Treatment of Abnormal Eye Movements That Impair Vision: Strategies Based on Current Concepts of Physiology and Pharmacology

R. John Leigh, MD,*‡ Lea Averbuch-Heller, MD,* Robert L. Tomsak, MD, PhD,*† Bernd F. Remler, MD,*† Stacy S. Yaniglos, OD,§ and Louis F. Dell'Osso, PhD*

Certain abnormal eye movements, especially pathological nystagmus, degrade vision and cause illusory motion of the seen environment. These symptoms are due to excessive movement of images of stationary objects on the retina. Recently, the pathophysiology underlying several types of nystagmus and saccadic oscillations was better defined by the development of animal models and by experimental pharmacological studies. Despite this, few reliable therapies are currently available for these abnormal eye movements. In clinical studies, a number of drugs reportedly helped individual patients, but few drugs have been subjected to double-blind trials. An alternative approach to pharmacological suppression of abnormal eye movements is optical stabilization of images on the retina, which is helpful in selected patients. Weakening of the extraocular muscles, using botulinum toxin or surgery, is prone to cause diplopia and may induce plastic-adaptive changes that render the effect temporary. In some patients, treatment of an underlying condition, such as the Arnold-Chiari malformation, reduces nystagmus and improves vision. There is a need for multicenter trials to evaluate systematically potential treatments of abnormal eye movements that impair vision.

Leigh RJ, Averbuch-Heller L, Tomsak RL, Remler BF, Yaniglos SS, Dell'Osso LF. Treatment of abnormal eye movements that impair vision: strategies based on current concepts of physiology and pharmacology. Ann Neurol 1994;36:129–141

In this review, we discuss current treatments for abnormal eye movements that interfere with clear vision, especially pathological nystagmus and saccadic intrusions [1]. Nystagmus is a repetitive, to-and-fro motion of the eyes that is initiated by a slow phase. Saccadic intrusions include single, rapid movements and sustained oscillations that disrupt steady fixation. In the past, treatment of these disorders was largely empirical, but a body of basic knowledge has now accrued that makes it possible to formulate a logical basis for therapy in certain patients. In this review, we first summarize the requirements that normal eye movements must fulfill to provide clear and stable vision, and describe how abnormal eye movements lead to visual symptoms. Second, we identify the differences between normal eye movements and eye movements that interfere with clear vision. Third, we review recent ideas about the pathophysiology and pharmacology of nystagmus and saccadic intrusions. Finally, we suggest available methods for treating these disorders, including strategies for selecting patients.

Ocular Motor Requirements for Clear and Stable Vision

Normal Mechanisms

What visual needs must eye movements satisfy? Stated briefly, clear vision of an object requires that its image be held *fairly steadily* on the foveal region of the retina. Just *how steadily* do images of the world have to be held on the retina in order for vision to be clear and stable? Our perception of the world, as viewed with our heads still, is one that is stationary, and so we tend to assume that images of the world on the retina are also stationary. In fact, our eyes are in constant motion due to drifts and saccades, and so are the retinal images of stationary objects. This movement of images on the retina, due to small eye movements, transforms a spatial pattern into a spatiotemporal pattern [2, 3]. Although it is often stated that if the speed of retinal drift of a visual stimulus increases then it will be seen less clearly, this is not completely true. In fact, changing the retinal image speed shifts the "spatial-frequency window" through which we can clearly view the out-

From the Departments of *Neurology, †Ophthalmology, ‡Neuroscience, and §Optometry, Department of Veterans Affairs Medical Center, University Hospitals and Mount Sinai Medical Center, Case Western Reserve University, Cleveland, OH.

Received Feb 14, 1994, and in revised form Mar 16. Accepted for publication Mar 17, 1994.

Address correspondence to Dr Leigh, Department of Neurology, University Hospitals, 2074 Abington Road, Cleveland, OH 44106.

side world [2, 3]. This not only means that if the speed of retinal image drift increases, we see high spatial frequencies (e.g., a conventional Snellen chart) less well, but also means that we will see lower spatial frequencies (e.g., large objects) *better.* This relationship was studied as subjects attempted to detect a single bar moving across a screen [2]. Figure 1 shows how the threshold for detecting the bar depends on both its width (spatial frequency) as well as its speed. It is also evident from Figure 1 that for detection of objects smaller than 1 degree, retinal slip should generally be held below about 5 degrees/sec; above this threshold, visual acuity declines in a logarithmic fashion [4]. (A special exception to these general rules concerns eye rotations about the line of sight—torsional movements—for which a different set of rules seems to apply [5].) Measurements of ocular drift while attempting steady fixation give values of about 0.15 degree/sec with the head held stationary, and up to 3 degrees/sec during walking [6]. So for the image motion induced by these eye movements, there is little change in the spatial filtering properties of the visual system [3, 7]. During fixation, saccadic eye movements also occur; these produce high-speed movement of images on the retina—too high for clear vision. Indeed, we generally do not see during saccades, mainly due to a "backward masking" effect; the brain finds it relatively easy (in normal lighting conditions) to ignore the smeared retinal signal due to the saccade since the images at the beginning and at the end of the saccade are, by comparison, so clear [8].

For best vision of a *single feature* of the world, its image not only must be held fairly steady on the retina, but also must be brought close to the center of the fovea. Visual acuity declines steeply from the fovea to the retinal periphery [3], and so the image of the object of regard should in general be within 0.5 degree of the center of the fovea.

Abnormal Mechanisms

Abnormal eye movements interfere with clear and stable vision by causing excessive drift of images on the retina and by displacing the image of an object of interest from the fovea. Patients with excessive image drift complain of impaired vision and oscillopsia—the illusory movement of the environment. These symptoms interfere with activities requiring steady fixation (e.g., reading and watching television), and oscillopsia can be distressing to the patient. Patients in whom inappropriate saccades repeatedly misdirect the fovea often complain of difficulty with reading.

Whereas the relationship between retinal image velocity and visual acuity is a fairly direct one (see above), the correlation between retinal image velocity and the development of oscillopsia is less consistent, and varies among subjects. With acquired nystagmus, the magnitude of oscillopsia is usually less than the magnitude of nystagmus. For example, in patients with downbeat nystagmus, the amplitude of oscillopsia is on average about one third of the amplitude of the nystagmus [9]. Furthermore, individuals with congenital nystagmus, who may intermittently have images moving across the retina with speeds exceeding 100 degrees/sec, seldom complain of oscillopsia [10]. A number of mechanisms may independently contribute to preservation of a perception of visual constancy in patients with nystagmus. In individuals with congenital nystagmus, it seems that this is partially due to "foveation periods"—brief epochs during each cycle of the nystagmus when the fovea is pointing at the object of interest and the eye is temporarily still [11, 12] (Fig 2A). Thus it is proposed that individuals with congenital nystagmus principally view their worlds during these brief, stationary "snapshots," and somehow suppress the visual perception that accompanies the high-speed portions of the waveform, when images are smeared across the retina. The mechanism for such suppression of visual smear is uncertain, but might be similar to the way we suppress a smeared visual percept during normal saccades [8].

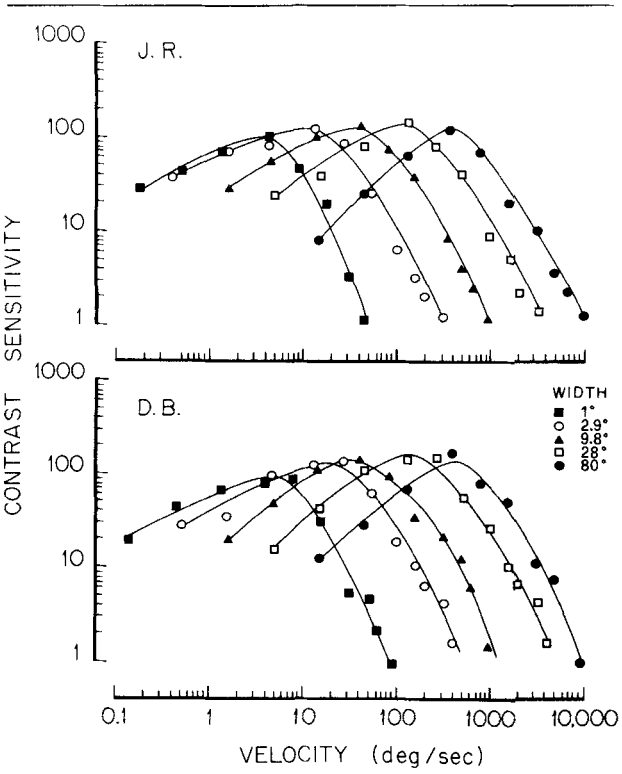

Fig 1. Contrast sensitivity of 2 subjects to moving bars (each a single cycle of sine wave grating) of various widths as a function of image velocity. Note how contrast sensitivity depends on both image velocity and spatial frequency. For bars subtending 1 degree, contrast sensitivity starts to fall when retinal image velocity exceeds about 5 degrees/sec. (Reproduced with permission from [2].)

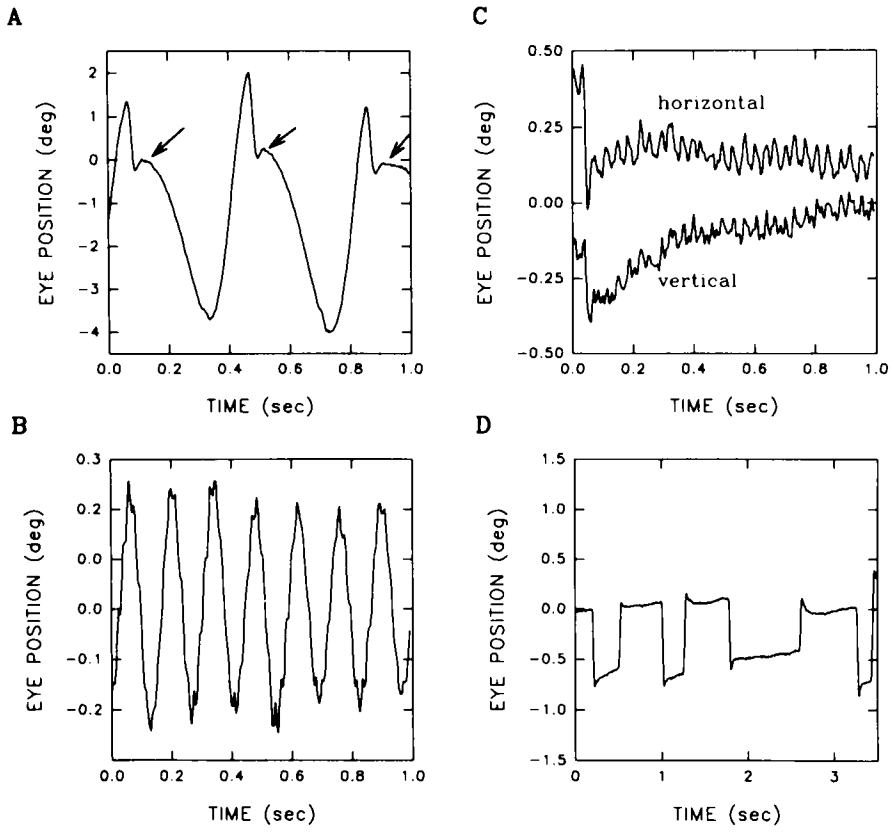

Fig 2. Examples of abnormal eye movements and their effect on vision. (A) A pendular type of congenital nystagmus waveform with superimposed quick phases. Note that following each quick phase, "foveation periods" (indicated by arrows) *occur, at which time the eye is close to the desired fixation point (0 degree) and eye velocity is low (i.e., the image is on the fovea and image slip is low). This patient experienced no oscillopsia. (B) A pendular type of acquired nystagmus in a patient with multiple sclerosis who complained of blurred vision and oscillopsia. Note the absence of foveation periods. Although the amplitude of these oscillations is low (being not much greater than the angular size of the fovea), their frequency is high (7 Hz) and their velocity is consequently large enough to impair vision. (C) Sustained saccadic oscillations that interfere with clear vision. The amplitudes of the horizontal and vertical components of this diagonal microsaccadic flutter are low, but the high frequency of these oscillations impaired vision in the patient, who was otherwise well. Clinically, these oscillations could only be discerned with an ophthalmoscope. (D) An example of saccadic intrusions (square waves) that repeatedly moved the image of regard off the fovea; the patient had progressive supranuclear palsy. Note that the scales differ in each panel. All eye movements are horizontal unless otherwise specified. Upward deflections indicate rightward or upward eye movements.*

However, it should be noted that individuals with congenital nystagmus also acquire visual information at times other than the foveation period [13].

Foveation periods are not present in patients with acquired nystagmus (Fig 2B), and so other mechanisms must be acting to suppress at least partially their oscillopsia. An old hypothesis that has received recent support is that the brain takes account of the nystagmus by monitoring an "efference copy" of the neural command signals for eye movements, and interprets its visual perceptions accordingly [14, 15]. Whatever the mechanism, it has been shown experimentally that if retinal image drift in patients with acquired nystagmus can be reduced below about 5 degrees/sec, then oscillopsia is usually abolished and vision is improved [14]. In the torsional plane, tolerance for retinal slip is higher [5] and, for example, the torsional component of nystagmus is less likely to impair visual acuity and cause oscillopsia.

Physiological and Pathological Nystagmus

The normal function of eye movements can be related to the visual prerequisites of holding images of the world fairly steady on the retina and bringing the image of an object of interest to the fovea. Thus, eye movements can be thought of as serving two main functions:

gaze-holding and gaze-shifting [1]. The purpose of *gaze-holding movements*—visual fixation, and the vestibulo-optokinetic reflexes—is to hold images of stationary objects fairly steady on the retina; failure to do so can cause the slow phases of pathological nystagmus. The purpose of *gaze-shifting movements*—saccades, smooth pursuit, and vergence—is to point the foveas at objects of interest that may be stationary or moving; failure to do so can limit foveal vision.

Nystagmus serves a *physiological* function in normal subjects during self-rotation. Most head movements are brief and require only small compensatory eye movements to maintain the stability of gaze. However, any sustained head rotation would cause the eyes to lodge at the corners of the orbit, in extreme contraversive deviation, where they no longer could make appropriate movements. Usually, this does not occur because of the *quick phases* of nystagmus, which reset the eyes so that they can then continue to make a compensatory movement. Quick phases are the evolutionary forerunners of voluntary saccades; they move the eye rapidly in the orbit in the same direction as that of head rotation and so enable perusal of the oncoming visual scene. In contrast, *pathological* nystagmus causes excessive drift of images of stationary objects on the retina, leading to impaired vision and oscillopsia. Just as the slow phase of physiological nystagmus acts to hold images of the world steady on the retina and preserve vision, so the slow phase of pathological nystagmus causes excessive motion of retinal images and impairs vision. Furthermore, the slow phase of pathological nystagmus usually reflects the underlying disorder of gaze-holding. *Saccadic intrusions* are abnormal gaze-shifting movements that disrupt steady foveal fixation [1]; some examples are shown in Figures 2C and 2D. Individual saccadic intrusions take the image of the object of regard away from the fovea and may, for example, interfere with reading. Sustained saccadic oscillations can cause the complaint of oscillopsia. Besides nystagmus and saccadic intrusions, other disorders of eye movements can disrupt clear and stable vision; one example is superior oblique myokymia, which is probably an abnormality of the trochlear motor units [16].

Although this review concerns nystagmus as a cause of oscillopsia and blurred vision, these symptoms are also reported by patients who have abnormalities of the vestibulo-ocular reflex or weakness of an extraocular muscle, but only when they move their heads [1]. When oscillopsia is caused by ocular oscillation such as nystagmus, it occurs even when the head is still. Rarely, oscillopsia is the complaint in patients who do not have excessive retinal image motion (i.e., have no nystagmus) but rather who seem to have a disorder of those central mechanisms that normally ensure a sense of visual constancy [17].

New Concepts Concerning the Pathogenesis of Nystagmus and Saccadic Intrusions

A better understanding of several types of acquired nystagmus has been obtained over the past decade and, in some cases, an animal model has been developed (see below). Nevertheless, some types of nystagmus remain poorly understood. The pathophysiological processes that are known to produce nystagmus can be thought of in terms of disorders of the three main subsystems that normally act to hold gaze steady: visual fixation, the mechanism for holding the eye in an eccentric position in the orbit (the "neural integrator"), and the vestibulo-optokinetic reflexes. Thus, with the head still, and the eyes close to primary position, the visual fixation system is of primary importance for holding gaze steady. When the eyes are turned to an eccentric position in the orbits, the neural integrator mechanism makes it possible to hold the eyes steady by sustaining tonic innervation of the extraocular muscles. During head rotations, vestibular, optokinetic, and fixation eye movements work together to keep the eyes pointed at a stationary object. A disturbance of any of these three mechanisms can cause the eyes to drift as a slow phase of nystagmus [1]. However, it should be noted that the anatomical pathways underlying these gaze-holding mechanisms (especially connections of the vestibular nuclei and cerebellum) show some overlap so that with clinical lesions, all three functions may be impaired. We start by reviewing forms of nystagmus for which an animal model exists or about which there is substantial understanding.

Forms of Nystagmus for Which an Animal Model Exists or That Are Well Understood

Nystagmus can be produced by lesions of the peripheral or central vestibular system. Such nystagmus is due to an imbalance in the level of tonic neural activity in the vestibular nuclei. The effects of *peripheral vestibular lesions* have been quantified in monkeys during the acute and recovery phases [18]; nystagmus from acute, peripheral vestibular disease rarely persists, due to the brain's remarkable ability to recover from these lesions. It has also been possible to induce a *central form of vestibular nystagmus—downbeat nystagmus*—by creating a lesion in either the cerebellar flocculi or the midline floor of the fourth ventricle [19, 20]. This nystagmus can be conceptualized as being due to a central imbalance of inputs from the vertical semicircular canals. Specifically, the upward drifts may represent greater "tone" in the central connections of the anterior semicircular canals, which mediate upward eye movements, than in those of the posterior canals, which mediate downward eye movements. Thus, either loss of inhibition of the anterior canal projection due to flocculectomy or disruption of posterior canal projections due to a lesion in the fourth ventricle floor can cause

downbeat nystagmus. Although *upbeat nystagmus* has not been produced experimentally, discrete lesions in humans also make it likely to reflect a specific disruption of the central projections from the anterior semicircular canals [1]. Similarly, *torsional nystagmus,* which occurs with pontomedullary tegmental lesions and syringobulbia, also can be regarded as a disorder of central vestibular connections [21].

It has also become evident that the medial vestibular nucleus and the adjacent prepositus hypoglossi nucleus are essential for normal neural integrator function. To hold the eye steady in an eccentric position in the orbit requires a tonic contraction of the extraocular muscles. This is achieved by a "step" eye position signal that is generated by the neural integrator. Experimental lesions of the neural integrator cause so-called *gaze-evoked nystagmus* [22]; due to a deficient eye position signal, the eyes cannot be maintained at an eccentric orbital position and they drift toward the primary position. Corrective quick phases move the eyes back toward the desired location. Gaze-evoked nystagmus frequently accompanies other vestibular eye signs with central vestibular lesions. It also can be caused by structural or toxic lesions that involve the vestibulocerebellum or its connections with the brainstem nuclei [19], and is most commonly produced by anticonvulsants, sedatives, and alcohol. A selective lesion of the medial vestibular nucleus and nucleus prepositus hypoglossi causing complete neural integrator failure was documented in a patient who died of lithium intoxication [23].

Much more is known about a rarer form of central vestibular nystagmus—acquired *periodic alternating nystagmus* (PAN). This is a spontaneous horizontal nystagmus, present in primary gaze, that reverses its direction about every 2 minutes. Acquired PAN occurs most commonly with disease involving the midline of the cerebellum [1]. Experimental ablation of the nodulus and uvula of the cerebellum in monkeys causes PAN when the animals are put into darkness [24]. One function of the nodulus and uvula is to control the time course of rotationally induced nystagmus (so-called velocity storage [25]). Thus, following ablation of the nodulus and uvula, the duration (velocity storage) of rotationally induced nystagmus is prolonged excessively, and it is postulated that normal vestibular "repair mechanisms" act to reverse the direction of this nystagmus, so producing the oscillations of PAN [24, 26]. 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.

Forms of Nystagmus That Lack an Animal Model and Are Less Well Understood

See-saw nystagmus is characterized by pendular oscillations, one half-cycle of which 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 [27]. In some patients, one half-cycle of see-saw nystagmus alternates with an oppositely directed quick phase [28, 29]; this has been called *hemi-see-saw nystagmus.* See-saw or hemi-see-saw nystagmus has been observed in patients with discrete lesions involving the interstitial nucleus of Cajal (INC) [29, 30]. These findings are in accord with experimental studies that implicate a central disturbance of otolithic inputs. Stimulation in the region of the INC in the monkey 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 [31]. The INC receives vestibular inputs, which probably include secondary otolithic projections. Moreover, eye movements similar to those obtained by stimulating the INC are also produced by stimulating the contralateral utricular nerve [32]. Both of these experimental responses are similar to one half-cycle of see-saw nystagmus. Thus, see-saw nystagmus could represent a sinusoidal oscillation involving central otolithic connections.

Another hypothesis for see-saw nystagmus arises from its frequent association with optic chiasm lesions. It has been suggested that interruption of subcortical pathways that carry signals to the inferior olive and cerebellar flocculus and that are normally used for adaptive control of vestibular responses may be important in the genesis of see-saw nystagmus [27].

Acquired pendular nystagmus is encountered with a variety of diseases, and of all forms of nystagmus, most frequently causes distressing visual symptoms. An example is shown in Figure 2B. The nystagmus often has both horizontal and vertical components; the oscillations may be disconjugate, disjunctive, and occasionally, purely monocular. The frequency of oscillations of acquired pendular nystagmus ranges from about 2 to 7 Hz, with a typical value of 3.5 Hz [33, 34]. The two most common causes of acquired pendular nystagmus are disorders of myelin (especially multiple sclerosis) and brainstem infarction [35]. In the latter, pendular nystagmus is a delayed consequence, often in association with palatal myoclonus; tremors of other parts of the body (e.g., larynx, head, limbs) may coexist. It has been postulated that the pathophysiological process responsible for oculopalatal myoclonus may be in the dentato-olivary connections, and since the projections of the inferior olive to the cerebellar flocculus are important in mediating adaptive properties of the vestibulo-ocular reflex, the ocular oscillations may be due to an instability of this adaptive mechanism [35].

Several hypotheses have been put forward to account for acquired pendular nystagmus in patients with myelin disorders. First, it is suggested that demyelination of the optic nerve is responsible, but its involve-

ment is not invariable and sometimes vision is only impaired due to the oscillations. Nonetheless, the nystagmus usually has a larger amplitude of oscillation in the eye with more severe involvement of the optic nerve [34]. Because of the common finding of midline cerebellar disturbance, the deep cerebellar nuclei have been incriminated [36]. The cerebellar signs, however, may be lacking and cerebellar lesions are not reported to produce disconjugate oscillations of the eyes. One possibility concerns the recently described cell groups of the paramedian tracts, which lie adjacent to the medial longitudinal fasciculus and relay projections from a variety of ocular motor structures to the flocculus [37]. Delay of transmission in this pathway might lead to acquired pendular nystagmus.

Saccadic Intrusions

Square-wave jerks are involuntary saccades that take the eyes off the target and are followed, after a nearly normal intersaccadic interval (130–200 msec), by a corrective saccade that brings the eyes back to the target (see Fig 2D). They can occur in normal individuals, and also with a variety of neurological disorders, most prominently cerebellar disorders and progressive supranuclear palsy [1]. Unless they are large and frequent, square waves seldom cause visual symptoms. Large (10–40 degrees) saccades, separated by intersaccadic intervals of about 100 msec, are called *square-wave pulses;* they have been observed in patients with multiple sclerosis (where they have also been called *macrosquare-wave jerks)* [38]. *Ocular flutter* is a burst of back-to-back saccades without an intersaccadic interval (see Fig 2C). Saccadic oscillations without an intersaccadic interval that have variable horizontal and vertical (and torsional) components are called *opsoclonus.* There appears to be a continuum between flutter and opsoclonus. Ocular flutter and opsoclonus are usually encountered in patients with signs of brainstem or cerebellar dysfunction (e.g., brainstem encephalitis and paraneoplastic syndromes) [1]. Occasionally, otherwise normal individuals show intermittent, small-amplitude, high-frequency saccadic oscillations that can only be observed with the ophthalmoscope ("microsaccadic flutter") [39]. We have encountered two patients in whom such oscillations had both horizontal and vertical components producing a repetitive diagonal motion (see Fig 2C). Patients with flutter and opsoclonus frequently complain of oscillopsia, even if the oscillations are of small amplitude; this is due to their high frequency, which causes large retinal slip velocities. Although there is no animal model for flutter and opsoclonus, qualitative hypotheses to explain these oscillations in terms of the brainstem neurons that generate and regulate saccades—"burst" and "pause" cells—have been proposed [39].

A final point on the pathogenesis of abnormal eye movements concerns the question of why the ocular motor system, which shows a considerable ability to "repair" a range of disturbances, cannot negate pathological nystagmus or saccadic intrusions. To some extent nystagmus can be negated, the best example being suppression of nystagmus due to peripheral vestibular disease by the normal visual fixation mechanism. However, most forms of nystagmus are associated with abnormal visual fixation; indeed, loss of vision itself leads to nystagmus [40]. A second possible factor is that the disturbance that causes the nystagmus also disrupts the normal repair mechanisms. However, this explanation is not wholly satisfactory since therapeutic paralysis of extraocular muscles with botulinum toxin to abolish nystagmus may set in motion plastic-adaptive changes to compensate for the muscle weakness (see below). Indeed, this preservation of certain reparative mechanisms may limit the success of procedures that attempt to lessen nystagmus by weakening the eye muscles.

Neuropharmacological Aspects of Nystagmus

Although much has been learned about the anatomy and physiology of the ocular motor system, the pharmacology is still being elucidated. In this section, we briefly review what is known, starting with the vestibular system and its connections.

The *vestibular nerve* has been shown to utilize aspartate, glutamate, and acetylcholine (ACh) [41, 42]. These same agents also have been found within the *vestibular nuclei;* in addition, γ-aminobutyric acid (GABA) has been identified [43]. A general principle concerning the *vestibular projections* is that inhibitory pathways to motoneurons mediating the vertical vestibulo-ocular reflex use GABA, whereas the inhibitory pathways to motoneurons mediating the horizontal vestibulo-ocular reflex utilize glycine [44]. Furthermore, glycine has been identified as the neurotransmitter of pause neurons, which inhibit saccadic burst neurons in the paramedian pontine reticular formation (PPRF) [45]. Disease affecting these pause neurons might cause saccadic oscillations such as opsoclonus (due to loss of burst cell inhibition) or slow saccades (if burst cell discharge became desynchronized).

One approach that may clarify the functional significance of these neurotransmitters is to study the behavioral deficits caused by microinjection of agents that inactivate certain neurotransmitters. Recently, Büttner and colleagues [46, 47] measured the ocular motor deficits produced by microinjection of the weak GABA antagonist bicuculline and the strong GABA agonist muscimol into the vestibular nuclei of monkeys. Bicuculline induced a vestibular imbalance manifesting as nystagmus with slow phases that had horizontal and vertical components; the horizontal quick phases were directed ipsilaterally or contralaterally. On

the other hand, muscimol caused a loss of neural integrator function, evident as gaze-evoked nystagmus with a shift in the "null" position away from the primary position. These findings indicate that GABA is an important neurotransmitter for the vertical and horizontal vestibulo-ocular reflexes, and also is involved in the gaze-holding mechanism, which depends heavily on the medial vestibular nuclei. Some patients with downbeat nystagmus, which may be due to a central vestibular imbalance, show improvement when given the GABA-B agonist baclofen [48].

There is also evidence that control by the nodulus and uvula of the dynamic property of the vestibulo-ocular reflex, referred to as velocity storage (see above), is achieved by inhibitory pathways that use GABA [49]. Thus, the GABA agonist baclofen is able to abolish PAN due to experimental or clinical lesions of the nodulus and uvula [24, 50]. The velocity-storage phenomenon in normal monkeys is also mildly enhanced by diazepam [51] and suppressed by baclofen [49] and picrotoxin [52].

Clinical evidence also has supported a role for acetylcholinergic mechanisms in vertical eye movements that are probably mediated by the vestibular system. First, it has been shown that nicotine can produce upbeat nystagmus in normal subjects in darkness [53, 54]. Second, intravenous physostigmine may increase the intensity of downbeat nystagmus [48]. Third, scopolamine suppresses downbeat nystagmus in some patients [55]. Fourth, increased ACh esterase activity and cholinergic denervation supersensitivity were observed in the hypertrophied inferior olivary nucleus of patients with palatal myoclonus [56, 57].

Experimental studies also have elucidated the pharmacology of a pathway important in the control of reflexive and voluntary saccades [58]. The nondopaminergic portion of the substantia nigra 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 on the superior colliculus. The caudate nucleus appears to facilitate the initiation of voluntary, self-generated types of saccades made in the context of learned behavior; in addition, the caudate appears to aid steady fixation by preventing unwanted reflexive saccades to stimuli which at that particular moment, would be disruptive. It has been shown that this nigrotectal pathway is GABA-ergic, and that injection of bicuculline into the superior colliculus increases the frequency and amplitude of the saccades, which take the form of square-wave intrusions [59].

Current Therapies for Nystagmus

In attempting to treat nystagmus or saccadic intrusions, it is helpful to recall that these abnormal eye movements may be manifestations of a variety of disorders. Therefore, it is not surprising that the list of proposed therapies is long, and drugs reportedly successful in one patient with nystagmus are only occasionally helpful in another. Furthermore, most treatments for nystagmus are symptomatic, with the aim of stopping either the oscillations or their visual consequences. Only a few treatments for nystagmus are directed toward the underlying mechanism.

We first discuss the existing pharmacological means of treating nystagmus, and then review in brief the remaining nonspecific methods. Generally, attempts to treat nystagmus with drugs originate from two main sources: the accumulating information concerning the neurotransmitters involved in its pathogenesis, and by analogy with presumably similar conditions, such as tremor. Several transmitters, both inhibitory and excitatory, take part in ocular motor control. One problem with attempting to augment inhibitory systems (e.g., GABA or glycine) or inhibit excitatory systems (e.g., glutamate) is that the relationship between different neurotransmitters is complex, involving such mechanisms as "double inhibition." For example, Büttner and colleagues [46] found that the GABA agonist muscimol actually *produced* nystagmus by impairing neural integrator activity. Because of the fragmentary knowledge of the pharmacology of the ocular motor system, caution is required in predicting the therapeutic effect of any given agonist or antagonist. Another factor that has confounded attempts to identify effective treatments for nystagmus and saccadic intrusions is the lack of double-blind clinical trials; most reports are based on uncontrolled observations (often without reliable measurement of eye movements) in a few patients.

Pharmacological Treatment of Nystagmus

PERIODIC ALTERNATING NYSTAGMUS. PAN is the best example of a form of nystagmus for which the drug treatment is based on known pathophysiology and pharmacology. PAN is thought to be produced by dysfunction of the GABA-ergic velocity-storage mechanism, and most but not all patients reported respond to the GABA-B agonist baclofen [50, 60] (Table). However, no control study has been performed. Patients with congenital PAN, which probably has a different pathogenesis, only occasionally respond to baclofen [61].

DOWNBEAT AND UPBEAT NYSTAGMUS. Clinical and laboratory evidence suggests involvement of GABA-ergic and cholinergic transmission in vertical vestibulo-ocular reflex, and both types of drugs were tried in patients with upbeat or downbeat nystagmus. Currie and Matsuo [62] studied the effect of the GABA-A agonist clonazepam; in all their patients downbeat nystagmus was reduced and oscillopsia eliminated by treatment

Disorders for Which Drug Treatments Have Been Reported as Effective

Disorder	Drug	References
Downbeat or upbeat nystagmus	Clonazepam	62
	Baclofen	48
	Scopolamine	55
Acquired pendular nystagmus	Scopolamine	33, 55
	Trihexyphenidyl	64, 65, 68
	Isoniazid	67
	Valproate	69
	Barbiturates	63
Periodic alternating nystagmus	Baclofen	50, 60, 61
See-saw nystagmus	Ethanol	70, 71
	Baclofen	61
Superior oblique myokymia	Carbamazepine	77, 79
	Propranolol	78
Saccadic oscillations	Clonazepam	73
	Phenobarbital	73
	Amphetamines	76
	Propranolol	39

with clonazepam. The authors proposed a 1- to 2-mg single-dose clonazepam test to determine whether long-term therapy was feasible. It should be noted that the cause of nystagmus in this series was diverse, and included structural, ischemic, degenerative, toxic, and demyelinative conditions. Dieterich and coworkers [48] administered the GABA-B agonist baclofen to 5 patients; 4 of them (2 with upbeat, 2 with downbeat nystagmus) showed reduction in both nystagmus velocity and oscillopsia. Here also, the cause varied from demyelinative to structural, ischemic, and paraneoplastic (the latter in a nonresponding patient). The same authors examined the effect of the cholinergic drug physostigmine (ACh esterase inhibitor) in a single intravenous injection in another 5 patients. Physostigmine worsened nystagmus in all of them; in 1 patient this adverse effect was partially reversed by an additional injection of the anticholinergic drug biperiden, implying that anticholinergic drugs might prove effective. Consistent with these observations, Barton and colleagues [55] found in a double-blind study (discussed below) that in 2 patients with downbeat nystagmus, scopolamine reduced both nystagmus and oscillopsia.

ACQUIRED PENDULAR NYSTAGMUS. The mechanism and neurotransmitters involved in this disorder are unknown. Early treatment was with barbiturates [63], but sedative side effects limit the use of this therapy. Because of similarities with palatal myoclonus, a condition with suggested cholinergic supersensitivity (discussed below), several groups recently tested anticholinergic agents [55, 64, 65]. Two double-blind studies comparing different anticholinergic agents were undertaken recently, with somewhat contradictory results. Leigh and colleagues [65] conducted a randomized, double-blind crossover trial of trihexyphenidyl and tridihexethyl chloride (a quaternary anticholinergic that does not cross the blood-brain barrier). Of the 10 patients in their study, 5 had pendular elliptical nystagmus; of these, only 4 completed the trials of both drugs. Surprisingly, 3 patients showed a decrease in nystagmus and an improvement of visual acuity while taking tridihexethyl chloride, whereas trihexyphenidyl was only effective in 1 patient. In spite of the visual benefits, none of the patients wished to continue with either drug because of anticholinergic side effects. In another double-blind study, Barton and colleagues [55] administered scopolamine, benztropine, and glycopyrrolate (a quaternary agent devoid of central nervous activity) intravenously. Confirming an earlier report [33], a single dose of scopolamine effectively reduced nystagmus and improved vision in all 5 patients with pendular nystagmus, whereas benztropine was less effective and glycopyrrolate had no significant effect. While the discrepancy between these two studies could be explained by different subtypes of receptors antagonized and habituation to the drug effect after long-term oral use, an additional double-blind study of transdermal or oral scopolamine is needed to settle the issue.

Provoked by a report of isoniazid effectiveness for postural cerebellar tremor [66], Traccis and associates [67] used this drug to treat acquired pendular elliptical nystagmus in 3 multiple sclerosis patients. In 2 of them the nystagmus was abolished and oscillopsia relieved. In the first author's experience (unpublished observations, 1982), isoniazid may not be effective, and potential side effects limit its use.

OCULOPALATAL MYOCLONUS. In this variety of pendular nystagmus seen in association with palatal myoclonus, lesions involving dentato-olivary connections with subsequent cholinergic denervation supersensitivity in the inferior olive are considered responsible [57]. Accordingly, anticholinergic medications were proposed to treat this condition. Trihexyphenidyl reportedly affected palatal movements in 4 patients without associated nystagmus [64]. A single patient with vertical pendular nystagmus identical to that seen in oculopalatal myoclonus, but without associated palatal movements, also improved with chronic trihexyphenidyl treatment [68]. Valproate reportedly reduces palatal myoclonus, and in 1 patient, it resulted in a striking decrease of nystagmus [69].

SEE-SAW NYSTAGMUS. Alcohol was beneficial in 2 reported patients [70, 71]. Baclofen with and without clonazepam improved both nystagmus and oscillopsia in 1 patient [61], suggesting possible GABA-ergic influences on the INC.

One rare condition that does uniformly respond to

treatment is the syndrome of *familial episodic ataxia with nystagmus;* the whole complex of symptoms, including nystagmus, is alleviated by acetazolamide [72].

SACCADIC OSCILLATIONS. Experimental evidence suggests that saccadic intrusions might reflect a loss of GABA-ergic inhibition on the superior colliculi [59]; therefore, treatment with GABA agonists might prevent inappropriate saccades. Indeed, GABA-A agonists, benzodiazepines, and barbiturates (diazepam, clonazepam, thiamylal, and phenobarbital) were effective in abolishing high-amplitude, square-wave jerks and macrosaccadic oscillations in 1 patient [73]. Certain other drugs may influence the frequency of saccadic intrusions of the square-wave type. Specifically, either depletion of catecholamines [74] or administration of L-tryptophan, given in combination with a tricyclic antidepressant and a monoamine oxidase inhibitor [75], can cause an increase of saccadic intrusions. On the other hand, amphetamines may suppress square-wave jerks [76]. Other drugs such as propranolol and verapamil reportedly diminish microsaccadic ocular flutter in individual patients [1, 39]. Superior oblique myokymia may be effectively treated, in some patients, with carbamazepine or propranolol [16, 77–79].

Optical Treatments

A number of optical devices have been suggested for treatment of nystagmus. One approach utilizes the fact that in certain patients, especially those with congenital nystagmus, the eyes are often "quieter" when they are moved into a particular position in the orbit—the "null region." The latter may be induced by a specific gaze angle (i.e., conjugate position of the eyes in the orbit) or by a convergence angle, or by both. Patients with a nystagmus null at a specific gaze angle may benefit by wearing version prisms, to place their eyes in the null region. For example, in patients with downbeat nystagmus that is less prominent on upgaze, prisms that turn the eyes up may be useful. Patients whose nystagmus damps with convergence may benefit by wearing base-out prisms. Although convergence suppression is common in congenital nystagmus, some patients with a variety of acquired ocular oscillations may show the same phenomenon [80]. Individuals with both types of null may take advantage of composite prisms that provide both a version shift and convergence. In our experience, this latter group benefits most from the convergence prisms; we prescribe 7.00-diopter base-out prisms with −1.00-diopter spheres added to compensate for accommodation. The spherical correction may not be needed in presbyopic individuals. Contact lenses sometimes suppress congenital nystagmus; this effect is not due to the mass of the lenses but is probably mediated via trigeminal afferents [81].

Another approach has been the development of an optical system to stabilize images on the retina [14, 82]. This system consists of a high-plus spectacle lens worn in combination with a high-minus contact lens (Fig 3). Theoretically, stabilization could be achieved if the power of the spectacle lens focused the primary image close to the center of rotation of the eye. A contact lens would then be required to extend back the focus 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 on the retina. One disadvantage of this system is that it disables the vestibulo-ocular reflex and voluntary eye movements, so that it is only useful while the patient is stationary.

We attempted to treat 10 patients with acquired nystagmus with the optical stabilization device. In practice, only 2 patients were able to persevere with it for more than a few months, and none have used it for more than a year. Our original rigid polymethylmethacrylate (PMMA) contact lenses were often uncomfortable; the high-power and resulting very-thick-edge configuration causes mechanical discomfort and diminishes oxygen diffusion to the cornea. We recently were able to obtain gas-permeable lenses in powers as high as −58.00 diopters, with higher oxygen transmission and better patient tolerance [83]. For patients who require lesser degrees of stabilization, and thus lower powers, soft contact lenses are available. Soft lenses, while usually more comfortable, require more diligent care and a level of dexterity that is often absent, for example, in patients with multiple sclerosis.

Botulinum Toxin as Treatment of Nystagmus

Several clinical reports suggested that injection of botulinum toxin either into selected extraocular muscles or into the retrobulbar space might be effective treatment for acquired nystagmus [84, 85]. In 2 patients with acquired pendular nystagmus with horizontal, vertical, and torsional components, botulinum toxin was injected into the horizontal rectus muscle of the right eye. This successfully abolished the horizontal component of the nystagmus in the injected eye in both patients for about 2 months [86]. Both patients showed a small but measurable improvement of vision in the injected eye; this improvement may have been limited by coexistent disease of the visual pathways. The vertical and torsional components of the nystagmus persisted in both patients. In 1 patient, the horizontal component of nystagmus in the noninjected eye increased, a finding that was ascribed to plastic-adaptive changes in response to paresis caused by the botulinum toxin. It was concluded that such plastic-adaptive changes and direct side effects of the injections, such as diplopia and ptosis, may limit the effectiveness of botulinum toxin in the treatment of acquired nystagmus. Neither

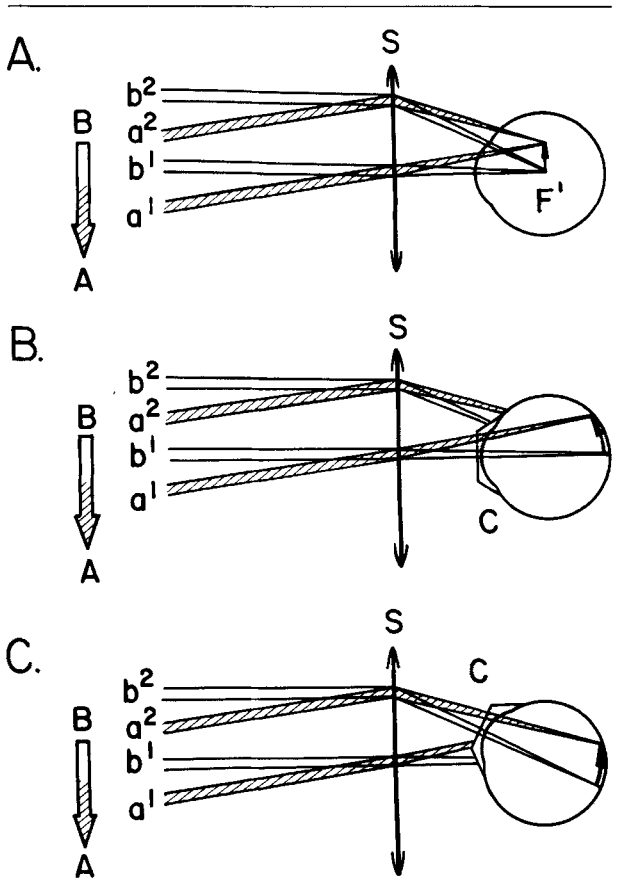

Fig 3. An optical method for stabilizing images of stationary objects on the retina. (A) When a distant object is viewed (AB), *a convergent spectacle lens* (S) *will focus rays of light* (b^1, b^2) *from a point of interest* (B) *on its focal point* (F^1), *which is close to the center of rotation of the globe. Thus, if the eyeball were to rotate, light rays from point B would remain focused at the same point as in the eye. (B) A strongly divergent contact lens* (C) *extends back the focus from the center of the globe to the retina. (C) Since the contact lens moves with the eye, it does not negate the effect of retinal image stabilization produced by the spectacle lens, and rays of light from point B remain focused on the foveal region of the retina. a^1 and a^2 = rays of light from point A. (Reproduced with permission from [14].)*

of these patients elected to repeat the botulinum treatment. Thus, the role of botulinum toxin in the treatment of nystagmus, injected either into specific muscles or into the retrobulbar space, has yet to be demonstrated.

Surgical Procedures

The Anderson-Kestenbaum procedure is an effective treatment for certain patients with congenital nystagmus [87–89]. This procedure aims to move the attachments of the extraocular muscles so that the null angle corresponds to the eyes' new primary position; it is best planned after careful measurements of eye movements and with a knowledge of the particular surgeon's "calibration factor" as to the amount of surgery necessary for the required shift in the position of the null region [90, 91]. The Anderson-Kestenbaum procedure both shifts and broadens the null region and results in decreased nystagmus outside the null region as well [90, 92, 93]. This procedure is of uncertain value in the treatment of acquired forms of nystagmus. In congenital nystagmus patients with stereopsis and a convergence null, the artificial divergence procedure modeled after Cüppers [94] is effective [95]. In all the above-mentioned procedures the increase in visual acuity is produced by prolongation of foveation time due to waveform changes and damping of nystagmus [90, 92, 93]. Studies comparing these different methods [93, 95, 96] concluded that the artificial divergence and combined operations gave better vision improvement than the Anderson-Kestenbaum procedure. Recently, large recession of the horizontal rectus muscles was proposed as treatment for patients with congenital nystagmus. Modest improvement of visual acuity was reported, but no reliable measurements of eye movements were made [97, 98].

Although most of the aforementioned reports dealt with congenital nystagmus, it is possible that the same measures could be applied to acquired nystagmus. However, a careful longitudinal study seems warranted to investigate this claim and determine whether factors such as the plastic-adaptive properties of the ocular motor system limit the beneficial effects as they may do after botulinum treatment. On the other hand, there is a consensus that neurosurgery does have a clear role in the therapy of Arnold-Chiari syndrome; suboccipital decompression reportedly improves downbeat nystagmus and prevents progression of other neurological deficits [99, 100].

Other Forms of Treatment

A variety of other treatments have been reported, principally for congenital nystagmus. Electrical or vibration stimulation over the forehead may suppress congenital nystagmus [101, 102]. Acupuncture administered to the neck muscles may suppress congenital nystagmus in some patients due to a similar mechanism [103]. Biofeedback also has been reported to help some patients with this condition [104, 105]. Its utility outside the laboratory in real-world situations, however, has yet to be demonstrated.

Evaluation of the Patient with Acquired Nystagmus: Selection of Appropriate Therapy

At the present time, there are relatively few reliable treatments for nystagmus, especially the acquired varieties. Thus, there is a great need for systematic evaluation of reported treatments, using reliable measurements of the nystagmus and visual acuity, and

systematic testing of all classes of eye movements. Whenever possible, evaluations should be double-blinded and drug assessments should be of oral or other preparations that the patient can take, rather than intravenous preparations. For the clinician not involved in such studies, referral to a center that can record eye movements *before* starting treatment is recommended, if only to identify the type of nystagmus. Although a careful clinical examination of the visual system and eye movements (including use of the ophthalmoscope and Frenzel goggles) may provide a clear diagnosis, congenital nystagmus or saccadic disorders can sometimes be mistaken for various types of acquired nystagmus, which would require different treatment. In these cases, quantification of the characteristics of the nystagmus (especially the slow phases) and systematic measurement of each class of eye movements (e.g., to detect subtle internuclear ophthalmoplegia) will indicate the nature of the ocular oscillation. In the patient in whom an acquired form of nystagmus is confirmed, it behooves the physician to look carefully for an underlying cause. Sometimes this may be obvious (e.g., multiple sclerosis), but it is worthwhile to look carefully for any treatable underlying condition such as the Arnold-Chiari malformation, Whipple's disease, thiamine deficiency, and paraneoplastic syndrome. Recent basic pharmacological studies of the vestibular and ocular motor systems are beginning to provide important information about the neurotransmitters involved. One great advantage of studying the ocular motor system is that it is organized more simply than other motor systems. Therefore, there is hope that in the next few decades, we will have a much better understanding of the pharmacological basis of pathological nystagmus, and so be better poised to treat its disabling visual consequences.

This work was supported by US Public Health Service grant EY06717, the Office of Research and Development, Department of Veterans Affairs, and the Evenor Armington Fund.

We are grateful to Nirav Sheth for help with the figures.

References

1. Leigh RJ, Zee DS. The neurology of eye movements. 2nd ed. Philadelphia: Davis, 1991
2. Burr DC, Ross J. Contrast sensitivity at high velocities. Vision Res 1982;22:479–484
3. Carpenter RHS. The visual origins of ocular motility. In: Cronly-Dillon JR, ed. Vision and visual function, vol 8. Eye movements. London: MacMillan, 1991:1–10
4. Demer JL, Amajadi F. Dynamic visual acuity of normal subjects during vertical optotype and head motion. Invest Ophthalmol Vis Sci 1993;34:1894–1906
5. Ott D, Seidman SH, Leigh RJ. The stability of human eye orientation during visual fixation. Neurosci Lett 1992;142: 183–186
6. Grossman GE, Leigh RJ, Bruce RJ, et al. Performance of the human vestibuloocular reflex during locomotion. J Neurophysiol 1989;62:264–272
7. Kelly DH. Motion and vision. II. Stabilized spatiotemporal surface. J Opt Soc Am 1979;69:1340–1349
8. Campbell FW, Wurtz RH. Saccadic omission: why we do not see a grey out during a saccadic eye movement. Vision Res 1978;18:1297–1303
9. Buchele W, Brandt T, Degner D. Ataxia and oscillopsia in downbeat-nystagmus vertigo syndrome. Adv Otorhinolaryngol 1983;30:291–297
10. Dickinson CM, Abadi RV. The influence of nystagmoid oscillation on contrast sensitivity in normal observers. Vision Res 1985;25:1080–1096
11. Dell'Osso LF, Leigh RJ. Foveation period stability and oscillopsia suppression in congenital nystagmus. Neuro-ophthalmology 1992;12:169–183
12. Dell'Osso LF, Leigh RJ. Ocular motor stability of foveation periods. Required conditions for suppression of oscillopsia. Neuro-ophthalmology 1992;12:303–326
13. Goldstein HP, Gottlob I, Fendick MG. Visual remapping in infantile nystagmus. Vision Res 1992;32:1115–1124
14. Leigh RJ, Rushton DN, Thurston SE, et al. Effects of retinal image stabilization on acquired nystagmus due to neurological disease. Neurology 1988;38:122–127
15. Leigh RJ, Dell'Osso LF, Yaniglos SS, Thurston SE. Oscillopsia, retinal image stabilization and congenital nystagmus. Invest Ophthalmol Vis Sci 1988;29:279–282
16. Leigh RJ, Tomsak RL, Seidman SH, Dell'Osso LF. Superior oblique myokymia. Quantitative characteristics of the eye movements in three patients. Arch Ophthalmol 1991;109: 1710–1713
17. Bender MB. Oscillopsia. Arch Neurol 1965;13:204–213
18. Fetter M, Zee DS. Recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 1988;59:370–393
19. Zee DS, Yamazaki A, Butler PH, Gucer G. Effects of ablation of flocculus and paraflocculus on eye movements in primate. J Neurophysiol 1981;46:878–899
20. DeJong JMBV, Cohen B, Matsuo V, Uemura T. Midsagittal pontomedullary brain stem section: Effects on ocular adduction and nystagmus. Exp Neurol 1980;68:420–442
21. Noseworthy JH, Ebers GC, Leigh RJ, Dell'Osso LF. Torsional nystagmus: quantitative features and possible pathogenesis. Neurology 1988;38:992–994
22. Cannon SC, Robinson DA. Loss of the neural integrator of the oculomotor system from brain stem lesions in monkey. J Neurophysiol 1987;5:1383–1409
23. Corbett JJ, Jacobson DM, Thompson HS, et al. Downbeating nystagmus and other ocular motor defects caused by lithium toxicity. Neurology 1989;39:481–487
24. Waespe W, Cohen B, Raphan T. Dynamic modification of the vestibulo-ocular reflex by the nodulus and uvula. Science 1985;228:199–202
25. Cohen B, Henn V, Raphan T, Dennett D. Velocity storage, nystagmus, and visual-vestibular interactions in humans. Ann NY Acad Sci 1981;374:421–433
26. Leigh RJ, Robinson DA, Zee DS. A hypothetical explanation for periodic alternating nystagmus: instability in the optokinetic-vestibular system. Ann NY Acad Sci 1981;374:619–635
27. Nakada T, Kwee IL. Seesaw nystagmus. Role of visuovestibular interaction in its pathogenesis. J Clin Neuro Ophthalmol 1988;8:171–177
28. Halmagyi GM, Curthoys IS, Gresty MA, Hoyt WF. Hemi-see-saw nystagmus due to unilateral diencephalic lesion: a novel eye movement disorder. Ann Neurol 1987;22(suppl):147
29. Ranalli PJ, Sharpe JA, Fletcher WA. Palsy of upward and

downward saccadic, pursuit, and vestibular movements with a unilateral midbrain lesion: pathophysiologic correlations. Neurology 1988;38:114–122
30. Kanter DS, Ruff RL, Leigh RJ, Modic M. See-saw nystagmus and brainstem infarction. MRI findings. Neuro-ophthalmology 1987;7:279–283
31. Westheimer G, Blair SM. The ocular tilt reaction—a brainstem oculomotor routine. Invest Ophthalmol 1975;14:833–839
32. Suzuki J-I, Tokumasu K, Goto K. Eye movements from single utricular nerve stimulation. Acta Otolaryngol (Stockh) 1969; 68:350–362
33. Gresty MA, Ell JJ, Findley LJ. Acquired pendular nystagmus: its characteristics, localising value and pathophysiology. J Neurol Neurosurg Psychiatry 1982;45:431–439
34. Barton JJS, Cox TA. Acquired pendular nystagmus in multiple sclerosis: clinical observations and the role of optic neuropathy. J Neurol Neurosurg Psychiatry 1993;56:262–267
35. Nakada T, Kwee IL. Oculopalatal myoclonus. Brain 1986;109: 431–441
36. Aschoff JC, Conrad B, Kornhuber HH. Acquired pendular nystagmus with oscillopsia in multiple sclerosis: a sign of cerebellar nuclei disease. J Neurol Neurosurg Psychiatry 1974;37: 570–577
37. Büttner-Ennever JA, Horn AKE, Schmidtke K. Cell groups of the medial longitudinal fasciculus and paramedian tracts. Rev Neurol (Paris) 1989;145:533–539
38. Dell'Osso LF. Nystagmus, saccadic intrusions/oscillations, and oscillopsia. In: Lessell S, van Dalen JTW, eds. Current neuro-ophthalmology, vol 2. Chicago: Year Book Medical, 1989: 147–182
39. Ashe J, Hain TC, Zee DS, Schatz NJ. Microsaccadic flutter. Brain 1991;114:461–472
40. Leigh RJ, Thurston SE, Tomsak RL, et al. Effect of monocular visual loss upon stability of gaze. Invest Ophthalmol Vis Sci 1989;30:288–292
41. Raymond J, Dememes D, Nieoullon A. Neurotransmitters in vestibular pathways. Prog Brain Res 1988;76:29–43
42. Matsuoka I, Domino EF. Cholinergic mechanisms in cat vestibular system. Neuropharmacology 1975;14:201–210
43. Spencer RF, Wang S-F, Baker R. The pathways and functions of GABA in the oculomotor system. Prog Brain Res 1992;90: 307–331
44. Spencer RF, Wentold RJ, Baker R. Evidence for glycine as an inhibitory neurotransmitter of vestibular, reticular, and prepositus hypoglossi neurons that project to the cat abducens nucleus. J Neurosci 1989;9:2718–2736
45. Horn AKE, Büttner-Ennever JA, Wahle P. Neuroanatomical evidence for glycine as the transmitter of saccadic omnipause neurons. Soc Neurosci Abstr 1993;19:1591
46. Straube A, Kurzan R, Büttner U. Differential effects of bicuculline and muscimol microinjections into the vestibular nuclei on simian eye movements. Exp Brain Res 1991;86:347–358
47. Büttner U, Straube A, Kurzan R. Oculomotor effects of gamma-aminobutyric acid agonists and antagonists in the vestibular nuclei of the alert monkey. Ann NY Acad Sci 1992; 656:645–659
48. Dieterich M, Straube A, Brandt Th, et al. The effects of baclofen and cholinergic drugs on upbeat and downbeat nystagmus. J Neurol Neurosurg Psychiatry 1991;54:627–632
49. Cohen B, Helwig D, Raphan T. Baclofen and velocity storage: a model of the effects of the drug on the vestibulo-ocular reflex in the rhesus monkey. J Physiol (Lond) 1987;393:703–725
50. Halmagyi GM, Rudge P, Gresty MA, et al. Treatment of periodic alternating nystagmus. Ann Neurol 1980;8:609–611
51. Blair SM, Gavin M. Modifications of vestibulo-ocular reflex induced by diazepam. Experiments in the macaque. Arch Otolaryngol 1979;105:698–701
52. Gavin M, Blair S. Modification of the macaque's vestibulo-ocular reflex by picrotoxin. Arch Otolaryngol 1981;107:372–376
53. Sibony PA, Evinger C, Manning KA. Tobacco-induced primary-position upbeat nystagmus. Ann Neurol 1987;21:53–58
54. Sibony PA, Evinger C, Manning KA, Pellegrini JJ. Nicotine and tobacco-induced nystagmus. Ann Neurol 1990;28:198
55. Barton JJS, Huaman AG, Sharpe JA. Muscarinic antagonists in the treatment of acquired pendular and downbeat nystagmus: a double-blind, randomized trial of three intravenous drugs. Ann Neurol 1994;35:319–325
56. Koeppen AH, Barron KD, Dentinger MP. Olivary hypertrophy: histochemical demonstration of hydrolytic enzymes. Neurology 1980;30:471–480
57. Matsuo F, Ajax ET. Palatal myoclonus, denervation supersensitivity in the central nervous system. Ann Neurol 1979;5: 72–78
58. Hikosaka O, Wurtz RH. The basal ganglia. In: Wurtz RH, Goldberg ME, eds. The neurobiology of saccadic eye movements. Rev Oculomot Res 1989;3:257–281
59. Hikosaka O, Wurtz RH. Effects on eye movements of a GABA agonist and antagonist injected into monkey superior colliculus. Brain Res 1983;272:368–372
60. Furman JMR, Wall C III, Pang D. Vestibular function in periodic alternating nystagmus. Brain 1990;113:1425–1439
61. Carlow TJ. Medical treatment of nystagmus and ocular motor disorders. In: Beck RW, Smith CH, eds. Neuroophthalmology. Boston: Little, Brown, 1986:251–264
62. Currie JN, Matsuo V. The use of clonazepam in the treatment of nystagmus-induced oscillopsia. Ophthalmology 1986;93: 924–932
63. Nathanson M, Bergman PS, Bender MB. Visual disturbances as the result of nystagmus on direct forward gaze: effect of sodium Amytal. Arch Neurol Psychiatry 1953;69:427–435
64. Jabbari B, Rosenberg M, Scherokman B, et al. Effectiveness of trihexyphenidyl against pendular nystagmus and palatal myoclonus: evidence of cholinergic dysfunction. Mov Disord 1987;2:93–98
65. Leigh RJ, Burnstine TH, Ruff RL, Kasmer RJ. The effect of anticholinergic agents upon acquired nystagmus. A double-blind study of trihexyphenidyl and tridihexethyl chloride. Neurology 1991;41:1737–1741
66. Hallet M, Lindsey JW, Adelstein BD, Riley PO. Controlled trial of isoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. Neurology 1985;85:1374–1377
67. Traccis S, Rosati G, Monaco MF, et al. Successful treatment of acquired pendular elliptical nystagmus in multiple sclerosis with isoniazid and base-out prisms. Neurology 1990;40:492–494
68. Herishanu Y, Louzoun Z. Trihexyphenidyl treatment of vertical pendular nystagmus. Neurology 1986;36:82–84
69. Lefkowitz D, Harpold G. Treatment of ocular myoclonus with valproic acid. Ann Neurol 1985;17:103–104
70. Frisen L, Wikkelso C. Posttraumatic seesaw nystagmus abolished by ethanol ingestion. Neurology 1986;36:841–844
71. Lepore FE. Ethanol-induced resolution of pathologic nystagmus. Neurology 1987;37:887
72. Zasorin NL, Baloh RW, Myers LB. Acetazolamide-responsive episodic ataxia syndrome. Neurology 1983;33:1212–1214
73. Fukazawa T, Tashiro K, Hamada T, Kase M. Multisystem degeneration: drugs and square wave jerks. Neurology 1986;36: 1230–1233
74. Tychsen L, Sitaram N. Catecholamine depletion produces irrepressible saccadic eye movements in normal humans. Ann Neurol 1989;25:444–449
75. Baloh RW, Dietz J, Spooner JW. Myoclonus and ocular oscillations induced by L-tryptophan. Ann Neurol 1982;11:95–97

76. Currie JN, Goldberg ME, Matsuo V, FitzGibbon EJ. Dyslexia with saccadic intrusions: a treatable reading disorder with a characteristic oculomotor sign. Neurology 1986;36(suppl 1): 134
77. Susac JO, Smith JL, Schatz NJ. Superior oblique myokymia. Arch Neurol 1973;29:432–434
78. Tyler RD, Ruiz RS. Propranolol in the treatment of superior oblique myokymia. Arch Ophthalmol 1990;108:175–176
79. Rosenberg ML, Glaser JS. Superior oblique myokymia. Ann Neurol 1983;13:667–669
80. Lavin PJM, Traccis S, Dell'Osso LF, et al. Downbeat nystagmus with a pseudocycloid waveform: improvement with base-out prisms. Ann Neurol 1983;13:621–624
81. Dell'Osso LF, Traccis S, Abel LA, Erzurum SI. Contact lenses and congenital nystagmus. Clin Vis Sci 1988;3:229–232
82. Rushton D, Cox N. A new optical treatment for oscillopsia. J Neurol Neurosurg Psychiatry 1987;50:411–415
83. Yaniglos SS, Leigh RJ. Refinement of an optical device that stabilizes vision in patients with nystagmus. Optom Vis Sci 1992;69:447–450
84. Crone RA, de Jong PTVM, Notermans G. Behandlung des Nystagmus durch Injektion von Botulinustoxin in die Augenmuskeln. Klin Monatsbl Augenheilkd 1984;184:216–217
85. Helveston EM, Pogrebniak AE. Treatment of acquired nystagmus with botulinum A toxin. Am J Ophthalmol 1988;106: 584–586
86. Leigh RJ, Tomsak RL, Grant MP, et al. Effectiveness of botulinum toxin administered to abolish acquired nystagmus. Ann Neurol 1992;32:633–642
87. Anderson JR. Causes and treatment of congenital eccentric nystagmus. Br J Ophthalmol 1953;37:267–281
88. Kestenbaum A. Nouvelle operation de nystagmus. Bull Soc Ophthalmol Fr 1953;6:599–602
89. Kestenbaum A. Clinical methods of neuro-ophthalmologic examination. 2nd ed. New York: Grune & Stratton, 1961
90. Dell'Osso LF, Flynn JT. Congenital nystagmus surgery. A quantitative evaluation of the effects. Arch Ophthalmol 1979; 97:462–469
91. D'Esposito M, Reccia R, Roberti G, Russo P. Amount of surgery in congenital nystagmus. Ophthalmologica 1989;198: 145–151
92. Flynn JT, Dell'Osso LF. Surgery of congenital nystagmus. Trans Ophthalmol Soc UK 1981;101:431–433
93. Zubkov AA, Stark N, Weber A, et al. Improvement of visual acuity after surgery for nystagmus. Ophthalmology 1993;100: 1488–1497
94. Cüppers C. Probleme der operativen Therapie des okulären Nystagmus. Klin Monatsbl Augenheilkd 1971;159:145–157
95. Sendler S, Shallo-Hoffmann J, Mühlendyck H. Die Artifizielle-Divergenz-Operation beim kongenitale Nystagmus. Fortschr Ophthalmol 1990;87:85–89
96. Kaufmann H, Kolling G. Operative Therapie bei Nystagmuspatienten mit Binokularfunktionen mit und ohne Kopfzwangshaltung. Berl Dtsch Ophthalmol Ges 1981;78:815–819
97. Helveston EM, Ellis FD, Plager DA. Large recession of the horizontal recti for treatment of nystagmus. Ophthalmology 1991;98:1302–1305
98. von Noorden GK, Sprunger DT. Large rectus muscle recession for the treatment of congenital nystagmus. Arch Ophthalmol 1991;109:221–224
99. Pedersen RA, Troost BT, Abel LA, Zorub D. Intermittent downbeat nystagmus and oscillopsia reversed by suboccipital craniectomy. Neurology 1980;30:1239–1242
100. Spooner JW, Baloh RW. Arnold-Chiari malformation. Improvement in eye movements after surgical treatment. Brain 1981;104:51–60
101. Dell'Osso LF, Leigh RJ, Daroff RB. Suppression of congenital nystagmus by cutaneous stimulation. Neuro-ophthalmology 1991;11:173–175
102. Dell'Osso LF, Sheth NV, Leigh RJ. Afferent stimulation in congenital nystagmus. Invest Ophthalmol Vis Sci 1994;35: 1409 (abstract)
103. Ishikawa S, Ozawa H, Fujiyama Y. Treatment of nystagmus by acupuncture. In: Highlights in neuro-ophthalmology: proceedings of the sixth meeting of the international neuro-ophthalmology society (INOS). Amsterdam: Aeolus Press, 1987:227–232
104. Abadi RV, Carden D, Simpson J. A new treatment for congenital nystagmus. Br J Ophthalmol 1980;64:2–6
105. Ciuffreda KJ, Goldrich SG, Neary C. Use of eye movement auditory biofeedback in the control of nystagmus. Am J Optom Physiol Optics 1982;59:396–409