eccentrically. This is an aberration of the computed field and not true sparing. Humphrey fields demonstrate a dense homonymous hemianopia with some sparing near the midline.
• Figure 17.49. (continued)
D. A CT scan of the same patient reveals a subtle but definite right occipital infarct.

• Figure 17.49. (continued)
E. Another case of Humphrey representation of spurious sparing.
• Figure 17.50.
A. Homonymous hemianopia that spares 3° around fixation indicates an occipital lobe lesion. B. Humphrey representation.
- Figure 17.51.
Some patients with occipital lobe lesions exhibit paracentral defects. In this example, a paracentral homonymous congruous hemianopsia, the lesion is in the left occipital lobe.

- Figure 17.52.
Spinal field of hystere. All points marked are with the same test object. x represents the first time the field is tested; o, the second time; and O, the third time. Note the progressive contraction of the peripheral field.
Cowey's experiments are the most interesting in this regard. In monkeys who had undergone occipital lobectomies, Cowey performed single-cell recording in the foveal receptor area of the other occipital lobe. When he stimulated a single retinal foveal cell, he got responses in the foveal area corresponding to the area served by the extinguished occipital lobe from the other side. The assumption then is that the surviving occipital lobe has projections to both sides of the vertical meridian of the fovea. McIwain came to a similar conclusion from experiments on the LGN.

Advocates of the bilateral representation theory point to surgical cases in which unilateral total occipital lobe removal resulted in a complete homonymous hemianopia with sparing. The final evidence to explain this phenomenon has not yet been put forward. The most recent evidence for bilateral representations was put forth by Bunt and Minckles, who confirmed the work of Stone. They demonstrated with neurosonography using horseradish peroxidase that a 1° strip of cells along the vertical meridian of the dorsal lateral geniculate nuclei represented both ipsilateral and contralateral ganglion cells. In the area of foveal representation, this area increased to 3°. These labeled ganglion cells were found along both the nasal and temporal rim of the foveola, suggesting bilateral representation.

Inouye and Holmes studied the correlation of visual fields and damage to the striate cortex in soldiers with war injuries, which led to their retinotopic map of the striate cortex. This has been the basis of our thinking since the early 1900s. They assign 25% of the striate cortex to the central 15° of vision. Early computer tomographic studies correlating injury to field loss seem to correlate closely to those figures. However, examination in the primates like the macaque monkey suggest that some 15% of central vision is represented by over 70% of the striate cortex. This is considerably more than previously attributed to the human striate cortex. Horton and Hoyt studied this discrepancy by using MRI on their patients and found a close correlation between human and macaque monkey striate cortex. Their findings compare favorably with the work of Daniel and Whitteridge and Van Essen, whose estimate was about 55 to 60% of striate cortex devoted to macular vision.

Daniel and Whitteridge mapped the macaque striate cortex and developed a theory called the linear magnification factor. They theorized about the amount of cortex represented per degree of visual field. This ratio begins at a ratio of 40:1 and decreases toward the periphery.

One of the cases of Horton and Hoyt demonstrated macular sparing. They concluded that the macular magnification factor is an explanation for macular sparing. The macular vascular supply is primarily via the posterior cerebral arteries. In about 25% of patients, that is also an extra vascular supply from the middle cerebral artery. If the posterior cerebral artery is occluded, then the branch from the middle cerebral artery may preserve a part of the macular projection. This is similar in theory to the chiasmatic artery preserving macular vision when the central artery is occluded. As mentioned above, the linear magnification factor of the macular projection allowed preservation of central vision of only a small area of striate cortex.

**COLOR DEFECTS**

As discussed above, the use of color as a reduced stimulus for measuring subtle field defects is well known. However, lack of appreciation of colored stimuli may also result from the differential effect of some diseases or fibers sensitive to color, as occurs, for example, in early optic nerve disease. Another form of color defect is the congenital variety, which is seen to various degrees in about 6% of the male population. This latter type of color defect is throughout the entire visual field and should not cause a localized field defect. These defects in color testing are
commonly known by any perimetrist. A more rarely encountered form of color loss occurs secondary to a lesion of the central nervous system. Patients with central loss of color can be subdivided into two broad groups. Those in one group have an intellectual problem in recognizing or naming colors but have no specific color defect. Those in the second group are intellectually intact and have excellent acuity to perceive color but have a central color defect (cerebral dyschromatopsia) in the cerebral cortical area that appreciates colored information.

Patients with a specific aphasia for naming colors do exist, but commonly they also have other forms of aphasia. This color-naming aphasia can be demonstrated by testing patients with the pseudoisochromatic plates. They will see the most subtle plates if they have no congenital color defect, attesting to the fact that the defect is not in seeing colors; yet, they will miss naming the bright green color of a large watermelon, indicating that the defect is in naming colors and is acquired. This defect appears to be more common with left hemisphere lesions, according to Benson and Greenberg and to Geschwind, who believe that the lesion is in the corpus callosum. Some patients who have difficulty in naming colors appear to have visual agnosia. There is some controversy concerning the existence of this particular disorder, but there have been several excellent cases to support its existence. Patients with visual agnosia cannot recognize objects and thus cannot name the appropriate colors. There is nothing wrong with their ability to see the object (acuity) or their color appreciation, since they see the subtle, hidden symbols in the color plates. Furthermore, such patients can name the correct color of an object if given other sensory stimuli, such as touching the object. For example, a patient who feels a banana and knows it is a fruit that is long and slim can recognize it as a banana and make the appropriate association.

In experimental studies with monkeys, Zeki demonstrated color-responsive cells in the fourth visual area. This area may be considered comparable to an area in the human occipital cortex that has been implicated in cerebral dyschromatopsia. In the few cases studied postmortem, the comparable area in humans involves the fusiform and lingual gyri.

Determining whether an individual patient has a congenital color defect or acquired cerebral dyschromatopsia can be difficult. Green and Lessell noted three differential features between the two conditions: In cerebral dyschromatopsia, the color defect is random and does not follow any pattern such as protanopia or deutanopia. If patients with cerebral dyschromatopsia are tested with the pseudoisochromatic plates, they do not see the confusion numbers. Patients with cerebral dyschromatopsia also exhibit field defects, although these field defects cannot account for their extensive loss of color appreciation. Vascular disorders are the most common cause of cerebral dyschromatopsia, but Green and Lessell reported two cases secondary to a tumor.

The disproportionate loss of color function versus loss of acuity, field, or other cerebral functions may be secondary to selective loss of certain groups of cells. Zeki identified, in monkeys, columns of cortical cells that were responsive to certain color stimuli. Although it is hard to imagine that a vascular episode or even less so, a mass lesion would disproportionately affect such a small population of cells, nevertheless it occasionally does occur. One explanation may be suggested from experiments demonstrating a decrease in color function at high altitudes, where there is lower oxygen saturation. In these altitude experiments, color was affected before vision and fields. This may also be the case in cerebral ischemia.

POSITIVE PERVERSION OF THE VISUAL SYSTEM

Alterations in vision or field may be negative or positive. Decreases in visual acuity or hemianopic field defects are examples of
negative alterations in the visual system. Hallucinations, allesthesia, perseveration, and palinopsia are examples of positive alterations in the visual system.

Visual perseveration is a continuation or repetition of a visual stimulus after it is no longer present and actively stimulating the retina. Visual perseveration occurs as a normal phenomenon, such as the afterimage of a strobe light shined in an eye. The length of time the phenomenon lasts is related to the intensity of the stimulus and the length of time of exposure. That is why a bright light such as a strobe light has a longer afterimage than a weak flashlight or a table lamp. All stimulate the retina and may do so for the same interval of time, but all do not have the same intensity effect on the retina.

Palinopsia is an abnormal extrapolation of the normal phenomenon of perseveration. The patient may see a face on television and at different times have that face appear as though it were on the TV at that moment. This differs from hallucinations, since this visual phenomenon actually occurred as the initial episode. It also differs from the visual phenomena of patients with migraine, retinal detachment, or posterior vitreous detachment, which constitute abnormal stimulation of the visual system. Tumors, vascular lesions, and, occasionally, trauma have been reported to cause palinopsia. Palinopsia occurs with other defects in the visual system and usually means involvement of the occipital parietal area.

Visual allesthesia is the transference of images from one half-field to the other, with palinopsia of those images. Studies on a small number of patients with visual allesthesia reported EEG abnormalities also in the parietal occipital area. These patients had not only field defects but also other evidence of seizure activity.

**FUNCTIONAL VISUAL LOSS**

Hysteric and malingering types of visual loss are similar; only the underlying psychologic reasons for the loss vary. This discussion, therefore, treats both types of functional visual loss and the tests used to establish the functional nature of the conditions.

As in most branches of medicine, in ophthalmology, the most difficult patient to evaluate is the one who has an organic disorder with a lot of functional overlay. Therefore, in every patient in whom a functional loss of vision is suspected, every effort must be made to rule out organic disease; and the patient must be reexamined and the regular intervals to check the clinical findings.

**Loss of Central Visual Acuity**

The loss of central vision is a common functional complaint. If the loss is related to emotional gain rather than to financial gain, it is usually bilateral. Bilateral loss of vision allows persons to become completely dependent and to retreat from whatever it is that they feel they can no longer cope with emotionally. Persons with loss of vision in only one eye would still be expected to cope with their problems. Monocular functional loss of vision does occur, however, and the condition is usually related to accidental trauma to or around the eye. Frequently, the patient is involved in litigation concerning an insurance claim. In organic monocular loss of vision, some clinical findings should exist in support of the patient's complaints, for example, changes in the fundus (such as destructive lesions), changes in the macula, optic atrophy, and cataract. A common exception to this rule occurs in retrolubular neuritis, in which nothing is shown initially on ophthalmologic examination except the afferent pupillary defect.

Patients with bilateral organic loss of vision are more difficult to diagnose. Organic lesions at the chiasm may not show optic atrophy for some time. Persons with occipital cortical blindness do not show any changes on ophthalmoscopy, and their pupils are essentially normal.

Patients who complain of loss of central vision but who have a full peripheral field should be considered as having an organic
lesion. Those with functional loss of central vision usually have severe contraction of the field. The person with retrobulbar neuritis has loss of central vision, a normal fundus, and usually a full peripheral field; however, it cannot be inferred that the opposite clinical finding—loss of central vision with severe contraction of the field—is always functional.

TESTING OF VISUAL ACUITY
A painstaking examination of only the visual acuity may be all that can be accomplished on the patient’s first visit. The examination may take an inordinate amount of time. (In such an examination, the patient’s vision has been referred to as “iron maiden vision,” since the physician seems to be like the torturer of old, applying repeated pressure until the “correct” answer is forthcoming from the patient.) As the physician uses different techniques to measure acuity, the patient’s vision may slowly improve from 20/200 to close to 20/20. A return of normal acuity on prolonged testing indicates that the initial loss of acuity was functional. Thirty minutes of testing does not improve organic loss of vision.

Another form of acuity testing involves comparing near and distance acuity. In organic disease, both types of acuity are either the same or within one Snellen line of each other.

In monocular loss of vision in which an obvious cause cannot be determined by ophthalmoscopy, the use of the afferent pupillary defect may be of value in establishing organic optic nerve disease. The method of eliciting this sign is discussed elsewhere.

Acuity testing can be done at distances other than 20 feet or 14 inches. For instance, have the patient walk 10 feet to the chart and then read the letters. The letters that were 20/100 at 20 feet will then be equal to 20/200, a relationship that can be applied proportionately to all the other lines of letters.

CYCLOPLEGIC TEST
A carefully done refraction, with and without a pinhole test, is always the first step in evaluating decreased vision. The second step is cycloplegic refraction, which can rule out such problems as spasm of accommodation and latent hyperopia.

In monocular functional visual loss, a cycloplegic refraction can also be of value. Both eyes should be completely corrected for distance, and the acuity of each eye then tested separately. Since patients are aware of when the eye with the poor vision is being tested, they give the same response about poor vision as before. The physician then puts a plus 2.50 sphere in the Phoroptor before the eye with the alleged decreased acuity. The sphere blurs that eye for distance. The visual acuity is then tested with both eyes uncovered behind the Phoroptor, and the patient reads the distance chart again. Patients do not usually resist this test since they can explain a correct reading of the chart by the fact that they were reading the chart with just the good eye. The physician should then flip down the near card at 16 inches and ask the patient to read it, again with both eyes. Since the normal eye is under cycloplegia without an appropriate add, the affected eye, which has the proper add, is the only eye capable of reading the chart at 16 inches. Since the patients know that the eye they are complaining about was blurred at a distance with both eyes open, they assume that it will be blurred at 16 inches. If the test is done quickly—before the patients think to close each eye separately to check which eye is seeing at close range—they fall into the obvious mistake.

RED-GREEN TEST
Another useful test for revealing functional loss of vision with the Phoroptor involves the red-green filters. To do this test, the physician seats the patient behind the Phoroptor and does the same refraction with the proper correction for distance. A red filter is placed in front of one eye and a green filter in the other so that the patient sees the green only. The patient reads the chart with the eye for distance, and the eye which is seeing the letters, however, the phy...
filter in front of the other. Then the physician puts the red-green slide in the projector so that the letters projected on the screen are green on one side and red on the other side. The patient sees the red letters with the eye with the red filter and the green letters with the eye with the green filter. This test is usually not very effective, because the patient can easily check which eye sees which set of letters. When a battery of tests is being done, however, any one of them may give the clue the physician seeks.

**POLARIZING TEST**

In a clever variation of the red-green filter test, polarizing lenses are used. The red-green slide is taken out of the projector and is replaced by a polarizing lens, which orients half the line of letters at 90° to the other half. Then the polarizing lenses are placed in front of each eye so that one eye sees the half of the chart that has its letters similarly polarized. At first glance, this test would seem to present the same problem as the red-green test. The patient can close each eye separately to check which eye sees which half of the chart. The difference between the tests, however, is that the polarization of the projected letters can be switched by changing the direction of the polarizing lenses with a silent twist of a knob. As a result, the patient’s right eye can be seeing the right half of the line of letters one instant and the left eye the right half of the line of letters the next instant. If the polarization is changed quickly and quietly and if the physician remembers which eye saw which half of the line of letters, the patient with a functional loss can be led into reading with the affected eye.

**OPTOKINETIC TEST**

Use of the optokinetic tape may be of value in examining patients who complain of such severe monocular or binocular loss of vision that they cannot even accurately count fingers placed directly in front of them. Patients should be instructed to look steadily ahead, even if they cannot see an object on which to fixate. The optokinetic drum or tape should be moved in the horizontal direction and any response sought. If a response occurs, the test should be repeated at different distances until no response occurs. Obviously, a response with small targets (like the stripes on the drum at 10 feet) and an inability to count fingers at even 6 inches are incongruous findings. The physician cannot give a Snellen evaluation of the patient’s vision but can certainly say that doubt exists as to the degree of the patient’s visual loss.

Sometimes, if patients show no response to horizontally displayed optokinetic targets, changing the targets so that they move in a vertical direction may catch them off guard; they may forget to ignore the optokinetic target and give a positive response.

**MIRROR TEST**

The mirror test is also used for patients complaining of extremely poor vision in one or both eyes. Patients are asked to look straight ahead and not move their eyes. The physician holds a 12- by 12-inch mirror about 2 feet in front of the patient’s eyes. When patients say that they cannot see the mirror, the physician reassures them that it is not necessary to see the mirror but it is necessary to hold their eyes still. While talking to the patient about something other than the test, the physician moves the mirror very slowly from side to side. Patients whose eyes move are able to see better than they admit, and the defect can therefore be considered functional.

**Peripheral Field Loss**

The traditional field defect of hysteria is the spiral field defect (Fig. 17.52). The spiral field gets progressively smaller as the peripheral isopters are reexamined—a phenomenon that can also be a sign of fatigue, particularly in very ill patients. The same
phenomenon is frequently seen in patients subjected to a protracted field examination. The length of time a patient can be expected to submit to a field examination varies from patient to patient, but the problem must be kept in mind as the perimetrist does the field tests.

Contraction of the peripheral field is a much more common finding in functional field loss than in spiral field defect. The organic causes of gun barrel fields have been discussed above. To distinguish functionally small fields from organically small fields, the examination should be done at two different distances. If the field defect at 1 m is 10° with a 1-mm test object, it should be 10° at any distance with a comparable test object. Therefore, to duplicate the testing circumstances, the patient should be moved back to 2 m from the tangent screen, and a 2-mm test object used (Figs. 17.53 and 17.54). The patient should again show a 10° field defect; however, the area in the tangent screen that was the 10° isoperter is now the 5° isoperter at 2 m, and the isoperter that previously was 20° is now the 10° isoperter. The field of vision, therefore, covers a larger area on the screen. The patient who does not see the 2-mm test object until it comes into the original 10° isoperter on the tangent screen has a functional field loss. This patient is reporting that the field is smaller at 2 m than it was at 1 m.

A mistake the perimetrist may make in doing this test is to forget to double the size of the test object when he or she doubles the testing distance. The physician who does not double the size of the test object is not duplicating the test. The 1-mm test object at 2 m is one-half the size of the 1-mm test object at 1 m on the retina; therefore, the test is not the same. A less sophisticated, but effective and dramatic, way to illustrate this fact is as follows. The patient demonstrates a 10° field to a 3-mm white test object at 1 m. The physician then backs away about 12 feet and asks the patient to cover one eye and to fix on the physician's nose with the other eye. The physician uses his or her hand as a test object and asks the patient to tell when the hand is seen. Obviously, the physician's hand is larger than 36 mm, which is the size of the test object that would have to be used to duplicate the test performed at 1 m. The physician then brings the hand in from the periphery until the patient sees it. If the area in which the patient sees the hand is no

- Figure 17.53.
Results of field examination with a 5-mm white test object at 1 m show a 10° field.

- Figure 17.54.
A patient with organic fields on the same screen subject twice the clinical appearance in terms of size and shape.
larger than the area the patient saw on the tangent screen at 1 m, the defect is a functional one.

The usual field-testing technique involves going from nonseeing to seeing. In patients with very small fields, it may be of value to go from seeing to nonseeing. The physician should ask patients to say when they do not see the test object. A considerably larger field may be found by this technique. The physician must judge whether it is a true field or whether the "larger" field has resulted from a slow response from a dull or obtunded patient.

As discussed above, color has its uses in testing for peripheral field loss. A functional loss may be revealed by determining fields with differently colored test objects. The size of fields in response to colored test objects differs in a specific way; that is, when all objects are the same size, the smallest field is obtained with a green object, the next larger field with a red object, and the next larger with a blue object. If any reversal of this order occurs, the defect should be considered functional. The test is administered so as to check for color recognition, not for color intensity. This test may not be reliable if the patient has some degree of red-green color blindness.

CORTICAL BLINDNESS

Three types of cortical blindness occur, and one of these types is frequently considered functional by the unwary physician. All three types result from lesions in the visual cortex of the occipital lobe. In one type of cortical blindness, patients have an infarction of both occipital lobes and see little or nothing. These patients say that they cannot see and act accordingly. In a second type of cortical blindness, patients have the same field loss but deny that they are blind. They probably have disturbances not only in visual cortex area 17 but also in association area 18. If these patients have Anton syndrome, they also have a Korsakoff-type reaction in that they confabulate about their
blindness. They have not learned from experience that they are blind, and they con- 

fable to justify their poor visual perfor-

mance.

It is the person with the third type of cortical blindness who frequently is said to have functional blindness. Such a person has a bilateral hemianopia typical of bilateral occipital lobe involvement, but has sparing of the tip of the occipital lobe, where the macular projection is located. In about 20% of people studied by arteriography, this area of the visual cortex has a secondary blood supply from the carotid system, a phenomenon

![Central 24-2 Threshold Test](image)

**Figure 17.55.**

A. Humphrey field demonstrates defects in all four quadrants of the right eye with sparing of the macular projection. The left eye of this patient could not be tested.
that is analogous to the secondary blood supply to the fovea from the choriocapillaries.

Figure 17.55. (continued)

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have to direct their small field to exactly the point in space that the physician indicates. For distance testing, the physician should direct these patients to sight down an arm, with the physician pointing the patient's arm as an aiming stake. I have examined patients whose field was so small that they could not see 20/200 letters but could see 20/50 letters.

Once this type of field defect is discovered, the usual tests (such as doubling and tripling the testing distance) can be performed to determine whether the defect is functional or organic. The bilaterality of the defect establishes that the lesion is located in the occipital lobe.

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