

Nystagmus and Related Ocular Motility Disorders

R. John Leigh and Janet C. Rucker

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GENERAL CONCEPTS AND CLINICAL APPROACH

This chapter concerns abnormal eye movements that disrupt steady fixation and thereby degrade vision. We now know a good deal about the normal anatomy, physiology, and pharmacology of ocular motor control (1). Our approach is to apply this knowledge to nystagmus and other ocular oscillations, since pathophysiology provides a sounder conceptual framework than a system based solely on phenomenology.

We first summarize the mechanisms by which gaze is normally held steady to achieve clear and stable vision (2). We then discuss the pathogenesis and clinical features of each of the disorders that disrupt steady gaze, including the various forms of pathologic nystagmus and saccadic intrusions. Finally, we summarize currently available treatments for these abnormal eye movements and their visual consequences.

NORMAL MECHANISMS FOR GAZE STABILITY

In order for us to see an object best, its image must be held steady over the foveal region of the retina. Although the visual system can tolerate some motion of images on the retina (3), if this motion becomes excessive (more than about 5°/second for Snellen optotypes), vision declines. Furthermore, if the image is moved from the fovea to peripheral retina, it will be seen less clearly.

In healthy persons, three separate mechanisms work together to prevent deviation of the line of sight from the object of regard. The first is fixation, which has two distinct components: (a) the visual system's ability to detect retinal image drift and program corrective eye movements; and (b) the suppression of unwanted saccades that would take the eye off target. The second mechanism is the vestibulo-ocular reflex, by which eye movements compensate for head perturbations at short latency and thus maintain clear vision during natural activities, especially locomotion. The third mechanism is the ability of the brain to hold the eye at an eccentric position in the orbit against the elastic pull of the suspensory ligaments and extraocular muscles, which tend to return it toward central position. For all three gaze-holding mechanisms to work effectively, their performance must be tuned by adaptive mechanisms that monitor the visual consequences of eye movements.

TYPES OF ABNORMAL EYE MOVEMENTS THAT DISRUPT STEADY FIXATION: NYSTAGMUS AND SACCADIC INTRUSIONS

The essential difference between nystagmus and saccadic intrusions lies in the **initial** eye movement that takes the line of sight off the object of regard. For nystagmus, it is a slow drift (or "slow phase"), as opposed to an inappropriate saccadic movement that intrudes on steady fixation. After the initial movement, corrective or other abnormal eye movements may follow. Thus, nystagmus may be defined as a repetitive, to-and-fro movement of the eyes that is initiated by a slow phase (drift). Saccadic intrusions, on the other hand, are rapid eye movements that take the eye off target. They include a spectrum of abnormal movements, ranging from single saccades to sustained saccadic oscillations.

DIFFERENCES BETWEEN PHYSIOLOGIC AND PATHOLOGIC NYSTAGMUS

It is important to realize that not all nystagmus is pathologic. **Physiologic nystagmus** preserves clear vision during self-rotation. Under most circumstances, for example during locomotion, head movements are small and the vestibulo-ocular reflex is able to generate eye movements that compensate for them. Consequently, the line of sight remains pointed at the object of regard. In response to large head or body rotations, however, the vestibulo-ocular reflex alone cannot preserve clear vision because the eyes are limited in their range of rotation. Thus, during sustained rotations, quick phases occur to reset the eyes into their working range: **vestibular nystagmus**. If rotation is sustained for several seconds, the vestibular afferents no longer accurately signal

head rotation, and visually driven or **optokinetic nystagmus** takes over to stop excessive slip of stationary retinal images. Additional examples of physiologic nystagmus are **arthrokinetic** and **audiokinetic nystagmus** (discussion following). In contrast to vestibular and optokinetic nystagmus, **pathologic nystagmus** causes excessive drift of stationary retinal images that degrades vision and may produce illusory motion of the seen world: **oscillopsia** (4–7). An exception is congenital nystagmus, which may be associated with normal visual acuity and which seldom causes oscillopsia (8).

Nystagmus, both physiologic and pathologic, may consist of alternating slow drifts (slow phases) in one direction and corrective, resetting saccades (quick phases) in the other: **jerk nystagmus** (Fig. 23.1A). Pathologic nystagmus may,

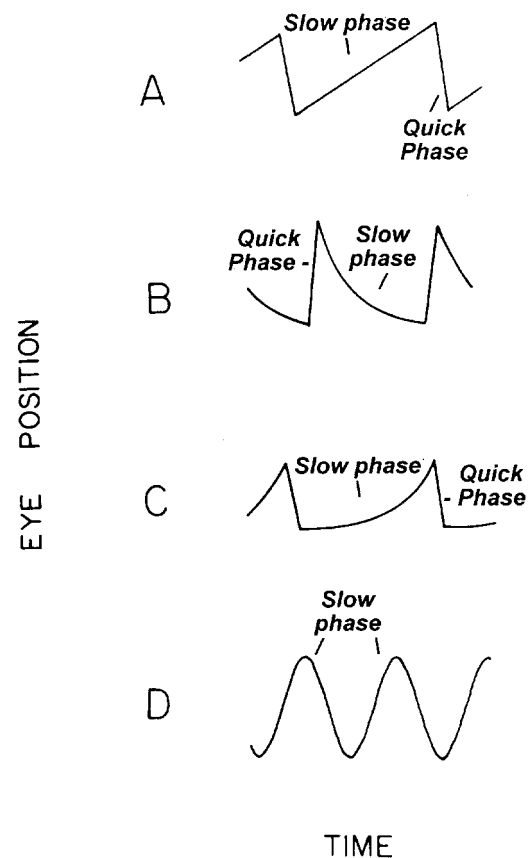


Figure 23.1. Four common slow-phase waveforms of nystagmus. A, Constant velocity drift of the eyes. This occurs in nystagmus caused by peripheral or central vestibular disease and also with lesions of the cerebral hemisphere. The added quick-phases give a "saw-toothed" appearance. B, Drift of the eyes back from an eccentric orbital position toward the midline (gaze-evoked nystagmus). The drift shows a negative exponential time course, with decreasing velocity. This waveform reflects an unsustained eye position signal caused by a "leaky" neural integrator. C, Drift of the eyes away from the central position with a positive exponential time course (increasing velocity). This waveform suggests an unstable neural integrator and is usually encountered in congenital nystagmus. D, Pendular nystagmus, which is encountered as a type of congenital nystagmus and with acquired brainstem disease. (From Leigh RJ, Zee DS. *The Neurology of Eye Movements*. Ed 3. New York, Oxford University Press, 1999.)

however, also consist of smooth to-and-fro oscillations: **pendular nystagmus** (Fig. 23.1D). Conventionally, jerk nystagmus is described according to the direction of the quick phase. Thus, if the slow movement is drifting up, the nystagmus is called “downbeating”; if the slow movement is to the right, the nystagmus is “left-beating.” Although it is convenient to describe the frequency, amplitude, and direction of the quick phases of the nystagmus, it should be remembered that it is the slow phase that reflects the underlying abnormality.

Nystagmus may occur in any plane, although it is often predominantly horizontal, vertical, or torsional. Physiologic nystagmus is essentially conjugate. Pathologic nystagmus, on the other hand, may have different amplitudes in the two eyes (dissociated nystagmus); it may go in different directions leading to different trajectories of nystagmus in the two eyes; or may have different temporal properties, i.e., phase shift between the two eyes, leading to movements that are sometimes in opposite directions (disconjugate nystagmus).

METHODS OF OBSERVING, ELICITING, AND RECORDING NYSTAGMUS

It is often possible to diagnose the cause of nystagmus through careful history and systematic examination of the patient (9,10). History should include duration of nystagmus, whether it interferes with vision and causes oscillopsia, and accompanying neurological symptoms. The physician should also determine if nystagmus and attendant visual symptoms are worse with viewing far or near objects, with patient motion, or with different gaze angles (e.g., worse on right gaze). If the patient habitually tilts or turns the head, the physician should determine whether or not these features are evident on old photographs.

Before assessing eye movements, the physician must examine the visual system, looking for signs of optic nerve demyelination or malformation, or ocular albinism which often suggests the diagnosis. The stability of fixation should be assessed with the eyes close to central position, viewing near and far targets, and at eccentric gaze angles. It is often useful to record the direction and amplitude of nystagmus for each of the cardinal gaze positions. If the patient has a head turn or tilt, the eyes should be observed in various directions of gaze when the head is in that position as well as when the head is held straight. During fixation, each eye should be occluded in turn to check for latent nystagmus. The presence of pseudonystagmus and oscillopsia in patients with head tremor who have lost their vestibulo-ocular reflex must be differentiated from true nystagmus.

Subtle forms of nystagmus, due to low amplitude or inconsistent presence, require prolonged observation over 2–3 minutes. Low amplitude nystagmus may be detected only by viewing the patient’s retina with an ophthalmoscope (11). (Note, however, that the direction of horizontal or vertical nystagmus is inverted when viewed through the ophthalmoscope.) The effect of **removal of fixation** should always be determined. Nystagmus caused by peripheral vestibular imbalance may be apparent **only** under these circumstances.

Removal of fixation is often achieved by eyelid closure; nystagmus is then evaluated by recording eye movements, by palpating the globes, or by auscultation with a stethoscope. Lid closure itself may affect nystagmus, however, and it is better to evaluate the effects of removing fixation with the eyelids open. Several clinical methods are available, such as Frenzel goggles which consist of 10- to 20-diopter spherical convex lenses placed in a frame that has its own light source. The goggles defocus the patient’s vision, thus preventing fixation of objects, and also provide the examiner with a magnified, illuminated view of the patient’s eyes. An alternative is to use two high-plus spherical lenses from a trial case, or to determine the effect of transiently covering the viewing eye during ophthalmoscopy in an otherwise dark room.

Evaluation of nystagmus is incomplete without a systematic examination of each functional class of eye movements (vestibular, optokinetic, smooth-pursuit, saccades, vergence) and their effect on the nystagmus, since different forms of nystagmus can be directly attributed to abnormalities of some of these movements. Physiological optokinetic nystagmus occurs during self-rotation, but it can be elicited at the bedside using a small drum or tape with alternating black and white lines, although larger displays are more effective in patients with voluntary gaze palsies. The slow phases represent visual tracking, including smooth pursuit; the resetting quick phases are saccadic in origin (12). In children and patients with impaired voluntary gaze, an optokinetic stimulus often provides useful information about both pursuit and saccadic systems (13–17). Vestibular nystagmus can be conveniently induced by rotating the patient in a swivel office chair for 30 seconds and then stopping: post-rotational nystagmus and vertigo are induced, which may help patients identify the nature of any paroxysmal attacks of dizziness. Caloric and other forms of induced vestibular nystagmus are described below.

It is often helpful to **measure the nystagmus waveform** because the shape of the slow phase often provides a pathophysiological signature of the underlying disorder (18,19). To properly characterize nystagmus, it is important to measure eye position and velocity, as well as target position, during attempted fixation at different gaze angles, in darkness, and during vestibular, optokinetic, saccadic, pursuit, and vergence movements. Common slow-phase waveforms of nystagmus are shown in Figure 23.1.

Conventionally, nystagmus is measured in terms of its amplitude, frequency, and their product: intensity. However, visual symptoms caused by nystagmus usually correlate best with the speed of the slow phase and displacement of the image of the object of regard from the fovea (7).

There are many different methods now available for recording eye movements, and these are discussed more fully elsewhere (20,21). Because many patients with nystagmus cannot accurately point their eyes at visual targets, precise measurement is best achieved with the magnetic search coil technique (Fig. 23.2), since the contact lens that the patient wears can be precalibrated on a protractor-gimbal device. In addition, this is the only technique that permits precise measurement of horizontal, vertical, and torsional oscilla-



Figure 23.2. A method for precise measurement of horizontal, vertical, and torsional eye rotations. The subject is wearing a Silastic © annulus embedded in which are two coils of wire, one wound in the frontal plane (to sense horizontal and vertical movements) and the other effectively in the sagittal plane (to sense torsional eye movements). When the subject sits in a magnetic field, voltages are induced in these search coils that can be used to measure eye position. (From Leigh RJ, Zee DS. *The Neurology of Eye Movements*. Ed 3. New York, Oxford University Press, 1999.)

tions over an extended range of amplitudes and frequencies. Although originally introduced as a research tool, the technique is now widely used to evaluate clinical disorders of eye movements, and is well tolerated (22). We have studied over 500 patients with this method.

CLASSIFICATION OF NYSTAGMUS BASED ON PATHOGENESIS

Our classification of nystagmus starts by relating the various forms of nystagmus to disorders of visual fixation, the vestibulo-ocular reflex, or the mechanism for eccentric gaze-holding. In addition, the adaptive processes that optimize these eye movements may be affected by disease, and we discuss these recalibration mechanisms as we deal with each class of nystagmus. Some forms of nystagmus can be better explained than others by this scheme. Nonetheless, our goal is to provide current hypotheses for nystagmus and saccadic intrusions whenever possible. Some hypotheses are backed by substantial evidence, whereas others are more tentative. The justification for this approach is that it provides explanations for clinical findings when knowledge allows, but also provides provisional hypotheses for other disorders that can be tested in future studies.

NYSTAGMUS ASSOCIATED WITH DISEASE OF THE VISUAL SYSTEM AND ITS PROJECTIONS TO BRAINSTEM AND CEREBELLUM

ORIGIN AND NATURE OF NYSTAGMUS ASSOCIATED WITH DISEASE OF THE VISUAL PATHWAYS

Disorders of the visual pathways are often associated with nystagmus. The most obvious example is the nystagmus that invariably accompanies blindness (23,24). How does this arise? At least two separate mechanisms can be identified: the visual fixation mechanism itself and the visually mediated calibration mechanism that optimizes its action.

The smooth visual fixation mechanism stops the eyes from drifting away from a stationary object of regard (25,26). For example, if a normal subject attempts to fixate on the remembered location of a target while in darkness, the eye drifts off target several times faster than if the subject fixates the visible target (27). Uncorrected drifts are eventually remedied by a saccade that places the image back on the fovea. This fixation mechanism depends upon the motion detection (magnocellular) portion of the visual system (28) which is inherently slow, with a response time of about 100 milliseconds that encumbers all visually mediated eye movements, including fixation, smooth pursuit, and optokinetic responses. If the response time is delayed further by disease of the visual system, then the attempts by the brain to correct eye drifts may actually add to the retinal error rather than reduce it, and may lead to ocular oscillations (29).

Vision is also needed for recalibrating and optimizing all types of eye movements. These functions depend on visual projections to the cerebellum, the structure called by Robinson "the ocular motor repair shop" (30). Thus, signals from secondary visual areas concerned with motion-vision project

to the cerebellum via the pontine nuclei and middle cerebellar peduncle (see Chapter 17). For example, neurons in the dorsolateral pontine nuclei and Purkinje cells in the cerebellar flocculus both encode visual-motion signals (31,32). Visual signals for recalibration may also pass via the inferior olive, which sends climbing fibers to the cerebellum (33,34). If the ocular motor system is to be recalibrated, visual signals need to be compared with eye movement commands. At present, it is not certain how or where this function is performed. One possibility is a group of cells in the paramedian tracts (PMT) in the lower pons, which receive inputs from almost all ocular motor structures and which project to the cerebellar flocculus (35). Lesions at any part of this visual-motor recalibration pathway can deprive the brain of signals that hold each of the eyes on the object of regard, the result being drifts of the eyes off target, leading to nystagmus.

Disease affecting any part of the visual system, from retina to cortical visual areas, or interrupting visual projections to pons and cerebellum, may be associated with nystagmus. In this section, we first catalogue the features of nystagmus reported with disease localized to the different sites in this pathway. We then describe features of acquired pendular nystagmus, one of the most common forms of nystagmus associated with disease affecting the visual system or its brainstem-cerebellar projections.

CLINICAL FEATURES OF NYSTAGMUS WITH LESIONS AFFECTING THE VISUAL PATHWAYS

Disease of the Retina

Congenital or acquired retinal disorders causing blindness, such as Leber's congenital amaurosis, lead to continu-

ous jerk nystagmus with components in all three planes, which changes direction over the course of seconds or minutes (Fig. 23.3A). The drifting “null point”—the eye position at which nystagmus changes direction—probably reflects inability to calibrate the ocular motor system, and it has also been reported after experimental cerebellectomy (36). This nystagmus often shows the increasing-velocity waveform (Fig. 23.1C) that was once thought to be specific for congenital nystagmus (discussion following). Recent developments in gene therapy for retinal disorders suggest that if vision can be restored, nystagmus will be suppressed (37,38).

Disease Affecting the Optic Nerves

Optic nerve disease is commonly associated with pendular nystagmus. With unilateral disease of the optic nerve, nystagmus largely affects the abnormal eye (monocular nystag-

mus), with prominent, vertical, low-frequency, bidirectional drifts (Fig. 23.3B); horizontal drifts are generally unidirectional with corrective quick-phases (24,39). When disease affects both optic nerves, the amplitude of nystagmus is often greater in the eye with poorer vision (the Heimann-Bielschowsky phenomenon) (40). This phenomenon is not confined to primary optic nerve disease, however, and also occurs in patients with profound amblyopia, dense cataract, and high myopia (24,39,41). Oscillations may disappear when vision is restored or they may persist (42), leading to oscillopsia. The former findings support the contention that these ocular oscillations are primarily caused by loss of vision rather than by any primary disorder of the ocular motor system. The origin of vertical drifts that occur in a blind eye is unknown but has been attributed to disturbance of either the vertical vergence mechanism (41), or to a monocular visual stabilization system (24).

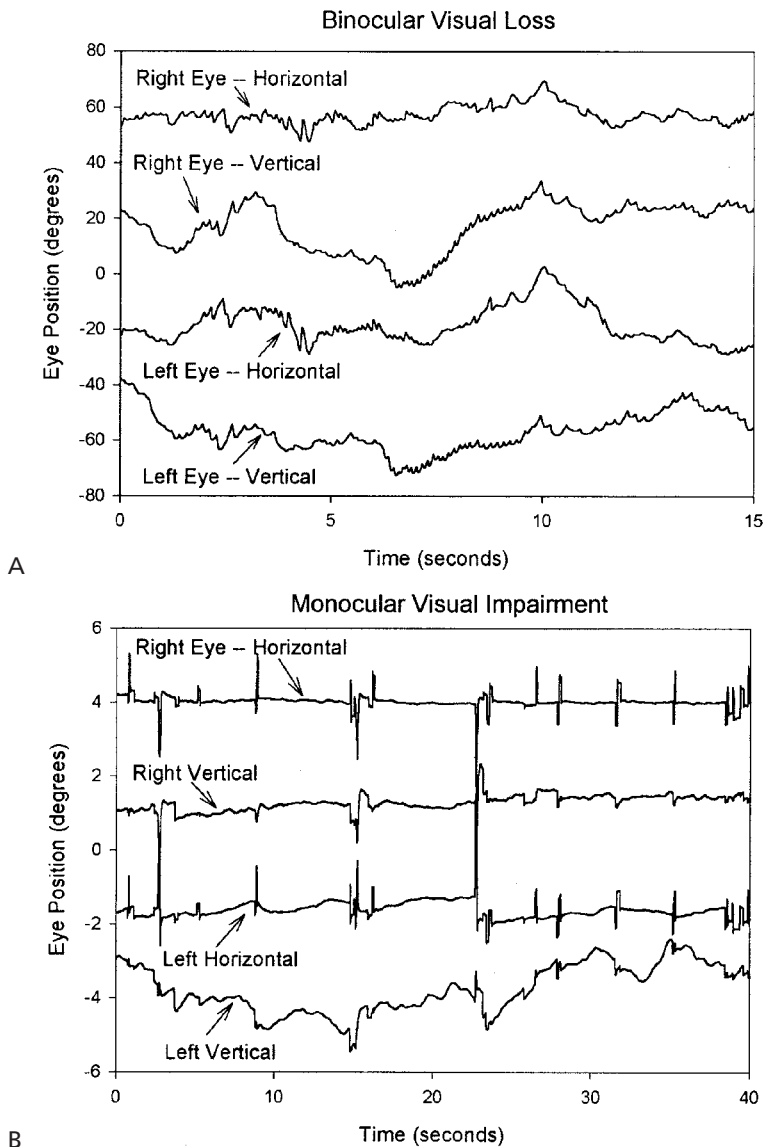


Figure 23.3. Nystagmus and gaze instability associated with visual loss. *A*, Binocular blindness since birth due to Leber’s congenital amaurosis. In the horizontal plane, nystagmus changes direction (evident in velocity channels) and there is a “wandering null point.” Slow-phase waveforms are variably linear decreasing velocity or, especially in the vertical plane, increasing velocity. *B*, Patient who had defocused vision since childhood following eye trauma and removal of his left lens. Following implantation of an artificial lens at age 35 years, his corrected visual acuity was 20/20 OD and 20/25 OS, but he was unable to maintain steady fixation with the left eye and suffered from variable diplopia and abnormal motion of vision in his left eye that he could not control. His left eye shows the Heimann-Bielschowsky phenomenon, vertical instability of fixation with slow drifts (17).

In infants, the appearance of monocular, vertical pendular nystagmus raises the possibility of optic nerve tumor and neuroimaging studies are indicated (43,44). However, monocular oscillations in children are sometimes due to spasmus nutans (45,46); this condition is discussed below. Monocular visual impairment, such as amblyopia, also leads to horizontal nystagmus and, if present from birth, the features are those of latent nystagmus, which is discussed in a later section.

Disease Affecting the Optic Chiasm

Parasellar lesions such as pituitary tumors have traditionally, albeit rarely, been associated with **seesaw nystagmus**, which is discussed in detail in a later section. Seesaw nystagmus also occurs in patients and in a mutant strain of dogs that lack an optic chiasm (47–49). It remains possible that visual inputs, especially crossed inputs, are important for optimizing vertical-torsional eye movements and if interrupted, might lead to seesaw oscillations (50,51).

Disease Affecting the Postchiasm Visual System

Horizontal nystagmus is a documented finding in patients with unilateral disease of the cerebral hemispheres, especially when the lesion is large and posterior (52). Such patients show a constant-velocity drift of the eyes toward the intact hemisphere (i.e., quick phases directed toward the side of the lesion, which are often low amplitude). Such patients usually also show asymmetry of horizontal smooth pursuit, brought out at the bedside using an optokinetic tape or drum (53,54); the response is reduced when the stripes move, or the drum is rotated, toward the side of the lesion. This asymmetry of visual tracking has led to the suggestion that nystagmus in such patients reflects an imbalance of pursuit tone as the cause (52). Whether this asymmetry occurs primarily from impairment of parietal cortex necessary for directing visual attention (55), or from disruption of cortical areas important for processing motion-vision (28,56,57), remains unclear.

ACQUIRED PENDULAR NYSTAGMUS AND ITS RELATIONSHIP TO DISEASE OF THE VISUAL PATHWAYS

Acquired pendular nystagmus (Fig. 23.4) is one of the more common types of nystagmus and is associated with the most distressing visual symptoms. Its pathogenesis remains undefined, and more than one mechanism may be responsible. It is encountered in a variety of conditions (Table 23.1).

Acquired pendular nystagmus usually has horizontal, vertical, and torsional components with the same frequency, although one component may predominate. (In congenital pendular nystagmus, however, the oscillation usually is predominantly horizontal, with a small torsional and negligible vertical component.) If the horizontal and vertical oscillatory components are in phase, the trajectory of the nystagmus is oblique. If the horizontal and vertical oscillatory components are out of phase, the trajectory is elliptical (Fig. 23.4B). A special case is a phase difference of 90° and equal amplitude

Table 23.1
Etiology of Pendular Nystagmus

Visual loss (including unilateral disease of the optic nerve)
Disorders of central myelin
Multiple sclerosis
Pelizaeus-Merzbacher disease
Peroxisomal assembly disorders
Cockayne's syndrome
Toluene abuse
Oculopalatal myoclonus
Acute brainstem stroke
Whipple's disease
Spinocerebellar degenerations
Congenital nystagmus

of the horizontal and vertical components, when the trajectory is circular. When the oscillations of each eye are compared, the nystagmus may be conjugate, but often the trajectories are dissimilar, and the size of oscillations is different (sometimes appearing monocular), and there may be an asynchrony of timing (phase shift). The latter may reach 180°, in which case the oscillations are convergent-divergent (29).

The temporal waveform usually approximates a sine wave, but more complex oscillations have been noted (29). The frequency of oscillations ranges from 1–8 Hz, with a typical value of 3.5 Hz (58). For any particular patient, the frequency tends to remain fairly constant; only rarely is the frequency of oscillations different in the two eyes (59). In some patients, the nystagmus stops momentarily after a saccade. This phenomenon is called postsaccadic suppression (60). A more common feature is that the oscillations are “reset” or phase-shifted by saccades (61). Acquired pendular nystagmus may be suppressed or brought out by eyelid closure (62,63) or evoked by convergence (64). In some patients with this condition, smooth pursuit may be intact, so that despite the oscillations, tracking eye movements occur with nystagmus superimposed (58).

Acquired Pendular Nystagmus with Demyelinating Disease

Acquired pendular nystagmus is a common feature of acquired and congenital disorders of central myelin, such as multiple sclerosis (MS) (64), toluene abuse (65), Pelizaeus-Merzbacher disease (66), and peroxisomal disorders (67). Since optic neuritis often coexists in patients with MS who have pendular nystagmus, prolonged response time of the visual processing might be responsible for the ocular oscillations. However, the nystagmus often remains unchanged in darkness, when visual inputs should have no influence on eye movements. In normal subjects, it is possible to induce spontaneous ocular oscillations by experimentally delaying the latency of visual feedback during fixation (Fig. 23.4C); however, the frequency of these induced oscillations is less than 2.5 Hz, which is lower than in most patients with pendular nystagmus (29). When this experimental technique is applied to patients with acquired pendular nystagmus, it does not change the characteristics of the nystagmus, but instead

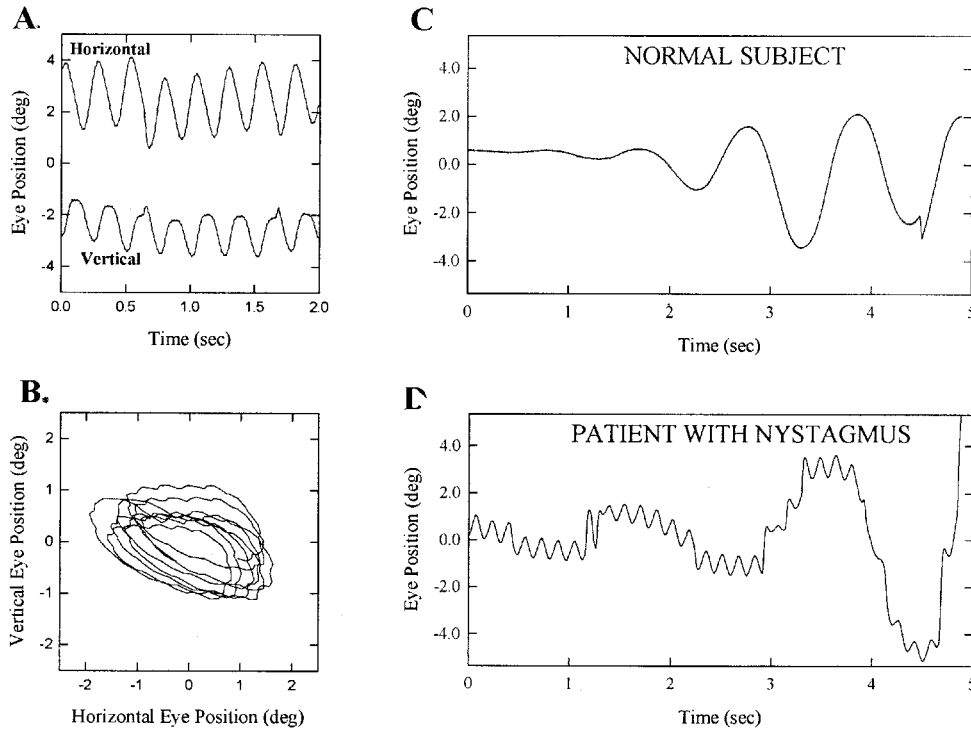


Figure 23.4. Acquired pendular nystagmus. *A*, Time plots of nystagmus of the patient’s right eye while fixating a central visual target. The horizontal and vertical records have been offset from zero eye position for convenience of display. Upward deflections correspond to rightward or upward eye rotations. *B*, Nystagmus trajectory seen as a scan path of eye movements in the horizontal and vertical planes corresponding to the time plot in *A*. The scan path corresponded to the direction of oscillopsia that the patient reported. *C and D*, Examples of ocular oscillations induced by imposing an effective delay in visual feedback. *C*, Normal subject. An effective delay in visual feedback of 480 msec was imposed at time zero. The subject developed ocular oscillations at about 1.0 Hz. *D*, Patient with multiple sclerosis and acquired pendular nystagmus. The effects of imposing an electronic delay of 480 msec. The oscillations of her nystagmus (unchanged at 6.5 Hz) were superimposed upon growing 0.67 Hz oscillations induced by the electronic manipulation. (Panels *C and D* adapted from Averbuch-Heller L, Zivotofsky AZ, Das VE, et al. Investigations of the pathogenesis of acquired pendular nystagmus. *Brain* 1995;188:369–378.)

superimposes lower-frequency oscillations similar to those induced in normal subjects (Fig. 23.4D). Thus, disturbance of visual fixation from visual delays can not be held accountable for the high-frequency oscillations that often characterize acquired pendular nystagmus.

A more likely possibility is that visual projections to the cerebellum are impaired, leading to instability in the reciprocal connections between brainstem nuclei and cerebellum that are important for recalibration. The high prevalence of internuclear ophthalmoplegia (INO) in these patients, suggests involvement of paramedian brainstem regions, including the cell groups of the paramedian tracts (PMT) (35,68–70). PMT cell groups send a neural copy of ocular motor signals to the cerebellum, and seem important for the integration and calibration of eye movement commands. The observation that acquired pendular nystagmus is “reset” or phase-shifted after saccades (more so with large saccades) suggested that the oscillations arise in the brainstem-cerebellar gaze-holding network (the neural integrator for eye movements—which is discussed in the section “Nystagmus Due to Abnormalities of the Mechanism for Holding Eccentric Gaze”) (61).

Oculopalatal Myoclonus (Oculopalatal Tremor)

Acquired pendular nystagmus may be one component of the syndrome of oculopalatal (pharyngo-laryngo-diaphragmatic) myoclonus (71–73). This condition usually develops several months after brainstem or cerebellar infarction, although it may not be recognized until years later. Oculopalatal myoclonus also occurs with degenerative conditions (74). The term “myoclonus” is misleading, since the movements of affected muscles are to and fro and are approximately synchronized, typically at a rate of about 2 cycles per second. The palatal movements may be termed “tremor,” rather than myoclonus, and the eye movements are really a form of pendular nystagmus (75). Although the palate is most often affected, movements of the eyes, facial muscles, pharynx, tongue, larynx, diaphragm, mouth of the eustachian tube, neck, trunk, and extremities may occur.

The ocular movements typically consist of to-and-fro oscillations, less sinusoidal than with demyelinating disease, and often with a large vertical component, although they may also have small horizontal or torsional components. The movements may be somewhat disconjugate (both horizon-



Figure 23.5. Pathology of oculopalatal myoclonus. A section through the cerebellum and medulla shows marked demyelination of the right dentate nucleus and restiform body (*double arrows*). The left inferior olive is hypertrophic and shows mild demyelination (*arrow*). (From Nathanson M. *Arch Neurol Psychiatr* 1956;75:285–296.)

tally and vertically) (58), with some orbital position dependency (72), and some patients show cyclovergence (torsional vergence) oscillations. Occasionally, patients develop the eye oscillations without movements of the palate, especially following brainstem infarction. Eyelid closure may bring out the vertical ocular oscillations (62). The nystagmus sometimes disappears with sleep, but the palatal movements usually persist. The condition is usually intractable, and spontaneous remission is uncommon (76). Vertical pendular oscillations sometimes occur in the acute period following pontine infarction (77), but the pathogenesis of these movements is probably different than that of oculopalatal myoclonus, since they often resolve spontaneously.

The main pathologic finding with palatal myoclonus is hypertrophy of the inferior olivary nucleus (Fig. 23.5), which may be seen during life using magnetic resonance (MR) imaging (74). There may also be destruction of the contralateral dentate nucleus (71). Histologically, the olivary nucleus has enlarged, vacuolated neurons with enlarged astrocytes. Functional scanning demonstrates increased glucose metabolism (78). Guillain and Mollaret proposed that disruption of connections between the dentate nucleus and the contralateral inferior olivary nucleus, which run via the red nucleus and central tegmental tract, is responsible for the syndrome (71). However, neither the dentate nucleus nor the red nucleus has been shown to have a specific role in ocular motor

control. Thus, it has thus been postulated that the nystagmus results from instability in the projection from the inferior olive to the cerebellar flocculus, a structure thought to be important in the adaptive control of the vestibulo-ocular reflex (69,72). It is also possible that disruption of projections from the cell groups of the paramedian tracts (PMT) (35) to the cerebellum leads to the ocular oscillations.

Whipple's Disease and Other Predominantly Convergent-Divergent Pendular Oscillations

Comparatively little has been written about vergence pendular oscillations, which are often small in amplitude, and there is some evidence that they are often overlooked by clinicians. More widespread use of the magnetic search coil technique has made it easier to identify the convergent-divergent components of this form of nystagmus. Averbuch-Heller and colleagues reported three patients with pendular oscillations that were about 180° out of phase in the horizontal and torsional planes but had conjugate vertical components (29). In one of these patients, the torsional component of the oscillations had the largest amplitude. Thus, the patient actually had a cyclovergence nystagmus.

Vergence pendular oscillations occur in patients with MS (79), brainstem stroke (58), and cerebral Whipple's disease (80). In Whipple's disease, the oscillations typically have a frequency of about 1.0 Hz and are accompanied by concurrent contractions of the masticatory muscles, a phenomenon called oculomasticatory myorhythmia. Supranuclear paralysis of vertical gaze also occurs in this setting and is similar to that encountered in progressive supranuclear palsy (81).

At least two possible explanations have been offered to account for the convergent-divergent nature of vergence pendular oscillations: a phase shift between the eyes, produced by dysfunction in the normal yoking mechanisms, or an oscillation affecting the vergence system itself (79). The latter explanation is more likely, because patients who have been studied show no phase shift (i.e., are conjugate) vertically, and because the relationship between the horizontal and torsional components is similar to that occurring during normal vergence movements (excyclovergence with horizontal convergence) (29). Under experimental conditions, the vergence system can be made to oscillate at frequencies up to 2.5 Hz—lower than that reported in patients with conditions other than Whipple's disease (30,80). To account for these higher-frequency oscillations, it seems necessary to postulate instability within the brainstem-cerebellar connections of the vergence system, for example, between the nucleus reticularis tegmenti pontis and cerebellar nucleus interpositus, which may help hold vergence angle steady (29,82).

NYSTAGMUS CAUSED BY VESTIBULAR IMBALANCE

Nystagmus related to imbalance in the vestibular pathway can be caused by damage to peripheral or central structures. Because the nystagmus varies, it usually is possible to distinguish nystagmus caused by peripheral vestibular imbalance from nystagmus caused by central vestibular imbalance.

NYSTAGMUS CAUSED BY PERIPHERAL VESTIBULAR IMBALANCE

Clinical Features of Peripheral Vestibular Nystagmus

Disease affecting the peripheral vestibular pathway (i.e., the labyrinth, vestibular nerve, and its root entry zone) causes

nystagmus with linear slow phases (Fig. 23.1A). Such unidirectional slow-phase drifts reflect an imbalance in the level of tonic neural activity in the vestibular nuclei. If disease leads to reduced activity, for example, in the vestibular nuclei on the left side, then the vestibular nuclei on the right side will drive the eyes in a slow phase to the left. In this example, quick phases will be directed to the right—away from the side of the lesion. Paradoxically, some patients show nystagmus with a horizontal component that beats toward the side of the lesion. Such cases may be “recovery nystagmus” (83), which represents the effects of a central adaptation process. An imbalance of vestibular tone usually also causes vertigo and a tendency to fall toward the side of the lesion. Apart from these attendant symptoms, two features of the nystagmus itself are useful in identifying the vestibular periphery as the culprit: its trajectory (direction) and whether it is suppressed by visual fixation.

The trajectory of nystagmus can often be related to the geometric relationships of the semicircular canals and to the finding that experimental stimulation of an individual canal produces nystagmus in the plane of that canal. Thus, complete unilateral labyrinthine destruction leads to a mixed horizontal-torsional nystagmus (the sum of canal directions from one ear), whereas in benign paroxysmal positional vertigo (BPPV), a mixed upbeat-torsional nystagmus reflects posterior semicircular canal stimulation. Pure vertical or pure torsional nystagmus almost never occurs with peripheral vestibular disease, because this would require selective lesions of individual canals from one or both ears, an unlikely event.

Nystagmus caused by disease of the vestibular periphery often is more prominent, or may only become apparent, when **visual fixation is prevented**. The reason for this is that when visually generated eye movements are working normally, as they usually are in patients with peripheral vestibular disease, they will slow or stop the eyes from drifting.

Another common, but not specific, feature of nystagmus caused by peripheral vestibular disease is that its intensity increases when the eyes are turned in the direction of the quick phase—**Alexander’s law** (84). This probably reflects an adaptive strategy developed to counteract the drift of the vestibular nystagmus and so establish an orbital position (i.e., in the direction of the slow phases) in which the eyes are quiet and vision is clear. This phenomenon forms the basis for a common classification of unidirectional nystagmus. Nystagmus is called “first degree” if it is present only on looking in the direction of the quick phases, “second degree” if it is also present in the central position, and “third degree” if it is present on looking in all directions of gaze.

Although these clinical features help make the diagnosis of peripheral vestibular disease, it is important to realize that brainstem and cerebellar disorders may sometimes mimic peripheral disease and, especially in elderly patients or those with risk factors for vascular disease, careful observation is the prudent course.

Nystagmus Induced by Change of Head Position

Vestibular nystagmus is often influenced by changes in head position. This feature can be used to aid in diagnosis,

especially of **benign paroxysmal positional vertigo** (BPPV). Patients with BPPV complain of brief episodes of vertigo precipitated by change of head position, such as when they turn over in bed or look up to a high shelf. The condition may follow head injury or viral neurolabyrinthitis (85).

To test for nystagmus and vertigo in a patient with possible BPPV, the examiner should turn the patient’s head toward one shoulder and then quickly move the head and neck together into a head-hanging (down 30–45°) position. About 2–5 seconds after the affected ear is moved to this dependent position, a patient with BPPV will report the onset of vertigo, and a mixed upbeat-torsional nystagmus, best viewed with Frenzel goggles, will develop. The direction of the nystagmus changes with the direction of gaze. Upon looking toward the dependent ear, it becomes more torsional; on looking toward the higher ear, it becomes more vertical. This pattern of nystagmus corresponds closely to stimulation of the posterior semicircular canal of the dependent ear (which causes slow phases mainly by activating the ipsilateral superior oblique and contralateral inferior rectus muscles). The nystagmus increases for up to 10 seconds, but it then fatigues and is usually gone by 40 seconds. When the patient sits back up, a similar but milder recurrence of these symptoms occurs, with the nystagmus being directed opposite to the initial nystagmus. Repeating this procedure several times will decrease the symptoms and make the signs more difficult to elicit. This habituation of the response is of diagnostic value, since a clinical picture similar to that of BPPV can be caused by cerebellar tumors, MS, or posterior circulation infarction. With such central processes, however, there is no latency to onset of nystagmus and no habituation of the response with repetitive testing. Some patients present with the lateral canal variant of BPPV (86,87); sudden horizontal head turns as the patient lies supine may induce a paroxysm of horizontal nystagmus beating toward the ground and vertigo.

Studies show that otolithic debris in the respective canals (canalolithiasis) interferes with the flow of endolymph or movement of the cupula and is probably responsible for BPPV and its variants (88,89). Neck movement causing vertebral basilar kinking and vertigo as an isolated manifestation of transient brainstem ischemia is an uncommon mechanism; in such cases, associated neurologic symptoms are usually present (90).

Nystagmus that persists after a horizontal change in head position (e.g., with the subject supine and the head turned to the right or left) is less specific than transient nystagmus induced by changes in head position. Indeed, some otherwise normal subjects develop nystagmus that is horizontal with respect to the head and becomes evident behind Frenzel goggles during static, horizontal positional testing. Such positional nystagmus may remain beating in the same direction whether the head is turned to the right or left, or it may change direction with lateral head turn such that it is either always beating toward the earth (geotropic) or away from the earth (ageotropic or apogeotropic). Sustained geotropic and ageotropic nystagmus probably reflect the effects of changing otolithic influences and may be encountered with

either peripheral, or central vestibular lesions (90,91). Only if such nystagmus is present during visual fixation does it suggest the possibility of central disease. Occasionally, disease affecting central vestibular connections, such as a cerebellar tumor (92), infarction (93,94), or MS may produce nystagmus associated with postural vertigo and severe nausea with vomiting. These manifestations may suggest a peripheral lesion; however, the characteristics of the nystagmus are usually central, rather than peripheral. Alcohol is well known to cause positional nystagmus, and both central and peripheral mechanisms contribute (95).

In patients who have symptomatically recovered from a unilateral, peripheral vestibulopathy, nystagmus can often be induced following vigorous head shaking in the horizontal or the vertical plane for 10–15 seconds (96–98). After horizontal head shaking, patients may show horizontal nystagmus with quick phases directed away from the side of the lesion. Vertical nystagmus following horizontal head shaking (an example of “perverted nystagmus”) often implies central vestibular disease (99,100). After vertical head shaking, patients with unilateral peripheral vestibular lesions may show less prominent nystagmus with horizontal quick phases directed toward the side of the lesion. Hyperventilation-induced nystagmus occurs in patients with schwannoma and other tumors of the 8th cranial nerve (9,101). Indeed, hyperventilating 25 deep breaths is useful in the evaluation of the dizzy patient. Patients with cerebellar disease may show transient downbeating nystagmus after horizontal head shaking or hyperventilation (102).

Nystagmus Induced by Proprioceptive and Auditory Stimuli

It is uncertain whether or not an imbalance of cervical inputs can produce a nystagmus similar to that caused by peripheral vestibular disease. In normal human subjects, eye movements generated from cervical proprioception—the cervico-ocular reflex (COR)—play little role in the stabilization of gaze (103), although the COR does increase in responsiveness in individuals who have lost vestibular function (104,105), and in certain patients with cerebellar disease (106).

The perception of passive body motion relies primarily on vestibular and visual information. However, an illusion of body rotation accompanied by a conjugate, horizontal, jerk nystagmus—**arthrokinetic nystagmus**—can be induced when the horizontally extended arm of a normal, stationary subject is passively rotated about a vertical axis in the shoulder joint (107). The slow phase of the nystagmus is in a direction opposite to that of the arm movement. The mean slow-phase velocity increases with increasing arm velocity, and the nystagmus continues for a short time following cessation of arm movement (arthrokinetic after-nystagmus). The existence of arthrokinetic circularvection and nystagmus suggests that there exists in normal humans a functionally significant somatosensory-vestibular interaction within the central vestibular system, at least for afferent pathways carrying position and kinesthetic information from the joints.

Normal stationary subjects in darkness may experience illusory self-rotation when exposed to a rotating sound field (108,109). This illusion is generally accompanied by **audio-kinetic nystagmus**, which is conjugate and horizontal, with the slow phase in the direction opposite to that of the experienced self-rotation (110). This nystagmus indicates that apparent, as well as actual, body orientation can influence ocular motor control. Neither the illusory self-rotation nor the nystagmus occurs when the subject is exposed to a rotating sound field in the light, i.e., when a stable visual environment is present, suggesting that visual information must dominate auditory information in determining apparent body orientation and sensory localization (110). Patients who develop vestibular symptoms and nystagmus when exposed to certain sounds—**Tullio’s phenomenon**—often have dehiscence of the superior semicircular canal or pathologic stimulation of otolithic organs (111–116).

Peripheral Vestibular Nystagmus Induced by Caloric or Galvanic Stimulation

Nystagmus induced by caloric stimulation of one ear has all the features of that caused by unilateral or asymmetric peripheral vestibular disease. During caloric stimulation, a temperature gradient across the temporal bone induces a convection current in the endolymph of a semicircular canal if it is orientated vertical to the earth (117). A second mechanism, which probably involves the effects of cooling the vestibular nerve, is less important (118,119). Before attempting to induce caloric nystagmus, the physician must first check that the tympanic membrane is visible and intact. The subject is then placed supine and the neck is flexed 30°. A cold stimulus (30°C) induces horizontal slow-phase components directed toward the stimulated ear (quick phases in the opposite direction). With a warm stimulus (44°C) and the same head orientation, quick phases are toward the stimulated ear (hence the mnemonic, **COWS**: cold-opposite, warm-same).

Caloric stimulation is an important way to test each peripheral labyrinth; details of quantitative testing are summarized elsewhere (91). Bedside testing with ice-cold water is especially useful in the evaluation of the unconscious patient (120,121). In this setting, tonic eye deviation indicates preservation of pontine function. Induction of caloric nystagmus is also a useful way to confirm preservation of consciousness in patients feigning coma. Suppression of caloric nystagmus by visual fixation depends on pathways important for visually mediated eye movements. For example, caloric nystagmus is impaired in patients with lesions of the cerebellar flocculus (122). Galvanic stimulation of the peripheral labyrinth also induces nystagmus but, at present, this is largely used as a research tool (91,123,124).

NYSTAGMUS CAUSED BY CENTRAL VESTIBULAR IMBALANCE

Clinical Features of Central Vestibular Nystagmus

In this section, we describe the clinical features of three common forms of nystagmus thought to be caused by imbal-

Table 23.2
Etiology of Downbeat Nystagmus

Cerebellar degeneration, including familial episodic ataxia, and paraneoplastic degeneration
Craniocervical anomalies, including Arnold-Chiari malformation
Infarction of brainstem or cerebellum
Dolichoectasia of the vertebrobasilar artery
Multiple sclerosis
Cerebellar tumor, including hemangioblastoma
Syringobulbia
Encephalitis
Head trauma
Toxic-metabolic
Anticonvulsant medication
Lithium intoxication
Alcohol
Wernicke's encephalopathy
Magnesium depletion
Vitamin B ₁₂ deficiency
Toluene abuse
Congenital
Transient finding in otherwise normal infants

ance of central vestibular connections: downbeat, upbeat, and torsional nystagmus. We also discuss the less common phenomenon of horizontal nystagmus caused by central vestibular imbalance. Finally, we offer a pathophysiologic scheme to account for these forms of central vestibular nystagmus.

Downbeat nystagmus occurs in a variety of disorders (Table 23.2), but it is most commonly associated with disease affecting the cerebellum, the craniocervical junction, or the blood vessels in these regions (125–128). It may also be a manifestation of drug intoxication, notably by lithium (129–133). Downbeat nystagmus is usually present with the eyes in central position, but its amplitude may be so small that it can only be detected by viewing the ocular fundus with an ophthalmoscope. In addition, it may occur intermittently (134). Generally, Alexander's law is obeyed: nystagmus intensity is greatest in downgaze and least in upgaze. Usually the waveform is linear, but it may be increasing in velocity (Fig. 23.1C). The latter is usually the case if Alexander's law is violated (i.e., when the nystagmus increases in upgaze). This phenomenon may reflect instability of the mechanism for eccentric gaze-holding. Most often, it is enhanced by having the patient look down and to one side. Downbeat nystagmus may also be evoked by placing the patient in a head-hanging position (135–137). Some normal subjects may show "chin-beating" nystagmus when they are placed upside down in darkness (or wear Frenzel goggles) (137,138); such nystagmus is usually absent in normal eyes during fixation (136). Convergence may influence the amplitude and frequency of the nystagmus or convert it to upbeat nystagmus. Some patients show combined divergent and downbeat nystagmus (139). In most patients, removal of fixation (e.g., with Frenzel goggles) does not substantially influence slow-phase velocity, although the frequency of quick phases may diminish.

A variety of ocular motor abnormalities often accompany downbeat nystagmus and reflect coincident cerebellar involvement. Vertical smooth pursuit and the vertical vestibulo-ocular reflex are abnormal because of impaired ability to generate smooth downward eye movements; such asymmetries cannot simply be attributed to superimposed nystagmus (126). Sometimes, the vestibulo-ocular reflex for upward eye movements is hyperactive, with a gain exceeding 1.0 (140). Impairment of eccentric horizontal gaze-holding, smooth pursuit, and combined eye-head tracking also commonly coexist. Vertical diplopia usually reflects associated skew deviation (126). The visual consequences of downbeat nystagmus are oscillopsia and postural instability (141).

Upbeat nystagmus that is present with the eyes close to central position occurs in many clinical conditions (Table 23.3). Nystagmus intensity is usually greatest in upgaze, and it usually does not increase on right or left gaze (126). As with downbeat nystagmus, slow phases are often increasing in velocity if Alexander's law is violated (Fig. 23.1C). Removal of visual fixation has little influence on slow-phase velocity. Convergence is variously reported to enhance, suppress, or convert upbeat nystagmus to downbeat (126, 142,143). Placing the patient in a head-hanging position increases the nystagmus in some individuals. It should be noted that the nystagmus in many patients with benign paroxysmal positional vertigo is upbeating. However, this is a transient phenomenon brought on by quickly placing the patient with the affected side down. Furthermore, the nystagmus of BPPV has a torsional component, and its direction depends upon the direction of gaze. As is the case with downbeat nystagmus, patients with upbeat nystagmus often show asymmetries of vertical vestibular and smooth pursuit eye movements, as well as associated cerebellar eye movement findings.

Torsional nystagmus is a less commonly recognized form of central vestibular nystagmus than downbeat or upbeat nystagmus. It is often difficult to detect except by careful observation of conjunctival vessels or by noting the direction of retinal movement on either side of the fovea, using

Table 23.3
Etiology of Upbeat Nystagmus

Cerebellar degenerations, including familial episodic ataxia
Multiple sclerosis
Infarction of medulla, midbrain, or cerebellum
Tumors of the medulla, midbrain, or cerebellum
Wernicke's encephalopathy
Brainstem encephalitis
Behçet's syndrome
Meningitis
Leber's congenital amaurosis or other congenital disorder of the anterior visual pathways
Thalamic arteriovenous malformation
Organophosphate poisoning
Tobacco
Associated with middle ear disease
Congenital
Transient finding in otherwise normal infants

Table 23.4
Etiology of Torsional Nystagmus

Syringobulbia, with or without syringomyelia and Chiari malformation
Brainstem stroke (Wallenberg's syndrome) or arteriovenous malformation
Brainstem tumor
Multiple sclerosis
Oculopalatal myoclonus
Head trauma
Congenital
Associated with the ocular tilt reaction

an ophthalmoscope or contact lens. Although both peripheral vestibular and congenital nystagmus may have torsional components, purely torsional nystagmus, like purely vertical nystagmus, indicates disease affecting central vestibular connections (see Table 23.4) (144–147). Torsional nystagmus shares many of the features of downbeat and upbeat nystagmus, including modulation by head rotations, variable slow-phase waveforms, and suppression by convergence (146). It is also probably a common finding in patients with the ocular tilt reaction (148). Nonrhythmic but continuous torsional eye movements may be a feature of paraneoplastic encephalopathy (149).

Horizontal nystagmus in central position from central vestibular imbalance is an uncommon but well-documented phenomenon. The underlying disorder usually is an Arnold-Chiari malformation (9,150). The slow-phase waveform in this form of nystagmus may be of the increasing-velocity type, making distinction from congenital nystagmus potentially difficult. However, patients with acquired central vestibular horizontal nystagmus typically report recent onset of visual symptoms, such as oscillopsia, and measurements usually demonstrate an associated vertical component that is absent in congenital nystagmus. Patients with horizontal nystagmus that is present in the central position always should be observed continuously for 2–3 minutes to exclude the possibility that the nystagmus is actually periodic alternating nystagmus (PAN, discussion following).

Pathogenesis of Central Vestibular Nystagmus

Our understanding of the pathogenesis of central forms of vestibular nystagmus has increased because of more cases with clinicopathological correlation, the development of animal and mathematic models, and the application of modern anatomy and physiology. Downbeat nystagmus is usually associated with lesions of the vestibulocerebellum flocculus, paraflocculus, nodulus, and uvula and the underlying medulla (126,151). Upbeat nystagmus is most commonly reported in patients with medullary lesions (Fig. 23.6) (152–156). These lesions variably affect the perihypoglossal nuclei and adjacent medial vestibular nucleus (structures important for gaze-holding), and the ventral tegmentum, which contains projections from the vestibular nuclei that receive inputs from the anterior semicircular canals (157). Upbeat nystagmus occurs in patients with lesions affecting the cau-

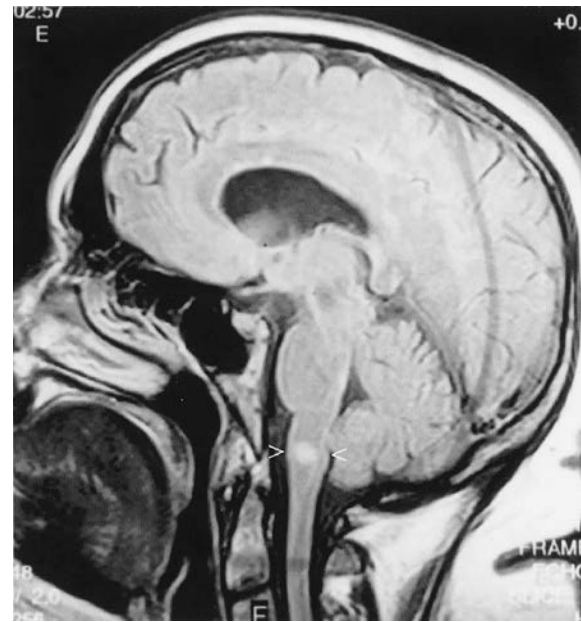


Figure 23.6. Magnetic resonance T2-weighted image showing a hyperintense signal in the medulla of a patient with upbeat nystagmus and multiple sclerosis (99). After horizontal head-shaking, she developed downbeating nystagmus (perverted head-shaking nystagmus) and tumbling vertigo.

dal medulla (158), anterior vermis of the cerebellum (152), or the adjacent brachium conjunctivum and midbrain (159–161). These cases suggest that lesions at several distinct sites can cause both upbeat and downbeat nystagmus. However, it is possible to account for these findings by considering the fundamental anatomic fact that, unlike the horizontal vestibular system which is right-left symmetric, the connections for vertical vestibular responses are dissimilar for upward or downward eye movements, both anatomically and pharmacologically. These up-down asymmetries involve connections subserving: (a) the vertical vestibulo-ocular reflex; (b) the otolith-ocular reflexes; (c) the vestibulocerebellum; (d) the network for eccentric gaze-holding (neural integrator); and (e) the smooth pursuit system.

Excitatory projections for the vertical vestibulo-ocular reflex from the posterior semicircular canals, which mediate downward eye movements, synapse in the medial vestibular nucleus and then cross dorsally in the medulla beneath the nucleus prepositus hypoglossi to reach the contralateral medial longitudinal fasciculus (MLF). Experimental lesions that damage this pathway cause upward eye drifts and downbeat nystagmus (162). On the other hand, it appears that excitatory connections from the anterior semicircular canals, which mediate upward eye movements, take different routes; more than one pathway may contribute (163). In addition, a central imbalance of otolithic inputs may contribute to vertical nystagmus (164), and account for “chin-beating” nystagmus when normal subjects are positioned upside down in darkness (137,138). The case for the cerebellar flocculus being an important structure in the production of downbeat nystagmus rests on the finding that Purkinje cells send inhib-

itory projections to the central connections of the anterior semicircular canal but not to the posterior canal (Fig. 23.7) (165–167). This asymmetry of inhibitory projections accounts for the finding that experimental flocculectomy causes downbeat nystagmus (168). This lesion disinhibits the projections to the anterior canal but not to the posterior canal, causing the eyes to drift up and producing downbeat nystagmus (167). A neural network that includes the vestibulocerebellum and the nucleus prepositus hypoglossi and adjacent medial vestibular nucleus is also thought to be important for the eccentric gaze-holding mechanism. Consistent with this hypothesis is the report of a patient with lithium intoxication, who had downbeat nystagmus and a complete failure of gaze-holding, and showed lesions in the nucleus prepositus hypoglossi (130). (However, a range of disorders of eye movements are reported with lithium [131,169–172], so more than one mechanism may be disrupted by it.) Lesions of the vestibulocerebellum may cause instability of this network, making the eyes drift at increasing velocity away from central position in the vertical or horizontal planes (150,173–175). It has also been suggested that the characteristics of downbeat nystagmus could be explained by a central imbalance in smooth pursuit with cerebellar lesions (140). Resolution of upbeat or downbeat nystagmus after the first few months of life in otherwise normal infants (176,177) may reflect calibration of pursuit or gaze-holding mechanisms as the visual system becomes fully myelinated.

PERIODIC ALTERNATING NYSTAGMUS

Periodic alternating nystagmus is a spontaneous horizontal nystagmus, present in central gaze, that reverses direction approximately every 90–120 seconds (Fig. 23.8). Because the period of oscillation is about 4 minutes, the disorder may be missed unless the examiner observes the nystagmus for several minutes. As the nystagmus finishes one half-cycle (e.g., of right-beating nystagmus), a brief transition period occurs during which there may be upbeating or downbeating nystagmus or saccadic movements before the next half-cycle (e.g., of left-beating nystagmus) starts. A congenital form of PAN also exists (discussed in the section ‘‘Congenital Nystagmus’’), but this is usually much less regular in the timing of reversal of direction and shows slow-phase waveforms typical of congenital nystagmus. PAN must also be differentiated from ‘‘ping-pong gaze,’’ an ocular deviation that reverses direction not over several minutes but every few seconds and that is encountered in unconscious patients with large bihemispheric lesions (178).

In most patients with acquired PAN, the nystagmus has the same characteristics in light or in darkness. Smooth pursuit and optokinetic nystagmus are usually impaired (179). Vestibular stimuli are able to reset the oscillations, and critically timed rotational stimuli can stop PAN for several minutes (179,180).

Acquired PAN occurs in association with a number of

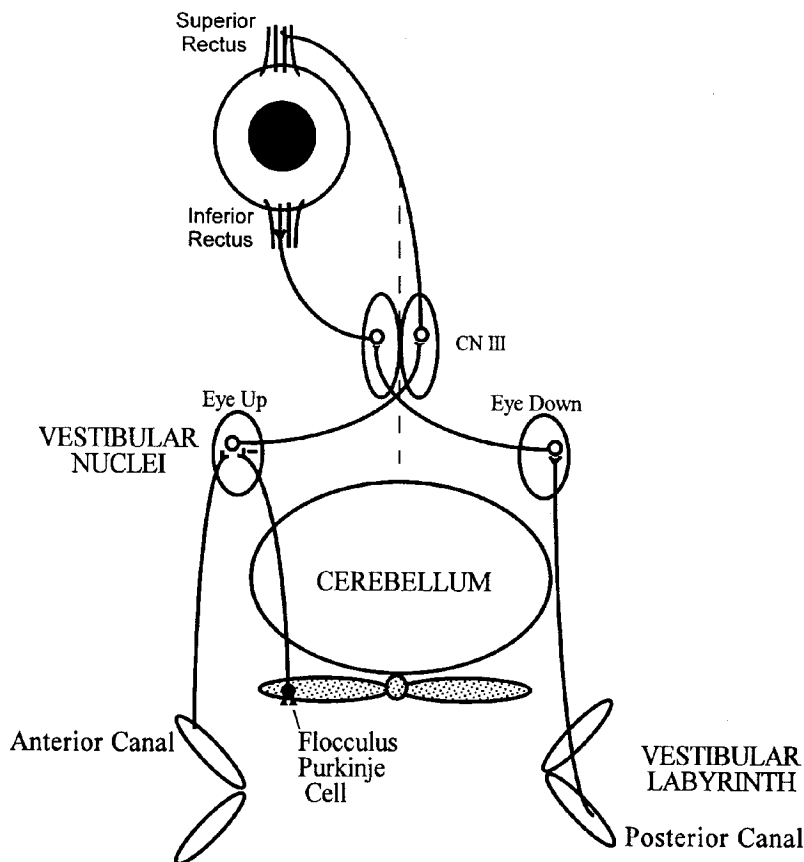


Figure 23.7. Schematic hypothesis for downbeat nystagmus. Inputs from the anterior semicircular canals of the vestibular labyrinth evoke upward eye movements via projections through the superior vestibular nuclei to motoneurons supplying elevator muscles, including the superior rectus (CN III is oculomotor nucleus). Inputs from the posterior semicircular canals evoke downward eye movements via projections through the medial vestibular nuclei to motoneurons supplying depressor muscles, including the inferior rectus. The flocculus of the cerebellum inhibits anterior but not posterior canal projections in the vestibular nuclei. If inhibition from the flocculus is impaired, the eyes will drift upward causing downbeat nystagmus. (Schematic based on Ito M, Nisimaru N, Yamamoto M. Specific patterns of neuronal connexions involved in the control of the rabbit’s vestibulo-ocular reflexes by the cerebellar flocculus. *J Physiol (Lond)* 1977; 265:833–854; Baloh RW, Spooner JW. Downbeat nystagmus: A type of central vestibular nystagmus. *Neurology* 1981;31:304–310.)

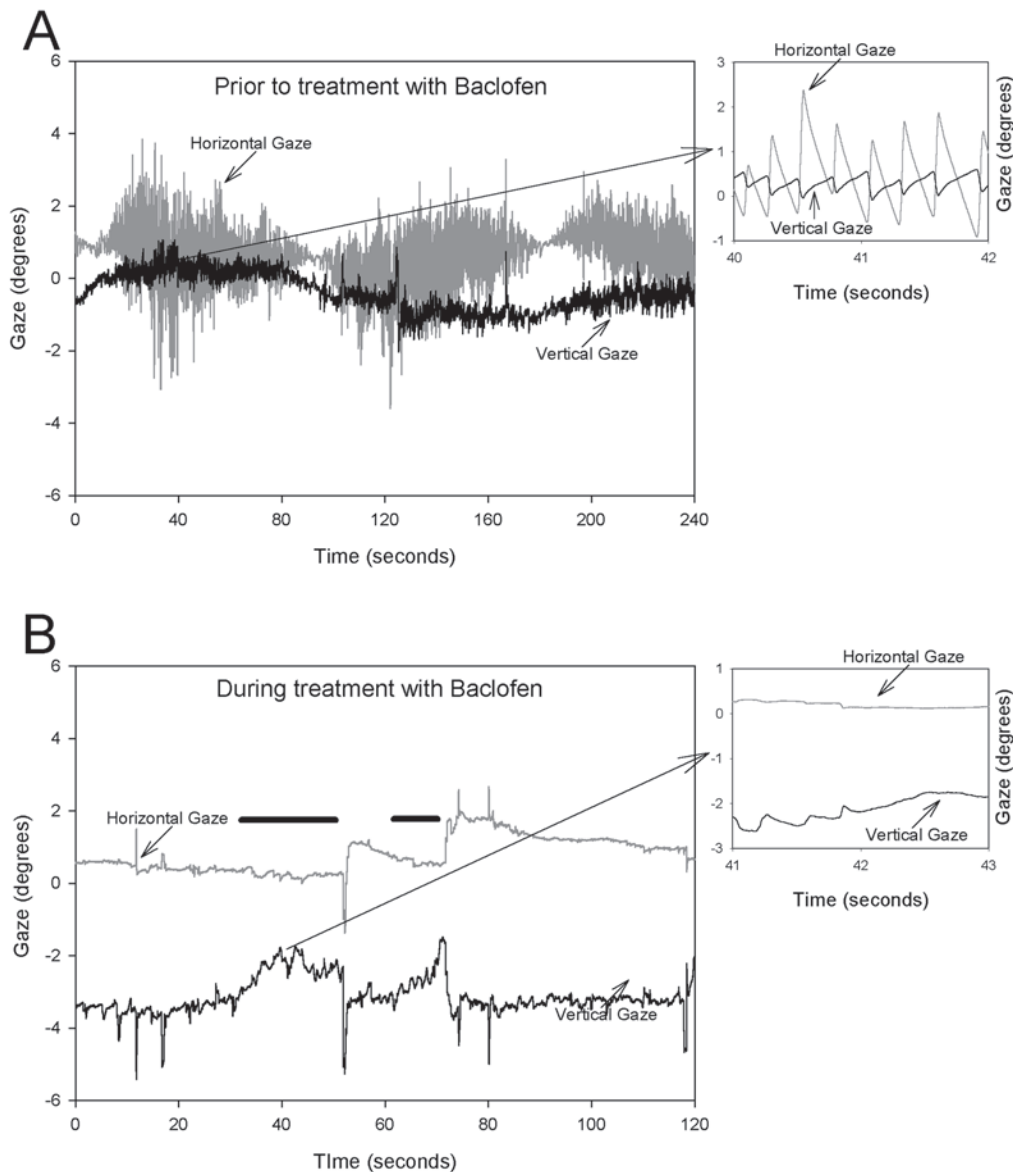


Figure 23.8. Periodic alternating nystagmus in a 24-year-old woman with multiple sclerosis prior to (A) and during (B) treatment with baclofen. Before treatment, PAN reverses direction approximately every 90 seconds; there is an associated downbeat nystagmus (evident in the *inset at right*, which has a magnified time scale). During treatment with baclofen, PAN is essentially abolished, even when the room was switched to complete darkness (indicated by horizontal bars in B, and shown in more detail in inset at right). Upward deflections indicate rightward or upward eye movements. (From Garbutt S, Thakore N, Rucker JC, Han Y, Kumar AN, Leigh RJ. Effects of visual fixation and convergence on periodic alternating nystagmus due to multiple sclerosis. *Neuro-Ophthalmology*, in press.)

conditions (Table 23.5), many of which affect the cerebellum. Experimental ablation of the nodulus and uvula of the cerebellum in monkeys causes PAN when the animals are placed in a dark room. Baclofen abolishes this nystagmus (181). One function of the nodulus and uvula is to control the time course of rotationally induced nystagmus—so-called “velocity storage” (182). Following ablation of the nodulus and uvula, the duration (velocity storage) of rotationally induced nystagmus is prolonged excessively. It is postulated

that normal vestibular repair mechanisms reverse the direction of this nystagmus, thus producing the oscillations of PAN (179,181,182). These oscillations would ordinarily be blocked by visual stabilization mechanisms that tend to suppress nystagmus, but disease of the cerebellum that causes PAN usually also impairs these mechanisms.

Two other unusual disorders may be related to PAN. The first is a variation of PAN, in which oscillations occurred in both the horizontal and vertical planes, 90° out of phase,

Table 23.5
Etiology of Periodic Alternating Nystagmus

Chiari malformations and other hindbrain anomalies
Multiple sclerosis
Cerebellar degenerations
Cerebellar tumor, abscess, cyst, and other mass lesion
Creutzfeldt-Jakob disease
Ataxia telangiectasia
Brainstem infarction
Anticonvulsant medications
Lithium intoxication
Infections affecting cerebellum, including syphilis
Hepatic encephalopathy
Trauma
Following visual loss (from vitreous hemorrhage or cataract)
Congenital nystagmus

and has been called **periodic alternating windmill nystagmus** (183). This phenomenon occurred in a blind patient. The second is the report of a patient with paroxysms of mixed torsional-horizontal-vertical nystagmus that occurred every 2 minutes in association with nausea (184). In this patient, the initial mechanism was probably caused by paroxysmal hyperactivity in one vestibular nucleus complex, unlike PAN, in which prolongation of the vestibular response is the initial mechanism. However, in both entities, an adaptive mechanism appears to influence the nystagmus every 2 minutes. This is perhaps the most direct evidence that dysfunction of an ocular motor recalibration mechanism can lead to nystagmus.

SEESAW AND HEMI-SEESAW NYSTAGMUS

In seesaw and hemi-seesaw nystagmus, one half-cycle consists of elevation and intorsion of one eye and synchronous depression and extorsion of the other eye; during the next half-cycle, the vertical and torsional movements reverse. The waveform may be pendular (185–188) or jerk. In the latter case, the slow phase corresponds to one half-cycle (189). A seesaw component is present in many central forms of nystagmus. Seesaw nystagmus may be congenital (185,190), or acquired (Table 23.6). Quantitative studies have done

Table 23.6
Etiology of Seesaw Nystagmus

Meso-diencephalic disease ^a
Parasellar masses
Brainstem stroke
Septo-optic dysplasia
Chiari malformation
Syringobulbia
Retinitis pigmentosa
Head trauma
Congenital form, including agenesis of optic chiasm, and as a transient finding in albinism

^a Includes hemi-seesaw nystagmus.

much to clarify the characteristics and pathogenesis of seesaw nystagmus. It has been proposed that jerk seesaw nystagmus (hemi-seesaw nystagmus) occurs in patients with lesions in the region of the interstitial nucleus of Cajal (INC) (189), although experimental inactivation of this structure has not produced this nystagmus (191). Such patients often have a contralateral **ocular tilt reaction**. With a right INC lesion, the reaction consists of a left head tilt, a skew deviation with a right hypertopia, tonic intorsion of the right eye and extorsion of the left eye, and misperception that earth-vertical is tilted to the left (189,192). Rarely, the ocular tilt reaction is paroxysmal in form, in which case it is ipsilateral to the INC lesion; however paroxysmal skew deviation is also reported with lesions of the cerebellar uvula (193). Some patients with this condition also show corresponding paroxysms of jerk seesaw nystagmus (189). The ocular tilt reaction is believed to be caused by an imbalance of central otolithic projections from vestibular nuclei to the INC. Stimulation in the region of INC in monkeys, for example, produces an ocular tilt reaction consisting of extorsion and depression of the eye on the stimulated side and intorsion and elevation of the other eye (194); somewhat similar results have been reported in humans (195,196). Thus, the various forms of the ocular tilt reaction are similar to the slow phase of jerk seesaw nystagmus. Isolated INC lesions may be characterized by ipsilesional torsional nystagmus and a restricted range of vertical saccades that are not slowed (197). If the adjacent rostral interstitial nucleus of the MLF (riMLF) is also damaged, however, either no quick phases (189), or contralesional quick phases (198), may be observed. (As discussed in Chapter 17, each riMLF contributes to upward and downward saccades but only to ipsilaterally directed torsional quick phases.)

Pendular seesaw nystagmus has most often been reported in patients with large tumors in the region of the optic chiasm and diencephalon (Fig. 23.9), and thus these oscillations

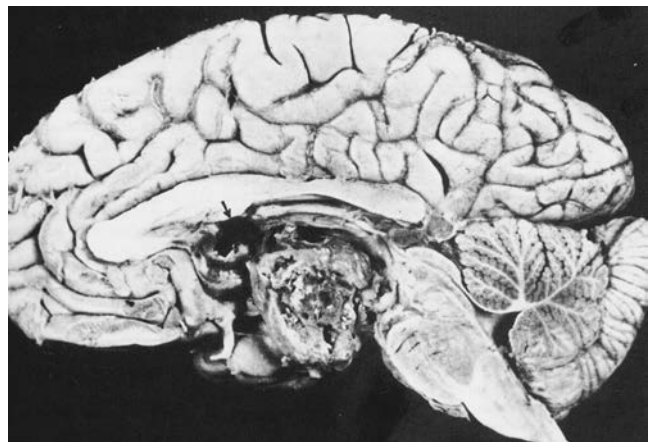


Figure 23.9. Pathology of seesaw nystagmus. A 47-year-old woman developed progressive visual loss and was noted to have bitemporal hemianopia and seesaw nystagmus. The patient died 8 months later, following subtotal removal of a craniopharyngioma. Note that the diencephalon and rostral mesencephalon are compressed and partially destroyed by the tumor that did not, however, obstruct the foramina of Monro (arrow).

have been attributed to either compression of the diencephalon or to the effects of chiasmal visual field defects. One aspect of the vestibular responses concerns movements to compensate for head roll motion if the subject looks at an object located off the midsagittal plane; in this case a seesaw rotation of the eyes is the geometrically appropriate compensation (199). Normal calibration of this response, which

would require that motion-visual information be sent to the cerebellum could be impaired with large suprasellar lesions, leading to the pendular variant of seesaw nystagmus (188). Thus, both the jerk and pendular variants of seesaw nystagmus probably arise from imbalance or miscalibration of vestibular responses that normally function to optimize gaze during head rotations in roll.

NYSTAGMUS DUE TO ABNORMALITIES OF THE MECHANISM FOR HOLDING ECCENTRIC GAZE

GAZE-EVOKED NYSTAGMUS

Nystagmus that is induced by turning the eye to an eccentric position in the orbit is called **gaze-evoked nystagmus**. It is the most common form of nystagmus encountered in clinical practice. Although the terms gaze-evoked nystagmus, end-point nystagmus, and gaze-paretic nystagmus are often used synonymously, gaze-evoked nystagmus is a general term that includes both physiologic and pathologic nystagmus. When the nystagmus is physiologic, the term end-point nystagmus is appropriate (see below). When the nystagmus is associated with a paresis of gaze, as in patients with ocular motor nerve palsies or weakness of the extraocular muscles, the term gaze-paretic nystagmus is appropriate.

Gaze-evoked nystagmus usually occurs on lateral or upward gaze, seldom on looking down. If fixation is impaired or prevented (e.g., in darkness), the slow phases consist of centripetal drifts that may have an exponentially decaying waveform (Fig. 23.1B). If visual fixation is possible, however, the slow phases have a more linear profile.

In order to understand how gaze-evoked nystagmus arises, one must consider the neural command required to hold the eye steadily at an eccentric position in the orbit. When the eye is turned toward a corner of the orbit, the fascia and ligaments that suspend the eye exert an elastic force to return toward central position. Overcoming this elastic restoring force requires a tonic contraction of the extraocular muscles. This is achieved by an eye position signal to the ocular motoneurons, called a step, that is generated by the gaze-holding network, also called the neural integrator. This network includes the vestibulocerebellum, the medial vestibular nucleus and adjacent nucleus prepositus hypoglossi in the medulla, and the interstitial nucleus of Cajal (INC) in the midbrain.

Gaze-evoked nystagmus is caused by a deficient step, such that the eyes cannot be maintained at an eccentric orbital position and are pulled back toward central position by the elastic forces of the orbital fascia. Corrective quick phases then move the eyes back toward the desired position in the orbit. Frequently, lesions that produce gaze-evoked nystagmus also impair visual fixation and smooth pursuit.

Gaze-evoked nystagmus may be caused by a variety of medications, including alcohol, anticonvulsants, and sedatives. Gaze-evoked nystagmus may also be caused by structural lesions that damage the gaze-holding neural network. Experimental lesions of the nucleus prepositus hypoglossi/medial vestibular nucleus region effectively abolish horizontal gaze-holding function (200–202), and also partially impair vertical gaze-holding. Inactivation of INC abolishes ver-

tical gaze-holding function (203). Experimental flocculectomy greatly, but not completely, impairs horizontal gaze holding (168) in addition to causing downbeat nystagmus.

Rarely, cerebellar lesions cause the gaze-holding mechanism to become unstable, so that the eyes drift with increasing velocity away from central position in either the vertical (173) or the horizontal plane (150). This “gaze-instability nystagmus” often violates Alexander’s law.

Another cause of gaze-evoked nystagmus is familial episodic ataxia type 2 (EA-2), which is characterized by attacks of ataxia and vertigo lasting hours, with interictal nystagmus. They nystagmus is typically gaze-evoked with a vertical component that can be downbeat or upbeat. Pursuit and optokinetic responses may be impaired, whereas vestibular responses may be normal or increased (204).

Differences between Physiologic End-Point Nystagmus and Pathologic Gaze-Evoked Nystagmus

Gaze-evoked nystagmus is commonly encountered in normal subjects, in which cases it is often called end-point nystagmus (205–207). It typically occurs on looking far laterally and is poorly sustained. The nystagmus is primarily horizontal. It is usually symmetric, but it may be asymmetric, being more prominent on looking to one side than to the other (207). In some normal persons, the nystagmus is sustained, occurs with less than full deviations of the eye, and may be slightly dissociated or have a torsional component. In addition, some normals show pendular oscillations in far eccentric gaze (208). In such individuals, this physiologic form of gaze-evoked nystagmus can usually be differentiated from that caused by disease, since the former has lower intensity (i.e., slower drift) and, most importantly, is not accompanied by other ocular motor abnormalities. Pathologic gaze-evoked nystagmus, in contrast, is accompanied by other defects of eye movements, such as impaired smooth pursuit (209).

Dissociated Nystagmus

A special type of pathologic gaze-evoked nystagmus is dissociated or “ataxic” nystagmus. This type of nystagmus is most commonly encountered with an **internuclear ophthalmoplegia** (INO). Dissociated nystagmus is, in fact, a series of saccades followed by postsaccadic drift that occurs when the patient attempts to look laterally away from the side of the lesion. Since the saccades initiate the oscillations, this ocular motor abnormality is not a true nystagmus, but rather a series of saccadic pulses. Consider, for example, a

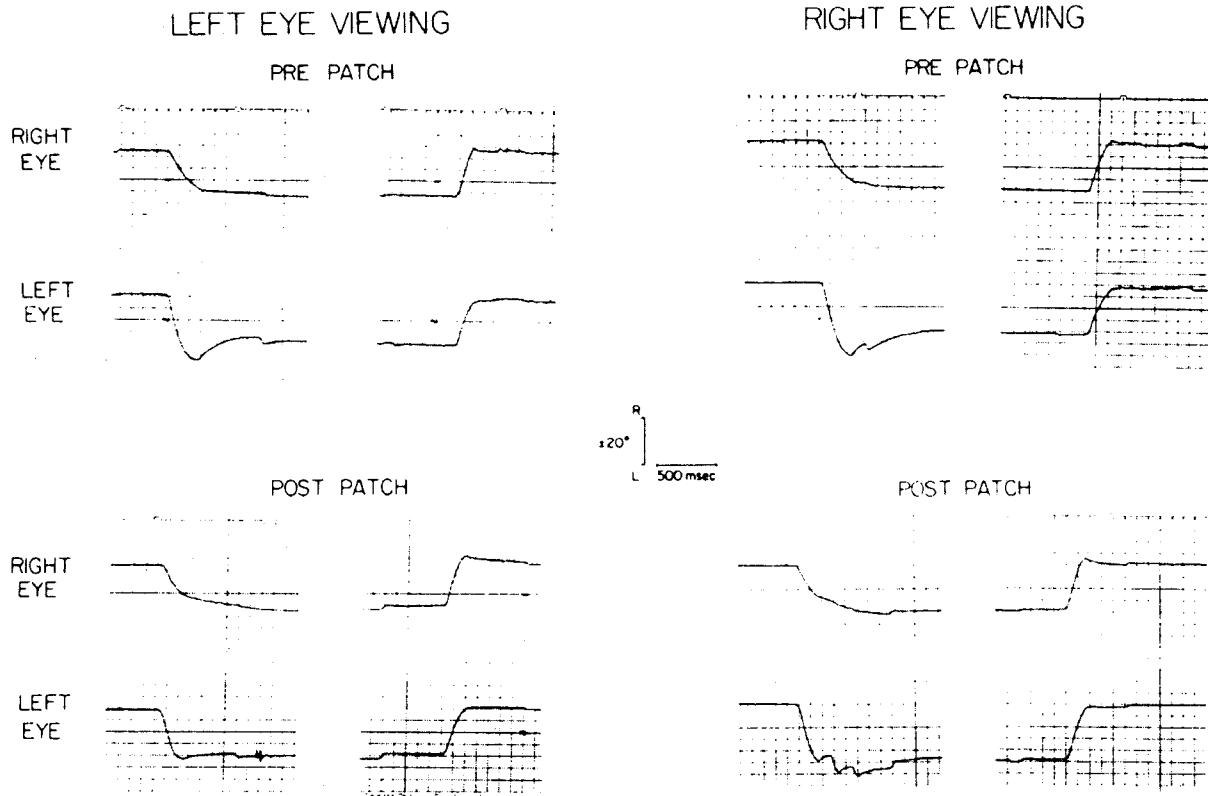


Figure 23.10. Effects of habitual monocular viewing on the eye movements of a patient with unilateral, right internuclear ophthalmoplegia. Pre-patch data were obtained after habitual binocular viewing, but the patient preferred to fixate with the right eye. Post-patch data were obtained after 5 days of patching of the right eye to ensure habitual left eye viewing. Left and right eye viewing refer to the viewing conditions at the time the eye movements were recorded. *Post-patch:* Note the decrease in the abduction nystagmus of the left eye (decrease in the size of the abduction saccadic pulse and of the backward postsaccadic drift), with a commensurate decrease in the size of the saccadic pulse and increase of the onward postsaccadic drift for the adduction saccades made by the right eye. These changes were independent of which eye was viewing during the recording session. Patching led to little change in the adducting saccades made by the left eye or abducting saccades made by the right eye (vertical bar indicates +20°; horizontal bar, 500 msec). (From Zee DS, Hain TC, Carl JR. Abduction nystagmus in internuclear ophthalmoplegia. *Ann Neurol* 1987;21:383–388.)

patient with a right-sided INO (Fig. 23.10, *top*). When the patient attempts to look to the left, the adducting saccades of the right eye are slow and hypometric. Each consists of a hypometric pulse, followed by a glissadic drift of the eye toward the target. Abducting saccades in the left eye are hypermetric, overshooting the target, and are followed by a glissadic backward drift of the eye. A series of such small saccades and drifts gives the appearance of dissociated nystagmus. Because of the difference in the velocity of the adducting saccades in the eye on the side of the lesion and the abducting saccades in the contralateral eye, comparison of horizontal saccades made by each eye is most useful in making the diagnosis of an INO. When the INO is subtle, moving an optokinetic tape or rotating an optokinetic drum toward the side of the affected medial rectus muscle induces asymmetric quick phases, with smaller-sized movements in the affected eye. Some caution is required in interpreting this sign, however, since abducting saccades are normally slightly faster than adducting saccades (210). In addition,

there are settings other than an INO in which patients may show an asymmetry of saccadic velocities, with the adducting eye moving more slowly than the abducting eye (discussion following). Nevertheless, when one observes slowed adducting saccades in one eye and normal abducting saccades in the opposite eye in a patient with no previous history of strabismus surgery, a diagnosis of INO is likely. Quantitative comparison of the velocity of the two eyes may be required to make the diagnosis of INO in subtle cases (211).

Several explanations have been offered to account for dissociated nystagmus in INO (9,212), but the most plausible suggestion is that it represents an attempt by the brain to adaptively correct hypometric saccades due to the weak medial rectus muscle. Acute experimental INO by local anesthetic blockade of the medial longitudinal fasciculus (MLF), produces paresis of the ipsilateral medial rectus, but does not produce abducting nystagmus in the contralateral eye (213). To compensate for the weakness of the medial rectus,

there may be an adaptive increase in innervation to the abducting eye and, because of Hering's law of equal innervation, a commensurate increase in the innervation to the normal, abducting eye results. Although this adaptive change may help get the paretic eye on target, it leads to overshooting saccades and postsaccadic drift of the abducting eye if the patient attempts to fixate with the ipsilesional eye. Support for this interpretation comes from the observation that patching the eye with the adduction weakness for several days almost abolishes the overshoot and pulse-step mismatch of the abducting eye when the latter eye fixates (Fig. 23.10, *bottom left*) (212). Additional support for the view that the abduction nystagmus of an INO is a compensatory response to a "peripheral" weakness comes from the observation that surgically caused medial rectus weakness leads to a similar nystagmus, which resolves if the eye with the weak medial rectus is patched for several days (214). In addition to previous extraocular muscle surgery, both myasthenia gravis (215) and the Miller Fisher syndrome (216) may produce a dissociated nystagmus similar to that seen in an INO.

Dissociated nystagmus characterized by larger movements in the **abducting** eye occurs when some patients with abducens nerve palsy look into the paretic field (9). Indeed, whenever a patient habitually prefers to fixate with a paretic eye, the normal eye will show a dissociated nystagmus while looking in the direction of action of the paretic muscle, regardless of the pathogenesis of the weakness.

Bruns' Nystagmus

Tumors in the cerebellopontine angle, such as meningiomas or schwannomas of the vestibulocochlear nerve, may produce a low-frequency, large-amplitude nystagmus when the patient looks toward the side of the lesion, and a high-frequency, small-amplitude nystagmus when the patient looks toward the side opposite the lesion. The nystagmus that occurs on gaze toward the side of the lesion is gaze-evoked nystagmus caused by defective gaze holding, whereas the nystagmus that occurs during gaze toward the side opposite the lesion is caused by vestibular imbalance. This special nystagmus is called **Bruns' nystagmus** (217,218).

CONVERGENCE-RETRACTION NYSTAGMUS

So-called convergence-retraction nystagmus is characterized by quick phases that converge or retract the eyes on attempts to look up. It is elicited either by asking the patient to make an upward saccade or by using a handheld optokinetic drum or tape and moving the stripes or figures down. This maneuver produces slow, downward, pursuit eye movements, but upward quick phases are replaced by rapid convergent movements, retractive movements, or both. Affected patients usually have impaired or absent upward gaze for both pursuit and saccadic eye movements; however, in some cases upward pursuit appears normal, whereas upward saccades are obviously abnormal. Convergence-retraction nystagmus is commonly produced by lesions of the mesen-



Figure 23.11. Pathology of convergence-retraction nystagmus. A pinealoma is compressing the dorsal midbrain of a 13-year-old boy who also had inability to elevate the eyes above the horizontal midline, limitation of downward gaze, and anisocoria.

cephalon that damage the posterior commissure, such as pineal tumors (219–221); an example is shown in Figure 23.11. It has been proposed that convergence-retraction nystagmus is, in fact, a saccadic disorder rather than nystagmus because the primary adductive movements are asynchronous abducting saccades (222). However, other studies have indicated that the movements may be vergence in origin (223); more studies are needed to resolve this issue. During horizontal saccades, the abnormal pattern of convergent innervation manifests itself as slowing of the abducting eye: "pseudo-abducens palsy" (219,221). Convergence-retraction nystagmus may also occur with a Chiari malformation or epileptic seizures (224,225). Convergence-retraction nystagmus is usually intermittent, being determined by saccadic activity, and it thus can be differentiated from other more continuous forms of disjunctive nystagmus, such as convergent-divergent pendular nystagmus (29,79) and the oculomasticatory myorhythmia characteristic of Whipple's disease (80).

Jerk-waveform **divergence nystagmus** is diagnosed infrequently, but it may occur in patients with cerebellar disease, such as the Chiari malformation. In such cases, combined divergent and downbeat nystagmus produces slow phases that are directed upward and inward (139).

CENTRIPETAL AND REBOUND NYSTAGMUS

If a patient with gaze-evoked nystagmus attempts to look eccentrically for a sustained period, the nystagmus may begin to decrease in amplitude and may even reverse direction, so that the eye begins to drift centrifugally ("centripetal nystagmus") (226). If the eyes are then returned to the central position, a short-lived nystagmus with slow drifts in the direction of the prior eccentric gaze occurs. This is called **rebound nystagmus** (227,228). Both centripetal and rebound nystagmus may reflect an attempt by brainstem or cerebellar mechanisms to correct for the centripetal drift of

gaze-evoked nystagmus. Rebound nystagmus typically occurs in patients with cerebellar disease, but it has been reported following experimental lesions in the region of the nucleus prepositus hypoglossi and medial vestibular nucleus (200), and in normal subjects with typical gaze-evoked nystagmus (207). Extreme gaze deviation away from the side of the lesion in one patient with a lateral medullary infarction was reported to cause this type of paroxysmal nystagmus and vertigo lasting about 1 minute (229). Such a phenom-

enon could be explained by a sustained eye position signal causing an imbalance of central vestibular mechanisms. Rebound nystagmus has been reported in a patient with a tumor confined to the flocculus (230); other ocular motor abnormalities, including impaired smooth pursuit and gaze-evoked nystagmus persisted after the tumor invaded the vestibular nuclei, but the rebound nystagmus disappeared. Such findings have suggested that rebound is due to the development of a bias within the vestibular nuclei.

CONGENITAL FORMS OF NYSTAGMUS

NATURE AND FORMS OF CONGENITAL OCULAR OSCILLATIONS

In this section, we review those forms of nystagmus that develop during infancy (231). Advances have been made with the identification of congenital forms of nystagmus in mutant dogs with abnormal anatomy of the visual system (47), and in normal monkeys that are deprived of binocular vision during early life (232). However, although some patients with congenital nystagmus show visual abnormalities, others with similar ocular oscillations do not. Furthermore, the characteristic waveforms, e.g., pendular (Fig. 23.1D) or jerk (Fig. 23.1A), do not specify pathogenesis or indicate whether the congenital nystagmus is associated with visual system anomalies (18). Thus, the underlying mechanisms are not fully understood. Three distinct syndromes are currently recognized: congenital nystagmus, latent nystagmus, and spasmus nutans.

Although there is no widely accepted classification of nystagmus in infancy, the Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group (233) has proposed that the term infantile nystagmus syndrome (INS) be used to encompass what has previously been called congenital nystagmus, including motor or sensory varieties. The main criteria for defining INS are infantile onset and accelerating slow-phase waveforms (Fig. 23.1C). However, a potential problem posed by the CEMAS classification for some ophthalmologists is that measurement of eye movements, which is necessary to characterize the waveforms, may not be available. In addition, CEMAS has called latent nystagmus Fusional Maldevelopment Nystagmus Syndrome (FMNS). In this chapter, we will continue to use the terms “congenital nystagmus” and “latent nystagmus” but the reader should note that a transition of terminology may occur in the neuro-ophthalmological community over the next few years.

CONGENITAL NYSTAGMUS

Clinical Features

Congenital nystagmus is usually diagnosed during infancy, but occasionally presents during adult life (234,235) when it may create a diagnostic problem, especially if the patient has other symptoms, such as headaches or dizziness. Certain clinical features usually differentiate congenital nystagmus from other ocular oscillations. It is almost always conjugate and horizontal, even on up or down gaze. A small

torsional component to the nystagmus is probably common (236), but is difficult to identify clinically. Only rarely is congenital nystagmus purely vertical (237–239). Congenital nystagmus is usually accentuated by the attempt to visually fixate an object and by attention or anxiety. Eyelid closure (240) and convergence usually suppress it (241–243), but occasionally congenital nystagmus is evoked by viewing a near target (79,244). Its intensity may also be influenced by viewing the vertical lines of an optokinetic tape (245). Congenital nystagmus often decreases when the eyes are moved into a particular position in the orbit, called the “null” region. In some patients, the direction of the nystagmus spontaneously reverses direction during sustained viewing of a fixation point (18,246,247). The direction of the nystagmus may also be influenced by which eye is viewing, with the nystagmus beating away from the covered eye; this is similar to latent nystagmus (see below).

The most distinctive feature of congenital nystagmus is its waveforms, the most common of which are increasing-velocity (Fig. 23.1C) and pendular (Fig. 23.1D). Frequently superimposed on these waveforms, which may be combined, are **foveation periods**—the hallmark of congenital nystagmus (18,248,249). During each cycle, usually after a quick phase, there is a brief period when the eye is still and is pointed at the object of regard. With jerk waveforms, the quick phases (saccades) may brake the oscillation (250) or bring the eye to the target. With pendular waveforms, the oscillation is flattened by a foveation period when the eye is closest to the target (Fig. 23.12). The particular waveform that is seen in a patient with congenital nystagmus depends in part upon the patient’s age. Most infants show large-amplitude “triangular” waveforms. Shortly thereafter, the waveform becomes pendular, but it changes again to a jerk type as the patient reaches about one year of age (251,252). These waveforms are so characteristic of congenital nystagmus that reliable records of eye position and velocity will often secure the diagnosis.

In those individuals with congenital nystagmus that spontaneously changes direction, the timings of reversal tend to be this irregular. This aperiodic alternating congenital nystagmus appears to have a different pathogenesis than acquired periodic alternating nystagmus (247,253,254).

Foveation periods are only rarely reported in acquired forms of nystagmus (255). They are probably one reason (along with elevated thresholds for motion detection) why most patients with congenital nystagmus do not complain of oscillopsia, despite otherwise nearly continuous move-

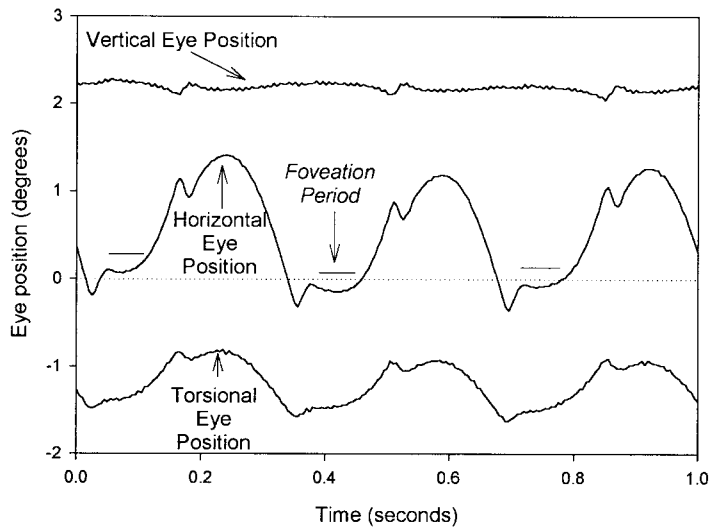


Figure 23.12. A pendular type of congenital nystagmus waveform with superimposed quick phases, showing the large horizontal component, smaller torsional component, and almost absent vertical component. Note that vertical and torsional channels have been offset to aid clarity of display. Foveation periods follow quick phases (when eye position is close to zero) and are indicated by horizontal bars. Upward deflections indicate rightward (horizontal), upward (vertical), or clockwise (torsional) eye rotations, with respect to the patient.

ment of their eyes (8,256–262), and why many have normal visual acuity (263,264). However, foveation periods are not invariably present in congenital nystagmus. When they are absent or poorly developed, vision is usually impaired (265).

Up to 30% of patients with congenital nystagmus also have strabismus (266). A commonly described associated finding in such patients is “inverted pursuit” or “reversed optokinetic nystagmus” (267). With a handheld optokinetic drum or tape, quick phases are directed in the same direction as the drum rotates or the tape moves. In fact, based on measurements made of tracking during the foveation period, it has been shown that both smooth pursuit and optokinetic eye movements are preserved in at least some individuals with congenital nystagmus (268,269). Similarly, vestibular responses are generally normal in patients with congenital nystagmus if judged by retinal image stability during foveation periods (270,271). Thus, their view of the world is similar whether they are stationary or in motion (272). In those patients with associated visual disorders such as albinism, however, vestibular responses to lower frequencies of head rotations and optokinetic responses may be impaired (273,274).

Occasional patients exhibit congenital nystagmus only during attempted smooth tracking (275), and others can voluntarily release or inhibit their congenital nystagmus, suggesting that fixation plays some role in the oscillations (276). Congenital nystagmus associated with congenital gaze-holding failure (i.e., leaky neural integrator) has been reported in a kindred (277) suggesting that, at least in this family, instability of the gaze-holding mechanism (neural integrator) is unlikely to have been the primary cause of the nystagmus.

Head turns are common in patients with congenital nystagmus and are an adaptive strategy to bring the eyes close to the null position in the orbit, where nystagmus is reduced (278). The observation of such a head turn in childhood photographs is often helpful in diagnosing congenital nystagmus. Another strategy used by patients with either congenital or latent nystagmus (discussion following) is to pur-

posely induce an esotropia to suppress the nystagmus. Such an esotropia requires a head turn to direct the viewing eye at the object of interest. This phenomenon is called the nystagmus blockage syndrome (279,280).

Some patients with congenital nystagmus also show head oscillations (271,281,282). Such head movements cannot act as an adaptive strategy to improve vision, however, unless the vestibulo-ocular reflex is negated. In fact, head movements are not compensatory in most patients with congenital nystagmus and tend to increase when the individual attends to an object, an effort that also increases the nystagmus. It seems possible, therefore, that the head tremor and ocular oscillations represent the output of a common disordered neural mechanism (282).

Pathogenesis of Congenital Nystagmus

As noted earlier, nystagmus developing early in life and showing some of the waveform characteristics of congenital nystagmus in humans also occurs in mutant dogs who lack the normal hemidecussation of fibers in the optic chiasm (47), and in normal monkeys who are subjected to monocular visual deprivation in infancy (232). It is also associated with a variety of visual system disorders, including ocular and oculocutaneous albinism (283–286), achromatopsia, retinal cone dystrophy, optic nerve hypoplasia, Leber’s congenital amaurosis, retinal coloboma, aniridia, corectopia, congenital stationary night blindness, Chédiak-Higashi syndrome, Joubert syndrome, and peroxisomal disorders (287). Because of the many diagnostic possibilities, a complete ophthalmologic evaluation and an electroretinogram must be performed in patients with congenital nystagmus associated with decreased visual acuity or visual dysfunction (287–289). Congenital nystagmus, both with and without associated visual system abnormalities, may be familial (290). Several modes of inheritance have been reported (231,291–293); in X-linked forms (292), the mothers may show subtle ocular motor abnormalities. Congenital nystagmus, with some similarities of waveform, has been reported

in monozygotic twins (294). However, there may be considerable differences in waveforms among members of a single family with hereditary congenital nystagmus (290).

The known anatomic variations of the anterior visual system in individuals with congenital nystagmus, such as excessive crossing at the chiasm in association with albinism (295–297), or absent crossing of nasal fibers in achiasmatic subjects with congenital seesaw nystagmus (47–49), have led to the development of models for congenital nystagmus based on “miswiring” of visual pathways (276,298). A model postulating that maladaptation to early visual deprivation leads to instability of the gaze-holding mechanisms has also been proposed (299). Further work is required to validate these models.

LATENT (OCCLUSION) NYSTAGMUS

Clinical Features

True **latent nystagmus** is a horizontal jerk nystagmus that is absent when both eyes are viewing but appears when one eye is covered. This conjugate nystagmus is characterized by quick phases of both eyes that beat toward the side of the fixating eye. In most patients, a low-amplitude nystagmus is also present when both eyes are viewing, and is called “manifest latent nystagmus” (300). It apparently occurs because only one eye is fixating, and vision from the other deviated eye is suppressed (301,302). Latent nystagmus usually reverses direction upon covering of either eye. In some patients, however, it is present when one eye is covered but is absent when the other is covered. Occasional patients can control their latent nystagmus at will (303). Latent nystagmus is usually associated with strabismus, typically esotropia (304). Amblyopia is frequent, whereas binocular vision with normal stereopsis is rare. Latent nystagmus has been described in identical twins (305).

The slow phase of latent nystagmus usually shows a decaying velocity waveform when the eyes are close to central position (Fig. 23.1B), in contrast to the increasing velocity waveform of congenital nystagmus. A number of studies suggest that foveation may occur during the slowest part of the drift if the amplitude of the nystagmus is large, and immediately after the quick phase if the amplitude is small (306). Latent nystagmus usually follows Alexander’s law, with the nystagmus being greatest on looking in the direction of the quick phases, away from the covered eye. Some patients turn the head to keep the viewing eye in an adducted position, where nystagmus is minimal. Occasionally, congenital and latent nystagmus coexist, in which case the waveforms may be quite complex. Rarely, in such patients, if vision is clearer with the latent nystagmus waveforms than with the congenital nystagmus waveforms, the patients switch from congenital to latent nystagmus as one eye becomes esotropic and the other takes up fixation (279). In addition to strabismus, patients with latent nystagmus frequently show an upward deviation of the covered eye (alternating sursumduction or dissociated vertical deviation) (307). In such patients, the nystagmus often has a torsional component (307). Latent nystagmus is quite common, and accurate diagnosis is important to avoid inappropriate inves-

tigations. It should be differentiated from gaze-evoked nystagmus in association with strabismus, especially abducting nystagmus occurring with INO, in which an exotropia may be present.

Pathogenesis of Latent Nystagmus

Latent nystagmus is thought to be caused by a defect in cortical motion processing that results from lack of development of binocular vision (308). It is a common feature of Down’s syndrome (309). Individuals with latent nystagmus often show impaired initiation of smooth pursuit in a specific pattern: nasal target motion evokes more vigorous pursuit than temporal motion, and vertical optokinetic motion evokes responses with horizontal components (17). A related theory is that latent nystagmus is caused by an imbalance in the subcortical optokinetic system (308), perhaps secondary to a loss of cortical motion detectors. This would account for the temporal-nasal directional predominance of monocular optokinetic responses shown by some patients with latent nystagmus and of normal infants prior to maturation of cortical vision (310). Animal models of monocular deprivation support this view (311). Another proposal is that latent nystagmus is caused by a defect in the influence of the internal representation of egocentric coordinates upon the direction of gaze. Support for this hypothesis comes from the observation that a patient with lifelong monocular blindness was able to reverse the direction of his latent nystagmus by attempting to view from his blind eye (312). It is also possible that an abnormality of extraocular proprioception predisposes to latent nystagmus (313), since extraocular proprioception is important for the normal development of binocularity (314). These proposed mechanisms may not be mutually exclusive, and their relative importance is unclear.

SPASMUS NUTANS

Spasmus nutans is characterized by the triad of nystagmus, head nodding, and an anomalous head position, such as torticollis (315). It usually begins in the first year of life, although it may not be detected until the child is 3 or 4 years old. Neurologic abnormalities are absent, although strabismus or amblyopia may coexist. The syndrome is sometimes familial and has been reported in monozygotic twins (316). Spasmus nutans spontaneously remits, usually within 1 to 2 years after onset, although it may last for over 8 years (317).

The most consistent feature of spasmus nutans is the nystagmus, although head nodding may be the first abnormality to be noticed (45,317–319). Because the nystagmus is usually intermittent and has a small-amplitude, high-frequency (3–11 Hz) pendular waveform, it can easily be overlooked. When recognized, however, it has a “shimmering” quality.

The nystagmus of spasmus nutans almost always differs in the two eyes, and it may even be uniocular (Fig. 23.13). Other distinguishing features are the variability of the amplitude of nystagmus in each eye and the difference in the phase relationship between the two eyes. Even over the course of a few seconds or minutes, the oscillations may variably be conjugate, disconjugate, dissociated, or purely monocular (Fig. 23.13). The plane of the nystagmus is predominantly

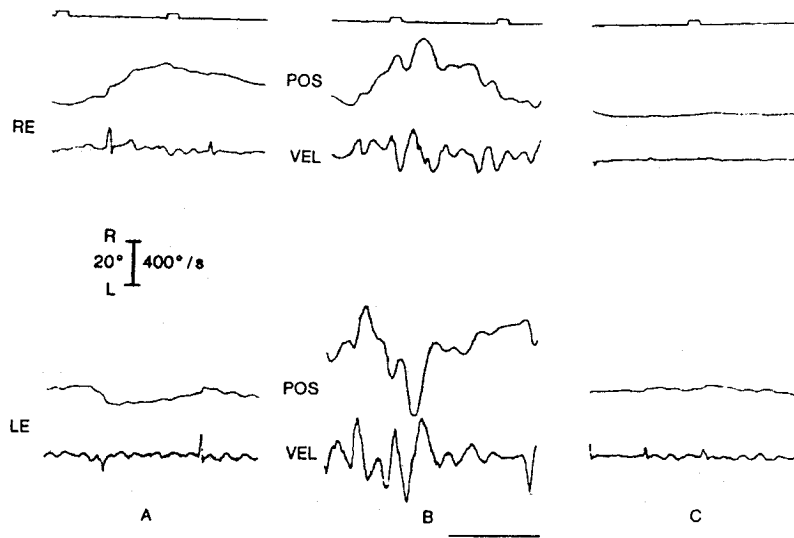


Figure 23.13. Examples of nystagmus of spasmus nutans from one child during a single recording session. *A*, There are binocular oscillations with no phase difference between the eyes. *B*, There are binocular oscillations with an approximately 180° phase difference between the eyes. *C*, There are unocular oscillations of the left eye. LE, left eye; RE, right eye; POS, position; VEL, velocity; timing marks at top of records indicate 1-second intervals. (From Weissman BM, Dell'Osso LF, Abel LA et al. Spasmus nutans: A quantitative prospective study. *Arch Ophthalmol* 1987;105:525–528.)

horizontal, but it may have vertical or torsional components. It may sometimes be brought out by evoking the near response (320).

The head nodding of spasmus nutans is irregular, with horizontal or vertical components. It is usually more prominent when the child attempts to inspect something of interest. About two-thirds of the patients have an additional head tilt or turn. In some patients, the head nodding appears to turn off the nystagmus (318,319); however, it is unclear whether head nodding, turning, or tilting are always adaptive strategies adopted to reduce the nystagmus or if they are simply another manifestation of the underlying abnormality in the central nervous system.

Two main clinical decisions must be made by the physician who sees a child with eye and head oscillations. The first is to determine if the nystagmus is associated with reti-

nal disease or a tumor of the visual pathway, particularly an optic chiasmal glioma (43,44,321). A careful ophthalmologic evaluation must be performed in all children, with particular emphasis on the anterior visual system. If there is any suggestion that the child has optic nerve or chiasmal dysfunction, neuroimaging studies should be performed. Some experts recommend that neuroimaging be performed on all children, given the difficulties inherent in eliciting a history of visual loss, and ophthalmoscopy, in small children. The second decision is to determine whether the ocular motor disturbance is actually spasmus nutans, which will resolve over time, or congenital nystagmus, which probably will not. Spasmus nutans usually can be differentiated from congenital and latent nystagmus by its intermittency, high frequency, and dissociated characteristics. If the child will cooperate, eye movement recordings often help differentiate between these two entities (45).

EYE MOVEMENTS DURING EPILEPTIC SEIZURES

Several forms of nystagmus occur as manifestations of epileptic seizures (322–326). Although such **epileptic nystagmus** is probably quite common, only rarely have eye movements been reliably measured during seizures.

Patients with epileptic foci affecting portions of the cortex concerned with the programming of smooth pursuit and saccades (see Chapter 17) may show either ipsiversive or contraversive eye deviation and nystagmus. In patients with epileptic saccadic activity, the underlying focus usually affects the occipito-temporo-parietal junction (322). In one such patient who had a right temporo-occipital focus, the seizure began with a contraversive (leftward) gaze deviation due to a staircase of small saccades (324). After a few seconds, left-beating nystagmus commenced, with slow phases that showed a decreasing-velocity waveform. The nystagmus was accompanied by high-voltage spike activity of 11–14 Hz that did not spread to the frontal cortex. At the end of the seizure, the eyes returned to central position. This patient was unresponsive, partly from a metabolic encephalopathy.

Her gaze deviation was initiated by saccades, and the subsequent nystagmus was probably caused by an impaired gaze-holding mechanism (i.e., a deficient neural integrator).

In another patient, who also had a seizure focus in the right temporo-occipital cortex, the initial eye movement was an ipsiversive gaze deviation, followed by a left-beating nystagmus that had linear slow phases (326). During the nystagmus, sharp wave activity of 12–14 Hz occurred. The patient with the ipsiversive deviation was conscious throughout the entire attack. His gaze deviation may have been a smooth pursuit movement, with the resetting leftward-beating quick phases of nystagmus triggered by the eccentric eye position and ipsilateral rightward drift of the eyes.

Thus, contraversive quick phases in epileptic patients may result from two different mechanisms. First, they may be primary, contraversive saccades that are caused by epileptic activity in the saccadic regions, and that are followed by centripetal drift from impaired gaze-holding. Such drifts are often seen in patients taking antiepileptic medications. Sec-

ond, they may be secondary, reflexive contraversive saccades that are correcting a slow ipsiversive deviation across the midline that is caused by epileptic activation of either the smooth pursuit or optokinetic regions. The second mechanism produces true nystagmus, whereas the first is actually a saccadic disorder. Experimental studies in awake monkeys indicate that the threshold for stimulating pursuit eye movements is lower than that for stimulating saccades (327).

EYELID NYSTAGMUS

Several studies have defined the anatomic and physiologic links between eye and eyelid movements (329–332), and have evaluated the common effects of disease on both (330). Upward movements of the eyelids frequently accompany upward movements of vertical nystagmus. In fact, the absence of lid nystagmus in a patient with upbeat nystagmus may suggest disconnection between the premotor signals for the superior rectus and levator palpebrae superioris, implicating the region between the riMLF and the oculomotor nucleus. For the same reasons, lid nystagmus unaccompanied by vertical eye nystagmus may reflect midbrain lesions (333,334). In patients with long-standing compression of the central caudal nucleus, “midbrain ptosis” may occur (see Chapter 24), and this may lead to lid nystagmus (334).

Occasionally, twitches of the eyelid accompany horizontal

To induce epileptic nystagmus in awake patients, the frequency of discharge must be high (above 10 spikes per second) and must affect the temporo-parieto-occipital junction area (322). In patients with coexistent brainstem lesions, the only manifestation of such activity may be rapid, small-amplitude, vertical eye movements (328). The absence of horizontal movements in such patients reflects dysfunction of the paramedian pontine reticular formation (PPRF).

nystagmus. This phenomenon was described in a patient with Wallenberg’s lateral medullary syndrome (335), in whom lid nystagmus was inhibited by convergence. In other patients, eyelid nystagmus may be induced by convergence. This is called Pick’s sign (336–338). In both cases, lesions are often present in the medulla, cerebellum, or both structures (336,337). The curious association of eyelid nystagmus with convergence may occur because the eyelid normally retracts with near effort. Therefore, any compromise of lid function will become more evident on attempt to converge. Eyelid nystagmus has been likened to the pathologic form of gaze-evoked nystagmus that occurs in patients with cerebellar disease and that is often associated with downward drifts of the eyelids, followed by corrective rapid upward movements (337).

SACCADIC INTRUSIONS

COMMON FEATURES OF SACCADIC INTRUSIONS

Several types of inappropriate saccadic eye movements may intrude upon steady fixation. These are schematized in Figure 23.14, and actual recorded examples are shown in Figure 23.15. Saccadic intrusions must be differentiated from nystagmus, in which a drift of the eyes from the desired position of gaze is the primary abnormality, and from saccadic dysmetria (Fig. 23.14A), in which the eye over- or under-shoots a target, sometimes several times, before achieving stable fixation (339,340). Because all of these movements are often rapid and brief, it may be necessary to measure eye and target position, as well as eye velocity, in order to identify accurately the saccadic abnormality. In this section, we first describe the characteristics of each type of saccadic intrusion and then review possible mechanisms of pathogenesis.

SQUARE-WAVE JERKS

Square-wave jerks, also called *Gegenrucke*, are a common finding in healthy persons, particularly the elderly (341–344). They have a typical profile on eye movement records, and it is this profile from which their name is derived. They are small, conjugate saccades, ranging from 0.5 to 5.0° in size, that take the eye away from the fixation position and return it after about 200 milliseconds (Figs. 23.14C and 23.15A). They are often more prominent during smooth pursuit, are most easily detected during ophthalmoscopy, and are also present in darkness.

Square-wave jerks with an increased frequency (up to 2

Hz) occur in certain cerebellar syndromes (345,346), in progressive supranuclear palsy (347,348), and in cerebral hemispheric disease (349). When very frequent, they are called square-wave oscillations (350). These movements may be mistaken for nystagmus. Cigarette smoking increases the frequency of square-wave jerks (351,352).

MACROSQUARE-WAVE JERKS (SQUARE-WAVE PULSES)

Macrosquare-wave jerks are large eye movements, typically greater than 5°, that occur at a frequency of about 2–3 Hz. After taking the eye off the target, they return it after a latency of about 80 milliseconds (Fig. 23.14D) (353). These eye movements occur in light or darkness, and they occasionally are suppressed during monocular fixation (354). Macrosquare-wave jerks occur in bursts and vary in amplitude. They are encountered in disease states that disrupt cerebellar outflow, such as MS.

MACROSACCADIC OSCILLATIONS

Macrosaccadic oscillations usually consist of horizontal saccades that occur in bursts, initially building up and then decreasing in amplitude, with intersaccadic intervals of about 200 milliseconds (Figs. 23.14B and 23.15C). Described originally in cerebellar patients, macrosaccadic oscillations are thought to be an extreme form of saccadic dysmetria, in which the patient’s saccades are so hypermetric that they overshoot the target continuously in both directions and thus oscillate around the fixation point (355,356). They

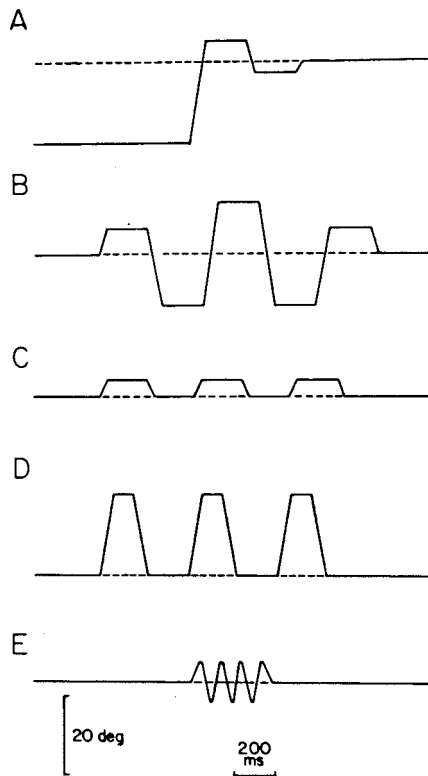


Figure 23.14. Schematic drawings of various saccadic oscillations. *A*, Saccadic dysmetria: Saccades with inappropriate amplitudes that occur in response to target jumps. *B*, Macrosaccadic oscillations: Hypermetric saccades about the position of the target. *C*, Square-wave jerks: Small, inappropriately occurring saccades away from and back to the position of the target. *D*, Macrosquare-wave jerks: Large, uncalled-for saccades away from and back to the position of the target. *E*, Ocular flutter: To-and-fro back-to-back saccades without an intersaccadic interval. (From Leigh RJ, Zee DS. *The Neurology of Eye Movements*. Ed 3. Philadelphia, FA Davis, 1991.)

are usually induced by a gaze shift, but they may also occur during attempted fixation or even in darkness (357). They are often visually disabling (358). They may have vertical or torsional components and, occasionally, the former may be quite prominent clinically (359). Macrosaccadic oscillations are occasionally encountered in patients with myasthenia gravis after administration of edrophonium (360). In such patients who have severe ophthalmoparesis, suddenly reversing the neuromuscular block with edrophonium reveals the adaptive efforts that the brain has been making—increasing innervation (gain) especially for saccades. Consequently, for a short period, saccadic gain is too high and the eyes oscillate either side of a visual target.

SACCADIC PULSES, OCULAR FLUTTER, AND OPSOCLONUS

Saccadic pulses are brief intrusions upon steady fixation. They are produced when a saccadic pulse is unaccompanied by a step command. The eye movement thus consists of a saccade away from the fixation position, with a rapid drift

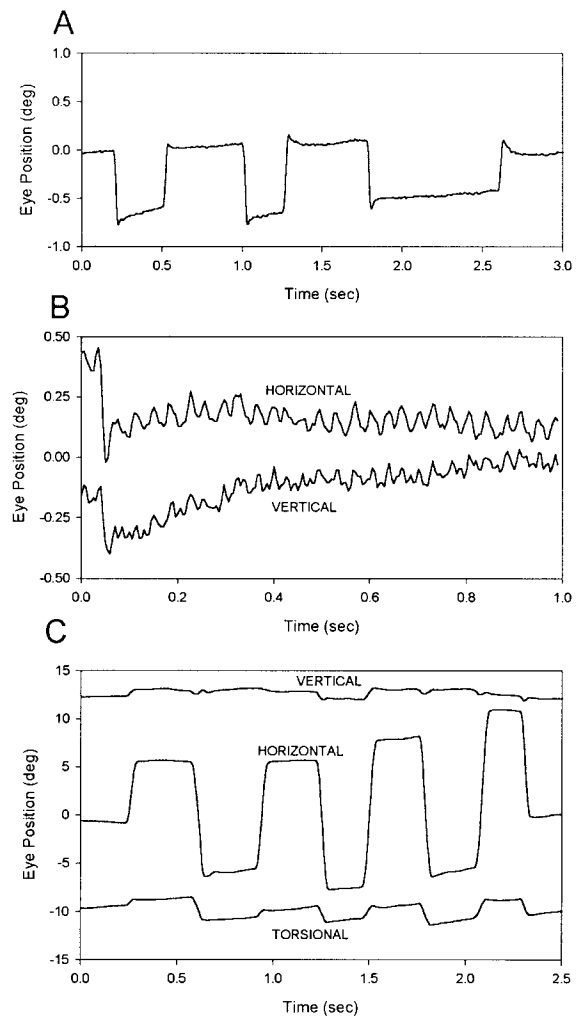


Figure 23.15. Actual recordings of saccadic oscillations. *A*, Horizontal saccadic intrusions (square-wave jerks) that repeatedly move the image of regard off the fovea. The patient had progressive supranuclear palsy. *B*, Diagonal microsaccadic flutter that was detectable only with an ophthalmoscope, but because of its high frequency it caused oscillopsia and impaired vision in this patient, who was otherwise well. *C*, Macrosaccadic oscillations from the right eye of a patient with a pontine infarction (357). Fixation is interrupted by bursts of saccadic intrusions that are time-locked in the horizontal, vertical, and torsional planes. The return saccade usually overshoots the central fixation point. Torsional and vertical tracings have been offset for convenience of display. Upward deflections correspond to rightward, upward, or clockwise eye rotations, with respect to the patient.

back. Saccadic pulses may occur in series or as doublets. They are encountered in some normal subjects and in patients with MS (361). Saccadic pulses may occur in other disorders (362). Their pathophysiology is not well understood.

There is a continuum between saccadic pulses and saccadic oscillations without an intersaccadic interval (363, 364). The latter may occur in one direction, usually the horizontal plane, in which case they are called **ocular flutter** (Fig. 23.14E), or they may be multivectorial, in which case

they are termed **opsoclonus** or **saccadomania**. The frequency of oscillations is usually high, typically 10–15 cycles per second, being higher with smaller-sized movements. Ocular flutter may be intermittent and mainly associated with voluntary saccades (flutter dysmetria) or convergence movements (365). Occasionally, the amplitude of the oscillations is very small (“microflutter”) (366). In such cases, the movements may be detected only with a slit lamp or an ophthalmoscope or by using eye movement recordings, even though they are producing oscillopsia or other visual symptoms. Sometimes such microflutter has components in all three planes (Fig. 23.15B).

Sustained opsoclonus is a striking finding, in which multidirectional conjugate saccades, usually of large amplitude, interfere with steady fixation, smooth pursuit, or convergence. These movements may persist during sleep. Opsoclonus is often accompanied by myoclonus—brief jerky involuntary limb movements—hence the term “opsoclonus-myoclonus.” In children, this syndrome is called “dancing eyes and dancing feet” (367). Ataxia and encephalopathy may also accompany opsoclonus.

The reported causes of ocular flutter and opsoclonus are summarized in Table 23.7. In about 50% of cases, the etiology remains obscure. In children, about half the cases of opsoclonus are associated with tumors of neural crest origin, such as neuroblastoma. In adults, opsoclonus occurs most often in association with small-cell lung, breast, and other cancers (368). Low CSF concentrations of 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) can often be demonstrated in children with the opsoclonus-myoclonus syndrome (369). However, CSF abnormalities may occur in opsoclonus associated with both tumor and encephalitis (370) and, therefore, do not help to distinguish between the infectious and paraneoplastic etiologies.

Various autoantibodies can be detected in sera of some

patients with opsoclonus. Of these, anti-Ri antibody is the most common (371–373), but various other antibodies have been demonstrated (374). Anti-Ri is reported in association with cancer of the breast or pelvic organs and, less commonly, in patients with small-cell lung or bladder cancer. Sometimes, however, no tumor can be found (375–377). A second antibody, anti-Hu, has been reported with opsoclonus in two children with neuroblastoma and in an adult with small-cell lung cancer (372,378). This is an antineuronal antibody that binds nuclear RNA and is usually associated with paraneoplastic sensory neuronopathy, cerebellar degeneration, and limbic encephalitis. A third type of antibody, directed against neurofilaments, was found in a child with paraneoplastic opsoclonus (379). Recent studies have emphasized the diversity of immunity to neuronal autoantigens (374), with only a minority of patients showing immunoreactivity to specific antineuronal antibodies (368).

The prognosis of idiopathic opsoclonus (including patients with manifestations of brainstem encephalitis) is generally good (368). Some patients with paraneoplastic opsoclonus myoclonus show spontaneous remissions, irrespective of the underlying tumor (372). Patients whose tumor can be identified and treated may recover neurologically; those who are not treated have a more severe course (368).

VOLUNTARY SACCADIC OSCILLATIONS OR VOLUNTARY NYSTAGMUS

Some normal subjects can voluntarily induce saccadic oscillations, usually by converging; this party trick has been called voluntary nystagmus but is really psychogenic flutter (380–382). Voluntary nystagmus is found in about 5–8% of the population and may occur as a familial trait (381). The oscillations are conjugate, with frequency and amplitude similar to those encountered in ocular flutter and opsoclonus. Although usually confined to the horizontal plane, voluntary nystagmus can occasionally be vertical or torsional (383), and may be accompanied by a head tremor (384). Voluntary nystagmus can be produced in the light or dark and with the eyes open or closed. It causes oscillopsia and reduced visual acuity and is often accompanied by eyelid flutter, a strained facial expression, and convergence. Individuals who are able to produce voluntary nystagmus may also be able to superimpose voluntary saccades on smooth movements during tracking of a target (385). The clinical challenge is to be able to distinguish voluntary forms of saccadic oscillations, which have no pathologic significance, from disorders such as ocular flutter and opsoclonus, which require a complete evaluation.

PATHOGENESIS OF SACCADIC INTRUSIONS

Neural Substrate

As discussed in Chapter 17, the brainstem circuits responsible for generating saccades are well worked out and provide a means for testing brainstem and cerebellar function (386). Thus, the saccadic command is generated by burst neurons of the brainstem reticular formation that project

Table 23.7
Etiology of Ocular Flutter and Opsoclonus^a

Viral encephalitis
As a component of the syndrome of myoclonic encephalopathy of infants (“dancing eyes and dancing feet”)
Paraneoplastic (occult tumor, especially small-cell lung and breast cancers)
Neuroblastoma
Other tumors
Trauma (in association with hypoxia and sepsis)
Meningitis
Intracranial tumors
Hydrocephalus
Thalamic hemorrhage
Multiple sclerosis
Hyperosmolar coma
Associated with systemic disease; e.g., viral hepatitis, sarcoid, AIDS
Side effects of drugs: lithium, amitriptyline, phenytoin, and diazepam
Toxins: chlordecone, thallium, strychnine, toluene, and organophosphates
Transient phenomenon of healthy neonates
Voluntary “nystagmus” or psychogenic flutter

^a Not all case reports have documented the abnormality with eye movement recordings.

monosynaptically to ocular motoneurons. The burst neurons for horizontal saccades are located in the PPRF (387), whereas the burst neurons for vertical and torsional saccades are located in the riMLF (388). Burst neurons discharge only during saccadic eye movements. The activity of all saccadic burst neurons is gated by omnipause neurons, which are crucial for suppressing unwanted saccades during fixation and slow eye movements. The omnipause neurons are located in the caudal pons within the raphe interpositus nucleus (RIP), adjacent to the abducens nucleus (389,390). Inputs into omnipause neurons arise in the superior colliculus, frontal eye fields, and mesencephalic reticular formation.

Square-Wave Jerks

During steady fixation, the threshold for electrical stimulation of saccades in either the frontal eye fields or the superior colliculus is elevated (391,392), which is probably mediated through the projections of these structures to the omnipause neurons. In the rostral superior colliculus, a distinct population of "fixation neurons" has been identified (393), whereas in the frontal eye fields, neurons active during suppression of saccades have been identified (391). Pharmacologic inactivation at both sites leads to disruption of fixation by saccadic intrusions, but not by flutter or opsoclonus (394,395). Furthermore, inactivation of the mesencephalic reticular formation may cause saccadic intrusions (396). Thus, impairment of any of these projections to the omnipause neurons can lead to saccadic intrusions, possibly explaining the increased incidence of square-wave jerks with cerebral hemispheric disease (349), and in progressive supranuclear palsy, in which the mesencephalic reticular formation and superior colliculus are both affected (397). We have also noted the development, and subsequent disappearance, of saccadic intrusions during recovery from peripheral extraocular muscle weakness, e.g., in the Miller Fisher syndrome or bilateral abducens palsy. It seems possible that this reflects central adaptation of saccadic commands in response to peripheral weakness.

Ocular Flutter and Opsoclonus

The pathogenesis of saccadic oscillations without an intersaccadic interval, e.g., ocular flutter and opsoclonus, seems closely related to the properties of the burst neurons themselves. Burst neurons have very high discharge rates (up to 1,000 spikes per second), and they discharge vigorously even for small saccades (398). The anatomical connections between burst neurons in the brainstem and their high discharge rates ("gain") predisposes to oscillations if the omnipause neurons are not actively inhibiting them and no specific saccadic command has been issued. Thus, normal subjects may show transient saccadic oscillations when, for example, they make a saccade in combination with a vergence movements (399). In this case, the saccade shifts the direction of gaze quickly, but the vergence movement takes much longer to align both eyes. While the vergence component is being completed, small conjugate horizontal oscillations are evident, indicating that the omnipause neurons are unable to

selectively shut off the saccadic burst neurons when their job is done (399). Theoretically, therefore, disease affecting omnipause neurons, or their afferents, might be expected to lead to saccadic oscillations such as ocular flutter and opsoclonus (363), especially if the membrane properties of the burst neurons became more excitable. Some experimental data are in conflict with this hypothesis, however, since chemical lesions of the omnipause neurons are reported to cause slowing of both horizontal and vertical saccades (400). Attempts to demonstrate histopathologic changes in omnipause neurons in some patients with paraneoplastic saccadic oscillations have usually failed to show any changes (401,402), although one study demonstrated complete absence of cells in the omnipause region of a patient with paraneoplastic saccadic oscillations (377). In this patient, intracellular deposits of anti-Ri IgG were discovered predominantly in the brainstem, especially in the reticular formation of pons and midbrain. Posner has suggested that, in paraneoplastic opsoclonus, the tumor and certain CNS structures share an epitope (372). This common epitope elicits an efficient immune response against the tumor, thus conferring a more indolent oncologic course, but it also elicits an immune response against normal neural tissue, causing the neurologic syndrome (see Chapter 36). One patient developed ocular flutter in association with an MS lesion in the PPRF region; as the lesion resolved, so did the oscillations (403). Furthermore, in two patients with presumed viral opsoclonus-myoclonus, MR imaging demonstrated lesions involving the pontine tegmentum (404).

There is some evidence that impaired glycinergic transmission may play a role in the pathogenesis of both ocular flutter and opsoclonus (405). First, poisoning with a glycinergic antagonist, strychnine, can produce both myoclonus and opsoclonus (406). Second, in generalized myoclonic conditions, such as hyperekplexia, abnormal receptors to glycine are found (407). The concurrent appearance of opsoclonus with myoclonus may suggest a similar mechanism. Third, glycine is identified as the neurotransmitter of the omnipause neurons (390). Since the latter are often implicated in the pathogenesis of saccadic intrusions, glycinergic dysfunction, presumably caused by autoantibodies, might be responsible for the opsoclonus-myoclonus syndrome.

Cerebellum and Saccadic Oscillations

Cerebellar dysfunction has traditionally been blamed for ocular flutter and opsoclonus (402,408,409). Functional imaging in patients with opsoclonus has shown activation of deep cerebellar nuclei (410). However, experimental lesions of the cerebellum do not produce these oscillations, even though striking saccadic dysmetria can be produced, especially when the caudal fastigial nuclei of the cerebellum are inactivated (411,412). Reliable measurements of eye movements are often necessary to make the distinction between severe forms of saccadic dysmetria and saccadic oscillations without an intersaccadic interval, such as ocular flutter and opsoclonus; such records are often absent from clinical reports.

OSCILLATIONS WITH DISEASE AFFECTING OCULAR MOTONEURONS AND EXTRAOCULAR MUSCLE

SUPERIOR OBLIQUE MYOKYMIA (SUPERIOR OBLIQUE MICROTREMOR)

Superior oblique myokymia (SOM) was first described by Duane in 1906 (413), but clinicians became generally aware of the disorder following the description by Hoyt and Keane in 1970 (414). Typical symptoms include monocular blurring of vision, tremulous sensations in the eye (414–417), brief episodes of vertical or torsional diplopia, and vertical or torsional oscillopsia. Attacks last less than 10 seconds and may occur many times per day; they may be elicited on by looking downward, by tilting the head toward the side of the affected eye, and by blinking. The majority of patients with SOM have no underlying disease, although cases have been reported following trochlear nerve palsy, after mild head trauma, in the setting of MS, after brainstem stroke, and in patients with cerebellar tumor (414–420).

The eye movements of SOM are often difficult to appreciate on gross examination, although they are usually apparent during examination with the ophthalmoscope or slit-lamp biomicroscope. They consist of spasms of cyclotorsional and vertical movements. Measurement of the movements of SOM using the magnetic search coil technique reveals an initial intorsion and depression of the affected eye, followed by irregular oscillations of small amplitude and variable frequency (418–421). Some resemble jerk nystagmus, with frequencies of 2–6 Hz, but superimposed upon these oscillations are low-amplitude, irregular oscillations with frequencies ranging up to 50 Hz.

Electromyographic recordings from superior oblique muscles affected by SOM reveal some fibers that discharge either spontaneously or following contraction of the muscle (414,422,423). These muscle potentials are abnormal, with increased duration (greater than 2 milliseconds) and amplitude, and they are polyphasic, with a spontaneous discharge rate of approximately 45 Hz. Spontaneous activity is absent only with large saccades in the “off” (upward) direction and is less affected by vestibular eye movements. Some firing units show an irregular discharge following muscle contraction before subsiding to a regular discharge of 35 Hz. These findings suggest that the etiology of SOM is neuronal damage and subsequent regeneration, leading to desynchronized contraction of muscle fibers. Indeed, experimental le-

sions of the trochlear nerve demonstrate regenerative capacities such that the remaining motor neurons increase their number of axons to hold the total constant (424). Superior oblique myokymia only rarely is preceded by an ipsilateral trochlear nerve palsy (414,425), but the possibility remains that mild damage to the trochlear nerve could trigger the regeneration mechanism for maintaining a constant number of axons in the nerve. Some of these cases might be predisposed to develop SOM.

OCULAR NEUROMYOTONIA

This rare disorder is characterized by episodes of diplopia that are usually precipitated by holding the eyes in eccentric gaze, often sustained adduction (426–431). Most reported patients have undergone radiation to the parasellar region, but idiopathic cases have been reported (432).

The episodic nature of the diplopia associated with ocular neuromyotonia often suggests myasthenia gravis, but anticholinergic medicines are ineffective in this condition. Other conditions that may mimic ocular neuromyotonia include superior oblique myokymia, thyroid eye disease, and cyclic oculomotor palsy.

The symptoms of ocular neuromyotonia are caused by involuntary, and at times painful, contraction of the lateral rectus muscle, the superior oblique muscle, or one or more extraocular muscles innervated by the oculomotor nerve (the latter case is particularly common). Extraocular muscles innervated by more than one ocular motor nerve may occasionally be affected, and rare patients with bilateral ocular neuromyotonia have been reported (433). Comparing symptoms with attempts at eccentric gaze-holding may aid in making the diagnosis, as symptoms may be absent in primary position but evoked by sustained eccentric gaze.

The mechanism responsible for ocular neuromyotonia is unknown, although both ephaptic neural transmission and changes in the pattern of neuronal transmission following denervation have been suggested, since spontaneous activity is seen in the ocular electromyogram of some affected patients (427,428). Axonal hyperexcitability caused by dysfunction of potassium channels has also been implicated in the production of neuromyotonia by analogy with systemic neuromyotonia (434).

SPONTANEOUS EYE MOVEMENTS IN UNCONSCIOUS PATIENTS

The examination of eye movements often provides important diagnostic information in unconscious patients (121,435,436). Deviations of one or both eyes and vestibular eye movements (induced by head rotation or caloric stimulation) are discussed in Chapters 17 and 18. In this section, we summarize spontaneous eye movements. Although some of these eye movements have been regarded as saccadic intrusions, this issue remains unclear because, for example, it is not possible to elicit quick phases of nystagmus with caloric stimulation in unconscious patients. There is a

great need for investigation of the pathogenesis of these disorders.

Slow conjugate or disconjugate roving eye movements are similar to the eye movements of light sleep, but they are slower than the rapid movements of paradoxical or rapid eye movement (REM) sleep. The presence of these eye movements suggests that the brainstem gaze mechanisms are intact (435).

Ocular bobbing consists of intermittent, usually conjugate, rapid downward movement of the eyes followed by a

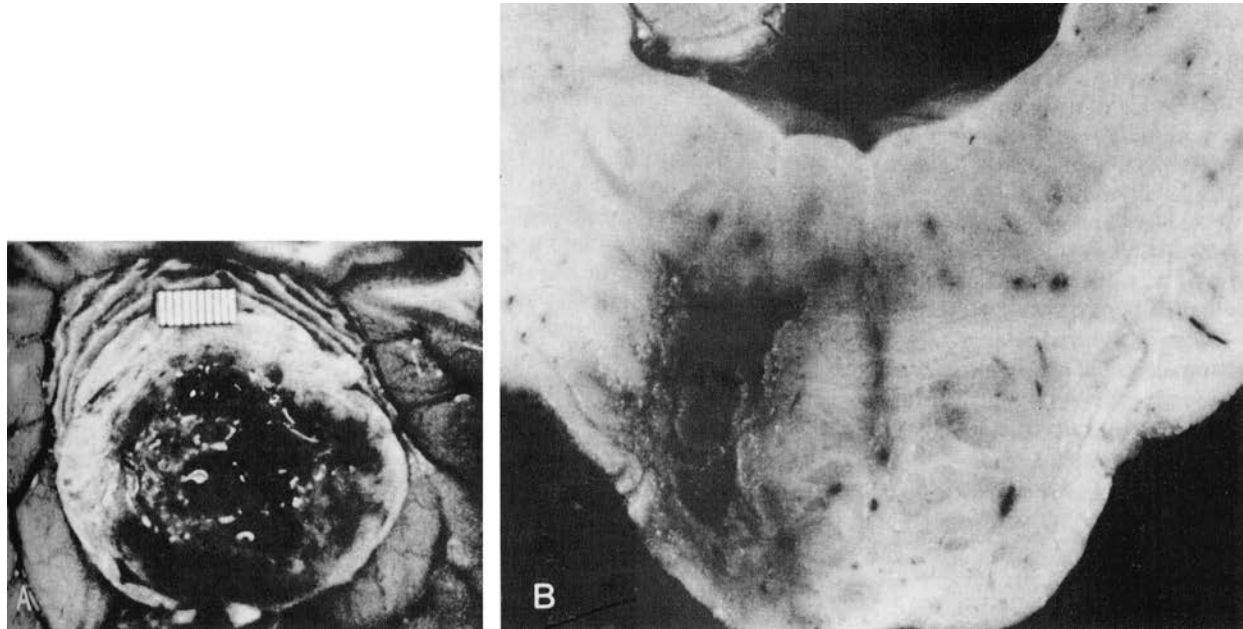


Figure 23.16. Pathology of ocular bobbing. *A*, Section through the midpons demonstrating a massive area of hemorrhage and necrosis in a 2-year-old girl with a pontine glioblastoma who developed a left hemiparesis, obtundation, seizures, and ocular bobbing. *B*, Organizing hematoma in the caudal portion of the basis pontis on the right side in a 57-year-old woman who developed a right gaze palsy, right facial palsy, and obtundation. (*A*, From Daroff RB, Waldman J. *J Neurol Neurosurg Psychiatry* 1965;28:375–377. *B*, From Katz B, Hoyt WF, Townsend J. *J Clin Neuroophthalmol* 1982;2:193–195.)

slower return to central position. Reflex-induced horizontal eye movements are usually absent. Classic ocular bobbing is a sign of intrinsic pontine lesions, usually hemorrhage (Fig. 23.16), but it has also been reported in patients with cerebellar lesions that compress the pons (437–446) and in patients with metabolic and toxic encephalopathies (447,448). An inverse form of ocular bobbing is characterized by a slow downward movement and rapid return to midposition: “ocular dipping” (449–455). “Reverse bobbing” is characterized by a rapid deviation of the eyes upward and a slow return to the horizontal (456), whereas the terms “reverse dipping” or “converse bobbing” describe a slow upward drift of the eyes followed by a rapid return to central position (457,458). In general, the variants of ocular bobbing are less reliable for localization than is the classic form. Nevertheless, because some patients show several types of bobbing, a common underlying pathophysiology is possibly responsible (459,460). Since the pathways that mediate upward and downward eye movements differ anatomically and pharmacologically, it seems possible that these movements represent a varying imbalance of mechanisms

for vertical gaze. Repetitive vertical eye movements, including variants of ocular bobbing, that contain convergent-divergent components may indicate disease affecting the dorsal midbrain (461,462).

Ping-pong gaze consists of slow, horizontal, conjugate deviations of the eyes alternating every few seconds (178). Ping-pong gaze usually occurs with bilateral infarction of the cerebral hemispheres or of the cerebral peduncles (463). Transient oscillations with a similar periodicity to ping-pong gaze can sometimes be induced by a rapid horizontal head rotation in patients with bilateral hemispheric disease (464).

Periodic alternating gaze deviation, in which conjugate gaze deviations change direction every 2 minutes, occurs in some patients with hepatic encephalopathy (465). This phenomenon is related to PAN, which is discussed above.

Rapid, small-amplitude, vertical eye movements may be the only manifestation of epileptic seizures in patients with coexistent brainstem injury (328). Rapid monocular eye movements with horizontal, vertical, or torsional components may also indicate brainstem dysfunction.

TREATMENTS FOR NYSTAGMUS AND SACCADIC INTRUSIONS

RATIONAL BASIS FOR TREATMENT

Ideally, knowledge of the pathogenesis of a form of nystagmus should suggest the treatment. Perhaps the best example for this is the acquired form of PAN, for which an animal model exists, pharmacologic mechanisms have been established, and drug treatment (baclofen) is usually effective.

Although such knowledge is still lacking for many forms of nystagmus and saccadic intrusions, headway has been made. In this section, we summarize current concepts of relevant pharmacology and the best therapies for the various disorders. It should be noted that although a number of drugs have been reported to improve nystagmus in individual pa-

tients, few have been subjected to controlled clinical trials. When drug treatments fail or effective drugs cannot be tolerated by the patient, certain optical devices may be used to either suppress the nystagmus or negate its visual consequences. Finally, surgery can be performed to either weaken the extraocular muscles or reattach them to the globe in such a way that the resting position of the eyes is at the null position.

It is essential to carefully evaluate patients before and during therapy for abnormal eye movements. In the case of new treatments, it is best to carry out a controlled, masked evaluation. Careful measurements of visual acuity using near and far test charts and systematic eye movement examination are essential. It is also very useful to record the oscillations. This can be achieved semiquantitatively by video, but it is best performed using one of several recording techniques, ideally the magnetic search coil method (Fig. 23.2).

PHARMACOLOGIC TREATMENTS (466,467)

Nystagmus from Vestibular Imbalance

Peripheral Vestibular Imbalance

Nystagmus caused by peripheral vestibular lesions usually resolves spontaneously over the course of a few days. Present approaches use vestibular suppressants for 24–48 hours, primarily for severe vertigo and nausea. If the nystagmus persists after this time, exercises are used to accelerate the brain's ability to redress the imbalance (468). In the case of BPPV, maneuvers to displace otolithic debris from the affected semicircular canal and exercises to sustain recovery are usually effective (90,469–472).

Central Vestibular Mechanisms—Pharmacologic Basis

The technique of pharmacologic inactivation by microinjection of drugs into the brainstem and cerebellum has provided some useful insights and clues to clinicians interested in treating abnormal eye movements. Thus, unilateral microinjection of the GABA_A agonist muscimol into the medial vestibular nucleus and nucleus prepositus hypoglossi of the monkey and cat produces bilateral gaze-evoked nystagmus (201,473,474). In addition, there is evidence that prolongation of the peripheral vestibular signal by central mechanisms, called velocity storage, by the nodulus and uvula of the cerebellum is regulated by inhibitory pathways that use GABA_B (475). The velocity-storage phenomenon in normal monkeys is suppressed by the GABA_B agonist baclofen (475), and mildly enhanced by both diazepam (476) and picrotoxin (477). Acquired PAN, which is thought to be partly caused by abnormal prolongation of velocity storage, is abolished by baclofen, and this response occurs with both experimental and clinical lesions of the nodulus and uvula (181,478). Microinjection of drugs with effects on glutamate receptors into medial vestibular nucleus/nucleus prepositus hypoglossi also effects gaze-holding ability (474). There is also evidence that nicotinic acetylcholinergic mechanisms play a role in vestibular-mediated vertical eye movements. Nicotine can produce upbeat nystagmus in normal subjects in darkness (479,480) and intravenous physostigmine may

increase the intensity of downbeat nystagmus (481). In addition, intravenous opioids have been reported to induce downbeat nystagmus (482,483).

Downbeat and Upbeat Nystagmus

The GABA_A agonist clonazepam is reported to be effective in reducing downbeat nystagmus (484). A single dose of 1–2 mg of clonazepam was administered to determine whether long-term therapy was likely to be effective. Baclofen may reduce the velocity of both upbeat and downbeat nystagmus and reduce associated oscillopsia (481). Barton and colleagues performed a double-blind study in which two patients with downbeat nystagmus experienced reduction in nystagmus after intravenous scopolamine (485). Improvement of occasional patients with downbeat nystagmus with trihexyphenidyl has been reported (486). However, all of these therapies are ineffective in many patients with downbeat nystagmus.

A new approach to the treatment of downbeat nystagmus arose out of the seminal observation by Griggs that nystagmus occurring in episodic ataxia type 2 responds to acetazolamide (487); this disorder is now known to be a calcium channelopathy (488,489). This led to a study of 3,4-diaminopyridine, a potassium channel blocker, as a treatment for downbeat nystagmus. Strupp and colleagues studied 17 patients with downbeat nystagmus due to a range of disorders (490). Ten of the patients showed a decrease of more than 50% in their nystagmus 30 minutes after ingesting 20 mg of 3,4-diaminopyridine. This medication was generally well tolerated, although it is known to induce seizures in some subjects. The possible mechanism of action of 3,4-diaminopyridine relates to one hypothesis for downbeat nystagmus described earlier in this chapter (167).

The cerebellum inhibits vestibular circuits mediating upward, but not downward, eye movements (Fig. 23.7) (165,166). Consequently, impaired cerebellar inhibition could cause uninhibited upward drifts of the eyes, which evoke corrective rapid downward movements: downbeat nystagmus. Potassium channels are abundant on cerebellar Purkinje cells—the output neurons from cerebellar cortex—and a related agent, 4-aminopyridine, is reported to increase the discharge of these neurons by affecting the slowly depolarizing potential. Enhancement of Purkinje cell activity due to 3,4-diaminopyridine could restore to normal levels the inhibitory influence of the cerebellar cortex upon vertical vestibular eye movements. Studies are under way to determine the long-term effects of these drugs on nystagmus and its visual consequences, and to compare 3,4-diaminopyridine and 4-aminopyridine; the latter penetrates the blood-brain barrier better, has a longer half-life, and is generally better tolerated.

The recent demonstration that a patient with downbeat nystagmus showed antiglutamic acid decarboxylase antibodies in the vestibular complex raises the possibility of evaluating drugs with glutamate effects in patients with downbeat nystagmus (491).

Periodic Alternating Nystagmus

As noted before, this is the best example of a form of nystagmus for which drug treatment is based on known

pathophysiology and pharmacology. Most cases of acquired PAN respond to baclofen (180,478). The congenital form of PAN, which probably has a different pathogenesis than the acquired form, only occasionally responds to baclofen (492), but one child did show a response to dextroamphetamine (493).

Acquired Pendular Nystagmus

The neuropharmacology of acquired pendular nystagmus is unknown, and more than one mechanism may be involved. This type of nystagmus used to be treated with barbiturates (73), but sedative side effects limit the use of this class of drugs.

In the case of oculopalatal myoclonus, increased acetylcholine esterase activity and cholinergic denervation supersensitivity has been reported in hypertrophied inferior olivary nucleus (494,495), prompting trials of anticholinergic agents for acquired pendular nystagmus. Initial studies showed that individual patients may be helped by trihexyphenidyl (496,497). One double-blind crossover trial compared trihexyphenidyl with tridihexethyl chloride (a quaternary anticholinergic that does not cross the blood-brain barrier) in 10 patients, 5 of whom had acquired pendular nystagmus. Of these five, only two showed a decrease in nystagmus and an improvement of visual acuity when given tridihexethyl chloride. Trihexyphenidyl had no effect on the nystagmus in any patient. Significantly, neither of the two patients whose nystagmus improved with medication elected to continue the drug because of anticholinergic side effects. In another masked study, scopolamine, benztropine, and glycopyrrolate (a quaternary agent devoid of central nervous activity) were administered intravenously to five patients with acquired pendular nystagmus (485). The results, confirming an earlier report (58), demonstrated a single dose of scopolamine effectively reduced nystagmus and improved vision in all five patients, whereas benztropine was less effective, and glycopyrrolate had no significant effect.

Why did intravenous scopolamine suppress acquired pendular nystagmus, but oral trihexyphenidyl did not? One possibility is that trihexyphenidyl selectively antagonizes only the *m1* muscarinic receptors, whereas scopolamine probably affects all five subtypes of muscarinic receptors (498). However, this is not the whole story, because in an open trial of transdermal scopolamine, which included four patients with acquired pendular nystagmus, two showed a decrease, one showed no effect, and one showed an increase of nystagmus (499). Thus, scopolamine does not appear to be a promising treatment for acquired pendular nystagmus. Intravenous administration is not a practical therapy, and clouds the sensorium. Occasional patients show some improvement with transdermal scopolamine, but this is often not sustained (499), and prolonged use of this mode of therapy is also not without risk.

Reports that the neurotransmitter GABA contributed to the normal function of the gaze-holding mechanism (201,473,474) focused attention on drugs with GABAergic effects. Valproate is reported to help some patients with acquired pendular nystagmus (500). Isoniazid has also been

studied as treatment for acquired pendular nystagmus in three patients with MS, and reduced nystagmus and relieved oscillopsia in two (501). However, isoniazid has potential side effects, and better-tolerated drugs have become available, notably **gabapentin**, which has been evaluated in controlled trials (75). Of 15 patients with acquired pendular nystagmus studied in a double-blind comparison with baclofen, visual acuity improved with gabapentin, but not with baclofen; an example is shown in Figure 23.17. Gabapentin significantly reduced nystagmus in all three planes, but baclofen did so only in the vertical plane. In 10 of the 15 patients, reduction of nystagmus was substantial, and 8 elected to continue taking the medication. The main side effect of gabapentin was increased ataxia and unsteadiness. However, the demonstration that the more purely GABAergic agent vigabatrin failed to suppress nystagmus led to the

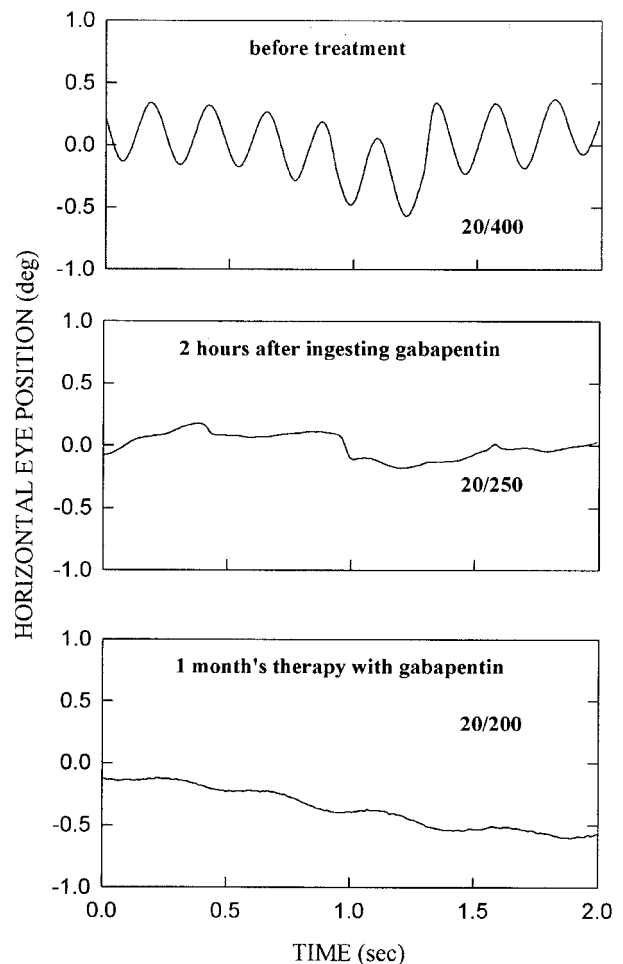


Figure 23.17. Effects of gabapentin on the horizontal component of pendular nystagmus in a 41-year-old woman with multiple sclerosis. After the initial recording (*top*), the patient was given 300 mg of gabapentin, which reduced her oscillations and improved her vision (*middle*). The effect was sustained two months later, when she was taking a dose of 300 mg three times per day. Visual acuity measurements of the recorded eye are shown at the *right* in each panel.

suggestion that gabapentin was probably working through a different transmitter mechanism, such as glutamate (502).

One agent with effects on glutamate receptors is memantine, which has recently received approval from the U.S. Food and Drug Administration for treatment of Alzheimer's disease. Memantine has been in use in Germany for over 20 years, and is known to be a safe and well-tolerated drug. It is a low-to-moderate uncompetitive (open channel) N-methyl-D-aspartate (NMDA) receptor antagonist. A study from the University of Munich reported that it suppressed acquired pendular nystagmus in patients with multiple sclerosis (503). There is need for a controlled study comparing memantine with gabapentin. At present, gabapentin has been shown to be effective in some patients with pendular nystagmus as part of the syndrome of oculopalatal tremor (75), but memantine has not been studied in this disorder. Palatal tremor may respond to carbamazepine in some patients (504,505). Occasional patients with acquired pendular nystagmus benefit from both gabapentin and surgical recession of muscles (506); the effects of surgery are described below.

Alcohol has been reported to suppress acquired pendular nystagmus (507). Smoking cannabis has been reported to suppress both acquired pendular nystagmus (508), and congenital nystagmus (509), but formal evaluations of this potential therapy are hindered at present by current social views on cannabis.

Seesaw Nystagmus

Improvement in seesaw nystagmus has been reported in some patients treated with alcohol (510,511). Clonazepam has reduced the nystagmus and associated oscillopsia in occasional patients (512). Two patients with pendular seesaw nystagmus showed reduction of their nystagmus with gabapentin, but more studies are needed to confirm this (75).

Familial Episodic Ataxia with Nystagmus

The attacks of episodic ataxia type 2 (EA-2), which is a calcium channelopathy, respond well to treatment with acetazolamide (489). However, the interictal nystagmus and ataxia (which in some patients is progressive) usually do respond. The briefer attacks of episodic ataxia type 1 (EA-1), which is a potassium channelopathy, respond to acetazolamide in some patients. The attacks of EA-1 spontaneously improve with time in some patients (489).

Saccadic Intrusions: Square-Wave Jerks

Both the frontal eye fields and the superior colliculus send brainstem projections that influence the omnipause neurons that gate saccades (discussed earlier). Experimental studies have elucidated the pharmacology of one part of this descending pathway (513). The nondopaminergic portion of the substantia nigra, the pars reticulata (SNpr), receives inputs from the caudate nucleus and selectively gates reflexive or voluntary saccades via the superior colliculus. This is accomplished, in part, by a phasic modulation of tonic inhibitory influence of the SNpr upon the superior colliculus. The caudate nucleus appears to facilitate the initiation of volun-

tary self-generated types of saccades and to aid steady fixation by preventing unwanted reflexive saccades to stimuli. The nigroretectal pathway is GABAergic, and injection of bicuculline into the superior colliculus increases the frequency and amplitude of the saccades, which take the form of square-wave intrusions (514). Furthermore, pharmacologic inactivation of the frontal eye fields with bicuculline causes saccadic intrusions (395). This experimental evidence suggests that treatment with GABA agonists might prevent inappropriate saccades. In fact, several benzodiazepines (diazepam, clonazepam) and the barbiturate phenobarbital were effective in abolishing high-amplitude square-wave jerks and macrosaccadic oscillations in one patient (515). There is also some evidence that amphetamines can suppress square-wave jerks in some patients (516). On the other hand, both nicotine (479) and opiates (483) are reported to induce square-wave jerks. Thus, more work is needed to better understand the pharmacology of saccadic intrusions and how they can be treated.

Ocular Flutter and Opsoclonus

Patients with parainfectious opsoclonus-myoclonus often improve spontaneously, but intravenous immunoglobulin may speed recovery (517). Similarly, although propranolol, verapamil, clonazepam, gabapentin, and thiamine have all been reported to diminish microsaccadic ocular flutter in individual patients (366,518,519), the effect may have been due to spontaneous remission. Opsoclonus associated with neural crest tumors in children usually responds to corticosteroid treatment (520); however, up to 50% of such children have persistent neurological disabilities, including ataxia, poor speech, and cognitive problems (372,518). Similar responses to steroids may occur in children with parainfectious or idiopathic opsoclonus (518). Treatment with steroids has not been uniformly successful in such cases, although plasmapheresis, intravenous immunoglobulin, and immunoadsorption therapy have occasionally proved effective (370,521,522).

Superior Oblique Myokymia and Ocular Neuromyotonia

Superior oblique myokymia spontaneously resolves in some patients (417), and others are not sufficiently bothered by their symptoms that they request treatment. Individual patients have responded to carbamazepine, baclofen, *b*-adrenergic blocking agents, or gabapentin given systemically or topically (415,416,419). Patients who do not respond to drug therapy, who develop side effects from the drugs, or who do not wish to take drugs for their condition, may experience complete relief of symptoms after extraocular muscle surgery (discussion following).

Ocular neuromyotonia is usually responsive to carbamazepine (432,433).

OPTICAL TREATMENTS

Convergence prisms provide one optical approach for patients with congenital or acquired nystagmus whose nystag-

mus dampens when they view a near target (242,523); a useful starting point is 7.00-diopter base-out prisms combined with -1.00 -diopter spheres to compensate for accommodation (although the spherical correction may not be needed in presbyopic individuals). In some patients with congenital nystagmus, the resultant improvement of vision is sufficient for them to qualify for a driver's license. Patients whose nystagmus is worse during near viewing may benefit from wearing base-in (divergence) prisms (64).

Theoretically, it should be possible to use prisms to help patients whose nystagmus is reduced or absent when the eyes are moved into a particular position in the orbit: the null region. For patients with congenital nystagmus, there is usually some horizontal eye position in which the nystagmus is minimized, whereas downbeat nystagmus may decrease or disappear in upgaze. In practice, patients use head turns to bring their eyes to the optimum position, and only rarely are prisms that produce a conjugate shift helpful.

A different approach to the treatment of nystagmus has been the use of an optical system that stabilizes images on the retina (524). This system consists of a high-plus spectacle lens worn in combination with a high-minus contact lens. The system is designed on the principle that stabilization of images on the retina could be achieved if the power of the spectacle lens focused the primary image close to the center of rotation of the eye. However, such images are then defocused, and a contact lens is required to extend the clear image back onto the retina. Since the contact lens moves with the eye, it does not negate the effect of retinal image stabilization produced by the spectacle lens. With such a system, it is possible to achieve up to about 90% stabilization of images upon the retina. There are several limitations to the system, however. One is that it disables all eye movements (including the vestibulo-ocular reflex and vergence) and thus is useful only when the patient is stationary and is viewing monocularly. Another limitation is that with the highest-power components (contact lens of -58.00 diopters and spectacle lens of $+32$ diopters), the field of view is limited. Some patients with ataxia or tremor (such as those with MS) have difficulty inserting the contact lens. However, initial problems posed by rigid polymethyl methacrylate contact lenses can be overcome by using gas-permeable, or even soft contact lenses (525). Most patients do not need the highest power components for oscillopsia to be abolished, and vision to be improved. We have found that in selected patients the device may prove useful for limited periods of time, for example, if the patient wishes to watch a television program (526).

Contact lenses alone sometimes suppress congenital nystagmus (527). This effect is not from the mass of the lenses but is probably mediated via trigeminal afferents (528); this issue is discussed further below.

A more recent innovation has been to use an electronic circuit to distinguish between the nystagmus oscillations and normal eye movements (529). This approach is most applicable in patients with pendular nystagmus. Eye movements are measured using an infrared sensor and, after filtering, fed to a phase-locked loop that generates a signal similar to the nystagmus but is insensitive to other eye movements,

such as saccades. This electronic signal is then used to rotate Risley prisms, through which the patient views the environment. When the Risley prisms rotate in synchrony with the patients nystagmus, they negate the visual effects of the ocular oscillations. Improvement and miniaturization of a prototype device may eventually lead to a spectacle-mounted device that selectively cancels out the visual effects of pathological nystagmus (529,530).

The main therapy for latent nystagmus consists of measures to improve vision, particularly patching for amblyopia in children (531).

BOTULINUM TOXIN TREATMENT OF NYSTAGMUS

An approach to treatment of nystagmus that has gained some popularity is injection of botulinum toxin into either the extraocular muscles or the retrobulbar space (532,533). Using both techniques, Ruben and colleagues reported improvement of vision in most of their 12 patients with a variety of diagnoses (534). The major side effect was ptosis. However, eye movements were not systematically measured and compared before and after injection. Repka and colleagues also described improvement of vision following retrobulbar injection of botulinum toxin in six patients and documented the effects on eye movements (535). The main reservation expressed by these authors was the temporary nature of the treatment and the necessity for repeated injections, with their attendant risks. We measured binocular eye rotations in three planes before and after monocular injection of botulinum toxin either into the horizontal recti (536), or into the retrobulbar space (537). Nystagmus was abolished or reduced in the treated eye for about 2–3 months, but no patient was pleased with the results because of ptosis, diplopia, increase of nystagmus in the noninjected eye or, in one patient, filamentary keratitis. No patient that we studied elected to repeat the procedure.

SURGICAL PROCEDURES FOR NYSTAGMUS

Two surgical procedures may be effective for certain patients with congenital nystagmus. One is the Anderson-Kestenbaum operation (538–540). This procedure is designed to move the attachments of the extraocular muscles so that the new central position of the eyes is at the null position. It is performed after first making careful eye movement measurements of nystagmus intensity with the eyes in various positions of gaze and determining the approximate null position. The appropriate extraocular muscles are then weakened or strengthened as necessary to achieve the required shift in the position of the null (541–543). The Anderson-Kestenbaum procedure not only shifts and broadens the null region, but also results in decreased nystagmus outside the region. It is of uncertain value in the treatment of acquired forms of nystagmus.

The second procedure is an artificial divergence operation (544,545). It may be helpful in patients with congenital nystagmus that dampens or is suppressed during near viewing and who have stereopsis. Studies comparing these two methods indicate that the artificial divergence operation generally

results in a better visual outcome than the Anderson-Kestenbaum procedure alone (543,545–547).

Several authors have recommended performing large recessions of all of the horizontal rectus muscles for treatment of patients with congenital nystagmus (548,549). Based on a long experience, Dell'Osso noted that any surgical procedure that detached and reattached the extraocular muscles tended to suppress congenital nystagmus. This led him to suggest that simply dissecting the perimuscular fascia and then reattaching the muscles at the same site on the globe might prove effective, especially in cases when convergence does not dampen the nystagmus. Results of this procedure on a canine model for congenital nystagmus supported this hypothesis (550). Reported lack of effect in monkeys concerns *latent nystagmus*, not typical congenital nystagmus (551,552). Preliminary results of a large, controlled clinical trial suggest that the operation is effective in some patients (242,553).

How could such a procedure damp congenital nystagmus? Recent studies by Büttner-Ennever and colleagues have indicated that the terminal portion of the extraocular muscles, near their site of their attachment, contains multiply-innervated muscle fibers (554). Using rabies toxin as an anatomic tracer, it has been possible to show that a separate group of ocular motor neurons (distinct from the classic oculomotor, trochlear, and abducens nuclei, and surrounding each of them) innervates these multiply-innervated fibers.

Finally, it is known that ocular proprioceptors (the palliade organs) lie at the insertion site of the extraocular muscles (554). Thus, procedures similar to those proposed by Dell'Osso may work by disrupting a proprioceptive feedback pathway that normally sets the tone of the extraocular muscles.

There is also some evidence that the tendino-scleral junction may contain neurovascular abnormalities in the eyes of patients with congenital nystagmus (555). This suggestion, and the "orbital revolution" set in motion by the discovery of pulleys for the extraocular muscles by Miller and Demer, promise the development of new therapies for congenital nystagmus (556).

The role of surgery in the treatment of acquired nystagmus is not well established, although individual patients may benefit from recession operations (506,557). However, it is clear that suboccipital decompression improves downbeat nystagmus in Chiari syndromes and also prevents progression of other neurologic deficits (558–560).

As noted above, SOM that does not respond to treatment with medication may respond to extraocular muscle surgery. The procedure used by most surgeons is a superior oblique tenectomy combined with myectomy of the ipsilateral inferior oblique muscle (414,415,417,422,561). However, Kosmorsky and colleagues reported successful treatment of a patient with SOM by performing a nasal transposition of the anterior portion of the affected superior oblique tendon, thereby weakening cyclorotation (562).

OTHER FORMS OF TREATMENT

A variety of methods other than those described above have been used to treat nystagmus, principally the congenital

variety. Electrical stimulation or vibration over the forehead may suppress congenital nystagmus (264). The mechanism of vibration on eye movements is uncertain, since vibration over the mastoid in patients who have lost vestibular function induces ocular torsion (563). However, it is postulated that the suppressive effect on congenital nystagmus, as well as suppression induced by wearing contact lenses (528), may be exerted via the trigeminal system, which receives extraocular proprioception (264,554).

Acupuncture administered to the neck muscles may suppress congenital nystagmus in some patients via a similar mechanism (564,565). Biofeedback has also been reported to help some patients with congenital nystagmus (566,567). The role of any of these treatments in clinical practice has yet to be demonstrated.

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