Development of New Treatments for Congenital Nystagmus

LOUIS F. DELL'OSSO

Ocular Motor Neurophysiology Laboratory, Veterans Affairs Medical Center; Department of Neurology, Case Western Reserve University and University Hospitals of Cleveland, Cleveland, Ohio 44106, USA

ABSTRACT: **The use of ocular motor data as the basis for the development of both nonsurgical and surgical therapies for congenital nystagmus (CN) has been underway since the mid-1960s. This paper presents three nonsurgical therapies (composite prisms, soft contact lenses, and afferent stimulation) and a new surgical therapy (four-muscle tenotomy) hypothesized from analysis of ocular motor data. The expanded nystagmus acuity function was developed to both predict and measure the effectiveness of CN therapies and for intersubject comparisons. Base-out prisms may be used to damp CN during distance fixation in patients whose CN damps during near fixation and who are binocular (i.e., they have no strabismus). Soft contact lenses may be used in those whose CN damps with afferent stimulation of the ophthalmic division of the trigeminal nerve. Cutaneous afferent stimulation (rubbing, vibration, or electricity) of the forehead or neck damps CN in some individuals. Finally, as first demonstrated in an achiasmic Belgian sheepdog and later in humans, tenotomy of the four horizontal rectus muscles and reattachment at their original sites may also damp CN. Taken together, these findings suggest the existence of one or more proprioceptive feedback loops acting to change the small-signal gain of the extraocular plant. Four-muscle tenotomy provides a needed therapeutic option for the many individuals with CN for whom other surgical therapies are contraindicated. Tenotomy may also prove useful in see-saw nystagmus (it abolished it in the aforementioned canine) or other types of nystagmus; further studies of the latter are required.**

KEYWORDS: **congenital nystagmus; composite prisms; soft contact lenses; afferent stimulation; tenotomy surgery**

INTRODUCTION

Research into ocular motor dysfunction consists of studying "experiments of nature" where neither the experiment nor the methods are totally under the researcher's control, but the outputs, in the form of eye movements, are accurately accessible using sophisticated measurement techniques. Nature stresses the ocular motor system in ways that are difficult or impossible to duplicate in the laboratory on a normal subject and thereby reveals otherwise hidden capabilities of the control system. The

Address for correspondence: L.F. Dell'Osso, Ph.D., Ocular Motor Neurophysiology Laboratory, Veterans Affairs Medical Center (127A), 10701 East Boulevard, Cleveland, OH 44106. Voice: 216-421-3224; fax: 216-231-3461.
lfd@po.cwru.edu

Ann. N.Y. Acad. Sci. 956: 361–379 (2002).

potential of this research approach has been appreciated for more than 150 years. When I helped build and subsequently joined the new Ocular Motor Neurophysiology Laboratory of Robert B. Daroff at the Miami VA Hospital in the early 1970s, we combined this approach with control-system analysis and applied it to the study of congenital and neurological conditions that resulted in ocular motor dysfunction. It has proven to be productive in exposing underlying control-system architecture, defining diagnostic criteria, and suggesting possible therapies. Our studies have also benefited from the interdisciplinary collaboration of biomedical engineering and neurology, ophthalmology, and neuro-ophthalmology. The former has particularly influenced studies into the underlying mechanisms of congenital nystagmus (CN) and other oscillations. Although our main emphasis was on understanding the basics of ocular motor control instability, we remained alert to the possibility of clinically exploiting our findings, regardless of the level of our understanding of their theoretical basis. Fortunately, to design a therapy that exploits an observed beneficial effect, one need not know all the underlying details of how the responsible action caused the effect. The basic paradigm consists of: accurately documenting the eye movements of subjects with CN in response to normal stimuli (visual and otherwise); analyzing the data in the context of control systems; attempting to exploit any damping present in each individual; and, finally, incorporating all observations into an ocular motor system model capable of simulating normal and abnormal responses.

Obtaining accurate eye-movement data was not possible from the existing literature (circa 1965). Eye movements, and specifically nystagmus, had been described clinically based on visual observation alone with only occasional recordings made with primative equipment. To their credit, some early clinical observers were quite insightful, limited only by characteristics that could not be seen by the naked eye. One of the best of these pioneers was Alfred Kestenbaum, whose writing on the subject continues to reveal insights based on astute observation.[1] However, the absence of good data led to errors in interpretation and in the theories resulting from them. Despite the publication of ocular motility data from several investigators that contradicted some of those early theories, they continued to reappear in the literature, adding little but confusion.

Although the foregoing research approach has been fruitful in many ocular motor areas, this report will be limited to CN therapies that are based on: (1) exploiting inherent characteristics of the internally generated oscillation; (2) reducing the responsiveness of the ocular motor plant to that oscillation; or (3) interfering with the efferent CN signal. Some of the therapeutic suggestions that sprang from our data were straightforward and required little original thought. Others required that one ignore what was considered "common knowledge" and postulate an action unsupported (or even contradicted) by current theory. We hypothesized that the characteristics of responses from a stressed ocular motor system (e.g., one with CN) would provide insights into how the *normal* ocular motor system is organized (on a functional basis) and also suggest, via computer modeling, the functional source(s) of the CN waveforms. From these studies, possible therapeutic approaches might arise. Implicit in this approach was the presumption that the ocular motor system of an individual with CN was substantially the same as that of a normal person. We hypothesized that the complex waveforms that identify CN represented the otherwise normal ocular motor system's attempts to modify one or more simple, basic oscillations with the

aim of maximizing target foveation and visual acuity. Indeed, as will be discussed, the observations made in the primordial systems study of CN[2] led to our first nonsurgical, acuity-improving therapy for this disorder, composite prisms.

The joining of the disciplines of biomedical engineering and neurology became a model for other investigators in this new and soon-to-be rapidly expanding area of research. Our approach has proven to be successful in elucidating the structure and function of the normal ocular motor system, in providing diagnostic criteria, and in suggesting new therapies (the subject of this report). In addition to defining our work for more than three decades, the combination of a biomedical engineering systems approach and a neuroanatomical and neurophysiological medical approach has also benefited other investigators and (most importantly) patients with congenital and acquired neurological conditions.

METHODS

Several ocular motility recording methods have been used in the Ocular Motor Neurophysiology Laboratory and new methods tried as they were developed.

Recording

Some eye movement recordings are made using infrared reflection. The infrared signal from each eye is calibrated with the other eye behind cover to obtain accurate position information and to document small tropias and phorias hidden by the nystagmus. Eye positions and velocities (obtained by analog differentiation of the position channels) are displayed on a strip chart recording system. Other data are recorded by means of a phase-detecting revolving magnetic field technique. Eye position data are digitized and stored in a computer.

Protocol

Written consent is obtained from subjects before testing. All test procedures are carefully explained to the subject before the experiment begins and are reinforced with verbal commands during the trials. Subjects are seated in a chair with headrest and either a bite board or a chin stabilizer, far enough from an arc of red LEDs to prevent convergence effects. The room light can be adjusted from dim down to blackout. Experiments consist of from 1 to 10 trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials are kept this short to guard against boredom because CN intensity is known to decrease with inattention.

Analysis

Analysis is carried out in the MATLAB environment using software specifically written for each study as needed.

RESULTS

The nonsurgical and surgical therapies for CN that have resulted from ocular motility studies performed in the Ocular Motor Neurophysiology Laboratory will be discussed chronologically.

Nonsurgical Therapies

Optical Therapy— Composite Prisms

Individuals with CN who exhibit a gaze-angle null may benefit from the use of base-left or base-right version prisms that place their eyes at that angle. Similarly, those whose CN damps with convergence may benefit from base-out vergence prisms that induce convergence during fixation of a distant target. For individuals with both types of nulls, composite prisms combine the effects of shifting gaze and inducing convergence; they are base-out prisms of unequal powers. During my initial study of ocular motor control in a subject with CN, I observed that the intensity of the CN diminished with both gaze in the null region and near fixation.[2] When I presented these observations to Larry Stark while visiting his lab at Berkeley, we verified them with further recordings and converted the numbers into prism diopters that would provide both a gaze-angle shift to the null and induce convergence. Because the convergence induces unwanted accommodation, –1.00S O.U. was added to the refraction to ensure clear distance vision.[3] The prisms damped the CN significantly and improved visual acuity by two Snellen lines to 20/25.[4] Further explanations regarding the use of composite prisms appeared in subsequent reports.[4,5]

Optical Therapy—Soft Contact Lenses

To many ophthalmologists, the presence of CN was a contraindication for the use of contact lenses. The constant motion of the eyes was thought to cause lens slippage with possible irritation to the cornea. However, eye motion due to the CN is much less likely to cause slippage than the high eye accelerations of the many voluntary saccades performed daily by normal persons. We studied the effects of soft contact lenses on the CN waveform under normal conditions and with local anesthesia.[6] Contact lenses damped the CN over all gaze angles, but local anesthesia abolished the effect and returned the CN to baseline levels (i.e., with no contact lenses). Contact lenses with partial correction damped the CN but not as well as full correction.

Afferent-Stimulation Therapy—Vibration and Electrical

Discussions regarding possible mechanisms for the CN damping produced by contact lenses, led Bob Daroff to suggest we try excitation of the ophthalmic division of the trigeminal nerve by cutaneous stimulation above one eye.[7] It produced a 50% diminution of the CN amplitude. This led to studies of afferent stimulation using vibration and electrical stimuli of the forehead and the neck.[8,9] Both methods at both sites were successful. As FIGURE 1 shows, vibratory and electrical stimulation damped the CN and improved foveation periods. Vibratory stimulation had a positive effect in a larger number of subjects (9 of 13) than did electrical (3 of 10). Positive vibratory effects occurred in 19 of 30 (63%) trials, and positive electrical effects occurred in 5 of 11 (45%) trials. FIGURE 1b and c demonstrates that damping of CN is not necessary for improved acuity; lengthening foveation periods and reducing their position variation are the most important effects of therapy for functional improvement; amplitude reduction does result in cosmetic improvement.

The NAF(X). For this study, we further developed an objective measure of the CN waveform, the Nystagmus Foveation Function (NFF) used in earlier studies,[10–12] into the Nystagmus Acuity Function (NAF), named for its relation to predicted, best-

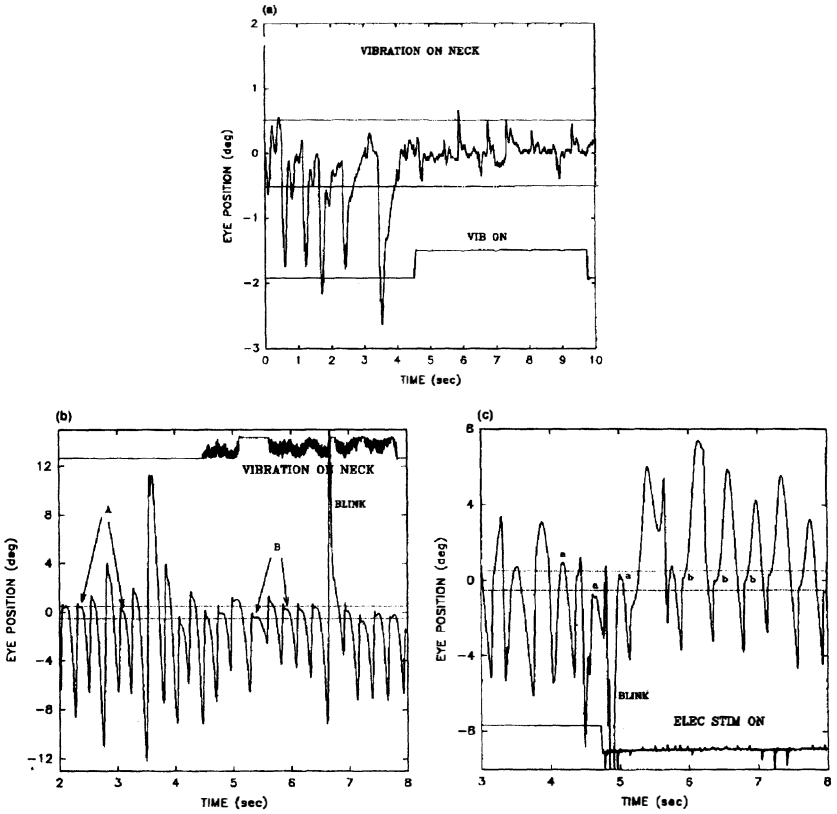

FIGURE 1. Positive effects of afferent stimulation showing (**a**) the reduction of amplitude of the nystagmus (from ~2-3 to ~0.2-0.5 degrees peak-to-peak) and longer foveation period durations during vibration on the neck and (**b**) an increase in the duration of the foveation periods during stimulation, but without much change in amplitude. Compare durations of foveation periods marked "A" (before stimulation) with those marked "B" (during stimulation). An effect of decreased variability in the positions of the foveation periods during stimulation is shown in **c**). Compare the alignment of the foveation periods marked "a" (before stimulation) with those marked "b" (during stimulation). The stimulus traces indicate only the intervals of stimulation and not the stimulus signals. Noise in the vibration traces resulted from the effects of the vibration on the resistive contact responsible for this signal. (From Sheth *et al.*, 1972.)

corrected visual acuity. Increases in this function when afferent stimuli were applied provided objective evidence of the beneficial effects. In the ensuing 8 years, the NAF has been used to assess subjects with CN and latent/manifest latent nystagmus (LMLN). Because some individuals cannot meet the stringent, well-developed foveation requirements of the NAF (i.e., repeated foveation of the target to within ±0.5 degrees and ±4 degrees/s simultaneously), the NAF's foveation window had to become expandable (based on an individual's foveation abilities) while maintaining the

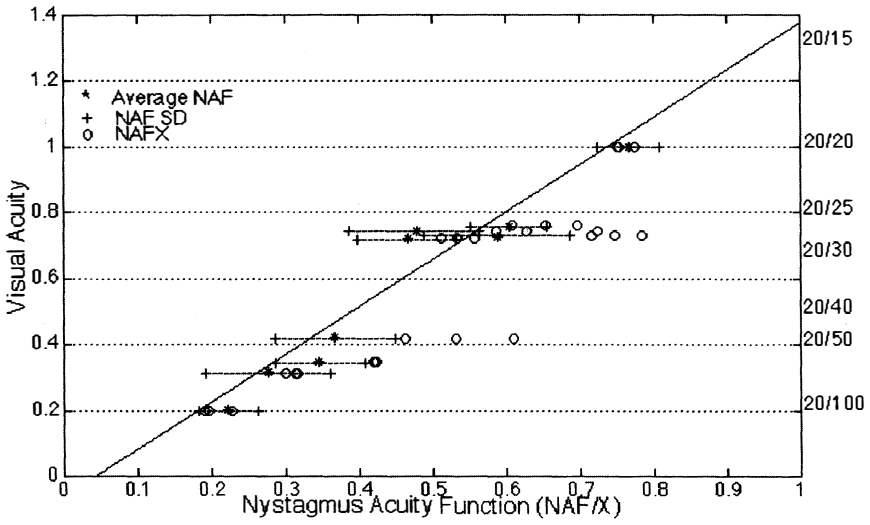

FIGURE 2. Nystagmus acuity function. Data from nine CN subjects with neither afferent deficits nor significant fixation-attempt effects on their waveforms, showing the linear relation between the NAF and potential, best-corrected visual acuity and the equivalent NAFX values calculated using arbitrary foveation-window sizes, determined by a protocol developed from our experience using the NAFX over the last 5 years. For clarity, the data points for two individuals (mean NAFs of 0.588 and 0.602) were slightly lowered or raised, respectively. Each individual had the same acuity (0.743 = 20/25-3) as the individual whose data are straddled (mean NAF of 0.478). (From Dell'Osso and Jacobs, 2001. In press.)

NAF's relationship to predicted, best-corrected visual acuity. The resulting eXpanded Nystagmus Acuity Function (NAFX) may be applied to any nystagmus waveform whose foveation variability (position and velocity) lies within foveation windows ranging from that of the original NAF up to the maximum expanded window of ±6 degrees and ±10 degrees/s.[13] Neither CN amplitude nor frequency is used to calculate any of these functions. FIGURE 2 demonstrates the relation between the NAFX and the predicted, best-corrected visual acuity of several subjects. This function has proven to be robust enough to allow analysis and acuity prediction of all subjects we have recorded thus far.

Surgical Therapies

The postulation and clinical trials of a new surgical therapy for CN with far-reaching theoretical implications had its roots in two areas of ocular motor research, documenting the effects of the Anderson-Kestenbaum recession-resection surgery on humans[14] and studying the eye movements of achiasmatic Belgian sheepdogs with CN and see-saw nystagmus (SSN).[15,16]

Anderson-Kestenbaum Surgery Results

In an early study of CN surgery (circa 1977), we noted a profound change in the shape of the nystagmus intensity versus gaze angle function. After Anderson-

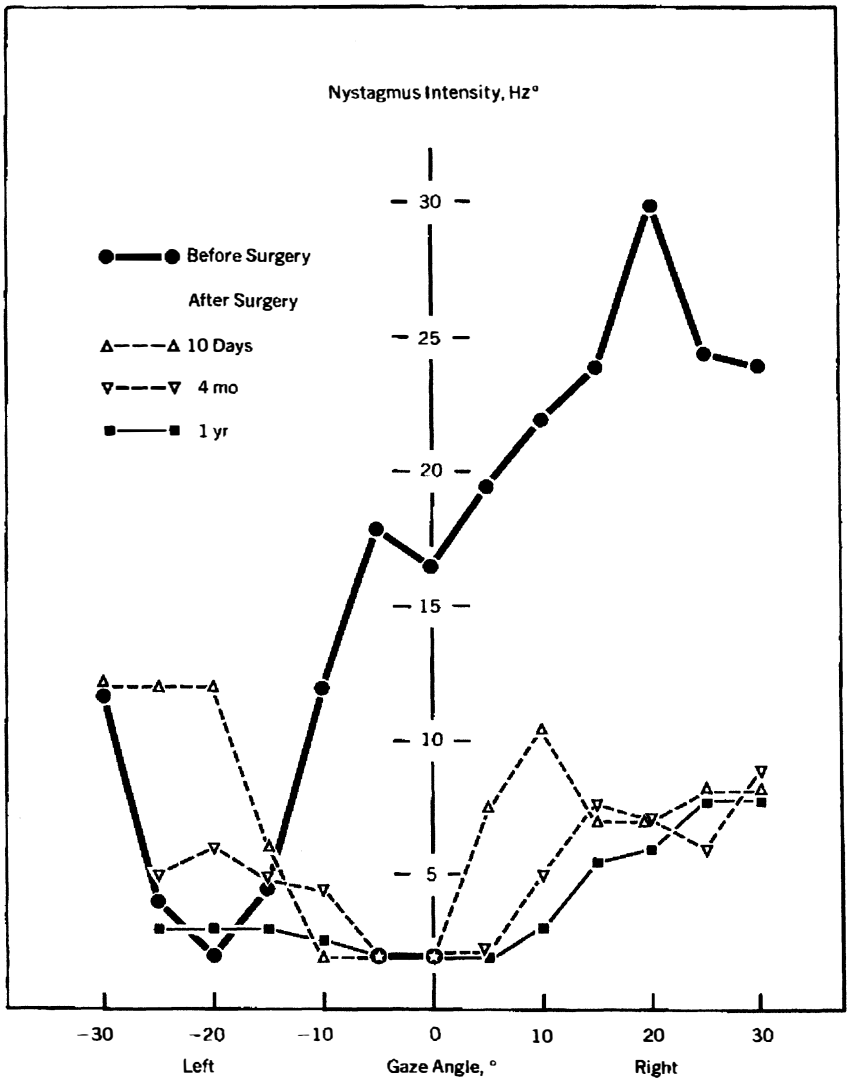

FIGURE 3. Pre- and postoperative plots of nystagmus intensity versus gaze angle for an individual, indicating the time course of improvement in primary and secondary effects of the Anderson-Kestenbaum surgery. (From Dell'Osso and Flynn, 1979.)

Kestenbaum surgery, in addition to the expected shift of this plot towards primary position, the breadth of the null region increased and the overall nystagmus intensity decreased.[14] FIGURE 3 shows these effects during the first year post-surgery; they remained unchanged after 5 years. We reasoned that there were two independent effects of this surgery due to different mechanisms. The expected null-shift towards primary position was mechanical due to the effective rotation of the globe opposite

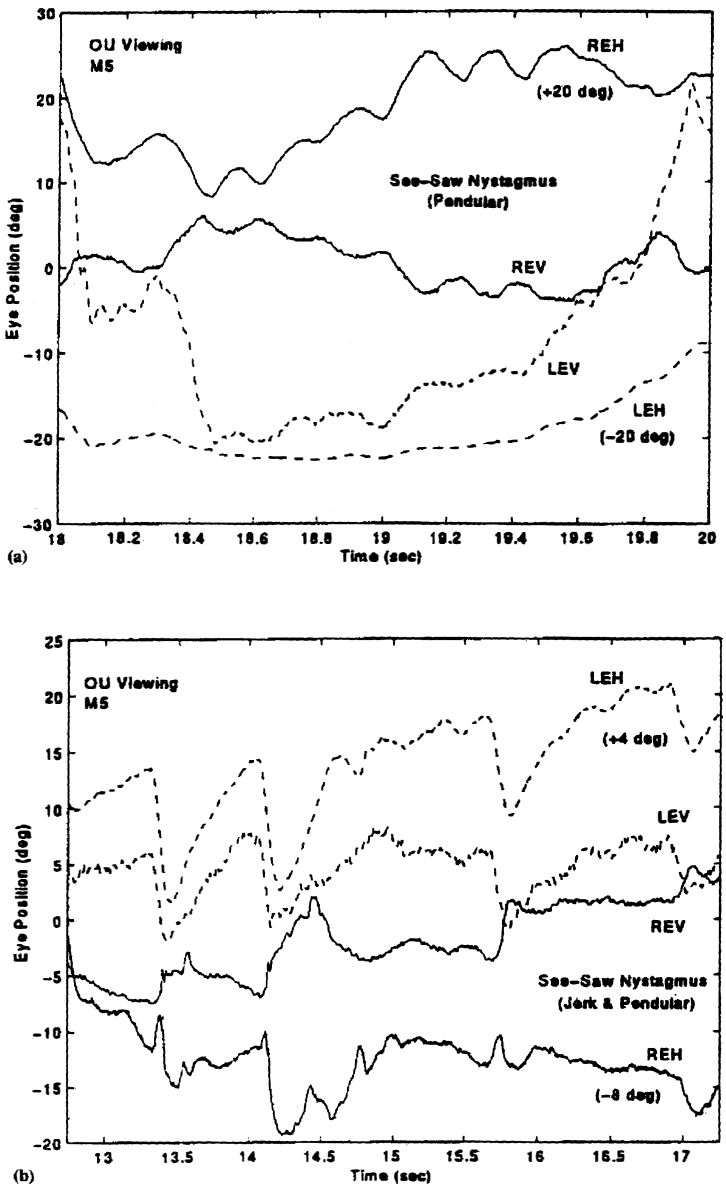

FIGURE 4. CN waveforms of an achiasmatic Belgian sheepdog. Right- and left-eye horizontal and vertical recordings during OU viewing. (**a**) Simultaneous pendular SSN and CN at the same frequency resulted in a diagonal pendular SSN, moving up-and-left (down-and-right) in the right eye and down-and-left (up-and-right) in the left eye. (**b**) Dual jerk (jerk plus pendular) SSN with simultaneous jerk-right CN resulted in a diagonal dual jerk SSN, beating up-and-left in the right eye and down-and-left in the left eye. During the slow phases, there was a superimposed diagonal pendular SSN, as in **a**. The horizontal traces in

the null angle and the subsequent innervation required to move the eyes back to primary position (i.e., the same innervation that placed the eyes in the null position preoperatively). Because the only surgery performed in addition to the resections and recessions was the accompanying tenotomies of the muscles, it was hypothesized that they alone were responsible for the CN damping at all gaze angles.[17] It was to take 20 years before we would have access to, and could test this hypothesis on, an animal model of naturally occurring CN (exhibiting the pathognomonic CN waveforms).

Achiasmatic Belgian Sheepdogs

In 1991, I was contacted by Robert W. Williams of the University of Tennessee, Memphis. He provided videos of the horizontal nystagmus of several achiasmatic Belgian sheepdogs, asking if they resembled human CN. I was struck by the similarity of the head posturing of the dogs and children with CN and arranged to document the waveforms to establish the diagnosis. The videos also revealed a see-saw nystagmus. In 1992, we documented horizontal CN waveforms and vertical-torsional see-saw nystagmus in the dogs.[15,16] This was the first time I had seen nystagmus waveforms (i.e., the horizontal components) from an animal that had the characteristics of human CN, including foveating and braking saccades. In subsequent recordings, we verified that all achiasmatic dogs had both CN and SSN,[18] including a dog with hemichiasma.[19] FIGURE 4 shows the pendular and jerk, horizontal and vertical waveforms of one of the achiasmatic dogs. The animal model for CN that we had been seeking to test our surgical hypothesis had been found. In addition, SSN was identified as a sign of chiasmal abnormalities in canines and humans.[20]

Four-Muscle Tenotomy Procedure

Canine. My colleague, Richard W. Hertle, performed the hypothetical tenotomy procedure in two stages: (1) all four horizontal recti were tenotomized and immediately reattached at their original insertion sites; and (2) 4 months later, the same procedure was performed on the four vertical recti and four obliques.[21] The first surgery tested the efficacy of tenotomy on horizontal CN, and the second, on SSN. The results were immediately obvious; there was a profound damping of the horizontal CN over a broad range of gaze angles (stage 1) and the SSN was abolished (stage 2). Eye movement recordings over the next 7 months verified the profound and persistent nystagmus damping. FIGURE 5 compares the pre- and postsurgical CN and SSN in this canine (note the expanded scales in B and D). The dog also exhibited immediate behavioral improvements that supported the prediction that the CN damping would increase his acuity.

Human. As a result of our hypothesis based on analysis of human eye movement data after Anderson-Kestenbaum procedures and demonstration that tenotomy damped the CN in a canine model of human CN, we began a clinical trial of this procedure under the auspices of the National Eye Institute with R.W. Hertle as the sur-

---

a and **b** were shifted by the indicated amounts for clarity. In this and FIGURE 5: RE, right eye; LE, left eye; OU or BE, both eyes; H, horizontal; V, vertical; upward (+) deflections indicate rightward (or upward) eye rotations; and viewing and fixation conditions are indicated. (From Dell'Osso *et al.*, 1998.)

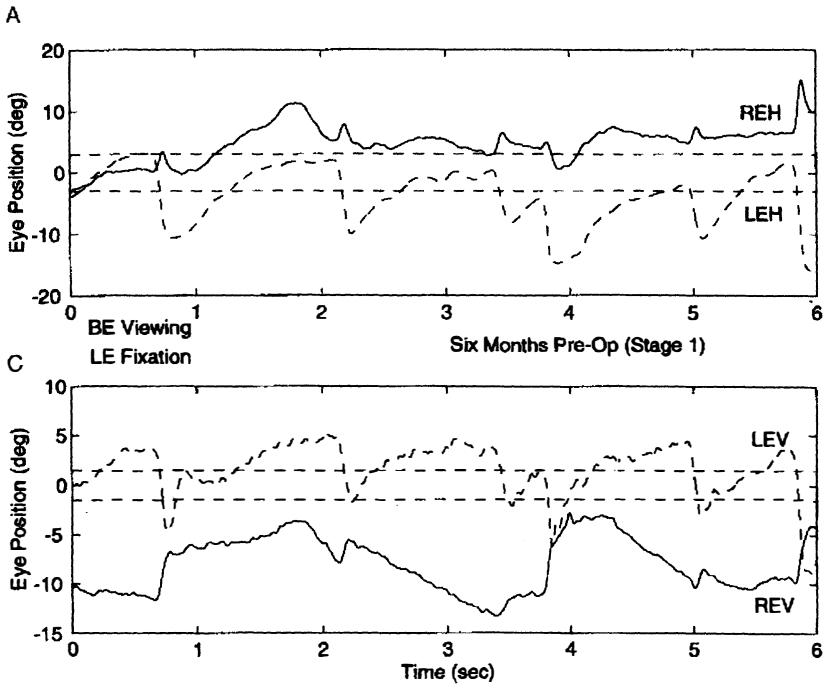

FIGURE 5. The effects of tenotomy on the CN and SSN in an achiasmatic Belgian sheepdog. (**A** and **C**) The horizontal CN and vertical SSN while fixating in primary position prior to stage 1 (horizontal recti) tenotomy. *Dashed lines* indicate the extent of the horizontal (±3 degrees) or vertical (±1.5 degrees) area centralis. (**B**,**D**) The horizontal and vertical CN, made during fixation in primary position 4 months postsurgical (stage 1) and 1 day postsurgical (stage 2). A 25-second interval of steady, right-eye fixation in both planes showing well developed centralization is shown. The CN was of low amplitude and no SSN was present. b, blink. (Modified from Dell'Osso *et al.*, 1999.)

geon.[21] Pre- and post-tenotomy eye movement data were recorded at the Laboratory of Sensorimotor Research, NEI, under the direction of E.J. Fitzgibbon. The data were blinded by D. Thompson and analyzed by this author at the Ocular Motor Neurophysiology Lab. The first phase included 10 adults and the second, 5 children. After the data up to 6 weeks post-tenotomy for the first five adult subjects were analyzed, they were unblinded to determine if phase 2 could be started. Preliminary results of these data showed improved NAFX scores and improved visual function.[22] FIGURE 6 shows the pre- and 6-weeks postoperative CN of one of the subjects (S2); tenotomy resulted in a 52% increase in the NAFX. As FIGURE 7 shows, the NAFX values for all patients improved (average improvement was 48%).

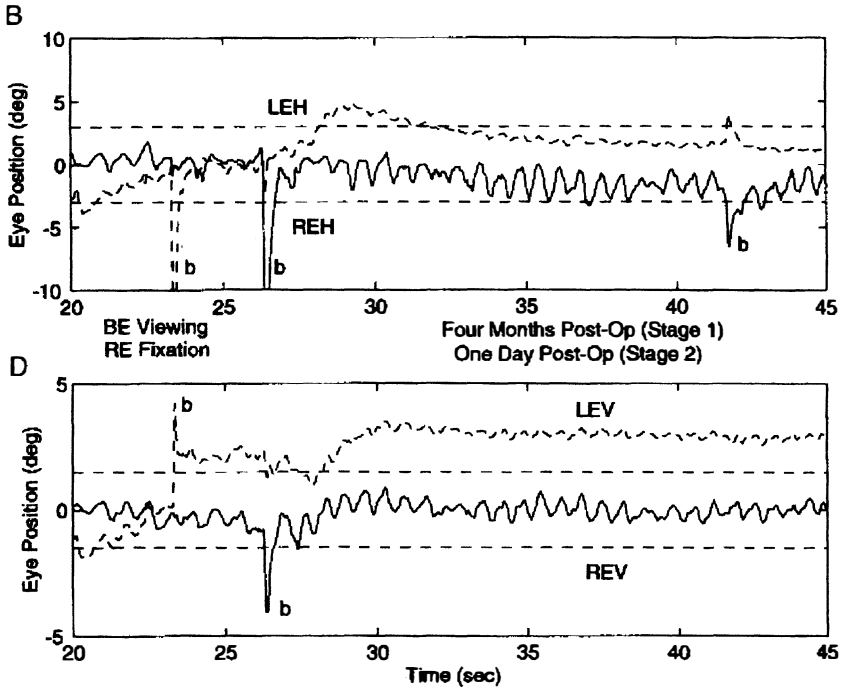

FIGURE 5. *Continued.*

DISCUSSION

Accurate diagnosis is the most important factor in the treatment of CN, or any medical condition. CN must be distinguished from a number of types of nystagmus that appear in infancy; their different waveforms imply different underlying mechanisms. Ocular motility data allow us to make these otherwise difficult differential diagnoses.[23–27] The variability in the success rates reported for CN surgery is, in great part, due to the absence of ocular motor data that would have produced more accurate diagnoses. Because of their different mechanisms and interrelationships with strabismus, CN, LMLN, the nystagmus blockage syndrome, and spasmus nutans do not respond to the same therapies; the lack of consistency in surgical results on patients diagnosed clinically without ocular motility data supports this view.

The first step, before considering therapies, was the establishment of definitive, differential diagnostic criteria for CN and other forms of nystagmus. Here, accurate ocular motor recordings quickly demonstrated that they were both essential and invaluable. The key waveform characteristics that are pathognomonic for CN became easily distinguishable.[23,28] No longer would "nystagmus" be an acceptable diagnosis. Eye movement recordings were to eventually be used to identify many different types of nystagmus and saccadic oscillations.[27,29] An integral part of waveform descriptions was identification of the portions of each cycle during which the image of

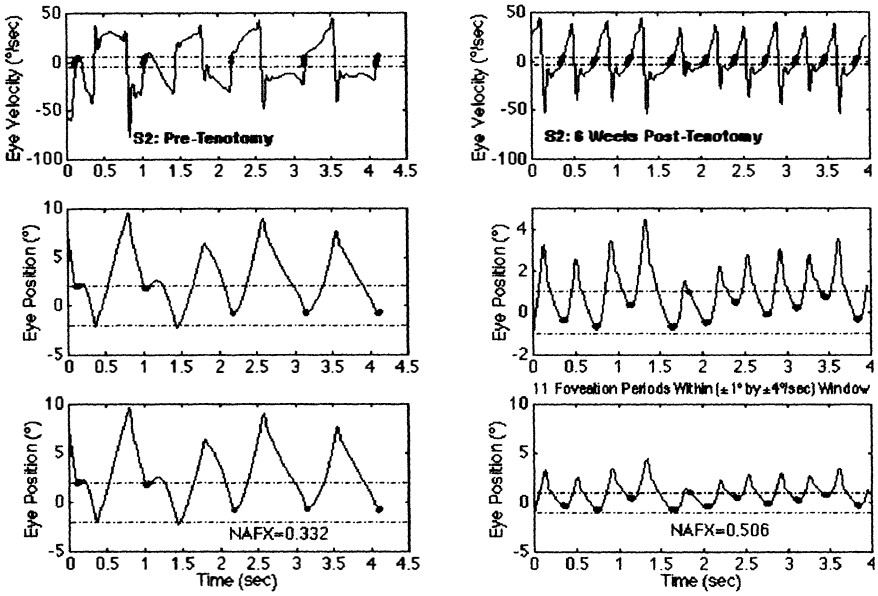

FIGURE 6. Effects of tenotomy on the CN in a human. Eye velocity (*top panels*) and position (*middle and bottom panels*) are shown with equivalent scales (*top and bottom panels*) for ease of comparison.

the target was on the fovea (foveation periods) during fixation[10,30] as well as during smooth pursuit and vestibulo-ocular movements.[11,12,31] Documentation of these important characteristics of CN waveforms by accurate ocular motor recordings provided the data necessary for both diagnosis and evaluation of the efficacy of specific therapies.

Evaluation and comparison of therapies require a quantitative measure of the change in the specific characteristic(s) that is the primary outcome of the therapy. Although the goals of CN therapy may be cosmetic and acuity improvements, they are not the primary outcomes. Because measured visual acuity is the result of several variables (e.g., stress, afferent deficits) whose relation to the CN waveform is idiosyncratic, it is not always a good measure of real-world acuity. CN amplitude is the characteristic most directly related to cosmetic appearance; however, amplitude is not a good predictor of acuity. A therapy that reduces amplitude may not improve acuity, and one that does improve acuity may not reduce amplitude. The waveform characteristics related to acuity are: foveation time and beat-to-beat foveation position and velocity variation. The NAFX is a quantitative function that includes all three of these primary characteristics. It predicts best possible visual acuity, which is ≤ *real-world* acuity which is ≤ measured acuity.

This paper has concentrated on the treatments stemming from studies conducted at the Ocular Motor Neurophysiology Lab. Other investigators have studied the effects on CN of acupuncture,[32,33] biofeedback,[34–42] and the injection of botulinum toxin.[43–48] These treatments have had variable success in both CN and acquired nys-

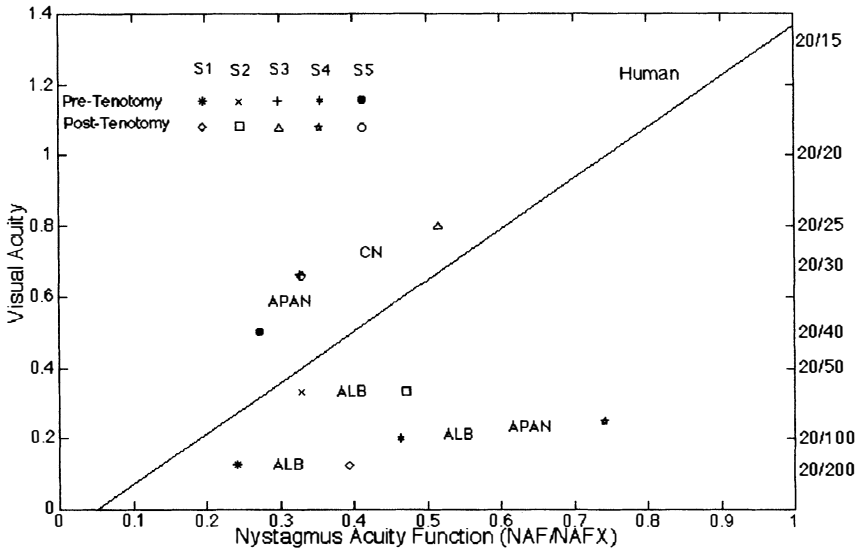

FIGURE 7. Expanded nystagmus acuity function. Effects of tenotomy on the NAFX of the CN in five human subjects (S1—S5). ALB, albino; APAN, asymmetric, (a) periodic alternating nystagmus.

tagmus. Others have also studied the effects on CN of prisms[49–51] and contact lenses.[34,52–56] The ocular motor effects of surgical procedures (Anderson-Kestenbaum and bimedial recession) have also received some attention.[57–59]

Composite Prisms

The mechanisms by which version and vergence prisms damp CN differ. The gaze-angle null exploited by version prisms is a region of reduced oscillation that increases as gaze is moved in either direction. By contrast, the vergence null exploited by base-out prisms appears to result from a reduction in the ocular motor plant's small-signal responsiveness (i.e., nonsaccadic gain) to the underlying oscillation. The mechanism is unknown, but it is probably related to repositioning of the extraocular muscle pulleys as a result of convergence. The resulting reduced gain is relatively unaffected by gaze angle, allowing the eye oscillation to remain damped as the latter changes.

Version prisms become impractical for null angles greater than 5 or 6 degrees due to the large prism size and the resulting chromatic aberration. Vergence prisms (with –1.00S O.U. added in prepresbyopic patients) do not have this limitation because the CN damping in most individuals occurs with less than 20D total convergence (i.e., 10D per eye). The use of composite prisms was an attempt to maximize the total damping by combining the required conjugate version shift to the gaze-angle null with the approximate vergence shift that damped the CN. Subsequent development of the NAFX allowed us to more accurately measure the visual-acuity-related effects at different vergence angles and identify the point of maximal damping. In an indi-

vidual who had initially worn 16D of convergence prism (relaxed to 14D several years later), we found that 12D yielded the maximal NAFX value, allowing further reduction in the prisms. Once converged, CN remains damped at most gaze angles (especially those in the central ±20 degrees of gaze); therefore, we now recommend equal-value, base-out prisms rather than composite prisms. This minimizes the amount of prism in each eye and reduces chromatic distortion. Thus, for the aforementioned individual, the initial values of 12D and 4D base-out were replaced with two 6D base-out prisms, with the same improved acuity. Prisms can also be used to fine tune the effects of less-than-adequate surgery (i.e., failure to fully shift the null to primary position). The use of base-out prisms to damp nystagmus has also been extended to acquired nystagmus.[60,61]

Soft Contact Lenses

The damping effect in CN produced by soft contact lenses may be due to either reducing the ocular motor plant's gain or interfering with the CN signal at a higher level. Soft lenses provide a nonsurgical therapy for individuals with no CN nulls. They are useful in sports, where spectacles might be an impediment, as well as in social situations, where an individual might feel more comfortable with contact lenses. Soft lenses can also be used interchangeably with prism glasses without a period of adjustment.

Afferent Stimulation

Presumably, the same mechanisms described for contact lenses apply to cutaneous stimulation of the forehead. Vibratory stimulation caused positive effects in a larger percentage of subjects and caused them more frequently. Vibration may stimulate deeper tissue and muscle, altering afferent proprioceptive signals to the nuclei of the upper spinal cord and brain stem. The greater effect of vibration on the neck than on the forehead may be due to the latter's absence of deep tissue. The suprathreshold electrical stimulation may have only stimulated cutaneous afferents. Not only did simple scratching of the forehead or vibration on the neck produce transient CN damping and increased acuity, but also air blowing on the forehead had a similar effect. Thus, for someone with CN, playing the outfield on a windy day should be easier than on a calm day!

Although afferent stimulation has not yet been reduced to a practical therapeutic device, it is not hard to imagine a battery-operated neck collar or head band that can provide either a vibratory stimulus or a mild electric shock at the press of a button when higher acuity is desired (e.g., as a street or traffic-control sign approaches while driving). Such vibratory collars are currently available for stress relief and can be used to damp CN.

Four-Muscle Tenotomy Procedure

The initial successes of tenotomy in the achiasmic canine and in humans have prompted us to speculate on the possible mechanism involved. We initially postulated that the surgery altered a proprioceptive loop in the EOM.[21] Motor fibers in the proximal ends of the distal tendons have recently been discovered.[62] Evidence of neural fibers in the distal ends of these tendons has also been found (personal communication, R.W. Hertle); in patients with CN, there were abnormalities in some of

these structures. Thus, in addition to the two proprioceptive gain-control loops (i.e., ophthalmic division of the trigeminal nerve and neck receptors) identified by contact lenses and afferent stimulation, there appear to be two others in the EOM itself. The efferent signals of one appear to be the motor fibers terminating in the EOM pulleys and of the other, motor fibers in the distal muscle and proximal tendon. The pulleys appear to provide gain-control mechanically by altering the point of action of the EOM. The second loop may provide gain-control by altering muscle tension. However, feedback loops require afferent as well as efferent information. We hypothesized that the fibers in the distal tendon provide that information. Others have provided evidence that proprioceptive inflow is used in ocular motor control.[63,64] Clearly, the demonstration of the efficacy of tenotomy has necessitated both a reevaluation of prevailing, simplistic concepts of the organization of the ocular motor plant and the differentiation between dynamic nystagmus procedures (aimed at reducing the oscillation) and static strabismus procedures (aimed at correcting a misalignment).

The use of tenotomy to damp CN in patients is now the subject of two clinical trials. Further analysis of the data taken in the first (described above) is currently under way. In the second study, patients from the Children's Hospital Medical Center of Akron are recorded pre- and postoperatively in the Ocular Motor Neurophysiology Lab; the surgery is accomplished by R.A. Burnstine. These data have not yet been analyzed but several of the patients have had improvements in their acuity, allowing them to pass the required tests to obtain a driver's license.

Combining Tenotomy with Other Procedures

If tenotomy proves to be an effective treatment for CN, it can also be combined with nystagmus procedures aimed at damping CN or with strabismus procedures in patients with CN. Thus, tenotomy of the lateral recti can be combined with bimedial recessions in binocular CN patients whose nystagmus damps with convergence;[21] both are nystagmus procedures. In cases of CN with no exploitable nulls plus strabismus, a one- or two-muscle strabismus procedure can be replaced by resections and recessions on both eyes, which will *de facto* include four-muscle tenotomies. Alternatively, the remaining muscles can be tenotomized to include the nystagmus-damping effects of this procedure. Note, these recommendations for combining tenotomy with strabismus procedures are for strabismus patients with CN, not LMLN.

FUTURE RESEARCH DIRECTIONS

The effectiveness of four-muscle tenotomy in LMLN or different types of acquired nystagmus (including SSN) needs to be assessed.

Chemical/Mechanical Tenotomy. Although surgical tenotomy has been shown to damp CN, it may be possible to achieve the same effect by microinjection of specific chemicals into the distal tendon (chemical tenotomy) or deform it with a hemostat (mechanical tenotomy). Alternatively, injection into the proximal tendon, where motor fibers have been identified, may prove beneficial. The NAFX provides an objective, quantitative measure of the effectiveness of various drugs, dosages, and injection sites; the studies remain to be done.

The Ocular Motor Plant. Prior to demonstrating that tenotomy of the extraocular tendons can damp CN, the plant was thought of and modeled as a passive low-pass filter (e.g., 2 poles or 2 poles + 1 zero). Clearly, although these representations may be useful in control-system models, the plant is a much more complex, actively controlled feedback system. The exact nature of the feedback loops and control signals (including those to the pulleys) needs to be studied. The functions of the neural fibers in the distal tendon and of the motor fibers in the proximal tendon need to be elucidated. Perhaps, with such knowledge, new and more precise therapeutic intervention will become possible for CN as well as other ocular motor disorders.

In summary, the foregoing therapies successfully damp CN by either exploiting the idiosyncratic null angle of the oscillation (version prisms or the Anderson-Kestenbaum procedure) or altering the responsiveness of the ocular motor plant to that oscillation (base-out prisms, bimedial recession, and four-muscle tenotomy). Contact lenses and afferent stimulation may use the latter mechanism or reduce the efferent CN signal. Ocular motility recordings and the NAFX have resulted in new therapies and have provided a means to objectively assess their efficacy.

ACKNOWLEDGMENTS

This work was supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs. I am deeply grateful to Robert B. Daroff who, in 1972, provided me with the initial opportunity to apply the systems approach towards our mutual goals of diagnosing, understanding, and treating conditions with ocular motor symptoms and signs. I was trained as a biomedical engineer (then, a new and virtually unknown discipline) and had neither a medical nor a neurophysiological background. Throughout our collaborative research, Bob was instrumental in the design, execution, and analysis of the results of many studies into acquired and congenital ocular motor oscillations and dysfunctions.

REFERENCES

1. KESTENBAUM, A. 1961. Clinical Methods of Neuro-Ophthalmologic Examination, 2nd Ed. Grune & Stratton. New York.
2. DELL'OSSO, L.F. 1968. A dual-mode model for the normal eye tracking system and the system with nystagmus. (Ph.D. dissertation). Ph.D. thesis. University of Wyoming, Laramie.
3. DELL'OSSO, L.F., G. GAUTHIER, G. LIBERMAN, *et al.* 1972. Eye movement recordings as a diagnostic tool in a case of congenital nystagmus. Am. J. Optom. Arch. Am. Acad. Optom. **49:** 3–13.
4. DELL'OSSO, L.F. 1973. Improving visual acuity in congenital nystagmus. *In* Neuro-Ophthalmology Symposium of the University of Miami and the Bascom Palmer Eye Institute, Vol. VII. J.L. Smith & J.S. Glaser, Eds: 98–106. CV Mosby Co. St. Louis.
5. DELL'OSSO, L.F. 1976. Prism exploitation of gaze and fusional null angles in congenital nystagmus. *In* Orthoptics: Past, Present, Future. S. Moore, ed. :135–142. Symposia Specialists. New York.
6. DELL'OSSO, L.F., S. TRACCIS, L.A. ABEL, *et al.* 1988. Contact lenses and congenital nystagmus. Clin. Vision Sci. **3:** 229–232.
7. DELL'OSSO, L.F., R.J. LEIGH & R.B. DAROFF. 1991. Suppression of congenital nystagmus by cutaneous stimulation. Neuroophthalmology **11:** 173–175.

8. SHETH, N.V. 1994. The effects of afferent stimulation on congenital nystagmus. (M.S. thesis). Ph.D. thesis. Case Western Reserve University, Cleveland.
9. SHETH, N.V., L.F. DELL'OSSO, R.J. LEIGH, *et al.* 1995. The effects of afferent stimulation on congenital nystagmus foveation periods. Vision Res. **35:** 2371–2382.
10. DELL'OSSO, L.F., J. VAN DER STEEN, R.M. STEINMAN, *et al.* 1992. Foveation dynamics in congenital nystagmus. I. Fixation. Doc. Ophthalmol. **79:** 1–23.
11. DELL'OSSO, L.F., J. VAN DER STEEN, R.M. STEINMAN *et al.* 1992. Foveation dynamics in congenital nystagmus. II. Smooth pursuit. Doc. Ophthalmol. **79:** 25–49.
12. DELL'OSSO, L.F., J. VAN DER STEEN, R.M. STEINMAN, *et al.* 1992. Foveation dynamics in congenital nystagmus. III. Vestibulo-ocular reflex. Doc. Ophthalmol. **79:** 51–70.
13. DELL'OSSO, L.F. & J.B. JACOBS. 2001. An expanded nystagmus acuity function: intra- and intersubject prediction of best-corrected visual acuity. Doc. Ophthalmol. In press.
14. DELL'OSSO, L.F. & J.T. FLYNN. 1979. Congenital nystagmus surgery: a quantitative evaluation of the effects. Arch. Ophthalmol. **97:** 462–469.
15. DELL'OSSO, L.F. & R.W. WILLIAMS. 1995. Ocular motor abnormalities in achiasmatic mutant Belgian sheepdogs: unyoked eye movements in a mammal. Vision Res. **35:** 109–116.
16. DELL'OSSO, L.F. 1996. See-saw nystagmus in dogs and humans: an international, across-discipline, serendipitous collaboration. Neurology **47:** 1372–1374.
17. DELL'OSSO, L.F. 1998. Extraocular muscle tenotomy, dissection, and suture: a hypothetical therapy for congenital nystagmus. J. Pediatr. Ophthalmol. Strab. **35:** 232–233.
18. DELL'OSSO, L.F., R.W. WILLIAMS, J.B. JACOBS, *et al.* 1998. The congenital and see-saw nystagmus in the prototypical achiasma of canines: comparison to the human achiasmatic prototype. Vision Res. **38:** 1629–1641.
19. DELL'OSSO, L.F., D. HOGAN, J.B. JACOBS, *et al.* 1999. Eye movements in canine hemichiasma: does human hemichiasma exist? Neuroophthalmology **22:** 47–58.
20. DELL'OSSO, L.F. & R.B. DAROFF. 1998. Two additional scenarios for see-saw nystagmus: achiasma and hemichiasma. J. Neuro-Ophthalmol. **18:** 112–113.
21. DELL'OSSO, L.F., R.W. HERTLE, R.W. WILLIAMS, *et al.* 1999. A new surgery for congenital nystagmus: effects of tenotomy on an achiasmatic canine and the role of extraocular proprioception. J. Am. Assoc. Pediatr. Ophthalmol. Strab. **3:** 166–182.
22. DELL'OSSO, L.F., R.W. HERTLE, E.J. FITZGIBBON, *et al.* 2000. Preliminary results of performing the tenotomy procedure on adults with congenital nystagmus (CN): a gift from "man's best friend." *In* Neuro-ophthalmology at the Beginning of the New Millennium. J.A. Sharpe, ed. :101–105. Medimond Medical Publications. Englewood.
23. DELL'OSSO, L.F. & R.B. DAROFF. 1975. Congenital nystagmus waveforms and foveation strategy. Doc. Ophthalmol. **39:** 155-182.
24. DELL'OSSO, L.F., D. SCHMIDT & R.B. DAROFF. 1979. Latent, manifest latent and congenital nystagmus. Arch. Ophthalmol. **97:** 1877–1885.
25. DELL'OSSO, L.F., J.C. ELLENBERGER, L.A. ABEL, *et al.* 1983. The nystagmus blockage syndrome: congenital nystagmus, manifest latent nystagmus or both? Invest. Ophthalmol. Vision Sci. **24:** 1580–1587.
26. DELL'OSSO, L.F., S. TRACCIS & L.A. ABEL. 1983. Strabismus: a necessary condition for latent and manifest latent nystagmus. Neuroophthalmology **3:** 247–257.
27. DELL'OSSO, L.F. 1985. Congenital, latent and manifest latent nystagmus: similarities, differences and relation to strabismus. Jpn J. Ophthalmol. **29:** 351–368.
28. DELL'OSSO, L.F. & R.B. DAROFF. 1976. Braking saccade: a new fast eye movement. Aviat. Space Environ. Med. **47:** 435–437.
29. DELL'OSSO, L.F. 1991. Nystagmus, saccadic intrusions/oscillations and oscillopsia. *In* Current Neuro-Ophthalmology, Vol. 3. S. Lessell & J.T.W. Van Dalen, Eds: 153–191. Mosby Year Book. Chicago.
30. DELL'OSSO, L.F. 1973. Fixation characteristics in hereditary congenital nystagmus. Am. J. Optom. Arch. Am. Acad. Optom. **50:** 85–90.
31. DELL'OSSO, L.F. 1986. Evaluation of smooth pursuit in the presence of congenital nystagmus. Neuroophthalmology **6:** 383–406.
32. ISHIKAWA, S., H. OZAWA & Y. FUJIYAMA. 1987. Treatment of nystagmus by acupuncture. *In* Highlights in Neuro-Ophthalmology. Proceedings of the Sixth Meeting of the

International Neuro-Ophthalmology Society (INOS). B.F. Boyd, Ed.: 227–232. Aeolus Press. Amsterdam.
33. BLEKHER, T., T. YAMADA, R.D. YEE, *et al.* 1998. Effects of acupuncture on foveation characteristics in congenital nystagmus. Br. J. Ophthalmol. **82:** 115–120.
34. ABADI, R.V., D. CARDEN & J. SIMPSON. 1979. Controlling abnormal eye movements. Vision Res. **19:** 961–963.
35. ABADI, R.V., D. CARDEN & J. SIMPSON. 1980. A new treatment for congenital nystagmus. Br. J. Ophthalmol. **64:** 2–6.
36. CIUFFREDA, K.J., S.G. GOLDRICH & C. NEARY. 1982. Use of eye movement auditory biofeedback in the control of nystagmus. Am. J. Optom. Physiol. Opt. **59:** 396–409.
37. KIRSCHEN, D.G. 1983. Auditory feedback in the control of congenital nystagmus. Am. J. Optom. Physiol. Opt. **60:** 364–368.
38. ABPLANALP, P. & H. BEDELL. 1987. Visual improvement in an albinotic patient with an alteration of congenital nystagmus. Am. J. Optom. Physiol. Opt. **64:** 944–951.
39. MEZAWA, M., S. ISHIKAWA & K. UKAI. 1990. Changes in waveform of congenital nystagmus associated with biofeedback treatment. Br. J. Ophthalmol. **74:** 472–476.
40. LEUNG, V., B. WICK & H.E. BEDELL. 1996. Multifaceted treatment of congenital nystagmus: a report of 6 cases. Optom. Vision Sci. **73:** 114–124.
41. EVANS, B.J., B.V. EVANS, J. JORDAHL-MOROZ, *et al.* 1998. Randomised double-masked placebo-controlled trial of a treatment for congenital nystagmus. Vision Res. **38:** 2193–2202.
42. SHARMA, P., R. TANDON, S. KUMAR, *et al.* 2000. Reduction of congenital nystagmus amplitude with auditory biofeedback. J. Aapos. **4:** 287–290.
43. CRONE, R.A., P.T.V.M. DE JONG & G. NOTERMANS. 1984. Behandlung des Nystagmus durch Injektion von Botulinustoxin in die Augenmuskeln. Klin. Mbl. Augenheilk. **184:** 216–217.
44. HELVESTON, E.M. & A.E. POGREBNIAK. 1988. Treatment of acquired nystagmus with botulinum A toxin. Am. J. Ophthalmol. **106:** 584–586.
45. LEIGH, R.J., R.L. TOMSAK, M.P. GRANT, *et al.* 1992. Effectiveness of botulinum toxin administered to abolish acquired nystagmus. Ann. Neurol. **32:** 633–642.
46. SPIELMANN, A. 1994. Nystagmus. Curr. Opin. Ophthalmol. **5:** 20–24.
47. CARRUTHERS, J. 1995. The treatment of congenital nystagmus with Botox. J. Pediatr. Ophthalmol. Strab. **32:** 306–308.
48. TOMSAK, R.L., B.F. REMLER, L. AVERBUCH-HELLER, *et al.* 1995. Unsatisfactory treatment of acquired nystagmus with retrobulbar injection of botulinum toxin. Am. J. Ophthalmol. **119:** 489–496.
49. RADIAN, A.B. 1980. [Electronystagmography and correction of congenital nystagmus by means of prisms]. Rev. Chir. Oncol. Radiol. O R L Oftalmol. Stomatol. Ser. Oftalmol. **24:** 173–176.
50. DICKINSON, C.M. 1986. The elucidation and use of the effect of near fixation in congenital nystagmus. Ophthal. Physiol. Opt. **6:** 303–311.
51. SENDLER, S., J. SHALLO-HOFFMANN & H. MÜHLENDYCK. 1990. Die Artifizielle-Divergenz-Operation beim kongenitalen Nystagmus. Fortschr. Ophthalmol. **87:** 85–89.
52. ABADI, R.V. 1979. Visual performance with contact lenses and congenital idiopathic nystagmus. Br. J. Physiol. Opt. **33:** 32–37.
53. ALLEN, E.D. & P.D. DAVIES. 1983. Role of contact lenses in the management of congenital nystagmus. Br. J. Ophthalmol. **67:** 834–836.
54. GOLUBOVIC, S., S. MARJANOVIC, D. CVETKOVIC, *et al.* 1989. The application of hard contact lenses in patients with congenital nystagmus. Fortschr. Ophthalmol. **86:** 535–539.
55. MATSUBAYASHI, K., M. FUKUSHIMA & A. TABUCHI. 1992. Application of soft contact lenses for children with congenital nystagmus. Neuroophthalmology **12:** 47–52.
56. SAFRAN, A.B. & Y. GAMBAZZI. 1992. Congenital nystagmus: rebound phenomenon following removal of contact lenses. Br. J. Ophthalmol. **76:** 497–498.
57. ROBERTI, G., P. RUSSO & G. SEGR. 1987. Spectral analysis of electro-oculograms in the quantitative evaluation of nystagmus surgery. Med. Biol. Eng. Comp. **25:** 573–576.
58. ABADI, R.V. & J. WHITTLE. 1992. Surgery and compensatory head postures in congenital nystagmus. A longitudinal study. Arch. Ophthalmol. **110:** 632–635.

59. ZUBCOV, A.A., N. STÄRK, A. WEBER, *et al.* 1993. Improvement of visual acuity after surgery for nystagmus. Ophthalmology **100:** 1488–1497.
60. LAVIN, P.J.M., S. TRACCIS, L.F. DELL'OSSO, *et al.* 1983. Downbeat nystagmus with a pseudocycloid waveform: improvement with base-out prisms. Ann. Neurol. **13:** 621–624.
61. TRACCIS, S., G. ROSATI, M.F. MONACO, *et al.* 1990. Successful treatment of acquired pendular elliptical nystagmus in multiple sclerosis with isoniazid and base-out prisms. Neurology **40:** 492–494.
62. BÜTTNER-ENNEVER, J.A., A.K.E. HORN, H. SCHERBERGER, *et al.* 2001 Motoneurons of twitch and non-twitch extraocular fibres in the abducens, trochlear and oculomotor nuclei of monkeys. J. Comp. Neurol. In press.
63. STEINBACH, M.J. & D. SMITH. 1981. Spatial localization after strabismus surgery: evidence for inflow. Science **213:** 1407–1409.
64. STEINBACH, M.J., E.L. KIRSHNER & M.J. ARSTIKAITIS. 1987. Recession vs. marginal myotomy surgery for strabismus: effects on spatial localization. Invest. Ophthalmol. & Visual Sci. **28:** 1870–1872.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 956

NEUROBIOLOGY OF EYE MOVEMENTS
FROM MOLECULES TO BEHAVIOR

Edited by Henry J. Kaminski and R. John Leigh

The New York Academy of Sciences
New York, New York
2002