

NYSTAGMUS IN INFANCY AND CHILDHOOD



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NYSTAGMUS IN INFANCY AND CHILDHOOD

CURRENT CONCEPTS IN MECHANISMS, DIAGNOSES, AND MANAGEMENT

Richard W. Hertle

Louis F. Dell'Osso

OXFORD
UNIVERSITY PRESS

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Oxford University Press is a department of the University of Oxford.
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Oxford New York
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Published in the United States of America by
Oxford University Press
198 Madison Avenue, New York, NY 10016

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Library of Congress Cataloging-in-Publication Data

Hertle, Richard W.
Nystagmus in infancy and childhood: current concepts in mechanisms, diagnoses, and management /
Richard W. Hertle, Louis F. Dell'Osso.
p. ; cm.
Includes bibliographical references.
ISBN 978-0-19-985700-5 (alk. paper)
I. Dell'Osso, Louis F. II. Title.
[DNLM: 1. Nystagmus, Pathologic. 2. Child. 3. Infant. WW 410]
618.92—dc23
2012005642.

1 3 5 7 9 8 6 4 2
Printed in the United States of America
on acid-free paper

This book is dedicated to my parents, Richard H. Hertle (1934–2008) and Anna Lena Hertle (1934–) who may seem from the outside as typical first-generation Americans from Brooklyn, New York, but for my family and me they were far from average. Their values, instilled in me (passion, education, hard work combined with a dedication to family and friends, and a spiritual soul), have become the cornerstone of a thoughtful and peaceful way of life.

Richard W. Hertle, MD

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.

—Sir William Lawrence Bragg, 1890–1971

This book is dedicated to my grandparents, who had the courage and foresight to emigrate to America, where they could forge a better life, and to my parents, Frank Dell’Osso (1914–2004) and Rose Perrone Dell’Osso (1915–2000), also first-generation Italian Americans from Brooklyn, New York. My genealogical research taught me that we are who they were. It is because of that lineage that I appreciated the pursuit of knowledge for its own sake, the satisfaction of a job well done (be it carpentry at home or my research), and the need to find balance while hunting the woods or fields, or playing on the golf course. They, and my large extended family, provided the confidence needed later in life to chart my own course and follow it despite the skepticism expressed by either my peers or other “experts.” Throughout my adult life I have been fortunate to have the love and support of two remarkable women. The insightful contributions and guidance in difficult times of Lyn Ferlo and, for the past 35 years, Charlene Morse were critical to any achievements I may have subsequently made. Therefore, this book is also dedicated to them.

Louis F. Dell’Osso, PhD

Not a single scientist in the meeting believed a word of what I said. Now, I know I am right.

—Hermann von Helmholtz (1821–1894)



R.W. Hertle and L.F. Dell’Osso in the latter’s Daroff-Dell’Osso Ocular Motility Laboratory office.

FOREWORD

A lot of intensely intelligent and highly dedicated workers have given their lives to this subject of nystagmus, and very little has come of it.

—Professor Frank A. Elliott, to R. B. Daroff (1965)

MY INTEREST in eye movements started on the first day of my neurology residency at Yale University, in July 1962, when we encountered a patient with a supranuclear ophthalmoplegia. Our attending asked me to read about eye movements and give a report to the group. I spent the next 2 months reading all that I could find on the subject and essentially became the Yale authority on eye movements while still only a PGY2. I decided to subspecialize in neuro-ophthalmology, a decision strengthened by a 3-month elective with J. Lawton Smith at the University of Miami during my PGY3 year.

I had an Army commitment after my residency and planned a neuro-ophthalmology fellowship thereafter that involved nystagmus research using ocular muscle electromyography (EMG). I discussed these plans with Professor Frank Elliott, one of my University of Pennsylvania Medical School Neurology mentors, and his negative response appears above. Elliott was

correct: in 1965, there was meager information about nystagmus, which my EMG plan wouldn't have increased. I had been impressed by Goodwin Breinin's ocular muscle EMG studies on gaze palsies, but except for convergence-retraction nystagmus, it has yielded no other useful information.

Fortunately, in the late 1960s and 1970s, several technologic advances led to enhanced understanding of eye movements in general and nystagmus in particular. As detailed by David Robinson, these included: the ability to record from single neurons in awake animals; the development of tracers to determine neuronal connections; computers that performed rapid data analysis; precise eye-movement recording techniques that noninvasively permitted minutes of arc measurements in all planes; and the popularization of a systems approach, where models provided the necessary hypotheses to focus basic and clinical research.

Such advancements, particularly the last, resulted from the entry of biomedical engineers into eye-movement research. These included David Robinson and Lou Dell'Osso, along with their multiple trainees, whose collaborations with clinicians focused studies that addressed relevant clinical issues. The teams included David Robinson with Dave Zee and John Leigh; and Lou Dell'Osso with me, Todd Troost, John Flynn, and more recently with the pediatric neuro-ophthalmologist and surgeon, Richard Hertle. Dell'Osso's own congenital nystagmus (now designated "infantile nystagmus syndrome") naturally sparked

his interest in understanding this previously understudied area.

Dell'Osso and Hertle described the book's organization in their Preface. I can only add that it is authoritative, reader friendly, and, indeed, brilliantly constructed. *Nystagmus in Infancy and Childhood* will now serve as the definitive source for the understanding and treatment of previously ill-understood and untreatable eye-movement disorders.

Robert B. Daroff, MD
Professor and Chair Emeritus of
Neurology, Case Western Reserve
University School of Medicine

PREFACE

Never write about nystagmus, it will lead you nowhere.

—Hermann Wilbrand (1851–1953) to Robert Wartenberg (1886–1956) in 1921

THIS BOOK describes, illustrates, and shares our current understanding, evaluation, and treatments of nystagmus in infancy and childhood. It has been over five decades since the pioneering works *Ocular Vertical Deviations and Nystagmus* by J. Ringland Anderson and *Clinical Methods of Neuro-Ophthalmologic Examination* by Alfred Kestenbaum described what was known about ocular oscillations and what could be accomplished to treat those disorders. Since then the amount of knowledge regarding the anatomy, physiology, molecular biology, and types of investigation techniques and treatment options for nystagmus have exponentially increased. We believe this work is timely, aligning it with advanced concepts of developmental brain-eye diseases and summarizing novel treatment paradigms. By using this medium to consolidate our combined experience, the authors hope to provide a comprehensive resource for both clinicians and scientists who care for infants and children with nystagmus.

This text will provide clinicians with algorithms for examination; descriptions of diagnostic techniques; and medical, surgical, and alternative treatments of the visual system in infants and children with nystagmus. Another important goal of this work is to provide scientists with details on methodologies of investigation, including analysis software, models of the ocular motor system, and current hypotheses on the pathophysiology of ocular motor oscillations. Modern media formats are included to visually illustrate the varied presentations of these disorders with their diagnostic electrophysiology.

The roots of this monograph are deep, stemming from seeds planted in a lecture, “Nistagmo Infantile” presented to Il Gruppo Italiano per lo Studio del Movimento Oculare, III Incontro Nazionale, I Corso di Aggiornamento Teorico-Pratico in Alghero (Sardinia) Italy in 1989. There, thanks to Dr. Sebastiano Traccis’ invitation to LFD to speak at this meeting and Dr. Josephine Shallo-Hoffmann’s suggestion

that a compilation of this information would be appreciated by clinicians treating these conditions, he began to collate ocular motor research about “congenital nystagmus,” “latent/manifest latent nystagmus,” the nystagmus blockage syndrome, and “spasmus nutans” with the aim of defining the critical factors in the differential diagnosis and treatment of these specific but easily confused types of nystagmus.

Clearly, the lure of new research kept this book on the back burner until the unbounded energy of Rich Hertle was applied to it. In the more than two decades that have elapsed since that first draft, not only has our knowledge base expanded tremendously but also the terminology has changed. In this handbook, we use the more modern CEMAS nomenclature and thereby avoid the misconceptions and errors inherent in the classical terminology. Eye-movement data and their analyses provide unambiguous, accurate, and repeatable waveform criteria and characteristics for infantile nystagmus syndrome, fusion maldevelopment nystagmus syndrome, nystagmus blockage syndrome, and spasmus nutans syndrome, allowing definitive diagnoses and determination of both the type and amount of the most efficacious therapy for each patient.

The resources used in this work include a summary (review) of much of the current knowledge regarding nystagmus in infancy and childhood, but, in addition, and uniquely, shares the authors’ combined 75 years of experience in studying, diagnosing, and treating thousands of patients with nystagmus. The book is structured in a logical way to allow a full cover-to-cover read or as a reference resource for those interested in a particular topic (e.g., eye-movement recording techniques, medical treatments, video appearance of periodic alternating nystagmus, etc.). Although one may concentrate on either the research or the clinical sections, the well-rounded reader would be better served by including both; they have been inseparable in our research approach and neither the “basic” nor the “clinical” aspects would exist without the other. We have included appendices that can be used in isolation for special purposes such as clinical examination sheets, patient information

sheets, algorithm for computer analysis of nystagmus waveforms, and so on. Additional resources—including patient, waveform, and canine videos—can be found on the companion website for this volume. Please visit www.oup.com/us/nystagmus for crucial tools and information for clinicians and scientists.

Chapter 1 covers the relevant anatomy involved in nystagmus or saccadic intrusions and oscillations. In Chapters 2–4, the results of ocular motor research into different types of nystagmus of infancy are summarized in a narrative manner, particularly the important ideas and observations that elucidate underlying neurophysiological mechanisms or have clinical relevance. We emphasize the latter since they form the foundations for both “clinical pearls” and the sections on therapeutic options that follow—“science-based,” rather than “evidence-based,” medicine. Just as the form and luster of real pearls stem from the grains of sand that are their foundation, the diagnostic and therapeutic value of these clinical pearls derives from the scientific foundations uncovered in research studies. Thus, our pearls remain scattered in their research beds, thereby maintaining close proximity to their scientific grains of sand. Chapter 5 is devoted to the differential diagnoses of both infantile types of nystagmus and saccadic disorders. Chapter 6 discusses the afferent-system clinical exam and Chapter 7, nystagmus treatments, including medical, surgical, and others.

Finally, Chapter 8 presents our summary and conclusions, including how, through the use of an eye-movement, data-driven function, the eXpanded nystagmus acuity function, we are now able to both provide a pre-therapy estimation of the beneficial effects of infantile nystagmus syndrome (INS) therapy on an individual patient, as well as directly measuring them post-therapy. The ability to estimate improvements in measured peak visual acuity and the breadth of the high-acuity gaze-angle region for individual INS patients with or without associated sensory visual deficits has never before been possible and cannot be accomplished using clinical measures alone. This eye-movement-based approach allows the physician to make more accurate diagnoses and to more confidently apply the most

suitable therapies to each patient. Hopefully, it will also discourage withholding beneficial therapies (“Your child has nystagmus and there is nothing that can be done”) and preclude applying therapies with little estimated visual function benefits; the net result should be improved visual function and patient satisfaction.

During the 2 years it took to organize, propose, write, and publish this work we have

learned how ignorant we remain regarding this group of disorders. It is our hope that it will serve as a resource for the next generation of clinicians and scientists, thereby encouraging a newer, deeper, and more profound set of discoveries.

Richard W. Hertle, MD

Louis F. Dell’Osso, PhD

ACKNOWLEDGMENTS

It is better to have nine of your ideas be completely disproved, and the tenth one spark off a revolution, than to have all ten be correct but unimportant discoveries that satisfy the skeptics.

—Francis Crick (1916–2004)

ALTHOUGH AUTHORED by two, this work could not have been accomplished without continuous support from colleagues and administrative personnel at multiple medical centers.

FOR R. W. HERTLE:

The Laboratory of Sensorimotor Research, The National Eye Institute, National Institutes of Health, Bethesda, MD; The UPMC Eye Center, Pittsburgh, PA; Akron Children's Hospital Medical Center, Akron, OH; Case Western Reserve University, Cleveland, OH. Granting agencies were as follows: The National Eye Institute, National Institutes of Health; The Veterans Administration Merit Review; and Fight for Sight. Anne Dellinger at Oxford University Press was tremendously helpful in advocating for, and assisting with, the huge task of publishing this work. Most important, this work could never have been completed without those patients and

their families who traveled from all parts of the world to many places in the United States to visit the author's professional offices.

The following people I could not do, or have done, without Dongsheng Yang, Robert Daroff, R. J. Leigh, Larry A. Abel, David Schaffer, Arthur Jampolsky, Marshal M. Parks, Jonathan Jacobs, Roy W. Beck, Raymond Kraker, Edmond F. Fitzgibbon, Susan B. Mellow, Mitra Maybodi, Robert Williams, David B. Granet, Deanna Stevens, William Anniger, Vanessa M. Hill, Joel S. Schuman, Hiroshi Ishikawa, Leah Reznick, Mingshia Zhu, Albert Maguire, Jean Bennett, Kenneth Adams, Matthew Kaufman, Eric Hald, Tara Cronin, Ellen Mitchell, Jai Jeng, Kristen Carey, Robert Burnstine, Shawn Lyden, Stephanie Knox, and Cathy Howe. Lastly, if were not for the love and support of my family, especially my wife, Gloriann, and children, Jessika and Jamie, my work on this project would never had been completed.

FOR L. F. DELL'OSO:

The Daroff-Dell'Osso Ocular Motility Laboratory (formerly The Ocular Motor Neurophysiology Laboratory), Case Western Reserve University, and Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH (formerly, University of Miami and Department of Veterans Affairs Medical Center, Miami, FL). Funding was from the following: The National Science Foundation (1972); Seeing Eye Foundation (1972–73); The National Eye Institute, National Institutes of Health (1972; 1978–79); and The Department of Veterans Affairs Merit Review (1973–2011). This work could never have been completed without the continuous stream of patients referred over the past 40 years by dozens of physicians (both in private practice and academia), and the many patients and families who traveled from all parts of the world to visit the author's laboratory for eye-movement recordings, diagnoses, and therapeutic recommendations to their referring physicians.

I am indebted to my many colleagues and students for their valuable contributions (both indirect, through their research and our long-term collaborations, and direct, during the preparation of this book). I have had the privilege and pleasure of collaborating with many excellent scholars; they are the silent authors, without whose contributions and collaborations this monograph would not have been possible. The following people played key roles in my research

and many, in my personal life: Robert B. Daroff (who facilitated my move to the Department of Neurology at a critical point early in my career and cemented our professional, symbiotic partnership that lasts to this day); Larry Stark (who insisted we write a paper based on my thesis and visit to his lab); Thorne Shipley, John T. Flynn, J. Lawton Smith, and Joel S. Glaser (the Bascom Palmer superstars who also were my teachers); Larry A. Abel (my first and most prominent post-doc); Jonathan B. Jacobs (grad student, postdoc, colleague, and Mac guru responsible for all our software); Robert M. Steinman; Dieter Schmidt; Sebastiano Traccis; Carl Ellenberger; R. J. Leigh; Han Collewijn; Akio Tabuchi; Barbara Weissman; Josephine Shallo-Hoffmann; Nirav Sheth; Lea Averbuch-Heller; Bernd Remler; Robert Williams; Robert Burnstine; Robert L. Tomsak; Jean Bennett; Greg Acland; Alessandro Serra; and Zhong I. Wang (my final and most prolific graduate student).

I am especially indebted to Ann Rutledge, my “secret weapon” who, for the past 16 years, insulated me from the ever-increasing administrative intrusions and overzealous committees imposing inane regulations on principal investigators that today stifle innovative research. Such intrusions destroy the uninterrupted “think time” required for a researcher to immerse himself in the work; because of my temperament and inability to “go along” with irrationality, Ann was the single most important factor allowing me to maintain the focus I needed.

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1

RELEVANT ANATOMY AND PHYSIOLOGY

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The ocular motor system can make the eyes do anything it wants to.

—Bert L. Zuber (circa 1972)

EYE MOVEMENTS bring visual stimuli to the fovea and also maintain foveal fixation of stationary and moving targets during head movements. These movements are performed by the ocular motor system that consists of ocular motor nerves and nuclei in the brainstem originating in the cerebral cortex, cerebellum, vestibular structures, and the extraocular muscles. Anatomically, the ocular motor system may be divided according to location into infranuclear, nuclear, internuclear, and supranuclear components. It is important to distinguish between supranuclear, internuclear, nuclear, and infranuclear (orbital, cranial nerves) disorders because the disturbances have highly varied causes and present different clinical pictures. Eye-movement abnormalities of supranuclear

origin are characterized by gaze palsies, tonic gaze deviation, saccadic and smooth pursuit disorders, vergence abnormalities, nystagmus, and saccadic oscillations. Supranuclear disorders such as nystagmus in infancy and childhood result from lesions above the level of the ocular motor nerve nuclei.

1.1 INFRANUCLEAR OCULAR MOTOR ANATOMY

1.1.1 Extraocular Muscles

The insertions of the rectus muscles extend from the equator of the eye to the limbus early on in development. By processes of disparate differentiation between the sclera and the rectus

tendon, posterior recession of the tendon from the limbus, and contemporaneous growth of the anterior segment of the eye, these tendons reach their adult location only between the ages of 18 months and 2 years.^{1,2} The tendons of origin and insertion of the extraocular muscles arise from mesenchymal tissue similar to that of their respective muscles. These tendon-muscle groups have developed from superior and inferior mesenchymal complexes. In humans there are three pairs of extraocular muscles in each orbit: a pair of horizontal rectus muscles, a pair of vertical rectus muscles, and a pair of oblique muscles.³ The four rectus muscles are attached to the sclera anterior to the equator near the cornea (see Fig. 1.1). The two oblique muscles approach the globe from in front, at the medial side of the orbit, and continue obliquely and laterally to insert on the sclera posterior to the equator on the temporal part of the globe. The rectus muscles are almost flat narrow bands that attach themselves with broad, thin tendons to the globe. There are four of these muscles: the medial, lateral, superior, and inferior. The origins of the rectus muscles, the superior oblique muscle, and the levator muscle of the upper lid are arranged in an approximately circular

fashion (the annulus of Zinn), surrounding the optic canal and in part the superior orbital fissure. Through this oval opening created by the origins of the muscles, the optic nerve, the ophthalmic artery, and parts of cranial nerves III and VI enter the muscle cone formed by the body of the rectus muscles. The interlocking of muscle and tendon fibers at the site of origin creates an extremely strong anchoring of the extraocular muscles. Attachments exist between the origins of the medial and superior recti and the dura of the optic nerve. The medial and lateral rectus muscles follow the corresponding walls of the orbit for a good part of their course, and the inferior rectus muscle remains in contact with the orbital floor for only about half its length. The superior rectus muscle is separated from the roof of the orbit by the levator muscle of the upper lid. If the rectus muscles were to continue their course in their original direction, they would not touch the globe; at about 10 mm posterior to the equator, the muscle paths curve toward the globe rather abruptly and eventually insert on the sclera at varying distances from the corneal limbus. The musculoorbital tissue connections (the muscle pulleys) are responsible for their changes in course. The insertions

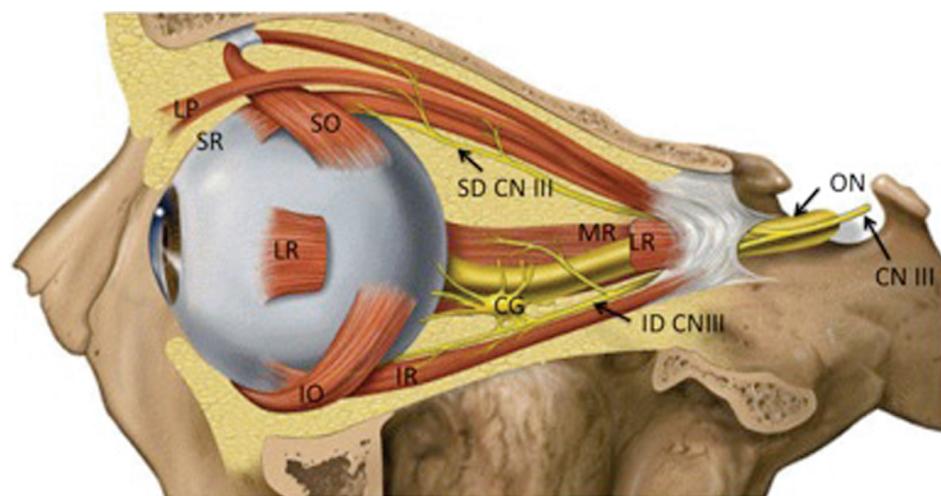


FIGURE 1.1 Orbital structures controlling eye movements. Parasagittal section of the orbit showing bones, extraocular muscles, and cranial nerve III (CN III) of the orbit. CG, ciliary ganglion; ID CN III, inferior division of cranial nerve III; IO, inferior oblique; IR, inferior rectus; LP, levator palpebrae superioris; LR, cut ends of lateral rectus; MR, medial rectus; ON, optic nerve; SD CN III, superior division of cranial nerve III; SO, superior oblique; SR, superior rectus.

of the rectus muscles do not lie on a circle that is concentric with it but rather on a spiral (the spiral of Tillaux). The insertion of the medial rectus muscle is closest to the corneal limbus, followed by the inferior, lateral, and superior rectus insertions, with the superior rectus insertion being the most distant. The lines of insertion are generally not straight; they are curved and sometimes even wavy. The straightest ones are the insertions of the medial and lateral rectus muscles, but these too are often slightly convex toward the corneal limbus. The distance of the tendon from the limbus may be influenced by age and axial length of the eye.

From its origin above and medial to the optic foramen, the superior oblique courses anteriorly in a line parallel with the upper part of the medial wall of the orbit, reaching the trochlea at the angle between the superior and medial wall. The trochlea is a tube 4 to 6 mm long formed in its medial aspect by bone (the trochlear fossa of the frontal bone). The rest of the circumference is composed of connective tissue that may contain cartilaginous or bony elements. After passing the trochlea, the superior oblique muscle turns in laterodorsally, forming an angle of about 54° with the pretrochlear or direct portion of the muscle. A fibrillar, vascular sheath surrounds the intratrocchlear superior oblique tendon. This portion of the tendon consists of discrete fibers with few interfibrillar connections. Each fiber of

the tendon moves through the trochlea in a sliding, telescoping fashion with the central fibers undergoing maximal excursion and the peripheral fibers the least excursion. The total travel of the central fibers appears to be 8 mm in either direction. A bursa-like structure lies between the trochlear "saddle" and the vascular sheath of the superior oblique tendon. At about the distal third of the direct portion (10 mm behind the trochlea), the muscle becomes tendinous and remains tendinous in its entire posttrochlear or reflected part. The tendon passes under the superior rectus muscle, fans out, and merges laterally with the sclera to the vertical meridian, forming a concave curved line toward the trochlea. The anterior end of the insertion lies 3.0 to 4.5 mm behind the lateral end of the insertion of the superior rectus muscle and 13.8 mm behind the corneal limbus (see Fig. 1.2). The posterior end of the insertion lies 13.6 mm behind the medial end of the insertion of the superior rectus muscle and 18.8 mm behind the corneal limbus. The width of the insertion of the superior oblique muscle varies greatly (from 7 to 18 mm) but is 11 mm on average. The medial end of the insertion lies about 8 mm from the posterior pole of the globe. Near its insertion the posterior border of the muscle is related to the superior vortex vein. The length of the direct part of the superior oblique muscle is about 40 mm and that of the reflected tendon is about 19.5 mm.

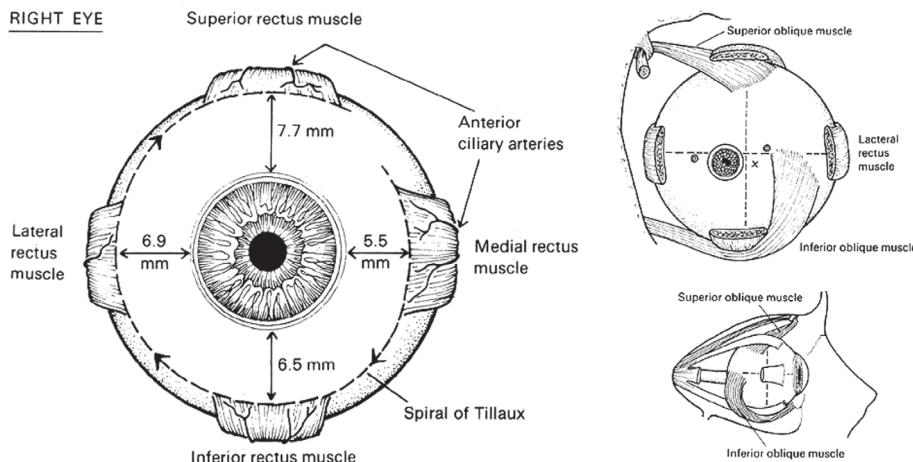


FIGURE 1.2 Insertional anatomy of the extraocular muscles. All numbers are averages in millimeters.

From a physiologic and kinematic standpoint, the trochlea is the origin of the muscle.

The inferior oblique muscle is the shortest of all the eye muscles, being only 37 mm long. It arises in the anteroinferior angle of the bony orbit in a shallow depression in the orbital plate of the maxilla near the lateral edge of the entrance into the nasolacrimal canal. The origin is readily located by drawing a perpendicular line from the supraorbital notch to the lower orbital margin. The muscle continues from its origin backward, upward, and laterally, passing between the floor of the orbit and the inferior rectus muscle. It inserts by a short tendon (1 to 2 mm) in the posterior and external aspect of the sclera. The width of the insertion varies widely (5 to 14 mm) and may be around 9 mm on average. The insertion forms a curved concave line toward the origin of the muscle. Its anterior margin is about 10 mm behind the lower edge of the insertion of the lateral rectus muscle; its posterior end is 1 mm below and 1 to 2 mm in front of the macula. Near its insertion, the posterior border of the muscle is related to the inferior vortex vein. Unlike the other extraocular muscles, the inferior oblique is almost wholly muscular. It forms an angle of about 51° with the vertical plane of the globe.

The medial and lateral rectus muscles have only horizontal actions. The medial rectus muscle is the primary adductor of the eye, and the lateral rectus muscle is the primary abductor of the eye. The superior and inferior

rectus muscles are the primary vertical movers of the eye. The superior rectus acts as the primary elevator; the inferior rectus acts as the primary depressor of the eye. This vertical action is greatest with the eye in the abducted position. The direction of pull of the muscles forms a 23° angle relative to the visual axis in the primary position, giving rise to secondary and tertiary functions. The secondary action of vertical rectus muscles is torsion. The superior rectus is an incyclotorter, and the inferior rectus is an excyclotorter. The tertiary action of both muscles is adduction. The superior and inferior oblique muscles are the primary muscles of torsion. The superior oblique creates incyclotorsion, and the inferior oblique creates excyclotorsion (Table 1.1).

1.1.2 Extraocular Muscle Pulleys

Modern imaging techniques such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) have revealed that the paths of the rectus muscles remain fixed relative to the orbital wall during excursions of the globe and even after large surgical transpositions.^{4,5} There is no sideslip of the rectus muscles in relation to the orbital walls when the eye moves from primary into secondary gaze positions. Demer and coworkers suspected from these findings that there must be musculo-orbital coupling through tissue connections that constrain the

Table 1.1 Functions of the Extraocular Muscles

MUSCLE	PRIMARY ACTION	SECONDARY ACTION	TERTIARY ACTION
Medial rectus	Adduction	— — —	— — —
Lateral rectus	Abduction	— — —	— — —
Superior rectus	Elevation	Incyclotorsion	Adduction
Inferior rectus	Depression	Excyclotorsion	Adduction
Inferior oblique	Excyclotorsion	Elevation	Abduction
Superior oblique	Incyclotorsion	Depression	Abduction
Levator palpebrae	Eyelid elevation	— — —	— — —

The superior muscles are incycloductors; the inferior muscles, excycloductors. The vertical muscles are adductors; the oblique muscles, adductors.

muscle paths during rotations of the globe.^{4–10} Subsequent studies with high-resolution MRI confirmed this notion by demonstrating retro-equatorial inflections of the rectus muscle paths. Gross dissection of orbits and histological and histochemical studies showed that these inflections are caused by musculo-orbital tissue connections in the form of fibroelastic sleeves that consist of smooth muscle, collagen, and elastin. During contraction the muscles travel through these sleeves, which act as pulleys by restraining the muscle paths. The orbital layer of the rectus muscle inserts directly on the pulley, whereas the global layer continues anteriorly to insert into the sclera.^{4–10} As Figure 1.3 shows, these pulleys are located in a coronal plane anterior to the muscle bellies and about 5 to 6 mm posterior to the equator. They are compliant rather than rigid, receive rich innervation involving numerous neurotransmitters in humans and

nonhuman primates, and change their positions as a function of gaze direction.^{4–10} For instance, the pulleys of the horizontal rectus muscle move posteriorly during muscle contraction. This adjustability of pulley positions and the different insertion sites of the global and orbital layers of extraocular muscles may play a major but still undefined role in ocular kinematics. Several lines of evidence, MRI, CT, gross examinations, surgical exposures, and histological studies in humans and monkeys strongly suggest that the orbital layer of each rectus muscle inserts on its corresponding pulley, rather than on the globe.^{4–10} These anatomic differences in the two muscle layers suggest differences in their functions: the orbital layer probably acts against the continuous elastic load of the pulley suspension, whereas the global layer acts against the intermittent, viscous load of the antagonist extraocular muscle.

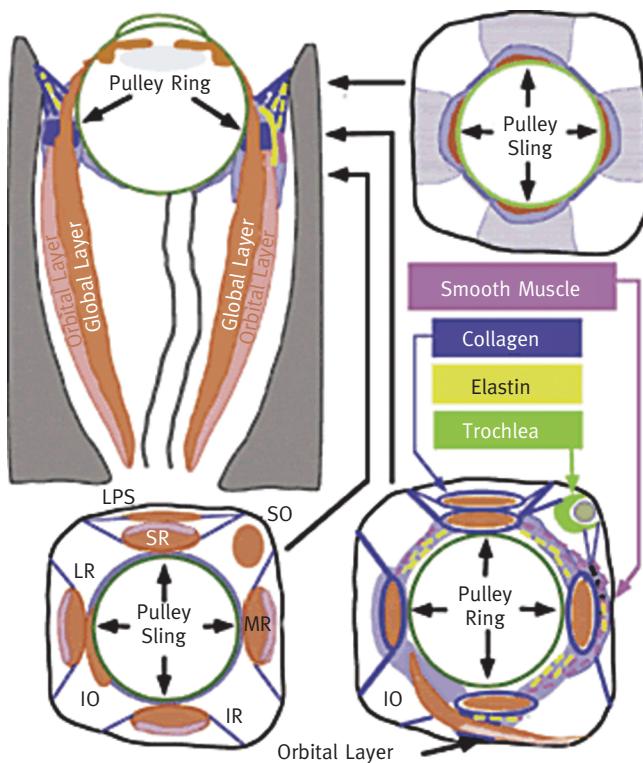


FIGURE 1.3 Anatomy of the extraocular muscle “pulley” system around the recti muscles. IR, inferior oblique; IR, inferior rectus; LG, lacrimal gland; LPS, levator palpebrae superioris; LR, lateral rectus; LR-SR, lateral rectus-superior rectus; MR, medial rectus; MR-IR, medial rectus-inferior rectus; MR-SR, medial rectus-superior rectus; SR, superior rectus; SOT, superior oblique tendon.

1.1.3 Orbital Tissues

The eyeball is suspended within the orbit by a system of fasciae. The bulk of the system is made up of Tenon's capsule, which is a condensation of fibrous tissue that covers the eyeball from the entrance of the optic nerve to near the corneal limbus, where it is firmly fused with the conjunctiva. Except for this area of fusion, the two structures are separated by the subconjunctival space. Tenon's capsule is also separated from the sclera. Between the two is the episcleral space. On its outer aspect the capsule is intimately related to the orbital reticular tissue. Its posterior edge is not clearly delineated; it is thin and more or less continuous with the meshwork of the orbital fat. In their extracapsular portions, the extrinsic eye muscles are enveloped by the pulley system and muscle sheath.^{1,11} This sheath is a reflection of Tenon's capsule and runs backward from the entrance of the muscles into the subcapsular space for a distance of 10 to 12 mm. At the lower aspect of the entrance, Tenon's capsule is reduplicated. At the upper aspect, it continues forward as a single membrane. The muscle sheaths of the four rectus muscles are connected by a formation known as the intermuscular membrane, which closely relates these muscles to each other. In addition, there are numerous extensions from all the sheaths of the extraocular muscles, which form an intricate system of fibrous attachments interconnecting the muscles, attaching them to the orbit, supporting the globe, and contributing to the pulley system.¹²

1.1.4 Extraocular Muscle/Orbit Nervous Anatomy

The oculomotor nerve (cranial nerve III) contains somatic motor fibers to the levator palpebrae, inferior rectus, medial rectus, superior rectus, inferior oblique, and sympathetic efferent fibers (preganglionic fibers) to the ciliary ganglion. The postganglionic fibers connected with these supply the ciliary muscle and the sphincter of the iris. The axons arise from the nucleus of the oculomotor nerve and pass in bundles through the posterior longitudinal bundle, the tegmentum, the red nucleus, and the

medial margin of the substantia nigra in a series of curves and finally emerge from the oculomotor sulcus on the medial side of the cerebral peduncle. The oculomotor nucleus lies in the gray substance of the floor of the cerebral aqueduct subjacent to the superior colliculus and extends in front of the aqueduct a short distance into the floor of the third ventricle. The inferior end is continuous with the trochlear nucleus. It is from 6 to 10 mm. The nucleus of the oculomotor nerve contains several distinct groups of cells that differ in size and appearance from each other and send their axons each to separate muscles. Much uncertainty still exists as to which group supplies which muscle. There are seven of these groups or nuclei on either side of the midline and one medial nucleus.^{13–16}

The trochlear nerve (cranial nerve IV) contains somatic motor fibers only. It supplies the superior oblique muscle of the eye. Its nucleus of origin, trochlear nucleus, is a small, oval mass situated in the ventral part of the central gray matter of the cerebral aqueduct at the level of the upper part of the inferior colliculus. The axons from the nucleus pass downward in the tegmentum toward the pons, but they turn abruptly dorsalward before reaching it and pass into the superior medullary velum, in which they cross horizontally to decussate with the nerve of the opposite side; they emerge from the surface of the velum, immediately behind the inferior colliculus. The nuclei of the two sides are separated by the raphé, through which dendrites extend from one nucleus to the other.^{16–19}

The trigeminal nerve (cranial nerve V) contains somatic motor and somatic sensory fibers. The motor fibers arise in the motor nucleus of the trigeminal and pass ventrolaterally through the pons to supply the muscles of mastication. The sensory fibers arise from the unipolar cells of the semilunar ganglion; the peripheral branches of the T-shaped fibers are distributed to the face and anterior two-thirds of the head; the central fibers pass into the pons with the motor root and bifurcate into ascending and descending branches that terminate in the sensory nuclei of the trigeminal ganglion. The motor nucleus of the trigeminal is situated in the upper part of the pons beneath the lateral angle of the fourth

ventricle. It is serially homologous with the facial nucleus and the nucleus ambiguus (motor nucleus of the vagus and glossopharyngeal) that belong to the motor nuclei of the lateral somatic group.^{19–26} The axons arise from large pigmented multipolar cells. The motor nucleus receives reflex collaterals and terminals from (1) the terminal nucleus of the trigeminal of the same and a few from the opposite side, via the central sensory tract (trigeminothalamic tract); (2) the mesencephalic root of the trigeminal; (3) the posterior longitudinal bundle; (4) and probably fibers in the *formatio reticularis*. It also receives collaterals and terminals from the opposite pyramidal tract (corticopontine fibers) for voluntary movements.^{19–26} The terminal sensory nucleus consists of an enlarged upper end, the main sensory nucleus, and a long more slender descending portion that passes down through the pons and medulla to become continuous with the dorsal part of the posterior column of the gray matter, especially the substantia gelatinosa of the spinal cord. The main sensory nucleus lies lateral to the motor nucleus beneath the superior peduncle. It receives the short ascending branches of the sensory root. The cells of the sensory nucleus are of large and medium size and send their axons into the *formatio reticularis*, where they form a distinct bundle, the central path of the trigeminal (trigeminothalamic tract), which passes upward through the *formatio reticularis* and tegmentum to the ventrolateral part of the thalamus.^{19–26} Most of the fibers cross to the trigeminothalamic tract of the opposite side. This tract lies dorsal to the medial fillet, approaches close to it in the tegmentum, and terminates in a distinct part of the thalamus. From the thalamus impulses are conveyed to the somatic sensory area of the cortex by axons of cells in the thalamus through the internal capsule and corona radiata.

The abducens nerve (cranial nerve VI) contains somatic motor fibers only that supply the lateral rectus muscle of the eye.^{15,16,27,28} The fibers arise from the nucleus of the abducens nerve and pass ventrally through the *formatio reticularis* of the pons to emerge in the transverse groove between the caudal edge of the pons and the pyramid. The nucleus is serially homologous with the nuclei of the trochlear and oculomotor

above and with the hypoglossal and medial part of the anterior column of the spinal cord below.^{15,16,27,28} It is situated close to the floor of the fourth ventricle, just above the level of the *striae medullares*. Voluntary impulses from the cerebral cortex are conducted by the pyramidal tract fibers (corticopontine fibers). The abducens nucleus probably receives collaterals and terminals from the ventral longitudinal bundle (tectospinal fasciculus)—fibers that have their origin in the superior colliculus, the primary visual center, and are concerned with visual reflexes.^{15,16,27,28}

The sensory innervation of the extraocular muscles is a contentious issue. Two distinct types of sensory receptors have been identified within human extraocular muscles, namely muscle spindles and palisade endings (myotendinous cylinders), but their precise function is not fully understood.^{19,22,23,25,29–35} The other main sensory receptors found within skeletal muscle, Golgi tendon organs, have as yet not been identified within human extraocular muscles, although they have been described in monkeys.^{24,33,34,36–38} Muscle spindles are found within the proximal and distal regions of human infant and adult extraocular muscles and are located at the junction of the orbital and global layers. Although they are found at a density similar to that of spindles in hand and neck muscles, suggesting a role in fine motor control, they also show features that hypothesize an ability to generate a proprioceptive signal. Palisade endings, a class of muscle receptor found exclusively within extraocular muscles, including those of humans, are located at the distal myotendinous junction of the multiply innervated non-twitch fibers of the global layer.^{24,33,34,36–38} They may be the principal source of proprioceptive feedback from extraocular muscles. Studies in the monkey suggest that proprioceptive signals ascend from the extraocular muscles to the central processing structures via the trigeminal nucleus. The precise pathway in humans has yet to be established. There is increasing scientific and clinical evidence that a nonvisual afferent signal, most likely to be derived from extraocular muscle proprioceptors, can under certain conditions influence visuomotor behavior. It may well be

that for the majority of individuals with normal visual function and normal oculomotor systems that vision itself, combined with efference copy, is sufficient to determine eye position. In such individuals, extraocular muscle proprioception may have little to contribute to the control of eye movements and the representation of visual space. However, under certain circumstances of reduced or impaired vision or in those with ocular motility disorders, afferent feedback from the extraocular muscles might assume greater significance.^{24,33,34,36–38}

1.2 SUPRANUCLEAR OCULAR MOTOR ANATOMY

1.2.1 Frontal Eye Fields

The saccade-related activity of the superior colliculus neurons is shaped by inputs from the posterior parietal cortex, the frontal eye fields, and the substantia nigra pars reticulata (see Fig. 1.4).³⁹ The posterior parietal cortex

is involved in the visual guidance of saccades by shaping the visual inputs to the superior colliculus.⁴⁰ The posterior parietal cortex contains neurons that are modulated by visual attention, that is, by how behaviorally relevant are visual stimuli. They respond more effectively when the stimulus is the target for an eye movement. The frontal eye fields form an executive center that can selectively activate superior colliculus neurons, playing a role in the selection and production of voluntary saccades.⁴⁰ The frontal eye fields are also involved in suppressing reflexive saccades and generating voluntary, nonvisual saccades. The complementary executive control exerted on saccade generation by the frontal eye fields and the superior colliculus is revealed by the effect of selective and combined ablation.^{39,41–43} Lesions of the superior colliculus prevent the generation short-latency reflexive saccades, whereas the generation of voluntary saccades is disrupted by frontal-eye-field lesions. Although saccades can still be produced after

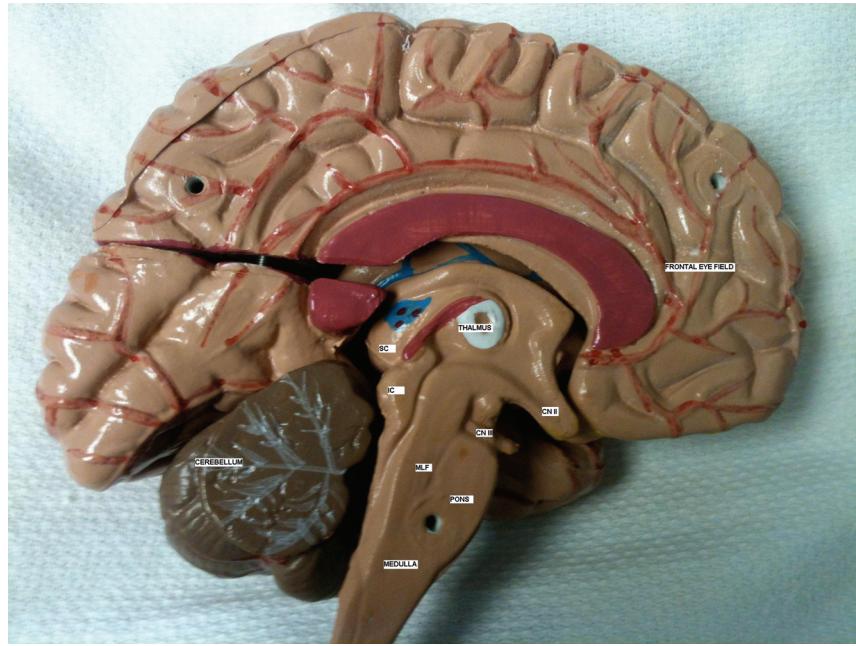


FIGURE 1.4 Brainstem structures controlling eye movements. Parasagittal section of the cerebrum and brainstem showing the areas of the ocular motor nuclei and brainstem structures involved with internuclear and supranuclear pathways. CN II, second cranial nerve (optic); CN III, third cranial nerve; MLF, medial longitudinal fasciculus; IC, inferior commissure; SC, superior colliculus.

the ablation of either the superior colliculus or the frontal eye fields, a combined ablation of these two structures results in the complete abolition of saccadic eye movements. The substantia nigra pars reticulata funnels inputs from the frontal cortex and acts as a gate for the voluntary control of saccades, keeping in check the superior colliculus activity.^{39,41–43} The neural activity in the substantia nigra maintains the superior colliculus tonically inhibited to prevent unwanted saccades. Prior to a voluntary saccade, this tonic inhibition is reduced by inputs from the caudate, which is activated by signals from the cortex. Experimental and clinical studies specify the role of frontal eye fields in the volitional, inhibitory control of visually triggered saccades. The parietal lobe instead seems mainly concerned with privileged target selection. A parallel processing of saccade-related signals occurs in corticostriatal circuits. Evidence for peristriate and parietal cortical areas to encode the information relevant to smooth pursuit generation is provided by animal and clinical studies.^{40,43}

1.2.2 Superior Colliculus

The superior colliculus provides both the motor command to the PPRF's burst neurons and the trigger command to the omnipause neurons.^{44–46} It is a laminated structure situated on the roof of the midbrain (see Fig. 1.5). It sends projections to both the horizontal (paramedian pontine reticular formation [PPRF]) and vertical gaze centers (rostral interstitial nucleus of the medial longitudinal fasciculus [riMLF]), providing the motor command to move the eye to an intended new position for the foveation of a visual stimulus.^{44–46} The superior colliculus contains a topographic motor map composed of neurons that discharge a high-frequency burst of action potentials immediately prior to saccades that have a specific vector, that is, a direction and amplitude, which is independent of the initial position of the eyes in the orbit.⁴⁷ The integrity of the superior colliculus is crucial for the production of short-latency reflexive saccades, including the “express” saccades whose latency approaches the fastest time for visual



FIGURE 1.5 The superior colliculus are a pair of oval masses composed of alternating layers of gray and white matter. They are centers for ocular movements. Some of the connections to the superior colliculus include the retina, visual and nonvisual cerebral cortex, inferior colliculus, paramedian pontine reticular formation, thalamus, basal ganglia, and spinal cord ventral gray horn. The fibers of the medial longitudinal fasciculus form a fringe on its ventrolateral side. 1-Superior colliculus, 2-Brachium of superior colliculus, 3-Medial geniculate nucleus, 4-Brachium of inferior colliculus, 5-Central gray substance, 6-Cerebral aqueduct, 7-Visceral nucleus of oculomotor nerve (Edinger-Westphal nucleus), 8-Nucleus of oculomotor nerve, 9-Medial lemniscus, 10-Central tegmental tract, 11-Medial longitudinal fasciculus, 12-Red nucleus, 13-Fibers of oculomotor nerve, 14-Substantia nigra, 15-Basis pedunculi.

signals to reach the oculomotor system and trigger a saccade.^{45,46,48,49} Lesions of the superior colliculus permanently abolish the production of express saccades.

1.2.3 Brainstem Control of Eye Movements

The problem of moving the eyes in the orbit entails two separate issues: controlling the amplitude of the movement (how far) and controlling the direction of the movement (which way).^{19,49,50} The amplitude of a saccade is determined by the activity in the lower motor neurons within the three oculomotor nuclei. The direction of a saccade is determined by which muscles are activated, as dictated by the activity in the premotor neurons within two separate gaze centers in the brainstem. The discharge frequency of extraocular motor neurons is directly proportional to the position and velocity of the eye.⁵¹ The saccade signal of motor neurons has the form of a pulse-step.⁵¹ The height of the step determines the amplitude of the saccade, while the height of the pulse determines the speed of the saccade. The duration of the pulse determines the duration of the saccade. The pulse is the phasic signal that commands the eyes to move. The step is the tonic signal that commands the eyes to hold in an eccentric position. The direction of saccades is dictated by premotor neurons in two gaze centers in the reticular formation: (1) the PPRF next to the abducens nucleus is the horizontal gaze center; and (2) the rostral iMLF in the midbrain reticular formation near the oculomotor nucleus is the vertical gaze center.^{45,47,51–53} To produce a rightward saccade, activation of premotor neurons in the right PPRF increases the activity of lower motor neurons in the right abducens nucleus, which innervate the lateral rectus muscle of the right eye. Activation in the right PPRF also increases the activity of internuclear neurons in the same (right) abducens nucleus, which send their axons along the medial longitudinal fasciculus to innervate the lower motor neurons in the left oculomotor nucleus, which in turn innervate the medial rectus muscle of the left eye.^{32,49,54} Omnipause neurons (OPNs) discharge at a relatively constant rate during fixation, but they stop

firing during saccades in all directions. The pause begins before the discharge of burst neurons and ends before the end of the saccade.^{32,49,54} Long-lead burst neurons (LLBNs) and excitatory burst neurons (EBNs) generate high-frequency bursts of activity before ipsilateral saccades. The burst of LLBNs are not as tightly coupled to saccade onset as the burst of EBNs.⁴⁷ EBNs make excitatory, monosynaptic connections with neurons in the ipsilateral abducens and provide the main source of excitatory drive for the saccade-related pulse of motor neuron activity.⁴⁷ The amplitude, duration, and velocity of saccades are coupled to the number of spikes generated, burst duration, and peak firing rate of the burst of activity, respectively.^{44,45,47,53} The tonic activity of many neurons in the nucleus prepositus hypoglossi and the medial vestibular nucleus is proportional to horizontal eye position, and these cells provide the excitation that is required for the step of motor neuron activity.^{44,45,47,53} Activity in the PPRF is specifically related to the control of horizontal saccades and the horizontal component of oblique saccades (see Fig. 1.6). Premotor neurons in the rostral midbrain produce the vertical pulse and step commands. Neurons in the riMLF generate a high-frequency burst before vertical saccades and convey this signal monosynaptically to the motor neurons (see Fig. 1.7).^{44,45,47,53} Vertical EBNs that discharge before upward saccades are intermingled with those that discharge before downward saccades in the riMLF. Neurons in the interstitial nucleus of Cajal (INC) and the vestibular nucleus discharge tonically at rates that are linearly related to vertical eye position, and provide the excitatory inputs that produce the step change in motor neuron activity.^{44,45,47,53} Many saccades have both horizontal and vertical components. Although the commands for the two components are generated in different regions of the brainstem, pontine OPNs inhibit both horizontal and vertical EBNs and tend to synchronize the onsets of the two components.

1.2.4 Vestibular Nuclei

The vestibular neurons are bipolar with their cell bodies located in Scarpa's ganglion in the internal auditory meatus.^{55–58} The superior and

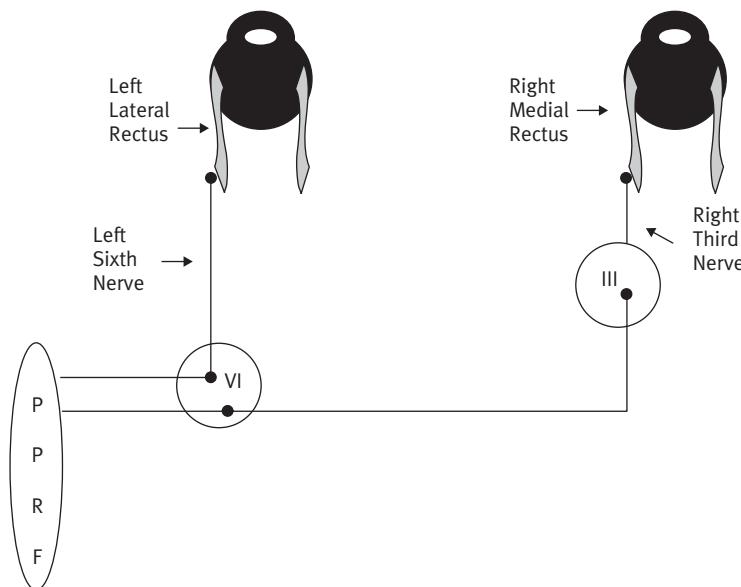


FIGURE 1.6 Schematic of brainstem pathways coordinating horizontal saccades. The PPRF, after receiving input from the ipsilateral cortical centers and superior colliculus, stimulates two sets of neurons in the abducens nucleus: (1) those that send axons to innervate the ipsilateral lateral rectus and (2) those whose axons join the medial longitudinal fasciculus and subsequently activate the medial rectus subnuclei of the contralateral third nerve. III, third cranial nerve nuclei; PPRF, paramedian pontine reticular formation; VI, sixth cranial nerve nuclei.

inferior vestibular nerves join to form a common bundle that enters the brainstem. These first-order neurons do not cross the midline. These afferent fibers terminate in the vestibular nuclei in the floor of the fourth ventricle. The nuclei are the superior vestibular nucleus, the lateral vestibular nucleus, the medial vestibular nucleus, and the descending vestibular nucleus. From the vestibular nuclei projections go to the cerebellum, extraocular muscle nuclei, antigravity muscles, and opposite vestibular nuclei.^{55–58} The semicircular canals detect head rotation and drive the rotational vestibulo-ocular reflex (VOR), whereas the otoliths detect head translation and drive the translational VOR. The main “direct path” neural circuit for the horizontal rotational starts in the vestibular system, where semicircular canals are activated by head rotation and send their impulses via the vestibular nerve through Scarpa’s ganglion and end in the vestibular nuclei in the brainstem.^{46,59,60} From these nuclei, fibers cross to the contralateral cranial nerve VI nucleus. There they synapse

with two additional pathways. One pathway projects directly to the lateral rectus of eye via the abducens nerve. Another nerve tract projects from the abducens nucleus by the abducens internuclear interneurons or abducens interneurons to the oculomotor nuclei, which contain motoneurons that drive eye muscle activity, specifically activating the medial rectus muscles of the eye through the oculomotor nerve.^{46,59,60} Another pathway directly projects from the vestibular nucleus through the ascending tract of Dieters to the ipsilateral medial rectus motoneurons.^{46,59,60} In addition, there are inhibitory vestibular pathways to the ipsilateral abducens nucleus. However, no direct vestibular neuron to medial rectus motoneuron pathway exists. Similar pathways exist for the vertical and torsional components of the VOR.^{61,62}

1.2.5 Cerebellum

The cerebellum plays an important role in eye movements.⁶³ Together with several brainstem

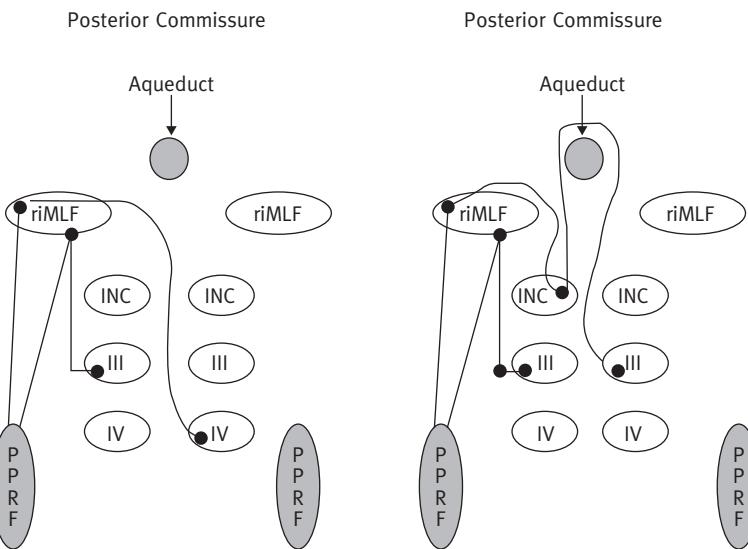


FIGURE 1.7 This shows schematics of brainstem pathways coordinating downward (SA) and upward (SB) saccades. In SA, the PPRF activates neurons in the riMLF that send fibers caudally to synapse upon the inferior rectus subnucleus of the ipsilateral third nerve and the contralateral superior oblique nucleus. Not shown in this diagram, fibers from the contralateral PPRF carry corresponding signals simultaneously. In SB, the PPRF activates neurons in the riMLF that send fibers through the posterior commissure to the superior rectus subnucleus of the contralateral third nerve and fibers to the inferior oblique subnucleus of the ipsilateral third nerve. Not shown in this diagram, fibers from the contralateral PPRF carry corresponding signals simultaneously. III, third cranial nerve nucleus; INC, interstitial nucleus of Cajal; IV, fourth cranial nerve nucleus; PPRF, paramedian pontine reticular formation; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus.

structures, including the nucleus prepositus hypoglossi and the medial vestibular nucleus, it appears to convert velocity signals to position signals for all conjugate eye movements through mathematical integration. Because of this, all of the structures involved in this process are often referred to as the neural integrator.⁶⁴ Patients with faulty neural integration may show gaze-evoked nystagmus, impaired smooth pursuit, inability to cancel the VOR during fixation, saccadic dysmetria, defective optokinetic nystagmus response, and/or rebound nystagmus.^{65–67} Various types of image-stabilizing reflexes are also “cerebellar” functions. Pursuit, VOR cancellation, and holding the eye steady for fixation, both immediately after saccades and in eccentric positions of gaze, are controlled by the flocculus (and probably paraflocculus).⁶⁸ The nodulus (and ventral uvula) modulates “low-frequency” aspects of vestibular responses and

hence controls the duration (time constant) of the VOR.⁶⁸ The dorsal vermis and underlying (posterior) fastigial nuclei participate in the control of the size of the saccadic pulse of innervation and hence saccadic accuracy.⁶⁸

1.3 AFFERENT SYSTEM

1.3.1 Retina

The retina is organized both vertically (in columns) and horizontally (in layers). The principal “vertically oriented” elements are receptors (rods and cones), the bipolar cells and the ganglion cells. The “horizontally oriented” elements are the horizontal, interplexiform and the Meuller cells. The human retina is approximately 0.2 mm thick and has an area of approximately 1100 mm². Each retina possesses about 200 million neurons. The human retina is “inverted,”

because the photoreceptor layer is located posteriorly and furthest from incident light. Rod and cone photoreceptors are easily distinguished by their outer segments.^{69–71} The outer segment contains photopigment in free-floating disks (rods) or folded layers (cones). Cone outer segments have a continuous outer membrane, whereas rods have discs, stacked like coins, in a sleeve.⁷⁰ The rod and cone outer segment membranes are constantly being replenished. The capture of individual photons by the photopigment molecules in the disk membranes is what initiates neural signaling. Photoreceptors are actually specialized hair cells, and the inner and outer segments are connected by the cilium. The human retina contains approximately 120 million rod and 1 million cone photoreceptors. Cone density is highest at the fovea, where recent estimates place it at approximately 300,000/mm;² rod density is highest at about 18° eccentric to the fovea (see Chapter 6 for electrophysiology).⁷⁰

1.3.2 Optic Nerve

The optic nerve (cranial nerve II) is considered to be part of the central nervous system as it is derived from an out-pouching of the diencephalon during embryonic development.^{71–73} Consequently, the fibers are covered with myelin produced by oligodendrocytes rather than the Schwann cells of the peripheral nervous system. Similarly, the optic nerve is ensheathed in all three meningeal layers (dura, arachnoid, and pia mater). The optic nerve is composed of retinal ganglion cell axons and support cells. It leaves the orbit via the optic canal, running posteromedially toward the optic chiasm, where there is a partial decussation (crossing) of fibers from the temporal visual fields of both eyes (see Fig. 1.8). Its diameter increases from about 1.6 mm within the eye, to 3.5 mm in the orbit, to 4.5 mm within the cranial space. The optic nerve component lengths are 1 mm in the globe,

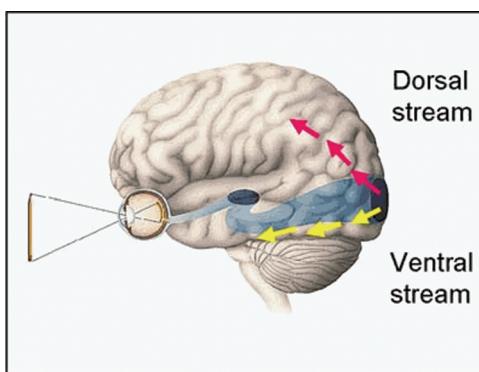


FIGURE 1.8 The retina consists of a large number of rod and cone photoreceptors. The photoreceptors synapse directly onto bipolar ganglion cells, which in turn synapse onto ganglion cells, which will then transmit signals through the optic nerve. The optic nerves from both eyes meet and cross at the optic chiasm, where information coming from both eyes is combined and then splits. Information from the right visual field (now on the left side of the brain) travels in the left optic tract. Information from the left visual field travels in the right optic tract. Each optic tract terminates in the lateral geniculate in the thalamus. The neurons of the lateral geniculate nucleus then relay the visual image via the optic radiations to the primary visual cortex. The visual cortex region that receives information directly from the lateral geniculate nucleus is called V1 or primary visual cortex. Visual information then flows through a cortical hierarchy that includes V2, V3, V4, and V5 medial temporal areas. After V1 is a further level of specialization of processing into two distinct pathways: the dorsal stream and the ventral stream occur. The dorsal stream, commonly referred to as the “where” stream, communicates with regions that control eye and hand movements. The ventral stream, commonly referred as the “what” stream, is involved in the recognition, identification, and categorization of visual stimuli.

25 mm in the orbit, 9 mm in the optic canal, and 16 mm in the cranial space before joining the optic chiasm. There, partial decussation occurs and about 53% of the fibers cross to form the optic tracts. Most of these fibers terminate in the lateral geniculate body.

1.3.3 Lateral Geniculate

The lateral geniculate nucleus (LGN) serves as a relay station in the projection of the visual pathway to the striate cortex.^{74–77} The microscopic structure of the LGN is characterized by a series of alternating gray matter and white matter layers.^{74–77} The LGN consists of six layers, with each alternating layer receiving inputs from a different eye, three layers for the left eye and three layers for the right. Layers 1, 4, and 6 correspond to information from the contralateral (crossed) fibers of the nasal visual field; layers 2, 3, and 5 correspond to information from the ipsilateral (uncrossed) fibers of the temporal visual field. The outer four layers are composed of small cells and, correspondingly, receive inputs from the small ganglion cells of the retina referred to as the parvocellular (P) ganglion cells; these cells dominate the fovea, are color sensitive, and are “fine-grained,” meaning their receptive fields are small enough that they can pick up a high level of detail. The two most ventral layers are referred to as the magnocellular layers and are composed of large cells, which receive their input from large ganglion cells referred to as the magnocellular (M) ganglion cells.^{76,78–80} These cells receive information from a wide radius of bipolar cells. They are mostly found in the peripheral retina, are insensitive to color, and are “coarse-grained,” meaning they are relatively insensitive to detail. Their main asset is that they are sensitive to motion. Therefore, it is evident that two types of information, motion versus color and form, are kept in separate layers in the LGN.

1.3.4 Geniculostriate

From the lateral geniculate body, fibers of the optic radiation pass to the visual cortex in the occipital lobe of the brain.^{73,78,81} The projections

of the magnocellular and parvocellular layers of the lateral geniculate body terminate in separate sublaminae of layer IV of striate cortex; a more superficial projection of the parvocellular layers to a narrow strip at the base of layer III (IVA in Brodmann’s terminology).^{73,78,81} Fibers carrying information from the contralateral superior visual field traverse Meyer’s loop to terminate in the lingual gyrus below the calcarine fissure in the occipital lobe, and fibers carrying information from the contralateral inferior visual field terminate more superiorly.

1.3.5 Association Cortex

As visual information passes forward through the visual hierarchy, the complexity of the neural representations increases. Whereas a primary visual cortex (V1) neuron may respond selectively to a line segment of a particular orientation in a particular retinotopic location, neurons in the lateral occipital complex respond selectively to a complete object (e.g., a figure drawing), and neurons in visual association cortex may respond selectively to human faces or to a particular object.^{77,78,81–83} Along with this increasing complexity of neural representation may come a level of specialization of processing into two distinct pathways: the dorsal stream and the ventral stream first proposed by Ungerleider and Mishkin.^{84–86} The dorsal stream, commonly referred to as the “where” stream, is involved in spatial attention (covert and overt) and communicates with regions that control eye movements and hand movements.^{84–86} More recently, this area has been called the “how” stream to emphasize its role in guiding behaviors to spatial locations. The ventral stream, commonly referred as the “what” stream, is involved in the recognition, identification, and categorization of visual stimuli.⁷⁸

1.3.6 Ocular Motor Proprioception

Nonhuman primates have eye muscle proprioceptive signals that provide information used in normal sensorimotor functions; these include various aspects of perception and of the control

of eye movement. It is possible that abnormalities of the eye muscle proprioceptors and their signals may play a part in the genesis of some types of ocular motor disorders. Studies of patients with these disorders in the course of their surgical or pharmacological treatment have yielded much interesting evidence about the central actions of the proprioceptive signals from the extraocular muscles. It is argued that such understanding of eye-muscle proprioception is a necessary part of the understanding of the physiology and pathophysiology of eye-movement control. The eye would seem to provide a unique system in which to study the way in which information derived within the brain about motor actions interacts with signals flowing in from peripheral receptors.²³ Muscle spindles are found within the proximal and distal regions of human infant and adult extraocular muscles and are located at the junction of the orbital and global layers.^{19,34,35} Palisade endings, a class of muscle receptor found exclusively within extraocular muscles, including those of humans, are located at the distal myotendinous junction of the multiply innervated non-twitch fibers of the global layer.^{19,34,35} They may be the principal source of proprioceptive feedback from extraocular muscles. Studies in the monkey suggest that proprioceptive signals ascend from the extraocular muscles to the central processing structures via the trigeminal nucleus.^{19,34,35} Based mainly on animal studies, Buttner-Ennever et al. have suggested that each layer of the extraocular muscles has its own type of sensory receptor to generate afferent signals, with the orbital layer utilizing muscle spindles and the global layer relying on palisade endings.¹⁹ These investigators also suggest that sensory signals from palisade endings form part of a proprioceptive feedback network that modulates the non-twitch motor neurons that innervate the slow non-twitch extraocular muscle fibers.

1.4 EFFERENT SYSTEM

The functional classes of eye movements are listed in Table 1.2 with their functions, stimuli, clinical tests, and latencies/speed.

1.4.1 Smooth Pursuit System

Smooth pursuit permits us to maintain a steady image of a moving object on our foveas and to thereby track moving targets with clear vision. The pathways for smooth pursuit have not been fully elucidated, but extrastriate cortex transmits information about the motion of both the target and the eyes to the dorsolateral pontine nuclei (DLPN).⁸⁷ This complex signal travels from the DLPN to the cerebellum, and from the cerebellum to the vestibular nuclei before reaching its final destination—the ocular motor nerve nuclei III, IV, and VI. Unilateral lesions along the pathway result in an ipsilateral deficit of smooth pursuit.⁸⁸

1.4.2 Saccadic System

Several forms of saccades, the fastest eye movements, can be observed: voluntary saccades to objects of interest, reflex saccades to unexpected new stimuli, spontaneous saccades that occur in normal inactive subjects, and saccades that form the quick phases of vestibular and optokinetic nystagmus.⁴⁷ Pathways descending from areas of cerebral cortex that govern saccades appear to decussate at the junction of the midbrain and pons.⁴⁷ The superior colliculus acts as an important relay for some of these projections. In the brainstem, the riMLF and the PPRF provide the saccadic velocity commands to cranial nerves III, IV, and VI.⁴⁷ Vertical and torsional components of saccades are generated in the riMLF, which is located at the mesencephalic-diencephalic junction, horizontal components are generated in the PPRF, which is found just ventral and lateral to the MLF in the pons. If an abnormality of saccadic eye movements is suspected, the quick phases of vestibular and optokinetic nystagmus can be easily evaluated in infants and young children.⁸⁹

1.4.3 Vergence System

Vergences are eye movements that turn the eyes in opposite directions (convergence, divergence, and cyclovergence) so that images of objects will fall on corresponding retinal points. Three

Table 1.2 Functional Classes of Human Eye Movements

EYE MOVEMENT	FUNCTION	STIMULUS	CLINICAL TEST	LATENCY/SPEED
Vestibular	Maintains steady fixation during head rotation	Head rotation, body, and head motion	Fixate on object while moving head	15 msec Up to 800°/sec
Saccades	Rapid refixation to eccentric stimuli	Eccentric retinal image	Voluntary movements, fast phases of OKN	200 msec 250–800°/sec
Vergence	Dysconjugate slow movements to maintain binocular vision	Binasal or bitemporal disparity, retinal blur, motion	Fusional amplitudes, near point convergence	160 msec 30–150°/sec
Optokinetic	Steadies images of the world on the retina during sustained head rotation	Head rotation, body and world movement	Optokinetic drum, motion	60 msec Supplements VOR during low-frequency movements
Pursuit	Conjugate continuous target tracking	Retinal slip (motion)	Horizontal and vertical moving target	125 msec 0–30°/sec

OKN, optokinetic nystagmus;VOR, vestibulo-ocular reflex.

major stimuli are known to elicit vergences: (1) retinal disparity that leads to fusional vergences, (2) retinal blur that evokes accommodative vergences, and (3) motion induces both disparity and accommodative vergence. The full neuroanatomic substrate for vergence eye movements remains unknown.^{19,49,90,91} Neurons in the medial superior temporal visual area (MST), the supplementary eye field (SEF), the frontal eye field (FEF), and the cerebellar vermis are active during vergence eye movements.^{39,49} MST and the caudal FEF neurons are likely to be involved in the initiation of vergence eye movements.^{46,49,91,92} Conjugate and vergence signals are generated independently and are combined at the extraocular motoneurons. Both convergence and divergence cells are found intermixed in the mesencephalic reticular formation outside the oculomotor nucleus, most within 1–2 mm of the nucleus.^{46,49,91,92} The vergence system has both a fast and a slow subsystem. Each subsystem has a different property.

The fast vergence system is best elicited by stimuli with large retinal disparity errors and/or velocities larger than 4°/sec.^{93,94} The slow vergence system is elicited by small disparity errors and/or disparity velocities of less than 3°/sec. Tectal and pretectal midbrain areas contribute to the near triad, which is simultaneous convergence, accommodation of the lens, and miosis, occurring during shifts in fixation between distance and near.^{93,94}

1.4.4 Vestibulo-Ocular System

The vestibular apparatus drives reflex eye movements, which allow us to keep images of the world steady on the retinas as we move our heads during various activities. The eyes move in the opposite direction to the movement of the head so that they remain in a steady position in space. The semicircular canals are the end organs that provide the innervation to the vestibular nuclei, which in turn drive cranial

nerves III, IV, and VI to compensate for rotations of the head.⁹⁵ In contrast, the otoliths respond to linear accelerations of the head and to gravity when the head is tilted. The principal brainstem areas of saccular nerve termination are the spinal vestibular nucleus, the lateral portion of the superior vestibular nucleus, ventral nucleus, and the external cuneate nucleus. The principal cerebellar projection is to the uvula. Principal brainstem areas of termination of the utricular nerve are the lateral/dorsal medial vestibular nucleus, ventral and lateral portions of the superior vestibular nucleus, and rostral portion of the spinal vestibular nucleus. In the cerebellum, a strong projection to the nodulus and weak projections to the flocculus, ventral paraflocculus, bilateral fastigial nuclei, and uvula are present.⁵⁰

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2

INFANTILE NYSTAGMUS SYNDROME

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*There are two unsolved questions in the neuronal physiology of nystagmus in the brainstem:
(1) The mechanism of the quick and slow phase; (2) The coordination of vestibular and optokinetic nystagmus.*

—R. Jung, discussing “Vestibular Connections in the Brainstem,” B. E. Gernandt, in *The Oculomotor System*, M. B. Bender, editor, Harper & Row, New York, 1964, p. 236

THERE ARE several types of benign nystagmus usually seen in infancy. The most common are those in the infantile nystagmus syndrome (INS; formerly known as “congenital” nystagmus [CN]). Others are the nystagmus of the fusion maldevelopment nystagmus syndrome (FMNS, formerly known as latent/manifest latent nystagmus [LMLN]) and the pendular nystagmus of the spasmus nutans syndrome (SNS). We use the nomenclature recommended by the Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group¹ that eliminates the confusing and misleading terminology of the classical names found in the literature. The CEMAS terminology, now more than a decade old, differentiates between a syndrome that includes nystagmus (often several, different types) and a specific type of nystagmus. For example, the nystagmus recorded in a patient with INS may be any combination of two or three *mechanistically different* types of nystagmus resulting in 16 specific waveforms. Using this terminology facilitates more accurate descriptions of each

type of nystagmus when required (e.g., pendular, pursuit-system nystagmus) while still allowing for the inclusion of several types found in each syndrome by simply appending the word “nystagmus” to the syndrome (e.g., INS nystagmus). Similarly, the shorthand “IN” is a general description encompassing all of the specific types of nystagmus possible in the INS; the same applies to “FMN.”

INS contains the most common types of benign nystagmus of infancy. Its constellation of waveforms and clinical signs allow positive identification using eye-movement recordings, but similarities in both areas to other types of nystagmus of infancy can result in misdiagnosis if the patient workup is limited to clinical signs alone. The past half-century has brought about remarkable advances in our understanding of the ocular motor system (OMS), both normal and abnormal. That can be directly traced to two things: (1) the development of accurate eye-movement measurement systems and (2) the application of the engineering approach to study neurological control. Engineering is a discipline

whose objective is to take what is either known or observed and use it to solve problems; the objective in science, on the other hand, is to understand the basic origins of nature.² Pioneers in the study of normal ocular motility were Larry Stark (who first applied control systems to model the normal pupillary response), his student, Laurence Young, and David Robinson (both of whom applied control systems to model the normal OMS). Each of these researchers was either an engineer or had engineering training. Because of Dell'Osso's interest in INS, he was the first to use his engineering training and apply control systems to model an abnormal OMS (i.e., one containing an internal oscillation simulating INS). The resulting behavioral model, and those that followed, demonstrated how, despite an internal oscillation, the OMS of INS patients was capable of accurately responding to pulse, pulse-step, step, ramp, and step-ramp target inputs.^{3,4} Each of these bioengineering pioneers used the top-down approach to modeling, concentrating on the functions necessary in each system rather than the details of the neurophysiology at each level or the anatomical sites of each group of neurons. Many of their students subsequently also applied the engineering approach to lower level portions of each functional block in the OMS (i.e., the bottom-up approach).

However, the goal of bottom-up modeling is as unachievable as it is misdirected. Duplication of an actual brain (~100 billion [10^{11}] neurons with 100 trillion [10^{14}] synapses) or even the billions of neurons and trillions of synapses comprising the OMS requires a complexity and magnitude of computer functions and interconnections that is unrealizable now, or for the foreseeable future. Even if that were not so, bottom-up (so-called neuromimetic—the action of a drug that mimics the response of an effector organ to nerve impulses) modeling of neurophysiological control perpetuates the fundamental mistake that classical behaviorism made, of commencing from the simple and moving upward. Paraphrasing the opinions of Thorne Shipley (1927–2009),⁵ nature has already solved for us the problem of going from the small and creating the complexities of human neurophysiology. Our task in modeling is to go the other way; it

is our destiny. Top-down modeling allows us to comprehend complex behavior. We do not wish to make virtual models of humans, to replace or remodel reality.

One key finding from the earliest INS model was that the OMS could not be adequately modeled as a simple retinal error-driven control system because, if that were the case, any oscillation would produce the perception of oscillopsia (world movement).^{3,4} INS patients do not normally experience oscillopsia; therefore, to make an OMS model that accurately responded to the above visual target inputs, it was necessary to use feedback of the outgoing motor signal (efference copy) to eliminate the effects of the unwanted retinal motion on the perceived target signal. Thus, the OMS responds to a “reconstructed perception” of target position and velocity, not directly to retinal error position and velocity. An OMS model based on efference copy has no oscillopsia (i.e., there exist internal signals that accurately reflect target position and velocity without the confounding oscillatory motion of the retina). Such models can also simulate the responses to nonvisual target inputs such as pursuit of the perceived absent hub of a “wheel” that consists of only its circular outline moving across the visual field; retinal error models cannot, since there is no “error” signal.

This chapter summarizes the results of relevant INS research conducted over the past 45 years that forms the foundation for the diagnostic criteria and therapies presented in Chapters 5 and 7, respectively. Sharply focused research studies posing mechanism-based questions of individual (or a small subset of) INS patients form the foundation for our present understanding of the mechanisms of INS, its accurate diagnosis, characteristics, etiology, objective measurements, and effective treatments; the order of the topics in this chapter was chosen to reflect this. Such “basic” clinical research is different from the evidence-based, statistical studies traditionally employed during interventional drug-related trials; the latter are necessary but not science⁶—the systematic study of the structure and behavior of the physical and natural world through observation and experiment. By their nature, clinical trials usually do

not address the types of questions necessary to advance both our understanding of underlying mechanisms of diseases but do have their place in determining effectiveness and the application of specific therapies to ameliorate their dysfunction. In addition, because the nature of our INS research combines both basic and clinical science, those restrictive adjectives were neither used nor considered in the organization of this chapter. A complete review of the literature on infantile nystagmus is not our purpose; that, along with other types of nystagmus and saccadic intrusions and oscillations can be found elsewhere.^{7–12} Finally, the results of this research have provided us with the answers to Jung's questions (see epigraph).

2.1 CHARACTERISTICS OF INFANTILE NYSTAGMUS SYNDROME

2.1.1 History and Background

Early research in INS was accomplished using electro-oculography (EOG) and allowed visualization of some of the waveforms exhibited by patients with INS. Because of alternating-current coupling, exact eye position was not retrievable from these records and the bandwidth was too low to reproduce the higher frequency components of INS waveforms. Therefore, these data provided little insight into the mechanism(s) causing the oscillations or of how visual acuity could be at or near normal levels in some INS subjects. Reliance on clinical observation alone gave rise to a number of *ophthalmological myths* about INS, its characteristics, and the effects of therapies that would not be disproven until the advent of more modern eye-movement data and data-analysis techniques.

2.1.1.1 ANCIENT DESCRIPTIONS AND THEORIES

The word *nystagmus* is derived from the Greek νυσταγμός (meaning “drowsiness”), which is derived from νυστάζειν (“to nod in one’s sleep”). The earliest description of head nodding with nystagmus was by Hadden in 1890,¹³ although

Zivatofsky uncovered what may be the earliest description of nystagmus dating as far back as 1,500 years ago.¹⁴ It was in a Talmudic account of albinism, photophobia, and nystagmus in a population living along the River Tigris. In the more recent past, the distinguished neuro-ophthalmologist Wilbrand once advised “never write on nystagmus, it will lead you nowhere.”¹⁵ Kestenbaum (a very astute observer) contributed much to the understanding of nystagmus in general and INS in particular.¹⁶ Kestenbaum’s book is a “must read” for all serious INS investigators, first, to familiarize themselves with what was observed and postulated before the modern era and second, to prevent “reinventing the wheel.” It contains a wealth of information with key insights continually emerging with each reading. Slightly later, Anderson, Bender, Jung and Kornhuber, and Cogan also made significant contributions despite the absence of modern, accurate eye-movement recording systems.^{17–20}

The nystagmus comprised in the INS is usually present at birth or noted in early infancy during the various sensitive periods defining the development of visual fixation,²¹ and it persists throughout life. The syndrome consists of one or more types of nystagmus with characteristic waveforms, head turns, tilts, or oscillations. Rarely, the nystagmus becomes manifest later in life,²² so the term “congenital” cannot be taken literally but rather as a congenital “predisposition” for this nystagmus. Unfortunately, it was one of Cogan’s papers²³ that led to overly simplistic, erroneous, and stubbornly persistent misinterpretations of the origins and characteristics of INS that were unintended, and later disavowed, by Cogan.²⁴ It was theorized that there were two types of INS (then called “congenital nystagmus” or “CN”); they were called “sensory-defect” and “motor-defect” (also known as “idiopathic”) CN, respectively. The first, “sensory nystagmus,” was putatively caused by an afferent defect in the visual system and was applied to INS patients who exhibited an associated sensory visual disorder. It was originally proposed that, in sensory nystagmus, the poor visual acuity interrupts sensory afferent input to the ocular motor control system, which

causes fixation to become unstable and leads to a pendular oscillation of the eyes. The second, “motor nystagmus,” implied that the oscillation is driven by a primary abnormality within the ocular motor circuitry and was applied to INS patients in whom the sensory visual system appears intact both clinically and electrophysiologically. Motor nystagmus was attributed to signal errors intrinsic to the ocular motor control centers, leading to a jerk nystagmus with relatively good visual acuity. However, the myth that the presence or absence of a primary sensory deficit can be predicted on the basis of the clinical appearance (i.e., pendular versus jerk nystagmus) has long been dispelled.²⁴ In fact, eye-movement recordings demonstrated that the specific types of nystagmus found in the INS had the *same* waveforms and underlying mechanisms, regardless of the coincidental/facilitating existence of any sensory deficits in both children and adults.^{25–27} INS is the direct result of an ocular motor control instability that may develop with or without an accompanying sensory deficit (see Section 2.2.3). Thus, where INS and a sensory deficit coexist, the latter is a subordinate factor in the development of the nystagmus, perhaps interfering with the normal calibration of one or more of the ocular motor subsystems, thereby precipitating instability. Eye-movement recordings of infants when they are attending to a visual task confirm that the development of foveation periods in INS waveforms begins early in infancy as acuity and fixation develop.

The presumption that a sensory defect could cause INS was made because of the association between INS and one or more afferent defects that were present in many, but not all, patients.

Pendular and jerk waveforms often coexist in the same individual with INS, so that waveform analysis alone cannot be used to predict the presence or absence of afferent visual pathway dysfunction.^{25,26} In the case of INS, all of the known waveforms have been recorded in patients with and without sensory visual deficits.^{28,29} INS has also been recorded in patients with visual acuities ranging from 20/20 to no light perception. Thus, infantile nystagmus does not “result” from poor acuity. Similarly, the age of onset for the nystagmus cannot be used to

predict the presence or absence of an underlying sensory visual deficit. The neurophysiological mechanism by which abnormal sensory visual input from both eyes precipitates or “unhinges” INS is unknown, although it is our hypothesis that the ocular motor subsystems require calibration and, in most individuals, poor visual input interferes with that calibration; in others, even excellent visual input is insufficient to aid in that calibration. This confusion of genetic association with true causality was unfortunate and resulted in further muddying of the waters when attempts were made to relate etiology to assumed waveform (see Section 2.1.2.1).

It is obvious that an afferent defect and the presumed failure to develop fixation reflexes cannot possibly explain a motor oscillation that is present at birth, as it is in some INS patients. The reasoning behind the assertions that nonvectorial defects such as achromatopsia, aniridia, blurring due to cataracts, ocular albinism, and so on should invariably result in the highly vectorial horizontal INS is obscure at best; no specific mechanisms have ever been proposed to explain exactly how nonvectorial sensory deficits could cause a vectorial oscillation (e.g., horizontal INS). Since many patients with INS have either minimal or no sensory defects, it follows that such defects are *not necessary* conditions for INS. Also, since many patients who have the aforementioned sensory defects do not have INS, these defects are *not sufficient* conditions for INS. Since they are neither necessary nor sufficient, they cannot be considered *causal*. Further discussion of the genesis and mechanisms of INS appears in Section 2.1.2.

2.1.1.2 CONNECTION TO FIXATION ATTEMPT

The effects of fixation, eyelid position, or ambient light on IN have long been areas of confusion. Different investigators arrived at contradictory conclusions concerning both or that IN might persist in darkness but not behind closed lids.³⁰ However, when the experiments were repeated while controlling for the subject’s visual and ocular motor intentions, it was found that the *attempt* to fixate or direct the eyes in a given direction

was the determining factor in the genesis of IN.³¹ This is independent of lid position or ambient illumination and provides an explanation for the observation that IN could sometimes cease completely when a subject is not attending to visual or ocular motor tasks (i.e., while “daydreaming”). It is also consistent with the common observation that any increased arousal or stress (anxiety, fear, anger, etc.) usually exacerbates IN.

Although visual problems themselves are not causal, they may represent simple genetic association and contribute to the intensity of the nystagmus. Most waveforms of INS nystagmus represent a high-gain instability in a slow-eye-movement subsystem,³² but “fixation attempt” (the effort to see) is the main driving force. The initial observation that increased fixation attempt exacerbated IN was made while patients attempted to read visual acuity charts; it did not separate the increasing visual demand with each smaller line from the stress associated with reading it accurately. Poor vision could increase fixation effort and the accompanying stress increase the intensity of the nystagmus.³¹ Moreover, a subclinical motor instability may become manifest by this exaggerated visual effort. The observation that IN sometimes persists with eyes open in darkness (when the subject will probably attempt to “see”) and damps behind closed lids (when the subject will, unless instructed to the contrary, reduce any attempt to “see”) is compatible with its genesis.³³ Because the defining criterion is fixation attempt, *not* retinal illumination or lid position, reports of the absence of nystagmus with lid closure or darkness without a description of the instructions to the subject, provide little useful information. Abel et al. demonstrated that although fixation attempt was responsible for the genesis of IN, stress was the key factor affecting the resulting intensity of IN.^{34,35} Because the driving force in IN is fixation attempt or effort, with or without actual fixation, IN is *not* a “fixation” nystagmus.

2.1.1.3 MODERN PHYSIOLOGICAL INVESTIGATION

The modern era of INS research began in the 1960s with the advent of accurate eye-movement

recording systems and the control-systems approach. Eye-movement data were analyzed with the intent of determining the underlying control-system mechanisms and producing a model of the OMS capable of simulating both normal and abnormal responses to controlled visual target inputs.³

2.1.2 Waveforms, Models, and Mechanisms

Quantitative ocular motor data have identified three underlying mechanistic slow-eye-movement defects that produce nystagmus: high gain instability, visual-vestibular tone imbalance, and integrator leak.

In some persons, because of abnormally high gain in a slow-eye-movement subsystem, a runaway (increasing velocity) movement or a pendular oscillation is evoked. The term “high gain” can also imply excessive delay for the gain present (i.e., the control loop may have a normal gain but an increased delay). Control theory suggests how particular changes in gain can result in either a pendular or a jerk nystagmus. Pendular nystagmus can be “congenital” (see Section 2.2) or acquired, whereas horizontal jerk nystagmus with slow phases of increasing velocity usually is associated with “congenital” nystagmus; however, the latter may result from an Arnold-Chiari malformation.³⁶ Vertical nystagmus with an exponential slow phase of increasing velocity may be secondary to acquired cerebellar disease.³⁷

Tonic imbalance of the visual-vestibular subsystem (i.e., the combined optokinetic and vestibular subsystems) results from the imposition of asymmetric input on an inherently normal horizontal gaze generator. If one vestibular apparatus (labyrinths, nerve, and brainstem nuclei) functions abnormally, if both sides are asymmetrically defective, or if there is a central imbalance of the optokinetic subsystem, such an asymmetric input results. The nystagmus produced has a linear (straight line) slow phase, reflecting a persistent tone to drive the eyes toward the side of the relatively damaged vestibular apparatus. The slow-phase amplitude is reduced by fixation and enhanced by darkness, Frenzel (high-plus)

lenses, or closing the eyes. Fixation inhibition may be related to an opposing smooth-pursuit force and requires the integrity of the cerebellar flocculus.

“Leaky integrator” nystagmus occurs only in an eccentric gaze position; thus, it is gaze-evoked (also called “gaze-paretic”) nystagmus. The eyes are unable to maintain the eccentric position and drift back to the primary position with a decreasing velocity, reflecting a passive movement resisted by the viscous forces of orbital soft tissues. The defect may reside in the brainstem “neural integrator” or its connections (such as in the cerebellum), which mediate eye deviation.

One can classify nystagmus based on whether it is “gaze evoked” or “gaze modulated”; the former category requires that there be no primary-position nystagmus. INS, FMNS (see Chapter 3), physiologic types (vestibular), and symptomatic types (vestibular) fall in the gaze-modulated category. Some physiologic types (end point) and symptomatic types (gaze paretic) are gaze evoked. Although these concepts of a control mechanism represent useful approaches toward a more meaningful classification of nystagmus, they are far from inclusive.

2.1.2.1 WAVEFORM TYPES

The recognition of INS is of extreme importance, particularly in the adult patient, and it

may obviate unnecessary neurodiagnostic procedures; its characteristics are listed in Table 2.1. INS is almost always binocular and rarely shows more than minor amplitude dissociation between the two eyes. Clinically, the nystagmus usually appears uniplanar. Like vestibular end-organ nystagmus, horizontal nystagmus remains horizontal when the eyes are deviated vertically and does not convert to vertical nystagmus. Unfortunately, clinical observation can only provide superficial, and often incorrect, characteristics of INS waveforms. In “pendular” nystagmus, the eyes appear to oscillate with “equal speed” in either direction and in “jerk” nystagmus, movement in one direction appears faster than in the other; unfortunately, some jerk nystagmus waveforms appear clinically to have equal speed in both directions, resulting in misdiagnoses.

Even with oculographic recordings, the direction of the fast phase may be misinterpreted unless velocity tracings are obtained.³³ In the absence of oculography, clinicians should describe the nystagmus carefully at different gaze angles, during convergence, and over time. The inability to accurately differentiate pendular from jerk INS waveforms using clinical observation alone was further evidence that one could not equate “pendular” waveforms with the so-called sensory CN and jerk waveforms with the so-called motor CN. Monocular

Table 2.1 Characteristics of Infantile Nystagmus

Binocular with similar amplitude in both eyes
Usually horizontal and torsional (vertical rare)
Pendular or increasing velocity slow phases
Distinctive waveforms with foveation periods and braking saccades
Asymmetric aperiodic alternation possible (Baclofen ineffective)
Provoked or increased by fixation attempt
Abolished in sleep or inattention to visual tasks
Gaze modulated, not gaze evoked
Diminished (damped) by gaze-angle or convergence nulls
Superimposition of latent component possible
“Inversion” of the optokinetic reflex (actually, null-shift-induced reversal of the infantile nystagmus)
Associated head oscillation (not compensatory) or turn
No oscillopsia except under rare conditions

visual deprivation induced, in some monkeys, a diagonal nystagmus whose horizontal component initially looked like FMN slow phases (see Chapter 3) and then developed to resemble IN slow phases. The deprivation took place from birth to 25 days and was followed by monocular deprivation of the other eye.³⁸ In monkeys, the role of the NOT in FMNS has been more clearly defined.^{39,40}

True pendular nystagmus is sinusoidal, and true jerk nystagmus begins with a slow phase *away from* the object of regard, followed by a fast, corrective (saccadic) phase *toward* the target. Despite the slow-phase genesis of all types of nystagmus, the direction of the fast component is used, by convention, to define the nystagmus direction. Although nystagmus can be described when the globes are inspected under slit-lamp magnification, or when the fundus is viewed, due to the complexity of INS waveforms and the probability of combinations of different types of nystagmus, only ocular motility recordings can guarantee accurate and repeatable diagnosis and assess complex waveform characteristics. It should be noted that nystagmus amplitude and intensity are purely cosmetic measures and do not accurately represent the potential visual acuity of INS waveforms. To do so, a foveation function, such as the eXpanded nystagmus acuity function (NAFX) is required since wavelet analysis is too insensitive and failed to identify the important foveation periods in INS waveforms.⁴¹ One should note the positions of gaze in which the nystagmus occurs and whether the intensity changes with gaze direction. Jerk nystagmus usually increases in amplitude upon gaze in the direction of the fast component, a characteristic referred to as Alexander's law⁴² (see Sections 2.2.3.1 and 2.2.3.2).

Accurate methods of ocular motility recording allowed identification of the various INS waveforms; this resulted in the ability to definitively diagnose INS and differentiate it from other types of nystagmus, both benign and symptomatic. A total of 12 waveforms were identified, not simply pendular or jerk, as had been claimed based on clinical observations alone.²⁵ Although INS waveforms could be classified into the general categories of pendular or jerk,

there are sufficient differences to further subdivide the latter into unidirectional and bidirectional jerk waveforms. The latter almost always have the clinical appearance of pendular IN and led to the clinical misimpression that pendular waveforms were more prevalent than they actually are.²⁵ In a study of 224 patients with INS Abadi et al. found conjugate, uniplanar horizontal oscillations were present in 174 (77.7%) while 32 (14.3%) had a torsional component.^{29,43} The most common oscillation in their group was a horizontal jerk with extended foveation ($n = 49$; 27%).

Eye-movement recordings of INS occasionally show a pure pendular waveform (sinusoidal) or a sawtoothed waveform (equiamplitude linear slow phase with foveating saccade) typically seen in vestibular nystagmus. These pure forms are neither frequent nor pathognomonic for INS. More often, INS manifests distinctive waveforms that are not present in acquired nystagmus. Complex INS waveforms are an expression of the attempts by the ocular motor control system to achieve and increase foveation time, imposed on inherently unstable slow control. The INS waveforms shown in Figures 2.1–2.3 (other than pure pendular or jerk) have never been recorded in acquired horizontal nystagmus.^{25,29} The target position is indicated by a dashed line; target position is problematic for pure and asymmetric pendular waveforms.

Our research and OMS modeling demonstrated that most of the INS pendular and jerk waveforms were manifestations of a single sinusoidal (pendular) velocity oscillation in the damping-control feedback loop of normally underdamped, smooth pursuit.^{4,44–52} Based on these recent demonstrations that most INS waveforms are derived from the same pendular velocity oscillations of an undamped smooth pursuit system and the documentation of a "dual-pendular" INS waveform, the original morphologically based classification can now be related to presumed ocular motor etiology (Figs. 2.1–2.3). This regrouping required differentiating linear slow phases from the more common accelerating slow phases of jerk nystagmus, based on presumed mechanisms (visual-vestibular and pursuit-system, respectively).

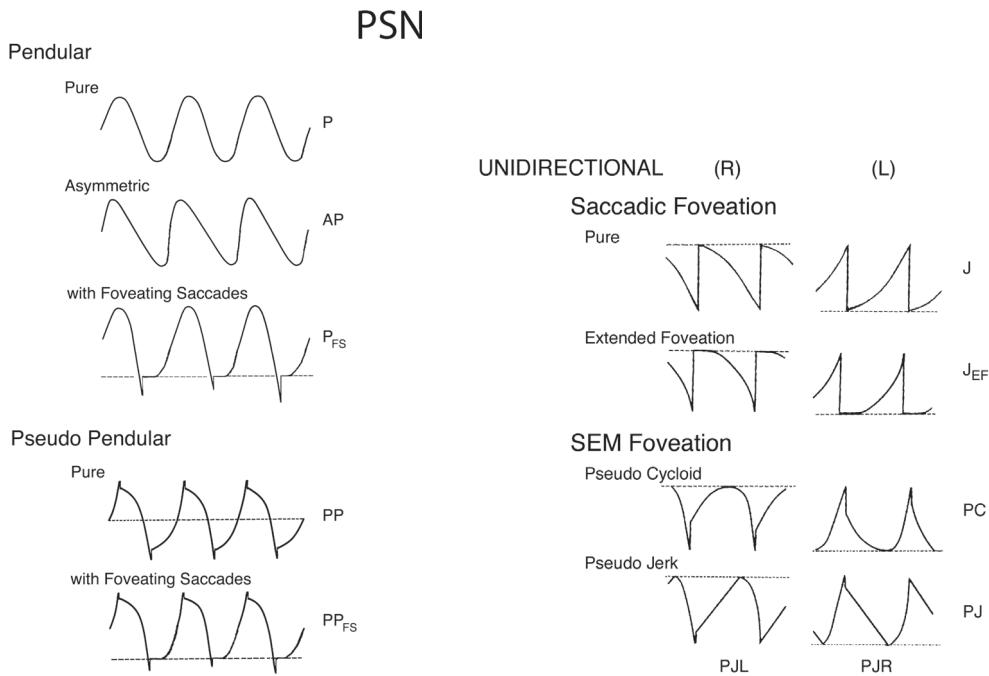


FIGURE 2.1 Illustrations of pendular and unidirectional jerk infantile nystagmus syndrome (pursuit-system nystagmus [PSN]) waveforms. Note the *accelerating* slow phases. Target (foveation) position shown by dashed lines. In all figures, by convention, eye motion to the right, up, and clockwise is up, and to the left, down, and counterclockwise is down; all directions are from the patient's point of view. When not labeled, data are from the foveating eye. AP, asymmetric pendular; J, jerk; J_{EF}, jerk with extended foveation; L, left; P, pendular; PC, pseudocycloid; P_{FS}, pendular with foveating saccades; PJ, pseudojerk; PP, pseudopendular; PP_{FS}, pseudopendular with foveating saccades; R, right.

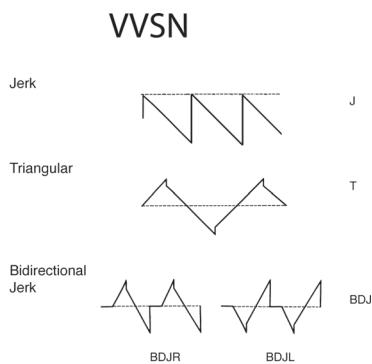


FIGURE 2.2 Illustrations of jerk infantile nystagmus syndrome (visual vestibular system nystagmus [VVSN]) waveforms. Note the *linear* slow phases. Target (foveation) position shown by dashed lines. BDJ, bidirectional jerk; J, jerk; L, left; R, right; T, triangular.

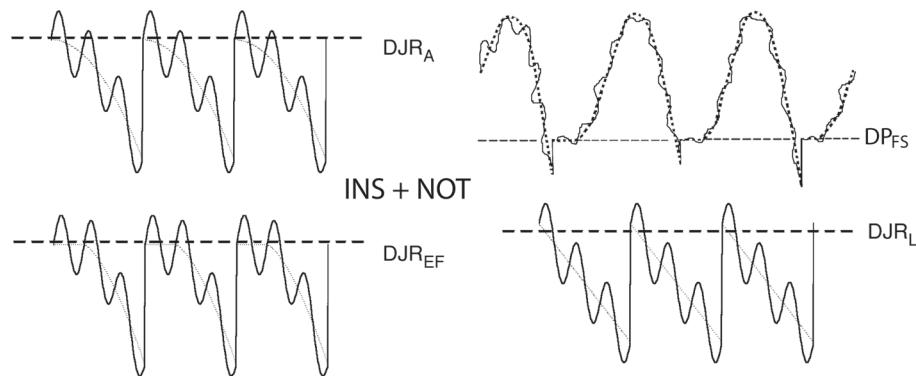


FIGURE 2.3 Illustrations of dual-jerk and dual-pendular INS + NOT waveforms. The DP_{FS} , DJR_A , and DJR_{EF} are pursuit-system nystagmus (PSN) and the DJR_L is visual vestibular system nystagmus (VVSN). DJR_A , dual-jerk right with accelerating slow phases; DJR_{EF} , dual-jerk right with extended foveation; DJR_L , dual-jerk right with linear slow phases; DP_{FS} , dual pendular with foveating saccades; INS, infantile nystagmus syndrome; NOT, nucleus of the optic tract.

The presence of dynamic overshoots in the fast phases (saccades) of INS waveforms (and in normal saccades) is both idiosyncratic and variable; for simplicity, we have not included them in Figures 2.1–2.3. Because dynamic overshoots are not an abnormality per se, their presence does not represent a “different” waveform.

The nine waveforms shown in Figure 2.1 are due to pursuit-system instability and are, therefore, “pursuit-system nystagmus” (PSN—Pendular and Pseudo Pendular and PSN—UNIDIRECTIONAL). The three in Fig. 2.2 are due to visual vestibular imbalance and are “visual vestibular system nystagmus” (VVSN). In addition, the four “dual” waveforms (PSN + NOT [DP_{FS} , DJR_A , and DJR_{EF}]; and VVSN +NOT [DJR_L]) shown in Fig. 2.3 are due to the low-amplitude, high-frequency pendular “nucleus of the optic tract” (NOT) nystagmus added to one of the pendular and three of the jerk INS waveforms shown in Figures 2.1 and 2.2 (although other combinations may occur, they have not yet been recorded). The term “dual” in the names refers to either (1) the two independent mechanisms (NOT instability plus either PS oscillation or VVS imbalance) responsible for the resulting nystagmus or (2) the superimposition of two waveforms (high-frequency, low-amplitude pendular plus the INS waveform identified in the particular

name). The dual-pendular nystagmus (DP_{FS}) was identified from the first recording of a high-frequency, pendular NOT nystagmus superimposed on a low-frequency, pendular with foveating saccades IN; it is shown in Figure 2.4 (see also Fig. 2.7 bottom right). Twelve of these waveforms are pathognomonic of INS; P, AP, J_L, and DJ_L are not.

For pendular waveforms, the target is foveated at the peaks that are more flattened, indicating extended foveation. The demonstration of extended foveation in an adult with lifelong nystagmus secondary to a congenital brainstem hamartoma and in an adult given gabapentin for treatment of nystagmus secondary to an arteriovenous malformation⁵³ supports the hypothesis that extended foveation periods in INS waveforms represent the action of a *normal* fixation system on the underlying INS oscillation. The pure pendular (P) and jerk (J) waveforms in Figures 2.1 and 2.2 are not conducive to good acuity because of the extremely short foveation times. Although these are common acquired waveforms, when afflicted with INS, the developing nervous system “modifies” pendular and jerk waveforms; therefore, foveation time (and thus acuity) is increased. Figure 2.5 demonstrates how these resultant waveforms serve to increase the time of foveal imaging. In the pendular nystagmus with foveating saccades

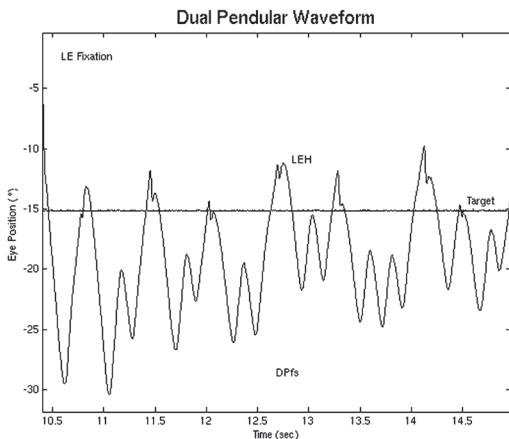


FIGURE 2.4 Illustration of the dual pendular with (leftward) foveating saccades (DPfs) INS + NOT waveform. It consists of an $\sim 5^\circ$, 3.5 Hz pendular NOT nystagmus superimposed on an $\sim 15^\circ$, 2 Hz pendular with foveating saccades INS waveform. DPfs, dual pendular with foveating saccades; H, horizontal; INS, infantile nystagmus syndrome; LE, left eye; NOT, nucleus of the optic tract.

waveform (P_{FS} —leftward foveating saccades shown), there is usually a substantial period of time after the foveating saccades when the target is imaged on the fovea and the eye is motionless (after instants 0 and 3 on the time axis). In jerk-right nystagmus with extended foveation (JR_{EF}), the position from times 0 to 1 or after 3 are when foveation takes place, and in the bidirectional jerk-left (BDJL) waveform, the position from instants 4 to 5 is conducive to good acuity.

Both adults and infants show dramatic changes in waveform when going from fixation to a state of low arousal.²⁹ In Figure 2.6, the INS waveforms of several subjects are shown. During fixation the waveforms were jerk or dual jerk with amplitudes up to 8° peak to peak and frequencies of 2–4 Hz, whereas during the low state of arousal the waveform became pendular, the amplitudes rose to 15° to 60° , and the frequency dropped to about 1 Hz. IN may

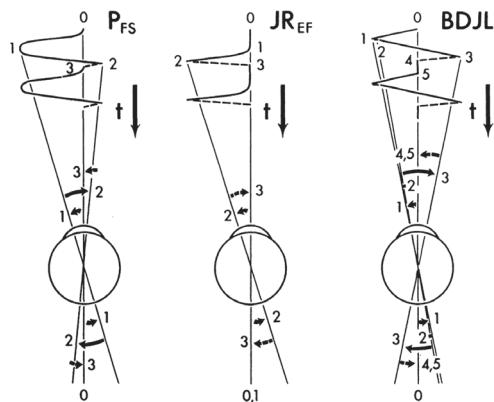


FIGURE 2.5 Illustrations of three infantile nystagmus syndrome waveforms with their respective eyeball rotations showing the periods of extended foveation following each waveform's foveating saccade. In the pendular with foveating saccades (P_{FS}) and jerk right with foveating saccades (JR_{EF}) waveforms, the foveation periods after foveating saccades “2–3” and in the bidirectional jerk-left (BDJL) waveform, after foveating saccade “3–4.”

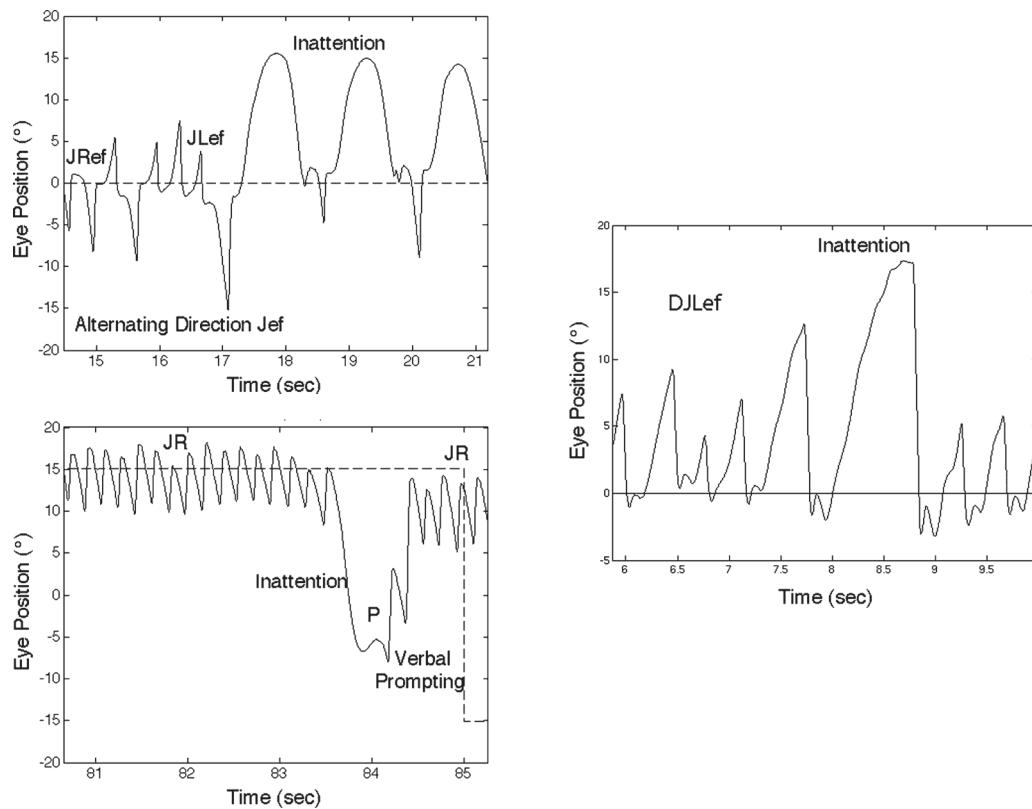


FIGURE 2.6 Illustrations of infantile nystagmus syndrome waveform changes of three patients during periods of inattention (pursuit-system nystagmus) waveforms. Target (foveation) position shown by dashed lines (left top and bottom) or solid line (right). DJ, dual jerk; J, jerk; Jef, jerk with extended foveation; L, left; P, pendular; R, right.

also be present during various stages of sleep. This dramatic slowing and/or damping of IN with inattention results in intervals of data that must be eliminated from analysis when attempting to assess the potential visual acuity of the patient's INS waveform during visual attention to a nonstressful target (e.g., a laser spot or LED). That, and the possibility of alternation of the fixating eye during an interval of attempted fixation on a target, precludes accurate, automatic analysis of long intervals of eye-movement data if that analysis is to correlate to visual function. We typically analyze only 2–5 seconds of data from the fixating eye (easily determined from monocularly calibrated eye-movement data) at each fixation point and do so several times to ensure accuracy. One cannot presume the “dominant” or “favored”

eye always accomplishes that fixation; in fact, eye-movement data show that it often does not. Analysis of the nonfixating eye cannot be used to predict visual function.

It should be emphasized that the superimposed pendular component of dual-jerk or dual-pendular INS waveforms is not synonymous with the pendular INS waveforms. The latter are of lower frequency and higher amplitude than this superimposed pendular component of dual waveforms, suggesting different mechanisms and sites of origin. Another distinction is that pendular INS waveforms may be improved by braking and foveating saccades. In fact, Tusa et al. demonstrated in monkeys that this low-amplitude, high-frequency pendular nystagmus was due to an abnormality in the circuitry of the NOT.³⁸ This NOT nystagmus may appear super-

imposed on either INS or FMNS (see Chapter 3) waveforms and, when INS is damped (e.g., due to convergence, gaze angle, or time variation), the NOT nystagmus may persist or be damped to a lesser degree (Fig. 2.7). The data in the top panel are from identical twins who both showed INS damping with convergence but little damping of the NOT component. The bottom panel is from a patient with only a *uniocular* NOT component that also damped minimally compared to the INS component. The bottom data show both DJ and DP waveforms at near, the latter, due to inattention. These observations support several conclusions. First, the mechanisms for NOT and pendular INS waveforms differ. Second, neuroanatomical sites may also differ. Finally, based on Figure 2.7, the responses of NOT and INS waveforms to therapy can differ,

making accurate diagnosis of the nystagmus critical before attempting to determine the best therapy or assess its effects on the INS waveform (see Chapter 7).

Figure 2.8 shows outputs from our behavioral OMS model during fixation at 0°. As shown in the top left and right panels, these model outputs accurately simulate patient eye-movement recordings of different waveforms. The bottom panel demonstrates the accuracy of foveation periods in PP_{FS} and J_{EF} waveforms as well as the transitions from PP_{FS} to either JR_{EF} or JL_{EF} including centripetally accelerating slow phases, as gaze is directed to the right or left of the neutral zone, respectively. Bias shifts that alter the foveation periods from one side of a pendular nystagmus to the other (common in INS) are simulated during fixation on the target 5° to the

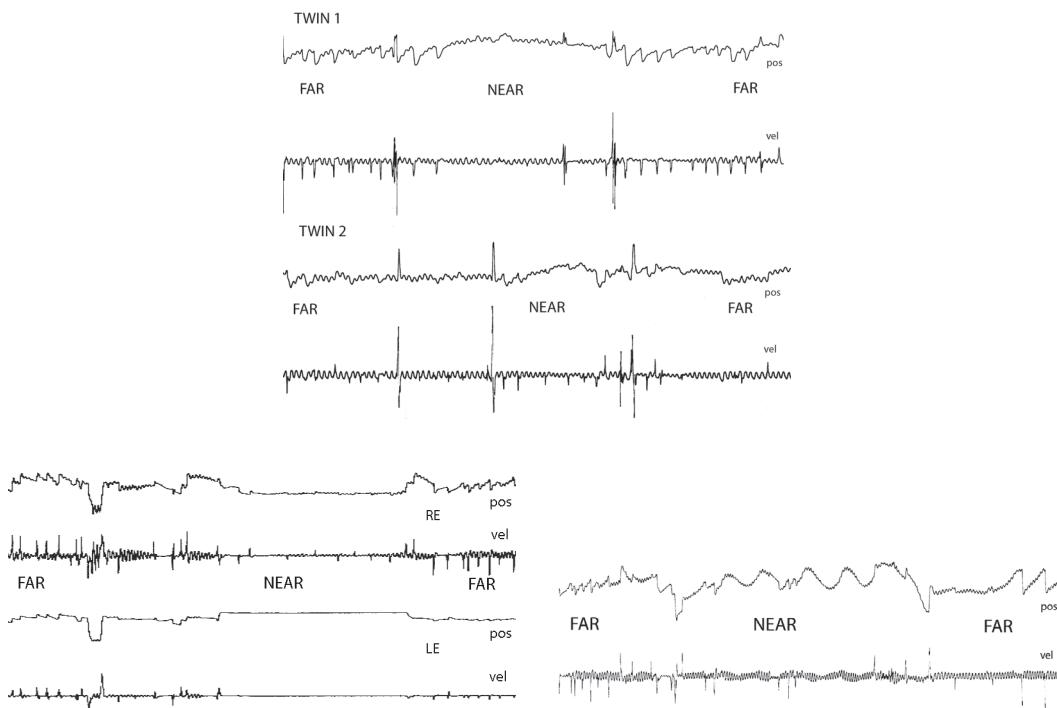


FIGURE 2.7 Illustrations of the effects of convergence on both the infantile nystagmus syndrome (INS) (1.5 Hz) and nucleus of the optic tract (NOT) (5 Hz) components of dual-jerk and pendular waveforms in identical twins (top) and a patient with a *uniocular* NOT (8 Hz) component (bottom). Both twins show greater INS-component damping than NOT-component damping. The *uniocular* NOT component in the bottom tracings also was damped less than the INS component. The dual pendular waveforms (INS, 0.5 Hz) at near occurred when the patient was inattentive (bottom right tracings). Note the square-wave jerk during the far to near transition. Large spikes in the data are due to blinks. LE, left eye; RE, right eye.

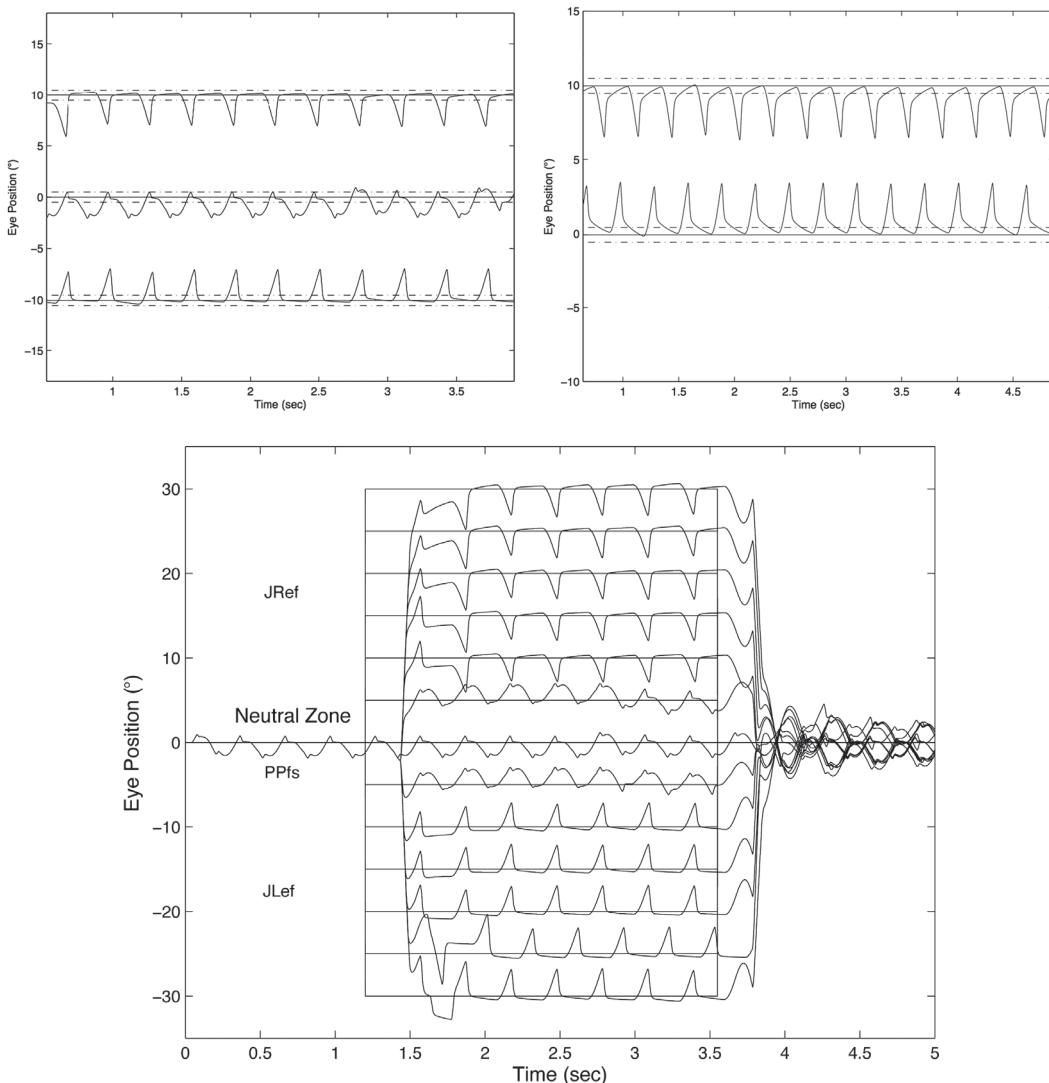


FIGURE 2.8 Behavioral ocular motor system model simulations of foveation accuracies and waveform transformations at different gaze angles. In top left panel, accurate foveation at 0° with pseudopendular with foveating saccades (PP_{fs}), jerk-right nystagmus with extended foveation (JR_{EF} [upper trace]), and jerk-left nystagmus with extended foveation (JL_{EF} [lower trace]) are shown (the latter two shifted for clarity). In the top right panel, right pseudocycloid (RPC [upper trace]) and left pseudopsycloid (LPC [lower trace]) are also shown with RPC shifted. In the bottom panel, both waveform transitions from PP_{fs} to $JRef$ and $JLef$ and amplitude increases are shown as gaze is directed away from the neutral zone. Note the bias shift at 5° . Foveal extent ($\pm 0.5^\circ$) is indicated by dash-dot lines.

right; this is one of the many emergent properties of the model.

In an attempt to determine whether the pendular part of dual-jerk waveforms was truly sinusoidal, Reccia et al. used spectral analysis.⁵⁴ Unfortunately, the data were obtained using

low-bandwidth, bitemporal EOG. By subtracting the power spectrum of a pure sawtooth waveform from the dual-jerk waveform, the authors were able to emphasize the pendular component. Their statistical analysis concluded that a sinusoidal fit would better approximate

the data than an exponential fit; the latter was suggested by Optican and Zee in their attempt to model one of the waveforms of INS.^{10,55}

Sensitive techniques for recording torsional eye movements documented small but significant torsional components in the nystagmus of subjects previously thought to have purely horizontal INS.⁵⁶ Because the prominent horizontal movement masks the usually smaller torsional component, the latter appears to be a common characteristic of “horizontal” INS. In most patients, rightward movements were accompanied by clockwise torsion and leftward movements by counterclockwise torsion.⁵⁷ We also documented a subclinical seesaw nystagmus in INS (see Fig. 2.15 in Section 2.1.10).⁵⁸

2.1.2.2 BRAKING AND FOVEATING SACCADES

One important feature of INS waveforms is the presence of “braking saccades” that act to stop runaway slow phases. Braking saccades serve to brake, or even stop, IN slow phases. Their identification in a study of INS waveforms uncovered a stimulus for saccades that was unknown prior to that point.⁵⁹ That is, saccades could serve solely to stop runaway eye movements rather than their normal function to reposition the eyes. In INS waveforms, braking saccades could perform both functions simultaneously; they are then called “foveating saccades.” Subsequent studies demonstrated that braking saccades were triggered by eye velocity approximately 40 msec prior to their execution and did effectively brake the slow phases of IN.⁶⁰ They are triggered by extraretinal eye-velocity information and when the superimposed slow-phase velocities are taken into account, braking saccades have the same velocity-amplitude characteristics as normal saccades and are generated by the same mechanism; the latter was demonstrated using an OMS model.⁶¹

2.1.2.3 THE FOVEATION PERIOD

More important than the various waveforms was the demonstration that during each IN cycle the eyes begin on target and remain

there for some time before the oscillation causes them to accelerate away from the intended position.³¹ These “foveation periods” are repeatable and could last several hundred milliseconds. This demonstration by retinal cinematography and accurate eye-movement recordings was counter to the prevailing clinical description that INS caused the eyes to oscillate about the intended line of regard. That putative description failed to account for the high acuity possible in INS, whereas the discovery of the foveation periods does. They provide the needed time for foveal imaging of a target while retinal slip velocity is low enough not to degrade vision appreciably. The identification of foveation periods in INS waveforms was the pivotal discovery responsible for the development of eye-movement data analysis methods coupling the quality of foveation periods to the best potential visual acuity of any INS waveform (see Section 2.1.9).

2.1.2.4 FOVEATION ACCURACY

Although eye-movement recordings suggested that each foveation period brought the eyes to the same position vis-à-vis the target, it was not until scleral search coils were introduced that a method sensitive and stable enough to study the accuracy of foveation periods during fixation, smooth pursuit, or VOR was available.^{62–64} The knowledge gained from those seminal studies allowed intelligent use of infrared measurement systems, which were replaced, decades later, by high-speed digital video systems. If foveation periods could not place the image in the foveal area on a beat-to-beat basis, acuity would suffer and the added problem of oscillopsia could result. The absence of oscillopsia in most INS subjects (under normal viewing conditions) was initially taken as strong evidence that the foveation periods, by allowing consistent target foveation at least once during each beat of IN, also suppressed oscillopsia (see Section 2.1.10).

Increased foveation time is the most effective determinant of increased acuity.^{31,65–67} The combination of foveation time along with foveation-position and foveation-velocity accuracies are

the three key elements determining foveation quality and, therefore, potential visual acuity. Clearly, they should be measured and serve as primary therapeutic outcome measures; ideally a function like the NAFX, containing all three, should serve that purpose (see Sections 2.1.9.1 and 2.3.1.1). In most INS subjects, the best waveform (i.e., most foveation time per cycle) is in the null region associated with a particular gaze or convergence angle. When it is not, the gaze or convergence angle that yields the best waveform is used, even if not the waveform with the least amplitude. Because decreased amplitude is the major determining factor in cosmetic improvement, a young patient's parents appreciate it. Despite a damping of the nystagmus, an individual with INS may not show an increase in peak acuity with convergence if the resulting waveform still has little foveation time per cycle (i.e., low NAFX), or if acuity is primarily limited by a visual deficit (i.e., the waveform at distance already had well-developed foveation and a high NAFX). However, even in such cases, broadening of the range of gaze angles where the patient's acuity is highest will still improve visual function sufficiently to justify therapy. The fixation system of someone with INS is able to repeatedly foveate a target within minutes of arc, almost as accurately as a normal person.^{62,65,68} That first use of "phase-plane" analysis in INS allowed definition of a "foveation window" ($\pm 0.5^\circ$ by $\pm 4.0^\circ/\text{second}$) for the study of fixation, smooth pursuit, and the vestibulo-ocular reflex (VOR).^{62–64} These studies demonstrated the extremely accurate fixation, pursuit, and VOR possible in individuals with INS. In Figure 2.9, the tight overlap of foveation periods within the foveation window in the phase plane demonstrates how accurate the cycle-to-cycle target foveation in INS can be despite the variation during the rest of the waveform. The foveation window defines the time when the eye is within $\pm 0.5^\circ$ of the target and moving with less than $\pm 4^\circ/\text{sec}$. Thus, despite an ocular oscillation whose amplitude is well outside the foveal extent and whose velocity exceeds $\pm 30^\circ/\text{sec}$, the OMS can foveate the target with extreme accuracy and allow normal visual acuity.

2.1.2.5 TARGET ACQUISITION TIME

Extended target acquisition time (i.e., the length of time required to acquire and accurately fixate each new target in the field of view) is one of the limitations to overall visual function experienced by those with INS—they are "slow to see." Yet this is not routinely measured either in the clinic or the laboratory. In normals, it is very fast, being limited only by saccadic latency and intersaccadic reaction time; each is on the order of 200 msec. However, despite having approximately the same saccadic limitations in latency and intersaccadic reaction time, persons with INS may take 1–2 seconds to accomplish the same task.⁶⁹ That does not include the extra time and stress involved if one has only a narrow range of gaze angles where one's acuity is highest (the so-called null region discussed in Section 2.1.5). Thus, in a common, real-world situation of entering a crowded room and finding and identifying those persons you know, what is a simple, easily and quickly done task becomes a longer and more stressful one. Target acquisition time is an important visual function measure that should be included in therapeutic outcome measures.

2.1.2.6 SMOOTH PURSUIT

Understanding the smooth pursuit system is essential to the understanding of the mechanisms underlying INS. Evidence from the first study of INS by Dell'Osso implicated smooth pursuit in the generation of INS.³ Subsequent external feedback experiments on a subject with INS produced exacerbated IN rather than the saccadic oscillations seen in normals.³² That is, the normally underdamped smooth pursuit system became undamped in INS and its oscillations grew larger with externally altered feedback of eye motion. Although the exact anatomical location of the source of the instability present in INS nystagmus is unknown, we hypothesized that the various pendular waveforms (and some jerk waveforms) are due to a gain/delay problem in an *internal* (brainstem) feedback loop in the pursuit subsystem (i.e., not the actual smooth-pursuit gain, which

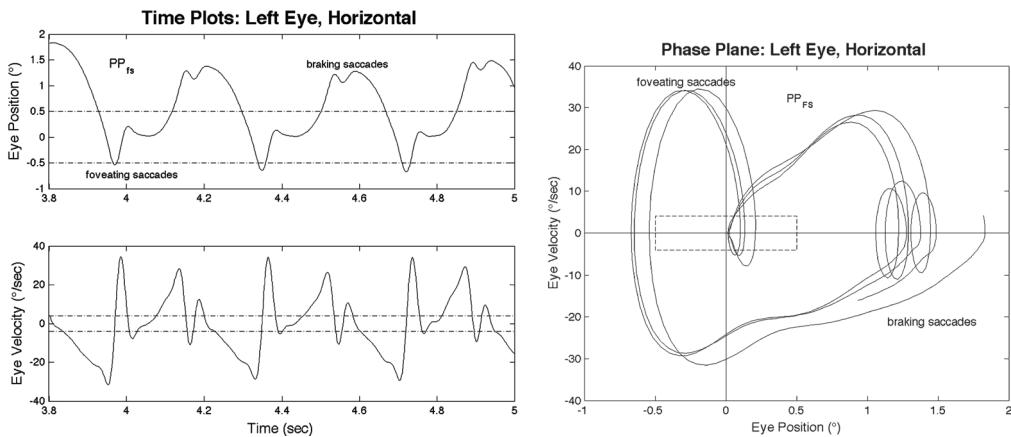


FIGURE 2.9 Three cycles of infantile nystagmus syndrome data showing the foveation accuracy of a pseudopendular with foveating saccades (PP_{FS}) waveform. Eye position and velocity (left panel) and phase plane (right panel) data contain foveation periods within the $\pm 0.5^\circ$ foveal and $\pm 4^\circ/\text{sec}$ retinal slip boundaries (dash-dot lines) for good vision. These boundaries determine the foveation window (dashed lines) in the phase plane.

is normal).³² Later studies of smooth pursuit demonstrated that despite the superimposed INS oscillations, the smooth pursuit system performed its task of tracking moving targets normally.^{63,70,71} Thus, the pendular (and most jerk) nystagmus waveforms of INS identified as “pursuit-system” nystagmus (PSN) in Figures 2.2–2.4 are actually a velocity oscillation, modified by the saccadic system’s attempts to foveate the target and the fixation subsystem’s attempt to extend foveation (position alterations). This hypothesis is embodied in a physiologically realistic, behavioral OMS model.^{4,44,45,47} Version 1.5 of this model is shown in Figure 2.10. This model contains each of the ocular motor subsystems necessary for simulation of fixed-head responses to common target inputs. Provision has also been made in the model for adding both vestibulo-ocular and optokinetic subsystems. The model is based on reconstructed target position and velocity signals to drive the responses and provide oscillopsia-free perceived target signals. Also, the neural integrator function is split into two portions, each responsive to different types of signals, in accordance with current neurophysiological data. All sensory input and efference-copy motor signals are utilized by

the “internal monitor” (i.e., the “brains” of the model) to determine ocular motor responses. Simulations from this model are used to illustrate INS characteristics.

Additionally, this behavioral OMS model demonstrated how the *same* pendular oscillation in the smooth pursuit’s damping control could produce both the pendular and jerk waveforms of INS.^{50,51} The body of this research provided strong support for the hypothesis that the *direct* cause of INS is an uncalibrated (and, therefore, undamped) smooth pursuit system. See Section 2.1.4.2 for a discussion of smooth-pursuit responses in INS. Recent studies in juvenile macaques support our hypothesis that the pendular oscillations that are the basis for most INS waveforms are due to oscillation in the smooth-pursuit damping circuitry.⁷²

The much greater frequency of horizontal-torsional nystagmus, compared with vertical or diagonal nystagmus, probably reflects inherent differences in the stability of the respective pursuit subsystems (i.e., the horizontal is more unstable than the vertical). Although there is no torsional smooth pursuit system per se, the torsional component of the nystagmus reflects instability in torsional control.⁵⁶ Another factor in support of the hypothesis of PSN is that

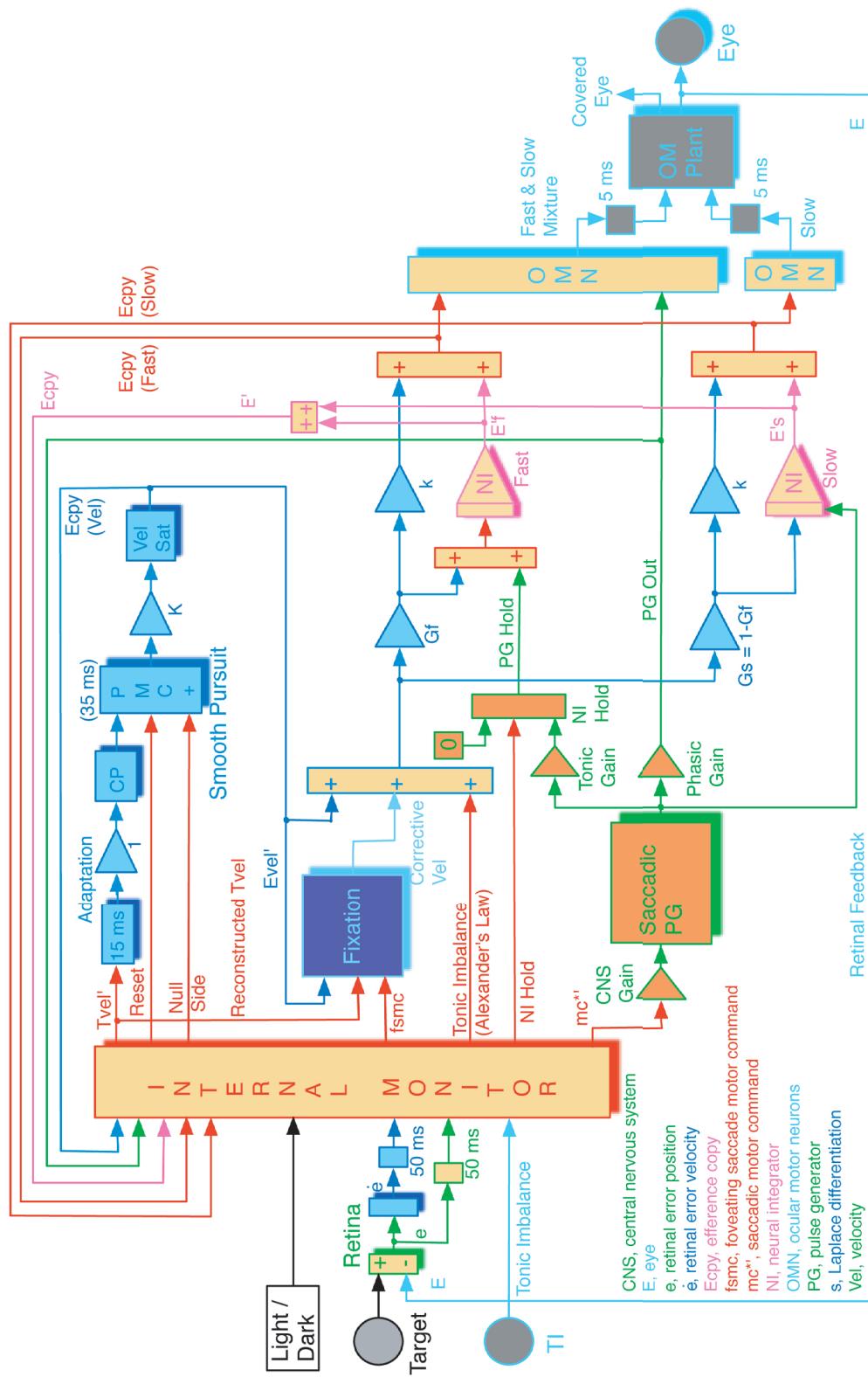


FIGURE 2.10 Block diagram of version 1.5 of a behavioral ocular motor system (OMS) model capable of simulating normal and abnormal (various types of nystagmus and saccadic intrusions and oscillations) responses to various target inputs. In addition to the saccadic, smooth pursuit, and fixation subsystems are two types of neural integrator networks, provision for efference copy of motor commands, an internal monitor to reconstruct needed target position and velocity signals that are free of oscillopsia, and the ocular motor plant.

no oscillopsia is perceived from oscillations in pursuit velocity, not in normals and not in those with INS. Thus, no additional “adaptation” mechanism need be proposed to account for the absence of oscillopsia in INS; it is suppressed by the same efference-copy mechanism by which normals suppress it during pursuit (see Section 2.1.10).

Initially, we proposed that excessive positive feedback around the common neural integrator might be responsible for the accelerating slow phases of INS nystagmus.⁷³ We subsequently demonstrated that the common neural integrator is *not* the site of the INS instability.⁷⁴ However, several models have been proposed that attempt to explain the genesis of some INS waveforms, based on that disproved premise.^{55,75,76} Although each can generate limited, specific INS waveforms, such models exhibit behaviors inconsistent with data from individuals with INS and, more important, do not simulate the known broad range of human ocular motor responses (both normal and during nystagmus) to common stimuli. Thus, they are simply demonstrations of putative computer mechanisms to generate waveforms rather than physiologically realistic models capable of simulating OMS behavior.

Because INS appears to be activated and intensified by fixation attempt accompanied by stress,³⁴ the deficit may also be linked to the fixation subsystem. Stress is the major factor in modulating IN. One study found that task-induced stress and motivation reduced foveation periods.³⁵ However, increased fixation attempt due to increased visual demand in the absence of stress may increase foveation times,⁷⁷ suggesting that the fixation system, like the saccadic system, is corrective and part of the OMS’s attempts to overcome the basic INS oscillation (i.e., it is not the *cause* of INS). The coexistence of a high-frequency pendular oscillation with a low-frequency INS waveform (resulting in one of the dual waveforms) in some INS subjects and also in dual-jerk FMN supports the hypothesis that the high-frequency pendular oscillation is due to an instability at a *different* site and is not an INS waveform. Available evidence points to the NOT as the site of this oscillation shared

by patients with either the INS or FMNS.⁷⁸ Goldstein suggested that INS might be caused by oscillations at two frequencies whose interactions may approximate some of the known INS waveforms.⁷⁹ However, such interactions do not produce the absolutely motionless (i.e., “flat”) periods of extended foveation (300–400 msec) recorded in many patients.

Clinical Pearl: Based on the research of the past 50 years, the INS in all patients is directly caused by instability in smooth pursuit damping plus a variable amount of tonic imbalance in the visual-vestibular system. Thus, INS is a motor oscillation with known motor causes, making the adjective “motor” (e.g., motor nystagmus or congenital motor nystagmus) redundant. Similarly, the terms “sensory” and “idiopathic” are both incorrect and misleading. None of these terms should be used in describing INS.

Therefore, the aforementioned terms are not used herein.

2.1.3 The Static Neutral Zone/Region

The static neutral zone is the range of gaze angles in which a reversal of direction of jerk nystagmus occurs and in which either no nystagmus, any of several bidirectional waveforms, or pendular nystagmus is present. During fixation of stationary targets, many individuals with INS also have a permanent null region representing the gaze angle at which the nystagmus is minimal and the waveform most conducive to highest NAFX and acuity. In most cases of IN, the neutral region straddles the null and contains either pendular or bidirectional jerk waveforms. To the left of the static neutral zone, the IN is jerk left and to the right, jerk right. The term “static” indicates that the region was measured during fixation of stationary targets at different gaze angles. In INS, the static neutral zone may be a function of static gaze angle or the fixating eye (INS with a latent component, next section). INS patients often turn their heads to permit straight-ahead viewing with the eyes in the null region. Such patients benefit from appropriate version prism

spectacles that alleviate the necessity for the head turn and the resulting increased stressful fixation attempt.^{33,80} However, if the IN damps with convergence, the higher NAFX values will persist over a broader range of gaze angles than during fixation on a far target (see Section 2.1.6). This allows higher acuity over most useful gaze angles and demonstrates the advantage of either base-out prisms or the bimedial rectus recession procedure over therapies aimed at moving a gaze-angle null to primary position.

2.1.3.1 LATENT COMPONENT

Some INS patients exhibit a “superimposed latent” component that induces null shifts toward an eye that is covered. Figure 2.11 shows the latent shift for an esotrope (top left panel) and an exotrope (top right panel) for either the left or right eye fixating; both IN magnitude and NAFX values are shown with their respective nulls and peaks. For example, in an esotrope fixing with the left eye, the null (or NAFX peak) shifts into right gaze; the opposite occurs for right-eye fixation. If the null shift is sufficient, a direction reversal of jerk IN in primary position will be observed each time cover is reversed. The right panel shows how an exotrope may exhibit an opposite shift. The bottom panel demonstrates the latent-component shifts in another way that helps visualize the INS direction reversal. For example, when the right eye is occluded, the null shifts right, moving primary position into the jerk-left INS field and vice versa. Because the static neutral zone shifts away from the fixating eye when the other eye is occluded, the direction of jerk nystagmus may reverse with alternate cover.⁸¹ This clinical observation may be mistaken as an indication of FMNS. However, without eye-movement recordings to differentiate the two conditions based on the slow phases of the two waveforms, INS with a latent component may be misdiagnosed as FMNS or vice versa. Such misdiagnoses can result in improper surgeries with problematic results.

Demonstration of such a shift and maintenance of any of the INS waveforms establishes the nystagmus as belonging to INS rather than the FMNS (see later). The mechanism

underlying the null shift is thought to stem from the Alexander’s law alteration of slow-phase velocity with gaze angle that is part of the visual vestibular subsystem (see also Chapter 5, Table 5.4). Rarely, a null shift is toward the viewing eye.³³ There have been, and continue to be, clinical reports of INS patients with “two” nulls. Indeed, one such report contained eye-movement recordings purported to demonstrate different nulls during near and far fixation.⁸² However, careful review of the eye-movement data in the aforementioned paper suggests that the patient had INS plus a latent component (and, based on the waveforms during near fixation, INS plus FMNS). That combination resulted in the expected shift of the null in the direction opposite to the fixating eye. At distance, fixation was with the left eye, resulting in jerk-left nystagmus with a null to the right and at near, fixation with the right eye resulted in jerk-right nystagmus with a null to the left. Multiple-gaze-angle monocular calibration records for each eye would have made this evident and prevented the misinterpretation. In every case we have recorded, the appearance of more than one null in INS resulted from a shift in the fixating eye in a patient with INS plus a latent component.

Clinical Pearl: Patients with INS and two static (or multiple) head postures should be examined for a latent component, FMNS or APAN.

2.1.4 The Dynamic Neutral Zone/Region

If one measures the characteristics of INS waveforms at various gaze angles while the subject is tracking a moving target, the amplitudes will also vary but the neutral zone (and “null” angle) will usually be found to be at an angle displaced from the static neutral zone in the direction opposite to the pursuit direction (target motion). This neutral zone is referred to as the *dynamic neutral zone* and its position is a function of superimposed eye velocity, both speed and direction (due to pursuit, optokinetic, or vestibulo-ocular eye movements). The importance of recognizing the existence of dynamic shifts in the static

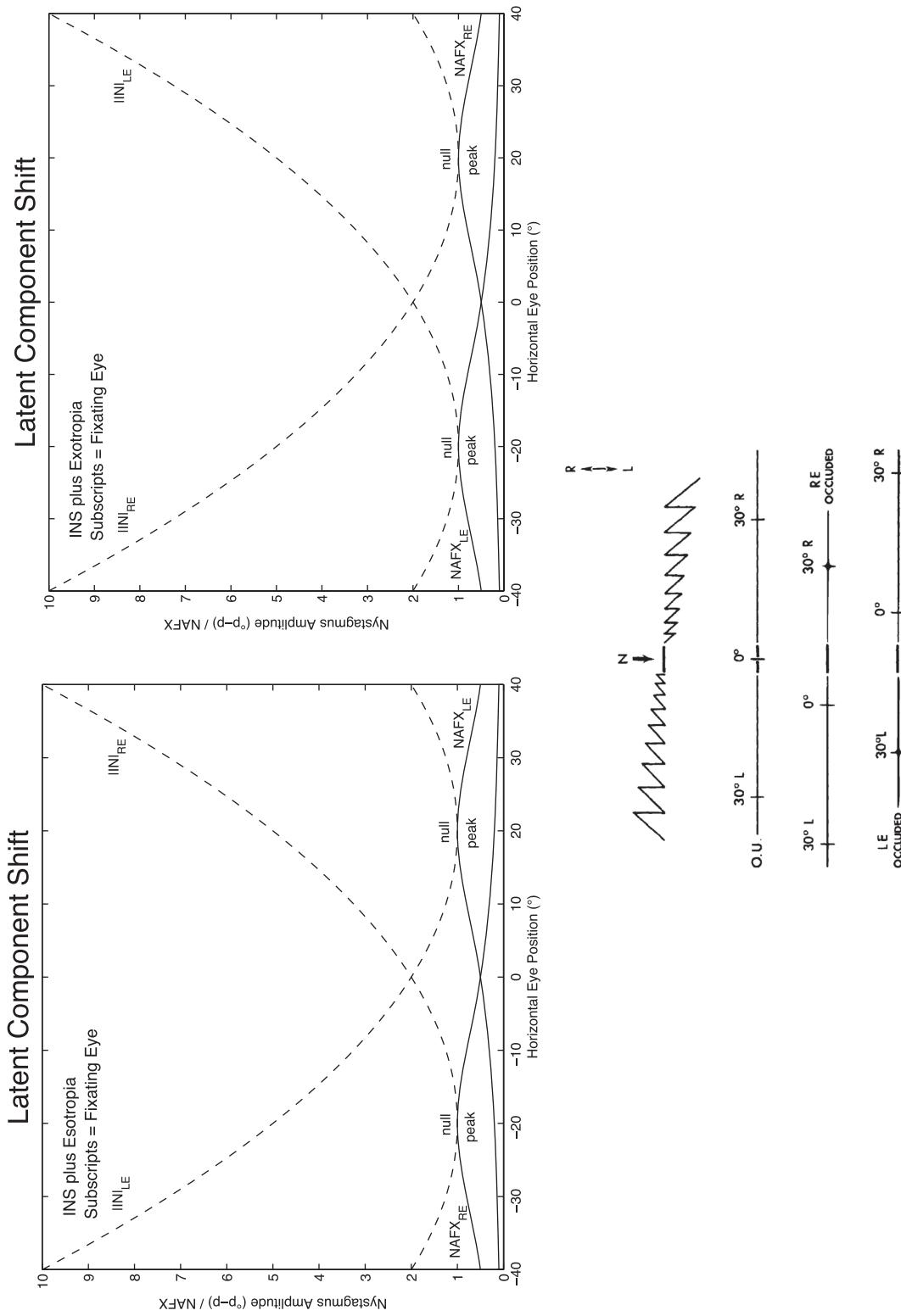


FIGURE 2.11 Illustrations of latent component shifts (exPanded nystagmus acuity function [NAFX] peak and infantile nystagmus syndrome [INS] null) with alternate occlusion for an esotrope (top left) and an exotrope (top right). The bottom panel illustrates how such shifts affect the movement of primary position with respect to the INS null.

neutral zone became evident when analyzing the variable and confusing responses measured during optokinetic, pursuit, and vestibulo-ocular stimulation. The dynamic neutral zone shifts occur instantaneously during smooth pursuit (or optokinetic or vestibulo-ocular eye movements) and are evident as waveform changes and null shifts during these movements.^{32,63,64,70} Based on the instantaneous open-loop responses to step-ramp stimuli (i.e., before visual or proprioceptive feedback is possible),⁸³ we hypothesize that the dynamic null shifts are initiated by either the reconstructed target velocity, background velocity, or head velocity signals or the subsequent motor commands they elicit.

2.1.4.1 ASYMMETRIC, (A)PERIODIC ALTERNATION

Most clinicians are familiar with this oscillation as acquired periodic alternating nystagmus (PAN). Acquired PAN has a specific pattern identified by the presence of spontaneous nystagmus in the primary position, which beats horizontally in one direction for 1 or 2 minutes, followed by a quiet period, and then reappearance of the nystagmus in the opposite direction for a similar length of time.⁸⁴ It is usually seen in association with vestibular cerebellar

disease, neurodegenerative conditions such as Friedreich's ataxia, or vision loss.

The dynamic neutral zone in INS may also vary spontaneously with time while fixating a static target. However, such INS patients exhibit an asymmetric, (a)periodic alternating nystagmus (APAN).^{29,81} Unlike acquired PAN, APAN is usually asymmetric, with unequal time periods of jerk nystagmus in each direction. APAN has all the characteristics of INS except that the null point shifts position in either a regular (periodic) or irregular (aperiodic) pattern and is usually also asymmetric (unequal intervals of jerk nystagmus in each direction).^{81,85–87} This results in changes in the intensity and/or direction of the nystagmus from seconds to minutes. APAN encompasses all idiosyncratic variations in intra- and intercycle timing and amplitudes; more specific nomenclature can be applied when these characteristics are known (see Chapter 5, Table 5.2). In some cases, aperiodic or periodic changes in intensity but not direction or direction but not intensity occur; they represent extremes in the broad spectrum of time variation in IN.

Figure 2.12 illustrates how the amplitude and direction of APAN vary with the time function describing the null shift. The direction, rate of change, and duration of the null

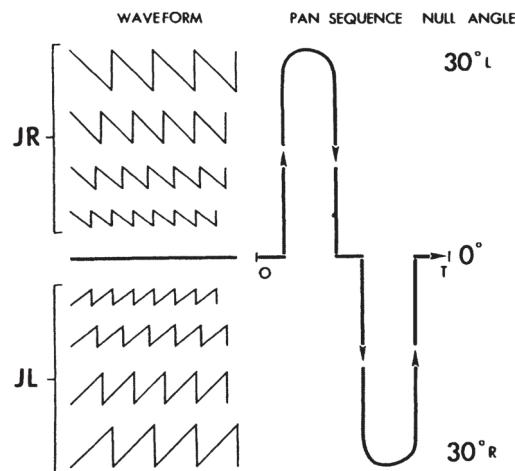


FIGURE 2.12 Illustration of how a shifting infantile nystagmus syndrome null angle accounts for the direction of asymmetric, (a)periodic alternating nystagmus (APAN), the rapidity of its amplitude increases, decreases, and durations at its maximal values. JL, jerk left; JR, jerk right.

shift determine the direction of the jerk IN (opposite to the null shift), how rapidly the jerk IN increases or decreases, and how long it remains at its maximal value. Also, APAN may exhibit different (aperiodic) or the same (periodic) times for each full period of nystagmus reversals; in some cases, the reversals are sporadic. Thus, for any give patient, one's INS neutral zone may be a function of gaze angle, eye velocity, fixating eye, or time. The amount that each of these parameters affects the neutral zone is idiosyncratic. APAN has been attributed to a time-varying (shifting) null region.⁸¹ Albinism has also been linked with APAN.⁸⁸ The occurrence of APAN in INS was thought to be rare, but Shallo-Hoffmann et al. suggested otherwise.⁸⁹ They also found switching between accelerating and linear slow phases in the two directions and asymmetries, even in those patients whose APAN was essentially periodic. The appearance of both accelerating and decelerating slow phases, sometimes seen during the neutral phase of APAN, has been shown to result from a single mechanism summing linear and pendular components.⁹⁰ The recognition of both PAN and APAN is essential when surgery is being considered for either acquired nystagmus or INS.⁹¹ Nine to 33% of patients with INS will have an inherent, rhythmic, periodic, or aperiodically changing nystagmus *intensity and/or direction* over time.

Abadi and Pascal studied 25 subjects with oculocutaneous albinism (16 tyrosinase negative and 9 tyrosinase positive) and 7 with ocular albinism (5 X-linked and 2 autosomal recessive) and found that 12 exhibited APAN.⁸⁵ The nystagmus waveforms encountered during the APAN active phases were either jerk-with-extended-foveation or pseudocycloid, whereas a variety of oscillations (including triangular and bidirectional) were evident during the quiet phases. For most of the 12 subjects, there was an asymmetric variation in nystagmus intensity during each APAN cycle. Although neuroimaging is obtained in almost all cases of clinically evident PAN, the definitive diagnosis of the ocular oscillation is made using eye-movement recordings. APAN is more common in patients with oculocutaneous albinism and is usually not

associated with serious central nervous system pathology.^{85,89}

Gradstein et al. diagnosed APAN in 18 (9%) of their 200 patients with infantile nystagmus, although most had not been diagnosed with APAN before referral, despite changing nystagmus reported by referring clinicians.⁸⁶ In those 18 patients they found 5 to have ocular or oculocutaneous albinism and 16 had an alternating anomalous head posture (AHP). The APAN cycle was of variable duration, often with asymmetric right- and left-beating components. Although horizontal jerk nystagmus with accelerating slow phase was predominant, other waveforms were encountered in the active phase of APAN. In the quiet phase (close to null zone), similar, but less intense, oscillations than those in the active phase were characteristic. Half of the patients showed a combination jerk and pendular waveforms in both phases. In another report the same authors found ocular oscillations consistent with INS evident in 24 of 27 patients with oculocutaneous albinism and Hermansky-Pudlak syndrome (HPS) and half showed periodic alternating nystagmus.⁹² They concluded that most patients with HPS have INS, and many have periodic alternating nystagmus.

Shallo-Hoffman et al. studied 18 patients with INS and found 7 of the 18 patients had APAN (median cycle: 223 seconds, range 180–307 seconds).⁸⁹ The periodicity of the cycles for each adult patient was regular, although the phases within a cycle were often asymmetric. Six of the 7 patients had an AHP, and in 5 of 7 with the AHP it was in only one direction (static). Except for one patient, the APAN waveforms had an increasing slow-phase velocity in at least one phase of the cycle; in the other phase they were linear. They concluded that the AHP was dependent on, and could be predicted from, the waveforms containing the longest foveation times. Although the waveforms and foveation times may differ among the phases of the APAN cycle, the periodicity of the cycle was usually regular and therefore predictable.

Hosokawa et al. found periodicity in the time-frequency distribution in 3 of 13 patients (23%) with INS.⁹³ Eighteen of 91 (19.8%) patients with

infantile nystagmus who were seen in the Teikyo University School of Medicine were diagnosed with APAN. They found that face turning was seen between the ages of 3 and 9 years. Visual acuity no worse than 20/40 with correction was obtained in all their patients and almost all the patients had an asymmetric null cycle manifested in an aperiodic alternating head posture.

Hertle et al. reported 78 patients with APAN and found that 46% had an associated diagnosis of oculocutaneous or ocular albinism.⁸⁷ Most of their patients had strabismus (72%) and an AHP (87%) with one-third having a visually preferred eye. The clinical head/face position was evenly split between those patients with a static head posture and a dynamic (alternating) posture. Interestingly, those patients with strabismus were more likely to have a static head posture, even with a periodic rhythm detected on eye-movement recordings. Most of their patients had best binocular acuity in the 20/50 to 20/100 range, which probably reflects the large number of patients with associated sensory system deficits that were referred to their study centers. The patients were also evenly split between those with a periodic and aperiodic eye-movement rhythm. The periodic rhythm averaged between 3 and 4 minutes.

The occurrence of APAN is not as rare as previously suggested and can be missed because of long or irregular cycles and the patient's preference for only one AHP. The changing null period is easier to recognize using eye-movement recordings, but in most clinical environments this is not available. The clinician may be able to diagnose this disorder if an INS patient is examined in the following way:

Clinical Pearl: Occlude the nonpreferred eye and examine the preferred eye with the head straight and gaze in primary position over at least 5–7 minutes. A regular or irregular changing oscillation intensity and/or direction indicates APAN.

Identification of APAN and possibly its waveform characteristics are essential in cases in which surgical or medical treatment is considered for correction of strabismus, nystagmus, and/or an

associated AHP. Some patients exhibit brief periods during which their IN stops; they lie at one end of the APAN spectrum—very aperiodic.

Clinical Pearl: Patients with INS whose measured visual acuity changes from one office visit to the next may have short periods when the nystagmus stops and acuity peaks; this is an exaggerated form of APAN.

2.1.4.2 OPTOKINETIC, PURSUIT, AND VESTIBULO-OCULAR RESPONSES

Unfortunately, the notions of “inverted pursuit movements” and “inverted optokinetic responses” have created confusion regarding the roles of both in INS. The smooth pursuit waveform in the INS does not appear clinically normal, and it is widely recognized that patients with INS often show an apparent reversal of their optokinetic responses (i.e., during pursuit of leftward optokinetic stimuli, a left-beating nystagmus rather than a right-beating nystagmus is seen).⁹⁴ The absence of any symptoms of such grave deficits and the normal abilities of individuals with INS in sports should have precluded the notions that either of these important ocular motor subsystems was actually reversed. Also, the perceptions of individuals with INS of both the direction and magnitude of movements in the periphery and on the fovea are normal.

When an individual with INS is placed in an optokinetic drum, where the stripes surround the subject, the perceived circularvection is in the *same direction* as for a normal (personal observation by LFD in the laboratory of David Cogan, circa 1970). Unfortunately, the clinical appearance of the nystagmus of a subject with INS during optokinetic stimulation is in the “wrong” direction and led some to conclude that “reversed optokinetic nystagmus (OKN)” was a clinical indication of INS. True inversion of the optokinetic reflex would contradict the normal perceived circularvection experienced by someone with INS. Eye-movement recordings cleared up the mystery when Halmagyi et al. documented that, as Dell’Osso et al. demonstrated for pursuit,^{32,70} the neutral region during OKN also shifted in the direction opposite to the stimulus

and resulting slow optokinetic eye movement.⁹⁵ The resulting nystagmus is either damped or opposite in direction from what would be anticipated because the evoked OKN simply summates with the ongoing nystagmus. “Inversion” of the optokinetic reflex is present in 67% of INS patients; this clinical observation establishes the nystagmus as IN. Kawai studied the effects of an optokinetic background on INS.⁹⁶ He concluded (in agreement with Dell’Osso’s observations earlier) that the perceived circularvection is in the proper direction for the background movement and, furthermore, that the OKN dynamics were normal in INS subjects.

There is another problem with the analysis of OKN in INS: whether presenting a slowly moving stimulus to such a person is an adequate OKN stimulus.⁸ In normals, such a stimulus results in slow motion across the retina; that is not the case in INS, where the retina is in rapid motion in both directions. Despite that, the subject perceives the correct drifting gratings and that perception produces a correct OKN response superimposed on the INS oscillation; that is further evidence that the OMS responds to perceived target motion, not merely retinal motion. Abadi and Dickenson reached the same conclusion from their study of OKN and INS.⁹⁷

The fundamental error of equating the summation of smooth pursuit movements plus the superimposed INS waveform with the pursuit movement alone inevitably leads to the erroneous conclusion that there is an inherent defect in the pursuit system, and during pursuit of a visual target, the slow phases of IN consist of normal pursuit movements plus the nystagmus itself but that the eye position consistently matches the target position during foveation periods.^{63,64,70,98} It is well documented that the attempts to pursue a slowly moving target significantly alter IN (e.g., the static neutral zone is shifted in the direction opposite to the pursuit). Thus, the actual IN amplitude at a given gaze angle is different during pursuit than when viewing a stationary target. It may be greater, less than, or even oppositely directed depending on whether the gaze angle is farther from or nearer to the dynamic null during pursuit than during steady fixation. For example, if the static null is at -20°,

the jerk-right INS at 0° will increase if pursuing to the right and either decrease or become jerk left if pursuing to the left (the latter will depend on the speed of pursuit). It is common to record a high-amplitude IN waveform during pursuit of rapidly moving targets across the whole field of gaze, from 20° left to 20° right, despite the fact that the same subject might have a broad null region somewhere in this range when looking at stationary targets.

Two interesting cases of INS that became manifest only during unidirectional pursuit were reported.⁹⁹ In these subjects, no IN was present during fixation of stationary targets at any gaze angle. However, when pursuing targets moving in one direction, a nystagmus developed that had increasing velocity exponential slow phases and was diagnosed as being INS. These patients’ complaints of oscillopsia only during such pursuit have been with them throughout their life. It is interesting that the normal suppression of oscillopsia seen in INS subjects was not present in these cases where the nystagmus was only manifest during unidirectional pursuit. Given the effects of smooth pursuit on the INS null, the most parsimonious explanation for these observations is that these patients had a very broad null region (see Section 2.1.5) that encompassed their whole range of gaze angles when viewing static targets. When they attempted to pursue in one direction, that null region was shifted in the opposite direction, causing a nystagmus in the same direction as the pursuit. These would be two extreme examples of the well-known null/neutral-zone shift seen in most INS subjects.

In a study of smooth pursuit, VOR, and OKN in individuals with INS, Kurzan and Büttner supported the hypothesis that the measured waveforms are caused by a shift in the static neutral zone to a new position (the dynamic neutral zone).⁷¹ In agreement with Dell’Osso et al.’s observations, they found that even low stimulus velocities caused large shifts in the neutral zone and higher velocities caused an increased shift. They also confirmed that this shift has no measurable latency. This shift in a subject with INS was later quantified.⁶³ Given their verification of the neutral-zone shift, they concluded that smooth pursuit was *normal* and that retinal slip

velocity is adequately utilized for the generation of smooth pursuit eye movements in individuals with INS.

Dell'Osso et al. studied the foveation periods of an individual with INS during smooth pursuit and VOR and demonstrated near unity gains for both over target velocities ranging from a few degrees per second to 215°/sec and for rotations in the normal gaze-angle range.^{63,64} During the vestibulo-ocular responses, the same type of neutral-zone shift seen during optokinetic and pursuit responses was documented. Also, despite the often confusing and misinterpreted combinations of INS waveforms superimposed on VOR eye movements, it was shown that the VOR was normal in subjects with INS. They also demonstrated, using phase-plane analysis, that both smooth pursuit and VOR were normal during foveation periods. By subtracting the target position and velocity from those of the eye, they reconstructed the retinal error phase planes during pursuit and VOR and showed them to virtually duplicate the phase plane of eye movement during fixation of a stationary target. Thus, by two unrelated methods, these subsystems were proved to be *normal* in INS, and that hypotheses or models claiming deficits in either of their gains or directions as the cause of INS were invalid.

Just as the INS waveform is distorted by slow eye movements (creating periods of extended foveation) during fixation of a stationary target, the pursuit system generates pursuit movements with a direction and velocity that match those of a moving target during INS foveation periods.^{63,70,71} This ensures extended foveation of the moving target and results in accurate smooth pursuit while the target image is on the fovea. Pursuit during foveation is all that is necessary for good acuity; the same conditions are met during smooth pursuit as during fixation of a stationary target.

Six patients in whom INS emerged in later life also exhibited the null shift with pursuit and OKN that is a characteristic of INS.²² Lueck et al. studied a patient who presented with episodes of oscillopsia with smooth pursuit and OKN responses that exhibited nystagmus slow phases in the direction opposite to the stimulus.¹⁰⁰ Several different mechanisms for the etiology

of this nystagmus were presented; this may have been a rare form of INS that is related to the two unidirectional pursuit cases discussed earlier.⁹⁹ This patient exhibited a jerk-left IN in far left gaze and when tracking from the right to the left. Thus, his neutral zone, which was in left gaze when fixating stationary targets, shifted to the right so that the jerk-left IN was superimposed on leftward pursuit movements. This case is the missing link between normal INS (where the nystagmus is present while viewing stationary targets and the neutral zone can easily be seen to shift during pursuit) and those cases previously recorded (where there was no nystagmus during fixation of stationary targets and a shift in neutral zone with pursuit caused the nystagmus to become manifest). The pursuit-induced neutral zone shift was the explanation offered for the mechanism involved in producing the IN in the two patients previously reported and that explanation is also supported by this patient. In a study of smooth pursuit in several cases of hereditary INS, Takahashi demonstrated smooth pursuit during the foveation periods of his subjects.¹⁰¹ The finding that there was a distinct difference in the IN of the male subjects from that of the female subjects during pursuit has neither been reported before nor noted in our data.

Many attempts to evaluate the VOR in subjects with INS have failed to successfully separate the slow-phase velocity associated with the underlying nystagmus from that due to the VOR itself. Because of the superimposition of an ever-present and changing INS waveform on the eye movements resulting from the normal VOR, the measured responses do not resemble normal ones. As previously discussed for smooth pursuit, the calculation of the VOR gain in INS must also be limited to foveation periods.⁶⁴ At any other point in the INS cycle (when there is neither target foveation nor clear vision due to the obligate retinal slip), the calculation of VOR gain is meaningless, both in the mathematical sense and as an indication of the performance of the VOR.

2.1.5 The Null Angle/Zone/Region

The field of gaze in which nystagmus intensity is minimal is termed the “null zone” and it usually,

but not always, overlaps with the “neutral zone.” A gaze-angle null results in an AHP that allows use of the null to fixate targets that are directly in front of the patient.¹⁰² Nystagmus therapy aimed at improving visual function is best accomplished and more accurately measured using the peak and breadth of the NAFX versus gaze angle curve, not nystagmus amplitude or intensity, which are not accurate predictors of visual function.

There are several reasons why an AHP should not be used either as a measure of therapy necessary or as an outcome measure. First, an AHP is under the direct control of the patient and is, therefore, unreliable (especially postoperatively in children who know the intent of the surgery was to “straighten the head”). Second, it is often variable, depending on the prevailing conditions, sharpness of the NAFX versus gaze angle curve, and need to accurately fixate the target. Third, it is more difficult to measure accurately than eye position. Fourth, it is not the primary problem but rather a patient’s compensatory response to the primary problem (i.e., the gaze angle with the best foveation). Finally, an AHP only translates into the necessary measurement of required gaze-angle shift if the body is perfectly aligned, straight ahead. Usually both the head and body are turned toward the target so the required gaze-angle shift is actually the sum of head-on-body rotation and body rotation. For these reasons, the discussion of AHP has been placed in this section on null angles and does not have its own section.

By measuring the amplitudes and frequencies of INS waveforms at various gaze angles, it was found that there usually is a small range of gaze angles within which one or both decrease.³¹ This damping of IN allows better acuity at that gaze angle (the “null” angle) and, in some cases, results in the subject turning the head opposite to the null angle to place objects of interest at the null angle. Early attempts at surgical correction in INS were directed at the cosmetic improvement in straightening the head and only secondarily (and sometimes not at all) was acuity improvement considered.

Clinical Pearl: Patients who (taking advantage of their null) move their heads word to word across the line while reading (even those with high acuity) may have INS with a narrow range of gaze angles where their acuity is highest.

The null angle is usually at the center of the neutral zone. A definition of an INS null is in order. For a gaze-angle position of low-amplitude nystagmus to be a true null (i.e. in the mathematical sense), the nystagmus must be more intense (amplitude × frequency) at gaze angles to either side of it. Those patients who turn their head in one direction so their eyes are in extreme lateral deviation do not fulfill this definition. It is well known that many patients with FMNS put their fixating eye in extreme adduction and take advantage of Alexander’s law to minimize their nystagmus; this is not a true null angle. Similarly, some patients with INS also adopt an extreme head turn forcing their eyes laterally and minimizing their nystagmus; this too is not a true null since the eyes cannot be deviated further to test whether the nystagmus increases at those gaze angles. INS patients with true nulls have only one such position but those with APAN may appear to have two. Since the earliest recordings of INS, “bias reversals” during steady fixation were noted.^{29,31} Some individuals with INS exhibit frequent, sporadic bias reversals and the resulting direction reversals of their IN may be considered one end of the spectrum of APAN, the most aperiodic.

An attempt has been made to use electromyographic (EMG) recordings to examine the possibility that there are two types of gaze-angle nulls present in INS.¹⁰³ One type was attributed to the active blockage of the nystagmus by an increase in the discharge of the synergistic extraocular muscles responsible for the gaze angle adopted. The second type was the classical null position for which no good explanation has been proven, and it is thought to result from an equilibrium position between the forces present in the push-pull OMS. According to this paper, the blockage type of null occurs at angles greater than 10° from primary position and the so-called Kestenbaum null occurs closer to primary

position. The key to differentiation, according to these authors, is analysis of time histograms of the EMG signal since ocular motor activity reflected in the EOG is the same for both types of nulls. We have measured the IN of patients who have true nulls at most gaze angles as well as some whose nulls were so far in lateral gaze that it could not be proven that it was a true null. It is too simplistic to pick a number like 10° and say that true nulls occur at smaller angles and that beyond 10° only the so-called blockage null occurs. All nulls will exhibit the change in EMG histograms described earlier since increased activity will result in a broader, flatter curve. Furthermore, if the mere increase in activity of a muscle can be used to block the nystagmus, then all such patients should be able to do this in both directions. This is not seen in INS patients with good binocular function; it is observed in INS patients with strabismus and in FMNS patients. Also, this increase in synergistic activity is not equivalent to the blockage of IN with convergence where the increase in activity is in antagonistic muscles and affects the push-pull system in a different way.

2.1.6 The Convergence Null

In some subjects, IN also damps during convergence on a near target. This convergence null allows for near acuities that are normal despite poor distance acuities in these subjects. As Figure 2.13 shows, not only does convergence increase the peak NAFX but it also broadens the range of gaze angles over which the NAFX (and therefore, acuity) remains high. Such broadening greatly improves visual function by allowing for rapid and accurate saccadic fixation of lateral targets without the need to align the head for each refixation. The variety of clinical conditions under which this occurs suggests that this effect is determined by the convergence angle rather than the state of accommodation. In fact, binocular viewing or binocular function is unnecessary to illicit convergence damping in those patients with INS in whom it is present.¹⁰⁴ Also, asymmetrical convergence damps IN (this is the basis for the use of composite prisms) and, once converged, gaze angle plays no important role in IN amplitude (if it did, convergence prisms or bimedial recession operations would not be

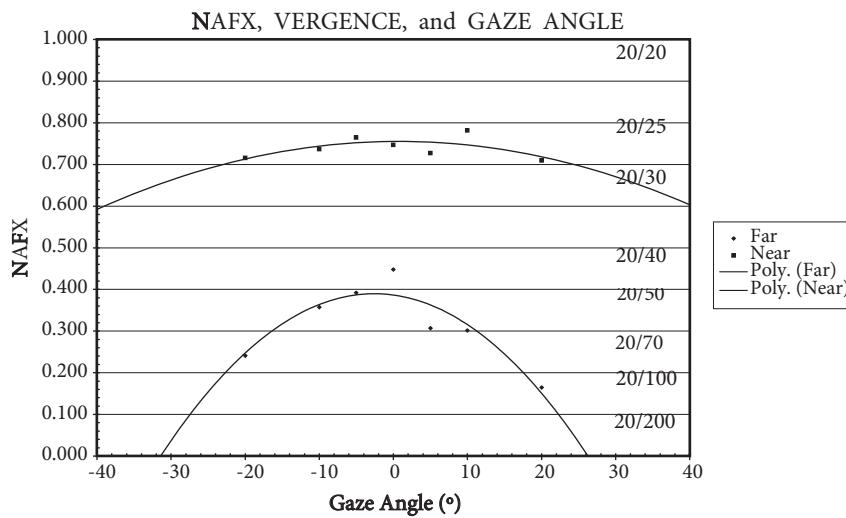


FIGURE 2.13 Plots of eXpanded nystagmus acuity function (NAFX) versus gaze angle for both far and near viewing showing increased values at near. Snellen acuities on left correlate with NAFX values and demonstrate the precipitous decrease in acuity at far compared to the maintained acuity at near as gaze is directed away from the position with the peak NAFX value.

of much value since real-life situations require looking in all fields of gaze).

Clinical Pearl: Patients with INS whose near visual acuity is greater than distant may have INS that damps with convergence.

Although the exact mechanism responsible for this damping is unknown, there was speculation that it might result from co-contraction of antagonist muscles of *each* eye during convergence. However, Miller found no co-contraction.¹⁰⁵ We hypothesized that damping during convergence might result from an effective increase in the stiffness of the ocular motor plant brought about by the increased innervation to the two medial recti (i.e., co-contraction of antagonist muscles of the *two* eyes, rather than of *each* eye). The Orbit 1.8 simulation (J. M. Miller, personal communication) predicted that the 8 g primary-position tension in the medial rectus increased to 13 g at 20° adduction (40° of convergence) and to 18 g at 30° adduction (60° of convergence), 75% and 125% increases, respectively. Because convergence results in a change in the muscle pulley system,^{106,107} the latter may play a part in increasing stiffness. However, when the eyes are converged by equivalent amounts, the muscle tension decreases.¹⁰⁵ This decrease may be accomplished by lowered γ -innervation to a proprioceptive feedback loop controlling steady-state muscle tension.^{108,109} The observations of convergence-induced damping of other types of nystagmus support this “peripheral” mechanism in preference to one relying on an inherent property of the nystagmus. Serra et al. made the interesting observation that divergence, in addition to convergence, resulted in higher NAFX values (i.e., better foveation quality).¹¹⁰ They discovered a hysteresis effect of vergence on IN that suggests that during divergence the same peripheral mechanism may be operating that damps IN during convergence.

Waveform, gaze-angle nulls, and convergence nulls are affected by heredity.²⁸ Members of the same family show more specific combinations of waveforms or of either having only a convergence null or no convergence null (i.e., having only a gaze angle null) than do members of the general INS population. We found

greater damping of INS nystagmus with convergence than with gaze angle, in patients who exhibited both types of null, and this translated into acuity increases.⁶² Comparison of the results of the Anderson-Kestenbaum and artificial divergence procedures also favored the latter.¹¹¹

In summary, most patients with INS have periods where the nystagmus intensity (amplitude \times frequency) is least. It is usually in these quiet periods (null/neutral times/zones/positions) that visual function is the best due to improved foveation quantity and quality during each beat of nystagmus. These null times/zones result from a complex combination of individual afferent and efferent patient characteristics. However, there are both static and dynamic components, present to some degree in all patients. The static components that either produce or modify a null/quiet period include a consistent horizontal/vertical/torsional position of gaze (eye in orbit, static gaze angle = N_g) and convergence at near or distance (vergence damping, nystagmus blockage, static convergence = N_c).^{112,113} Most patients’ static null position is in the three-dimensional midline, that is, straight ahead. However, 10% to greater than 50% of children have their null zone in an eccentric position of gaze relative to midline (horizontally, vertically, torsionally, or a combination of all three). The null zone/period in patients with INS also has multiple dynamic components. The dynamic components that either produce or modify a null/quiet period include the following: a movement of the null toward a covered eye (causing a clinical “latent component,” dynamic fixing eye = F_d), null movement in the direction opposite of smooth pursuit, OKN, and VOR stimuli (giving the impression of low-gain pursuit [saccadic] and “reversal” of OKN induced eye movements, Dynamic SP-VOR-OKN = E_o), and finally a change over time in both the short term (minutes—periodic/aperiodic) and over the long term (years—associated with age) (Dynamic (A)PAN = ΔT). Other well-recognized and highly associated developmental or congenital abnormalities of the visual system affect the oscillation of infantile nystagmus in general and the null/quiet periods in particular.

These include high spatial frequency vision (acuity) compromise due to optic nerve and retinal disease, heterotopias (and eye dominance), and amblyopia.

Possibly, all of the variables listed earlier (i.e., the static components, dynamic components, and other visual system affecters) combine in a mathematical way to produce the clinical null period that is observed and used to guide much of the medical and surgical treatment of INS (Fig. 2.14). The perturbations of the basic INS oscillation as a result of gaze, time, binocular/monocular viewing, acuity, heterotopia, and motion are probably directed by complex developmental connections between the multiple parallel pathways in the afferent visual and efferent vestibular, vestibular ocular, and

velocity storage systems.^{26,102,113–115} Based on the data from this and other reports of patients with APAN, it is probable that the rhythmic component of APAN and the associated head posturing are heavily influenced by associated heterotopia with visual and motor dominance.

2.1.7 The Saccadic Response

Early studies of INS noted that responses to changes in target position were often combinations of hypometric saccades and the slow phases of the INS waveform.³² This observation led to an early hypothesis that IN was secondary to a primary abnormality in the saccadic system; we have long since realized that the saccadic system is normal and the direct cause of

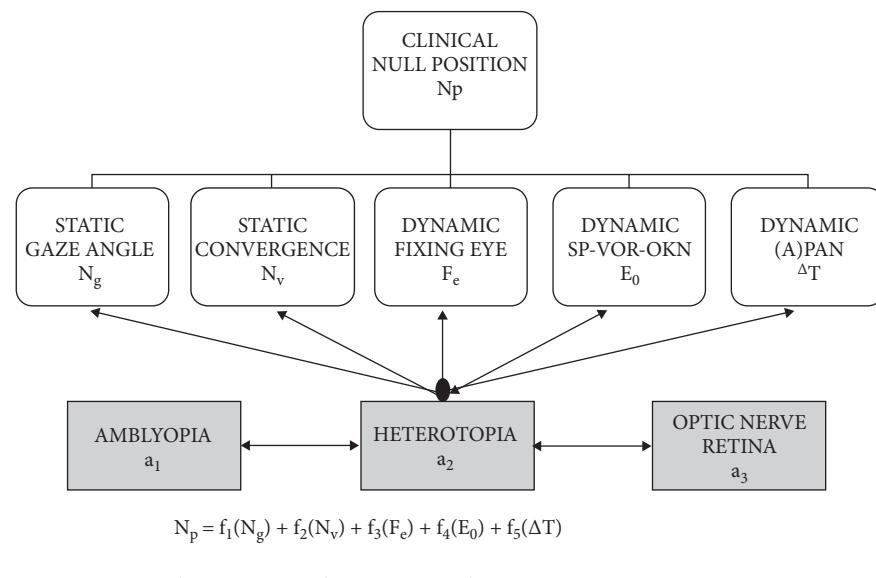


FIGURE 2.14 A hypothetical model showing how the clinical null or quiet period is influenced, and ultimately determined, by a complex and changing combination of dynamic and static factors. These factors interact in a hierarchical and temporal way to change how any one patient with infantile nystagmus syndrome may have what appears to be a clinically “changing” null or “multiple” null positions. N_p = overall null position; $f_1(N_g)$ = static gaze null (horizontal, vertical or torsional) as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_2(N_v)$ = static convergence damping as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_3(F_e)$ = dynamic null influenced by a fixing eye (“latent component”) as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_4(E_0)$ = dynamic null influenced by smooth pursuit, vestibular ocular reflex, or optokinetic responses as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3); $f_5(\Delta T)$ = dynamic null influenced by an underlying regular or irregular rhythm (periodicity) as a function of amblyopia (a_1) plus heterotopia (a_2) plus optic nerve or retinal disease (a_3).

INS is in the pursuit system. The responses to step changes in target position exhibited by INS subjects contain hypometric saccades or slow-phase responses that occur most frequently when the target is displaced in the direction of the slow phase.¹¹⁶ Since the retinal stimulus produced by step change in a target position is the same stimulus that normals receive from a step change followed by a ramp motion back toward the fovea, comparison was made to responses of normals to the standard Rashbass stimulus. Looked at in that way, the ocular motor responses of INS patients are *normal* saccadic responses to the sequence of retinal image motion produced by this stimulus and not contributions from the pursuit system in response to position displacements on the retina, as has been suggested by others. The responses of INS patients with albinism were less likely to contain saccades and may be attributed to their impaired sensory functioning. Thus, there is now additional evidence supporting the hypothesis that both the saccadic and pursuit systems of INS subjects *function normally* given the ongoing oscillation; this hypothesis was contained in the earliest model of the saccadic and pursuit systems operating in the presence of an ongoing oscillation.³

Although visual feedback provides a means of sampling and assessing the accuracy of foveation periods in INS, a number of observations suggest that fast phases are not produced in response to a retinal displacement error signal between the fovea and the target image. Worfolk and Abadi have offered the following evidence to support this supposition: jerky IN can continue with the eyes closed; IN continues and its parameters remain unchanged as individuals track paracentral afterimages; and in pendular IN with foveating saccades the retinal displacement error signal is opposite in sign to the forthcoming fast phase, allowing insufficient time to program the quick phases using visual information.¹¹⁷ Saccades and gaze holding are normal in INS, and the saccades contained within the nystagmus waveforms are always corrective, and not the initiating movement responsible for the nystagmus.⁶² In examining how the ocular stabilization systems function in the setting of

INS, one must confine the analysis to the foveation periods. It is during this portion of the INS waveform that the oscillation is least, vision is clearest, and some degree of ocular stabilization is possible. Eye movement recordings and phase-plane portraits in INS demonstrate the following: the oscillations of INS supersede the ocular stabilization systems but do not extinguish them; these systems exert their primary influence on vision during foveation periods; and defects in ocular stabilization are neither the cause nor the necessary result of INS.^{62–64}

2.1.8 Static and Dynamic Head Posturing

Many children with INS exhibit spontaneous head oscillations; adults, when they are concentrating on a visual task (real or imaginary), may also but they usually learn to keep their heads still because it is socially unacceptable to allow the head shaking. These head oscillations use existing pathways in the neck muscles. EMG in the neck muscles show that when normals make saccades to the left, the innervation is seen in the left-turning neck muscles and when they made them to the right, it is seen in the right-turning neck muscles. Normally, when we look left we are going to turn our head left. The pathways exist and, if there is an instability causing the eyes to oscillate and one records from the neck muscles, the same waveform is seen. When the oscillation grows large enough, the head will start oscillating. This is *not* something willed by the patient to compensate for the IN¹¹⁸; it is a manifestation of an existing oscillation on existing pathways to the neck. It used to be thought that head oscillations were compensatory. The head was supposed to be moved equally and oppositely to the IN to stabilize the eye in space. If that were true, the VOR gain would have to be zero. Accurate objective observations of the head movements in patients with INS do not support that hypothesis.¹³ In individuals with INS, the VOR is normal; it is not affected by INS.^{64,71}

Therefore, the head oscillations of most with INS are merely an extension of the IN and during the foveation periods, the eyes do not

move in space and acuity is unaffected by head movements.^{13,119,120} Basically, the head oscillations of an individual with INS and a normal VOR are equivalent to those of a normal person moving his or her head and acuity does not change.⁶⁴ For most INS patients (who have good foveation periods), there is no advantage to shaking the head; if the foveation periods are flat, head motion *cannot* help the patient and head shaking is, therefore, *not* an adaptation designed for increasing acuity.¹¹⁸ A normal VOR is incompatible with a head movement that compensates for an eye movement. Even with no VOR the head would have to move in complex ways opposite to the INS waveforms to achieve stability; that is clearly impossible. The head has too much mass to duplicate the waveforms of INS. The compensatory hypothesis, when you understand the VOR, cannot work. Realistic compensation could theoretically be accomplished if one could suppress a normal VOR to near zero and *only* move the head equally and oppositely to any movements of the eye during the INS foveation periods. This would achieve gaze stability during that part of the waveform and is a possible form of compensation useful *only* if the foveation periods of an individual were not stable with the head still.

The head tremor in INS can be distinguished from that in acquired disease; it is easily suppressed voluntarily in the former but not in the latter.

Clinical Pearl: Point out the head tremor to the patient. If it stops, the nystagmus is that of INS; if it persists, both are more likely acquired.

For those interested in accurate head posture measurement with minimal artifact, an apparatus was described by Young¹²¹ and another, more recently by Yang et al.¹¹⁵ However, head posture is neither a repeatable nor an accurate indicator of IN gaze-angle nulls, pre- or post-operatively. There is too much variability that can be introduced by the subject. It is best to fix the head and record the IN at known, and more accurately measured, gaze angles.

2.1.9 Foveation and Visual Acuity (High Spatial Frequency Vision)

Dell'Osso et al. studied the accuracy and cycle-to-cycle repeatability of the foveation periods in congenital nystagmus (INS) because visual acuity is directly related to these indices.⁶² During a 5-sec interval of fixation, the SD of mean horizontal foveal position was ± 13 minarc (± 5 minarc vertical) and mean foveation time was 59 ms. There were 1-sec intervals of fixation with SDs of 0 minarc. Position and velocity histograms reflected the increase in data about the zero position and velocity points caused by the foveation periods of the waveforms. Phase-plane analysis of the INS waveforms demonstrated beat-to-beat overlap in the position and velocities during the foveation periods (see Fig 2.9). Contrary to the notion that INS was due to *poor* fixation reflexes, they concluded that the fixation reflexes in subjects with INS were remarkably *strong* and *accurate* despite the large oscillation always present. Even in albinos, where the fovea is not normal, INS foveation periods were found to approximate those with normal foveae.⁶⁸ In a study of various indices of INS waveforms, the highest correlations were found to be between (1) foveation time and the maximum rate of the histogram indicating the rate of duration of the eye in each spatial position, (2) amplitude and intensity, and (3) mean slow-phase velocity and intensity.¹²² Of the three, visual acuity correlated best with foveation time. The presence of foveation periods in the waveforms of individuals with late-onset INS proves that the ability to suppress an acceleration of the eyes off target is part of our normal ocular motor arsenal and not something developed in early life by those with INS.²²

Abadi and Dickenson found both accurate and inaccurate foveation during fixation.²⁹ Bedell et al. found similar foveation-period variations (13–67 minarc horizontally and 8–20 minarc vertically).⁶⁵ They attributed the vertical variation to crosstalk from the horizontal IN. Based on their finding of a correlation between the variations in the horizontal and vertical meridians in both idiopaths and albinos, they

correctly concluded that INS is a *motor* and not a *sensory* disorder in *both* populations. They further concluded that subjects with nystagmus might also exhibit *normal* ocular motor behavior under certain conditions.

The accuracy, repeatability, and duration of the foveation periods are the most critical features of INS waveforms' effect on visual acuity. As a result of his studies of the dynamics of the foveation periods in INS, Dell'Osso developed a nystagmus foveation function (NFF) that was the first indicator of the gaze angle of best acuity in an individual and a means of correlating waveform characteristics and acuity between subjects, something that IN intensity cannot do.⁶² This function was formed by the quotient of the product of foveation period per cycle and IN frequency in the numerator and the product of the SDs of the mean foveation-period position and velocity in the denominator. Preliminary data demonstrated the direct relation between the value of the NFF and the gaze and convergence angles of best acuity.

Abadi and Worfolk studied the relationship between visual acuity and the duration of low velocity in IN slow phases.⁶⁶ They found a significant correlation between the duration of slow-phase velocities below 10°/sec and acuity. Although this was a somewhat cruder measure of the foveation periods, it does illustrate their importance in acuity. This paper contains velocity histograms of various waveforms and their effect on good foveation. Other studies also found a correlation between acuity and foveation-period duration⁶⁷ or variability.⁶⁵ This latter study did not find a correlation in albinos, whose acuity is limited by afferent defects. One study of acuity and several waveform variables did not find a correlation across patients.¹²³ This does not mean that correlations do not exist in specific individuals; experience has proven that damping IN and increasing foveation-period duration *will* improve acuity if it is not severely limited by afferent defects. The reason for the variability in the results of these studies is probably due to the correlations of several variables, and it is for this reason that the NFF described earlier yielded good results. The NFF contained *all* the motor variables relevant to acuity.

A paper on the use of telescopic aids for low-vision patients (with and without nystagmus) found that head motion was an important factor in preserving the stable retinal images necessary for good acuity.¹²⁴

Hatayama et al. examined several patients with and without base-out prisms.¹²⁵ Unfortunately, they used bitemporal EOG to record the eye movements. Four of the five patients showed a damping of the INS waveform during fixation in primary position. However, only three of the five showed an increase in acuity and one of the three was the patient in whom no damping of the IN was seen. The use of base-out prisms will usually damp IN and, more important, increase foveation time. However, in order to improve acuity, -0.50 to -1.00 sphere may need to be added to the refraction of patients with ample accommodation to negate the effect of the convergence-accommodation induced myopia stimulated by the base-out prisms. It was not clear whether this spherical correction was added to the refraction of these patients. We would anticipate that, had this been done, the acuity would have increased in more of the patients.

2.1.9.1 THE EXPANDED NYSTAGMUS ACUITY FUNCTION

The NFF led to the development of a more sensitive function, the NAF,¹²⁶ which, after testing and use in a number of INS patients, was altered to accommodate the larger foveation windows required by many INS patients.¹²⁷ The result was the NAFX, which has undergone over 15 years of testing, improvements, automation, and use in hundreds of patients with uniplanar or biplanar INS.¹²⁸ The current version has a GUI and automatic calculations that make its use easy and rapid (see Appendix F.1.2 for methodological details). Since, like its predecessors, it contains the three waveform factors (foveation time, position variation, and velocity variation) that define well-developed foveation periods and affect acuity the most, its value is linearly proportional to the best-corrected visual acuity of INS patients with no afferent deficits. That is, because the NAFX is only a function of the INS waveform characteristics, it is independent of the state of

the patient's visual sensory system. More specifically, only the foveation characteristics of the waveform are used in its calculation; all other, non-acuity-affecting portions of the waveforms are automatically discarded. Clearly, for a given INS waveform, the resulting visual acuity will be better when the SD of the foveation-period position is small than when it is large. The same applies for the SD of the foveation-period velocity. Since they may vary independently, both are necessary factors in a function that is related to potential visual acuity.

The inclusion of the aforementioned factors makes the NAFX a powerful tool in determining, *a priori*, what improvements in visual function may be expected by INS therapies that affect only the nystagmus (e.g., EOM surgery, prisms, soft contact lenses) and do not affect any afferent deficit that might or might not also be present. Using the NAFX, the physician can, for the first time, estimate not only improvements in peak visual acuity but also the more important improvements in the range of gaze angles over which the patient has his or her highest acuity (see Chapter 7, Section 7.5). These estimations can then form data-driven foundations for therapeutic decisions to be made by the physician and the patient. Used properly, the NAFX can more specifically delineate expected visual function improvements and thereby guide the patient's expectations.

Part of the NAFX methodology is the graphical determination of the position and velocity boundaries of the foveation window. Although the NAFX was developed to be relatively independent of those boundaries for a given data interval, using a larger-than-necessary window (either in position or velocity) raises the possibility of including extraneous data that might satisfy the enlarged foveation criteria; that could lessen the accuracy of the NAFX's correlation to potential visual acuity and compromise its ability to estimate therapeutic improvements. Measures of INS that do not identify and quantitate well-developed foveation periods are unable to provide the relationship between measured acuity and its INS component ("potential" acuity) that is necessary to separate the latter from the sensory component due to an afferent visual

deficit. That is why IN amplitude, frequency, and their product, intensity, are not good indicators of visual function and should not be used as outcome measures for therapeutic intervention.

There have been several subsequent attempts to duplicate the NAFX, albeit without including all of the three acuity-specific, waveform factors of the NAFX. Indeed, during the development of the NAF, the NAFP, which was limited to position variation, was included.¹²⁶ Functions that measure only variations in foveation-period position¹²⁹ and the others, only velocity¹³⁰ might provide a measure equivalent to the NAFX for certain specific waveform characteristics (e.g., if the SD of velocity was near zero, a function considering only position would suffice and if the SD of position was near zero, a function considering only velocity would suffice). To do so, such functions would have to be applied only to the fixating-eye data during periods of attention; claims to be able to apply them to larger data intervals with little attention to accurate calibration stretch credibility. As was found from comparisons of the NAFP and NAF (prior to developing the NAFX), given the idiosyncratic nature of INS waveforms and their intrasubject variation with gaze and convergence angle, such "simpler" methods cannot provide the NAFX's accuracy over all patients and waveforms. Attaching the word "acuity" to fundamentally deficient functions is merely an exercise in reification. No such functions have been shown to accurately reflect posttherapeutic, measured visual acuity changes and therefore cannot be expected to duplicate the NAFX's ability to provide a pretherapeutic estimate of therapeutic improvements. Finally, attempts to use more general signal-classifying approaches (e.g., wavelet analysis) to measure the foveation quality of INS waveforms have been proven to be too insensitive.⁴¹ Negative conclusions regarding therapeutic efficacy that are based on wavelet analysis in INS have no scientific basis and cannot serve to dispute the demonstrated, NAFX-based improvements in foveation quality.

2.1.10 Oscillopsia Suppression

Most types of nystagmus result in the perception of oscillopsia; however, in INS, it is almost

never constantly present.^{131,132} In those rare INS patients with intermittent oscillopsia, it tends to occur at gaze angles in which the nystagmus is maximal or after a new sensory system defect develops (e.g., retinal disease).^{133–135} The absence of oscillopsia is usually not helpful in distinguishing INS from acquired nystagmus in children as it is in adults since, even with nystagmus acquired in the first decade of life, children rarely have a continuation of this complaint.

Several mechanisms have been proposed to account for the stability of the perceived world in the face of nearly constant motion across the retinas in individuals with INS.^{133,134,136,137} These include the notion of visual information sampling only during foveation periods with suppression at other times, use of an extraretinal signal to cancel out the visual effects of eye motion, central elevation of motion detection threshold, and postsaccadic backward masking of motion. The thresholds for motion detection in INS differ from normal and may also have a role in oscillopsia suppression.^{138,139} However, such differences are slight compared to the high velocities of IN slow phases. Based upon these experimental results, an abnormally low sensitivity to oscillatory target motion cannot be invoked to explain the absence of oscillopsia in individuals with INS. Oscillopsia may occur in some patients with very poor foveation stability¹⁴⁰ or may occur in later life secondary to afferent deficits.¹³⁵ Perturbations in the INS cycle related to external or internal factors (e.g., head trauma, medications) can result in oscillopsia. Finally, certain viewing conditions may cause oscillopsia in some patients with INS.¹⁴¹

The striking difference in oscillopsia between INS and acquired nystagmus led Dell'Osso et al. to investigate the possible mechanisms that produce oscillopsia by studying subjects with INS or FMNS who somehow suppress oscillopsia.^{133,142–145}

2.1.10.1 FOVEATION DYNAMICS

One hypothesis for oscillopsia suppression in INS was the requirement that waveforms have repeatable, well-developed foveation periods. It is only during foveation periods

that clear and stable images of targets are visible. This was supported by studies that induced oscillopsia in a subject with INS and in the study of a subject with INS who experienced oscillopsia after loss of consciousness, which suggested that it was these foveation periods that were necessary for the suppression of oscillopsia. The mechanism suggested incorporated efference copy. Dell'Osso et al. demonstrated that some individuals with INS appear to require well-defined, repeatable foveation periods from one cycle to the next to perceive a nonmoving visual world.^{25,28} In two patients with INS plus an acquired nystagmus, their acquired oscillopsia seemed to be related to an inability to maintain repeatable periods of good foveation in a particular plane.^{142,143} However, that inability was an epiphenomenon caused by the addition of a transitory acquired nystagmus to the ever-present INS nystagmus.¹⁴⁶

2.1.10.2 TEMPORAL SAMPLING

A second hypothesis for oscillopsia suppression in INS was the requirement that waveforms have repeatable, well-developed foveation periods of sufficient time durations simultaneously in both the horizontal and vertical planes. Furthermore, temporal sampling of these stable foveation periods may result in normal visual acuities despite INS. These clear and stable “snapshots” allow for high acuity despite being superimposed on the less useful, continuous visual input. A phase-plane study of a subject with diagonal INS supported the aforementioned hypotheses¹⁴³ as did a study of a subject with FMNS who had 20/15 visual acuity.¹⁴⁷ The same foveation-window criteria necessary for good acuity and oscillopsia suppression in INS were found to be necessary in FMNS.¹⁴⁸

The suggestion that individuals with INS periodically sample their visual environment only during foveation periods with total suppression at all other times (i.e. “stroboscopic” vision) was a simplistic inference drawn from the observation that clear and stable vision was possible only during foveation periods, and it has been dispelled. Temporal modulation

studies demonstrate that individuals with INS process retinal information continuously rather than selectively during saccade periods. Bedell et al. found no evidence of decreased sensitivity to oscillatory target motion in patients with INS when comparing them to control patients viewing a target with sinusoidal or ramp motion to simulate the retinal image motion that occurs with retinal eye movements.^{123,131,134,137} Suppression of the perceptions of oscillopsia and motion smear may be mediated by different but overlapping mechanisms in INS.¹⁴⁹

2.1.10.3 EFFELENCE COPY

The third hypothesis for oscillopsia suppression in INS was the presence and use of an efference copy of ocular motor signals to cancel the components of eye movements in retinal motion signals. Comparison of the saccade dynamics of subjects with INS, FMNS, and both pendular and jerk forms of AN argued against the saccade-period hypotheses and concluded that the use of efference copy alone was sufficient to suppress oscillopsia in all subjects and individually in each plane of eye motion.¹⁴⁴ When a person with INS has an afterimage (e.g., after a bright flash bulb), that afterimage oscillates with respect to the rest of the visual scene, which is perceived as stable (LFD, personal observation, circa 1945). Thus, the retinally stable afterimage is perceived as oscillating, whereas the retinally moving images of the world are perceived as stable. Individuals with INS respond normally to all of the common target inputs (pulse and step changes in position, ramps, and step ramps, etc.) despite their retinal images, confounded by the INS.³ Efference copy was postulated as the means by which that is achieved. Retinal image stabilization produces oscillopsia in individuals with INS, suggesting that an extraretinal signal (efference copy) may be used by the brain to cancel out the INS waveform.¹³³

We also studied oscillopsia of a migraine aura in an individual with INS,¹⁴⁵ as well as vertical oscillopsia secondary to a decompensated phoria; the latter event led to the discovery of subclinical seesaw nystagmus in

the horizontal-torsional waveforms of INS (see Section 2.1.12.1).^{58,150} The cortically stable migraine aura is similar to a retinally stable afterimage and both produce oscillopsia. The aforementioned studies of oscillopsia suppression in INS, and its absence in FMNS, disproved several possible hypothetical mechanisms. When taken together, these studies led to the conclusion that efference copy of motor signals was the mechanism by which oscillopsia is suppressed despite retinal-image oscillation in INS and other types of nystagmus.^{70,132,133,137,146–148,151,152}

As discussed at the beginning of this chapter, one of the first conclusions produced by the study of INS was that the normal OMS could not be adequately represented by models whose sole inputs in the determination of eye-movement responses was retinal error signals.³ Because subjects with INS exhibited normal responses to various target inputs, such simplistic models of the normal OMS, which were incapable of reproducing the normal INS responses, were determined to be a poor representation of the OMS. Instead of retinal error signals, the OMS responses had to be driven by perceived target positions and velocities. That is, target position and velocity signals had to be reconstructed within the OMS from the retinal error signals and efference-copy signals. All of our subsequent models of INS capable of exhibiting the OMS behavior of INS subjects (as well as that of other ocular motor disorders) were based on that first model's use of efference copy.^{4,44–51,153} These behavioral OMS models had the added advantage of containing signals devoid of the INS waveforms that could be responsible for the perceived target position and velocity signals of INS subjects (i.e., the absence of oscillopsia).

2.1.11 Afferent Stimulation

The response to external trigeminal stimulation, when present, is robust and stimulus independent; touch, pressure, vibration, and subliminal electrical stimulation have all been found to damp IN.¹⁵⁴

2.1.11.1 CUTANEOUS TRIGEMINAL STIMULATION

Studies of the effects of afferent (cutaneous) stimulation of the ophthalmic division of the trigeminal nerve on IN were based on observations of the effects of contact lenses (see Section 2.4.2.2). Dell’Osso et al. documented 50% decreases in IN amplitude with pressure, vibration, or electrical stimulation.¹⁵⁴ They hypothesized that the afferent stimulation was affecting the proprioceptive calibration of the extraocular muscles since these fibers travel in the trigeminal nerve. These results infer that there is a strong effect on eye movement of changing the proprioceptive bias to the extraocular muscles despite the absence of a classical stretch reflex. Making the transition from experimental to therapeutically useful methods of external stimulation remains. However, these early observations were to be used in developing a new surgical therapy for INS, the tenotomy and reattachment (T&R) procedure (see Section 2.4.3.4) and a topical drug therapy (see Section 2.4.2.3).

Sheth et al. found afferent stimulation could increase foveation duration and developed an “acuity function” (NAFP),^{126,155} based on a prior function (NFF),⁶² that was the precursor to the NAFX (see Section 2.1.9.1). Their data, derived from both vibration and electrical stimulation applied to the forehead, identified foveation duration as the single most important factor determining acuity.

2.1.11.2 DEEP MUSCLE STIMULATION

Acupuncture involves the insertion of a needle in specific points in the neck muscle and mechanically or electrically stimulating it. Ishikawa et al. found a reduction in the intensity of nystagmus in 9 of 16 patients.¹⁵⁶ Vibration applied on the neck was found to be more effective than electrical stimulation in increasing INS foveation times and changing waveforms.¹⁵⁵ Acupuncture applied to the sternocleidomastoid muscles also produced improved foveation in 4 of 6 patients with two maintaining improvement after removal of the needles; INS waveforms were also modified in this latter study.¹⁵⁷

2.1.11.3 CONTACT LENSES

Abadi found that contact lenses damped the nystagmus and improved contrast sensitivity in a patient with INS¹⁵⁸ and others also found increased acuities in seven of eight patients.¹⁵⁹ Although eye-movement data documented that soft contact lenses damped IN, when used with anesthetic (to block afferent input), they did not.¹⁶⁰ That latter study, based on an observation of J. Lawton Smith (personal communication to LFD), established for the first time that exteroceptive feedback of the oscillation (via the inner eyelids and the ophthalmic division of the trigeminal nerve) could be used by the brain to damp IN. Slight pressure on the eyelid using a cotton swab also damped the INS waveform. The contact lenses damped the IN by more than 50% and increased acuity by 60% (20/40 to 20/25).

2.1.11.4 BIOFEEDBACK

Auditory biofeedback has been shown to damp IN and improve acuity.^{161–163} Ciufreda also found similar effects of biofeedback on INS.¹⁶⁴ Kirschen reported IN damping of 41%–73%.¹⁶⁵ In addition to damping IN, biofeedback has also been reported to increase foveation times by up to 180%.¹⁶⁶

2.1.12 Canine Nystagmus (Achiasmic Belgian Sheepdog)

After searching in vain for an animal model for INS that could be used in ocular motor research (Siamese cats notwithstanding) one was finally located in a family of achiasmic Belgian sheepdogs.^{167,168} Eye-movement recordings verified the presence of INS waveforms along with unyoked movements.¹⁶⁹ In contradiction to the then current concepts of vertebrate physiology,¹⁷⁰ these mammals had no crossing optic nerve fibers; essentially they were “anti-chameleons” and almost “anti-albinos.” This discovery, and the documentation of seesaw nystagmus in the achiasmic Belgian sheepdogs, would later give rise to the serendipitous

identification of human achiasma along with seesaw nystagmus.¹⁷¹

2.1.12.1 SEESAW

Because of the identification of seesaw nystagmus in two species with either achiasma or hemichiasma, its importance as a sign of these structural abnormalities was realized and led to the recommendation that a magnetic resonance image (MRI) of the optic chiasmal area was indicated in infants with seesaw nystagmus.¹⁷² We documented seesaw nystagmus in all of the achiasmatic mutant Belgian sheepdogs and compared it to that found in the human achiasmat.¹⁷³ We also studied the seesaw nystagmus in canine hemichiasma and suggested, based on our findings, that human hemichiasma might also exist.¹⁷⁴ Human hypochiasma was latter found to exist and also exhibited seesaw nystagmus.¹⁷⁵ It would latter be found that “horizontal” INS could also contain both torsional and subclinical seesaw components.⁵⁸ Careful and sensitive recording techniques are necessary to reveal the subclinical seesaw component to the IN.

As Figure 2.15 (top panel) shows, the subclinical seesaw nystagmus in INS is phase locked with the horizontal and torsional components, allowing foveation periods to occur in all planes simultaneously. Torsional motion does not seem to impair orientation perception thresholds, perhaps due to extraretinal information.¹⁷⁶ We hypothesized that subclinical seesaw nystagmus results from slight mismatches between the forces exerted by the vertical recti and oblique muscles, and it does not represent a true vertical-system instability; this contrasts with clinically visible seesaw nystagmus that accompanies achiasma (Fig. 2.15, bottom panel).

2.1.12.2 PENDULAR

The pendular IN recorded in the two eyes of achiasmatic Belgian sheepdogs could be independent in amplitude and phase.¹⁶⁹ This reflected the loose yoking of canine eye movements in general. Because of their large temporal monocular fields, they are able to move their eyes independently when necessary. Pendular nystagmus also

coexisted with jerk nystagmus (i.e., dual-jerk waveforms) in the canines.

2.1.12.3 TENOTOMY AND REATTACHMENT PROCEDURE

In addition to studying INS in a canine model and the discoveries associated with achiasma, the achiasmatic mutant Belgian sheepdogs presented us with a unique opportunity to test a decades-old hypothesis regarding the effects of extraocular muscle surgery on INS. Based on observations made during the study of the eye-movement improvements in human patients after the Kestenbaum procedure,¹⁷⁷ it was hypothesized that the important secondary benefits of broadening the null region and off-null damping were due solely to the tenotomy and reattachment of the muscle tendon, independent of its repositioning.¹⁷⁸ A new surgical procedure, the T&R procedure, was hypothesized to provide these therapeutic benefits to INS patients with either no lateral or convergence nulls, with a narrow null in primary position, or with APAN. We performed the T&R procedure on an achiasmatic mutant Belgian sheepdog in two stages separated by 4 months: (1) all four horizontal rectus muscles and (2) all four vertical rectus and four oblique muscles.¹⁷⁹ After each T&R stage, the dog showed immediate and persistent visible, behavioral, and eye-movement changes. Both the horizontal IN and the seesaw nystagmus were markedly damped (the latter appeared clinically gone). Fixation ability was improved as was the ability to maintain target centralisation (i.e., within the area centralis) (see Section 2.3.1.1 and Figs. 2.20b and c). Not only was this demonstration therapeutically successful but also it reaffirmed the importance to ocular motor control of the proprioceptive feedback loop controlling extraocular muscle tension. The addition of a proprioceptive tension control loop to the ocular motor system is illustrated in Figure 2.16. Proprioceptive muscle tension information and efference copy of motor signals are fed back to higher centers where target information is reconstructed, motor calculations and decisions are made, and motor control signals sent to the

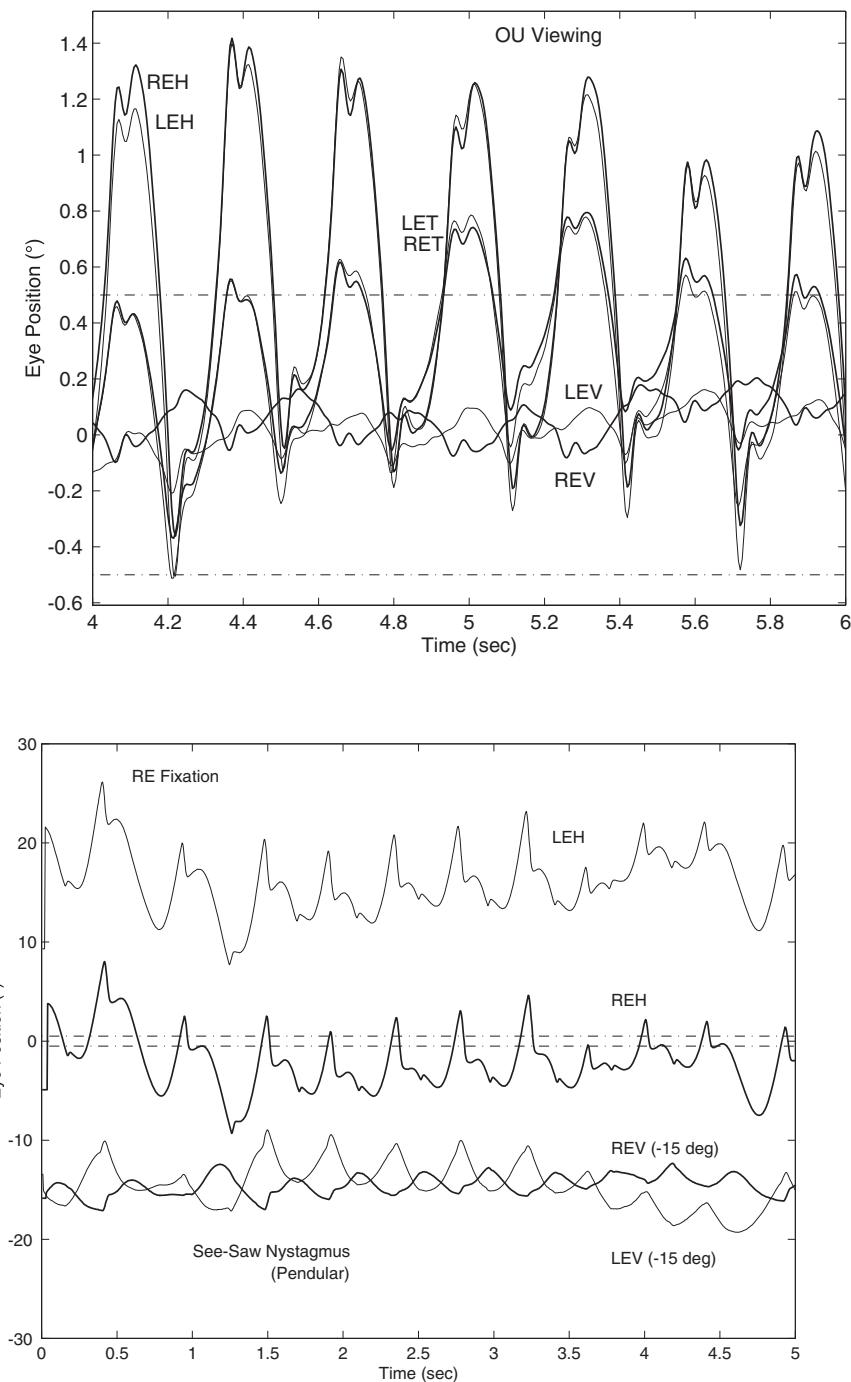


FIGURE 2.15 Horizontal, vertical, and torsional infantile nystagmus syndrome (INS) data demonstrating the phase relationships between the components in each plane of a patient with a subclinical seesaw vertical component (top panel). The horizontal and vertical data in the bottom panel are from INS with a clinically visible vertical component. In both patients, the horizontal INS was conjugate and the vertical, disconjugate; the torsional component in the top panel was in phase with the horizontal component. The foveation periods coincided in all planes. H, horizontal; RE, right eye; LE, left eye; T, torsional; V, vertical. In the bottom panel, the vertical data were shifted by -15° for clarity.

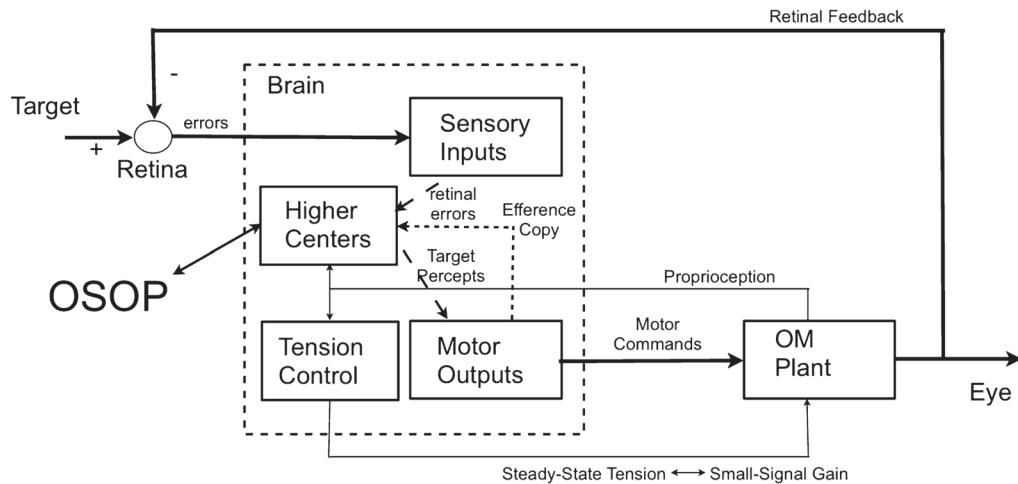


FIGURE 2.16 Block diagram showing how a proprioceptive tension-control feedback loop provides information from the ocular motor (OM) plant (specifically the extraocular muscles) that, combined with efference copy of motor signal outputs, aids in the reconstruction of target information from retinal input signals. The presence or absence of oscillopsia (OSOP) depends on the accuracy of these signals and the internal calculations that result.

ocular motor plant. The suppression of oscillopsia depends on the accuracy of these signals and the internal calculations that result.

2.1.13 Canine Model of Infantile Nystagmus Syndrome with RPE65 Retinal Degeneration (Briard)

Not only has the ocular motor study of “man’s best friend” resulted in the discovery of mammalian achiasma and a new INS therapy, but dogs have also played a key role in a new genetic treatment for Leber’s congenital amaurosis and the accompanying damping of the associated IN. A colony of Briard dogs with RPE65 deficiency was used to document the INS changes subsequent to gene therapy applied subretinally.¹⁸⁰ The NAFX values were substantially increased after gene therapy as the IN was clinically undetectable. In a second study, the time course of improvements was studied.¹⁸¹ INS waveforms were pendular, jerk, and dual-jerk in different dogs. It was found that the INS improvements occurred no sooner than 10 weeks after treatment in all but one case, which occurred in 4 weeks. Both unilateral treatment leading to bilateral IN damping and bilateral treatment (but unilateral electroretinogram

response) leading to either unilateral or bilateral IN damping were seen in different dogs. This pioneering work led to successful safety and efficacy trials of AAB2-mediated gene transfer in these canines¹⁸² and in humans.¹⁸³

2.2 ETIOLOGY OF INFANTILE NYSTAGMUS SYNDROME

The term “congenital” is fundamentally inaccurate since the nystagmus only occasionally appears at birth. When questioned, parents and relatives will usually relate an onset of nystagmus between 8 and 12 weeks of age.¹⁸⁴ In hereditary cases, however, INS has been documented at birth by the obstetrician and the families, who are aware of the possibility and carefully observe the baby’s eyes.^{33,185} Rarely, INS can manifest for the first time in the teens or beyond, and it can cause blurred vision and oscillopsia by disrupting the long-standing sensory and motor adaptations that the patient has developed to remain asymptomatic.¹

Although numerous studies have described INS pathophysiology and its effect on the visual system, until recently its etiology remained elusive. Defects involving the saccadic, optokinetic,

smooth pursuit, and fixation systems as well as the neural integrator for conjugate horizontal gaze have been proposed. Many clinical conditions, including genetic predisposition, are associated with the INS oscillation. Regardless of these clinical associations, nearly all patients with INS have infantile onset in common; strongly suggesting that this oscillation is most likely to occur in an immature ocular motor system.^{186–189}

Early theories regarding the cause of INS focused on the notion that the oscillation must result from an inherent abnormality in one of the ocular stabilization systems (i.e., the smooth pursuit system, the optokinetic system, the VOR, or the fixation system). Patients with INS do not have any known “focal lesion,” only miscalibrated motor control systems. Dell’Osso et al. have proposed that INS seems to conform to an increase in the damped oscillation of the normally functioning pursuit system.^{49,190} This loosely translates as an error in “calibration” of smooth pursuit that becomes evident during attempted fixation or other ocular motor tasks. A behavioral, biomedical control-system model based on that hypothesis has reproduced INS waveforms, characteristics, and ocular motor responses.

As has been previously stated, in addition to IN, other types of nystagmus (and saccadic oscillations) may also occur at, or shortly after, birth and should not be confused with, or lumped together with, IN. The other types of nystagmus are different from IN in waveform (mechanism) and clinical characteristics. Other benign types of nystagmus appearing in infancy are the nystagmus of FMN, spasmus nutans, and the nystagmus blockage syndrome (NBS). The physician need not be concerned with whether the nystagmus appeared “at birth” or in the first few weeks after birth as INS has been documented to appear at any time from birth through infancy; indeed in rare cases, it may appear later in life.²² More important is (1) determining whether this is a benign nystagmus or one that suggests disease and, (2) if benign, determining whether it is INS, FMNS, spasmus nutans, or the NBS.

The *motor eye sign*, IN, is defined as follows: either a pendular or jerk nystagmus resulting from a slow eye movement instability producing

periodic motion of the eyes away from and back to an intended gaze angle or target (*not* across the target).³¹ The pendular waveforms of INS look sinusoidal, but they are usually distorted by both flattening and the presence of small foveating saccades on the peaks corresponding to where target foveation occurs. The jerk waveforms of INS are caused by an instability that leads to an acceleration of the eyes away from the intended gaze angle or target and requires a saccade (“braking” saccade) in the opposite direction to stop that runaway. This braking saccade might return the eyes back to the target (“foveating” saccade) or begin a slow eye movement back to the target for refoveation. The direction of IN is defined by the direction of that saccade, although it is the slow eye movement that causes the IN. This is consistent with the convention used to define the direction of all types of jerk nystagmus. IN is usually horizontal but occasionally may have vertical components in some patients; torsional components are common and there may be a subclinical seesaw component.⁵⁸

Because INS is a motor instability, its direct cause in all patients with INS is the failure of one or more parts of the OMS to develop (calibrate) properly in order to maintain stable eye position. Many different types of afferent visual deficits may contribute to, or even facilitate, that failure in ocular motor calibration but none of them are truly causative. Harris and Berry proposed the INS may develop as a developmental response to reduced contrast sensitivity to high-spatial frequencies in an early critical period.¹⁹¹ In many INS patients, there are no afferent visual deficits. Therefore, it is both misleading and incorrect to infer causality by (1) classifying IN as consisting of “sensory” and “motor” subtypes; (2) to state that IN is a disorder indicative of “a primary disturbance of either the ocular *motor* or visual sensory systems”; or (3) using the term “idiopathic” when no sensory abnormality is found. *The primary disturbance responsible for all IN is known and it lies within the OMS (see Section 2.2.3).*

2.2.1 Familial (Gene Defect)

INS may appear spontaneously or, in some families INS is hereditary, as can be seen by its

presence in more than one member. However, when information about other members of the family is unavailable or if the individual with INS is the only known member of the family to have this disorder, one still cannot rule out a heredity component (spontaneous genetic mutation, capable of familial transmission).

Shallo-Hoffmann et al. studied the eye movements of family members of subjects with INS.¹⁹² In each of five families, abnormalities of seemingly nonaffected members were demonstrated; in four, saccadic instabilities were found and in the fifth, an INS waveform. Increased frequencies of square-wave jerks and square-wave oscillations were seen in family members. This is a curious finding since INS is due to a slow-eye-movement instability, not saccadic. Neither the reason why unaffected family members would demonstrate saccadic instabilities nor the relationship of such instabilities to INS is clear. The results of this study suggest that, in isolated cases of INS, the presence of saccadic instabilities in family members might be indicative of hereditary INS. Hereditary vertical pendular IN was documented in two sisters¹⁹³ and carriers of blue-cone monochromatism may have vertical (upbeat and downbeat) nystagmus and FMNS.¹⁹⁴ Nystagmus has been reported with many other hereditary conditions, but these reports usually do not contain accurate eye movement records and preclude the identification of the nystagmus as IN.^{195–201} In one report of three patients with congenital absence of conjugate horizontal eye movements and nystagmus, recordings did show a pendular nystagmus in two of the three.²⁰²

An interesting Japanese pedigree of hereditary INS in five generations was attributed to X-linked irregular dominant transmission.²⁰³ Absence of male-to-male transmission and generation skipping was noted. The INS waveforms were predominately pendular and there was good central vision and an absence of sensory defects in this pedigree. These patients are further examples that waveform cannot be used to classify IN as “sensory-defect” nystagmus. In another paper, five male infants who showed findings of abnormal auditory brain-stem response and pendular IN were reported.²⁰⁴ Also exhibited were hypotonia of head

and limbs in the early infantile period and later paresis. Unfortunately, the method for recording the eye movements was poor and it was impossible to identify the INS waveforms from the figures provided. If the time constant given was correct, the recordings more accurately reflect eye velocity than position. Given their other abnormalities, it is possible that these patients had both INS and other neurological disorders as suggested by the authors. Leigh and Khanna raised the possibility that INS could result from a congenital channelopathy, which causes similar hereditary acquired forms of nystagmus such as episodic ataxia type 2.²⁰⁵

An animal model for IN was thought to have been produced in monkeys by monocularly depriving them of vision at birth, then reversing their sutures 25 days later.³⁸ A variable nystagmus that could be jerk, pendular, or combinations of both was observed; the slow phases of the jerk nystagmus were of increasing velocity. Also, a latent component was noted on cover testing. At the time of that study, there was no known animal model for IN and one would not be confirmed until the eye movements of members of a family of achiasmic Belgian sheepdogs were recorded.^{167,173,206}

Hereditary INS may be sex-linked, recessive or dominant; the dominant form has been linked with chromosome 6p12.²⁰⁷ A genetic study of INS (including APAN) revealed mutations of the FRMD7 gene in 10 families; however, not all in those families had APAN.²⁰⁸ In recent years, there has been an explosion of genetic studies of INS families.^{185,209–223} One study found no causative mutations and no correlation between nystagmus and X-linked ocular albinism.²²⁴

We know that the FRMD7 mutation, which is associated with X-linked INS, is expressed in the ventricular layer of the forebrain, mid-brain, cerebellar primordium, spinal cord, and the developing neural retina.^{210,225} To date, five nystagmus loci (NYS 1–5) have been described in the literature associated with INS; they are shown in Table 2.2.^{185,210,225} Within the NYS1 locus (Xq26.2), the FRMD7 gene was identified. Subsequently other groups have also confirmed this.^{226–228} This protein is homologous to another protein that is known to alter the length

Table 2.2 Genetic Loci of Infantile Nystagmus

LOCUS	OMIM NO.	GENE	INHERITANCE	PUBLICATION
NYS 1 (Xq26.2)	310700	FRMD7	X-linked	(Tarpey et al., 2006)
NYS 2 (6p12)	164100	No	Autosomal dominant	(Kerrison et al., 1996)
NYS 3 (7p11.2)	608345	No	Autosomal dominant	(Klein et al., 1998)
NYS 4 (13q31–33)	193003	No	Autosomal dominant	(Ragge et al., 2003)
NYS 5 (Xp11.4-p11.3)	300589	No	X-linked	(Cabot et al., 1999)

and degree of branching of neurons as they develop in the midbrain, cerebellum, and retina, which could provide a motor and combined visual and motor underpinning for the occurrence of INS. The expression of FRMD7 has been shown in neuronal tissue in the developing retina, midbrain, and hindbrain, although it is not clear which specific gaze control systems may be involved.^{210,225} The predominant clinical phenotype associated with FRMD7 mutations has also been characterized and it has been reported that unaffected carriers can have a subnormal OKN gain.¹⁸⁵ Recently it was shown in Neuro-2A cells that FRMD7 has a role in neuronal outgrowth and development.²²⁵

Furthermore, detailed discussion of genetics is beyond the scope of this chapter. However, it should be remembered that even in “hereditary” INS, an identified gene variant is *not* the direct cause of INS and the conclusions reached in many genetic studies of INS claiming causality are both premature and unwarranted. There is neither proof of causality nor any specific mechanism known by which that particular gene variant causes INS. The tendency by some to consider genes as if they acted alone, is simplistic and inaccurate. Specific genes act in concert with *all other genes*, not in a vacuum. Researchers studying the genetics of INS face the danger of making the same unfounded logical errors, as did their predecessors who erroneously attributed causality to sensory deficits that were merely associated with INS. Like the plethora of associated sensory deficits, the ever-increasing gene variants found in families with INS should be considered *associated, facilitating*

factors to the direct cause of most INS waveforms (i.e., a developmental failure in the delicate calibration of the smooth pursuit damping circuitry).⁴⁸

Claiming several different “genetic causes” of INS²²⁹ mimics the aforementioned logical error exactly—many “causes” means a failure to identify the direct cause. The continued use of the term “idiopathic,” restricted to only those with no clear “sensory” deficit, perpetuates the discredited notion of sensory causality for some cases of INS. Failure to identify a single cause for the IN in any of the putative patient subtypes leads to the conclusion that they should all be called “idiopathic.” The driving force behind the aforementioned paper appears to be the medical classification of subtypes of INS *patients* rather than of IN itself, although the distinction went unappreciated.

Clearly, INS patients with various types of sensory deficits (including none) differ medically and therapeutically, although not so much as had been thought regarding IN treatment. Just as clearly, eye-movement data from thousands of INS patients (recorded in several laboratories) demonstrate that their IN, or its direct cause, does not differ. Despite extensive investigation, only some “subtle” differences in IN frequency (uncorrelated to visual function) were found from the sample of patients with albinism in that study; all other IN characteristics important to visual function (e.g., foveation time and the NAFX values) were the same.²²⁹ Unfortunately, the IN data were taken only in the $\pm 15^\circ$ range of gaze angles, thereby limiting amplitude and, more important, waveform variations. It is not

surprising that patients with foveal hypoplasia would be slower to insert braking and foveating (i.e., resetting) saccades into their “pendular” waveforms, thereby exhibiting a slightly lower frequency—that does not equate to either a different type of nystagmus or a different cause.

Although the genetic association listed earlier provides a possible causal relationship, the etiology of the INS oscillation may be multifactorial (genetic, inflammatory, developmental, infectious, etc.) if the final common pathway is interference with ocular motor calibration during a developmental period of “sensitivity,” at which time an insult results in possibly irreversible changes. Sensitive periods during development of visual functions are well recognized, for example, contrast sensitivity, stereopsis, visual acuity, and binocularity.^{230,231} Motor-system calibration is an active process that may start in utero and continues at least through early infancy. Sensory-system development is a parallel visual process that has been more thoroughly studied and also continues to develop through the first decade of life. Previous studies have documented connections between parallel visual processes (cross-talk) that modify, instruct, and coordinate these systems, resulting in smooth and coordinated function.^{232,233} Although INS may result from a primary genetic defect directly affecting ocular motor calibration, it may also result from abnormal cross-talk from a defective sensory system to the developing motor system at any time during the motor system’s sensitive period. This can occur from conception due to a sensory defect (e.g., retinal dystrophy), during embryogenesis due to a developmental abnormality (e.g., optic nerve hypoplasia), or after birth during infancy (e.g., congenital cataracts). This theory of the genesis of INS incorporates a pathophysiologic role for the sensory system in its genesis and modification. While the set of physiologic circumstances may differ, the final common pathway is abnormal calibration of the ocular motor system during its sensitive period. The primary ocular motor instability underlying INS is the same but its clinical and oculographic expression are modified by both initial and final developmental integrity

of all parallel afferent visual system processes. As mentioned previously, this new knowledge caused us to abandon the classic “motor” and “sensory” classification introduced by Cogan over 30 years ago.²⁴

The block diagram in Figure 2.17 summarizes the concepts regarding the direct cause of INS and those other conditions that may facilitate the development of INS in a particular subject. The ocular motor oscillation in INS develops directly from deficits within the smooth pursuit (most waveforms) and visual vestibular (some waveforms) subsystems. Many factors determine whether miscalibration of these subsystems develops or to what degree that miscalibration develops in each. These factors may facilitate miscalibration to various degrees but cannot be considered the direct cause of INS. As Figure 2.17 indicates, ocular motor research has eliminated many of the components of the OMS as possible causes of INS, including fixation, saccadic, and final common neural integrator.

2.2.2 Developmental Disturbance of the Ocular Motor System with Associated Sensory System Deficit

Several papers emphasize the associated sensory defects found in individuals with INS.^{234–236} Some have stressed the high percentage of INS patients with these defects, but this may reflect the authors’ patient population more than the INS population in general. Whatever the numbers, two things are clear: (1) physicians do have to look for any sensory defects that may be present in an individual with INS and treat them; (2) no matter what the sensory defects are, the INS is still a *motor* instability. The sensory defects discussed next are commonly associated with INS of all waveforms.

INS is caused by a primary motor defect and there is no preponderance of any specific waveform with the presence or absence of an associated sensory defect. One of the initial findings that resulted from accurate eye-movement recordings was that both the etiology and the mechanisms underlying INS waveforms are independent of accompanying sensory

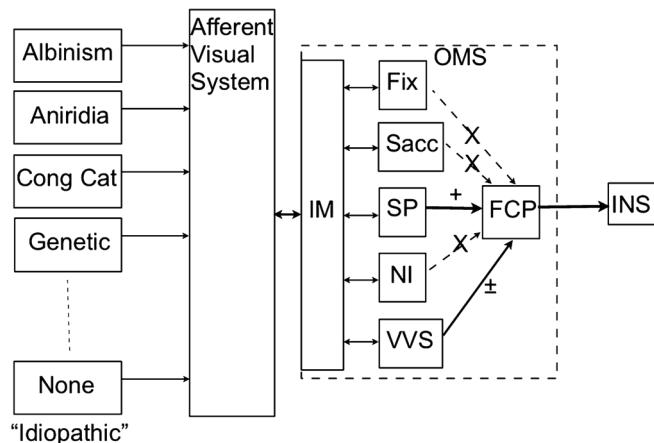


FIGURE 2.17 Block diagram summarizing the differences between the many possible conditions that may facilitate the development of infantile nystagmus syndrome (INS) in an individual and the final direct cause of INS itself. Cong Cat, congenital cataracts; FCP, final common pathway; Fix, fixation subsystem; IM, internal monitor; NI, neural integrator; OMS, ocular motor system; Sacc, saccadic subsystem; SP, smooth pursuit subsystem; VVS, visual vestibular subsystem; X, subsystems whose deficits do not cause INS; + and \pm , subsystems whose deficits do cause INS.

defects.³³ Therefore, although there is an association between many sensory defects and the presence of INS,²³⁵ the former appear to be secondary factors provoking the manifestation of INS in individuals where there is already a primary predisposition for the latter. In many patients, sensory defects are the precipitating factors of INS. This correlation is particularly high in chiasmal disorders, such as found in albinism or in achiasma (Belgian sheepdogs^{167,169} or human^{172,173}). In the former there are too many crossing fibers and in the latter, none. Thus, two opposite deficits induce the same ocular motor instability; this supports the hypothesis that any disruption to the afferent visual system in the early stages of development may result in INS. To put it quite simply, due to the inherent instability in normal ocular motor development, INS is a disorder waiting to happen.

Despite the eye-movement data that prove conclusively that INS is a unitary entity (i.e., a motor sign indicating ocular motor instability) the early, erroneous idea that there existed two types of INS, “sensory” and “motor,” persists.^{23,235} The term “motor INS” is redundant and “sensory INS” is misleading (meaningless) for the reasons discussed earlier; neither should be used. Rather

than accepting the factual data, some have inverted (perverted) them by claiming that eye movement data “cannot differentiate” between these two putative types of INS.¹¹⁸ That is similar to claiming that fingerprint analysis cannot differentiate between two prints left by the *same* person. Totally lost in such an argument are the facts that the same sensory defects (including albinism, which has incorrectly been claimed to always be accompanied by INS) exist in patients without INS, and INS exists in many individuals who have no sensory defects. Simple logic dictates that sensory defects are neither the necessary nor sufficient conditions for the development of INS.

One should not, however, ignore the association between sensory defects and INS present in many individuals. Since *any* of several different sensory abnormalities (each affecting the primary visual signal in unrelated ways) can affect the developing motor system such that it becomes unstable, the following possibilities are suggested: (1) a small percentage of individuals are born with a motor system that is precariously close to oscillation or (2) nature has evolved the OMS in such a way that the horizontal system is close to instability in many individuals. The reason for the latter hypothesis may lie in our

need for rapid horizontal eye motion to survive. Whatever the underlying reason, the developing motor system seems to require early visual input to assure its stability and any sensory defect interfering with the acquisition of that early visual input *might* result in the INS instability. In those individuals actually born with INS, the motor system may have developed with such a strong instability (owing to hereditary or spontaneous genetic factors) that even the presence of adequate visual input after birth (i.e., no sensory defects) is not enough to stabilize it. This latter group, where the INS is truly “congenital,” can include both those with only INS and those with associated sensory defects, not just the former.

In individuals who have a sensory defect, it, instead of the nystagmus, may be the limiting factor for acuity and even halting eye motion using forceps may not result in an acuity improvement; in other such individuals, acuity can be improved by damping the IN. One must perform the necessary diagnostic tests (e.g., the electroretinogram, visual evoked response, etc.) to correctly assess the functional integrity within the visual system and diagnose any sensory abnormalities present but that diagnosis is *not* sufficient to describe the motor defect causing the nystagmus. The latter requires motility recordings for absolute diagnosis since those with sensory defects might have one of the other types of nystagmus and not IN. If a patient with nystagmus has a best-corrected binocular visual acuity worse than 20/40, one should look carefully for other associated sensory system defects. Sensory defects may be more prominent in pediatric patient populations than in adult populations where there is a higher incidence of INS unassociated with visual defects.²³⁵ It is possible that there are two different genes with variable probabilities of the one facilitating the slow-eye-movement instability, IN and the other, the afferent defect. The presence of either of these genes might be related to the presence of the other by some third probability. Another possibility is that there is one gene with different probabilities for an afferent defect and INS; a patient may have both,

one, or the other; this has not been worked out and is outside the scope of this chapter. The diagnosis and treatment of the various sensory system abnormalities that may accompany INS also will not be extensively covered in this text; rather, we will concentrate on the proper management of INS and other forms of nystagmus in infancy and childhood.

2.2.2.1 ALBINISM

One specific group of patients who usually have INS are those with albinism. Here, as with INS, what was once a “clinical” diagnosis can now be made definitively by a simple diagnostic test based on the visual evoked potential (VEP). If performed properly using a pattern-onset paradigm, the VEP is highly sensitive and specific.^{237,238} This paradigm uses full-field, monocular pattern (checkerboard) onset/offset stimuli instead of pattern reversal stimuli; the latter contain motion artifacts and should *not* be used in individuals with IN or any other nystagmus. For children below the age of about 4 years, reliable results are obtained with a luminance flash paradigm. This paradigm demonstrated the unequivocal dissociation between the misrouted fibers found in albinos and their INS since no individuals with hereditary or only INS had misrouting. Thus, the hypothesis that misrouting is the cause of INS is incorrect and lacks physiological foundation; misrouting is but one of several sensory defects that *may* impede the development of a stable OMS.

One area that has received much attention and is the result of some confused ideas about the etiology of INS is in individuals with albinism. Most, but not all, albinos also have IN. All albinos exhibit asymmetry in the monocular visual evoked potential (VEP).²³⁹ However, not all albinos demonstrate nystagmus and therefore the link between aberrant projections and organization of the OMS in nonalbinos with INS is in question. They found no crossed projections in a nonalbino with nystagmus. A case of albinism with FMNS has also been reported.²⁴⁰ Apkarian and Spekreijse also reported another nonalbino with nystagmus who had

no crossed fibers.²⁴¹ In a test of 14 patients with INS, they found *none* with optic pathway misrouting (personal communication to LFD). In a study of 18 albinos, 5 of which had no noticeable nystagmus, all showed global stereopsis.²⁴² These findings are interesting when contrasted with the investigations in albino animal models where a paucity of binocularly driven cortical neurons is found in visual areas 17, 18, and 19. Other studies have also verified that albinos demonstrate VEP asymmetries, whereas those with only INS do not.^{243,244} Thus, since electrophysiological evidence has proven that individuals with INS do *not* have crossed fibers, hypotheses and models that rely on crossed fibers and “reversed” pursuit have no basis in fact.^{55,63,70,71}

Rosenberg and Jabbari suggested that a horizontal grating stimulus might be used where the conventional check stimulus for VEP produces poor results due to horizontal nystagmus. In a paper on the recognition and management of albinism, Abadi and Pascal described twin girls who had similar INS waveforms but whose fast phases were in opposite directions. In this paper the authors stated that all forms of albinism are characterized by nystagmus; this appears to be in contradiction to the studies mentioned earlier. As a final note on albinism and INS, it has been suggested that although acuity is primarily limited in albinism by retinal factors, reducing the IN can lead to an improvement.²⁴⁵ The value of the electroretinogram in the evaluation of children with early-onset nystagmus has also been examined.²⁴⁶

2.2.2.2 ACHIASMA

After the discovery of achiasma and hemichiasma in canines,^{167,174} it was confirmed and studied in humans.^{102,175,247–251} As in albinism, the absence or diminished number of crossing optic fibers is strongly associated with INS and additionally, with seesaw nystagmus.^{173,248,252} Indeed, the latter is a sign that imaging of the chiasm is indicated. The addition of achiasma to the long list of sensory deficits associated with INS and specifically its opposite effect on crossing fibers than albinism should finally lay to rest any

putative causal mechanism causing INS that is related to “reversed” signals.

2.2.2.3 INFANTILE STRABISMUS

Strabismus may or may not accompany INS, unlike in FMNS, where it is mandatory. Strabismus complicates both the differential diagnosis and treatment of INS. Because those with strabismus can change their fixating eye, the analysis of eye-movement data is made difficult, especially when trying to determine the foveation qualities of INS waveforms in the fixating eye. Without accurate monocular calibration, such determinations are highly problematic and may lead to errors in determination or prediction of visual acuities correlated to foveation functions applied to INS waveform data.

The problem of strabismus is misalignment of the eyes (i.e., a relatively static problem) and the aim of strabismus therapy is correct alignment of the two eyes (i.e., a static outcome, easily measured by the position of the eyes). Although restoring binocularity is also a medically desirable outcome, it is not the standard measure for successful strabismus therapy. INS, in contrast, causes an oscillation of both eyes that degrades foveation of targets of interest (i.e., a dynamic problem), and the aim of INS therapy is to reduce the oscillation and improve foveation quality (i.e., a dynamic outcome, easily measured by analysis of eye-movement data). Although improvement of peak visual acuity is also one of the medically desirable outcomes, it is not the standard measure for successful INS therapy. A far more important medical outcome is improvement of the range of gaze angles with high acuity; in some cases, that may be the standard measure. Other INS problems may include a head posture, adopted to exploit the gaze angle with maximal acuity. Head posture is not the variable to measure to quantify the problem nor is it the means to determine the therapeutic outcome of INS therapy. Rather, in all such cases, only measurements made from eye-movement data provide direct outcome measures of each of these INS-induced problems.

2.2.2.4 NONVECTORIAL VISUAL SENSORY DEFICITS

Visual sensory deficits that are nonvectorial but yet have been claimed to cause horizontal INS include achromatopsia (lack of color vision); aniridia (absence of irides); congenital stationary night blindness (deficient rod-cell response); foveal hypoplasia (maldevelopment of the fovea); optic nerve aplasia/dysplasia/hypoplasia/atrophy/colobomas; infantile retinal dystrophy/degeneration; and infantile visual deprivation. To date, no mechanistic hypotheses have been presented to support such claims. The incidence of congenital achromatopsia in a group of otherwise undiagnosed children was 29%, with 40% being erroneously classified as having “idiopathic” INS.²⁴⁶ The authors concluded that there was a need to use the electroretinogram in children where the diagnosis was uncertain. It has been claimed that those with congenital achromatopsia have a slow buildup of OKN in the temporal-to-nasal direction compared to the nasal-to-temporal direction, whereas others with INS do not.²⁵³

2.2.3 The Direct Cause(s) of Infantile Nystagmus Syndrome with or without Sensory/Genetic Deficits

A significant portion of this chapter contains information that dispelled long-held myths, misinformation, and erroneous conclusions regarding the direct cause(s) of INS. The diagnostic characteristics for each of the benign types of nystagmus of infancy are unambiguous. Each type can be differentiated by simple eye-movement recordings that simultaneously provide the data necessary for effective therapeutic intervention. Regardless of time of onset, the waveforms recorded from individuals with INS are overlapping combinations from the same group. Not only are the waveforms the same but also the motor mechanism(s) in all instances are the same; there is only one INS, independent of time of onset or associated sensory or genetic deficits. With the aid of recorded eye movements, the diagnostic criteria for INS are definitive. Many of the 12 waveforms that were

originally identified in INS²⁵ are pathognomonic of INS except pure pendular or linear (sawtooth) jerk; either of these could be an acquired nystagmus and the latter, FMNS. However, the pendular nystagmus of INS is usually distorted so the patient can foveate, whereas in acquired nystagmus it is not. In acquired nystagmus, the slow phases can be linear, of increasing velocity, of decreasing velocity, or pendular. IN slow phases can be pendular, increasing velocity, or some may be linear. Within the pendular or jerk major INS waveform categories, three different forms of pendular and eight of jerk (four unidirectional and four bidirectional) were identified. Additionally, dual-jerk is the superimposition of a high-frequency, low-amplitude pendular nystagmus of different origin on a jerk INS waveform with either increasing velocity or linear slow phases; illustrations and examples are available in the literature^{25,254} and in Figure 2.4. In a group of patients with INS, 87% had more than one INS waveform; they had various combinations of the 12 originally described waveforms. A small percentage of patients (13%) exhibited only one waveform. Distinguishing the subtle characteristics of INS waveforms required DC-coupled, high-bandwidth recordings of both eyes simultaneously.

2.2.3.1 LOSS OF SMOOTH-PURSUIT DAMPING

Most INS waveforms are directly caused by a failure in calibration of an internal feedback loop in the smooth pursuit subsystem; they are the pendular and most jerk waveforms and are identified in Figure 2.2 as PSN. Our behavioral ocular motor system model demonstrates how this simple, albeit evolutionarily probable, miscalibration in an otherwise normal ocular motor system can produce the complex waveforms recorded in INS. For all INS waveforms, the intersection of the Alexander’s law relationships (see Section 2.2.3.2) in the two directions results in a null centered in primary position, and asymmetry of those relationships results in an eccentric null position. The steeper the slopes of the Alexander’s law relationships, the faster will be the rise in IN amplitude as gaze is

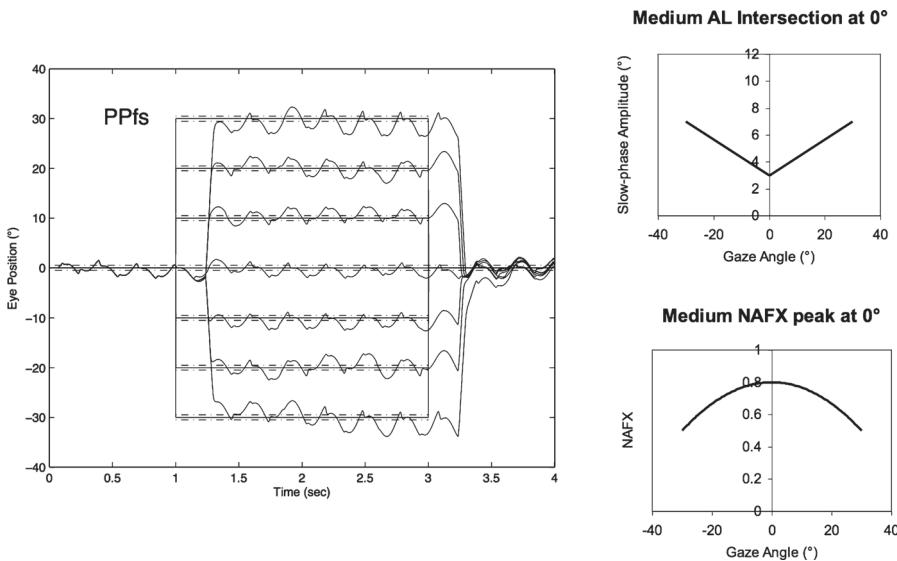


FIGURE 2.18 Simulation of pseudopendular with foveating saccades (PPfs) waveform variation as a result of a centered intersection of the Alexander's law (AL) relationships with moderate slopes. As gaze is directed away from the null, the infantile nystagmus syndrome amplitude increases slowly. The eXpanded nystagmus acuity function (NAFX) versus gaze angle curve corresponding to such a variation is also shown with its moderate sharpness.

directed away from the null position. To illustrate the effects of different Alexander's law relationships on INS without the confounding influence of changing waveforms, Figures 2.18

and 2.19 show simulations of an individual with INS whose waveforms remain constant with gaze angle rather than the more common simulations shown in Figure 2.8, where neutral-zone

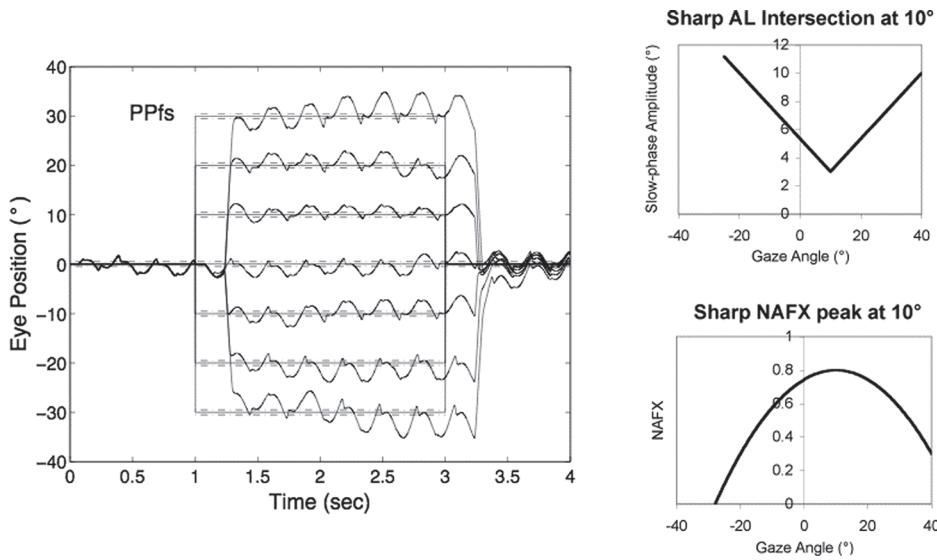


FIGURE 2.19 Simulation of pseudopendular with foveating saccades (PPfs) waveform variation as a result of a right-gaze intersection of the Alexander's law (AL) relationships with steep slopes. As gaze is directed away from the null, the infantile nystagmus syndrome amplitude increases rapidly. The sharp eXpanded nystagmus acuity function (NAFX) versus gaze angle curve corresponding to such a variation is also shown.

pendular waveforms become jerk waveforms with lateral gaze. Figure 2.18 shows the gradual rise in PP_{FS} waveform amplitudes produced by relatively moderate slopes intersecting at primary position. The corresponding NAFX versus gaze angle curve is shown below the Alexander's law relationship. In Figure 2.19, the steeper slopes and eccentric intersection produce a null in right gaze and a rapid increase in PP_{FS} amplitudes with corresponding sharper NAFX curve, as gaze is directed lateral to that null (see also Chapter 5, Table 5.3).

2.2.3.2 TONIC VISUAL VESTIBULAR IMBALANCE

A small number of INS waveforms are directly caused by a tonic imbalance of steady-state neural signals in the visual vestibular subsystem; they are those with linear slow phases identified in Figure 2.3 as VVSN. Our behavioral ocular motor system model produces linear slow phase jerk nystagmus when such a tonic imbalance is present. The model contains Alexander's law relationships that increase the tonic imbalance as gaze is directed laterally.

2.3 VISUAL FUNCTION DEFICITS AND MEASUREMENTS OF INFANTILE NYSTAGMUS SYNDROME

2.3.1 Static Deficits

Static visual function in INS is diminished in several ways that are not adequately detected or measured by current clinical examination. The restriction of the patient's high-acuity range of gaze angles by the characteristic worsening of the INS waveform at gaze angles lateral to the "null" is a major impediment to good visual function. Simply assessing the BCVA, either in primary position, at the "null" angle, or both does not identify the true visual function deficit in INS. Such restricted measures also fail to differentiate the amount of visual function loss that is directly attributable to either an associated visual sensory loss or to the INS itself. This can only be done using analysis of eye-movement data.

Finally, changes in peak visual acuity is a poor direct outcome measure of INS therapy and, in some cases, may show no improvement despite significant improvements in other factors defining overall visual function; that can obscure the success of INS therapies by incorrectly classifying these patients as "not improved." INS deficits are an addition to, and complicated by, those caused by associated visual sensory deficits. It is important to both understand the differences between INS deficits and purely visual deficits, to be able to separate and quantify both types of deficits, and to be able to measure and predict the improvements to the former (i.e., INS deficits) from INS therapies. Only then can the proper treatment be prescribed and its expected effects accurately measured.

2.3.1.1 THE EXPANDED NYSTAGMUS ACUITY FUNCTION AND LONGEST FOVEATION DOMAIN MEASURES

The nystagmus acuity function (NAF) provides an objective determination of potential visual acuity from measurements of the key characteristics of the INS waveform: foveation time and the standard deviations of foveation position and velocity means (for NAF) or position mean alone (NAFP).¹⁵⁵ For those subjects whose foveation ability is not *well developed* (i.e., the target image always falls within the default foveation window), the window used for its calculation can be enlarged and the "expanded" NAF (NAFX) plotted versus gaze or convergence angle. Thus, the NAFX reverts to the original NAF when the default foveation window is chosen. Because of inter- and intrasubject variation in INS waveforms, the relative impact of each of the three foveation characteristics on visual acuity varies. Thus, despite claims to the contrary, attempts to correlate only one or two of them to visual acuity^{130,255} can only be approximate or limited to specific waveforms and cannot accurately duplicate either the analytic or predictive abilities of the NAFX in most cases.

The current NAFX software can assess horizontal, vertical, or multiplanar foveation quality.¹²⁸ The software calculates the NAFX from eye-movement data and provides a quantitative

method for evaluating different therapies for their effect on potential visual acuity.¹²⁷ Plots of the NAF or NAFX versus visual acuity reveal the linear relationship that allows intersubject prediction of potential visual acuity.¹⁹⁰ The NAFX can also be used to compare potential acuity across subjects with different types of nystagmus (IN or FMN) or to predict the acuity increase possible after therapeutic intervention in a given subject. The latter is accomplished by plotting the NAFX versus gaze or convergence angle. Figure 2.20a shows the NAFX outputs during far and near and far fixation from a subject with achiasma, recorded in Laboratory of

H. Collewijn in Rotterdam (see Albinism and Achiasma sections 2.2.2.1 and 2.2.2.2).¹⁷¹ As the NAFX clearly shows, conditions for highest visual acuity occurred during near fixation where (as the bottom panels show) a smaller foveation window could be used to calculate the NAFX. Figure 2.20b shows the NAFX outputs from an achiasmatic Belgian sheepdog, pre- and post-T&R, demonstrating the effectiveness of the T&R treatment. As the bottom panels show, the post-T&R nystagmus is subclinical and well within the boundary of the area centralis; the nystagmus during the whole interval qualified as a foveation period. Figure 2.20c shows the

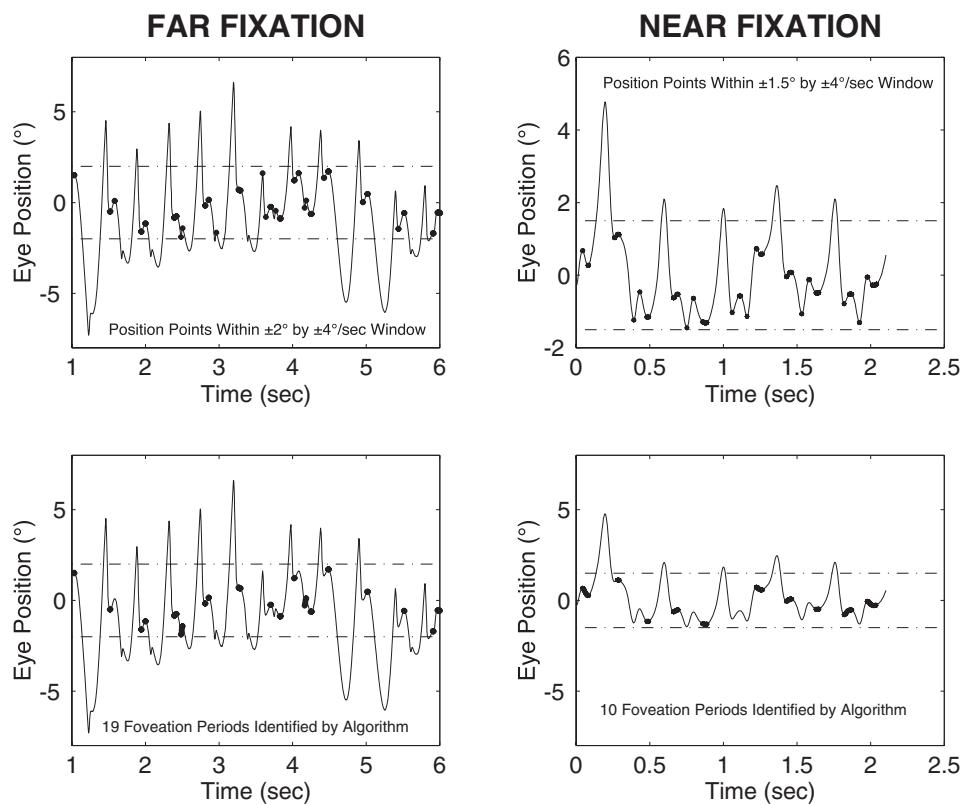


FIGURE 2.20 (A, above) The eXpanded nystagmus acuity function (NAFX) output for a subject with achiasma during far and near fixation, demonstrating improvement at near by the smaller foveation window and lower variation of foveation position. (B) The NAFX for an achiasmatic Belgian sheepdog demonstrating dramatic postoperative improvement by the relative sizes of the nystagmus and the $\pm 3^\circ$ centralis window. (C) NAFX versus visual acuity for both humans and canines, demonstrating improvement at near fixation (humans S1 and S2), at far with base-out prisms (S1), and after tenotomy and reattachment (canine S3). The dot-dashed lines indicate the extent of the foveal window (humans) or area centralis (canines). The thickened areas identify foveation (human) or centralisation (canine) periods in NAFX outputs.

(continued)

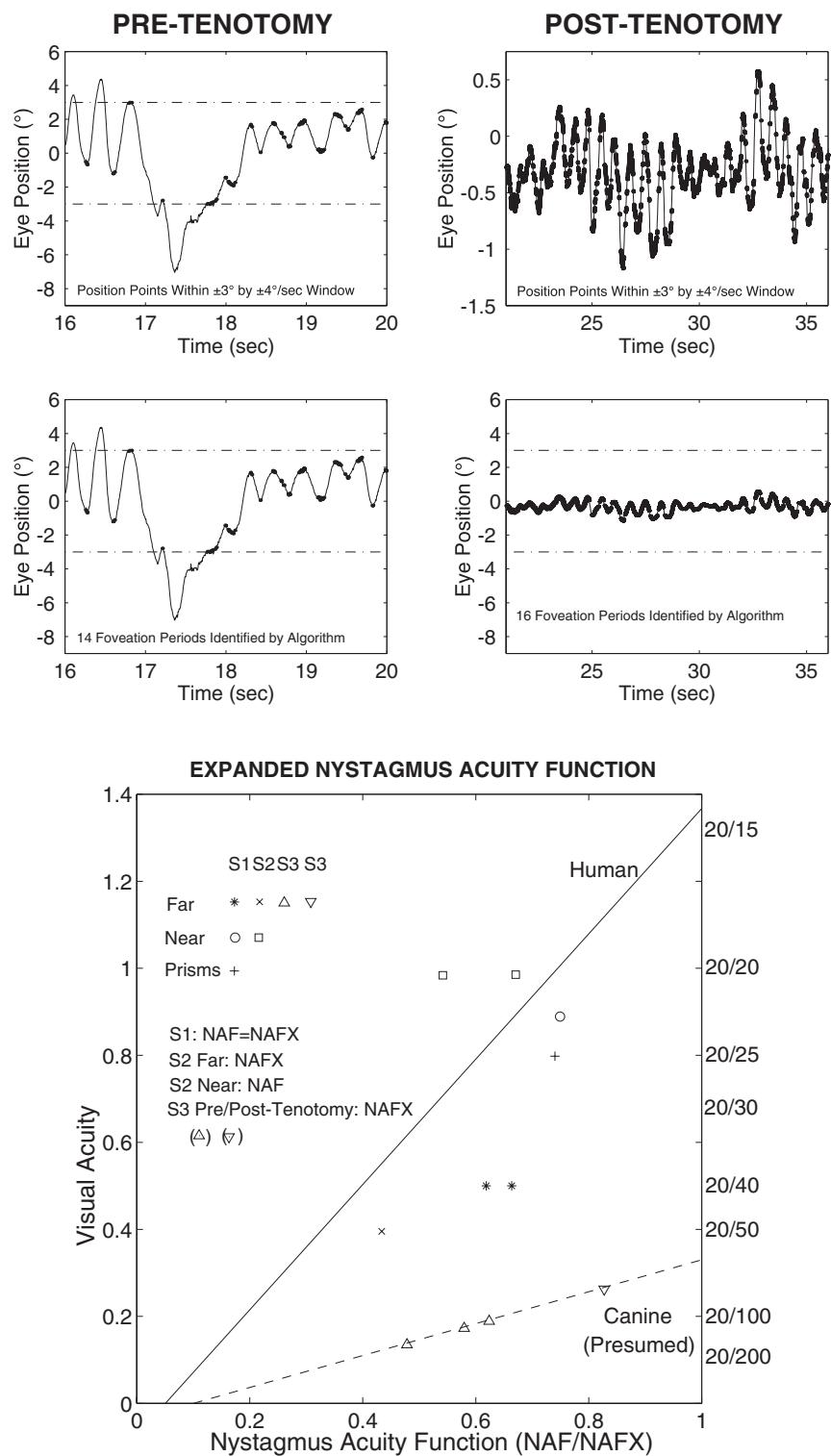


FIGURE 2.20 B. top, C. bottom.

NAFX versus potential (solid and dashed lines) and measured (symbols for the human data) visual acuity for two humans (S1 and S2) and a canine (S3). The NAFX (and potential visual acuity) is higher at near than at far (S1 and S2) or while using base-out prisms at far (S1). For the canine, the post-T&R NAFX is higher than preoperatively and the dashed line is inferred from veterinary data.

Because of its direct relationship to potential visual acuity (specifically, the motor component of visual acuity), the NAFX is the best available outcome measure of therapies designed to affect the INS waveform.²⁵⁶ Although amplitude is related to cosmetic appearance, neither it nor frequency is closely correlated with acuity. Bedell suggested that some INS patients have amblyopia that is amenable to treatment with proper refraction.²⁵⁷ Although that may be true, INS itself does not produce amblyopia since improving foveation periods in INS by surgical, optical, or other means immediately results in improved visual acuity in most INS patients. It appears that the existence of foveation periods in the INS waveforms is sufficient to prevent amblyopia in cases where there is no other underlying cause present.

For multiplanar INS, the foveation periods in each plane must be phase locked for maximum acuity. As a practical matter, the horizontal and vertical foveation periods are more important since torsion contributes little retinal motion at small distances from the center of the fovea.⁵⁶ Fortunately, from data taken so far, it appears that the foveation periods in all three planes are phase locked (see Fig. 2.15). The horizontal foveation periods are phase locked to both the subclinical torsional and seesaw components of the oscillation. The current NAFX software can be used to measure the potential acuity of multiplanar INS.¹²⁸

2.3.2 Dynamic Deficits

In addition to the static deficits in visual function (lower peak visual acuity and narrow range of gaze angles with high acuity), there are *dynamic deficits* associated with INS. They include increased times to acquire (i.e., foveate)

both new stationary targets and moving targets. Thus, the usually simple and rapid task of scanning a room full of people to identify familiar faces becomes both difficult and slow; also, performance in sports is diminished. Currently, neither these visual function measures nor their possible improvement after therapy is assessed clinically. That omission, plus the failure to use eye-movement data to assess all of the pre- and posttherapy measures, introduces false-negative findings in clinical trials limited to peak visual acuity or other static measures as their outcome measures.^{115,258}

2.3.2.1 TARGET ACQUISITION TIME (STATIONARY TARGETS)

Wang et al. found that the acquisition time to static targets is increased in INS patients; that is, they are “slow to see.”⁶⁹ The saccadic latency (i.e., time from target step to first saccade) is not appreciably different from normal in INS. However, it takes several IN cycles before the new target is foveated; thus, target acquisition times are longer than simple saccadic latencies. The amount of time added to acquire new targets was related to the interaction between target motion and intrinsic saccades in INS waveforms. Target steps occurring at or near foveating or braking saccades increases target acquisition times. Our behavioral ocular motor system model predicted this when simulations were run with targets stepping at different times in the IN cycle. The OMS model simulations in Figure 2.21 demonstrate that despite similar saccadic latencies, target acquisition times for step-change targets are longer for individuals with INS.

2.3.2.2 TARGET ACQUISITION TIME (MOVING TARGETS)

In addition to longer acquisition times for stationary targets, the time to acquire a moving target is similarly increased in INS if target motion begins near the intrinsic saccades within the INS waveforms.²⁵⁹ Furthermore, the timing of these saccades sometimes introduces errors in calculating target position, resulting

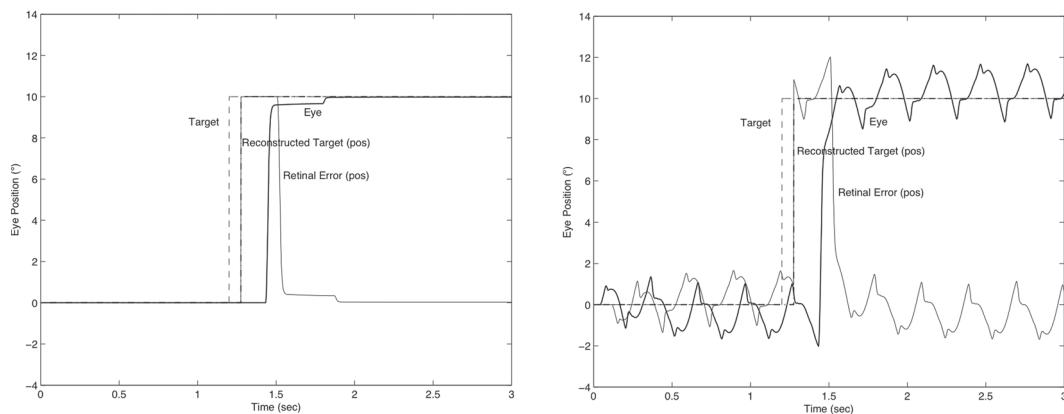


FIGURE 2.21 Step response simulations of the behavioral ocular motor system model for a normal subject (left panel) and one with a pseudopendular with foveating saccades (PP_{FS}) infantile nystagmus syndrome waveform. Note that although the saccadic latencies are similar, the target acquisition time is much longer for the subject with infantile nystagmus syndrome. Shown are target motion (dashed), reconstructed target motion (dot-dashed), retinal error position (thin trace), and eye (heavy trace).

in steady-state position errors during smooth pursuit of moving targets. Thus, although the eyes move with the correct (i.e., target) velocity, they are consistently behind the moving target. Our behavioral ocular motor system model predicted both the acquisition time increases and the steady-state position errors during pursuit simulations. These deficits negatively affect the patient's professional and personal

life and impair his or her abilities in tasks such as driving and sports (e.g., lagging a flying clay or game bird results in shooting behind it and missing the target). The OMS model simulations in Figure 2.22 demonstrate that despite similar smooth pursuit latencies, target acquisition times for ramp-change targets are longer for individuals with INS. In Figure 2.23, the model simulations show how target timing

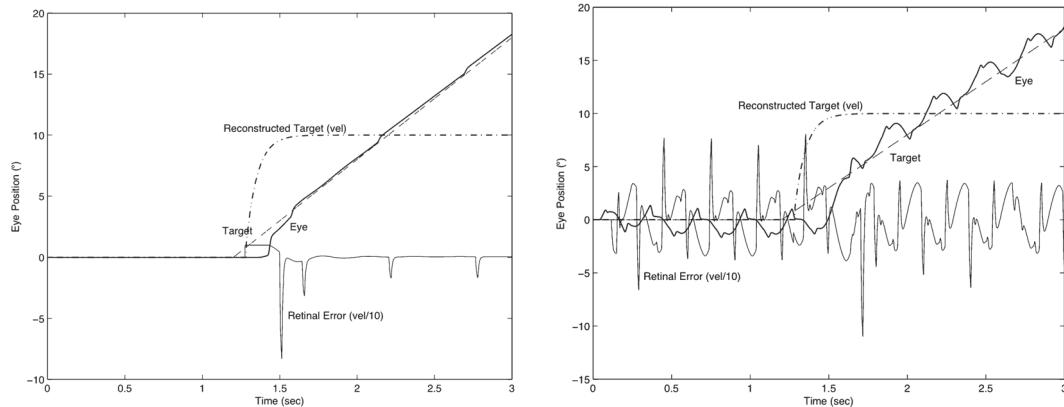


FIGURE 2.22 Ramp response simulations of the behavioral ocular motor system model for a normal subject (left panel) and one with a pseudopendular with foveating saccades (PP_{FS}) infantile nystagmus syndrome (INS) waveform. Note that although the saccadic latencies are similar, the target acquisition time is much longer for the subject with INS. Shown are target motion (dashed), reconstructed target motion (dot-dashed), retinal error velocity/10 (thin trace), and eye (heavy trace).

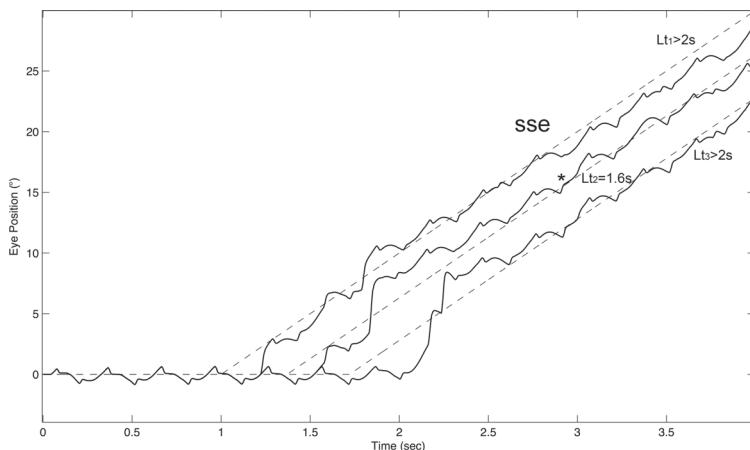


FIGURE 2.23 Ramp response simulations of the behavioral ocular motor system model for a subject with a pseudopendular with foveating saccades (PP_{FS}) infantile nystagmus syndrome (INS) waveform when the target velocity onset occurs at different times in the INS cycle. Motion onsets (earliest to latest) are as follows: during the foveation period, during the slow phase, and during the breaking saccade. The respective target acquisition times (L_t) are >2 sec, 1.6 sec, and >2 sec, respectively. Also there is a steady-state position error for the first response.

can introduce steady-state position errors during pursuit. Not only does target motion near intrinsic INS saccades extend target acquisition times but it also causes calculation errors leading to steady-state eye position errors.

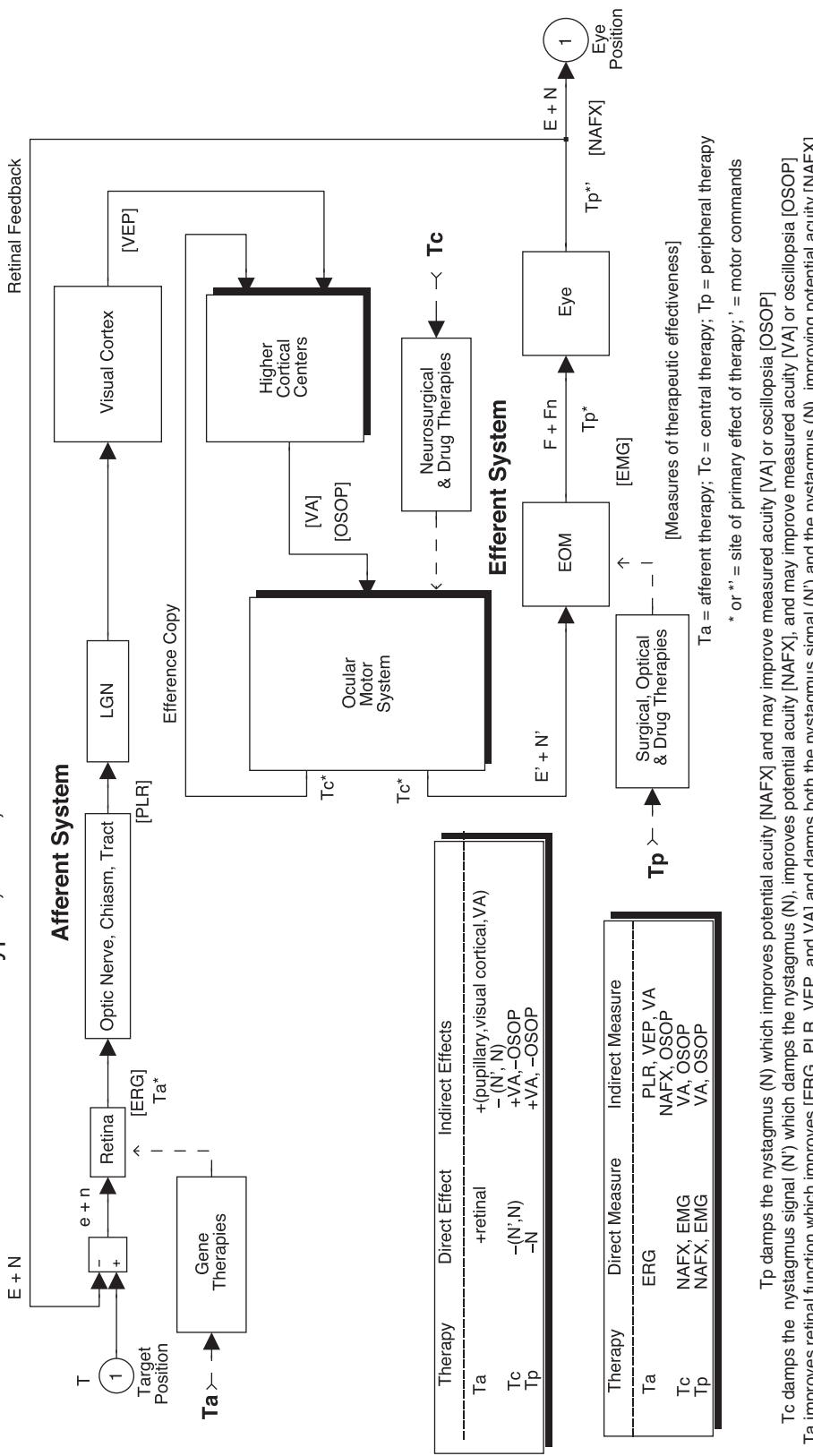
2.3.3 Clinical

Visual acuity is a secondary measure of INS therapy; because of its idiosyncratic variation with stress and monocular occlusion, it is not a reliable outcome measure, especially if patients have not been screened for the foveation quality of their waveforms. Also, because of the latter variation, monocular acuity is not a valid outcome measure. A clinical study of the effects of T&R, or the Anderson procedure plus T&R of the remaining two extraocular muscles (EOM) (as was suggested by the positive results of the T&R procedure), supported our predictions.²⁶⁰ However, this and similar clinical studies (not cited herein) have had the expected variable and confounded results. First, they failed to use the direct outcomes of EOM surgery (e.g., the peak NAFX and, more important, the broader ranges of gaze angles where the NAFX was either within 10% of the peak—the longest foveation domain [LFD] or greater than

pretherapy values—the therapeutic improvement domain [TID]¹¹⁰) or even clinical measures of gaze-dependent visual acuity. As a result, such studies do not provide useful information about either the mechanisms important to the improvements of each procedure or the specific visual function improvements that resulted, and they are also subject to false-negative outcomes. Second, studies that used measures of head posture were *doubly confounded* by lack of accurate measurement and patient control of that outcome measure; the shift in NAFX peak is a much more accurate and repeatable outcome measure. Several reviews of the therapies for INS and other forms of nystagmus incorporate current research findings.^{261–263} The block diagram in Figure 2.24 illustrates the anatomical sites and physiological signals that determine both the therapeutic options and the best direct outcome measures of each type of therapy. Despite the central source of the INS, therapies may be aimed at the afferent system (Ta), centrally (Tc), or, as is most often the case, peripherally (Tp). Direct and indirect effects of each type of therapy are listed, as are the direct and indirect outcome measures of each. For both central and peripheral therapies, the NAFX is the most accurate direct outcome measure of INS therapy.

Nystagmus Therapies

Types, Sites, and Measures



T_a dampens the nystagmus signal (N') which improves potential acuity [NAFX] and may improve measured acuity [VA] or oscilllopia [OSOP]
 T_c improves retinal function which improves [ERG, PLR, VEP, VEP, and VA] and damps both the nystagmus signal (N') and the nystagmus signal (N), improving potential acuity [NAFX]
 T_p dampens the nystagmus signal (N') which damps the nystagmus (N), improves potential acuity [NAFX], and may improve measured acuity [VA] or oscilllopia [OSOP]
 Ta improves the nystagmus (N) which improves potential acuity [NAFX] and may improve measured acuity [VA] or oscilllopia [OSOP]

FIGURE 2.24 Block diagram illustrating afferent (Ta), central (Tc), and peripheral (Tp) intervention points for infantile nystagmus syndrome therapies and examples of each. Also shown are the outcome measures that are possible at each anatomical site.

2.3.3.1 VISUAL ACUITY AT DIFFERENT GAZE ANGLES

A reduction in contrast sensitivity for medium to high spatial frequency vision and increased pattern detection thresholds in INS impairs the detection of vertically oriented stationary and moving grating patterns more so than horizontal ones. The increased contrast sensitivity and pattern detection thresholds are secondary to the oscillation itself and improve when the INS oscillation is reduced.^{264,265}

Individuals with INS suffer reduced visual acuity as they direct their gaze lateral to their null region. That is the major visual function limitation attributable to INS in most patients, not low peak acuity. As the NAFX versus gaze angle curves demonstrate, visual acuity can drop off sharply as gaze is directed away from its peak. Thus, patients cannot simply and rapidly scan their visual environment by using saccades to acquire lateral targets; if they do so, they may not be able to identify such targets (e.g., people's faces) because their INS waveforms have poor foveation quality. That necessitates the time-consuming and less accurate strategy of turning one's head for each target so that it appears at the null angle. This deficit in visual function is neither appreciated by most clinicians nor tested for, either before or after therapy. Broadening the range of gaze angles with high acuity should be the major outcome measure of the effectiveness of any INS therapy. Unlike peak acuity, which can be diminished by various sensory deficits as well as INS, the breadth of this function is solely due to the characteristics of the INS and is a direct outcome measure. The therapeutic effects of broadening the range of gaze angles with high acuity can be appreciated from the figures in the next section.

2.4 TREATMENTS OF INFANTILE NYSTAGMUS SYNDROME

The past 50 years have produced numerous studies of the effects of INS treatment, both nonsurgical and surgical. Most important, in terms of increasing our understanding of INS, have been those studies that utilized eye-movement data

as their foundation. INS treatments and their application are discussed in detail in Chapter 7, but it is important to note that INS research using eye-movement data analysis has uncovered both the inadequacy of using clinical measures alone as outcome measures and the danger of using them as primary outcome measures. The most common measure, peak visual acuity, is both indirect and insufficient and peak acuity may not improve in some *successful* cases of INS therapy. The following summarizes the contributions to INS treatment made by ocular motor research.

Weiss et al. suggested that improving foveation-period quality would *not* improve acuity in INS associated with albinism, and that the acuity of such patients was not related to the INS but rather, to macular hypoplasia.²⁶⁶ In light of the number of such patients whose visual function improvement following EOM surgery has been documented in the literature, both the assumptions and methods used to arrive at those contrary conclusions need to be seriously reexamined. First, only in those few cases where both the pretherapy NAFX and LFD values are high is the presumption that acuity is not related to the INS true and, therefore, there would be limited expectation of improvements. Second, contrary to the suggestion that those with visual sensory deficits that limit their peak visual acuity would not benefit from INS therapy, five decades of eye-movement-based INS research demonstrates conclusively that not only will they benefit but also the percentage improvement in their outcome measures will be greater than those INS patients with higher pretherapy acuity.²⁶⁷

Clinical Pearl: INS therapy is not contraindicated in patients with associated visual sensory deficits; in fact, these patients have the greatest chances for significant (i.e., life-changing) improvements in their visual function.

2.4.1 Goals

The goals of INS therapy that emerge from our research are to improve the foveation

characteristics of the waveforms such that one or more of the following is achieved: (1) the range of high NAFX values is broadened; (2) the peak NAFX value is increased; and (3) target acquisition speed is increased. These therapeutic improvements will translate into a broader range of high-acuity gaze angles, higher peak acuity, and reduction of the “slow-to-see” phenomenon. The actual improvements in each of these visual function factors will depend on the values of pretherapy NAFX and LFD and may be estimated before therapy (see Chapter 7, Section 7.5).

2.4.2 Nonsurgical

Nonsurgical therapies for INS include the use of optical methods (prisms, both version and vergence, soft contact lenses), oral and/or topical medications, and a variety of nontraditional medical approaches (e.g., biofeedback, acupuncture). When indicated, low-vision aids are used for associated visual system deficits.

2.4.2.1 PRISMS

The various therapies available for INS, based on the presence or absence of gaze and

convergence nulls, is summarized in Table 2.3. Note that for patients with both convergence and gaze-angle nulls, exploitation of the former (surgically or with vergence prisms) usually damps the nystagmus and increases acuity most; it is necessary to add -1.00 S (OU) to vergence prisms for pre-presbyopic patients (and to remove it later in life when presbyopia appears). Studies of the broad damping effects of convergence (at all gaze angles) on IN (see Fig. 2.13 and discussion of convergence in Section 2.1.6) suggest that the originally used composite prisms (unequal base-out)³² are not necessary in these cases; vergence prisms (equal base-out) will achieve the same damping.²⁶⁸ As indicated in Table 2.3, regardless of the presence of nulls, afferent stimulation can be used in all patients who exhibit nystagmus damping with active stimulation.

2.4.2.2 CONTACT LENSES

In many individuals with INS, afferent stimulation of the ophthalmic division of the trigeminal nerve or of the neck may damp the nystagmus and improve the waveform, allowing increased visual acuity.^{154,155} Neck or forehead vibration prolonged

Table 2.3 Therapies for Infantile Nystagmus (IN)

If the IN nulls ONLY with lateral gaze:

- Resection and recession (four-muscle)
- Version prisms (useful only for small angles)
- Afferent stimulation (passive or active)

If the IN nulls ONLY with convergence:

- Bimedial recession¹ (artificial divergence)
- 7D BO vergence prisms with -1.00 S¹ (OU)
- Afferent stimulation (passive or active)

If the IN nulls with BOTH lateral gaze and convergence:

- Bimedial recession¹ possibly combined with resection and recession
- 7D BO vergence prisms with -1.00 S¹ (OU)
- Afferent stimulation (passive or active)

If the IN nulls with NEITHER lateral gaze nor convergence or is asymmetric aperiodic alternating IN:

- Four-muscle tenotomy and reattachment
- Afferent stimulation (passive or active)

Therapies include surgical, optical, and mechanical; for drug therapies, see text.

¹Damps IN only for nonstrabismic, binocular patients.

foveation periods, yielding higher values of the NAF and improved visual acuity in 9 of 13 patients with INS.¹⁵⁵ This noninvasive and benign therapy (active afferent stimulation) may prove useful in both INS and acquired nystagmus. The use of contact lenses (of any materials) to improve the acuity of individuals with INS takes advantage of the damping effect on nystagmus of (passive) afferent stimulation.^{158–160,269} Contact lenses damp the IN and broaden the LFD using an exteroception mechanism that is

similar to the proprioception mechanism of the T&R and convergence therapies.²⁷⁰ Figure 2.25 demonstrates the effects of contact lenses and compares them to convergence in the same subject. Note from panels (a)–(c), that the NAFX values of INS waveforms are not determined by amplitudes; (a) and (c) have the same NAFX despite the difference in amplitudes and (b) has the highest NAFX value despite an amplitude between those in (a) and (c). In (d), the contact lenses achieved the same gaze-angle broadening as

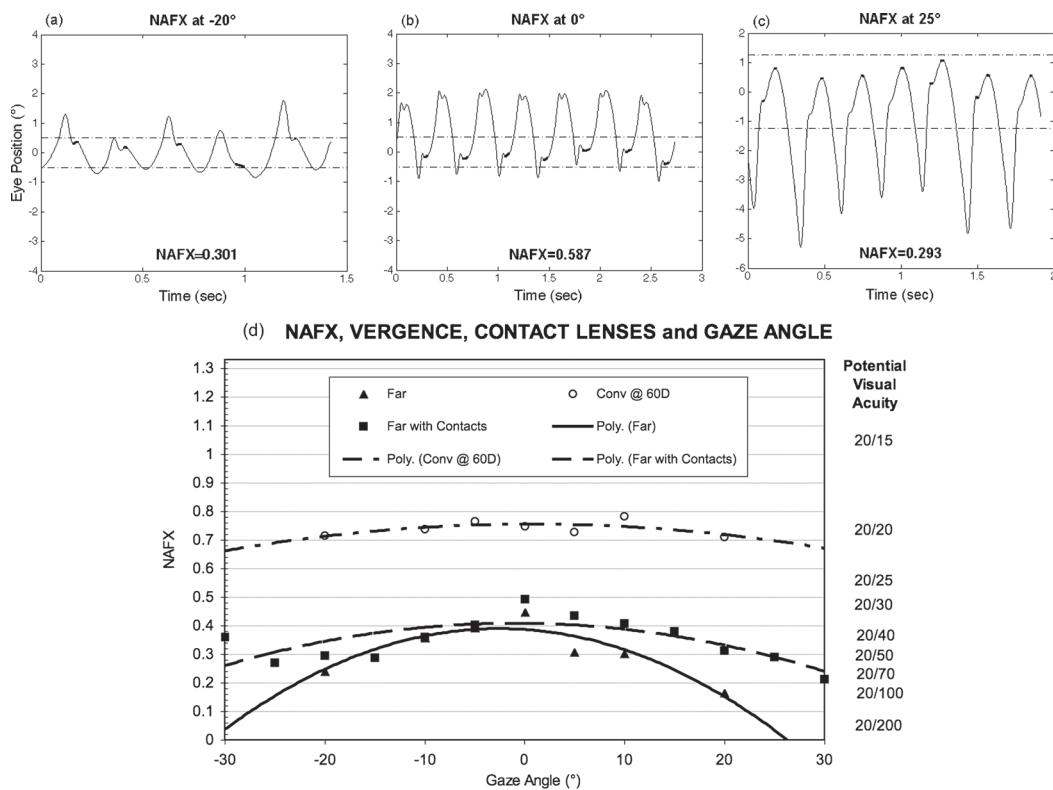


FIGURE 2.25 The effects of contact lenses compared to convergence in a subject with infantile nystagmus syndrome. Fixation data (eye position vs. time) for the subject during far viewing with contact lenses at different gaze positions: -20° (a), 0° (b), and 25° (c). The corresponding eXpanded nystagmus acuity function (NAFX) values are also shown. The NAFX algorithm automatically thickened foveation periods. The area between the dash-dotted lines represents the foveation position window used to calculate the NAFX. In (d), plots of NAFX versus gaze angles for far viewing, far viewing with contact lenses, and while converged (60 PD). Fitted polynomial curves are shown. NAFX-correlated potential visual acuities are adjusted for the subject's age. Conv, convergence. The dot-dashed lines indicate the extent of the foveal window. The thickened areas identify foveation periods in NAFX outputs.

convergence albeit with a lower peak NAFX value.

Clinical Pearl: Contact lenses are not contraindicated in INS and can provide better acuity than spectacles in patients whose nystagmus damps with afferent stimulation. Plano soft contact lenses can be used if no refractive correction is required. Four advantages of contacts in the INS patient are better optical quality, improvement in nystagmus foveation, move with eye to utilize eccentric gaze null, and ability to decrease light sensitivity/interference via tinting or painting.

2.4.2.3 DRUGS

Both memantine and gabapentin may improve INS waveforms and visual acuity.^{271–274} More recently, an oral systemic carbonic anhydrase inhibitor (CAI) (acetazolamide) was shown to improve visual function in INS by both increasing peak NAFX and LFD values.²⁷⁵ With the use of a topical CAI (brinzolamide), a whole new area of INS-therapy research that may revolutionize the treatment of INS has now been demonstrated to improve visual function.²⁷⁶ This potentially far-reaching finding was suggested

by the hypothesized proprioceptive mechanism of the T&R procedure. The effects of four different types of therapy on the same INS patient and their comparison to the effects of the T&R on other patients is shown in Figure 2.26. The left panel shows that, as expected, the highest percent increase in peak NAFX was during convergence. Both systemic acetazolamide and topical brinzolamide achieved results comparable to the T&R procedure, and contact lenses had less of an effect on peak NAFX. In the right panel, again convergence had the greatest broadening effect on the LFD with systemic acetazolamide and contact lenses comparable to the T&R procedure with topical brinzolamide slightly lower. Our ability to study the effects of these therapies on the same patient provided the data for this unique figure.

2.4.2.4 GENE-TRANSFER THERAPY

We were fortunate to have the opportunity to study the eye movements of RPE65-deficient canines both pre- and post-gene therapy.¹⁸⁰ These canines had the equivalent of human congenital stationary night blindness, whereas in humans, this retinal function deficiency causes Leber congenital amaurosis (LCA), a

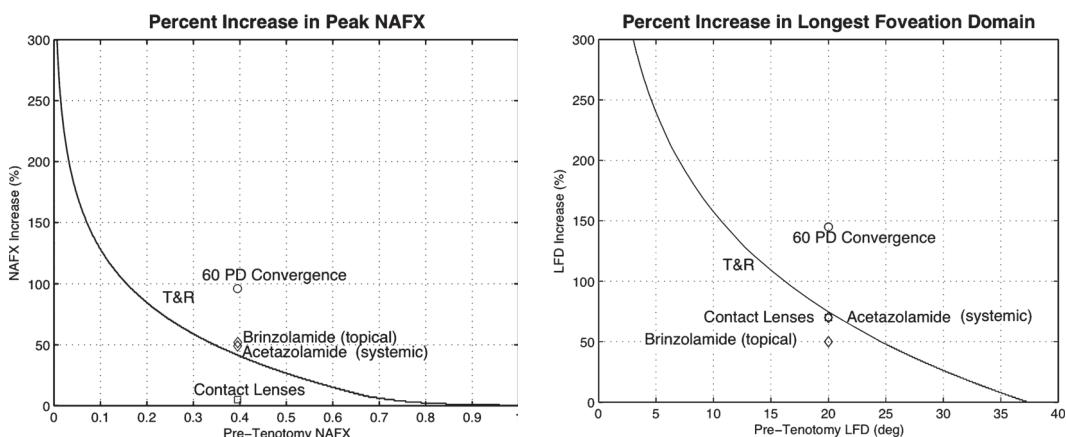


FIGURE 2.26 Plots of the percent increase in peak expanded nystagmus acuity function (NAFX) (left panel) and longest foveation domain (LFD) (right panel) after treatments with base-out prisms, contact lenses, systemic acetazolamide, and topical brinzolamide in the same infantile nystagmus syndrome patient. Shown for comparison are the respective curves from tenotomy and reattachment (T&R) data averaged for other patients.

previously untreatable, autosomal-recessive retinal dystrophy. Both humans with LCA and these canines have INS. Thus, the second animal model of INS whose eye movements we were able to study were also canines. Gene therapy applied to the retina virtually abolished (i.e., not clinically detectable 90% of the time) the IN in these canines. Posttreatment NAFX values were higher than pretreatment. Unicocular treatment also was able to damp the IN in both eyes. Figure 2.27 shows the difference in nystagmus of littermates, one untreated and the other treated; the latter being of much lower amplitude. The IN of the treated dog was clinically undetectable and comparison of the area centralis indicated on each figure shows that the oscillation never left that high-acuity area in the treated dog, whereas it was mostly outside in the untreated dog. Figure 2.28 (top panels) shows the large pre- to posttreatment increases in the NAFX in two canines. In one, the NAFX increases from 0.46 to 0.73 (58.7%), with the initial DJ waveform damped to only its small pendular component, and in the other, from 0.0.375 to 0.74 (97.3%).

Translating the latter dog's improvements to a human patient with poor vision due to both a sensory deficit (like LCA) and INS means that this therapy not only would improve acuity by increasing retinal function but also would improve the motor portion of peak visual acuity (i.e., that due to the INS waveform) by nearly 100%. We have no data on how or if the LFDs of patients will improve after gene therapy but, if they do not, a T&R (or other INS surgery) can be used to achieve this important visual function improvement.

Data taken to assess the time course of the INS improvements showed improvements in from 4 (1 dog) to 10 weeks.¹⁸¹ Figure 2.28 (bottom panel) shows the posttreatment damping in one dog and the difference between the damping in one treated eye and the other eye that did not respond to treatment. There were no adverse effects in the canines. A study of the safety and efficacy of gene therapy using an optimized adeno-associated virus was successful.¹⁸² In a subsequent study, in patients, there was mini-

mal adverse effect and modest improvement in retinal function.¹⁸³

An important finding from our canine studies is that the ocular motor system appears to be capable of recalibration when the visual deficit that interfered with that calibration is removed. That recalibration damps the IN significantly and seems to be possible even in later life; that is, the OMS does not have a sensitive period beyond which change is precluded.

2.4.2.5 BIOFEEDBACK

Some studies of the effectiveness of auditory biofeedback on INS have claimed that the techniques learned in the laboratory can be maintained and used later.^{162,163,277} It is not clear however that when needed most, that is, when under stress, such techniques can be applied to increase acuity. Unlike other therapies that reduce the baseline INS oscillation and improve foveation quality so that any deterioration due to stress begins from a much better waveform, biofeedback requires maintenance of a state of mind to damp the INS waveform; that is the very thing that would be interfered with during stressful conditions. Other investigators did not find that their patients could maintain improved acuity after training.^{166,278} Therefore, biofeedback has not proven to be a widely useful or practical therapeutic approach to improving INS waveforms and, with them, acuity.

2.4.3 Surgical

Surgical therapies for INS have two main goals: (1) mechanical, that is, reposition the eye(s) to treat associated strabismus, move an eccentric INS "null" region to primary position, or exploit the convergence-induced INS damping; and (2) neurological, to improve the INS waveform characteristics. Operations used to treat nystagmus have been classified based on analysis of hundreds of nystagmus operations into nine types. A clinical algorithm for clinicians and details of all those procedures are presented in Chapter 7. A detailed analysis of the more common operations is discussed in the following sections.

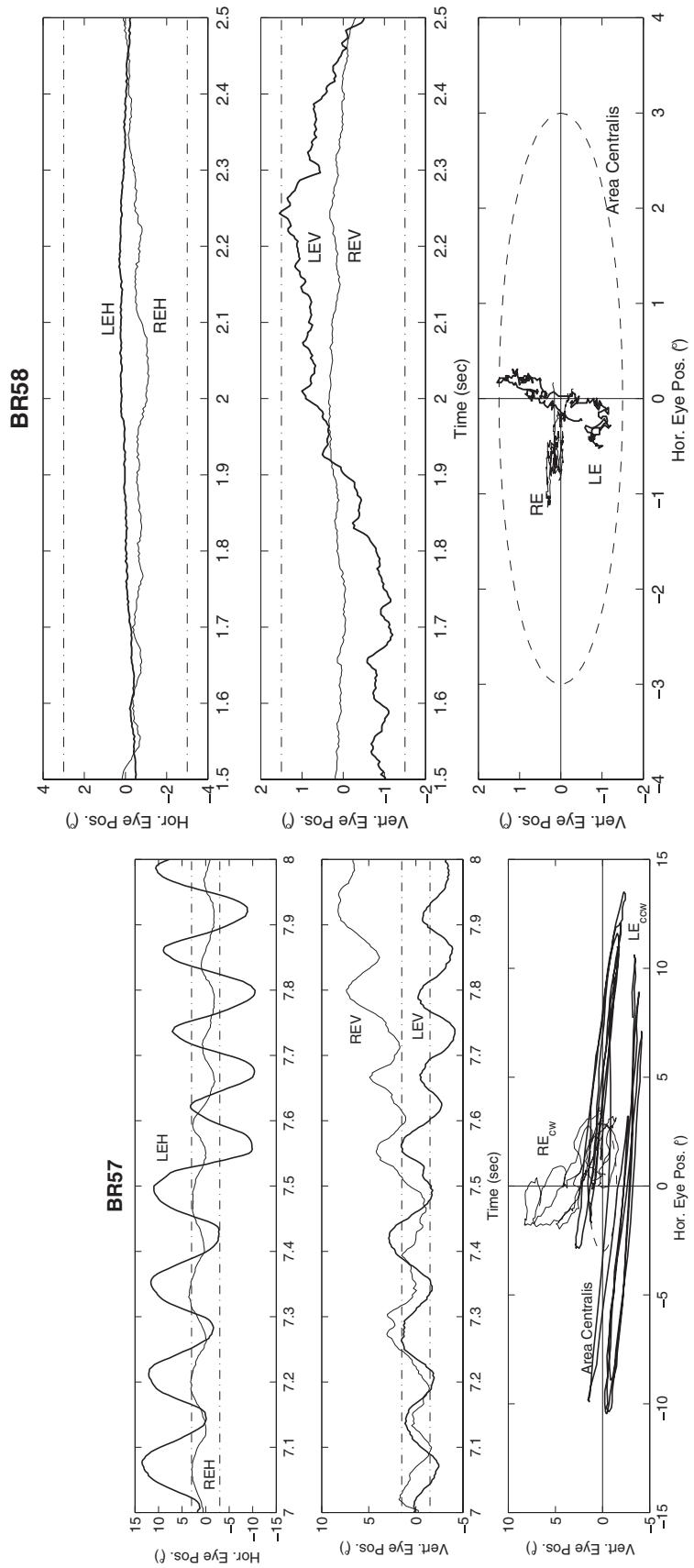


FIGURE 2.27 Horizontal (H) and vertical (V) right (RE) and left (LE) eye-position and scan-path data from an untreated RPE65-deficient canine (BR57) and a littermate (BR58) treated with gene therapy. The dot-dashed lines indicate the area centralis.

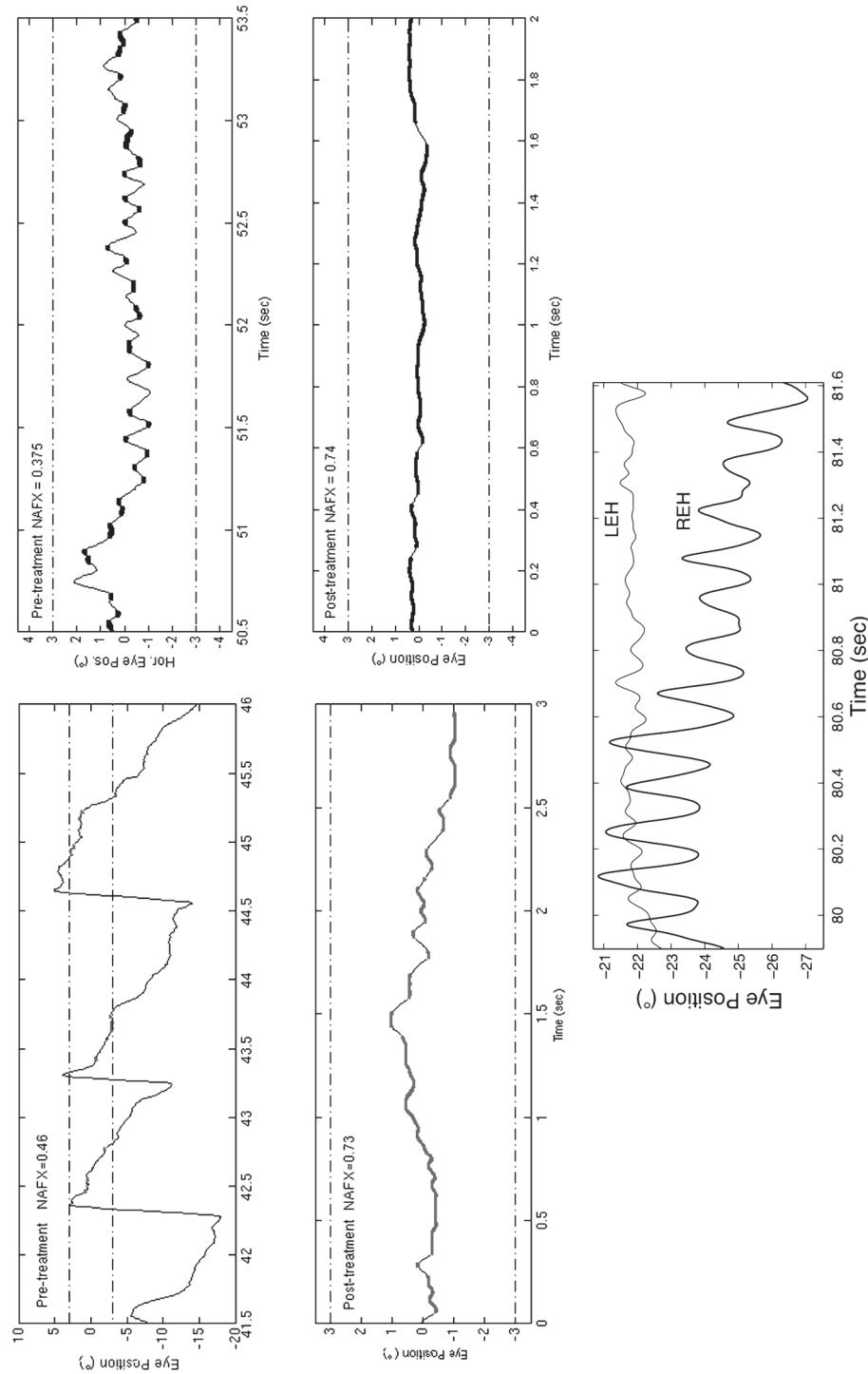


FIGURE 2.28 eXpanded nystagmus acuity function (NAFFX) pre- and post-gene-therapy outputs from two RPE65-deficient canines, one with jerk (top left panel) and one with pendular (top right panel) infantile nystagmus syndrome. Horizontal (H) right (RE) and left (LE) eye-position data from a gene-therapy-treated RPE65-deficient canine showing the difference between the successfully treated LE and the unsuccessfully treated RE (bottom panel). The dot-dashed lines indicate the extent of the area centralis. The thickened areas identify centralisation periods in NAFFX outputs.

2.4.3.1 FOUR-MUSCLE RESECTION AND RECESSION PROCEDURE (OPERATION 1) (ALSO KNOWN AS KESTENBAUM, ANDERSON-KESTENBAUM, OR ANDERSON PLUS GOTO)

In 1979 the first eye-movement study of the results of the Kestenbaum procedure was published.^{177,279} It demonstrated that this four-muscle recession and resection procedure had several therapeutically beneficial effects beyond the shifting of an eccentric INS null to primary position. Prior to this study with eye-movement data, it was mistakenly believed that the only effect was to shift the null region to primary position with no improvements in visual acuity. The expected (based on the then current literature) and actual effects of this procedure are illustrated in Figure 2.29. In fact, the most important effect was the broadening of the null area so that it allowed better acuity over a larger range of gaze angles than preoperatively. As Figure 2.29 shows, INS magnitude was also lowered at all gaze angles, also improving acuity. Subsequent longitudinal eye-movement studies verified that these therapeutic effects were permanent and dispelled the myth that “the eccentric null returned” at a later date.²⁸⁰ We attribute those erroneous observations to the combination of

using the patient’s head turn both to estimate the surgery necessary and as an outcome measure and the use of fixed formulae, not tailored to each patient (see later). The null broadening observation was to have a profound effect on our understanding of the effects of extraocular muscle surgery and would lead to the hypothesis, and later demonstration, of the T&R procedure.

Accurate eye-movement data also were responsible for producing a curve that allowed the determination of the total amount of surgery necessary for each desired amount of null shift. Figure 2.30 shows this curve that provides the physician with an accurate method of determining the surgery necessary and predicting the resulting postoperative null shift. For example, a 20° shift would require 10 mm (5 mm recession and 5 mm resection) of rotational surgery on each eye. Not only can it be used to determine the necessary surgery but also (as the authors showed), in cases where too little surgery was performed, it can be used to determine the amount needed to center the null in primary position. This is a far better approach than using a fixed formula for all patients based on whether their required null shift was large or small. To the extent that the tenotomy (enthesiotomy) and reattachment contained within the Kestenbaum procedure caused

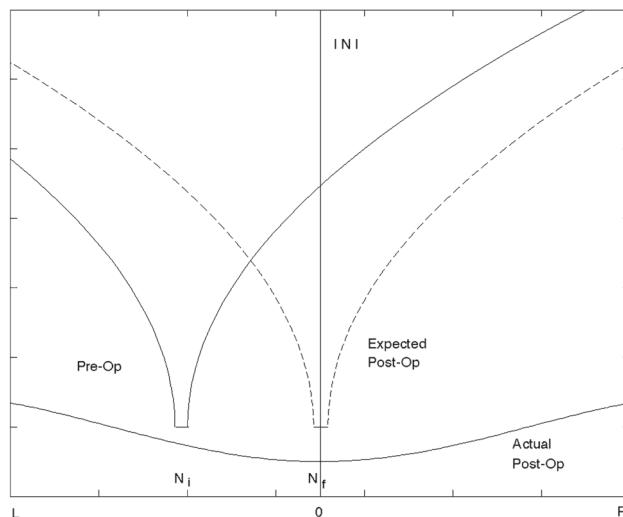


FIGURE 2.29 Illustration of the expected and actual results of resection and recession surgery. L, left; |N|, nystagmus magnitude; N_f, final null; N_i, initial null; R, right.

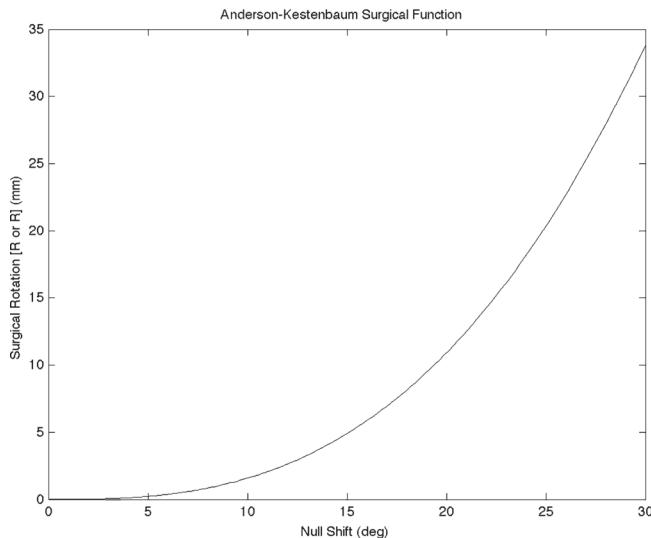


FIGURE 2.30 The relationship to determine the total amount of resection and recession surgery needed for each eye to achieve the required shift in the eXpanded nystagmus acuity function (NAFX) peak.

null broadening, the errors inherent in such fixed formulae were ameliorated and good results were possible despite the coarse approach. However, with the use of this more accurate eye-movement data, the null can be shifted to accurately place it in primary position regardless of its initial eccentricity. To maintain homeostasis as much as possible, the total amount of surgery dictated by the curve was split evenly into the recession and resection amounts. This approach to nonstrabismic INS surgery remains as the gold standard.

Although the cosmetic disfigurement and possible neck problems of the patient's compensatory AHP were appreciated, they would disappear once the primary deficit, the eccentric position of the best INS waveforms, was broadened and moved to primary position. The authors of that 1979 study neither measured nor used AHP in their treatment. Although the use of IN intensity was not optimal and the authors recognized that saccade time (which would later be replaced by the NAFX) would be a better indicator of visual acuity, the important but little appreciated therapeutic effects of the Kestenbaum procedure were demonstrated. This study documented visual acuity improvements in these patients and dispelled the myth that they did not occur; the authors stated that

acuity in primary position that exceeded that at the preoperative null should be anticipated.

2.4.3.2 TWO-MUSCLE RECESSION PROCEDURE (OPERATION 1A) (ALSO KNOWN AS ANDERSON)

About the same time as Kestenbaum proposed the four-muscle recession and resection procedure, Anderson proposed the two-muscle recession procedure that could be used for smaller lateral gaze nulls.²⁸¹ Although it is clear that, for moderate angles, the null-shifting goal may be accomplished by recessions alone, it has not been demonstrated that this two-muscle procedure will result in broadening of the NAFX peak or, if it does, that the broadening will equal that from four-muscle procedures. Until a carefully done study of the NAFX changes following two-muscle recessions is done and comparison made to the therapeutic benefits from four-muscle procedures on patients with different initial peak NAFX values,²⁶⁷ we recommend that Anderson recessions be augmented by T&R of the other two horizontal rectus muscles. We have documented that, when all four muscles are operated on in this way, the same NAFX peak broadening results.

2.4.3.3 BILATERAL MEDIAL RECTUS RECESSION PROCEDURE (OPERATION 8) (ALSO KNOWN AS BIMEDIAL RECESSION)

Cüppers proposed the bimedial recession procedure to treat INS.²⁸² As the research presented in this chapter demonstrates, the single most effective INS therapy is the inducement of convergence in those patients who have sufficient fusional vergence and whose IN damps with convergence. In all such patients we found greater damping with convergence than with gaze angle and in those we studied, therapy that induced convergence (e.g., near targets or base-out prisms) always produced the greatest improvements in peak NAFX and LFD. Kaufmann and Kolling discussed the advantages of bimedial recession in those patients with CN who have good binocular function and a decrement of IN intensity during near vision.²⁸³ They recommend this operation regardless of whether the patient has an abnormal head position, that is, a lateral null angle, and claim that the results are better than the Kestenbaum/Anderson operation.

Although we initially recommended that the two lateral rectus muscles receive a T&R procedure in addition to recessing the two medial rectus muscles, current research casts doubt that there is an additional benefit to associated lateral rectus T&R. The increased damping secondary to convergence and its relaxation of steady-state muscle tension exceeds that obtained from surgery on the four extraocular muscles. Thus, the bimedial recession procedure is the only two-muscle surgery recommended for INS in those patients for whom it is indicated. The bimedial recession procedure, like the T&R, is indicated in only a small percentage of INS patients, but for them it has no equal.

2.4.3.4 TENOTOMY AND REATTACHMENT PROCEDURE (OPERATION 6)

Prior to 2000, there were no surgical therapies for INS patients that did not have associated strabismus, a static eccentric gaze-angle null position, or convergence null (i.e., they

had no null, a primary-position null, or possibly APAN). However, the first study of the Kestenbaum (four-muscle resection and recession) procedure using analysis of eye-movement data uncovered secondary improvements in the INS characteristics that resulted in improvements in visual function that had gone unrecognized.¹⁷⁷ It was found that the null region was broadened, its peak reduced in intensity, as well as shifted to primary position. No explanation for these improvements was evident at the time, but they did result in a hypothetical new procedure, the T&R procedure.¹⁷⁸ This procedure consisted of performing an enthesial tenotomy, dissection, and reattachment at its original insertion of each of the four horizontal rectus muscles. The efficacy of the T&R procedure was first demonstrated on an achiasmatic Belgian sheepdog with INS and seesaw nystagmus.¹⁷⁹ In two procedures (first, T&R of the four horizontal rectus muscles and, after 4 months, T&R of the four vertical rectus and four oblique muscles), the INS was damped and the seesaw nystagmus abolished. A proprioception hypothesis was advanced to explain the improvements in INS waveforms.

Results of a masked clinical trial of this surgery were positive in a Phase 1 study of adults^{284,285} and Phase 2, in children.²⁸⁶ Since those initial studies, there have been a number of others demonstrating the positive therapeutic effects of the T&R procedure in INS and even acquired pendular nystagmus.^{258,267,287–290} The T&R procedure was to be used for INS patients with no nulls and added to those other procedures that did not include all four muscles. For example, the Anderson (two-muscle recession) procedure would be augmented by performing a T&R on the other two horizontal rectus muscles. That was shown to add the therapeutic benefits of a four-muscle T&R to the null shifting of the two-muscle recession procedure.²⁸⁸ Although it was originally thought that a two-muscle T&R should also be added to the bimedial recession procedure for INS patients with convergence damping, data from base-out prisms indicated that convergence alone produced these desired benefits; thus, no additional T&R was necessary for that procedure.¹¹⁰

The positive therapeutic effects of the T&R procedure specifically, thus all eye muscle surgical procedures generally, includes higher peak NAFX values and broader LFD values. The therapeutic benefits documented for horizontal INS were also found in the vertical plane.²⁹¹ Visual function deficits that were not improved by therapy were both the increased target acquisition times and position errors introduced during smooth pursuit that are characteristic of INS.²⁹² Preliminary evidence indicates that this is a limitation present in the normal smooth pursuit mechanism.²⁹³ Our experience is that for patients in whom convergence damps their IN, the increases in peak NAFX, LFD, and TID are greater after induced convergence (by prisms or bimedial horizontal rectus recession surgery) than by any other therapeutic measures (e.g., surgical, contact lenses, or pharmaceutical).^{110,270,275,276}

The currently accepted mechanism responsible for the damping effects of T&R is alteration of a proprioceptive tension-control loop.^{179,289,294} This is supported by the discoveries of the neural substrate for such a loop in both the musculotendon^{295–304} and enthesial end of the tendon (where the surgery takes place).³⁰⁵ Proprioceptive signals representing the eye in head are also present in the cortex.³⁰⁶ In rabbit, T&R and recession surgeries both cause the same adaptive changes in EOM, suggesting that it is the former that is responsible.³⁰⁷ Thus, the alteration of a proprioceptive feedback loop controlling steady-state muscle tension in a manner that reduces that tension shares the same mechanism by which convergence can reduce IN (see earlier). That is, lowered γ -innervation reduces muscle tension, placing it on a lower gain portion of the length-tension curve, thereby decreasing the IN. Proprioception has become an important factor in new therapies for INS,³⁰⁸ as well as given rise to a hypothetical modification to existing surgeries that needs to be investigated for efficacy.³⁰⁹ Before any surgery is contemplated, INS should be definitively diagnosed using ocular motility recordings.³¹⁰ Figure 2.31 shows the improvements in NAFX outputs of three patients after either a four-muscle T&R²⁶⁷ or two-muscle T&R combined with either unequal vertical (i.e., vertical Anderson plus

vertical strabismus) or equal horizontal strabismus recessions.²⁸⁸ The top and second panels show the left and right eye data, respectively, from an exotropic INS patient (lateral rectus recessions plus medial rectus T&R procedures). The third (left eye in primary position) and fifth (right eye in primary position) panels show data from a patient with acquired downbeat nystagmus and vertical strabismus (unequal superior rectus recessions plus inferior rectus T&R procedures). The fourth panel shows the data from an INS patient (T&R procedure). Starting at the top with the lowest preoperative values, the NAFX improvements were 0.107 to 0.696 (550%); 0.279 to 0.609 (118%); 0.391 to 0.733 (87.5%); 0.565 to 0.748 (32.4%); and 0.652 to 0.845 (29.6%). NAFX percent improvements translate directly into visual acuity percent increases. As the figure demonstrates, the T&R portion of each procedure damped the IN and improved the waveforms. Both the saccade times per cycle and the mean saccade positions improved and the postoperative saccade windows were smaller in position, velocity, or both for all but the 0.652 case, where the minimum window was used preoperatively.

In Figure 2.32 the results of T&R in four cases are shown. In the top left panel, a low, sharp NAFX peak was improved to a high, broad peak. In the top right panel, a medium, broad NAFX peak was improved to a high, broad peak. In the bottom left panel, a high, sharp NAFX peak was improved to a high, broad peak. In each of these cases, visual function is improved, albeit differently. In the bottom right panel are the results from an exotropic patient who, by virtue of alternating fixation, appeared clinically to have two “nulls.” As the preoperative data show, there was a high, sharp peak in left gaze when the left eye was fixating and a high, sharp peak in right gaze when the right eye was fixating; this led to low NAFX values (poor vision) in primary position. After bilateral, lateral rectus recessions and bilateral, medial rectus T&R, the data show that despite the alternate fixation, the composite NAFX peak was high, broad, and centered in primary position. This 43% increase in primary position NAFX resulted in a 92.3% increase (20/150 to 20/80) in visual acuity.

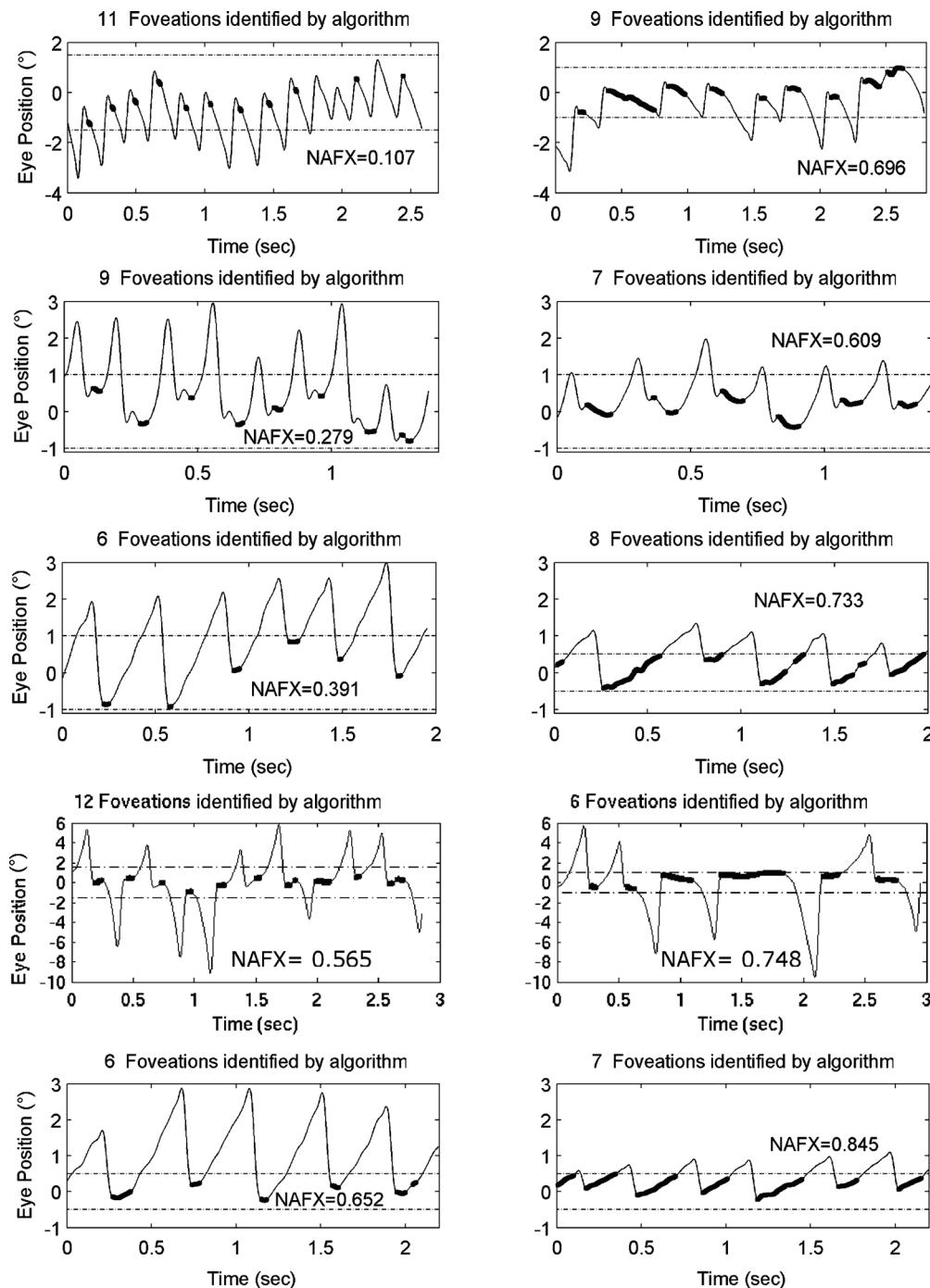


FIGURE 2.31 Patient data showing the pre- (left panels) and postoperative (right panels) eXpanded nystagmus acuity function (NAFX) outputs for three patients (one shown with either eye fixating and one, at two gaze angles) whose preoperative values ranged from 0.107 to 0.652 (see Section 2.4.3.4). The pre- and postoperative scales are the same for ease of comparison and the dash-dot lines define the position boundaries of the foveation windows used to calculate the NAFX. The improvements are due to longer foveation periods per cycle and a smaller foveation window in position, velocity, or both in four of the panels. The dot-dashed lines indicate the extent of the foveal window. The thickened areas identify foveation periods in NAFX outputs.

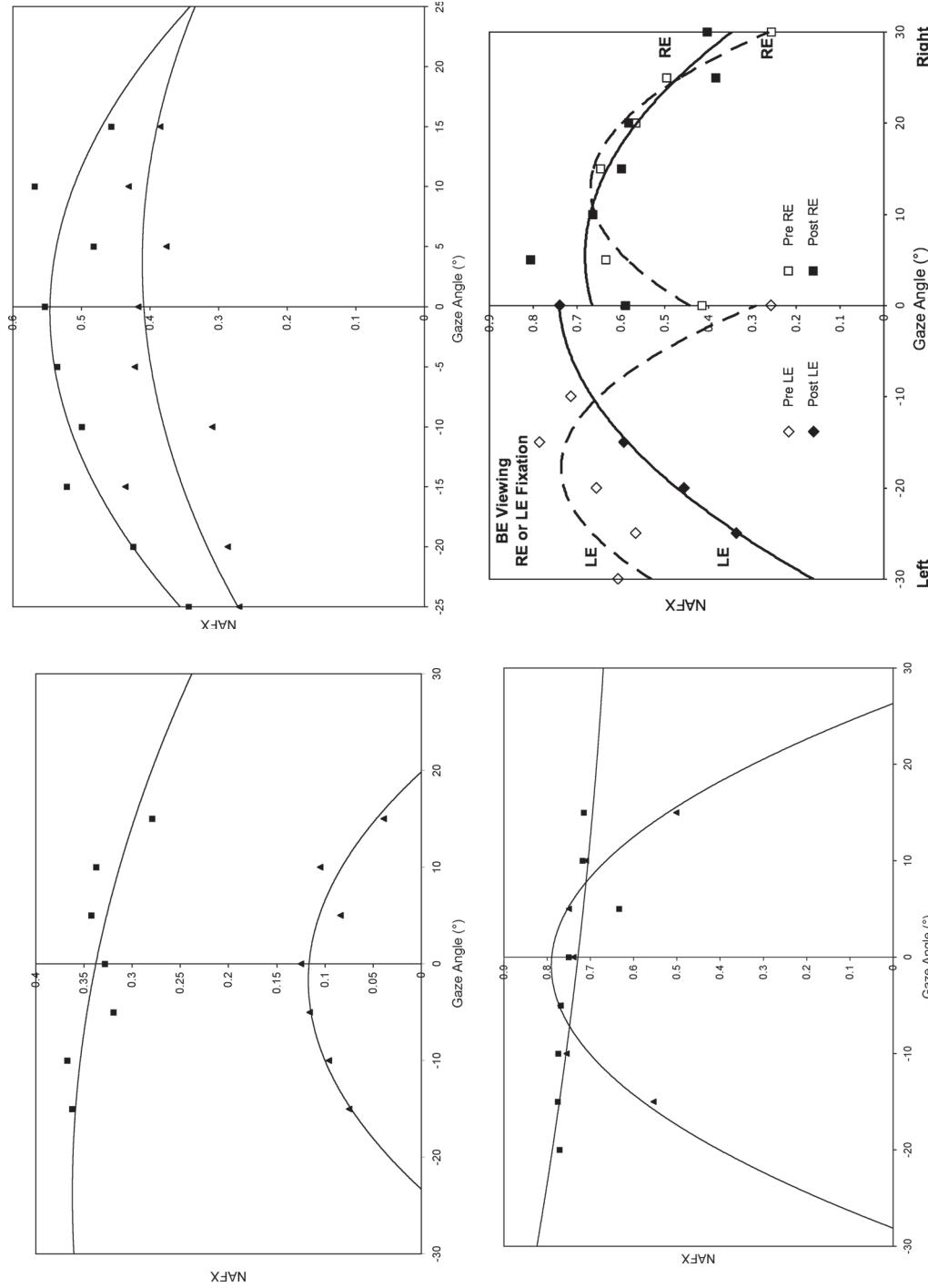


FIGURE 2.32 Pre- and post-tenotomy and reattachment (T&R) eXpanded nystagmus acuity function (NAFX) versus gaze angle data for patients with a low, sharp peak (top left); medium, broad peak (top right); or high, sharp peak (bottom left). Also shown are the data from a patient with alternate fixation (bottom right). In all cases, visual function improved. BE, both eyes; LE, left eye; RE, right eye.

A number of research publications into the effects of the T&R procedure and eye muscle surgery in general on INS further supported the proprioception hypothesis and demonstrated new therapeutic improvements in visual function. Foveation was improved over a larger range of gaze angles.²⁶⁷ It was shown that saccades were not affected but “small signals” were.²⁹⁴ The “slow-to-see” description of the longer target acquisition times of INS patients was demonstrated⁶⁹ and the T&R procedure was shown to reduce target acquisition times.²⁹⁰ It was also demonstrated that target acquisition times were longer than normal and depended on target timing during smooth pursuit by a subject with INS.²⁵⁹ A new and interesting approach to INS research, the “null-zone fMRI technique,” suggests that the decline of the cerebellum is possibly involved in INS.³¹¹ Other reviews of INS therapies may be found elsewhere.^{102,312}

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3

FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

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Galileo may have been the only man of his day who believed the Earth revolved around the Sun, but he was right!

—S. F. Singer and D. T. Avery, *Unstoppable Global Warming—Every 1500 Years*

FUSION MALDEVELOPMENT nystagmus syndrome (FMNS, also known as latent/manifest latent nystagmus, LMLN) exhibits the following: a jerk nystagmus with either a linear or decreasing-velocity exponential slow phase identical to that of gaze-paretic nystagmus; strabismus; alternating hyperphoria/dissociated vertical deviation; and pendular torsional nystagmus in primary position.¹ The constantly present, conjugate, horizontal, jerk nystagmus increases in intensity by monocular occlusion, blurring, or reducing image brightness. A jerk nystagmus with a linear slow phase may

be present when both eyes are closed. Rarely, the nystagmus is only evoked by the “pure” or “true” latent condition (LN) and occurs only with unioocular viewing (i.e., the other eye being occluded). That is, there is no nystagmus when both eyes are viewing, but when one eye is occluded, jerk nystagmus develops in both eyes, with the fast phases toward the uncovered eye. The term “manifest latent nystagmus” was first defined by Kestenbaum as being present with both eyes open but only one being used for fixation.^{2,3} Using eye-movement recordings, mild FMN with both eyes viewing can

usually be detected in those patients who may appear to have “pure” latent nystagmus clinically. True/pure FMN “latent nystagmus vera” is uncommon. The intensity of FMN decreases when visual attention declines and increases during attempted fixation.^{4,5} FMN may clinically resemble other types of nystagmus (e.g., INS with a latent component) and require eye-movement recordings to differentiate it. Indeed, it can even present as spasmus nutans (see Chapter 4).⁶

Patients with FMNS always have strabismus and, to suppress diplopia, vision from the tropic eye is suppressed (“occluded”) in the cortex.⁷ The FMN present with both eyes open, but only one fixating, is the same nystagmus as the rare FMN that only appears with occlusion of one eye. Thus, the term FMN refers to this *single type* of nystagmus that is present in most FMNS patients with both eyes open while one is fixating but, in some patients, may only be present when one eye is occluded.

3.1 CHARACTERISTICS OF FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

3.1.1 Waveforms, Models, and Mechanisms

The slow phase of FMN is either linear or a slight decreasing-velocity exponential (initiating the

nystagmus) or a prominent decreasing-velocity exponential (following saccadic pulses) and the fast phase is always in the direction of the eye that is fixating, the straight eye. That is, the slow-phase rotation of the fixating eye is always in adduction and the fast-phase is in abduction; fixation with the right eye generates a right-beating nystagmus of both eyes, while fixation with the left eye produces a left-beating nystagmus of both eyes. Figure 3.1 illustrates the waveforms usually seen for binocular and monocular viewing. During binocular viewing, the slow phases are usually linear followed by corrective fast phases but upon occlusion, the nystagmus converts to a saccadic pulse train where the saccades defoveate the target and the decelerating slow phases return the fixating eye to the target.

It has long been known that, just as in normal saccades, the fast phases of FMN may contain dynamic overshoots³; the dynamic overshoots’ characteristics in both FMNS and INS are normal.⁸ Figure 3.2 shows FMN in two patients, one without dynamic overshoots (left panel) and one with dynamic overshoots (right panel). Dynamic overshoots are integral parts of the saccadic fast phases and not the beginnings of the slow phases. The uncommon occurrence of square-wave jerks (SWJ, see Chapter 5, Section 5.3.1) mimics their occurrence in normal observers, and their presence during binocular viewing

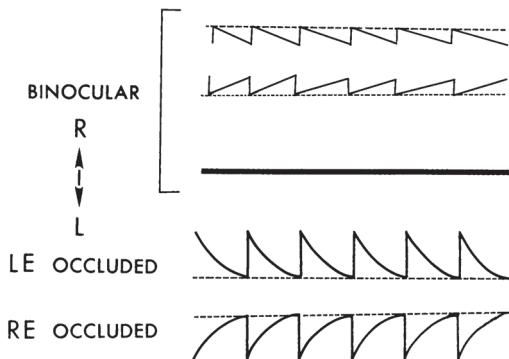


FIGURE 3.1 Illustrations of fusion maldevelopment nystagmus syndrome during binocular viewing (but monocular fixation) and during monocular viewing. Nystagmus with linear slow phases (top) may convert to defoveating saccadic pulses with decelerating slow phases (bottom). Dashed lines indicate target position. LE, left eye; RE, right eye.

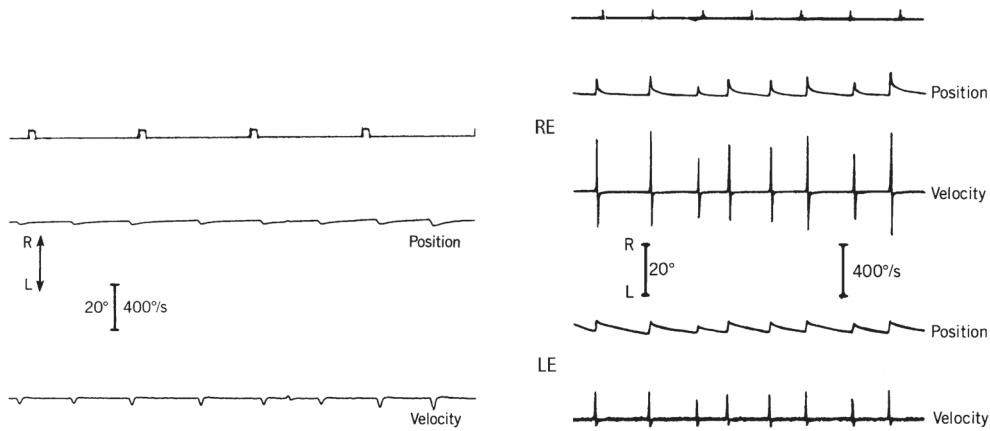


FIGURE 3.2 Fixating left eye of a patient with fusion maldevelopment nystagmus syndrome (left panel) and both eyes of another patient with fusion maldevelopment nystagmus syndrome during right-eye fixation. Note the prominent dynamic overshoots in the saccadic pulses of the fixating right eye and their sharp attenuation in the deviated left eye. Time markers indicate 1-sec intervals; LE, left eye; RE, right eye.

in FMNS is unpredictable and variable. Thus, the presence of either dynamic overshoots or SWJ does *not* represent a mechanistically different “type” of FMN⁸; it is merely the *same* FMN, including these common, normal saccadic dynamics or intrusions. This also applies to the occurrence of other types of nystagmus in addition to FMN (e.g., an undefined “torsional” nystagmus or the high-frequency pendular nystagmus thought to arise from the NOT, resulting in a dual-jerk waveform). In an individual patient, both FMNS and INS may coexist with another type of nystagmus or saccadic intrusion/oscillation. The clearest way to delineate a group of patients with two mechanistically independent eye-movement characteristics is to describe the two conditions (e.g., FMN with dynamic overshoots, FMN plus SWJ, or FMN plus “torsional” nystagmus). Attempts to define FMNS as consisting of multiple “types” based on the presence or absence of these normal occurrences is both confusing and not mechanistically justified. For simplicity, the basic FMNS waveforms shown in Figure 3.1 do not contain either dynamic overshoots in their fast phases or the confounding addition of other types of nystagmus.

3.1.1.1 TYPES (FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME PLUS NUCLEUS OF THE OPTIC TRACT)

Just as in INS, FMNS may also coexist with NOT nystagmus. That is, superimposed on the jerk FMN (with either linear or decelerating slow phases) will be a low-amplitude, high-frequency pendular nystagmus. When the additional pendular oscillation of NOT nystagmus is present, the resulting waveform would be the same as shown in Figure 2.3 for linear INS slow phases (DJR_L) or consist of the pendular oscillation superimposed on the decelerating slow phases illustrated in Figure 3.1.⁹ Figure 3.3 shows eye-movement data from patients with FMNS + NOT nystagmus (specifically, dual-jerk FMN) and demonstrates the independence of the two types of nystagmus; either one may be damped without affecting the other.

3.1.1.2 THE FIXATING EYE

The slow phases of FMN are either linear or decelerating, and the fast phases are always in the direction of the fixating eye.³ The nystagmus of patients with strabismus, alternating

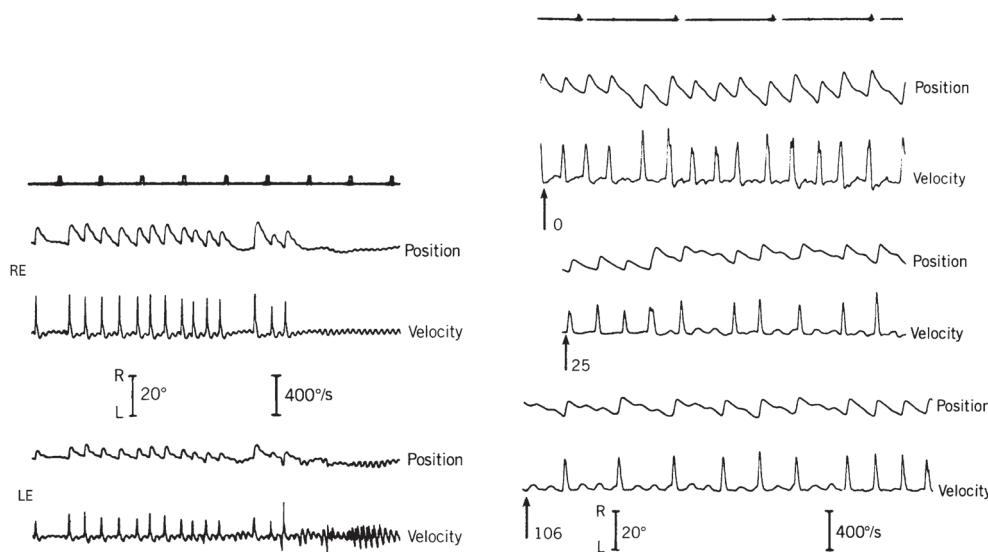


FIGURE 3.3 Eye movements (position and velocity) of patients with fusion maldevelopment nystagmus syndrome (FMNS) plus nucleus of the optic tract (NOT) nystagmus illustrating the independent variations of either component of the dual-jerk FMN waveforms. Shown are damped FMN but consistent NOT nystagmus (left panel) and time-variable NOT but consistent FMN nystagmus (right panel). Numbered arrows in right panel indicate the time in seconds from a continuous record. Time markers indicate 1-sec intervals; LE, left eye; RE, right eye.

fixation, and FMNS with both eyes open has fast phases that are always in the direction of the fixating eye. Such patients may be easily misdiagnosed as having INS, because the nystagmus is present with both eyes open. Recordings are required to document the decelerating or linear slow-phase waveforms characteristic of FMNS from the accelerating slow phases predominant in the INS.

Although “conjugate,” FMN exhibits some morphological differences between the fixating and deviated eye, the latter being less precise (so-called rubber-band conjugacy); this is evident in Figure 3.2 (right panel), where the deviated left eye mimics but does not duplicate the motion of the fixating right eye. It is also consistent with the hypothesis that the two eyes are driven independently and not by a single composite signal.¹⁰ Figure 3.4 shows the effects on FMN of reversing the occlusion of one eye in either an esotropic or exotropic patient. In addition to a reversal of the FMN, a position shift to take up fixation is accomplished by enhanced fast phases and diminished slow phases. Depending on the

directions involved, fast phases are sometimes also diminished.

In addition to occlusion, intent or darkness also may alter FMN. In Figure 3.5 a patient was able to change his FMN by merely attempting to fixate with either one or both eyes (left panel), and another patient’s FMN changed when placed in darkness (right panel). In both panels, both eyes were open at all times (i.e., manifest FMN). When the patient in the left panel switched intent from looking with the left eye to looking with both eyes, the manifest FMN damped considerably and the left eye became slightly esotropic while the right eye took up fixation with no manifest FMN. In the right panel, the patient’s jerk right manifest FMN immediately switched to jerk left in darkness, suggesting a predisposition for left-eye fixation (i.e., left-eye dominant).

The curious observation of a darkness-induced shift in the “fixating” eye shown in Figure 3.5 was clarified by our study of a patient with FMNS who had a prosthesis in his congenitally blind right eye.¹¹ Not surprisingly, he exhibited

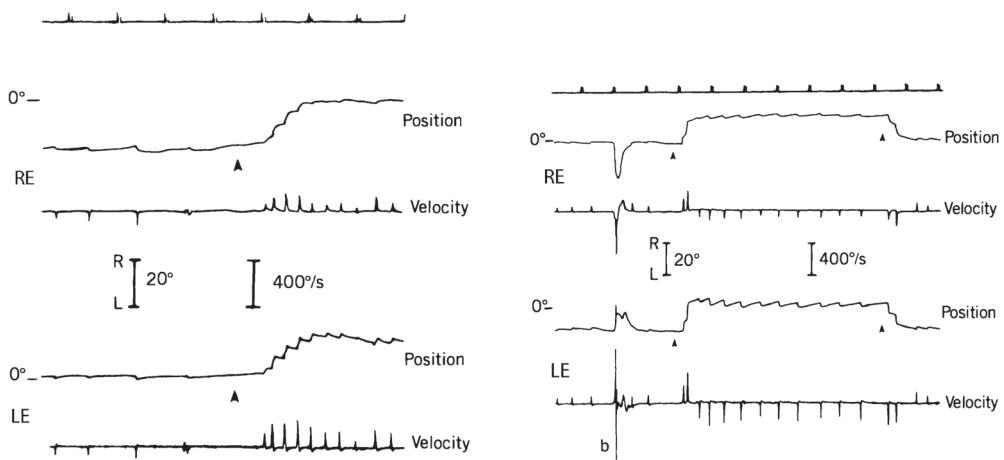


FIGURE 3.4 Eye movements (position and velocity) of patients with fusion maldevelopment nystagmus syndrome and either esotropia (left panel) or exotropia (right panel) upon reversing cover to the fixating eye. Both a direction reversal of the fusion maldevelopment nystagmus and a position shift of both eyes take place to allow fixation by the previously occluded and deviated eye. Arrowheads indicate reversal of cover from the right to left eye (left panel) and from the left to right and back to left eye (right panel). Time markers indicate 1-sec intervals; b, blink; LE, left eye; RE, right eye.

jerk-left FMN during normal fixation but, immediately after the lights were turned off, his “manifest” FMN switched to jerk right while his only intact left eye became esotropic; jerk-left FMN returned when the lights were turned back on (see Fig. 3.6, left panel). As we had observed with many FMNS patients with sight in both eyes, Figure 3.6 (right panel) shows that he also

was able to willfully choose his “fixating” eye (including the prosthetic eye) in the dark and by doing so, change the direction of his FMN. We concluded that eye dominance was cortically predetermined and not altered by visual abnormalities.

Therefore, just as fixation attempt is responsible for the genesis of IN (presumably by modulating

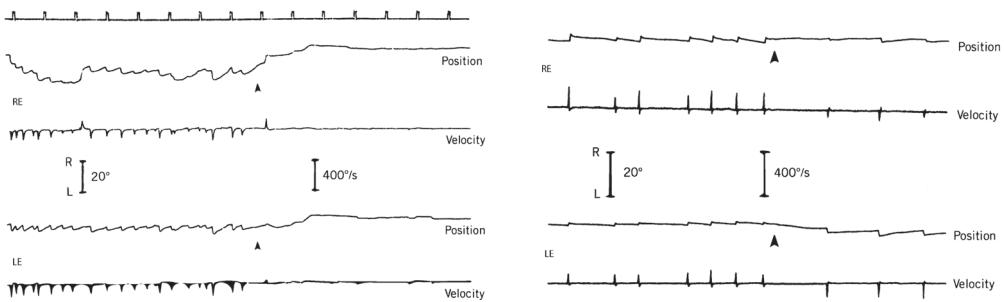


FIGURE 3.5 Eye movements (position and velocity) of patients with fusion maldevelopment nystagmus syndrome illustrating the effects of “looking” with one eye (left panel) or of darkness (right panel). Before the arrowhead in the left panel, the patient was “looking” with the left eye and after it, with both eyes. In the right panel, the patient was in the light and, at the arrowhead, was placed in the dark. Note the spontaneous reversal of direction in the manifest fusion maldevelopment nystagmus. Time markers indicate 1-sec intervals; LE, left eye; RE, right eye.

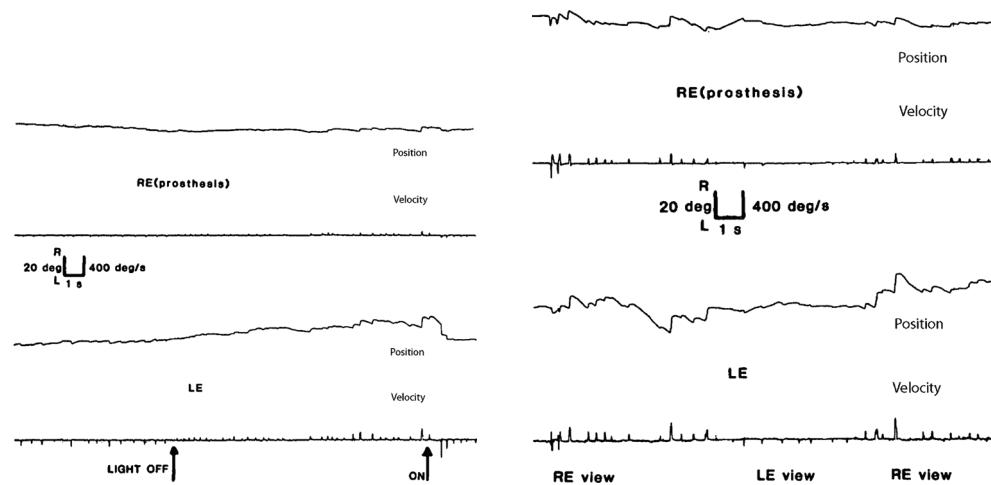


FIGURE 3.6 Eye movements (position and velocity) of a patient with fusion maldevelopment nystagmus syndrome and a right-eye prosthesis showing the effects of darkness (left panel) and willful changes in “viewing” eye in darkness (right panel). LE, left eye; RE, right eye.

the internal feedback loop that controls the damping of smooth pursuit), monocular/binocular fixation attempt is able to modulate the tonic imbalance (slow-phase velocity) driving FMN.

3.1.1.3 TARGET FOVEATION AND DUAL-MODE FAST PHASES

Because the good acuity of INS patients is related to the long, postsaccadic foveation periods of many waveforms, it was difficult to explain the equally good acuity of FMNS patients, given the absence of such periods. However, accurate studies of FMN foveation in a patient with 20/15 acuity revealed a dual strategy.¹² During the low-amplitude, linear-slow-phase FMNS waveform, the saccadic fast phases foveate the target, and the low-velocity slow phases take the eye away from the target with little effect on acuity. During the higher amplitude, decelerating slow-phase FMNS waveform, the saccadic fast phases defoveate the target, allowing foveation during the low-velocity, tail ends of the slow phases (see Fig. 3.7); this ensures the best acuity possible and was the first recorded demonstration of the saccadic system acting deliberately to defoveate the target. As the phase plane in Figure 3.7 (right panel) shows, most of the data (i.e., time) is during the slow phases and within the foveation window. There is very little

time spent during the high-velocity leftward fast phases or their rightward dynamic overshoots, which can be seen just above the slow-phase data points that appear as the large black area within the foveation window. In Figure 3.8, the effects of placing and removing cover over each eye are shown. Initially, both eyes were on target (within the foveal radius) and there was minimal FMN. Cover resulted in FMN with both foveating or defoveating fast phases and esotropia; cover removal damped the now manifest FMN.

Defoveating saccades result from generating a pulse, but not a step, of innervation to drive the fast phases of the FMNS nystagmus. Therefore, the common neural integrator controlling eye position must be kept from integrating these defoveating pulses by an internal signal representing the correct/desired eye position vis-à-vis the target. These hypotheses were combined in a physiologically realistic, behavioral OMS model (see Chapter 2) capable of simulating responses of an individual with FMNS.^{13–15} The model simulated FMN based on the tonic imbalance hypothesized to be its cause. In Figure 3.9, OMS model simulations of the effects on FMN of both alternate fixation (during binocular viewing) and alternate cover are shown. During alternate fixation, the foveating fast-phase waveform of FMN is likely to remain, whereas during alternate cover, defoveating fast phases are more likely.

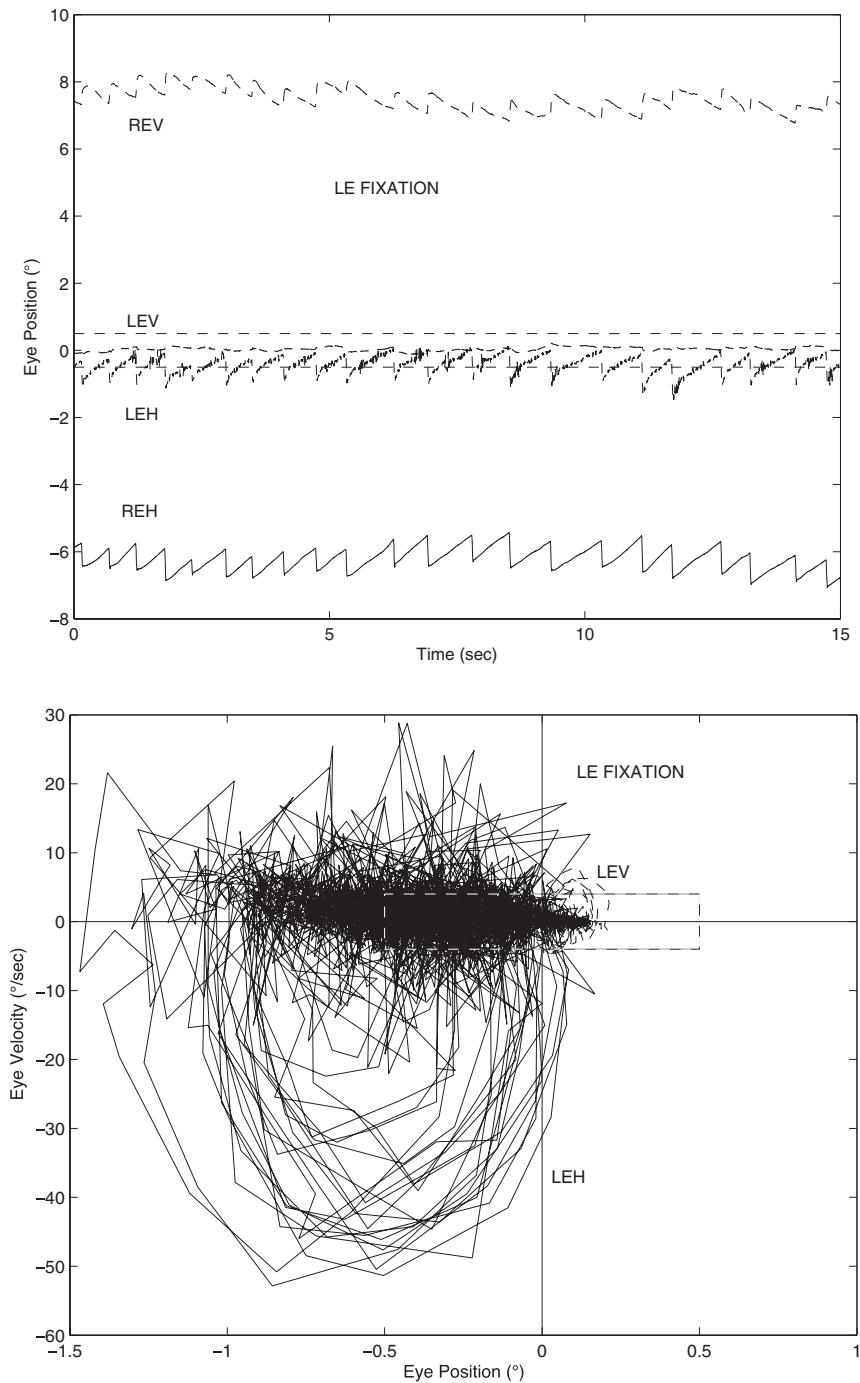


FIGURE 3.7 Horizontal (H) and vertical (V) eye movements of a patient with manifest fusion maldevelopment nystagmus (top panel) and phase plane of the fixating left eye (bottom panel). The fast phases are defocusing with dynamic overshoots allowing foveation during the decelerating slow phases. LE, left eye; RE, right eye; dashed lines, foveal extent (top panel) and the foveation window (bottom panel).

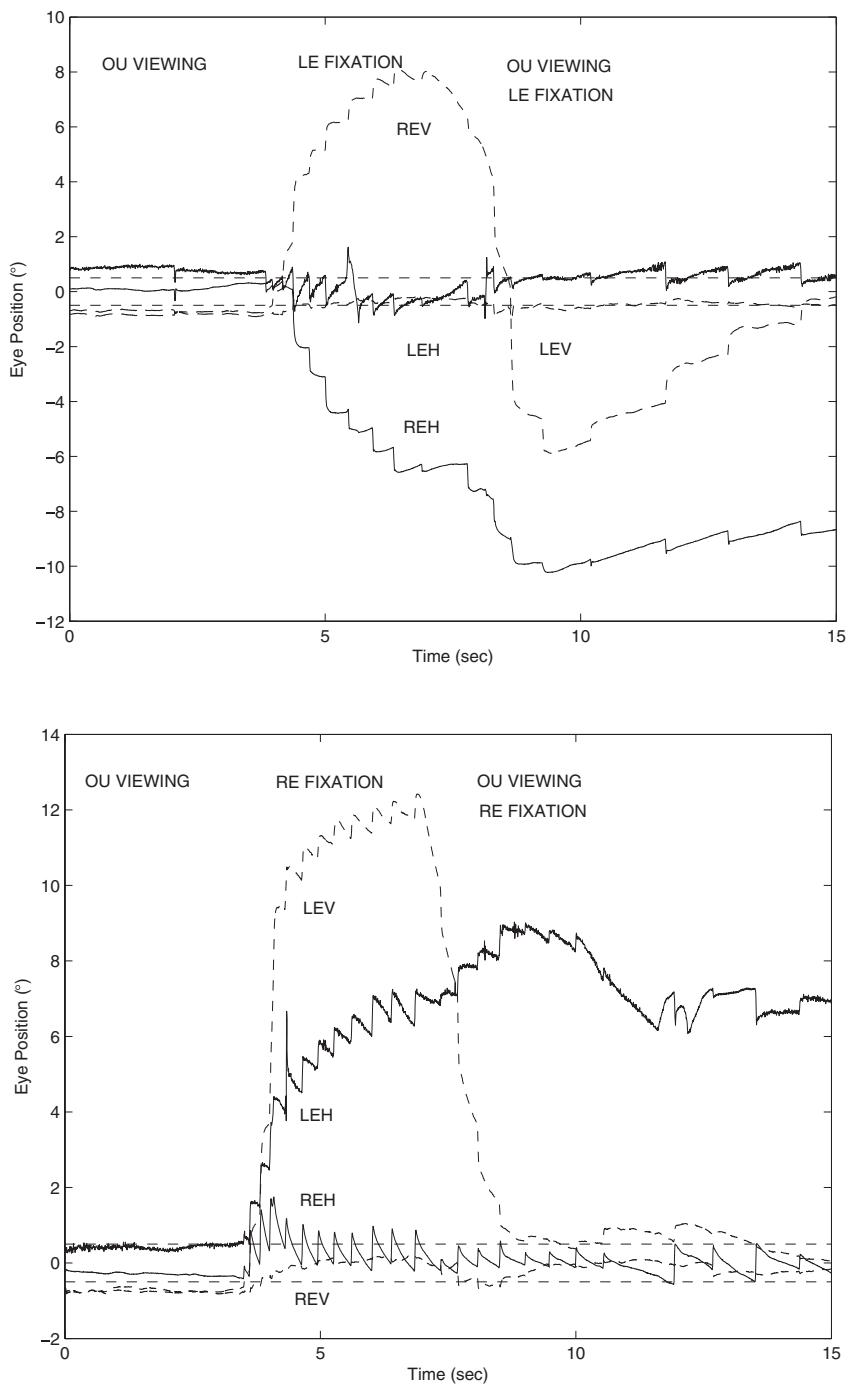


FIGURE 3.8 Horizontal (H) and vertical (V) eye movements of a patient with manifest fusion maldevelopment nystagmus showing the effects of placing and removing cover over the right (top panel) and left (bottom panel) eyes. LE, left eye; OU, both eyes; RE, right eye; dashed lines, foveal extent.

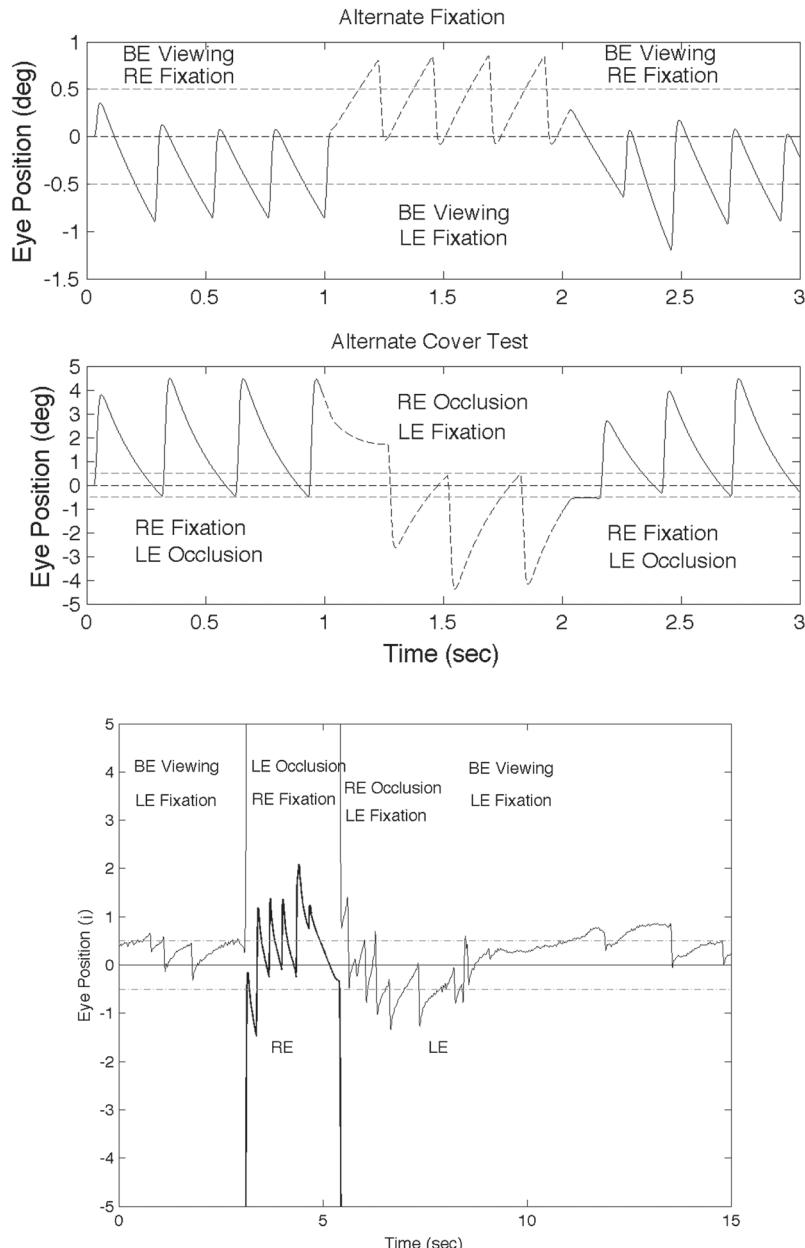


FIGURE 3.9 Behavioral ocular motor system model simulations of alternate fixation and alternate cover on fusion maldevelopment nystagmus (top panel) and of alternate cover in a fusion maldevelopment nystagmus syndrome patient for comparison. LE, left eye; RE, right eye.

3.1.1.4 FOVEATION ACCURACY

FMNS can cause the patient to have much worse monocular than binocular visual acuity. However, as the patient whose data are shown in Figures 3.7 and 3.8 demonstrates, accurate foveation is still possible under both conditions

in some patients, thereby preserving their visual acuity. Foveation can be just as accurate in some patients with FMNS as it is in others with INS. The fixation subsystem can either prolong foveation periods just after foveating saccades in INS or at the ends of decelerating, foveating

slow phases that follow saccadic pulses in FMNS. However, it cannot create foveation periods when there is a non-zero velocity slow phase immediately following a foveating slow phase; that is, as the dashed waveforms in Figure 3.10 illustrate, there exist no waveforms where extended foveation periods precede either linear or decelerating slow phases.

3.1.2 Variation with Gaze Angle

The intensity of FMNS is maximal in abduction and minimal in adduction, causing an “adduction” null with the fixing eye and not a true “gaze” (eye in orbit) null position (see Chapter 5, Table 5.3). In Figure 3.11, OMS model simulations of the Alexander’s law¹⁶ effects of gaze angle on FMN are shown for both small and large effects during both monocular occlusion and binocular viewing. For the same FMN in primary position, the larger amplitude variation with gaze angle results in a waveform transition at a more central gaze angle in both

conditions albeit with a more damped FMN for the manifest case.

Finally, to take full advantage of Alexander’s law in order to minimize the amplitudes of their nystagmus, many patients with FMNS alternate their fixing eye such that it is always the adducting eye. Thus, they fixate with the left eye when looking right and vice versa. Figure 3.12 shows OMS model simulations of the effects of this strategy for different gaze angles in both directions for small and large Alexander’s law effects.

3.1.3 Head Position

Because of the propensity to place the fixating eye in adduction, viewing targets directly in front of the patient necessitates rotation of the head in the opposite direction (e.g., right eye to the left, in adduction, with head rotated to the right). In addition to causing the anomalous head posture, this may give the mistaken clinical impression of a nystagmus (usually INS) with two “nulls” if the clinician fails to detect the change in the fixating

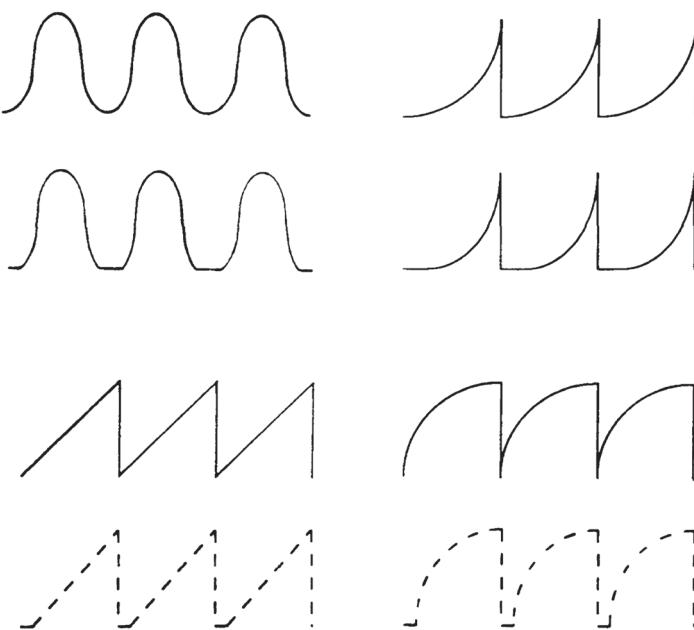


FIGURE 3.10 Illustrations of the four major nystagmus waveforms (clockwise from the top left, pendular, jerk with accelerating slow phases, jerk with linear slow phases, and jerk with decelerating slow phases) coupled with the addition of extended foveation periods in those waveforms where it is possible for the ocular motor system to produce them. Dashed waveforms do not exist.

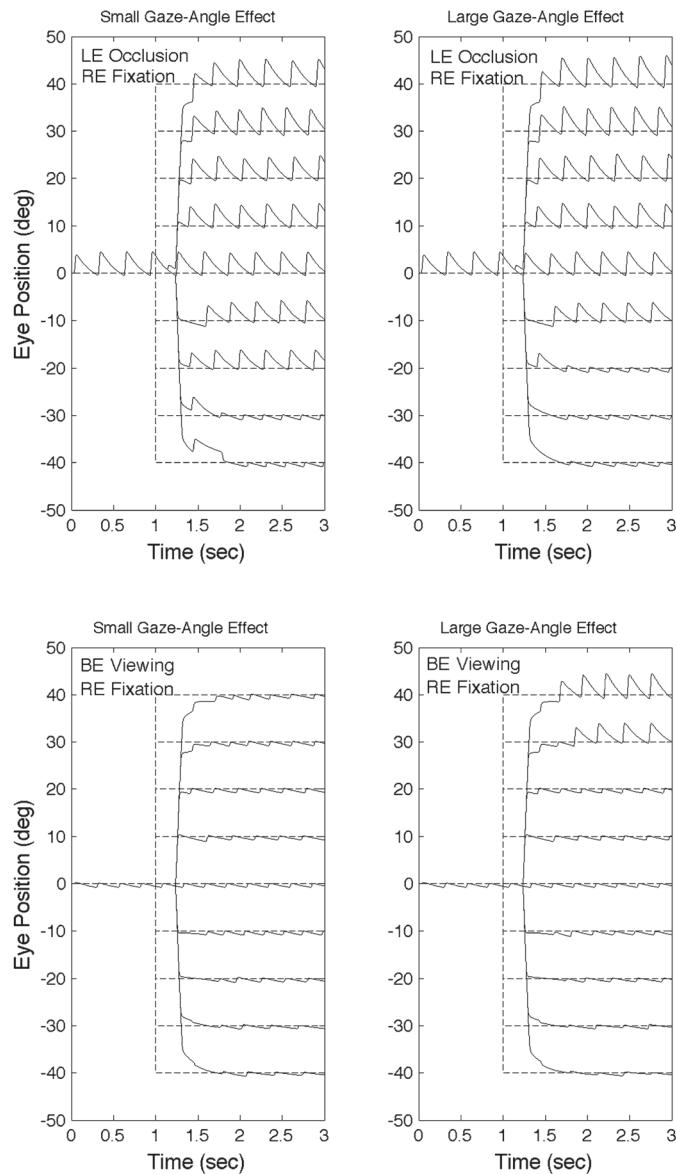


FIGURE 3.11 Behavioral ocular motor system model simulations of gaze angle on fusion maldevelopment nystagmus syndrome amplitude and waveform transition angle (for both small and large Alexander's law effects) during both monocular occlusion (top panels) and binocular viewing (bottom panels). BE, both eyes; LE, left eye; RE, right eye.

eye or realizes that there is no true null (i.e., the nystagmus does not increase as the eye is rotated further in adduction).

Using scleral search coil eye-movement recordings of 10 patients with dissociated vertical deviation and FMNS, Guyton et al. showed that nystagmus (horizontal, vertical, and torsional) practically always appeared initially,

when one eye was occluded, and became damped as a dissociated vertical deviation (DVD) developed with head tilting.¹⁷ The damping occurred over 0.3 to 3 seconds and was often only partial, identified as a decreasing slope of the nystagmus slow phases. Occasionally, if the DVD response diminished, the FMN reappeared. As was discussed earlier for FMN, the DVD

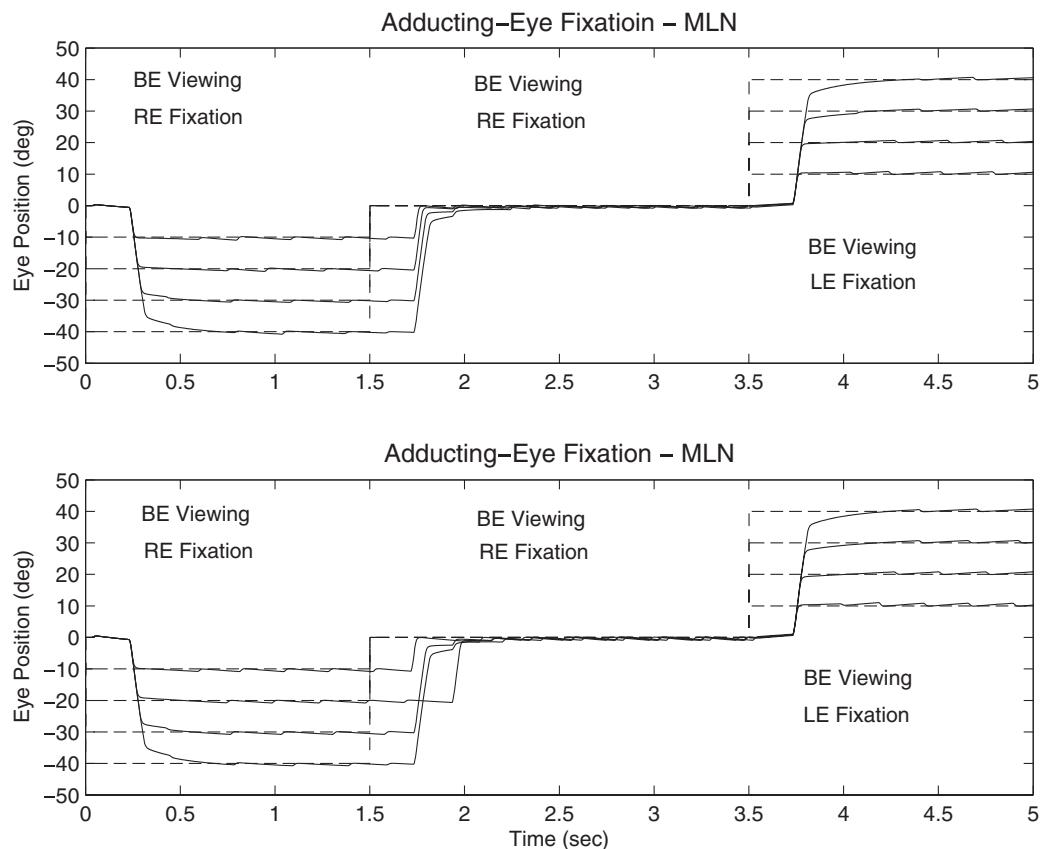


FIGURE 3.12 Behavioral ocular motor system model simulations of adducting eye fixation on fusion maldevelopment nystagmus syndrome for both small (top panel) and large (bottom panel) Alexander's law effects. BE, both eyes; LE, left eye; RE, right eye.

response could be recorded in total darkness in those individuals who could voluntarily imagine switching “fixation” (attention) from one eye to the other. A head tilt also damped the FMN and appeared to decrease the need for DVD. That evidence supports the view that DVD is an acquired (learned), often anticipatory, cyclovergence response, occurring upon taking up unilateral fixation, serving to improve vision by damping or blocking FMN.

3.1.4 Foveation, eXpanded Nystagmus Acuity Function, and Acuity

Despite the lack of extended foveation periods in FMN with linear or slightly decelerating slow phases, the low amplitudes of these slow

phases may still allow for good visual acuity. As long as sufficient data points fall within the foveation window of the eXpanded nystagmus acuity function (NAFX; centered at the ends of the fast phases) for each FMN cycle, the NAFX value, and visual acuity, will be high. When the FMN waveform consists of saccadic pulses whose decelerating slow phases foveate the target, the same applies since the NAFX window is now centered on the tail ends of the slow phases. We have documented visual acuities as high as 20/15 in a patient with both waveforms.¹²

3.1.5 Efference Copy, Foveation, and Oscillopsia Suppression

The discussion in Chapter 2, Section 2.1.10 regarding the roles of efference copy and

foveation in the suppression of oscillopsia in INS is equally applicable in FMNS. Patients with FMNS do not normally experience oscillopsia because their efference-copy signal of the FMN motor command is used to negate the nystagmus portion of the retinal signal, leaving the target portion uncontaminated and allowing for the perception of spatial constancy. Thus, in our OMS model of FMNS, that stable reconstructed target signal is produced internally by the same mechanism as in INS and is used to drive the correct ocular motor responses to target position and velocity—analogous to INS and FMNS patients, the model has no oscillopsia when simulating either.

3.2 ETIOLOGY OF FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

FMNS is “congenital” in the same sense as INS (i.e., a congenital predisposition). However, several cases have been recorded of the manifest form of FMNS (“MLN” occurring with both eyes open), associated with retrothalamic fibroplasia.³ Early theories postulated that a unilateral retinal stimulus was the necessary condition for FMNS, but this concept was discounted by observations of FMN in monocular fixation with a blind eye or with an acoustic stimulus in complete darkness. FMNS occurs in patients with strabismus who, although viewing with both eyes open, are fixing monocularly.

Strabismus is a necessary (but not sufficient) condition for FMNS.⁷ That is, all individuals with FMNS have strabismus, consisting of either a phoria or tropia under cover and a tropia with both eyes open, if nystagmus is present under these respective conditions. Conversely, FMNS is not significantly associated with early-onset strabismus.¹⁸ Rarely, on occlusion of a preferred eye, during which fixation with an amblyopic eye is forced, both eyes drift in the direction of the covered eye without corrections by fast phases; this is called “latent deviation.” Early surgical correction of infantile strabismus may convert the nystagmus of FMNS present with both eyes open (the manifest condition) to nystagmus present only upon occlusion of one eye (the “vera”

or “latent” condition),¹⁹ thereby supporting a previous hypothesis.⁷

In children with FMNS and fusion, the development of amblyopia with subsequent diminishing fusion or the recurrence of a frank tropia, thus disrupting binocular vision, will make an FMN become either more intense or manifest, thus the potential for creating visual symptoms due to the nystagmus where none were present before. The magnitude of the resulting manifest FMN is proportional to the degree of the interocular visual disparity. However, successful treatment of amblyopia or strabismus will decrease the intensity, occasionally giving the appearance of complete absence. FMNS has also been reported in children with unilaterally reduced vision and esotropia associated with congenital disorders such as cataract or optic nerve hypoplasia. These children will often maintain a head turn to position the fixating eye in adduction.^{11,20,21}

Various theories have been advanced to explain FMNS. These include a primitive vestibular tone imbalance, poor egocentric localization, a subcortical optokinetic system anomaly, a subcortical maldevelopment of retinal slip control, abnormal cortical motion processing, a disorder of proprioception, and a phylogenetic persistence of the dominance of the nasal half of the retina.^{3,22–31} In Chapter 2 we identified the direct cause of most IN waveforms as a failure of calibration in the damping mechanism of smooth pursuit. The direct cause of FMN is a tonic imbalance that drives the eyes with constant velocity (producing linear slow phases). The source of the imbalance may be the naso-temporal asymmetry present in normal infants that disappears as fusion develops or, as we hypothesized, egocentric direction confusion (see Section 3.2.3).

3.2.1 Familial (Gene Defect)

Just as in INS, there are some families whose members have FMNS. That suggests that, in those families, there is a genetic component that facilitates (*not causes*) the development of FMNS (see discussion of genetics and INS in Chapter 2, Section 2.2.1).

3.2.1.1 DOWN SYNDROME

FMNS is common in Down syndrome, where it may coexist with INS.³² Of 35 adult patients with Down syndrome, 6 (23%) had FMNS; none had INS. In addition, one child was studied who had some INS waveforms in addition to FMNS. This was far above the reported 15% prevalence of FMNS in the general population. Near stereopsis was preserved in two of the adults and some fusion (the Worth four-dot test) in two others. Five of the six preferred left-eye fixation and three were left handed, a high percentage suggesting an unusual pattern of hemispheric dominance.

3.2.2 Optokinetic Asymmetry

FMNS has been associated with nasotemporal asymmetry of the horizontal optokinetic response and smooth pursuit during monocular viewing. Roelofs first observed horizontal optokinetic asymmetry in patients with FMNS.³³ Kommerell suggested that FMNS could be regarded as the consequence of horizontal optokinetic asymmetry.²³ Hoffman developed a model to explain nasotemporal asymmetry based on combined cortical and subcortical input to the nucleus of the optic tract in the cat.³⁴ In 1983, Schor proposed that FMNS and nasotemporal optokinetic asymmetry are mediated by the nucleus of the optic tract.³⁵ Human nasotemporal asymmetry has received considerable attention because it persists throughout life in humans with early-onset infantile strabismus. Nasotemporal asymmetry is seen in rabbits, kittens, monkey infants, and human infants within the first 6 months of life.³⁵

However, the hypothesis that the FMNS is caused by nasal-temporal asymmetries in the optokinetic reflex is not supported by evidence that subjects with FMNS are able to use retinal slip information to adapt motion-detection sensitivities³⁶ and are able to pursue symmetrically.⁴ Also, because nasal-temporal asymmetries exist in individuals with strabismus but not FMNS,³⁶ this cannot be the primary causal factor in the genesis of the nystagmus. Asymmetries in the monocular optokinetic response of monkeys

deprived of binocular input early in life may result from, rather than cause, their nystagmus. In normal monkeys, each NOT is driven binocularly; in these monkeys, they are driven by the contralateral eye.³⁷ Although the resulting imbalance may provide the tonic signal that produces the FMN slow phases (inactivation of the NOT with muscimol abolishes the nystagmus), the cause of the imbalance appears to lie in higher centers. The spontaneous reversal of FMN in the dark has led to the speculation that eye dominance is predetermined.^{11,38} Shallo-Hoffmann et al. identified an alternating vertical component to FMNS³⁹ and Brodsky linked the genesis of FMNS and dissociated vertical divergence (DVD) to the dorsal light reflex present in many animals.⁴⁰ In cases of FMNS plus DVD, the nystagmus may have a vertical component.⁴¹

3.2.3 Egocentric Direction Confusion

Cortical switching that must occur in the calculation of egocentric direction when going from binocular to monocular viewing.³ Under binocular conditions, egocentric direction, referenced to the “cyclopean eye,” is obtained by summing the gaze angle of each eye with the other and dividing by two. However, with monocular viewing, egocentric direction depends *only* on the viewing eye, and the cortical operation of summing and dividing by two must be altered to process unchanged information from the viewing eye. We hypothesized that the shift in egocentric direction toward the non-viewing eye causes the slow drift of the eyes in that direction. Both eyes are then corrected by a saccade in the direction of the viewing eye, which brings the eyes to the target (or, in darkness, to the intended gaze angle). This hypothesis was supported by unilateral strabismus surgery causing central effects on egocentric localization.⁴² Thus, FMNS nystagmus may be generated by this inability to properly alter the cortical mathematical operation normally used to define egocentric direction (i.e., this deficit in higher centers may result in a tonic imbalance in the visual-vestibular subsystem, producing the linear slow phases of FMN). Our 1979 hypothesis for the cause of FMNS was also supported by Tychsen et al.,

who studied FMNS in patients and nonhuman primates.⁴³ They related egocentric direction confusion to unbalanced infantile, monocular interhemispheric MSTd drive, which they found was necessary and sufficient for FMNS. The shift to monocular egocentric localization can also produce this mode whereby the saccadic system generates defoeating saccades that momentarily carry the fixating eye past the target in a temporal direction, followed by a decelerating-velocity nasal drift back toward the target.¹²

Studies in subhuman primates have shown that FMNS arises after incomplete development of visual input from occipitotemporal cortex to subcortical vestibular pathways. In monkeys with FMNS, there is a loss of binocularity in the NOT, the subcortical structure that feeds into the vestibular system, with most cells driven by the contralateral eye.³⁵ The areas that normally provide binocular input to the NOT are the middle temporal (MT) visual area and the medial superior temporal (MST) visual area in occipitotemporal cortex.^{44,45} When strabismus was surgically induced in infant monkeys during the first 2 weeks of life, these monkeys also developed FMN and visual area MT/MST loses binocularity. If either eye is covered during infancy, visual area MT/MST and NOT develop normal binocularity, but the striate cortex still shows loss of binocularity and these monkeys do not develop FMN. This finding suggests that the initial cause of FMNS is loss of binocularity in visual area MT/MST from the misaligned eyes in early infancy. Neuroanatomical experiments have supported the Schor hypothesis that the NOT may be the site of FMN generation. FMNS occurs in nonhuman primates following artificial induction of esotropia within the first 2 weeks of life.^{44,45} Experiments have shown that a loss of binocular connections within striate cortex (area V1) in the first months of life may be the necessary and sufficient cause of FMNS.^{43,46,47}

The severity of FMNS increases systematically with longer durations of binocular decorrelation and greater losses of V1 connections. Decorrelation durations that exceed the equivalent of 2–3 months in human development result in an FMNS prevalence of 100% in the nonhuman primate model.^{43,46,47} No manipulation of

brainstem motor pathways was required in this model. The binocular maldevelopment originating in area V1 is passed on to downstream extrastriate regions of cerebral cortex that drive conjugate gaze, notably MST. Conjugate gaze is stable when MST neurons of the right and left cerebral hemispheres have balanced binocular activity. Fusion maldevelopment in infancy causes unbalanced monocular activity.^{43,46,47} If input from one eye dominates and the other is suppressed, MST in one hemisphere becomes more active. Acting through downstream projections to the ipsilateral nucleus of the optic tract, the eyes are driven conjugately to that side. The unbalanced MST drive is evident as the nasalward gaze-holding bias of latent FMN when viewing with either eye.

In summary, most patients have nystagmus from either the INS or the FMNS; some have both; and three unambiguous patient groups have been identified: INS, FMNS, and INS + FMNS.^{9,48,49} The three groups exhibit different clinical signs and relations to strabismus; most series of INS patients show that many have strabismus, but all FMNS are strabismic.^{50–53} Thus, INS and FMNS are specific, easily differentiated syndromes and do not, as has been suggested,²⁹ represent a unitary disorder with a broad spectrum of expression. Because no acquired, time-independent, primary-position jerk nystagmus reverses direction with alternate eye cover, a simple reverse-cover test can be a powerful clinical tool.

Clinical Pearl: To distinguish between benign (non-neurologically threatening), infantile, primary-position, jerk nystagmus and that which is neurologically threatening, first verify that there is no periodic alternation in direction and then perform bilateral, sequential, cover-uncover testing. If the cover test causes a reversal in the nystagmus direction consistent with FMNS, the nystagmus is benign (FMNS or INS with a latent component). If not, attempt to rule out INS (by history, clinical signs [see Table 2.1], and waveforms).

Clinical Pearl: If the results of an alternate-cover test indicate a benign, infantile,

primary-position, jerk nystagmus (i.e., it causes a reversal in the nystagmus direction consistent with FMNS or INS with a latent component), perform the test again but in far adduction of the fixating eye (e.g., far left gaze when the left eye is occluded). If the nystagmus again reverses (i.e., becomes jerk left in left gaze with left eye occluded), it is INS with a latent component. Repeat the test in adduction of the other eye fixating. If the nystagmus remains in the direction of the fixating eye, it may be either FMNS or INS with a large latent component.

3.3 TREATMENTS OF FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

When considering therapy for FMNS, it is important to understand the different components that contribute to the nystagmus and how (and at what site) each proposed therapy works. Similar to INS, there are both sensory and motor components. The absence of fusion is the sensory component that contributes to the tonic motor imbalance that drives FMN. The effect of gaze angle (Alexander's law) is the motor component modulating the FMN. Finally, the proprioceptively controlled small-signal gain of the extraocular muscles (a motor component) also can modulate the FMN. Therefore, different therapies and adaptations by the patient can act in distinct mechanistic ways to damp the FMN and, in some cases, restore fusion.

The primary treatment of FMNS is a combination of medical, optical, and surgical therapy to create, restore, or improve binocular function. Since the intensity of the FMN is related to the degree of binocular function, improving fusion will damp the FMN and improve visual function. The addition of nystagmus surgery, in the form of tenotomy and reattachment (T&R) of any horizontal rectus muscles not operated on to realign the eyes, should also further damp the FMN.

3.3.1 Fixation Preference

Patients with FMNS may be visually guided by one eye; this is due, in large part, to afferent

asymmetry associated with ametropia, amblyopia, or structural disease of the eye and brain. Many of these patients will prefer the fixing eye in adduction, thus adopting a head/face turn toward the fixing eye regardless of the primary position deviation. When forced to fixate with the nonpreferred eye, the intensity of the FMNS will increase, visual functions will decrease, and a new (opposite) head/face position will be evident. Some patients spontaneously switch fixating eyes while looking at a single target.

3.3.2 Alexander's Law

Taking advantage of Alexander's law is also a consideration when determining treatment options. It would be disadvantageous to move the fixating eye medially as it would require additional abduction innervation to fixate targets in either primary position or further in abduction. In esotropia, the fixating eye (or, both eyes) is moved into abduction so that the adduction innervation required to maintain fixation damps the FMN by taking advantage of Alexander's law (motor component of FMN). It is also possible to achieve fusion to damp FMN (sensory-motor component of FMN). However, in exotropia, if one moves the fixating eye medially to achieve the straightening effect on the exotropic eye for primary position targets, that may exacerbate the motor component of FMN unless the patient achieves fusion. In the latter case, the sensory-motor effect of fusion in decreasing the FMN could be greater than the abduction innervation in increasing the FMN. In those exotropic FMNS patients for whom fusion is impossible, recessions of all four horizontal recti with a large differential (more on the lateral than the medial recti) has proven successful in treating both the exotropia and the motor component of the nystagmus.

3.3.3 Eye-Muscle Surgery

It is also possible to surgically enhance the acuity of some patients with FMNS at the same time as correcting the strabismus and head posture. These operations are considered broadly as treatment of "strabismus and nystagmus with or

without an anomalous head posture" (see operation algorithm, Chapter 7, Appendix C, and Appendix D, Figs. D.2 and D.4). In summary, to address both the FMN, head posture (if not alternating), and strabismus in the same procedure, the two horizontal rectus muscles on the eye responsible for the head posture are recessed and resected to straighten the head while the two horizontal recti on the nonfixing eye are recessed and resected to correct the resulting strabismus. The advantage of operating on all four horizontal recti is that, in addition to treating the strabismus and head posture, there is the potential of fusion and further damping of the FMN produced by the T&R effect on the proprioceptive control of the small-signal gain of the extraocular muscles. Another advantage of the T&R additions to the strabismus procedure is that, in addition to damping the FMN, those muscles receiving a T&R are left intact and may be used for future strabismus adjustments that might become necessary.

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4

OTHER TYPES OF NYSTAGMUS OF INFANCY

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The greatest obstacle to discovery is not ignorance—it is the illusion of knowledge.

—Daniel J. Boorstin

IN ADDITION to infantile nystagmus syndrome (INS) and fusion maldevelopment nystagmus syndrome (FMNS), there are two rare syndromes found in infants and children: the nystagmus blockage syndrome (NBS) and the spasmus nutans syndrome (SNS).¹

4.1 NYSTAGMUS BLOCKAGE SYNDROME

The NBS was defined clinically as one in which a patient with nystagmus (type undefined) damps or changes that nystagmus (again type undefined)

by willfully deviating his fixating eye inward (e.g., “convergence”).^{2–6} The lack of specificity regarding the nystagmus types or waveforms present both before and after “convergence” led to problematic diagnoses and interpretations of the clinical symptoms. Because of this, the NBS remains both a poorly understood and an over-diagnosed phenomenon related to INS. As the name suggests, the nystagmus of these patients diminishes or disappears clinically with the act of *willed esotropia* while fixating a distant target. *This should not be confused with the damping of IN during true convergence on a near target.*

Based on our research, the NBS can now be more accurately defined as a syndrome in which a patient with INS plus a variable esotropia willfully deviates the fixating eye into adduction to accomplish either a damping of the IN or a switch from IN to a low-amplitude FMN.¹

The reported incidence of NBS in esotropic patients is quite variable and may reflect a geographical bias (10.2% in Europe and 4%–5% in America) as well as overdiagnosing in conjunction with a lack of quantitative data. Although Metz and Smith do discuss NBS,⁷ their recordings clearly show that their patient had FMNS and that the amplitude varied in accordance with Alexander's law.^{8–13} Hoyt, in a letter containing no eye-movement recordings, claimed that 8 of 32 patients with congenital esotropia had NBS.¹⁴ Without recordings, INS cannot be differentiated from FMNS, and the diagnosis of NBS cannot be verified.

4.1.1 Characteristics of Nystagmus Blockage Syndrome

4.1.1.1 MULTIPLE TYPES OF NYSTAGMUS

The first characteristic revealed by eye-movement data was that there were two mechanisms by which blockage of the ongoing nystagmus can be accomplished; that resulted in two different types of patients with the NBS.^{15,16} Patients with both types had IN when their eyes were aligned. In Type I, the IN either damped or stopped entirely upon willful esotropia, in much the same way as with true convergence. In Type II of NBS, the INS waveform converts to a low-amplitude FMNS waveform with the onset of the strabismus. Normally, the substitution of the FMNS slow phases for the INS waveforms that allow for better foveation would not be advantageous. However, in these few patients, the low FMNS amplitude results in better acuity than the larger INS amplitude. NBS is often misdiagnosed in FMNS patients with a strong Alexander's law variation of their nystagmus, which causes them to fixate with their adducting eye.¹⁵ Thus, the NBS encompasses two different types of infantile nystagmus and the ability to willfully change the amount of esotropia present to improve the

nystagmus waveform and, thereby, visual acuity. The NBS has been reported in an exotropic patient¹⁷ and also in a congenitally blind patient.¹⁸

4.1.1.2 WAVEFORMS AND MECHANISMS

During the pre-esotropia phase of the NBS, the waveforms of the nystagmus are those of INS (see Chapter 2, Section 2.1.2). However, upon the willful esotropia, they may be either damped INS waveforms or FMNS waveforms (see Chapter 3, Section 3.1.1). As discussed in Chapter 3, the underlying mechanism for the appearance of FMN is hypothesized to be a tonic imbalance related to the failure of fusion development. Although it is possible that the purposive esotropia induces an actual switch from IN to FMN, it is more probable that both types of nystagmus coexist and the FMN is revealed when the IN becomes sufficiently damped by the esotropia. The second possibility is supported by the demonstration that IN and FMN can both be present in some patients.¹⁶

4.1.1.2.1 Target Foveation. Target foveation depends on which type of waveform (INS or FMNS) is present and is described in Chapters 2 and 3. In some cases, the nystagmus is totally blocked by the purposive esotropia and foveation is essentially the same as in unaffected individuals.

4.1.1.2.2 Foveation Accuracy. Foveation accuracy also depends on which type of waveform (INS or FMNS) is present and is described in Chapters 2 and 3. In the case of complete nystagmus blockage, the accuracy is essentially the same as in unaffected individuals.

4.1.1.3 PURPOSIVE ESOTROPIA

It had been suggested that the nystagmus is actively blocked by convergence innervation, the esotropia thus being caused by sustained convergence and secondary changes in the medial rectus muscles. The differential diagnosis includes infantile esotropia with equal and alternating crossed fixation, bilateral sixth nerve paralysis, and bilateral Type I Duane syndrome. NBS is characterized

by a reduction of the nystagmus when esotropia increases. A useful clinical sign in differentiating NBS from other forms of convergence excess esotropia is the absence of pupillary constriction. These patients are not using their accommodative vergence mechanism to block the nystagmus but, instead, are depending upon some other mechanism to bring about damping of the nystagmus.

4.1.1.4 HEAD POSITION

Prior to the purposive esotropia (i.e., during the binocular IN phase), there is not likely to be a head turn. However, after esotropia (in both the NBS Types I and II), the fixating eye is the purposively esotropic eye, necessitating a head turn in the opposite direction. In Type II, because of the Alexander's law variation of FMN, a large head turn is common.

4.1.1.5 BLOCKAGE SYNDROME TYPES I AND II

The characteristics of both the NBS Types I and II and the differences from convergence damping

in INS are demonstrated in the following figures. The eye movements of a patient with Type II NBS are shown in Figures 4.1–4.3. The INS waveforms of this NBS patient during binocular fixation of a target in primary position are shown in Figure 4.1. The jerk and jerk with extended foveation waveforms are predominantly right beating with some cycles that are left beating. Figure 4.2 shows the waveforms of the same NBS patient binocularly fixating a target in right gaze. As the right eye becomes esotropic and the left eye remains on target, the INS waveform abruptly switches to a jerk-left FMN. When the right eye returns to the target, the nystagmus again becomes IN (dual jerk right with extended foveation).

Individuals with FMNS often fixate stationary targets with their adducting eye, as is illustrated in Figure 3.12. This strategy is also used during smooth pursuit, as is shown in Figure 4.3. Initially, as the target crosses the midline, the right eye takes up pursuit to the left, while the left eye remains esotropic, albeit moving with the same pursuit velocity. As the now rightward moving target again crosses the midline, the left eye takes up smooth pursuit while the right eye remains esotropic.

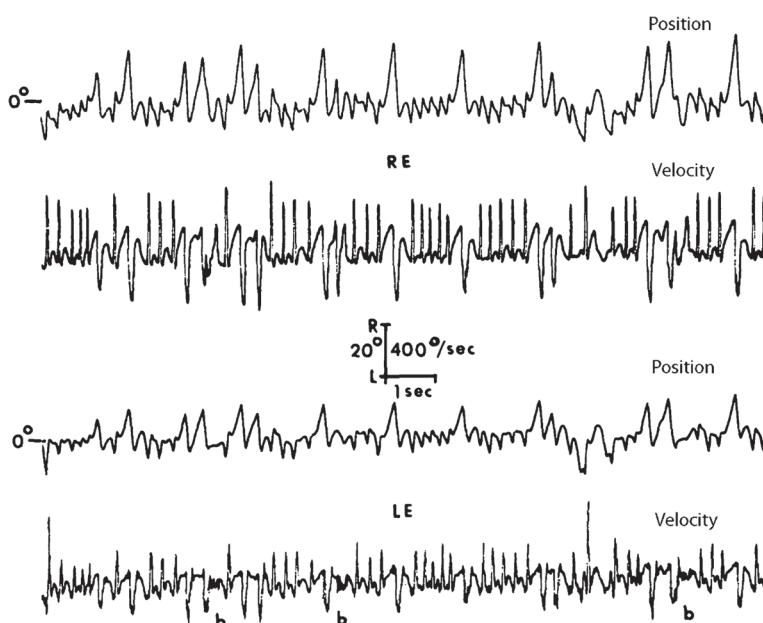


FIGURE 4.1 Horizontal eye position and velocity right- and left-eye data from a patient with nystagmus blockage syndrome showing infantile nystagmus syndrome waveforms when the eyes are aligned and fixating on a target in primary position. Time markers indicate 1-sec intervals. b, blink; LE, left eye; RE, right eye.

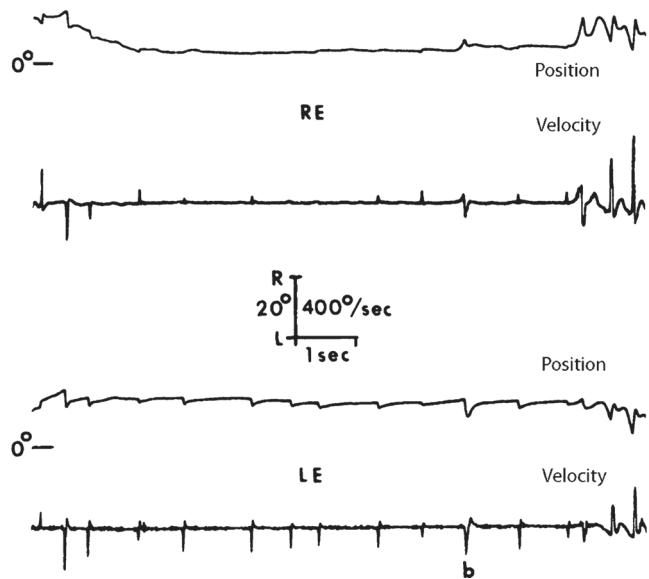


FIGURE 4.2 Horizontal eye position and velocity right- and left-eye data from the same patient shown in Figure 4.1 with nystagmus blockage syndrome showing infantile nystagmus syndrome waveforms when the eyes are aligned (beginning and ending of the interval shown) and conversion to jerk-left fusion maldevelopment nystagmus when the right eye became esotropic. Time markers indicate 1-sec intervals. b, blink; LE, left eye; RE, right eye.

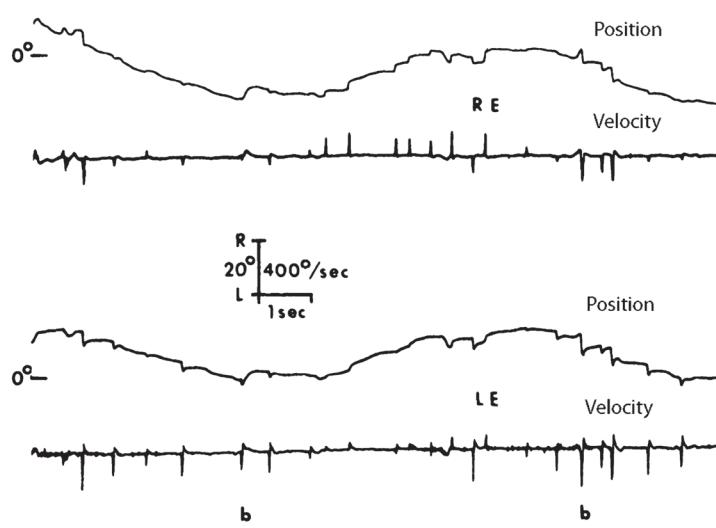


FIGURE 4.3 Horizontal eye position and velocity right- and left-eye data from the same patient shown in Figures 4.1 and 4.2 with nystagmus blockage syndrome during smooth pursuit with the adducting eye (i.e., pursuit by the right eye for target positions in left gaze and the left eye in right gaze). Time markers indicate 1-sec intervals. b, blink; LE, left eye; RE, right eye.

Without accurate, monocularly calibrated eye-movement data, the relative positions of each eye, the determination of the fixating eye, and differentiating between INS with a latent component, FMNS, or the NBS would not be possible. In Figure 4.4, the eye movements of a patient with INS with a latent component are shown during convergence on a primary position target moving from far to near and back to far. Throughout the record, the waveforms are those of INS only (initially jerk left with extended foveation, then jerk right with extended foveation); no FMNS were exhibited. The left eye tracked target motion inward (the right eye was esotropic); at near, the IN of both eyes was damped. However, the right eye tracked target motion outward (the left eye was esotropic). Note that, unlike in the NBS, there was no nystagmus damping during the times when either the right or left eye was maximally esotropic. This same lack of esotropia-induced damping is evident in Figure 4.5, where spontaneous reversals of the fixating eye occurred during fixation on a stationary, distant, primary position target.

In Figure 4.6 we see the eye movements of another patient who had INS plus a variable strabismus during fixation first on a distant,

primary position target and then a target 15° to the right (between the two was a period of conjugate wandering attributed to inattention). Again, only INS waveforms were exhibited; first was jerk right with extended foveation and then jerk left with extended foveation. No nystagmus damping accompanied the variable esotropia. In Figure 4.7, this patient demonstrated classic INS damping with convergence, despite the esotropia of the left eye. Thus, with eye-movement data one is able to differentiate these clinically similar types of nystagmus characteristics.

4.1.1.6 FOVEATION, EXPANDED NYSTAGMUS ACUITY FUNCTION, AND ACUITY

In Type I, the extended foveation periods will increase the eXpanded nystagmus acuity function (NAFX) over that measured during binocular fixation. The eye-movement data are indistinguishable from convergence damping in a binocular INS patient with the exception that only one eye is adducted in the NBS. In Type II, the very low amplitude FMN will also yield higher values of the NAFX. During the purposive esotropia, target foveation is accurate, the NAFX is high, and

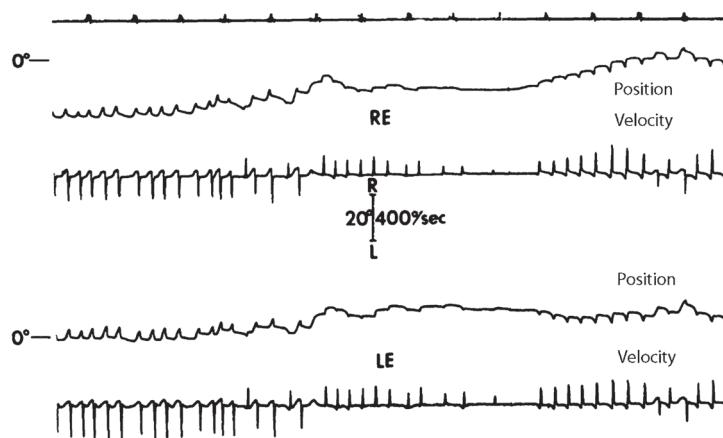


FIGURE 4.4 Horizontal eye position and velocity right- and left-eye data from a patient with infantile nystagmus syndrome (INS) with a latent component and esotropia shown fixating a distant target with the LE (RE esotropic) as the target is brought inward and then back to its original distant position. During the distant fixation and convergence, the INS waveform was jerk left while the LE adducts onto the near target. At near, the RE takes on fixation and the INS waveform reverses to jerk right. As the target moves outward, the formerly fixating LE remains adducted and the RE maintains fixation with a jerk-right INS waveform. Time markers indicate 1-sec intervals. LE, left eye; RE, right eye.

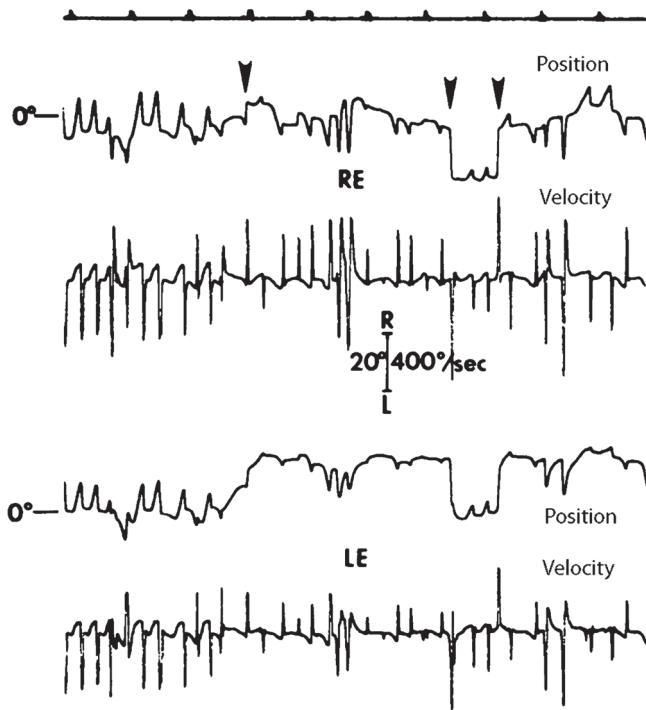


FIGURE 4.5 Horizontal eye position and velocity right- and left-eye data from the same patient shown in Figure 4.4 with infantile nystagmus syndrome with a latent component and esotropia during fixation on a distant target. At the first arrow, the LE became esotropic (RE fixation); at the second arrow the RE became esotropic (LE fixation); and at the third arrow, the LE again became esotropic (RE fixation). Time markers indicate 1-sec intervals. LE, left eye; RE, right eye.

visual acuity is at its maximum for the NBS patient regardless of whether it is Type I or II.

4.1.1.7 EFFERENCE COPY, FOVEATION, AND OSCILLOPSIA SUPPRESSION

As was discussed in Chapters 2 and 3, the built-in efference copy of motor commands in the OMS prevents the perception of oscillopsia in either IN or FMN. Thus, patients with the NBS do not normally experience oscillopsia regardless of whether it is Type I or II.

4.1.2 Treatments of Nystagmus Blockage Syndrome

The same mechanistic considerations discussed in Chapters 2 and 3 for INS and FMNS, respectively, apply in the NBS. One must first determine whether the patient is Type I or II. The therapeutic choice will depend on the patient's

individual nystagmus type(s) and characteristics. The medical and surgical therapies applied to IN and FMN utilize the respective characteristics of the nystagmus. In much the same manner, INS patients turn their heads to exploit the gaze-angle null of IN, and FMNS patients do the same to exploit the Alexander's law variation of their FMN. Patients with NBS also apply these same "therapeutic" maneuvers. Head turns, for whichever type of nystagmus they are used, may be cosmetically unattractive or even may lead to neck problems when severe. However, head turns are not defects associated with the INS, FMNS, or NBS, but rather, constitute purposive and therapeutic patient-administered "therapy." Successful amelioration of a head turn can only occur if its advantages, vis-à-vis better visual function, are otherwise achieved (e.g., surgically moving the IN null to primary position or inducing convergence that both damps and broadens the IN null).

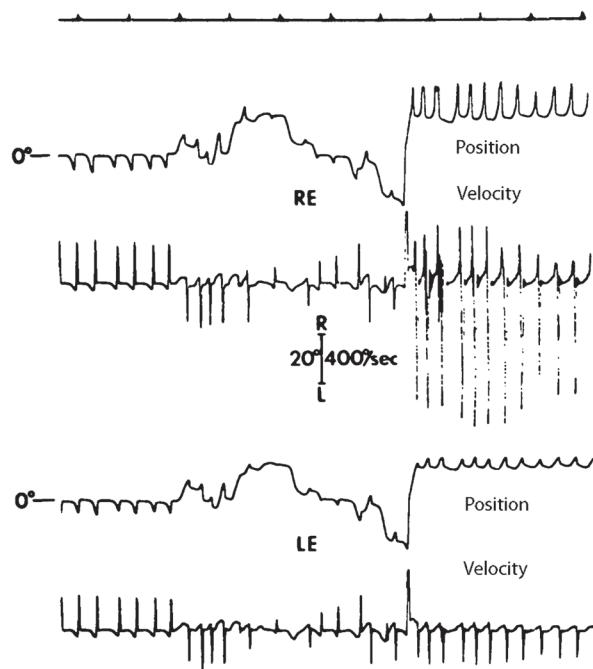


FIGURE 4.6 Horizontal eye position and velocity right- and left-eye data from a patient with infantile nystagmus syndrome (INS) and variable strabismus. Initially, the patient was fixating a primary position target with a jerk right with extended foveation INS waveform. Then there was a conjugate wandering (presumably due to inattention) until the instruction to look at a target at 15° (right gaze). After the refixating saccade, the INS waveform was jerk left with extended foveation. Time markers indicate 1-sec intervals. LE, left eye; RE, right eye.

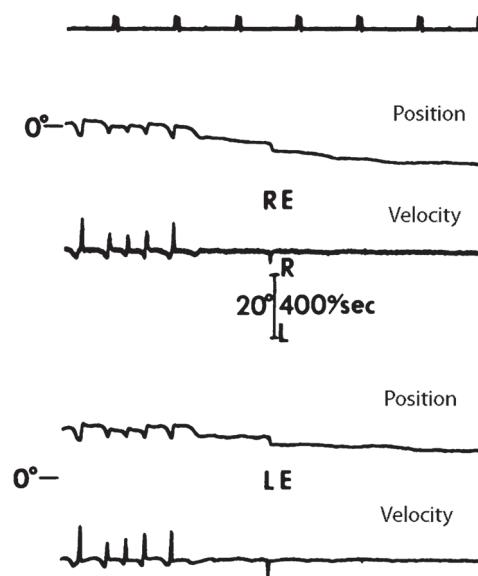


FIGURE 4.7 Horizontal eye position and velocity right- and left-eye data from same patient shown in Figure 4.6 with infantile nystagmus syndrome (INS) and variable strabismus while fixating a distant target with the RE (LE esotropic) as the target is brought inward. The jerk right with extended foveation INS waveform at distance damped completely at near. Time markers indicate 1-sec intervals. LE, left eye; RE, right eye.

4.1.2.1 FIXATION PREFERENCE

If the patient fixates with the straight eye in Type I NBS, there will be no head turn. If the newly esotropic eye is used, a head turn will be necessary and will depend on the amount of esotropia employed by the patient.

4.1.2.2 ALEXANDER'S LAW

The amount of Alexander's law variation with gaze angle is idiosyncratic. Its effects on the amplitude change in FMN were discussed in Chapter 3, Section 3.1.2 and demonstrated in Figure 3.11. Therefore, the presence or amount of head turn will also be idiosyncratic and could affect the optimal therapy.

4.1.2.3 SURGICAL

The surgery for NBS is aimed at reducing the head turn required after the patient utilizes esotropia to damp (Type I) or damp and change (Type II) the nystagmus. Because the patients are able to fuse and only manifest esotropia when they desire, standard strabismus-surgery approaches do not apply. If they have strong fusion reflexes, perhaps a bimedial recession procedure would produce the required damping for Type I NBS patients in the same manner as in binocular INS patients. For Type II NBS patients, if the INS damping produced by realigning the eyes is sufficient, perhaps the switch to FMN would not occur; if the underlying mechanism in Type II is not a switch to FMN but a manifestation of a low-amplitude FMN that coexisted with a more prominent INS, the FMN would then also appear.

4.1.2.3.1 Fixating Eye. As stated earlier, if fixation remains with the stationary eye as the other is deviated inward (as in Fig. 4.2), no head turn would be necessary and surgery would be problematic. If, however, fixation is taken up by the deviated eye (the most common scenario), a head turn results and surgery can be tailored to reduce that turn.

In the NBS, it is possible that the bimedial recession procedure could be therapeutically beneficial because the purposive esotropia is

different from ordinary strabismus; the latter is not under conscious control. Although it has been suggested that bimedial recession may help those with NBS, published studies are lacking. Similarly, the Faden operation may benefit those with NBS. Simple surgical correction in NBS has not proven successful.¹⁹

4.2 SPASMUS NUTANS SYNDROME

The spasmus nutans syndrome (SNS)¹ includes ocular oscillations, head nodding, and anomalous head positions that begin in infancy (usually between 4 and 18 months of age) and disappear clinically in childhood (usually before 3 years or age). The nystagmus is generally bilateral (but can differ in each eye and may even be strictly monocular), and it oscillates in horizontal, torsional, or vertical directions. The average duration of SNS is 12 to 24 months; rarely, it lasts a number of years. It was first described by Raudnitz in 1897,²⁰ followed by others, including several longitudinal studies.^{21–29} The pathogenesis of SNS remains obscure despite some ocular motor studies.^{16,30–33} SNS has been confused with other entities,^{34–37} but eye-movement recordings allow accurate differentiation (e.g., FMN or uniocular pendular nystagmus).³⁸ Prior to subsequent ocular motility studies, diagnosis was delayed until the clinical symptoms of nystagmus and anomalous head posture resolved.

4.2.1 Characteristics of Spasmus Nutans Syndrome

SNS appears as a high-frequency, asymmetric, dysconjugate ocular oscillation. It is usually horizontal in direction but may also be vertical or torsional. It is often described as an intermittent nystagmus that is asymmetrical in appearance and occasionally monocular. A key eye-movement recording observation is the variable phase difference between the two eyes, which is reflected clinically as an asymmetry in the oscillations between the two eyes. On lateral gaze, the dissociation may increase, with nystagmus of the abducting eye predominating.

Some case series suggest an increased prevalence of esotropia in SNS. Gottlob et al. found a high incidence of esotropia, latent nystagmus, dissociated vertical divergence, and amblyopia in children with SNS.²⁹ Conversely, rare patients with infantile esotropia display horizontal or vertical head oscillations that resolve following surgical realignment of the eyes. In contradistinction to INS, visual acuity is minimally affected in SNS.

4.2.1.1 WAVEFORMS AND MECHANISMS

The nystagmus waveform in SNS is a dissociated pendular nystagmus, and this dissociation may be so great that the nystagmus is uniocular.^{39,40} Ages of onset of the seven patients studied ranged from birth to 14 months; five had head nodding. The dissociated nystagmus is usually of a higher frequency than INS nystagmus, and the result can be disjunctive, conjugate, or uniocular. Early reports considered SNS to be pathogenetically related to diverse causes that included light deprivation, dietary factors, season, rickets, epilepsy, auto-arousal, and poor socioeconomic conditions.³⁴ Hermann noted a strong predisposition for the onset of SNS to occur during the winter months, with 70% of cases having their onset during December, January, and February.^{41–44} In 1897, Raudnitz published the classical description of SNS in which he collated previously reported cases with 15 cases of his own. He emphasized the fact that virtually all of his patients belonged to a certain dark quarter of Prague. When this district was later sanitized, no further cases of SNS developed. Raudnitz viewed darkness as the primary etiologic factor, speculating that the eyes of affected children were somehow damaged by the “irritant effect” of insufficient light during a critical period of fixation development. Raudnitz noted that pups that were reared in total darkness for several months developed eye nystagmus and head nystagmus.

Lower socioeconomic status may represent a risk factor for the development of SNS. In a study comparing SNS with infantile nystagmus, Wizov found African American or Hispanic ethnicity to be significantly more common in SNS.⁴⁵ Patients with SNS also had lower average gestational ages, lower home luminances at birth, fewer married

parents living together, and more psychiatric disorders, including alcohol and drug abuse.

For a century, numerous reports emphasized that SNS was a visually and systemically benign and self-limited clinical entity.^{26,46–52} Since 1967, however, many infants with some of the features of spasmus nutans have been found to have congenital suprasellar tumors (most commonly chiasmal gliomas). Suprasellar tumors can produce a constellation of neuro-ophthalmologic signs that are clinically and electrophysiologically indistinguishable from SNS. Congenital head nodding and nystagmus has been reported with cerebrocerebellar degeneration.⁵³ The clinical findings of hydrocephalus, café au lait spots, optic atrophy, or other clinical signs of neurofibromatosis make it more likely that a child with SNS will have a central nervous system glioma. A substantial proportion of patients presenting with SNS-like nystagmus have important underlying ocular, intracranial, or systemic abnormalities. Neurodegenerative disorders such as Pelizaeus–Merzbacher disease and Leigh disease may produce nystagmus and head nodding that are indistinguishable from SNS.^{52,54–57} These disorders should be suspected in children with clinical signs of ataxia or developmental delay or with magnetic resonance evidence of white matter signal abnormalities. Achromatopsia, congenital stationary night blindness, and Bardet Biedl syndrome can also masquerade as SNS.

Genetic factors were suggested by the descriptions of SNS in identical twins and the finding that it is more common in Black children.^{29,34,40,58,59} However, SNS occurs in neurologically normal children. Weissman et al. considered vergence, saccadic, and pursuit system abnormalities as possible causes of SNS but came to no definitive conclusion.⁴⁰ SNS is a diagnosis that can only be made using a combination of clinical characteristics and eye-movement findings, which exclude other visual or nervous system disease. The pathogenesis and neuroanatomical substrate of this developmentally acquired form of asymmetric, dysconjugate nystagmus are still unknown.

We hypothesize that SNS reflects a yoking abnormality, perhaps due to delayed development. Recordings show that SNS nystagmus

may not disappear completely but may recede to a subclinical level; neither INS nor FMNS disappears with age.

4.2.1.2 VARIABLE INTEROCULAR PHASE

The nystagmus of the SNS tends to be asymmetric in the two eyes, to vary in different directions of gaze, and to be rapid and of small amplitude. The pendular oscillation of SNS is characterized by a variable phase difference between the oscillations of each eye.⁴⁰ These phase differences can appear from minute to minute and during the child's development. As Figure 4.8 shows, the pendular oscillations of each eye may be phase locked, slightly out of phase, or even totally out of phase, and this can vary during the course of the recording anywhere from pure conjugacy to pure disconjugacy (0–180° phase shift).⁴⁰ The phase variation usually varies from minute to minute. Distinguishing this variable phase relationship between the pendular oscillations of both eyes requires DC-coupled, high-bandwidth recordings of both eyes simultaneously.

4.2.1.3 HEAD NODDING

The head nodding in SNS is curious. It is inconstant and irregular and can be horizontal or vertical, or both. The head nodding associated with SNS is a combination of vertical head nodding together with a lateral shaking of the head in an unpredictable pattern.^{57,60–62} The head nodding is of lower frequency than the nystagmus and becomes prominent when the child attempts to inspect something of interest. It disappears during sleep but may persist when the child is lying down. Since some children with INS also have head nodding, this finding alone cannot be used to confirm the diagnosis of SNS in the child with nystagmus. Studies of quantitative head- and eye-movement recordings indicate that the head movement may, using the normal VOR, actually serve to abolish the eye movements (see Fig. 4.9).³⁰ In some patients, it may be only compensatory with suppression of the VOR. Compare this to INS, where the head oscillation is an extension of the nystagmus and the VOR is normal (see Chapter 2, Section 2.1.8). Gresty et al.

examined patients with SNS in whom head nodding abolished the nystagmus, and a normal VOR stabilized the eyes during head movements.³² They demonstrated with eye-movement recordings that the head nodding in SNS is an adaptive behavior that serves to improve visual acuity by suppressing the nystagmus, rather than a separate pathological phenomenon. Eye-movement recordings from these patients demonstrated that the head nodding in SNS functions to abolish the nystagmus through some mechanism independent of the vestibulo-ocular response. Gottlob et al. confirmed and refined these conclusions in a large number of patients with SNS using eye-movement recordings.^{29,60} In their patients, the head nodding changed the SNS waveform from a fine, pendular, dissociated nystagmus of high frequency to a larger slower waveform that is symmetrical between the two eyes. There is now general agreement that head nodding in SNS is compensatory.

Because the vestibulo-ocular reflex (VOR) of these patients is normal, by willfully shaking of the head, the nystagmus is switched off and the eyes become stable in space because of a good VOR. A patient may have convergence nystagmus, one eye going left, the other eye going right at the same time (180° out of phase), while the head is still. When the patient starts shaking his or her head, the nystagmus stops and, owing to the normal VOR, the eyes begin moving conjugately equally and oppositely to the head, so gaze remains constant.

"Cultured" Clinical Pearl: Based on the observation that head nodding is compensatory in the SNS, if further research on the eye movements of the "SN-like" nystagmus associated with brainstem gliomas demonstrates that no head nodding is exhibited by these patients, the presence of deliberate, compensatory head nodding is an indication of SNS and is benign.

The head tilt in SNS is a variable finding that is present in less than half of cases. Although the reason for the associated head tilt is unclear, Gottlob et al. suggested that it may serve to directionalize the head nodding to its optimal trajectory.⁶⁰ Although early authors stated that

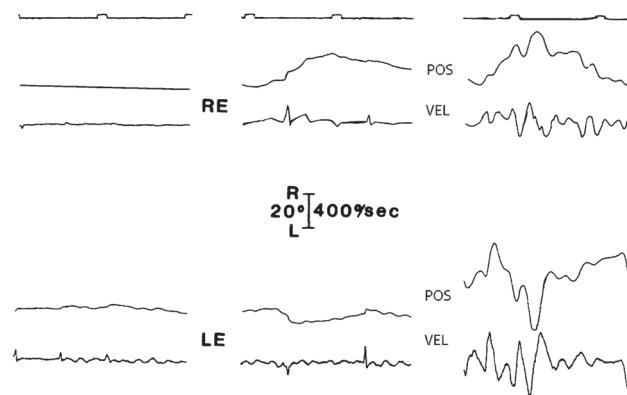


FIGURE 4.8 First example of the phase variation between the two eyes in spasmus nutans syndrome. (Left) A uniorcular, pendular nystagmus in the LE. (Middle) A binocular, pendular nystagmus with both eyes in phase. (Right) A binocular, pendular nystagmus with the eyes 180° out of phase. The three intervals were within seconds of each other. Time markers indicate 1-sec intervals. LE, left eye; POS, eye position; RE, right eye; VEL, eye velocity.

the head nodding was the first sign of SNS to appear and the last to resolve, it is now generally agreed that the nystagmus is the most constant feature of SNS and that it probably precedes the head nodding, although the head nodding may be the abnormality that first attracts attention. Weissman found persistence of the nystagmus in some of their patients, and Gottlob et al. found persistence of nystagmus using eye-movement recordings in all patients who had clinical

resolution of the condition, suggesting that the nystagmus diminishes to a subclinical level but does not entirely resolve.⁴⁰

4.2.2 Treatment of Spasmus Nutans Syndrome

In patients with “SN-like” nystagmus, accurate diagnosis is the most important factor. Therefore, until definitive eye-movement-based criteria are

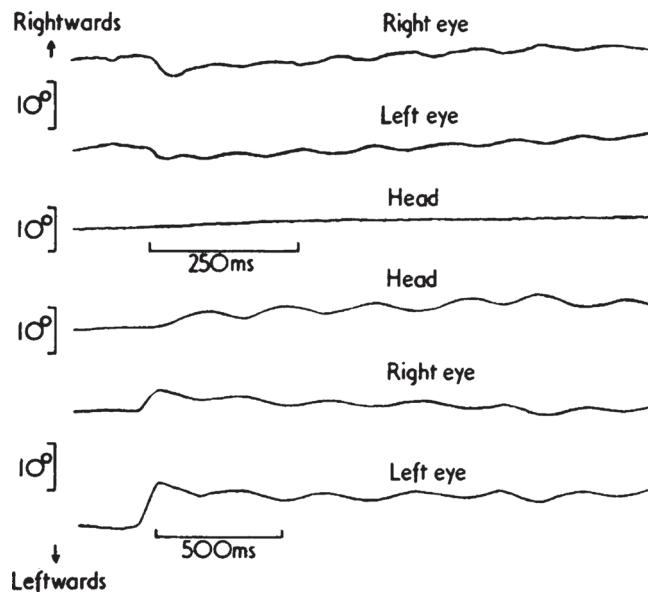


FIGURE 4.9 First demonstration that the head movements in spasmus nutans syndrome are both willful and compensatory. Time markers indicate 1-sec intervals (From Gresty et al., 1976.)

identified to differentiate SNS from other, more neurologically problematic conditions, imaging is a necessity. Because SNS is benign, once it is definitively diagnosed, SNS requires no treatment.

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5

DIFFERENTIAL DIAGNOSIS OF NYSTAGMUS IN INFANCY AND CHILDHOOD

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In the fields of observation, chance favors only the mind that is prepared.

—Louis Pasteur (1854, 1822–1895)

THE DIAGNOSTIC material in this chapter results from the past half-century of eye-movement-based research (summarized in Chapters 2–4) into the different types of nystagmus found in infancy; that research forms the foundation for the various “clinical pearls” that have also emerged from studying ocular motor data from patients exhibiting nystagmus. Also, Appendix D contains flowcharts and work sheets useful in differential diagnosis and therapeutic intervention. All forms of nystagmus are due to deficits in one or more slow-eye-movement subsystems, whereas saccadic intrusions and oscillations are due to deficits in fast-eye-movement subsystems.¹ There is a large literature on the many types of nystagmus listed in Table 5.1 that have been reviewed elsewhere.^{2–7}

5.1 NYSTAGMUS WITHOUT ASSOCIATED NEUROLOGICAL DISEASE—“BENIGN”

5.1.1 Infantile Nystagmus Syndrome

Familiarity with the clinical features of infantile nystagmus syndrome (INS; also known as congenital nystagmus [CN])⁸ is essential. INS is an ocular motor disorder with the hypothesized etiology of undamped smooth pursuit. It presents at birth or early infancy and is clinically characterized by involuntary oscillations of the eyes. The Leicestershire nystagmus survey estimated the prevalence of nystagmus in the general population to be 24.0 per 10,000.⁹ The most common forms of nystagmus are neurologic nystagmus (6.8 per 10,000 population)

and infantile nystagmus associated with low vision (3.4–4.2 per 10,000). Within ethnic groups, nystagmus was significantly more common in the White European population than in the Asian population (Indian, Pakistani, other Asian backgrounds). Other estimations of the incidence of INS vary enormously from 1 in 350 to 1 in 20,000, although the generally quoted estimated incidence to be 1 in 6,550 or .015%.¹⁰ These movements most commonly have a slow and fast phase, although they may be pendular, with or without braking and foveating saccades. They are usually horizontal with a small torsional component and may (rarely) have a vertical component. The intensity of INS increases on lateral gaze and becomes right beating in right gaze and left beating in left gaze. The fact that INS “disobeys” Alexander’s law under binocular conditions (which states that, in peripheral vestibular nystagmus, the direction of the nystagmus increases in the direction of the fast phase and decreases *but never reverses* in the direction of the slow phase) is often useful in distinguishing it from horizontal peripheral vestibular nystagmus.^{11–14} Other clinical characteristics of INS, with variable association, include the following: remains horizontal in upgaze (in contrast to acquired and/or vestibular nystagmus, which changes direction in vertical gaze); increases intensity with fixation attempt or stress and decreases with sleep or inattention; variable intensity in different positions of gaze (usually about a null position); changes direction in different positions of gaze (about a neutral position); decreased intensity (damping) with convergence; anomalous head posturing;

Table 5.1 Forty-Nine Types of Nystagmus

Acquired	Gaze-evoked	Pursuit-defect ¹
“Fixation”	Deviational	Pursuit-system
Anticipatory	Gaze-paretic	Infantile
Induced	“Neurasthenic”	Pseudospontaneous
Arthrokinetic	“Seducible”	Induced
Induced	“Setting-in”	Rebound
Somatosensory	Horizontal	Reflex
Associated	Induced	Baer’s
Induced	Provoked	Seesaw
Stransky’s	Infantile	Somatosensory
Audiokinetic	Congenital	Induced
Induced	“Fixation”	Spontaneous
Bartels’	Hereditary	Stepping around
Induced	Pursuit-system	Apparent/real
Bruns’	Intermittent vertical	Induced
Centripetal	Jerk	Somatosensory
Cervical	Lateral medullary	Torsional
Neck torsion	Lid	Rotary
Vertebral-basilar artery insufficiency	Miner’s ¹	Uniocular
Circular/elliptic/oblique	Occupational	Upbeat
Alternating windmill	Muscle-paretic	Vertical
Circumduction	Myasthenic	Vestibular
Diagonal	Nucleus of the optic tract	A(po)geotropic/geotropic
Elliptic	Optokinetic	Alternating current
Gyratory	Induced	Bechterew’s
Oblique	“Kinetic”	Caloric/caloric-after
Radiary	“Optic”	Compensatory
Convergence	Optomotor	Electrical/faradic/ galvanic
Convergence-evoked	Panoramic	Head shaking
Dissociated	“Railway”	Induced
Disjunctive	Sigma	L-
Downbeat	“Train”	Labyrinthine
Drug-induced	Optokinetic after-	Perverted
Barbiturate	Induced	Pneumatic/compression
Bow tie	Postoptokinetic	Positional/alcohol
Induced	Reverse postoptokinetic	Positioning
Epileptic	Pendular	Pseudocaloric
Ictal	Talantropia	Rotational/perrotary
Fusion maldevelopment	Periodic/aperiodic alternating	Secondary phase
Latent/manifest latent	Alternans	
Monocular “fixation”	Physiologic	
Unimacular	End-point	
Flash-induced	Fatigue	
Flicker-induced	Pursuit after-	
Induced	Induced	

Synonyms and other terms are indented under either the preferred (CEMS) or the more inclusive designation; some nystagmus types may be acquired or congenital; quoted terms are erroneous or nonspecific.

¹ May not exist.

strabismus; and the increased incidence of significant refractive errors. This history is useful in further distinguishing the nystagmus from peripheral vestibular nystagmus, which becomes worse with occlusion and is damped by fixation.¹¹ To confirm this observation, the examiner can observe one optic disc with the direct ophthalmoscope while periodically occluding the other eye. Increased nystagmus intensity with occlusion suggests a peripheral vestibular nystagmus, whereas no change, a direction reversal, or a decrease in nystagmus intensity suggests INS or fusion maldevelopment nystagmus syndrome (FMNS). Anxiety or fatigue will also increase the INS intensity and thereby degrade visual acuity. When evaluating an infant or child with INS for the first time, historical points suggest afferent visual pathway dysfunction. If the child's eyes are light sensitive, this suggests the presence of a congenital retinal dystrophy, degeneration, or albinism. If the child sees better in daytime or at night, this suggests congenital stationary night blindness or a rod-cone dystrophy.¹⁵

The presence or absence of an underlying visual sensory deficit does not affect the time of onset of INS. Often the infant is first evaluated in the first to third months of life when irregular eye movements are noted. When INS first appears, it is often arrhythmic and intermittent, consisting of a series of irregular horizontal and oblique deviations of the eyes from side to side. At this stage, the erratic eye movements may simulate opsoclonus.

INS often occurs in association with congenital or early onset (first 6 months of life) acquired defects in the visual sensory system (e.g., systemic and ocular albinism, achromatopsia, aniridia, congenital retinal dystrophies and degenerations, visual cortex anomalies, and congenital cataracts, glaucoma and corneal diseases). Children with this condition frequently present with a head turn, which is used to maintain the eyes in the position of gaze of the null point (point of minimum nystagmus).^{11,16,17} This is particularly prominent when the child is concentrating on a distant object, since this form of nystagmus tends to worsen with attempted fixation. The head turn is an attempt to improve

visual function under these conditions. In most individuals with INS, the head position corresponds roughly with the minimal intensity zone of the nystagmus. A clinical algorithm to aid in the determination of the etiology of anomalous head turns in the presence of strabismus and nystagmus is shown in Figure 5.1.

When the angle of the null zone exceeds 15°, however, the angle of the head turn may fall short of the null zone. In some children, the anomalous head position appears to be dictated by the velocity distribution of the slow phase (i.e., the percentage of time that the slow phase is less than or equal to 10° per second) and the nystagmus beat direction (which can be influenced both by the prior position of gaze and by the length of time a subject has maintained a fixed gaze position). Bagolini et al. suggested that some individuals with INS utilize large head turns to place their eyes in extreme side gaze and actively block their nystagmus.¹⁸ Unlike positioning the eyes in a null zone, in which foveation is optimum, the mechanism of such blockage is unknown. Head oscillations are common in INS, but they are not used as the strategy to improve vision, except in those rare patients with abnormal gain of their vestibulo-ocular reflex.¹⁹

The INS waveform shown in Figure 5.2 (JR_{EF}) is typical of many with periods of extended foveation. When foveation periods are 100 msec or greater, normal visual acuity is possible. Some studies of INS in infants and children suggest an age-dependent evolution of waveforms during infancy from pendular types to jerk types in some patients.^{20,21} This is consistent with the theory that jerk waveforms reflect modification of the INS oscillation by growth and development of the visual sensory system. However, we documented jerk waveforms in other infants with and without sensory deficits, suggesting that early development of the ocular motor system may be responsible.

In Figure 5.3, the interactions and effects between the developing afferent and efferent systems are depicted during several stages from conception to infancy. This "crosstalk" is essential to the normal development of both good vision and a stable ocular motor system. Any deficits in either during this developmental period

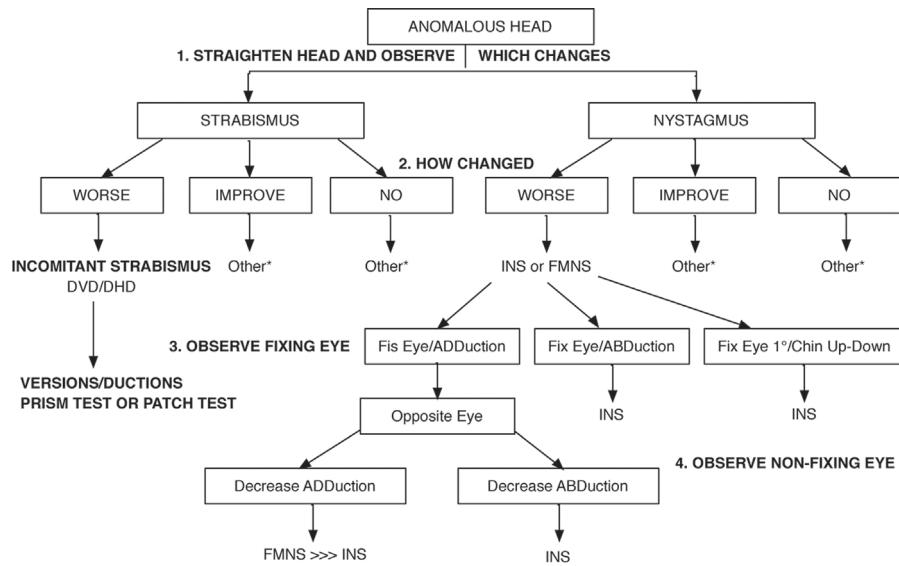


FIGURE 5.1 A clinical algorithm to aid in diagnosing the etiology of an anomalous head posture in the presence of strabismus and nystagmus. The first step is to reposition the patient's head to the neutral position and observe the consequences on the strabismus or the nystagmus (Step 1) and whether the change improves or worsens the condition (Step 2). The major clinical differentiation occurs at this step. If the nystagmus is worse, then differentiating between a "gaze" null due to infantile nystagmus syndrome (INS) and an "adduction" null due to fusion mal-development nystagmus syndrome (FMNS) can be made by looking at the fixing eye's (Step 3) and the opposite nonfixing eye's (Step 4) effect on the oscillation in aBDuction and aDDuction.

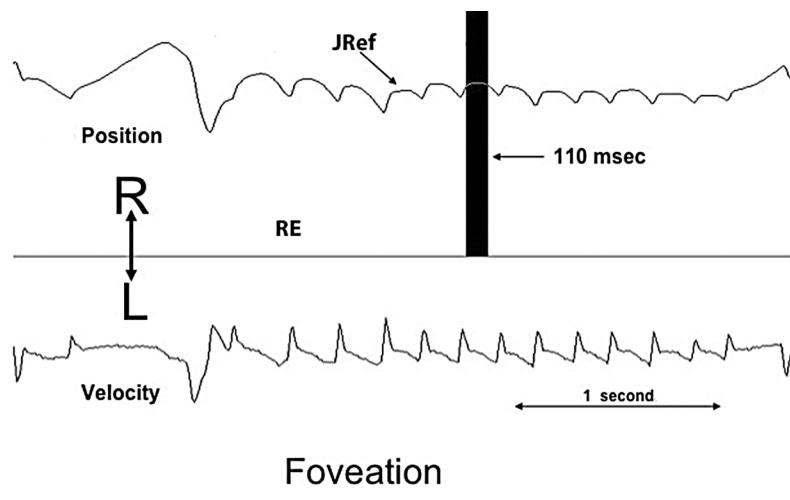


FIGURE 5.2 Eye-movement recording showing position and velocity of right eye of a patient with INS showing a typical jerk right with extended foveation (JRef) waveform. These 100-msec periods of high-quality foveation occur just after the fast phase of the nystagmus; time (in seconds) is shown at the bottom. The numbers outlined in red show details of foveation encompassed in the black rectangular area. L, left; R, right; RE, right eye.

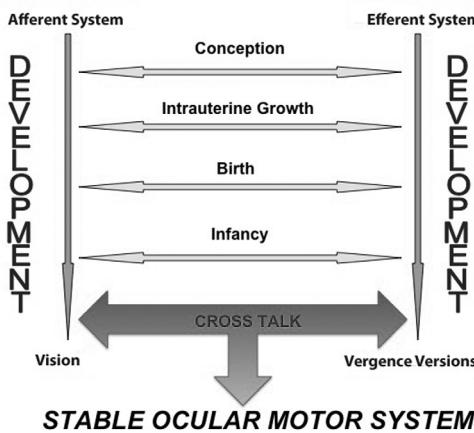


FIGURE 5.3 A model for development of infantile nystagmus syndrome (INS). Motor-system calibration is an active process that may start in utero and continue at least through early infancy. Sensory-system development is a parallel visual process that continues to develop through the first decade of life. Previous studies documented connections between parallel visual processes (cross-talk) that modify, instruct, and coordinate these systems, resulting in smooth and coordinated function. INS may result from a primary defect (familial, genetic) of oculomotor calibration. INS may also result from abnormal cross-talk from a defective sensory system to the developing motor system at any time during the motor system's development. This can occur from conception as a result of a primary defect (retinal dystrophy), during embryogenesis as a result of an intrauterine abnormality (optic nerve hypoplasia), or after birth during infancy (congenital cataracts). This hypothetical genesis of INS incorporates a pathophysiologic role for the sensory system. Although the physiologic circumstances may differ, the final common pathway is abnormal calibration of the ocular motor system. The primary ocular motor instability that underlies INS remains the same, but its clinical and oculographic expression are modified by both initial and final developmental integrity of all parallel afferent visual system processes. As the bidirectional arrows suggest, abnormal motor development also affects sensory development.

will negatively affect both the system with the deficit and the other system. Thus, motor deficits may interfere with visual development and visual deficits may interfere with motor development, as is explained in the figure caption.

Although INS is a lifelong condition, it may remain variable over time. This includes minute-to-minute variability and long-term changes associated with age and other ocular and systemic conditions. There are no good long-term, multisubject studies (greater than 10 years) that characterize the aging process and its effects on INS, but we do know that changes can occur in the INS oscillation as a result of aging, medications, and degenerative and neurological illnesses. This concept of INS as a dynamic disease process may be useful when evaluating and caring for patients with this condition over their lifetime. However, eye-movement data taken over decades in some subjects with INS (one,

over more than a 45-year span) showed no overall changes in the important waveform characteristics governing visual function.

5.1.1.1 ASSOCIATION WITH STRABISMUS

Estimates of the prevalence of strabismus in INS range from 16% to 50%.^{22–27} Strabismus is essential for FMNS but incidental to INS. Although FMNS is intrinsically more likely to be associated with strabismus than is INS, the greater frequency of INS means that any given patient with strabismus will still be more likely to have INS (53%) than FMNS (35%).²³ The presence and nature of an underlying sensory visual disorder seems to influence the likelihood of associated strabismus. In a study of 82 children with INS (diagnosed clinically), Brodsky and Fray found the prevalence of strabismus to be 82%

in children with optic nerve hypoplasia, 53% in children with albinism, 36% in children with congenital retinal dystrophies, and 17% in children with idiopathic INS.²⁸

5.1.1.2 CLINICAL SIGNS AND SYMPTOMS

Patients with INS typically have several different waveforms; one study found multiple waveforms in 87% of patients.²³ In addition to the quantifiable and definitively diagnostic characteristics of IN available through eye-movement recordings, there are clinical signs one can observe in the office. In INS, one should look for a null angle; an indication of which is the presence of a head turn. A teenager or an adult may not show a head turn because of societal pressures. They have learned to keep their heads straight at the expense of vision because it is not “appropriate” to walk around with their head turned, but a child will more likely exhibit a head turn. A positive family history and negative neurological examination also suggest INS. One study found that 48% of patients exhibited both convergence and gaze-angle nulls (28% had only convergence nulls and 9% only gaze-angle nulls) and 14% had no nulls.²³

If converging the eyes damps the IN, the patient will hold reading material close. The patient may have a latent component; that can be checked by the alternate-cover test. If the nystagmus direction reverses with monocular cover, one still does not know whether it is FMN or IN with a latent component (they are different types of nystagmus). They may also have head nodding that is *not* compensatory.

Many patients with IN exhibit an eccentric null angle of gaze, where the IN magnitude damps (“null”). A true null position is that position of gaze (eye in orbit) where changing gaze to either side of this minimal nystagmus intensity position increases the oscillation intensity. That is in contrast to FMN, where monotonic variation with gaze angle (Alexander’s law) causes patients to keep their eyes deviated to one side where the nystagmus is low. FMN does not have a true null because there is no increase on both sides. In IN, the position of the null is

a function of the angle of gaze and also a function of the velocity of the eyes.^{29–32} Thus, the null angle during fixation (static null) does not usually equal the null angle during pursuit, optokinetic nystagmus, or head movement, where the vestibulo-ocular reflex is stimulated (dynamic null). Usually, the null is shifted in the direction opposite to the eye movement. During pursuit to the left, the dynamic null moves to the right of the static null; and during pursuit to the right, the dynamic null moves to the left. In the IN population, 48% have both convergence and gaze angle nulls, 29% only convergence nulls, 9% only gaze angle nulls, and there are 14% with no nulls. Accurate measurement of the null position requires a well-calibrated, DC-coupled recording system. That measurement can then be used to prescribe prisms or determine the amount of surgery to be performed (see Chapter 7).

In cases with nystagmus plus strabismus, it is sometimes possible to differentiate INS from FMNS. For example, if the preferred gaze angle places the fixating eye in abduction, the nystagmus is most probably IN because, if it were FMN, the fixating eye would most probably be in adduction due to Alexander’s law. If the fixating eye is in adduction, either IN or FMN is possible.

Clinical Pearl: When the preferred fixating eye is kept in abduction, the nystagmus is most probably IN, not FMN. Caveat: It might still be FMN if the patient has exotropia or an angle kappa.

Children with IN and a static eccentric gaze null position automatically adopt a head turn to see better. They do not have to wait to be told about the null angle; they know where it is because all visual functions improve when they turn their head, placing their eyes at the static null angle. One may think of the null as a region of ocular motor equilibrium. The brainstem (left and right) generates forces pulling the eyes both ways, and there is a position of equilibrium of forces, not necessarily in primary position, where the nystagmus is minimal. When viewing targets at the null angle, many visual functions (including acuity) should increase; when there

is a severe afferent defect, or an INS waveform with well-developed foveation (i.e., high NAFX) across a large range of gaze angles (high LFD; see Chapter 2, Section 2.3.1.1), acuity may not increase measurably.

Sometimes a patient will tilt the head, and sometimes the patient will turn it (vertically or horizontally) and tilt it. Perhaps the oblique muscles are involved; this has not really been studied well. It represents innervation of muscles other than the horizontal muscles that are somehow helping to reach equilibrium in predominantly horizontal oscillations; most IN is primarily horizontal with little or no vertical components. Again, acuity increases with vertical or torsional head positions, especially if there are no afferent defects.

The mechanism causing an IN reversal when covering an eye is similar to when the person pursues; the null moves and can cause a direction reversal of the IN if gaze went from one side of the null to the other.³³ Although IN with a latent component looks clinically like FMN, it is not (because the waveform remains IN); only the IN direction changes because the null has moved with occlusion.

IN with a latent component can behave as though there were two null angles since, if the fixating eye changes with gaze angle, the induced null shift will appear to be a second null. In binocular individuals with IN, there is only one null and in those with strabismus, there is also only one null, although it shifts to a different gaze angle when fixation shifts to the other eye. A good recording system, properly calibrated for fixation with each eye, will detect shifts in the fixating eye (and the tropias of the nonfixating eye) and prevent misreading the records as showing two nulls. Also, IN and periodic (PAN) or asymmetric, (a)periodic (APAN) alternating nystagmus will mimic two nulls because of the null shift accompanying the direction reversal. Steady fixation in primary position for several minutes will disclose either form of alternation.

Table 5.2 summarizes the different types of APAN seen in INS patients and compares them to acquired PAN. The term *APAN* encompasses all idiosyncratic variations in

the timing and amplitudes of the intracycle jerk IN, including those that are periodic, but all have combinations of IN waveforms, whereas acquired PAN has a sawtooth jerk waveform. When the specific intra- and intercycle characteristics are known, the more specific nomenclature in Table 5.2 may be used. Note that the total intercycle periods (*T* in Table 5.2) for APAN are usually much longer than for acquired PAN.

5.1.1.3 DIFFERENTIAL DIAGNOSIS

The localizing significance of nystagmus is often a mere indication of dysfunction somewhere in the posterior fossa (i.e., vestibular end organ, brain stem, or cerebellum). However, certain nystagmus patterns are quite specific and permit reasonably accurate neuroanatomic diagnosis. When possible, the specific and nonspecific forms are separated on the basis of clinical appearance and associated signs and symptoms. Some of the characteristics of IN and their comparison to FMN are listed in Table 5.3. Specifically, the ocular motor sites of the deficits affect both waveforms and the shape of the NAFX peak (or “null” depth).

Individuals with both INS and FMNS are difficult to diagnose correctly; it is not usual, but some patients (~5%) have a combination of INS and FMNS.²³ One or the other might be dominant and result in complex waveforms and variations of nystagmus type with gaze angle. The best approach to diagnosing these patients is to first learn to accurately diagnose the more straightforward types. As Table 5.3 indicates, this combination results in many possible waveforms, NAFX peak variations, and also includes IN with a “latent component” or the nystagmus blockage syndrome.

5.1.1.4 ALTERNATE-COVER AND GAZE-ANGLE-COVER TESTS

It may be difficult to distinguish FMN from IN when strabismus and a “latent” component are present (fast phase movement toward uncovered eye and/or increased intensity of

Table 5.2 Time-Varying Types of Jerk Nystagmus

TYPE	INTRACYCLE DIRECTION			INTERCYCLE PERIOD (T) ¹	SPECIFIC TYPE OR CHARACTERISTICS
	DURATION	AMPLITUDE			
APAN	=	=	=	=	IN: PAN
	≠	=	=	=	Asymmetric duration PAN
	=	≠	=	=	Asymmetric intensity PAN
	≠	≠	=	=	Asymmetric duration and intensity PAN
	=	=	≠	≠	Symmetric AAN
	≠	=	≠	≠	Asymmetric duration AAN
	=	≠	≠	≠	Asymmetric intensity AAN
	≠	≠	≠	≠	Asymmetric duration and intensity AAN
	Acquired PAN	=	=	=	Symmetric duration and intensity PAN Saw-tooth waveform

Duration indicates the time period of oscillation in a given direction. Intensity indicates the amplitude × frequency of oscillation in a given direction.

¹T of APAN is usually >> T of acquired PAN.

T is the sum of left-beating, right-beating, and two neutral interval durations.

AAN, aperiodic alternating nystagmus; APAN, asymmetric (a)periodic alternating nystagmus; IN, infantile nystagmus (with any combination of IN waveforms); PAN, periodic alternating nystagmus.

Table 5.3 Comparative Characteristics of Infantile and Fusion Maldevelopment Nystagmus

TYPE	OCULAR MOTOR SUBSYSTEM DEFICIT			NAFX PEAK OR INTENSITY “NULL”	
	PURSUIT	VV	POSSIBLE WAVEFORMS	GAZE ANGLE	SHAPE
IN	Yes	No	IN: P-SW	Idiosyncratic or none ¹	Broad or none ¹
	No	Yes	IN: VVSW	None ¹ , with low NAFX (<<1)	Not applicable
	Yes	<<< Pursuit	IN: P-SW	Idiosyncratic	Broad
	Yes	< Pursuit	IN: P-SW	Idiosyncratic	Variable
	Yes	= Pursuit	IN: P-SW + VVSW	Idiosyncratic	Sharp or medium
	FMN	No	Yes	J _L , SPT	Far add of FE
IN + FMN ²	Yes	Yes	All of the above	Idiosyncratic	Linear ¹

FE, fixating eye; IN, infantile nystagmus; J_L, jerk with linear slow phase; NAFX, eXpanded nystagmus acuity function; P-SW, pursuit-system waveforms (see Chapter 2, Fig. 2.1); SPT, saccadic pulse train; VV, visual vestibular; VVSW, visual vestibular system waveforms (see Chapter 2, Fig. 2.2).

¹No mathematical peak/null but may vary with gaze angle.

²Includes IN with a latent component and the nystagmus blockage syndrome.

nystagmus with monocular cover) since the two patients will appear clinically identical. The only definitive way to distinguish between IN with a “latent component” and FMN is with the use of eye-movement recordings.^{34,35} The differences between IN with a “latent component” and FMN can be seen in Figure 5.4. FMNS patients have slow phases that are predominantly decreasing velocity and linear. Patients with frank esotropia may demonstrate FMN. Since these patients usually suppress one eye at a time, the nystagmus is present even without covering an eye. The direction of the nystagmus depends on which eye is fixating. Manifest FMN can clinically appear to be converted to “pure,” latent FMN if the strabismus treatment results in orthophoria. Two tests are useful in attempting to differentiate INS from FMNS.

The first is the “alternate-cover” test, where each eye is alternately occluded while the patient is looking straight ahead. If the patient has jerk nystagmus that is stationary with time (i.e., does not change direction while maintaining fixation on a primary-position target) and the direction does not reverse with

alternate cover, *it is IN* rather than FMN. However, if nystagmus direction reverses with alternate cover (with the direction of the nystagmus toward the fixating eye), then it could be either IN with a latent component or FMN. Reversal of nystagmus direction does *not* mean that it is FMN, although this test is often misinterpreted that way. One might be tempted to presume that if there is no strabismus and a reversal occurs, then the diagnosis should be INS since FMNS requires strabismus to be present (see Section 5.1.2). However, this is a clinical test and even an undetectable microtropia is sufficient for FMNS.

The second test, “the gaze-angle-cover” test, is useful in this latter case where a reversal occurred in primary position. While maintaining cover, move the fixation target into the adduction field of the fixating eye (e.g., move it into the patient’s left field when the right eye is fixating). If the right-beating nystagmus now reverses to a left-beating nystagmus in left gaze, *the nystagmus is IN with a latent component*; if not, it *still could be* either FMN or IN with a large latent component (i.e., the neutral-zone shift with occlusion was so

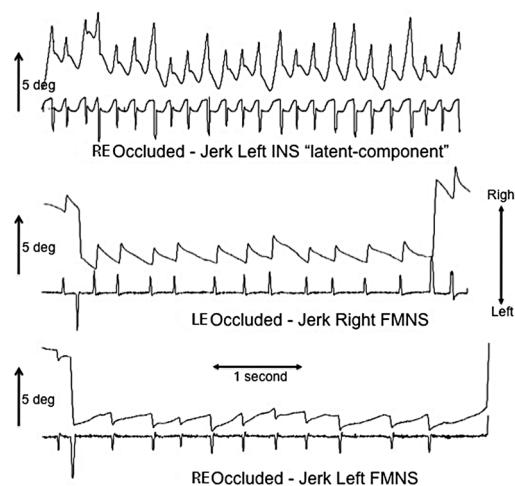


FIGURE 5.4 The differentiation between infantile nystagmus syndrome (INS) with a “latent component” and fusion maldevelopment nystagmus syndrome (FMNS). Both conditions are clinically identical, that is, horizontal nystagmus with both eyes open that changes in direction and/or intensity under monocular conditions. The top trace shows jerk-left INS under left-eye monocular fixation. This is different from the bottom two traces, which show jerk right with linear/decreasing velocity slow phases under right-eye monocular fixation and jerk left with linear/decreasing velocity slow phases with left-eye monocular fixation typical of FMNS. Deg, degrees; LE, left eye; RE, right eye.

great as to preclude transversing it in far left gaze and obtaining a nystagmus reversal back to left-beating nystagmus).

5.1.2 Fusion Maldevelopment Nystagmus Syndrome

Fusion maldevelopment nystagmus syndrome (FMNS, also known as latent/manifest latent nystagmus, LMLN)⁸ is a benign, binocular horizontal oscillation of infantile onset; there is always associated strabismus, and ocular motor recordings show four types of slow phases with jerk in direction of fixing eye.^{12,35–39} The oscillations appear conjugate, horizontal, and uniplanar, and there are usually no associated sensory system deficits (e.g., albinism, achromatopsia). This form of nystagmus in infancy is generally associated with the best binocular acuity potential of all the forms of childhood oscillations. The oscillations may change with exaggerated convergence, resulting in a head posture associated with fixing eye in adduction. There is no head shaking, the eyes may exhibit “reversal” with OKN stimulus, and there is no aperiodicity to the oscillation.^{12,35–39} Constant horizontal and dissociated strabismus is often present. The intensity decreases with increased fusion (binocular function) and movement of the fixing eye into adduction (toward the nystagmus slow phase) and with increasing age.

5.1.2.1 ASSOCIATION WITH STRABISMUS

FMNS implies strabismus, but the converse is not true; strabismus does not imply FMNS (50% have no nystagmus at all), but if an individual has FMNS, he or she also has strabismus (i.e., strabismus is a necessary, but not sufficient, condition for FMNS). Even if it is not evident clinically (it may be a microstrabismus that can be recorded), it is there. Distinguishing the FMNS waveform and the tropia of the nonfixating eye requires DC-coupled, high-bandwidth recordings of both eyes simultaneously. In logical terminology, strabismus is a necessary (but not sufficient) condition for FMNS (i.e., all

individuals with FMNS have strabismus, but not all with strabismus have FMNS). Summarizing, INS can occur with or without strabismus; all FMNS patients have strabismus.

5.1.2.2 CLINICAL SIGNS AND SYMPTOMS

As stated earlier, the pure, latent form of FMNS (pure LN) is extremely rare. That is, when you record pure FMN, you must find no nystagmus with eyes open at all gaze angles. There have been only a couple of cases proven by recordings to have this pure form. Many patients thought clinically to have latent FMN really have manifest FMN. When one records them or examines them with an ophthalmoscope, the FMN is visible. More common is latent FMN in primary position with manifest FMN in lateral gaze; most common is manifest FMN at all gaze angles.

The intensity of FMN is greatest with gaze toward the direction of the fast phase (Alexander’s law). Jerk-right nystagmus is greater in right than in left gaze and vice versa. These are not true nulls; one cannot show increased nystagmus because the patient is at the end of the excursion of the eye. Instead, this is an example of a monotonic relationship of gaze and amplitude. It would not be uncommon for a person who fixates with one eye and has FMNS, to keep that eye in adduction where Alexander’s law will reduce the nystagmus. In INS there is a null and increased amplitude (with increasing-velocity exponentials) as gaze is directed away from the null in both directions, whereas in FMNS (right eye or left eye fixating), there is an Alexander’s law relationship and decreasing-velocity exponentials. Patients with FMNS usually place their fixating eye in adduction to minimize the nystagmus and thereby maximize acuity. As in INS, the head turn minimizes the nystagmus and maximizes acuity. A patient might place his or her eye in other than the minimum position of nystagmus if he or she had an “angle kappa” that required eccentric fixation. Better acuity results, although the nystagmus might be a little higher where the patient places his or her gaze.

We have never recorded the FMNS waveform in patients with orthophoria; they all had

latent strabismus (when you cover one eye, the other does not remain straight). Similarly, FMNS has never been recorded in patients with binocular alignment; all had manifest strabismus. Both eyes are open, but one eye must be deviated (in or out) to have FMNS. If they can straighten their eyes, the FMN disappears; in the blockage syndrome, they have INS when their eyes are aligned.

5.1.2.3 DIFFERENTIAL DIAGNOSIS

Waveform is also the diagnostic criterion for FMNS (see Chapter 3, Fig. 3.1 and Table 5.3); recordings show a decreasing-velocity exponential slow phase. All patients (100%) with FMNS have strabismus. Included in the definition of strabismus is latent strabismus (i.e., the phoria resulting when you cover an eye). Thus, FMNS includes a pure latent form, where the eyes are straight with no nystagmus when both eyes are open and when you cover one eye, an eso- or exophoria will develop followed by manifest FMN in both eyes. This more common, manifest form of FMN is present with both eyes open and mimics the latent form exactly if it is bidirectional. When it is unidirectional and the patient fixates with one eye, there will be no nystagmus and the other eye will be esotropic, but when the patient fixates with the other eye and the formerly fixating eye is esotropic, the patient will have FMN. The latent form of FMN (i.e., no nystagmus with both eyes open) is rare. If you occlude the left eye and the right eye is fixating, jerk-right FMN with linear or decreasing-velocity slow phases results and vice versa.

The small group of patients with both INS and FMNS present a diagnostic dilemma. Some have mostly INS (designated “INS/FMNS”) and their waveforms are any of the INS waveforms (i.e., pendular or increasing-velocity slow phases) (see Table 5.3) and one other waveform called “dual jerk” or “dual pendular” (see Chapter 2, Fig. 2.3 and Chapter 3, Fig. 3.3). The latter is a waveform where a low-amplitude, high-frequency pendular nystagmus is superimposed on a decreasing-velocity slow-phase jerk waveform. They do not exhibit

the pure FMNS waveform (i.e., decreasing-velocity slow phases); therefore, INS is predominant. The other group has mostly FMNS (FMNS/INS) and their waveforms are FMNS and dual-jerk FMN. There are some who have INS and FMNS equally. At various times they exhibit the INS waveform, FMNS waveform, or the dual-jerk waveform. A linear slow phase is not diagnostic of either INS or FMNS. When a pendular waveform is superimposed on a jerk waveform and the slow phase is accelerating, it is a dual-jerk IN; if the slow phase is decelerating, it is a dual-jerk FMN. One has to carefully determine what is happening to the axis of the pendular slow phase (i.e., whether it is decelerating or accelerating) to properly categorize the nystagmus. This small but difficult group of patients *must* be recorded for accurate diagnosis. Distinguishing the INS and FMNS waveforms from the combination waveforms requires DC-coupled, high-bandwidth recordings of both eyes simultaneously.

Summarizing, within the different types of neurologically “benign” infantile nystagmus, there is a large category of pure INS, a significant category of pure FMNS, and a small category that is a mixture of the two; there are also individuals with the nystagmus blockage syndrome (NBS) or spasmus nutans syndrome (SNS). All are easily diagnosed with the aid of ocular motility recordings and just as easily misdiagnosed without them. There are twelve INS waveforms, two mixed INS waveforms (dual-jerk and dual-pendular IN), two FMNS waveforms, and one mixed FMNS waveform (dual-jerk FMN). If a patient walks into your office with wiggling eyes and you wish to guess what the patient has before you record him or her, your best guess would be INS. A large percentage (80%) will be INS and 15% FMNS with only a small percentage of mixtures. If you could consider just INS patients, 94% will be pure INS and only 6% a mixture. If you could restrict the population to FMNS patients, three-fourths of them will have only FMNS, but many will have mixtures. Thus, more patients with predominantly FMNS will also have some INS than patients with predominantly INS having FMNS.

5.1.2.4 ALTERNATE-COVER AND GAZE-ANGLE-COVER TESTS

The same two tests discussed in Section 5.1.1.4 apply here since their purpose is to help differentiate INS from FMNS. However, as can be seen from the conclusions that can be drawn from the various observations from the two tests, although INS can be identified conclusively in some cases, FMNS cannot.

5.1.3 Nystagmus Blockage Syndrome

The nystagmus blockage (blockierungs, compensation) syndrome (NBS)⁸ denotes a particular type of nystagmus: onset of esotropia in early infancy, pseudoabducens paralysis, head turn toward the side of the fixating eye, absence of nystagmus with the fixating eye in adduction, and appearance of a manifest jerky nystagmus as the fixating eye moves into primary position and abduction.^{40,41} Many reports have concluded from eye-movement recording analysis that patients who habitually hold their dominant eye in the position of least nystagmus (usually adduction) may develop suppression and esotropia in the fellow eye.^{38,40–42} Adelstein and Cuppers analyzed this condition further and coined the term “nystagmus blockage syndrome” (NBS).⁴³ In the majority of patients the eyes are in a convergent position; in others there is alternating fixation. Adelstein and Cuppers separated this syndrome from bilateral abducens paralysis and explained the esotropia on the basis of hypertonicity of the medial rectus muscles, resulting from the patient’s sustained effort to block the nystagmus by adducting the eye.⁴³

The diagnosis of nystagmus blockage syndrome can be made only when the ongoing waveform is of INS and the nystagmus markedly diminishes with esotropia.⁴⁴ Therefore, true NBS is indeed a “blockage” of an ongoing nystagmus (i.e., IN) present with both eyes open, produced by an added or increasing esotropia. The esotropia may reduce the nystagmus by one of two mechanisms: it may reduce an ongoing INS much in the same manner as true binocular convergence reduces the

amplitude of IN, or it may convert the nystagmus to a low-amplitude FMN.

The name “nystagmus blockage syndrome” reflects the prevalent assumption that patients block their nystagmus by adducting one eye. The adducted eye may be the fixing eye (i.e., accompanied by a head turn) or it may be the nonfixing eye (i.e., when a patient views an object in primary position with his or her head straight). In both cases, the nystagmus is reduced when the esotropia occurs. The diagnosis of NBS is difficult to make because precise and uniform diagnostic criteria are lacking; similar, more common disorders, such as esotropia associated with FMNS, are mistaken for NBS; and the diagnosis usually is made by clinical observation rather than by accurate eye-movement recordings.^{36,38,40–42,45–49} The patients commonly misdiagnosed as having NBS are those with FMNS and esotropia.

5.1.3.1 ASSOCIATION WITH STRABISMUS

Strabismus, albeit a variable strabismus, is a necessary but not sufficient condition for the NBS since a purposive esotropia is required to damp the IN and/or transform it into FMN. That is, all patients with NBS have strabismus, but clearly all with strabismus do not have NBS.

5.1.3.2 CLINICAL SIGNS AND SYMPTOMS

Patients with NBS willfully induce esotropia while fixating at distance. This is something that most with INS cannot do unless they have the ability to partially suppress the esotropic eye. If INS patients with normal binocular vision could make one eye esotropic, they would have oscillating diplopia. When NBS patients turn one eye in and suppress it, their nystagmus damps and they may adopt a head turn to place their fixating eye in adduction. The INS is either reduced in amplitude or converted to a low-amplitude FMNS by this purposive esotropia; the greater the esotropia, the lower the nystagmus and, as the fixating eye moves from adduction to abduction, the nystagmus increases and esotropia decreases.

5.1.3.3 DIFFERENTIAL DIAGNOSIS

The NBS is the source of some misunderstanding. Individuals with NBS use a convergence-like movement to damp their INS while viewing a distant target. Thus, the waveforms in NBS are those of INS when the patient is looking in the distance and the eyes are straight.⁴¹ With the imposition of the purposive esotropia (this is *not* a strabismus that occurs transiently but one that the patient either willfully or reflexively imposes because he or she has found that acuity is better under that condition) the waveform can either become a damped INS waveform (Type I NBS) or a small-amplitude FMNS (Type II NBS). Thus, the NBS implies ocular motor deficits capable of producing both IN and FMN waveforms (see Table 5.3). Even though the FMNS waveform is usually unsuitable for good acuity (because there are no long, postsaccadic foveation periods), it is of low amplitude and acuity increases. Thus, there are two types of blockage syndrome. NBS is often misdiagnosed in patients with FMNS and alternating fixation who place their fixating eye in adduction to reduce their FMNS. Since they do not have INS, and they do not have NBS. Distinguishing the INS from the FMNS waveforms and the purposive esotropia of one eye requires DC-coupled, high-bandwidth recordings of both eyes simultaneously.

5.1.4 Spasmus Nutans Syndrome

The term *spasmus nutans* (Latin for “nodding spasm”) refers to the constellation of nystagmus, head nodding, and torticollis. Although the term “acquired nystagmus” has been applied to the spasmus nutans syndrome (SNS)⁸ as a differentiating feature from INS, it should be remembered that INS is also “acquired” earlier in infancy.^{35,50–54} Unlike INS, which usually becomes apparent between 8 and 12 weeks of age (although it may appear at birth), the age of onset in SNS is generally quoted as 6 to 12 months of age, although cases with clinically apparent onset ranging from 2 weeks to 3 years of age have been documented. SNS may become clinically “silent” within 1 to 2 years of onset, but it persists for years if studied

with eye-movement recordings. There is no lasting direct effect on vision, although there is high incidence of ametropia and amblyopia in this population of patients.

5.1.4.1 ASSOCIATION WITH STRABISMUS

Gottlob et al. found a high incidence of esotropia, latent nystagmus, dissociated vertical divergence, and amblyopia in children with SNS.^{55,56} Conversely, rare patients with infantile esotropia display horizontal or vertical head oscillations that resolve following surgical realignment of the eyes.

5.1.4.2 CLINICAL SIGNS AND SYMPTOMS

SNS appears as a high-frequency, asymmetric, dysconjugate ocular oscillation. It is usually horizontal in direction but may also be vertical or torsional.^{35,50–54} It is often described as an intermittent nystagmus that is asymmetrical in appearance and occasionally monocular. The key eye-movement recording observation was the variable phase difference between the two eyes, which is reflected clinically as an asymmetry in the oscillations between the two eyes. On lateral gaze, the dissociation may increase, with nystagmus of the abducting eye predominating. Some case series suggest an increased prevalence of esotropia in SNS. In contradistinction to INS, visual acuity is minimally affected in SNS. SNS is more common in Black children and has been reported in several sets of identical twins.^{51,53,57}

Contrary what was commonly believed, eye-movement data showed that the asymmetric ocular oscillations of SNS did *not* always disappear.⁵³ There have been patients of 10 or 12 years of age whose SNS is still clinically evident. Many times it disappears to clinical observation (again, like FMNS) but when recorded, a pendular dissociated nystagmus will be found. As described in Chapter 4, Section 4.2.1.3, patients cancel the dysconjugate pendular oscillation of SNS (present with a still head) and substitute a conjugate vestibulo-ocular reflex (VOR) when the head is moving; as a result, acuity

increases. The oscillating diplopia that probably results from the out-of-phase oscillations may be the main reason that head shaking is used to cancel the nystagmus. Thus, unlike the low-amplitude, uncontrolled, noncompensatory head nodding sometimes seen in INS, the larger amplitude, purposive head nodding in SNS is compensatory.^{52,58,59}

5.1.4.3 DIFFERENTIAL DIAGNOSIS

SNS may appear at or after birth and usually, but not necessarily, ceases by the age of 3 years. The nystagmus is pendular, usually monocular or disconjugate, and is commonly accompanied by a head oscillation. Reports of “spasmus nutans” accompanying neurological disease (e.g., craniopharyngioma, optic nerve and chiasmal glioma,^{60–62} or cerebrocerebellar degeneration⁶³) have not all included eye-movement recordings to prove that the nystagmus was the same as that of spasmus nutans. Although the nystagmus may clinically resemble that recorded in SNS, until a proper study comparing the actual waveforms of SNS with those recorded in children with known neurological disease, they should not be presumed to be identical. The term “SNS” should be reserved for the specific, benign nystagmus that has been documented (see earlier) and should not also be used to describe the nystagmus accompanying neurological disease, even if the nystagmus itself is subsequently found to be identical. Rather, a descriptive name for the nystagmus should be used for the latter. Other signs are needed to distinguish true SNS from similar looking nystagmus associated with central nervous system (CNS) disease.⁵⁴

For a century, numerous reports emphasized that SNS was a visually and systemically benign and self-limited clinical entity.^{54,61,62,64–68} Since 1967, however, many infants with some of the features of spasmus nutans have been found to have congenital suprasellar tumors (most commonly chiasmal gliomas). Suprasellar tumors can produce a constellation of neuroophthalmologic signs that are clinically and electrophysiologically indistinguishable from SNS. The clinical findings of hydrocephalus, café au

lait spots, optic atrophy, or other clinical signs of neurofibromatosis make it more likely that a child with SNS will have a CNS glioma. A substantial proportion of patients presenting with SNS-like nystagmus have important underlying ocular, intracranial, or systemic abnormalities. Neurodegenerative disorders such as Pelizaeus–Merzbacher disease and Leigh disease may produce nystagmus and head nodding that are indistinguishable from SNS.^{54–56,69–73} These disorders should be suspected in children with clinical signs of ataxia or developmental delay or with magnetic resonance evidence of white matter signal abnormalities. Achromatopsia, congenital stationary night blindness, and Bardet Biedl syndrome can also masquerade as SNS. The diagnosis of SNS can only be made using a combination of clinical characteristics and eye-movement findings, which exclude other visual or nervous system disease. The pathogenesis and neuroanatomical substrate of this developmentally acquired form of asymmetric, dysconjugate nystagmus are still unknown.

SNS must first be distinguished from INS and FMNS. Despite the clinical similarities of SNS to INS or FMNS in some patients, eye-movement data can be used to make the correct diagnosis. The diagnostic criteria for SNS have also been defined by ocular motility recordings.⁵³ Based on that data we can now diagnose SNS immediately and distinguish it from INS and FMNS; it is no longer necessary to wait 3 or 4 years before making the diagnosis based on its possible clinical disappearance. The diagnostic key is the variable phase difference between the oscillations in both eyes, unlike INS and FMNS, where the oscillations are always phase-locked, if not totally conjugate.

At present, however, even positive identification of SNS or SNS-like waveform is insufficient to preclude further imaging studies to rule out neurological disease. However, if it is subsequently found that the nystagmus associated with neurological disease differs from that of SNS, then identification of the latter by eye-movement data could provide sufficient evidence to remove the need for expensive imaging studies. Similarly, eye-movement identification of a type of nystagmus that is found to be specific

for neurological disease would require imaging studies.

5.1.5 Nystagmus and Strabismus

The prevalence of strabismus in general population has been reported to be between 0.80% and 6.0%.^{15,74–77} Chia et al. in a study of 3009 Singaporean children, aged 6 to 72 months found a prevalence of strabismus of 0.80%.⁷⁸ The MEPEPS Study Group found that in 3007 African American children and 3007 Hispanic children, ages 30 to 72 months, incidence of strabismus was similar in both groups (2.4% for Hispanic children vs. 2.5% for African American children).^{79,80} Graham reported that the prevalence of strabismus is 5.66% based on a study done on 4784 children.⁸¹ Of 1187 children, 4.2% were found to have strabismus in a study done by Chew et al.⁸² In a study done in Sweden, the prevalence of strabismus was found to be 3.2%.⁸³ Compared to the general population, the prevalence of strabismus in patients with nystagmus is higher than in the general population. In a study by Forssman the prevalence of strabismus was reported to be 16%.^{84,85} In another study by Brodsky and Fray the prevalence of strabismus was reported to be 17%–50%.²⁸ Self et al. reported that the prevalence of strabismus is 44% in INS due to mutations in FRMD7.^{86,87} From a combination of studies of over 500 infants, children, and adults with childhood forms of nystagmus reported by multiple authors, incidences from 25% to 72% were reported.^{21,25,28,35–37,39,88–96} Thus, those eye care professionals who care for patients with strabismus are as likely, if not more so, as any in health care to be confronted with the disorders of nystagmus and other ocular oscillations.

5.2 NYSTAGMUS WITH ASSOCIATED NEUROLOGICAL DISEASE—“SYMPOMATIC”

In addition to the benign types of nystagmus in infancy discussed earlier, there are also symptomatic types of nystagmus that may appear

in infancy as well as adulthood. Various types of acquired nystagmus may be localized, as Figure 5.5 illustrates. Knowing how each type of nystagmus varies with gaze angle is important for differential diagnosis. In Figure 5.6, the waveforms and their variation with gaze angle of INS, FMNS (both linear and decelerating slow phases), GEN, and VN are illustrated. These variations are shown in Figure 5.7 as they would appear when recorded. The target position for the FMNS waveforms with decelerating slow phases has been corrected from illustrations published prior to the discovery of the substitution of saccadic pulse trains for linear FMNS when the slow-phase velocities were too high for good foveation.⁹⁷

5.2.1 Vestibular Nystagmus

Certain characteristics of vestibular nystagmus can localize the etiology to the peripheral or central neuronal pathways of the vestibular systems. Central vestibular nystagmus is frequently uniplanar in contrast to peripheral vestibular nystagmus, which is usually torsional or multiplanar.^{98,99} Visual fixation easily inhibits peripheral vestibular nystagmus, but not central vestibular nystagmus. Vertigo and tinnitus are common in peripheral vestibular nystagmus and uncommon in central vestibular nystagmus.

5.2.1.1 PERIPHERAL VESTIBULAR IMBALANCE

The child with peripheral vestibular nystagmus has, in many ways, similar etiologies, signs, symptoms, and treatment options as an adult. The VOR normally generates eye rotations, after a short latency, in the same plane as the head rotation that elicits them. Disorders of the vestibular periphery cause nystagmus in a direction that is determined by the pattern of involved labyrinthine-semicircular canals.^{99–106} The complete, unilateral loss of one labyrinth causes a mixed horizontal-torsional nystagmus that is suppressed by visual fixation. Another consequence of vestibular disease is a change in the size (gain) of the overall dynamic VOR response. As a result of this change, patients complain

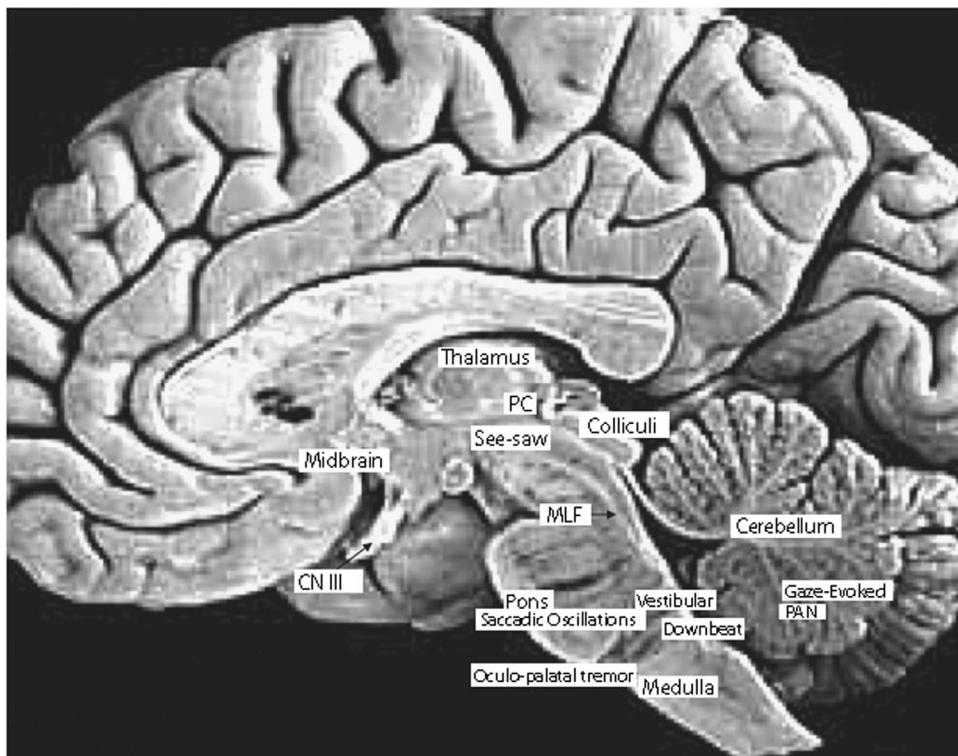


FIGURE 5.5 Sagittal section of brainstem, midbrain, cortex, and cerebellum. Anatomical areas responsible for ocular motor control and nystagmus types localized to brainstem and cerebellar areas are indicated. CN III, cranial nerve three; MLF, medial longitudinal fasciculus; PAN, periodic alternating nystagmus; PC, posterior commissure.

of oscillopsia during rapid head movements. A VOR gain larger than 1 (eye speed exceeds head speed) results from a disinhibition of the brainstem circuits responsible for the VOR and is caused by vestibulo-cerebellar dysfunction. Loss of peripheral vestibular function causes impaired vision and oscillopsia during locomotion, due to the inability to compensate for the high-frequency head perturbations that occur with body and head movements. Symptoms include vertigo, nausea, dizziness, and oscillopsia, and signs include mixed horizontal-torsional trajectory of the oscillation (which usually beats away from the side of a vestibular lesion), associated neurologic signs and symptoms, usually acute onset, and unsteady gait. Common associated findings include relatively preserved saccades and smooth pursuit, skew deviation, and an increase in the intensity of the oscillation when eyes are turned in the direction of the

quick phases (Alexander's law). The nystagmus is suppressed by visual fixation and increased when fixation is removed. The horizontal component is diminished when the patient lies with the intact ear down and is exacerbated with the affected ear down. The nystagmus is increased or precipitated by changes in head position, vigorous head shaking, hyperventilation, mastoid vibration, or Valsalva maneuver. There is unilaterally impaired ability to modulate spontaneous nystagmus. A magnetic resonance image (MRI) or computed tomography (CT) scan of the brain may show disease and, importantly, ocular motility recordings show linear (constant velocity) slow phases.^{99–106} The prognosis of the oscillation depends on underlying disease. The characteristics of peripheral vestibular nystagmus are listed in Table 5.4; peripheral positional nystagmus, in Table 5.5; and its variation with gaze angle is illustrated in Figures 5.6 and 5.7.

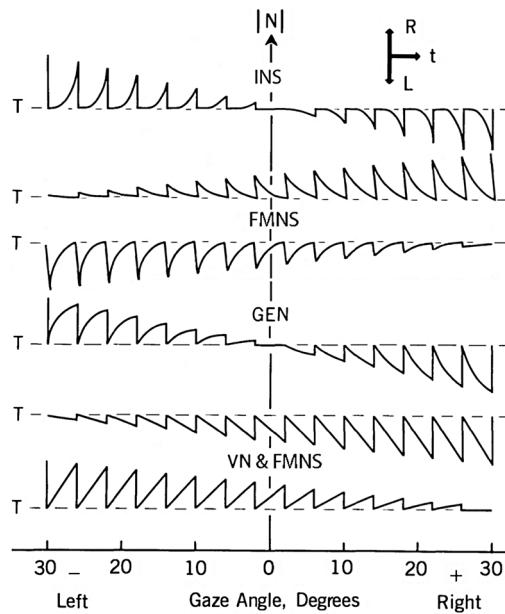


FIGURE 5.6 Waveform variation with gaze angle for different types of nystagmus. Note that the target positions for FMNS with decelerating slow phases are at the *ends* of the slow phases; thus, these are defoveating saccadic pulse trains, not true nystagmus. The basic FMNS waveforms (JR for right-eye fixation and JL for left-eye fixation) have linear slow phases and are shown with VN. FMNS, fusion maldevelopment nystagmus syndrome; GEN, gaze-evoked nystagmus; INS, infantile nystagmus syndrome; L, left; |N|, nystagmus magnitude; R, right; t, time; VN, vestibular nystagmus.

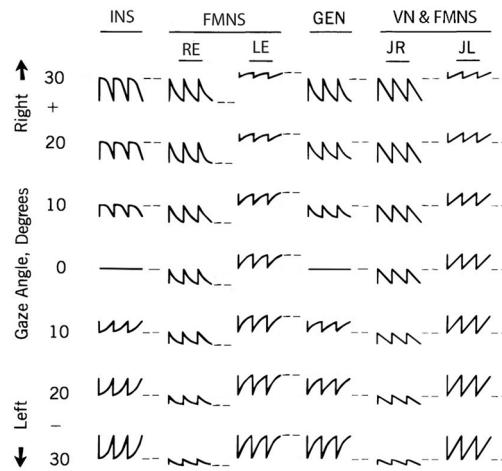


FIGURE 5.7 Waveform variation with gaze angle for different types of nystagmus as would be recorded by an eye-movement data acquisition system. FMNS, fusion maldevelopment nystagmus syndrome; GEN, gaze-evoked nystagmus; INS, infantile nystagmus syndrome; JL, jerk left; JR, jerk right; LE, fixation with left eye; RE, fixation with right eye; VN, vestibular nystagmus.

Table 5.4 Vestibular Nystagmus

SYMPTOM OR SIGN	PERIPHERAL (END ORGAN)	CENTRAL (NUCLEAR)
Direction of nystagmus	Unidirectional, fast phase opposite lesion	Bidirectional or unidirectional
Purely horizontal nystagmus without torsional component	Uncommon	Common
Vertical or purely torsional nystagmus	Never present	May be present
Visual fixation	Inhibits nystagmus and vertigo	No inhibition
Severity of vertigo	Marked	Mild
Direction of spin	Toward fast phase	Variable
Direction of past-pointing	Toward slow phase	Variable
Direction of Romberg fall	Toward slow phase	Variable
Effect of head turning	Changes Romberg fall	No effect
Duration of symptoms	Finite (minutes, days, weeks) but recurrent	May be chronic
Tinnitus and/or deafness	Often present	Usually absent
Common causes	Infection (labyrinthitis), Meniere disease, neuronitis, vascular, trauma, toxicity	Vascular, demyelinating, and neoplastic disorders

5.2.1.2 CENTRAL VESTIBULAR IMBALANCE

The child with central vestibular nystagmus also has, in many ways, similar etiologies, signs, symptoms, and treatment options as an adult. There is a mixed horizontal-torsional trajectory to the fast phase with beats away from the side of the vestibular lesion.^{98,103,107,108}

There are almost always associated neurologic signs and symptoms, that is, the acute onset of vertigo, nausea, dizziness, and oscillopsia, associated with other signs of vestibulocerebellar dysfunction. Common associated findings may include other ocular oscillations such as downbeat, upbeat, torsional, horizontal, jerk, and SSN. Slow phases may be linear or have increasing- or decreasing-velocity

Table 5.5 Positional Nystagmus

FEATURES	PERIPHERAL	CENTRAL
Latency	3–40 sec	None; nystagmus begins immediately
Fatigability	Yes	No
Rebound	Yes	No
Habituation	Yes	No
Intensity of vertigo	Severe	Mild
Reproducibility	Poor	Good
Directionality and waveforms	Stereotyped	Variable

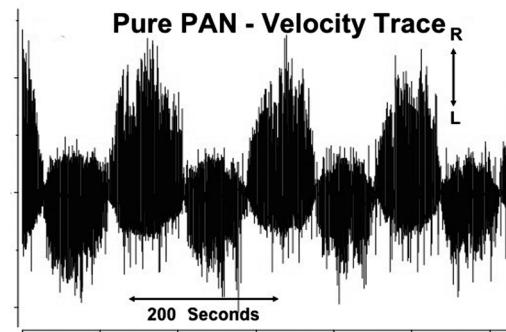


FIGURE 5.8 Velocity trace from eye-movement recordings of a patient with infantile nystagmus syndrome and periodic alternating nystagmus (PAN) looking in primary position for about 13 minutes showing classic rhythmic change in intensity and direction of the oscillation. Spontaneous nystagmus in the primary position, which beats jerk right with increasing then decreasing intensity for 1 to 2 minutes, followed by a quiet period, and then reappearance of the nystagmus in the opposite direction with similar crescendo-decrescendo in intensity for a similar length of time. Both eyes had same tracing.

waveforms. The nystagmus is poorly suppressed by fixation of a visual target and may be precipitated, exacerbated, or changed in direction by altering head position, vigorous head shaking (horizontal or vertical), or hyperventilation. Convergence may increase, suppress, or convert upbeat to downbeat

nystagmus and vice versa. The oscillation is commonly associated with impaired smooth pursuit, gaze-evoked nystagmus, gait instability, and ataxia. An MRI/CT scan of the brain reflects underlying disease. The prognosis depends on the underlying disease. The characteristics of central vestibular nystagmus are

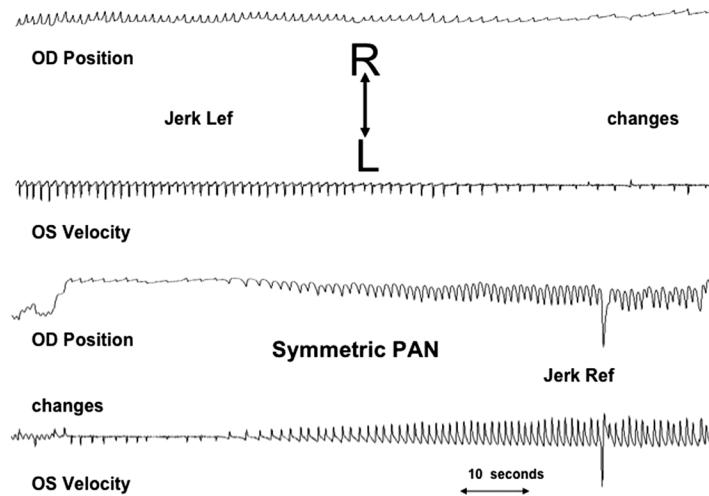


FIGURE 5.9 Eye-movement recording of right eye from a patient with symmetric infantile periodic alternating nystagmus (PAN) performed under binocular conditions over 200 seconds illustrating a typical periodic, symmetric, jerk right with extended foveation (Jerk Ref) when the infantile nystagmus syndrome direction was to the right and jerk left with extended foveation (Jerk Lef) when the direction was to the left. L, left; R, right; OD, right eye; OS, left eye.

listed in Table 5.4 and central positional nystagmus, in Table 5.5.

5.2.1.3 CENTRAL VESTIBULAR INSTABILITY (PERIODIC ALTERNATING)

Periodic alternating nystagmus (PAN) is an extraordinary ocular motor phenomenon in which a persisting horizontal jerk nystagmus periodically changes directions; it may be congenital or acquired. The congenital variety (i.e., INS nystagmus), which may be associated with albinism,^{109,110} has slow-phase waveforms of both linear and increasing velocity, usually lacks the well-defined stereotyped periodicity seen in acquired PAN (i.e., it is asymmetric (a)periodic alternating nystagmus, APAN), and can persist for many minutes in either direction or spontaneously change direction after a few seconds.^{111,112} The addition of variable pendular nystagmus to these APAN jerk waveforms can produce complex waveforms that may mimic those of FMNS nystagmus.^{113–115} The periodicity of INS APAN is markedly influenced by changes in gaze position, supporting the hypothesis that the direction reversals are a result of a temporal shift in the null zone (see Chapter 2, Fig. 2.12).³³ INS with APAN may also be hereditary.¹¹⁶

In contrast, the usual, fixed sequence in acquired PAN consists of about 90 seconds of nystagmus beating in one direction, 10 seconds of a neutral phase in which the eyes stop or beat downward irregularly, and 90 seconds of beating in the opposite direction (see Fig. 5.8 where the velocity trace demonstrated this periodicity). This periodicity is continuous during waking hours and may prevail during sleep. Some patients demonstrate asymmetries in the timing of the two major phases, but the basic pattern for each patient is usually invariable; for a contrast to APAN, see Table 5.2. In Figure 5.9 the symmetric PAN of a patient with INS is shown. The JLe waveform is shown gradually diminishing in amplitude and, after a neutral period, reversing to JRef and increasing in amplitude. In acquired PAN the waveform would be a sawtooth jerk nystagmus.

Acquired PAN is usually seen in older children or adults but may present in early

childhood. Causes of acquired PAN include head trauma, multiple sclerosis, posterior fossa lesions, vascular insufficiency, spinocerebellar degenerations, encephalitis, otitis media, syphilis, aqueductal stenosis, and Arnold–Chiari malformation.^{95,110,117} PAN may coexist with downbeat nystagmus, which also suggests a Chiari malformation. Unlike PAN in the INS, acquired PAN is usually associated with structural lesions involving the cerebellum or its central connections. Reports of acquired PAN following visual loss (e.g., vitreous hemorrhage or cataract) and its disappearance with restoration of vision provide an important clue to the underlying pathophysiology.

Patients with acquired PAN usually have vertigo, nausea, dizziness, and oscillopsia. It can be associated with other signs of vestibulocerebellar involvement (e.g., Arnold–Chiari, platybasia). The nystagmus is a mixed horizontal-torsional trajectory showing a peculiar, spontaneous, rhythmic, regular, crescendo-decrescendo intensity and directional change direction of the fast phase with the complete cycle lasting about 3 minutes. It is usually acute in onset and may be associated with periodic alternating head turns—the head turns in the direction of the quick phase, and the eyes are moved into a position in the orbit that is the same as the direction of the slow phase—thereby minimizing the nystagmus induced by Alexander’s law. The nystagmus cycle is not affected by visual fixation. Vestibular stimuli, such as head rotations, can change or transiently stop nystagmus, downbeat nystagmus and square-wave jerks may become more obvious in the brief null period when the horizontal nystagmus wanes and then reverses, MRI/CT scan of brain reflects underlying disease, and ocular motility recordings show linear (“constant velocity”) slow phases. The prognosis depends on the underlying disease.

Campbell described PAN secondary to phenytoin intoxication in a patient with alcoholic cerebellar degeneration.¹¹⁸ The antispasticity drug baclofen abolishes acquired PAN but does have some unpredictable effects on the INS variety.¹¹⁹ The drug abolished experimentally created PAN in the monkey,¹²⁰ as well as a single case of aperiodic alternating nystagmus in a patient

with vertebrobasilar insufficiency.¹²¹ Baclofen damped the APAN of some patients with INS,¹²² whereas memantine damped acquired PAN in a case where baclofen was ineffective.¹²³

PAN may be associated with a periodic alternating skew deviation.¹²⁴ Periodic alternating gaze deviation (“ping-pong gaze”), regardless of whether associated with alternating nystagmus or alternating head turning, is a rare, related phenomenon.¹²⁵ Periodic alternating gaze deviation is a cyclic disorder of eye (and head) movements characterized by slow, spontaneous, alternating, pendular, conjugate, horizontal eye and/or compensatory head movements. A complete cycle lasts seconds to minutes and consists of a conjugate horizontal eye movement to one side followed by a slow conjugate eye movement to the opposite side. This disorder is usually clinically evident as part of a larger cerebral dysfunction such as a cerebrovascular accident, brain tumor, obtunded states, sleep, anesthesia, and coma. Although the exact mechanism is unknown, the midline cerebellum, pons, and bilateral cerebral hemisphere dysfunction have all been postulated.

Animal experiments combined with additional data in humans suggest that acquired PAN probably requires concurrent CNS dysfunction at two separate levels.^{108,126} The nodulus and uvula of the cerebellum are believed to control postrotational nystagmus, which is prolonged following ablation. PAN can be produced in animals following ablation of these structures if visual deprivation is superimposed. It is believed that normal vestibular repair mechanisms act to reverse the direction of the nystagmus. Under normal circumstances, the oscillations of PAN would be blocked by visual fixation, smooth pursuit, and optokinetic mechanisms. When these visual stabilization systems do not work (in the setting of visual deprivation and disease of the cerebellar flocculus), removal of Purkinje cell inhibition upon the vestibular nuclei allows the central velocity storage mechanism to become unstable.

Pharmacological evidence suggests that the nodulus and uvula maintain inhibitory control on the vestibular rotational responses via the inhibitory neurotransmitter gamma-amino-butyric acid (GABA).^{117,119,127,128} Halmagyi et al. were the first to report the successful treatment

of the acquired form of PAN with the GABAergic drug Baclofen.¹¹⁹ The finding that acquired PAN is abolished by Baclofen, both in humans and in animals following ablation of the nodulus and uvula, further supports this pathogenetic mechanism in acquired PAN.

In a clinical and control-system study,¹²⁹ it was proposed that PAN arises from (1) a defect in the brainstem neural networks that generates slow phases of vestibular and optokinetic nystagmus, (2) the action of an adaptive network that normally acts to null prolonged, inappropriate nystagmus, and (3) an inability to use retinal-error velocity information. They proposed a control system model that denied access of visual signals to the visual vestibular system. This model is particularly appealing because of the occasional relationship between impaired vision and PAN. Support for their hypothesis of impairment in the velocity storage element was presented by Furman et al.,¹³⁰ who studied four PAN patients. PAN has occurred after bilateral vitreous hemorrhages (associated with a massive subarachnoid hemorrhage) and after cataracts and disappeared after bilateral vitrectomy and cataract surgery, respectively. Ablation of the nodulus and ventral uvula of the cerebellum in monkeys produces PAN.¹²⁰

5.2.2 Gaze-Holding Deficiency Nystagmus

There are several forms of nystagmus that are directly related to problems with gaze holding; they usually manifest at eccentric gaze angles, although one type may be present in primary position.

5.2.2.1 ECCENTRIC GAZE, GAZE-EVOKED, REBOUND

Gaze-evoked nystagmus (GEN) is a rhythmic oscillation of the eyes while attempting to maintain an eccentric eye position. It is caused by a deficiency, usually a structural lesion, in the neural integrator network.¹³¹ Gaze cannot be held at an eccentric position, and the eyes drift back toward the null point of the integrator, which often is straight-ahead gaze. A corrective

saccade is attempted to move the gaze back to the eccentric position, and the process repeats. The variation of GEN with gaze angle is illustrated in Figures 5.6 and 5.7.

Saccadic eye movements are made by a neural signal composed of a rapid increase in neural discharge (pulse) and then a rapid decrease to a new discharge rate (step). When the pulse component is not accurate, the eyes will over- or undershoot their target and then make a corrective second saccade to bring the gaze to the intended fixation. When the step component is not maintained, the eyes will drift back to primary gaze with a decelerating slow phase, make a corrective saccade, and repeat to cause GEN.¹²⁶ It is the neural integrator that is responsible for mathematically “integrating” the pulse of neural activity into a step discharge. If there is a minimal abnormality in integrator function, GEN will manifest itself only at extreme angles of gaze. However, if there is a major defect in function, GEN can appear in primary gaze. It should also be remembered that vertical GEN almost always indicates brainstem or cerebellar dysfunction. Gaze-evoked nystagmus is the most common form of nystagmus encountered in clinical practice.

There is an important difference between GEN and physiologic end-point nystagmus (EPN). With EPN, the eyes attempt a saccade out to an extreme gaze position and have an initial difficulty holding this position. After a short amount of jerk nystagmus with fairly linear slow phases, the eyes may be able to maintain the eccentric gaze. EPN is a normal finding and differs from GEN by the fact that GEN is a constant nystagmus with larger amplitude (defined as 4° or more) and is often asymmetric. Physiologic end-point nystagmus is not a type of GEN but a nystagmus that may be inconsistent and that is seen in most normal individuals, some when attempting to fixate an eccentric target of only 20°¹³² or even 10°.¹³³ The jerk phase may occur for a few beats, and then the integrators will hold and the nystagmus will disappear. Physiologic EPN has been found to occur in up to 60% of individuals and is maximally deviated after 30 seconds of eccentric gaze

holding (or attempted holding).¹³⁴ Included in the causes of GEN are medications and brainstem or cerebellar disorders. Brainstem and cerebellar lesions also cause pathological rebound nystagmus. After holding eccentric gaze between 30° and 45° from primary gaze for more than 30 seconds, a patient is directed to look straight (assume primary gaze). If an abnormal amount of rebound nystagmus is present (more than three beats of nystagmus), with the jerk directed away from the prolonged eccentric gaze, it is rebound nystagmus. Because the neural integrator is found in the brainstem, tumors that favor this area should be suspected when GEN is found.

5.2.2.2 GAZE INSTABILITY (“RUNAWAY”)

This is usually an acquired oscillation in which the slow phases are directed centrifugally (away from) primary position. There are often associated neurologic signs and symptoms. The nystagmus usually has an acute onset and is associated with other signs of vestibulocerebellar involvement. The nystagmus slow phases carry the eyes away from a fixing position and the slow phases show an accelerating velocity.¹³⁵ This is different from the accelerating slow phases of INS where they are directed back to the null position (see Chapter 2, Section 2.1.2.6, discussion of the neural integrator). The oscillation may have a vertical or horizontal or horizontal component. An MRI/CT scan of brain often reflects underlying diseases and eye-movement recordings show slow phases that are accelerating.¹²⁶ CNS pathology is almost always present.

Arnold et al. reported the effects on gaze stability of microinjections of eight different drugs into the NPH-MVN of monkeys.¹³⁶ Agents with either agonist or antagonist actions at GABA, glutamate, and kainate receptors all caused gaze-evoked nystagmus, while agents acting at the glycine receptor (glycine and strychnine) had no effect. In contrast, when muscimol was injected near the center of the MVN, the eyes sometimes drifted away from the central position with increasing velocity waveforms. Clinically, patients who show nystagmus with

increasing velocity waveforms have cerebellar, not brainstem, lesions.

5.2.3 “Vision-Loss” Nystagmus

Nystagmus may occur in complete blindness and may also accompany incomplete visual impairment due to lesions anywhere along the visual pathways. Visual loss may facilitate nystagmus in two ways—through loss of visual inputs to the fixation system that are used to detect and immediately correct ocular drift and through loss of visual signals that are used, over the long term, to calibrate the ocular motor systems.^{70,137}

The first of these components may be regarded as “visual fixation,” and it is easily demonstrated when a normal subject attempts to fixate on the remembered location of an eccentric target after the room is switched to darkness: the eye drifts centripetally off target several times faster than when the subject was actually viewing it. The visual fixation mechanism by which smooth eye movements correct for drifts of gaze depends on the motion vision system (especially portions of the cerebral cortex, such as the middle temporal area or VS). Although such visually mediated eye movements are important for maintaining steady fixation, they have one important limitation, a response time of longer than 70 milliseconds. If this response time is delayed further by disease of the visual system, then the brain’s attempts at correcting eye drifts might actually add to the retinal error rather than reducing it, leading to ocular oscillations. This type of nystagmus is similar to normal physiological “end-point” nystagmus.

The second component of the visual influence on gaze control concerns the need for continuous calibration and optimizing all types of eye movements.^{70,137} This optimization depends heavily on visual projections to the cerebellum. The cerebellum receives visual signals from motion vision areas of the cerebral cortex via the pontine nuclei. In addition, visual signals for calibration probably also pass to the cerebellum via the inferior olive nucleus on climbing fibers. Calibration of the ocular motor system requires that visual signals be compared with eye-movement commands (efference copy), and the latter probably reach the cerebellum from the cell

groups of the paramedian tracts, which lie diffusely throughout the midline of the brainstem and receive input from all premotor structures that project to ocular motor neurons. Lesions at any part of this visual motor calibration pathway deprive the brain of signals that are essential for fixation, resulting in drifts of the eyes away from the target, leading to nystagmus. This type of nystagmus is similar to that produced by a tonic imbalance from the visual vestibular system.

Thus, “vision-loss” nystagmus is not a specific type of nystagmus but rather nystagmus due to ocular motor system drifts and imbalances that may become manifest when the stabilizing effects of vision are absent.

5.2.3.1 PRECHIASMAL, OPTIC CHIASM, AND POSTCHIASMAL VISION LOSS

These ocular oscillations occur with loss of vision after early infancy (~6–9 months) and have associated afferent visual system eye and/or brain disease. Acquired prechiasmal bilateral visual loss in children causes continuous jerk nystagmus, with horizontal, vertical, and torsional components, and a drifting “null” position. Monocular visual loss causes slow vertical oscillations and low-amplitude horizontal, mainly pendular, nystagmus predominantly in the blind eye.²⁰ Lesions at the optic chiasm can result in SSN with bitemporal visual field loss. Postchiasmal vision loss results in low-amplitude horizontal nystagmus beating toward the side of the lesion.

5.2.4 Other Pendular Nystagmus Associated with Diseases of Central Myelin

Acquired pendular nystagmus usually has horizontal, vertical, and torsional components with the same frequency, although one component may predominate.^{126,137} If the horizontal and vertical oscillatory components are in phase, the trajectory of the nystagmus is diagonal (oblique). If the horizontal and vertical oscillatory components are out of phase, the trajectory is elliptical. A special case is a phase difference of 90° and equal amplitude of

the horizontal and vertical components, when the trajectory is circular. When the oscillations of each eye are compared, the nystagmus may be conjugate, but often the trajectories are dissimilar, and the size of oscillations is different (sometimes appearing monocular), and there may be an asynchrony of timing (phase shift). The latter may reach 180°, in which case the oscillations are again diagonal. The temporal waveform usually approximates a sine wave, but more complex oscillations have been noted. The frequency of oscillations ranges from 1 to 8 Hz, with a typical value of 3.5 Hz. For any particular patient, the frequency tends to remain fairly constant; only rarely is the frequency of oscillations different in the two eyes. In some patients, the nystagmus stops momentarily after a saccade. This phenomenon is called postsaccadic suppression. A more common feature is that the oscillations are “reset” or phase-shifted by saccades. Acquired pendular nystagmus may be suppressed or brought out by eyelid closure or evoked by convergence. In some patients with this condition, smooth pursuit may be intact. Acquired pendular nystagmus is a common feature of acquired and congenital disorders of central myelin, such as multiple sclerosis, toluene abuse, Pelizaeus-Merzbacher disease, and peroxisomal disorders. The observation that acquired pendular nystagmus is “reset” or phase-shifted after saccades (more so with large saccades) suggested that the oscillations arise in the brainstem-cerebellar gaze-holding network (the neural integrator for eye movements). This form of nystagmus also occurs with the syndrome of oculopalatal tremor and Whipple disease of the CNS.

5.2.4.1 OCULOPALATAL TREMOR OR “MYOCLONUS”

Acquired pendular nystagmus may be one component of the syndrome of oculopalatal (pharyngo-laryngo-diaphragmatic) myoclonus.^{138–140} This condition usually develops several months after brainstem or cerebellar infarction, although it may not be recognized until years later. Oculopalatal myoclonus also occurs with

degenerative conditions. The term “myoclonus” is misleading, since the movements of affected muscles are approximately synchronized, typically at a rate of about two cycles per second. The palatal movements may be termed “tremor,” rather than myoclonus, and the eye movements are really a form of pendular nystagmus. Although the palate is most often affected, movements of the eyes, facial muscles, pharynx, tongue, larynx, diaphragm, mouth of the eustachian tube, neck, trunk, and extremities may occur. The ocular movements typically consist of oscillations less sinusoidal than with typical multiple sclerosis, and often with a large vertical component, although they may also have small horizontal or torsional components. The movements may be somewhat dysconjugate (both horizontally and vertically), with some orbital position dependency. Some patients show cyclovergence (torsional vergence) oscillations.

Occasionally, patients develop the eye oscillations without movements of the palate, especially following brainstem infarction. Eyelid closure may bring out the vertical ocular oscillations. The nystagmus sometimes disappears with sleep, but the palatal movements usually persist. The condition is usually intractable, and spontaneous remission is uncommon. The main pathologic finding with palatal myoclonus is hypertrophy of the inferior olive nucleus, which may be seen during life using MRI.¹³⁹ There may also be destruction of the contralateral dentate nucleus. Histologically, the olivary nucleus has enlarged, vacuolated neurons with enlarged astrocytes. Guillain and Mollaret proposed that disruption of connections between the dentate nucleus and the contralateral inferior olive nucleus, which run via the red nucleus and central tegmental tract, are responsible for the syndrome.^{141,142} However, neither the dentate nucleus nor the red nucleus has been shown to have a specific role in ocular motor control. Thus, it has thus been postulated that the nystagmus results from instability in the projection from the inferior olive to the cerebellar flocculus, a structure thought to be important in the adaptive control of the VOR. It is also possible that disruption of

projections from the cell groups of the paramedian tracts to the cerebellum leads to the ocular oscillations.

5.2.4.2 PENDULAR VERGENCE NYSTAGMUS ASSOCIATED WITH WHIPPLE DISEASE

Vergence nystagmus has also been called “convergent-divergent” nystagmus, but that redundant term is needlessly convoluted (e.g., horizontal is not called “leftward-rightward” nor is vertical called “upward-downward” nystagmus). This ocular oscillation occurs with the gastrointestinal disease “Whipple;” thus, patients have associated signs and symptoms of gastrointestinal illness with neurological involvement.^{143,144} These dysconjugate, vergence, pendular oscillations are often small in amplitude and thus easily overlooked by clinicians. More widespread use of the magnetic search coil technique has made it easier to identify the vergence components of this form of nystagmus. Averbuch-Heller et al. reported three patients with pendular oscillations that were about 180° out of phase in the horizontal and torsional planes but had conjugate vertical components.¹⁴⁵ In one of these patients, the torsional component of the oscillations had the largest amplitude. Thus, the patient actually had a cyclovergence nystagmus. Vergence, pendular oscillations also occur in patients with multiple sclerosis and brainstem stroke. In Whipple disease, the oscillations typically have a frequency of about 1.0 Hz and are accompanied by concurrent contractions of the masticatory muscles, a phenomenon called oculomasticatory myorhythmia. Supranuclear paralysis of vertical gaze also occurs in this setting and is similar to that encountered in progressive supranuclear palsy. At least two possible explanations have been offered to account for the vergence nature of these pendular oscillations: a phase shift between the eyes, produced by dysfunction in the normal yoking mechanisms, or an oscillation affecting the vergence system itself. Patients who have been studied show no phase shift (i.e., are conjugate) vertically. Under experimental conditions, the vergence system

can be made to oscillate at frequencies up to 2.5 Hz—lower than that reported in patients with conditions other than Whipple disease. To account for these higher frequency oscillations, it seems necessary to postulate instability within the brainstem-cerebellar connections of the vergence system, for example, between the nucleus reticularis tegmenti pontis and cerebellar nucleus interpositus, which may help hold vergence angle steady.

5.2.5 Convergence/Convergence-Evoked Nystagmus

The act of convergence usually damps INS (see Chapter 2, Section 2.1.6). Convergence can also damp¹⁴⁶ or evoke¹⁴⁷ lid nystagmus and may damp or enhance downbeat nystagmus.¹⁴⁸ Upbeat nystagmus may change to downbeat with convergence.¹⁴⁹ A slow divergence movement followed by a rapid convergence to the primary position is called “repetitive divergence.” It occurs at irregular intervals, distinguishing this from nystagmus.¹⁵⁰ The only reported instance of this phenomenon was in a patient with hepatic encephalopathy; an entire cycle lasted from 4 to 10 seconds, and the interval between cycles was 1 to 15 seconds.

Conjugate nystagmus evoked by convergence (convergence-evoked nystagmus) is not the same as “convergence nystagmus” (a vergence nystagmus) and convergence-retraction “nystagmus” (a saccadic oscillation discussed in Section 5.3.6). The latter is a manifestation of the dorsal midbrain syndrome; because the initiating convergence movements are saccadic,¹⁵¹ it is not a true nystagmus. Fast divergent movements, followed by a slow convergence, associated with epileptic electroencephalographic activity, occurred in a neonate with an intraventricular hemorrhage.¹⁵² Vergence nystagmus must also be distinguished from psychogenic flutter (the so-called voluntary “nystagmus” discussed in Section 5.3.14), which is often best induced when the eyes are slightly converged. With the exception of pure convergence nystagmus in infants with SNS, true pendular convergence nystagmus is rare but does occur most commonly in Whipple

disease. Three patients with convergence nystagmus with phase shifts of about 180° in both the horizontal and torsional planes with conjugate nystagmus in the vertical plane were studied.¹⁵³ Convergence increased the nystagmus in two of the patients. The waveforms were either sinusoidal or complex sums of sinusoids, and in one patient they were cycloidal. There were no initiating saccades to these cycloidal movements, unlike the pseudocycloid waveform of INS. A visually mediated vergence instability was hypothesized to induce low-frequency vergence nystagmus, whereas instability of brainstem pathways associated with vergence might have induced high-frequency forms. Backward and forward motion in the ground plane can also induce vergence nystagmus in normals.¹⁵⁴

Nystagmus evoked by convergence is unusual and may be either conjugate or disjunctive, congenital or acquired.¹⁵⁵ No definite clinical correlation could be made with a specific lesion in the two cases reported. The neuropathologic examination revealed no morphologic explanation for nystagmus in the patient with congenital convergence-evoked nystagmus; the patient with the acquired form had demyelinating disease with a spastic paraparesis and no cranial nerve abnormality other than the ocular motor findings. Horizontal pendular nystagmus rarely is evoked by accommodative vergence.¹⁵⁶

5.2.6 Upbeat Nystagmus

Upbeat nystagmus that is present with the eyes close to central position occurs in many clinical conditions.^{157,158} Nystagmus intensity is usually greatest in upgaze, and it usually does not increase on right or left gaze. Removal of visual fixation has little influence on slow-phase velocity. Convergence is variously reported to enhance, suppress, or convert upbeat nystagmus to downbeat. Placing the patient in a head-hanging position increases the nystagmus in some individuals. As is the case with downbeat nystagmus, patients with upbeat nystagmus often show asymmetries of vertical vestibular and smooth-pursuit eye movements, as well as associated cerebellar eye-movement findings. Upbeat nystagmus is present with the eyes close

to the central position and usually increases on upgaze. Causes of upbeat nystagmus are lesions in the ascending pathways from the anterior canals (and/or the otoliths) at the pontomesencephalic or pontomedullary junction, near the perihypoglossal nuclei, most often seen after medullary lesions. The main causes are multiple sclerosis, tumors of the brainstem, Wernicke's encephalopathy, cerebellar degeneration, and intoxication (e.g., nicotine).

5.2.7 Downbeat Nystagmus

Downbeat nystagmus occurs in a variety of disorders, but it is most commonly associated with disease affecting the cerebellum, the craniocervical junction, or the blood vessels in these regions.^{126,158,159} It may also be a manifestation of drug intoxication, especially lithium. Downbeat nystagmus is usually present with the eyes in central position, but its amplitude may be so small that it can only be detected by viewing the ocular fundus with an ophthalmoscope. The nystagmus intensity is greatest in downgaze and down and lateral gaze and least in upgaze. Usually the waveform is linear. Downbeat nystagmus may also be evoked by placing the patient in a head-hanging position. Some normal subjects may show "chin-beating" nystagmus when they are placed upside down in darkness (or wear Frenzel goggles). Convergence may influence the amplitude and frequency of the nystagmus or convert it to upbeat nystagmus. Some patients show combined divergent and downbeat nystagmus. In most patients, removal of fixation (e.g., with Frenzel goggles) does not substantially influence slow-phase velocity, although the frequency of quick phases may diminish. A variety of ocular motor abnormalities often accompany downbeat nystagmus and reflect coincident cerebellar involvement.¹⁶⁰ Vertical smooth pursuit and the vertical VOR are abnormal because of impaired ability to generate smooth downward eye movements. Sometimes, the VOR for upward eye movements has a gain exceeding 1.0. Impairment of eccentric horizontal gaze holding, smooth pursuit, and combined eye-head tracking are coincident findings. Vertical

diplopia usually reflects associated skew deviation.¹⁶¹ The visual consequences of downbeat nystagmus are oscillopsia and postural instability. Visual fixation has little effect on its slow-phase speed; convergence may suppress or enhance it in some patients. In general, the nystagmus is accompanied by a vestibulocerebellar ataxia. The pathophysiological mechanism of downbeat nystagmus appears to be due to a central imbalance of the vertical VOR to an abnormality of the vertical-torsional gaze-holding mechanism (neural integrator). The most common cause of downbeat nystagmus is cerebellar degeneration (hereditary, sporadic, or paraneoplastic). Other important causes are Chiari malformation, multiple sclerosis, and a rare congenital form. In practice cerebellar atrophy, Arnold–Chiari malformation, various cerebellar lesions (multiple sclerosis, vascular, tumors), and idiopathic causes account for approximately one-fourth of the cases each. Downbeat nystagmus occurs in the channelopathy episodic ataxia type 2.¹⁶²

5.2.8 Torsional Nystagmus

Torsional nystagmus is a less commonly recognized form of central vestibular nystagmus than downbeat or upbeat nystagmus.¹⁶³ To retain consistency with other forms of nystagmus, the clockwise and counterclockwise torsional directions are based on the patient's point of view. Thus, clockwise torsional movement describes motion of the top of the eyeball toward the patient's right shoulder. It is often difficult to detect except by eye-movement recordings, careful observation of conjunctival vessels, or by noting the direction of retinal movement on either side of the fovea using an ophthalmoscope or contact lens. Although both peripheral vestibular and INS may have torsional components, purely torsional nystagmus, like purely vertical nystagmus, indicates disease affecting central vestibular connections. Torsional nystagmus shares many of the features of downbeat and upbeat nystagmus, including modulation by head rotations, variable slow-phase waveforms, and suppression by convergence. Nonrhythmic but continuous

torsional eye movements may be a feature of paraneoplastic encephalopathy.¹⁶⁴

5.2.9 “Seesaw” Nystagmus

In pendular and jerk seesaw nystagmus (SSN), one half-cycle consists of elevation and intorsion of one eye and synchronous depression and extorsion of the other eye; during the next half-cycle, the vertical and torsional movements reverse.^{165,166} The waveform may be pendular or jerk. In the latter case, the slow phase corresponds to one half-cycle. A seesaw component is present in many central forms of nystagmus. Seesaw nystagmus may be congenital or acquired.^{167–169} Quantitative studies have done much to clarify the characteristics and pathogenesis of SSN. It has been proposed that jerk SSN (hemi-SSN) occurs in patients with lesions in the region of the interstitial nucleus of Cajal (INC), although experimental inactivation of this structure has not produced this nystagmus. With a right INC lesion, the reaction consists of a left head tilt, a skew deviation with a right hypertropia, tonic intorsion of the right eye and extorsion of the left eye, and misperception that earth-vertical is tilted to the left. Isolated INC lesions may be characterized by ipsilesional torsional nystagmus and a restricted range of vertical saccades that are not slowed. Pendular SSN has most often been reported in patients with large tumors in the region of the optic chiasm and diencephalon; thus, these oscillations have been attributed to either compression of the diencephalon or to the effects of chiasmal visual field defects. Both the jerk and pendular variants of SSN probably arise from imbalance or miscalibration of vestibular responses that normally function to optimize gaze during head rotations in roll.

The frequency is lower in pendular (2–4 Hz) than in jerk SSN.¹⁷⁰ The latter has been attributed to unilateral meso-diencephalic lesions, affecting the interstitial nucleus of Cajal and its vestibular afferents from the vertical semicircular canals. The term “hemi seesaw” has been used to describe jerk SSN; it is neither accurate (a full cycle of jerk SSN is the same as for the pendular variety) nor descriptive (hemi seesaw motion would stop after one-half cycle). The pendular

form is associated with lesions affecting the optic chiasm. Loss of crossed visual input seems to be the crucial element in the pathophysiology of pendular SSN.

In the early 1990s a remarkable new visual system abnormality (canine “achiasma”) was first described by Williams et al. in a group of Belgian sheepdogs in whom optic nerve fibers fail to cross at the optic chiasm and who manifested SSN.^{26,169,171,172} Williams et al. reported that the optic nerves, in seven of eight dogs studied, did not approach each other to form a chiasm. Achiasma or “nondecussating retinal fugal fiber syndrome” was subsequently recognized in two children who presented with poor distant vision.¹⁷³ They had asymmetries in the distribution of the monocular, pattern-onset, visually evoked potential (VEP) and SSN, similar to that seen in the achiasmatic dogs; the latter was recognized by Dell’Osso in 1993 from a video of one of these achiasmatic children¹⁷⁴ (see Appendix F, Section F1.4). These findings suggested a chiasmal anomaly that subsequent MRI scans confirmed. Hertle et al. reported and reviewed a total of 11 cases and found that in all a “crossed asymmetry” (right cortex receives the right eye’s visually evoked response and the left cortex receives the left eye’s visually evoked response) in the monocular VEP occipital distribution existed; this is consistent with a paucity of fibers crossing at the chiasm.¹⁷⁵ Experimental analysis of the achiasmatic mutant Belgian sheepdogs demonstrated that the entire nasal hemiretina with its misdirected ipsilateral projection made functional connections in the thalamus and in the ipsilateral primary visual cortex.^{169,172} A critical finding was that input from nasal and temporal sides of the same retina was integrated at the cortical level. Adjacent neurons often responded to visual stimuli that were far apart—often on opposite sides of the vertical meridian. Given this radical misarrangement of maps of visual space, it is not surprising that the ocular motor system of these achiasmatic dogs did not develop normally.

The syndrome is associated with INS, SSN, and strabismus. This condition is a developmental anomaly of the midline CNS that may or may not have other systemic findings, for example,

craniofacial or heart. In children this condition presents in early infancy or childhood with decreased visual behavior, nystagmus, and strabismus (a fairly common combination of clinical characteristics). The outstanding clinical sign is the presence of SSN in addition to the more typical oscillation of INS.^{169,175} There are findings of optic pathway (nerve/disc) anomalies (hypoplasia, dysplasia, and coloboma) in all patients seen clearly with three-dimensional volumetric MRI acquisition. Other systemic or CNS signs or symptoms can be present. Due to this we recommend that these patients be followed for signs of central pituitary dysfunction. The presence of the triad of SSN/ISN, strabismus, and optic disc anomalies should prompt the clinician to conduct further electrophysiologic and/or radiographic investigations in search of structural abnormalities of the optic chiasm.

5.2.10 Lid Nystagmus

Upward movements of the eyelids frequently accompany upward movements of vertical nystagmus. In fact, the absence of lid nystagmus in a patient with upbeat nystagmus may suggest disconnection between the premotor signals for the superior rectus and levator palpebrae superioris, implicating the region between the riMLF and the oculomotor nucleus.^{176,177} For the same reasons, lid nystagmus unaccompanied by vertical eye nystagmus may reflect midbrain lesions. In patients with long-standing compression of the central caudal nucleus, “midbrain ptosis” may occur and this may lead to lid nystagmus. Occasionally, twitches of the eyelid accompany horizontal nystagmus. In other patients, eyelid nystagmus may be induced by convergence. This is called Pick’s sign.¹⁷⁶ In both cases, lesions are often present in the medulla, cerebellum, or both structures. Eyelid nystagmus has been likened to the pathologic form of gaze-evoked nystagmus that occurs in patients with cerebellar disease and that is often associated with downward drifts of the eyelids, followed by corrective rapid upward movements. Eyelid nystagmus can be classified into three types.¹⁷⁸ The most common is associated with vertical ocular nystagmus with the

lid movement being synchronous with the eyes, but with greater amplitude. The second type is associated with gaze-evoked horizontal nystagmus and may occur in the lateral medullary syndrome, and the third is Pick's sign.

5.3 SACCADIC INTRUSIONS/OSCILLATIONS

In addition to benign and symptomatic types of nystagmus in infancy, there are also other

types of ocular motor instabilities that may appear in infancy as well as adulthood. They take the form of either saccadic intrusions or saccadic oscillations. There is a large literature on the many types of saccadic intrusions and oscillations listed in Table 5.6 that have been reviewed elsewhere.^{2–7} Several types of inappropriate saccadic eye movements may intrude upon steady fixation (see Fig. 5.10). Saccadic intrusions must be differentiated from nystagmus, in which a drift of the eyes from the

Table 5.6 Saccadic Intrusions and Oscillations

Bobbing/dipping	Saccadic lateropulsion
Inverse bobbing	Ipsipulsion
Reverse bobbing	Contrapulsion
Convergence-retraction "nystagmus"	Saccadic pulses/pulse trains
"Nystagmus" retractoris	Abduction "nystagmus"
Double saccadic pulses (single/multiple)	Ataxic "nystagmus"
Saccadic intrusions/oscillations	Saccadic intrusions/oscillations
Dynamic overshoot	Stepless saccades
"Quiver"	Square-wave jerks/oscillations
Dysmetria	Gegenrucke
Flutter	Hopping "nystagmus"
Flutter dysmetria	"Lightening eye movements"
Macrosaccadic oscillations	Myoclonus
Myoclonus	Saccadic intrusions/oscillations
Laryngeal "nystagmus"	Zickzakbewegungen
"Lightning eye movements"	Square-wave pulses (bursts/single)
Pharyngeal "nystagmus"	"Macro square-wave jerks"
Opsoclonus	Kippdeviationen/ "Kippnystagmus"
"Dancing eyes"	"Pendular macro-oscillations"
"Lightning eye movements"	Saccadic "nystagmus"
Saccadomania	Saccadic oscillations/intrusions
Psychogenic flutter	Staircase saccadic intrusions
Hysterical flutter	Superior oblique myokymia
Hysterical "nystagmus"	
>Ocular fibrillation"	
>Ocular shuddering"	
Psychological "nystagmus"	
Voluntary flutter	
Voluntary "nystagmus"	

Synonyms and other terms are indented under either the preferred or the more inclusive designation; quoted terms are erroneous or misleading.

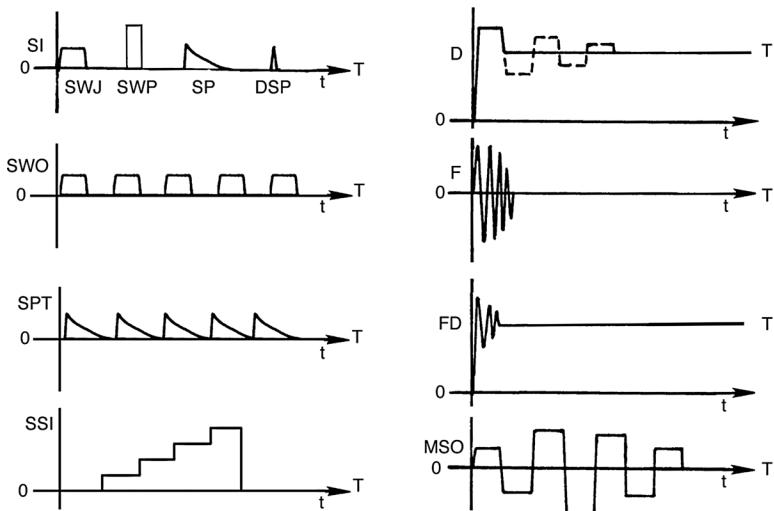


FIGURE 5.10 Diagrammatic representation of ocular motility recordings of major types of saccadic disorders. 0, point of origin of eye; D, dysmetria; DSP, double saccadic pulses; F, flutter; FD, flutter dysmetria; MSO, macrosaccadic oscillations; SP, saccadic pulses; SPT, saccadic pulse trains; SSI, staircase saccadic intrusions; SWJ, square-wave jerks; SWO, square-wave oscillations; SWP, square-wave pulses; T, target; t, time axis.

desired position of gaze is the primary abnormality, and from saccadic dysmetria, in which the eye over- or undershoots a target, sometimes several times, before achieving stable fixation. Because all of these movements are often rapid and brief, it may be necessary to measure eye and target position, as well as eye velocity, in order to identify the saccadic abnormality accurately.

The saccadic command is generated by burst neurons of the brainstem reticular formation that project monosynaptically to ocular motoneurons.^{179–181} The burst neurons for horizontal saccades are located in the PPRF, and the burst neurons for vertical and torsional saccades are located in the riMLF. Burst neurons discharge only during saccadic eye movements. The activity of all saccadic burst neurons is gated by omnipause neurons, which are crucial for suppressing unwanted saccades during fixation and slow eye movements. The omnipause neurons are located in the caudal pons within the raphe interpositus nucleus (RIP), adjacent to the abducens nucleus. Inputs into omnipause neurons arise in the superior colliculus,

frontal eye fields, and mesencephalic reticular formation.

5.3.1 Square-Wave Jerks and Oscillations

Square-wave jerks (SWJ, also called Gegenrucke) are a common finding in healthy persons. They have a typical profile on eye-movement records, and it is this profile from which their name is derived.^{182–184} As illustrated in Figure 5.10, they are small, conjugate saccadic intrusions, ranging from 0.5 to 5.0° in size, that take the eye away from the fixation position and return it after about 200 milliseconds. They are often more prominent during smooth pursuit, are most easily detected during ophthalmoscopy, and are also present in darkness. SWJ with an increased frequency (up to 2 Hz) occur in certain cerebellar syndromes, in progressive supranuclear palsy, and in cerebral hemispheric disease. The characteristics of SWJ are summarized in Table 5.7.

Although present in many normals, when they are prominent during fixation, they should

Table 5.7 Characteristics of Saccadic Instabilities

	SQUARE-WAVE JERKS	SQUARE-WAVE OSCILLATIONS	SQUARE-WAVE PULSES*	MACROSACCADIC OSCILLATIONS
Amplitude	0.5°–5° ¹	0.5°–5° ¹	4°–30°	1°–30°
	Constant	Constant	Variable	Increasing then decreasing
Time course	Sporadic/bursts	Bursts	Bursts/sporadic	Bursts
Latency	200 msec	200 msec	50–150 msec	200 msec
Foveation	Yes	Yes	Yes	No
Presence in darkness	Yes	Yes	Yes	No

*Previously designated macro square-wave jerks.

¹Occasionally up to 10°.

be considered abnormal, although lacking diagnostic specificity, much like saccadic pursuit. SWJ are a subtle disturbance that is easily missed clinically. However, they are obvious with eye-movement recordings, which also allow other types of saccadic intrusions to be identified.¹⁸⁵ Because the individual saccades in SWJ are usually small, they may contain dynamic overshoots. Clinically, they are often best identified during slit-lamp biomicroscopy or funduscopy, but they may be difficult to distinguish from other intrusions (e.g., square-wave pulses). As was pointed out in earlier chapters, SWJ may also appear in individuals with nystagmus (benign or symptomatic); they are merely superimposed on the nystagmus and do not represent a different type of nystagmus.

SWJ is significantly more common in the elderly population than in young subjects. Their appearance at a rate greater than 9/minute in young patients is considered abnormal. SWJ frequency in normals is approximately 7/min and they were unidirectional in 94% of the subjects.¹⁸⁶ Other types of saccadic intrusions were also found in this study: saccadic pulses and double saccadic pulses (see later) were found in 22% and 68% of the subjects, respectively. The effect of age on the prevalence of SWJ is unclear as that study did not find an age factor. However, a subsequent study did find an increase with age.¹⁸⁷

SWJ are also found in 70% of patients with acute or chronic focal cerebral lesions and are the rule in progressive supranuclear palsy and Parkinson disease. Schizophrenic patients and their parents¹⁸⁸ exhibit SWJ, which are also present during smooth pursuit and have been mistaken for a deficit in the pursuit system. The frequency and metrics of SWJ are influenced by the task being performed.¹⁸⁹ A post-flight increase in SWJ in an astronaut may have been responsible for his increased postflight dynamic visual function.¹⁹⁰ The mechanism of SWJ may be linked to attention and its effect on the balance between fixation and saccade generation¹⁹¹; endogenous rather than exogenous attention was the major factor.¹⁹² SWJ correlated with the velocities of steady drifts were found in albinos without INS, suggesting that both might be related to a failure in saccadic system development.¹⁹³

When SWJ form a continuous train, they are called square-wave oscillations (SWO). These continuously occurring SWJ have been recorded in patients with a variety of neurologic deficits (see Fig. 5.10). The characteristics of SWO are identical to those of SWJ (see Table 5.7). In a patient with progressive supranuclear palsy, SWO appeared to be part of a continuum with SWJ; at times, single or several SWJ occurred, and at other times there were long runs of SWJ that were identified as SWO.¹⁹⁴

During steady fixation, the threshold for electrical stimulation of saccades in either the frontal eye fields or the superior colliculus is elevated, mediated through the projections of these structures to the omnipause neurons.¹⁹⁵ In the rostral superior colliculus, a distinct population of “fixation neurons” has been identified and in the frontal eye fields, neurons active during suppression of saccades have been identified. Pharmacologic inactivation at both sites leads to disruption of fixation by these saccadic intrusions, but not by flutter or opsoclonus. Impairment of any projections to the omnipause neurons can lead to saccadic intrusions.

Mechanistically, SWJ and SWO are hypothesized to occur when there is dysfunction in the internal reconstruction of target position, as shown in Figure 5.11. When this hypothesis was incorporated into our behavioral ocular motor system model, SWJ were generated, as demonstrated in Figure 5.12, top left and top right panels.

5.3.2 Square-Wave Pulses

Square-wave pulses (SWP), originally given the misleading name “macro square-wave jerks,” are usually larger in amplitude than SWJ (typically greater than 5°), are related to fixation, and have a frequency of about 2 Hz.^{182,183,196,197} They generally occur in bursts but may appear as a single saccadic intrusion. Both eyes suddenly and conjugately move off target with a saccade, and after a latent period of only about 80 milliseconds, a non-visually evoked reflex saccade brings them back on target (see Fig. 5.10). SWP are not merely large SWJ; the characteristics of both are summarized in Table 5.7. These saccadic intrusions occur in light or darkness. SWP usually occur in patients with marked extremity ataxia suggestive of cerebellar outflow disease, especially when the patient has demyelinating lesions.¹⁹⁶ A unique variety of SWP, present with binocular fixation at distance but stopping when either eye was closed, prompted the designation “inverse latent SWP.”¹⁹⁸

The underlying mechanism for SWP was hypothesized to rely on efference copy of the motor output signal that could program the short-latency return saccade in response to

the initial spurious saccade that initially drove the eyes off target.¹⁹⁶

5.3.3 Staircase Saccadic Intrusions

We identified a unique type of saccadic intrusion in a patient with cerebellar atrophy, named “staircase saccadic intrusions” (SSI) because of its appearance in eye-movement recordings.¹⁹⁹ Fixation would be interrupted by a series of saccades in one direction or the other with normal intersaccadic intervals (see Fig. 5.10). The individual saccades could be of equal amplitude or could vary. Staircase saccadic intrusions were also present during smooth pursuit. In normals, such “staircase” eye movements can be generated by feeding back the eye-movement signal and allowing it to move the target in the same direction. This produces a constant retinal error signal that drives the saccadic system in a staircase manner with normal intersaccadic intervals, as shown in the simulation of Figure 5.12, bottom left panel. We modeled SSI using a behavioral OMS model²⁰⁰ by simultaneously interfering with the retinal error signal and creating a constant reconstructed error signal (see Fig. 5.11); the simulation is shown in Figure 5.12, bottom right panel. The individual hypotheses for SWJ/SWO and SSI embodied in the model were severely tested during simulation of the eye movements of a patient with Joubert syndrome, shown in Figure 5.13, who exhibited SWJ, SWO, and SSI in various mixtures.²⁰¹ By combining our hypothetical mechanisms for each of the simultaneous dysfunctions, the model accurately simulated the mixtures recorded from the patient (see Fig. 5.14), ruled out the loss of efference copy as a cause, and led us to the specific mechanisms for each that are shown in Figure 5.11.

5.3.4 Macrosaccadic Oscillations

Macrosaccadic oscillations (MSO) usually consist of horizontal saccades that occur in bursts, initially building up and then decreasing in amplitude, with intersaccadic intervals of about 200 milliseconds. The characteristics of MSO

OMS Block Diagram: Saccadic/Pursuit Dysfunctions

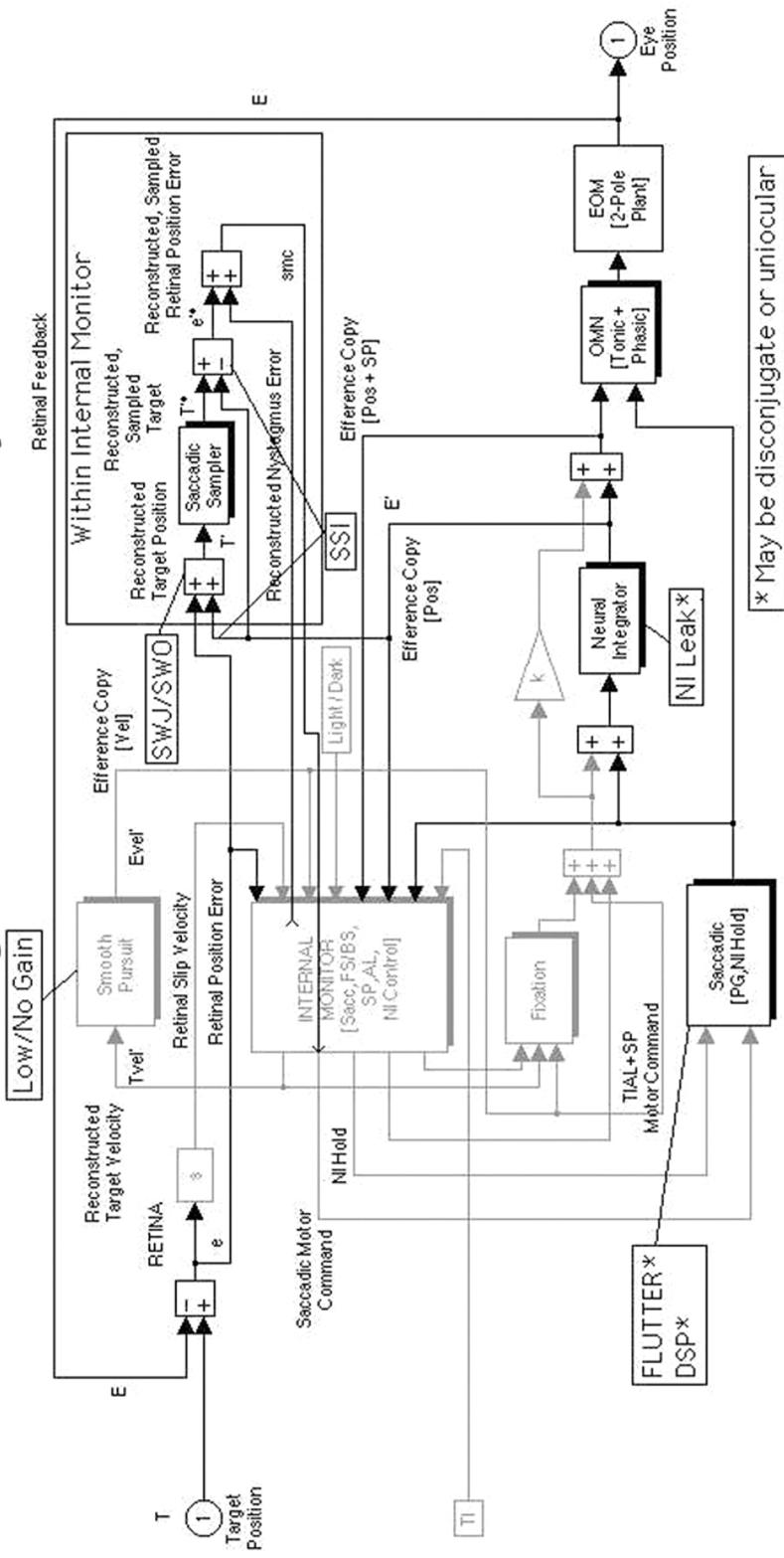


FIGURE E.11 Behavioral ocular motor system (OMS) model with an expanded view (dark lines) of the portion of the relevant functional circuitry within the internal monitor that is responsible for target reconstruction from retina error and efference copy of eye position, reconstructed sampled target position (i.e., perceived target position), reconstruction of retinal position error (sampled), and generation of the saccadic motor command after accounting for internally generated eye movement (e.g., nystagmus). Shown are the mechanistic sites of dysfunction producing square-wave jerks/oscillations (SWJ/SWO), staircase saccadic intrusions (SSI), flutter (FLUT), double saccadic pulses (DSP), neural integrator leak (NI), or low/no-gain smooth pursuit.

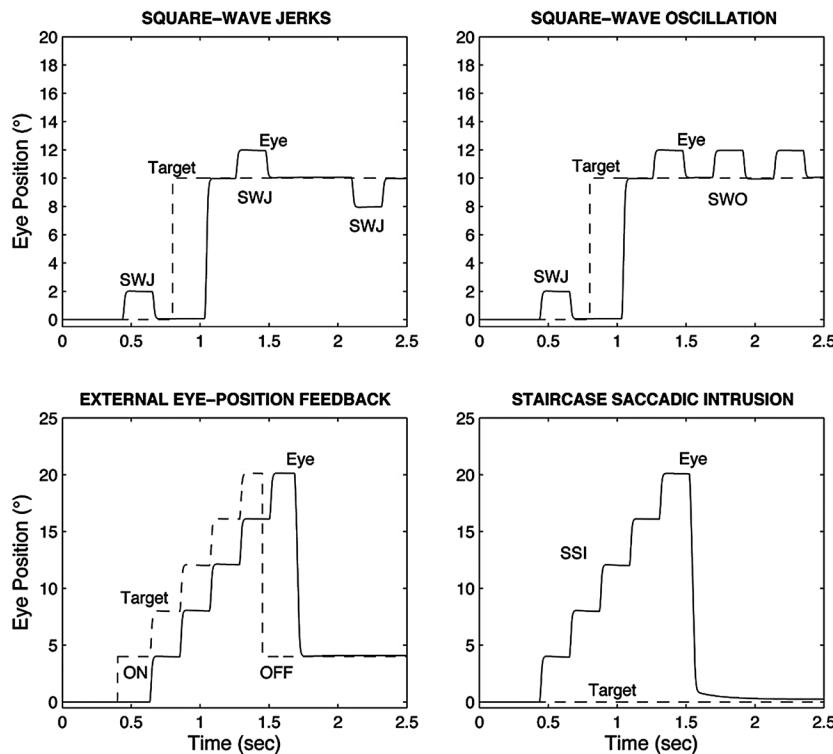


FIGURE 5.12 Behavioral ocular motor system (OMS) model simulations of the individual components of the saccadic intrusions and oscillations found in subjects with cerebellar atrophy or Joubert syndrome. (Top left) Square-wave jerks (SWJ) before and after response to a step change in target position. (Top right) SWJ before and square-wave oscillations (SWO) after response to a step change in target position. (Bottom left) Simulation of a rightward, equal-step staircase saccadic intrusions (SSI) due to opening the retinal loop. (Bottom right) Simulation of a rightward, equal-step SSI during fixation.

are summarized in Table 5.7. Described originally in cerebellar patients, MSO are thought to be an extreme form of saccadic dysmetria, in which the patient's saccades are so hypermetric that they overshoot the target continuously in both directions and thus oscillate around the fixation point.^{182,183,197} They are usually induced by a gaze shift, but they may also occur during attempted fixation or even in darkness. They are often visually disabling and have vertical or torsional components. MSO are occasionally encountered in patients with myasthenia gravis after administration of edrophonium.²⁰²

5.3.5 Saccadic Pulses (Single and Double)

Saccadic pulses (SP), originally called “stepless saccades,” are brief intrusions on fixation caused

by a spurious pulse of innervation, provided by the burst cells without the usual accompanying step. The resultant eye movement consists of a saccade away from the fixation position followed immediately by a glissadic drift back to the target (see Fig. 5.10). The glissadic drift in SP represents failure of the neural integrator to produce a step of innervation from the burst producing the SP. This difference from SWJ suggests dysfunction in the pause cell/burst cell circuitry for SP and a more central dysfunction for SWJ. Saccadic pulses may occur in series or as doublets.^{164,203} They are encountered in some normal subjects and in patients with multiple sclerosis.

Saccadic pulse trains (SPT) are continuous runs of SP and, as Figure 5.10 shows, may be easily confused with nystagmus. Even on good eye-movement records, SPT cannot

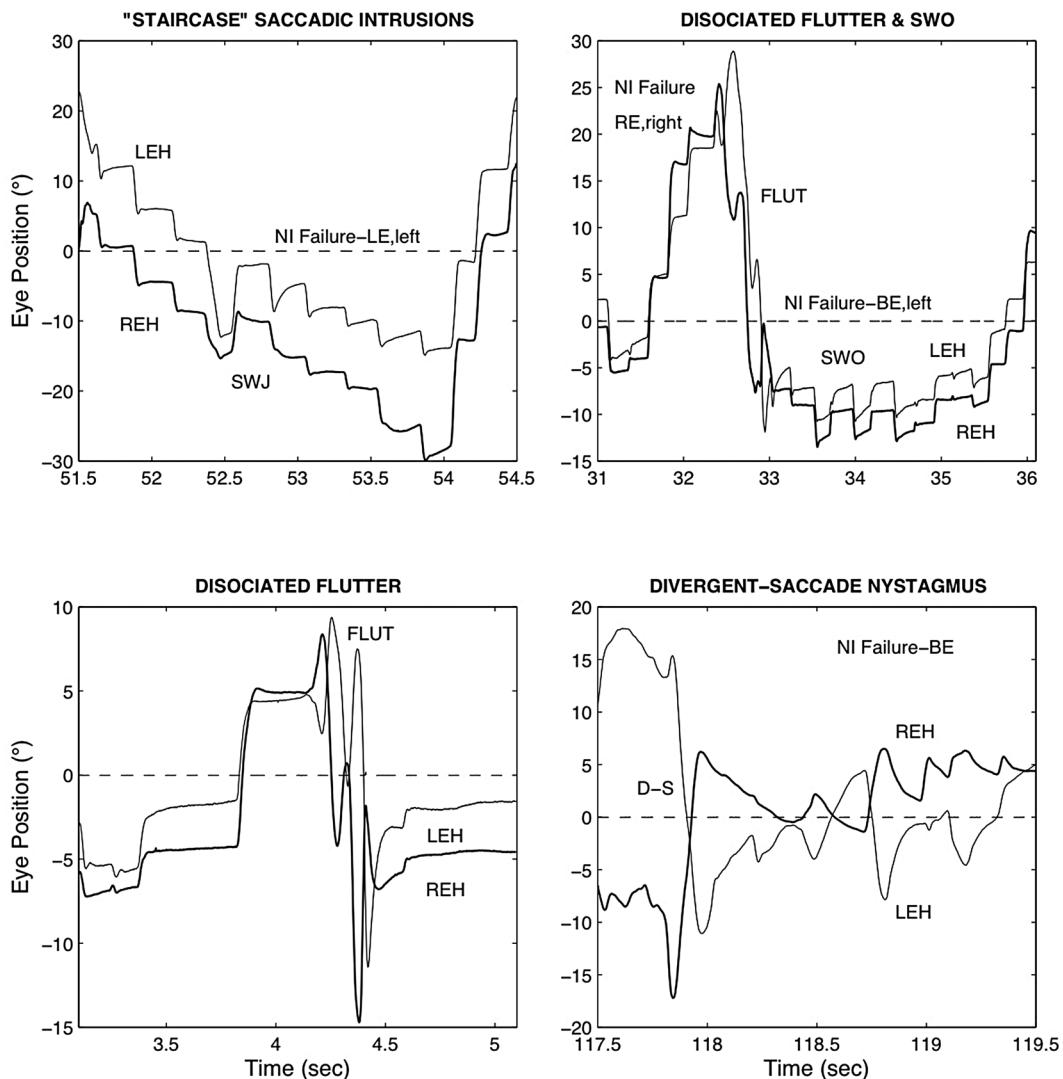


FIGURE 5.13 Examples of the complex ocular motor disorders occurring during attempted fixation of a target in primary position from a subject with Joubert syndrome. (Top left) Leftward, equal-step staircase saccadic intrusions (SSI) including a leftward square-wave jerks (SWJ) and uniocular neural integrator leak of the left eye in left gaze (LE, left). (Top right) Rightward, unequal-step SSI with uniocular neural integrator leak of the right eye in right gaze (RE, right) followed by flutter during the refixation and SWO with neural integrator leak of both eyes in left gaze (BE, left). (Bottom left) Rightward, unequal-step SSI followed by divergent flutter during the refixation. (Bottom right) Divergent-saccade (D-S) followed by D-S nystagmus with neural integrator leak of both eyes. FLUT, flutter; LEH, left eye horizontal (thin trace); REH, right eye horizontal (heavy trace), and both eyes were viewing.

be distinguished from jerk nystagmus with decreasing-velocity slow phases, unless both eye position and target position are known. The initiation of an SP is a saccade off target, whereas jerk nystagmus is initiated by the slow phase off target, with the saccadic

fast phase bringing the eye back to the target. The so-called abduction “nystagmus” of internuclear ophthalmoplegia is an SPT.²⁰⁴ Several patients with congenital achromatopsia thought to have INS did not contain any of the known INS waveforms but instead had

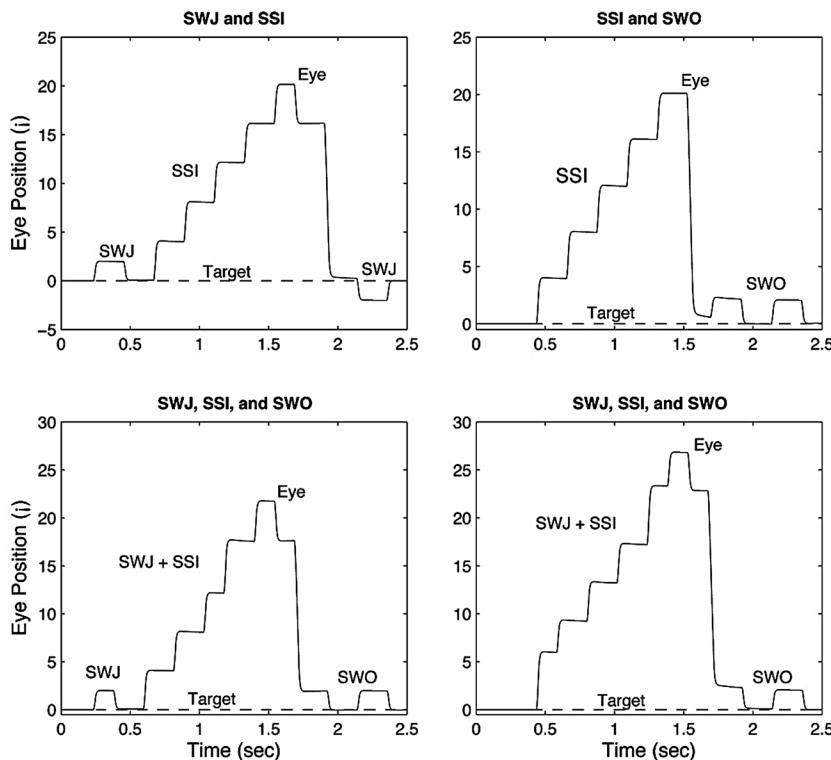


FIGURE 5.14 Behavioral ocular motor system (OMS) model simulations of the complex saccadic intrusions and oscillations found in a subject with Joubert syndrome by different combinations of their individual components. (Top left) Square-wave jerks (SWJ) before and after a rightward, equal-step staircase saccadic intrusions (SSI) and refixation during attempted fixation. (Top right) Square-wave oscillations (SWO) after a rightward, equal-step SSI and refixation during attempted fixation. (Bottom left) Simulation of a rightward, unequal-step SSI during fixation, preceded by a SWJ and followed by a SWO. (Bottom right) Simulation of a rightward, unequal-step SSI during fixation, followed by a SWO.

oscillations consistent with SPT. Although the waveforms mimicked those of FMNS, there were no effects of monocular fixation.

5.3.6 Convergence-Retraction “Nystagmus”

Convergence-retraction “nystagmus” is a misnomer since the abnormality is in the vergence and fast eye movement systems.^{153,205} It is characterized by quick phases that converge or retract the eyes on attempts to look up. It is elicited either by asking the patient to make an upward saccade or by using a handheld optokinetic drum or tape and moving the stripes or figures down. This maneuver produces slow, downward, pursuit eye movements, but upward quick phases are replaced by rapid convergent movements,

retractive movements, or both. Affected patients usually have impaired or absent upward gaze for both pursuit and saccadic eye movements; however, in some cases upward pursuit appears normal, whereas upward saccades are obviously abnormal. Convergence-retraction “nystagmus” is commonly produced by lesions of the mesencephalon that damage the posterior commissure, such as pineal tumors. It is probable that convergence-retraction nystagmus is, in fact, a vergence and saccadic disorder rather than nystagmus because the primary adducting movements are asynchronous adducting saccades and some studies have indicated that the movements may be vergence in origin. Convergence-retraction “nystagmus” may also occur with a Chiari malformation or epileptic seizures.²⁰⁶ It is usually intermittent, being determined by

saccadic activity, and it thus can be differentiated from other more continuous forms of disjunctive nystagmus, such as pendular vergence nystagmus and the oculomasticatory myorhythmia characteristic of Whipple disease. A jerk-waveform divergence nystagmus is rare, but it may occur in patients with cerebellar disease, such as the Chiari malformation. In such cases, combined divergent and downbeat nystagmus produces slow phases that are directed upward and inward. Other components of this clinical syndrome include light-near dissociation, dorsal midbrain lesions, and vertical gaze palsy.

5.3.7 Dissociated Ocular Oscillations

In dissociated nystagmus, there is a significant asymmetry in either amplitude or direction of the two eyes. The pendular nystagmus in patients with multiple sclerosis is usually dissociated. There are a variety of nystagmus dissociations with lesions of the posterior fossa (e.g., asymmetric vertical nystagmus greater in one eye on looking up and in the other eye on looking down).

A common type of dissociation occurs in internuclear ophthalmoplegias, where the most marked oscillation is in the abducting eye. However, this abduction "nystagmus," sometimes designated by the confusing term "ataxic" nystagmus, is not really a nystagmus. Instead, it is a saccadic oscillation secondary to lesions of the medial longitudinal fasciculus and is discussed in Section 5.3.5.

5.3.8 Dysmetric Saccades

Ocular dysmetria is provided by refixation saccades and consists of undershooting (hypometria) or overshooting (hypermetria) followed by brief small-amplitude saccadic oscillations before the eyes come to a new fixation point, or conjugate overshooting followed by a single corrective saccade to bring the eye back to the target. There is an intersaccadic latency between the various corrective saccades. One type of dysmetria, hypermetria, is illustrated in Figure 5.10. Dysmetria is a common sign of cerebellar system disease.²⁰⁷

5.3.9 Ocular Flutter

The pathogenesis of saccadic oscillations without an intersaccadic interval, for example, ocular flutter and opsoclonus, seems closely related to the properties of the burst neurons themselves.¹⁶⁴ Burst neurons have very high discharge rates (up to 1000 spikes per second), and they discharge vigorously even for small saccades. The anatomical connections between burst neurons in the brainstem and their high discharge rates ("gain") predisposes to oscillations if the omnipause neurons are not actively inhibiting them and no specific saccadic command has been issued. Disease affecting omnipause neurons, or their afferents, might be expected to lead to saccadic oscillations such as ocular flutter and opsoclonus. Contrary to this, studies have shown that chemical lesions of the omnipause neurons are reported to cause slowing of both horizontal and vertical saccades. Attempts to demonstrate histopathologic changes in omnipause neurons in some patients with paraneoplastic saccadic oscillations have usually failed to show any changes. It has been suggested that, in paraneoplastic opsoclonus, the tumor and certain CNS structures share an epitope.²⁰⁸ This common epitope elicits an efficient immune response against the tumor, thus conferring a more indolent oncologic course, but it also elicits an immune response against normal neural tissue, causing the neurologic syndrome. There is some evidence that impaired glycinergic transmission may play a role in the pathogenesis of both ocular flutter and opsoclonus. Poisoning with a glycinergic antagonist, strychnine, can produce both myoclonus and opsoclonus and in hyperekplexia, abnormal receptors to glycine are found. The concurrent appearance of opsoclonus with myoclonus may suggest a similar mechanism. Glycine is identified as the neurotransmitter of the omnipause neurons and their glycinergic dysfunction, presumably caused by autoantibodies, might be responsible for the opsoclonus-myoclonus syndrome.

Cerebellar dysfunction has traditionally been blamed for ocular flutter and opsoclonus. Functional imaging in patients with opsoclonus has shown activation of deep cerebellar nuclei.

However, experimental lesions of the cerebellum do not produce these oscillations, even though striking saccadic dysmetria can be produced, especially when the caudal fastigial nuclei of the cerebellum are inactivated.^{209,210}

5.3.10 Flutter Dysmetria

Flutter dysmetria (FD) is the occurrence of flutter immediately after a saccade (Fig. 5.10).²¹¹ It superficially resembles dysmetria, but eye-movement recordings reveal that FD is an oscillation about the intended fixation angle and consists of back-to-back saccades with no intersaccadic latencies. This contrasts with dysmetria in which the saccadic oscillation has normal intersaccadic latencies. FD is seen in a setting of cerebellar disease.

5.3.11 Opsoclonus

There is a continuum between saccadic pulses and saccadic oscillations without an intersaccadic interval. The latter may occur in one direction, usually the horizontal plane, in which case they are called ocular flutter. If they are multivectorial, they are termed “opsoclonus” or “saccadomania.” The frequency of oscillations is usually high, typically 10–15 Hz, being higher with smaller-sized movements. Ocular flutter may be intermittent and mainly associated with voluntary saccades (flutter dysmetria) or convergence movements. Occasionally, the amplitude of the oscillations is very small (“microflutter”). In such cases, the movements may be detected only with a slit lamp, an ophthalmoscope, or eye-movement recordings. Sustained opsoclonus is a striking finding, in which multidirectional conjugate saccades, usually of large amplitude, interfere with steady fixation, smooth pursuit, or convergence. These movements may persist during sleep.

5.3.11.1 OPSOCLONUST-MYOCLONUS

Opsoclonus is often accompanied by myoclonus—brief jerky involuntary limb movements—hence the term “opsoclonus-myoclonus.” In children, this syndrome is called “dancing eyes and dancing feet.” Ataxia and encephalopathy

may also accompany opsoclonus. In about 50% of cases, the etiology remains obscure. In children, about half the cases of opsoclonus are associated with tumors of neural crest origin, such as neuroblastoma.²⁰³ Low cerebrospinal fluid concentrations of 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) can often be demonstrated in children with the opsoclonus-myoclonus syndrome. However, cerebrospinal fluid abnormalities may occur in opsoclonus associated with both tumor and encephalitis; thus, they may not help to distinguish between the infectious and paraneoplastic etiologies. Various autoantibodies can be detected in sera of some patients with opsoclonus. Of these, anti-Ri antibody is the most common.^{212,213} Anti-Hu antibody has been reported with opsoclonus in two children with neuroblastoma and in an adult with small-cell lung cancer. This is an ant neuronal antibody that binds nuclear RNA and is usually associated with paraneoplastic sensory neuronopathy, cerebellar degeneration, and limbic encephalitis. The prognosis of idiopathic opsoclonus (including patients with manifestations of brainstem encephalitis) is generally good. Some patients with paraneoplastic opsoclonus myoclonus show spontaneous remissions, irrespective of the underlying tumor. Patients whose tumor can be identified and treated may recover neurologically; those who are not treated have a more severe course.

5.3.12 Superior Oblique Myokymia

Superior oblique myokymia (SOM) was first described by Duane in 1906, but clinicians became generally aware of the disorder following the description by Hoyt and Keane in 1970.²¹⁴ Typical symptoms include monocular blurring of vision, tremulous sensations in the eye, brief episodes of vertical or torsional diplopia, and vertical or torsional oscillopsia.²¹⁵ Attacks last less than 10 seconds and may occur many times per day; they may be elicited on by looking downward, by tilting the head toward the side of the affected eye, and by blinking. The majority of patients with SOM have no underlying disease, although cases have been reported following trochlear nerve palsy, after

mild head trauma, in the setting of multiple sclerosis, after brainstem stroke, and in patients with cerebellar tumor.

The eye movements of SOM are often difficult to appreciate on gross examination, although they are usually apparent during examination with the ophthalmoscope or slit-lamp biomicroscope. They consist of spasms of cyclotorsional and vertical movements. Measurement of the movements of SOM using the magnetic search coil technique reveals an initial intorsion and depression of the affected eye, followed by irregular oscillations of small amplitude and variable frequency.²¹⁶ Some resemble jerk nystagmus, with frequencies of 2–6 Hz, but superimposed upon these oscillations are low-amplitude, irregular oscillations with frequencies ranging up to 50 Hz. Electromyographic recordings from superior oblique muscles affected by SOM reveal some fibers that discharge either spontaneously or following contraction of the muscle. These muscle potentials are abnormal, with increased duration (greater than 2 milliseconds) and amplitude, and they are polyphasic, with a spontaneous discharge rate of approximately 45 Hz. Spontaneous activity is absent only with large saccades in the “off” (upward) direction and is less affected by vestibular eye movements. Some firing units show an irregular discharge following muscle contraction before subsiding to a regular discharge of 35 Hz. These findings suggest that the etiology of SOM is neuronal damage and subsequent regeneration, leading to desynchronized contraction of muscle fibers. Indeed, experimental lesions of the trochlear nerve demonstrate regenerative capacities such that the remaining motor neurons increase their number of axons to hold the total constant. Superior oblique myokymia only rarely is preceded by an ipsilateral trochlear nerve palsy.

Ocular neuromyotonia is a rare disorder characterized by episodes of diplopia that are usually precipitated by holding the eyes in eccentric gaze, often sustained adduction.²¹⁷ Most reported patients have undergone radiation to the parasellar region, but idiopathic cases have been reported. The episodic nature of the diplopia associated with ocular neuromyotonia often suggests myasthenia gravis,

but anticholinergic medicines are ineffective in this condition. Other conditions that may mimic ocular neuromyotonia include superior oblique myokymia, thyroid eye disease, and cyclic oculomotor palsy.

The symptoms of ocular neuromyotonia are caused by involuntary, and at times painful, contraction of the lateral rectus muscle, the superior oblique muscle, or one or more extraocular muscles innervated by the oculomotor nerve. Extraocular muscles innervated by more than one ocular motor nerve may occasionally be affected, and rare patients with bilateral ocular neuromyotonia have been reported. Comparing symptoms with attempts at eccentric gaze holding may aid in making the diagnosis, as symptoms may be absent in primary position but evoked by sustained eccentric gaze. The mechanism responsible for ocular neuromyotonia is unknown, although both ephaptic neural transmission and changes in the pattern of neuronal transmission following denervation have been suggested, since spontaneous activity is seen in the ocular electromyogram of some affected patients. Axonal hyperexcitability caused by dysfunction of potassium channels has also been implicated in the production of neuromyotonia by analogy with systemic neuromyotonia.

5.3.13 Ocular Bobbing

Ocular bobbing is a distinctive spontaneous vertical eye-movement disturbance, readily distinguished from downbeat nystagmus and ocular myoclonus. Bobbing refers to fast downward jerks of both eyes followed by a slow drift to midposition.²¹⁸ The downward jerks may be disjunctive in the two eyes, and often the eyes remain deviated for several seconds before returning to midposition. Bobbing can be divided into three types: typical, monocular, and atypical.²¹⁹

5.3.13.1 TYPICAL

Ocular bobbing consists of intermittent, usually conjugate, rapid downward movement of the eyes, followed by a slower return to primary position. Reflex horizontal eye movements are usually absent; that is, it appears in patients with

paralysis of horizontal conjugate eye movements. The pathophysiology of all types of ocular bobbing is uncertain, but putative hypotheses are numerous. Bobbing usually occurs in comatose patients with extensive destruction of the pons, but extrapontine compressions, obstructive hydrocephalus, metabolic encephalopathy, and encephalitis occasionally are causative.²²⁰

5.3.13.2 MONOCULAR

Monocular bobbing reflects coexisting contralateral third-nerve paresis.²¹⁹ In two cases, a pontine lesion plus an oculomotor lesion resulted in monocular bobbing²²¹; in some cases, no explanation could be found.²²²

5.3.13.3 ATYPICAL

The third category, atypical bobbing, includes downward bobbing with convergence movements, asymmetric bobbing without an associated oculomotor palsy, and bobbing with intact spontaneous or reflex horizontal eye movements; the latter variety suggests diffuse encephalopathy, hydrocephalus, or organophosphate poisoning, rather than severe intrinsic pontine disease.²²³ Atypical bobbing may be disconjugate.²²² Associated signs and symptoms of pontine damage, inverse bobbing has an initial downward movement that is slow and the return to midposition is rapid; this has also been called ocular dipping.²²⁴

Reverse ocular dipping or converse bobbing has been used to describe a slow upward drift of the eyes followed by a rapid return to central position; variants of ocular bobbing are less diagnostically specific. Two reports of comatose patients who demonstrated a slow downward eye movement, followed, after a variable delay, by a quick saccade up to midposition. This disorder was called “inverse bobbing” in one report²²⁵ and “ocular dipping” in the other.²²⁶ The latter term (dipping) seems to have achieved favor.^{227–230} The upward jerking of the eyes is occasionally associated with contraction of the orbicularis oculi.²³¹ The phenomenon is regarded as mechanistically similar to the sustained downgaze deviation seen occasionally in comatose patients and has

occurred in a patient with a pinealoblastoma. A depressed level of consciousness is not a prerequisite for its appearance. Some patients in coma may demonstrate all three types of spontaneous vertical movements: ocular bobbing, ocular dipping, and reverse bobbing.²³² Ocular dipping may lead to a vertical gaze paresis (e.g. in Jacob-Creutzfeldt disease)²³³ or may coexist with ping-pong gaze (e.g., hypoxic encephalopathy).²³⁴

In addition to these three types of bobbing (typical, monocular, and atypical), we described a phenomenon designated “reverse bobbing,” in which the eyes jerked upward with a fast movement and then slowly returned to the horizontal; the patients were deeply comatose as a result of metabolic encephalopathy. Reverse bobbing may coexist with typical bobbing with lesions of the dorsal median portion of the pontine tegmentum.²³⁵

5.3.14 Psychogenic Flutter (Voluntary “Nystagmus”)

Voluntary (hysterical, psychological) “nystagmus” is not nystagmus at all but a series of back-to-back saccades, interrupting fixation, whose timing is such that the waveform traced out appears to be pendular (i.e., a psychogenic or voluntary flutter). The most accurate and inclusive term for this oscillation (which has also been called “ocular fibrillation” and “ocular flutter”) is “psychogenic flutter,” introduced in 1980.²

Psychogenic flutter consists of bursts of an extremely rapid, conjugate, horizontal oscillation that appears pendular but actually consists of back-to-back saccades.²³⁶ As shown in Table 5.6, voluntary “nystagmus” is actually flutter.²¹¹ It may be used as a party trick or as a conscious attempt to feign illness. The oscillation is readily identified by the extreme rapidity (approximately 20 Hz, with a range of 8 to 23 Hz) and brevity of each burst (maximum duration usually less than 30 seconds). Most subjects do not sustain the oscillation for more than 10 seconds and manifest facial distortions with eyelid closure to “rest” their eyes in preparation for another outburst. The ability to perform this stunt may be hereditary, and it is present in about 5%–8% of the population but in 79% of their relatives.^{237,238}

Rarely, psychogenic flutter may be vertical²³⁹ or multidirectional, mimicking opsoclonus.²⁴⁰ In a family we recorded in the 1970s, it was exhibited by a father and two sons, with the father able to maintain it the longest, less by the elder son, and least by the younger son. A study of two families with members capable of generating psychogenic flutter found similarities in durations, frequencies, and amplitudes.²⁴¹ There is an association between generating psychogenic flutter and converging the eyes; it may also occur with accommodation spasm.²⁴²

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6

AFFERENT VISUAL SYSTEM—CLINICAL EXAMINATION PROCEDURES

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One cannot be a good observer unless one is a good theorist.

—Charles Darwin (1809–1882)

THE RELATIONSHIP between development of visual function(s) and an ongoing ocular oscillation in infancy and childhood is complex and dynamic. In addition to an age-dependent suppression of oscillopsia, the oscillation has a direct effect on visual acuity, contrast sensitivity, motion detection, visual recognition time, gaze-dependent acuity, size of functional visual space, possible accommodation, and the creation of motion-induced amblyopia.^{1,2} In over 50% of infants and children with ocular oscillations, there are, in addition, many possible types of associated afferent system deficits (i.e., foveal dysplasia/hypoplasia, photophobia/light interference, optic nerve dysplasia/hypoplasia, retinal dystrophy/degeneration, amblyopia, ametropia, cortical-subcortical visual impairment, and delayed visual maturation).³ The coexisting presence of nystagmus and an afferent system deficit imposes multifactorial limitations on all aspects of visual development.

To measure afferent system function separately, a number of subjective and objective tests can be used in infants and children with nystagmus. There is a voluminous amount of material available to the reader describing the general history, application, methodology, and results of these tests.^{3–6} It is our purpose here to focus on how these tests are interpreted, implemented, and/or modified for those infants and children with nystagmus with emphasis on infantile nystagmus syndrome (INS) and fusion maldevelopment syndrome (FMNS).

6.1 SUBJECTIVE TESTING

6.1.1 Teller Acuity Card Procedure

In 1958, Berlyne and Fantz independently observed what was to be termed preferential looking (PL) or forced-preferential looking (FPL) behavior.^{7–9} PL behavior is based on the

infantile preference to look at a pattern rather than a homogenous background. PL was first used in 1962 to test visual acuity by comparing visual data to mean acuity of specific age groups. In the 1970s, Teller introduced the forced-choice preferential looking test, which yielded more individualized data.^{7–9}

The acuity card procedure was developed to allow the rapid measurement of grating visual acuity in infants and young children in both clinical and laboratory settings (Fig. 6.1). Initially, acuity cards were constructed of gray cardboard, with a grating that varied in spatial frequency from card to card mounted behind an aperture on one side of the card, and a high spatial frequency grating, composed of very fine black-and-white stripes, mounted behind an aperture on the other side of the card. After the initial success of the cards in clinical settings, a commercially produced version of the acuity cards became available (Teller Acuity Cards™ [TAC], Vistech Consultants, Inc., Dayton, OH). The commercially produced acuity cards differed from the prototype cards in three important ways: (1) the patch of grating that varied from card to card was square, rather than circular, (2) the grating was printed on the card rather than being mounted behind an aperture, and (3) there was no well-defined, high spatial frequency “blank” target on the

side of the card opposite the patch of grating. Despite these differences, the acuity values obtained with the commercially produced cards were similar to acuity values obtained with the prototype cards.

After the introduction of the commercially produced TAC, a number of investigators published normative monocular and binocular grating acuity data for infants and young children.^{10–13} The company that produced the TAC (Vistech Consultants, Inc.) went out of business, and another company (Stereo Optical Co., Inc., Chicago, IL) began producing a modified version of the cards, the Teller Acuity Cards™ II (TAC II). The TAC II differs from the original TAC in two important ways. First, the face of each of the new cards is laminated, producing lower contrast in the gratings on the new cards. Second, improved production technology has eliminated the “edge artifact” that appeared as a visible line around the patch of grating on the card in the original TAC that contained the highest spatial frequency grating (38 cycles/cm). Recently Clifford et al. found that acuity scores obtained with the original TAC (Vistech Consultants, Inc.) are approximately 0.5 octave (one card step) better than acuity scores obtained with the newly developed TAC II (Stereo Optical Co., Inc.).¹⁴



FIGURE 6.1 Example of Teller acuity card held vertically in front of an infant with nystagmus.

In infants and children with nystagmus it is best to begin the presentation protocol at the shortest distance with the 0.32 cycles/cm card. It is also important to hold the TAC vertically so that the gratings are horizontally oriented. Binocular acuity is tested first. Patients should be tested in their preferred head position. After binocular testing, the right eye is tested first, followed by the left. Although it is generally agreed that reliable Snellen-equivalent visual acuity measurements cannot be obtained until assessed with a recognition test using linear letters or symbols, grating acuity can be used to assess a reduction, change, or variation from normal visual function in the first 3 years of life.⁸

6.1.2 Visual Acuity Testing (High Spatial Frequency Vision)

Recognition of black letters on a white screen or its measure (Snellen, Early Treatment Diabetic Retinopathy Study, Cardiff, Landolt-C, Lea Symbols, and HOTV acuity) is understandably important to clinicians and their patients. Unfortunately, high spatial frequency vision was, is, and continues to be a poor “primary” measure of ocular motor function. For example, a patient with INS and a latent component has multiple optotype measures of acuity depending on mental state, attention, and whether fixation is monocular, binocular, at distance or near, or at eccentric gaze angles. Another 17% to 33% of patients with INS have a periodically changing cycle in which their null zone and best visual function exist not only at a place in space but also during a period in time, making measures of acuity not only statically but also dynamically dependent. Vision, used as a measure of visual function in patients with ocular oscillations, must be explicit, because there are at least five psychophysical measures of acuity (i.e., detection, recognition, resolution, hyperacuity, and localization).¹⁵

In patients with INS, measuring best-corrected binocular vision in and during the null zone is a visually unique ocular motor variable because of the nature of the oscillation. Almost all patients with acquired forms of ocular oscillations will have varied measured visual acuity

based on gaze, ocular laterality, mental state, and time.

We prefer to test visual acuity in the patient’s preferred null zone (INS), determined by the use of clinical evaluation, head posture measuring system, or eye-movement recordings, or in adduction of the fixating eye (FMNS). This is accomplished while the patient is wearing his or her best optical correction, first, binocularly, then monocularly, using the PEDIG Study group ATS HOTV[®] protocol for subjects ages 3 to < 7 years and the ATS Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS[®]) protocol for subjects ages ≥ 7 years (see Table 6.1).^{16,17} This type of testing has shown validity and reliability across all age groups. Almost 20% of otherwise normal 2-year-olds are able to reliably perform matching acuity. Using it allows the clinician to accurately assess the natural progression/regression or the impact of interventions on a standard measure of high spatial frequency vision in these patients (Fig. 6.2).

6.1.3 Stereo Testing

Stereopsis is a neurologically dependent on normal binocular vision. Its presence or absence is an important indicator of the state of binocularity in patients with all ocular motility disorders. Several studies using different paradigms such as line stereograms and a preferential looking procedure, random dots with a forced-choice preferential looking technique, and random dots with visually evoked responses have shown stereopsis is absent in almost all infants less than 3 months old, after which it rapidly develops to normal levels, which are reached by the sixth month of life. Patients with nystagmus and good binocular function will be able to respond appropriately when tested for stereopsis.

Equipment for testing stereopsis ranges from simple equipment to complex laboratory apparatus (Fig. 6.3). The two eyes must be dissociated; that is, each eye must be presented with a separate field of view, and each of the two fields or targets must contain elements imaged on corresponding retinal areas. In the Polaroid

Table 6.1 Electronic–Early Treatment of Diabetic Retinopathy Study (E-ETDRS) Vision Testing

E-ETDRS SCREENING PHASE

Objective: With single-letter presentations, determine smallest logMAR level at which a letter is correctly identified

Show one letter per level starting at 20/400 in three-level steps until a letter is missed (20/400, 20/200, 20/100, 20/50, 20/25, 20/12)

- Uses V, R, K, D letters (letter set is limited to intermediate difficulty letters that have approximately equal difficulty)
- If 20/400 is missed, go to 20/800 and if correct, continue with single letters at 20/640 and 20/500 until one is missed
- If a letter smaller than 20/400 is missed:
 - 1) Go up two levels from the missed level (i.e., one level smaller than last correct level) and continue with one letter at each level until a letter is missed
 - Note: a letter missed the first time will end up being retested unless a larger letter is missed (*this protects against an inadvertent miss well above threshold*)
 - 2) If the first letter in this step (step b2) is missed, go back up one level at a time until a letter is correct (*this protects against a lucky guess below threshold*)

Scoring: The score in screening phase is the last correct level

E-ETDRS THRESHOLD PHASE

Objective: Based on screening phase score, test five letters at each level until smallest level with 5/5 correct and the smallest level with 0/5 correct are determined.

Start testing letters by intermixing letter sizes of screening phase score and one level smaller.

- Uses same letter sequence for each level as on ETDRS chart
- If a letter is missed at a level, one level larger is added to the testing mix
- If a letter is correct at a level, one level smaller is added to the testing mix

Stop testing a level once five letters at that level have been presented

Continue to add larger levels to the testing mix as long as one letter is missed at a level

Continue to add smaller levels to the mix as long as one letter is correct at a level

Test ends when both the smallest level with 5/5 correct and smallest level with 0/5 correct have been determined.

Scoring: The letter score is calculated as the number of letters correct on the test plus the number of letters above the “5 of 5” line through 20/800.

Vectograph® test a gross stereoscopic pattern representing a housefly is provided to orient the patient and to establish whether there is gross stereopsis (threshold: 3000 seconds of arc). The Polaroid test also contains three rows of animals, one animal in each row imaged disparately (thresholds: 100, 200, and 400 seconds of arc, respectively). The Titmus® test contains nine sets of four circles arranged in the form of

a lozenge. In this sequence the upper, lower, left, or right circle is disparately imaged at random with thresholds ranging from 800 to 40 seconds of arc. Both of these tests are used for testing near vision. The vectograph test can be supplemented with a projected vectograph test at distance fixation (Polaroid Vectographic Project-O-Chart®, American Optical Reichert) or with the B-VAT® (Mentor) projection device.



FIGURE 6.2 Demonstration of amblyopia treatment study single surrounded HOTV vision testing, which is a computerized visual acuity testing method of single surrounded HOTV optotypes developed by the Pediatric Eye Disease Investigator Group.



FIGURE 6.3 The standard testing methods for use in measuring stereopsis.

To avoid monocular visual clues that could confound the Polaroid tests, random-dot stereograms are much more useful for accurate stereo testing. Reinecke and Simon introduced the random-dot E test, which contains three cards and Polaroid spectacles. One card is a base-relief model of the stereo test figure and is used to show the child what to look for. One of the two other test cards contains the E stereo figure, and the other is stereo blank with an identical random-dot background. The test is perception of an image in depth. The TNO® test is graded to provide retinal disparities ranging from 15 to 480 seconds of arc.

Occasionally, young children will refuse to wear Polaroid or red-green spectacles, and observing the position of the eyes while the patient is being tested for stereopsis may be desirable. To overcome these difficulties, Lang developed a test based on pantographic presentation of a random-dot pattern. Glasses are not needed to recognize the stereoscopic images of a star, a car, and a cat embedded in random dots on the test card. A separate image is provided to each eye through cylindrical lenses imprinted on the surface lamination of the test card. A revised version of this test (Lang II Test®) with smaller disparities and a less dense arrangement of random dots is available. The advantage of the Lang I test is that it can be performed in children as young as 6 months of age.¹⁸ If the baby stares for a few seconds at the card, one can infer the presence of stereopsis, following the same reasoning underlying the preferential looking testing technique. Stereo tests that use random dots are an accurate and established method to measure stereo acuity; however, the results obtained with different tests will vary widely. Testing based on random dots exposes the child to visual demands that are different from and more difficult than those prevailing under more casual conditions of seeing. Only when the images from the right and left eye are combined at the neural level and the object is seen in depth does recognition take place.

The information obtained by testing for stereopsis in patients with nystagmus allows the clinician to assess other aspects of the visual system (binocular function, vergence,

accommodation) that may be helpful in planning, and/or evaluating the effectiveness of, nystagmus treatments. Of 57 patients with infantile nystagmus tested for stereopsis by Liu et al., only 8 had normal testing. They found damaged stereopsis in most patients with “pendular” and more than half with “jerk” nystagmus. They found that the better the acuity, the less the stereopsis was damaged.¹⁹

6.1.4 Color-Vision Testing

Proper color discrimination requires the presence of normal cone function. Color deficiency is common, with as many as 8% of males and 0.4% of females having some level of color deficiency. Most color vision abnormalities in children are present at birth. Color vision improves greatly over the first 3 postnatal months, and it approaches adult values rapidly over the first 6 months of life.²⁰ The overall insensitivity of infants to contrast is likely to provide a satisfactory explanation of the poor color vision of infants. The critical immaturity primarily responsible for the high thresholds and poor color vision of infants is probably after the site of visual adaptation, although lower level factors may also play a role.²⁰ Color-vision deficits associated with nystagmus are usually caused by concomitant optic nerve or retinal disease (e.g., optic nerve hypoplasia, optic nerve atrophy, achromatopsia, foveal dysplasia, cone-rod dystrophy etc.).

Color-vision testing can be achieved with a variety of tests (Fig. 6.4). Pseudo-isochromatic plates, such as those available with the Ishihara® and the Hardy-Rand-Rittler® tests, are commonly used color vision tests. More advanced tests, such as the Farnsworth D-15® and Farnsworth-Munsell 100 Hue® tests, may be used to better characterize the deficit noted on screening tests, especially in older children.

Pseudoisochromatic plate tests have limited effectiveness for young children. At present, there are few tests that are appropriate for young children that demonstrate good validity, are inexpensive, allow rapid assessment, and are commercially available. A new pseudo-isochromatic color plate test specifically



FIGURE 6.4 The matching (drawing) test used in preverbal children to test color vision.

designed for young children, “Color-Vision Testing Made Easy” (CVTME), has recently been introduced. Results of a validation study indicate that CVTME has a high degree of efficacy as a color-vision testing young children and may be well suited to those with nystagmus. CVTME was 100% compatible with the Ishihara with the same specificity and sensitivity. There were no false positives. The response patterns of normal and color-deficient children were very clear-cut so that a diagnosis was easy and made with a high degree of confidence. The selection of Part II (dog, boat, balloon), together with the demonstration replicas, allows most children 3

years of age or older to be easily tested. Verbal identification, drawing over the figure, or selecting the matching demonstration replica can all be used as testing methods.

6.1.5 Contrast-Sensitivity Testing

The current gold standard in the assessment of vision, visual acuity, provides only a limited amount of information, obtained under artificial conditions. Contrast-sensitivity testing (CST) measures a range of visual performance under real-life conditions. It measures the least amount of contrast needed to detect a visual stimulus and gives a more complete quantification of

patients' visual capabilities. Contrast sensitivity is present in early infancy and improves in visually normal children until about 7 years of age.^{21,22} Several contrast test systems are available (Fig. 6.5). The key differences are whether an optotype or a sine wave grating target is used for testing. The Pelli-Robson® chart determines the contrast required to read large letters of a fixed size. The Regan® chart, a low-contrast letter chart having differently sized letters, reduces the contrast levels of a standard Snellen-type letter acuity chart, resulting in several charts. The Functional Acuity Contrast Test (FACT™) and Vector Vision™ both use sine-wave gratings, which measure specific visual channels. Most of the commercially available CST can be used successfully in older children with nystagmus under binocular and monocular conditions.

The absence of stimulation of the size-selective detectors processing high spatial frequencies may account for a previously described abnormal shape of the CST curve in patients with some forms of nystagmus. A reduction in CST for medium to high spatial frequency vision and increased pattern detection thresholds in patients with nystagmus impairs the detection of vertically oriented stationary and moving grating patterns more so than horizontal ones. Previous studies have shown that results for contrast sensitivity in some, but not

all, subjects with nystagmus alone are poorer than that in normal observers under conditions of comparable retinal image motion. Dickinson and Abadi reported that CST did not improve in many INS subjects when the oscillation was damped by convergence.²³ There is psychophysical evidence that retinal motion may contribute to vision loss via an amblyopic component in patients with INS separate from ametropic and strabismic components.

6.1.6 Gaze- and Time-Dependent Acuity Testing

Different positions of gaze result in different oscillation intensities in children with many forms of nystagmus. The null zone is defined as that position of gaze where nystagmus intensity (amplitude × frequency) is least and is greater for gaze in either direction lateral to the null. Children with nystagmus often adopt an anomalous head posture (e.g., chin up or down, head turned or tilted) to improve their vision by maintaining gaze in the direction of an eccentric null zone. Both their gaze angle and the duration of visual stimulus presentation are important factors when determining visual function in nystagmus patients. We record "binocular gaze-dependent visual acuity" as measured using single-surrounded optotypes while

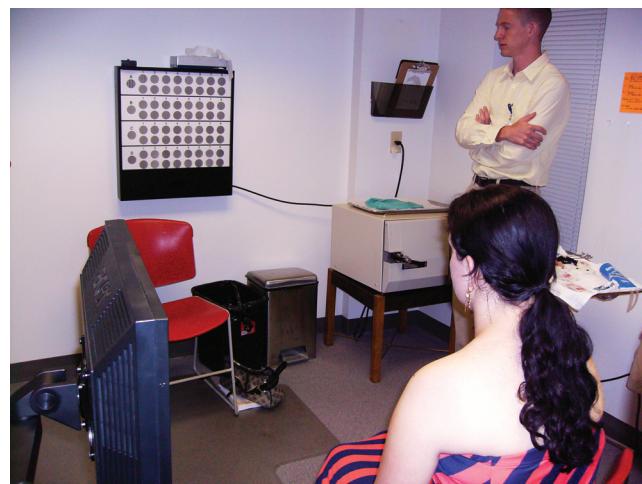


FIGURE 6.5 Example of a contrast sensitivity chart that can be used binocularly and monocularly with spatial frequency gratings easily tested in patients with nystagmus.

the heads of subjects are moved between varying angles horizontally and vertically. Optotype recognition has been shown to be dependent on gaze angle in nystagmus patients versus normal controls.^{24,25} This suggests that an INS patient's "real-world" vision, with a panorama of objects presented for variable periods, may be functionally less than the visual acuity measured in a controlled clinical setting.

If eye-movement recordings are not part of the clinical examination, binocular visual acuity measurements should be made at a minimum of five gaze angles (e.g., 0°, ±15°, and ±30°). Although not as accurate or sensitive as a plot of the NAFX versus gaze angle (see Chapter 2, Section 2.1.9.1 and Figs. 2.13, 2.18, 2.19, 2.25, and 2.36), plotting these acuities versus gaze angle will allow determination of the decrement of visual acuity at gaze angles lateral to the null angle. A sharp reduction in acuity is indicative that therapy would improve overall visual function.

The additional variable of time to recognition of a visual stimulus is another visual system measure that is anomalous in patients with nystagmus.^{24–26} This measure manifests in real-world situations during body and/or world motion. The measure of changes in visual recognition time may, therefore, be a useful measure of function in patients with nystagmus and has been shown to improve after intervention(s) for their oscillation. In one study of patients with nystagmus 50% of patients showed two or more lines difference in their visual acuity across gaze, while all control subjects showed none.^{24,25} During a time-restricted paradigm (TR) acuities were significantly decreased in eccentric gaze positions relative to non-time-restricted (NTR) paradigms in all nystagmus patients whereas the TR and NTR acuities were equal across gaze in all control subjects.^{24,25,27}

6.1.7 Visual Field Testing

Visual field assessment should be incorporated into the initial, comprehensive examination of the infant and child with nystagmus. Associated disease of the pre- or postchiasmal visual pathway and retina in patients with nystagmus often

results in compromised visual field function. It is important for the clinician to understand how focal or generalized, static or progressive, defects in the visual field of patients with nystagmus add to overall visual system dysfunction. The additional information regarding the integrity of the visual field may assist with diagnosis, prognosis, and treatment options of the patient's nystagmus in particular, and visual system in general.

In infants and young children, testing is accomplished by attracting the child's attention directly forward while introducing a target (small toy) from the periphery. As the child perceives the object approaching from the periphery, usually a sudden refixation saccade is apparent. The examiner also observes the child for any changes in attention or behavior. This same technique can be performed monocularly in each of the four quadrants if the child will tolerate it. A drawback of confrontation visual field testing is the subjective interpretation of its results.

Simple examination methods such as the arc perimeter can test the visual fields of young children.^{27–31} The arc perimetry test has the child orient to flashing lights on four oblique meridians at 20° and 30°. The device has four black arms at the major oblique meridian (45°, 135°, 225°, and 315°). At the 36-cm test distance, the arms extend to 110°. A 6° white sphere attracted the child's gaze toward the intersection of the arcs. A small white ball travels from the periphery to the center along an arc perimeter while the child fixes on another ball straight ahead. Once the child perceives the peripheral ball, a point on the perimeter is measured, indicating the extent of the visual field in that direction. The arc perimeter has been shown to be of benefit in the measurement of visual field size in healthy infants and infants with visual or neurologic abnormalities.

The hemispheric perimetry test is the next step up from the arc perimetry (Fig. 6.6). It is suited for babies who can sit upright. The child looks in a dome, which uses smaller static lights at the periphery. The results are plotted similarly to the Goldmann[®]. It yields more quantitative data than the arc, though not as detailed as the Goldmann[®].^{27–31}



FIGURE 6.6 Example of a behavioral method of testing visual field in preverbal patients.

Once a developmentally normal child has reached the age of 7 to 8 years, visual field testing is best performed using Goldmann® or automated visual field testers. Goldmann® perimetry test is done by having the child look into a globe with a central target to fixate upon. The eye that is not being tested is covered. The globe shows a light at the periphery that is gradually moved inward until the child presses a buzzer indicating that he or she sees the light. This is done with many lights from different peripheral points. The points the child sees are plotted to make a graph of the child's visual field. The main advantages of the Goldmann® test is that it yields the most quantitative results. Unfortunately, it requires a lot of cooperation and ability to sit still, so it is difficult to do with very young or very impaired children.^{27–31}

Computerized or automated visual field testing is available by many manufacturers using many protocols. We use a Humphrey® automated testing machine and a standard SITA program, which is excellent for evaluating visual field defects in children. The shortened test time and decreased variability described for adults are also present for children. Using the 24–2 rather than the 30–2 program can also reduce variability and test time; it shortens test time by approximately 30% and improves (lessens) variability. The periphery of the visual field is not tested with either of these programs. Patients with degenerative retinopathies should be tested with

kinetic (Goldmann®) perimetry. Table 6.2 summarizes each of the visual field tests.

6.2 OBJECTIVE TESTING

6.2.1 Visual Evoked Potentials

The visual evoked potential (VEP) is an evoked electrophysiological potential that can be extracted, using signal averaging, from the electro-encephalographic activity recorded at the scalp (Fig. 6.7a). The VEP can provide important diagnostic information regarding the functional integrity of the visual system. In patients with nystagmus it is important to go slightly beyond the current international society for clinical evaluation of vision (ISCEV) criteria.³² Because chiasmal and retrochiasmal diseases may be missed using a single channel, three channels using the midline and two lateral active electrodes are suggested. Pattern reversal is the preferred technique for most clinical purposes but is less reliable in patients with unstable fixation or nystagmus. The results of pattern-reversal stimuli are less variable in waveform and timing than the results elicited by other stimuli. The pattern-onset/offset technique can be more useful in patients with nystagmus, and the flash VEP is particularly useful when optical factors or poor cooperation makes the use of pattern stimulation unreliable.^{33,34}

Stimuli for VEP testing are patterns and flashes. Pattern VEP uses black-and-white

Table 6.2 Visual Field Testing Methods

1. Confrontation Visual Field
 - a. Easy and rapid to perform
 - b. Examiner tests the visual field of the patient under sequential monocular testing conditions using his or her own eye as a control
 - c. A reasonable screening study but lacks sensitivity, especially for small defects
2. Amsler Grid
 - a. Excellent tool for assessing the central field subjectively
 - b. Useful for small central or paracentral defects within a few degrees of fixation and for assessing distortion in shape (i.e., metamorphopsia) or size (i.e., micropsia, macropsia)
3. Tangent Screen
 - a. Useful for rapid testing of the central field
 - b. Especially helpful for demonstrating a nonorganic tunnel visual field that does not expand at 1-m and 2-m testing distances
4. Goldmann Perimetry
 - a. Operator dependent tool
 - b. Qualitative assessment of visual field
 - c. Kinetic and static testing possible
 - d. Technician can reassure, reeducate, and retest specific areas of interest in a subject
 - e. Can test central or peripheral visual field with different size and brightness stimuli
 - f. Qualitative (subjective) reports of technician can assess patient reliability during testing
5. Automated Computerized Perimetry
 - a. Provides quantitative (visual threshold) information that is useful for following progression of disease (e.g., glaucoma or idiopathic intracranial hypertension)
 - b. Reproducible and reliable technique
 - c. Formal quantitative assessments of reliability
 - d. Computerized fixation and eye-movement monitoring
 - e. Automated testing and retesting protocols for selected points (false-positive and false-negative results)

checkerboard stimulation. Flash VEP is a white flash. The VEP is measured and evaluated in latency (time from stimulation to peak response) and amplitude of peak response (P100). All VEPs in children with or without nystagmus should be compared with appropriate age-related normal values. When recording the VEP in infants, the sweep duration should be increased due to the increased peak latency in this population. By 6 months of age the peak latency of the main positive peak of the pattern reversal VEP for larger checks (>30 sec) is usually within 10% of adult values.^{33,34}

The waveform of the VEP depends upon the temporal frequency of the stimulus. At rapid rates of stimulation, the waveform becomes approximately sinusoidal and is termed steady state (Fig. 6.7b). At low temporal frequencies, the waveform consists of a number of discrete deflections and is termed a transient VEP. Only transient VEPs form a part of the ISCEV standard. VEP peak latency, amplitude, and waveform are age dependent. VEP peak latency refers to the time from stimulus onset to the maximum positive or negative deflection or excursion; thus, the term “VEP peak latency” corresponds

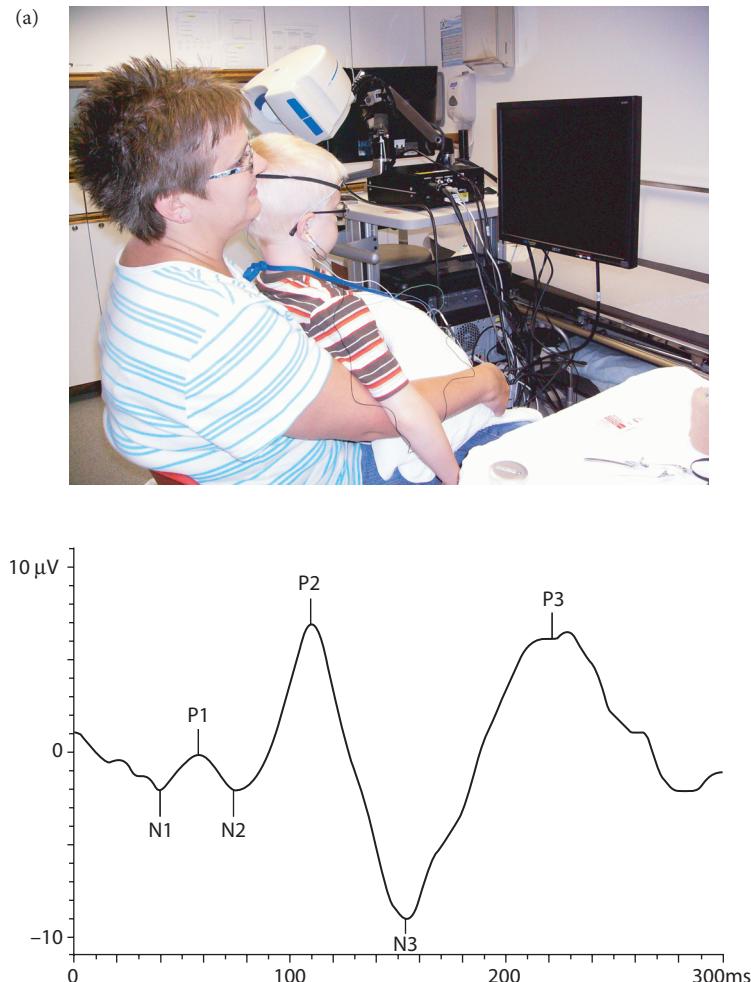


FIGURE 6.7 Child seated with electrodes in place on the scalp in front of LCD screen for flash visual evoked potential (VEP) testing (a). Normal appearance of positive and negative wave of a normal flash evoked response (b).

to the term “implicit time” used to describe the time from the stimulus to the maximum deflection. VEP peak latency may also be referred to as “time to peak” or peak time.

The pattern reversal VEP has relatively low variability of waveform and peak latency both within a subject and over the normal population. Therefore, it is the preferred procedure in most circumstances. For pattern reversal, the VEP consists of N75, P100, and N135 peaks. The nomenclature consists of designating peaks as negative and positive followed by the typical mean peak latency. It is recommended to measure the amplitude of P100 from the preceding

N75 peak. The peak latency of P100 shows relatively little variation between subjects, minimal within-subject interocular difference, and minimal variation with repeated measurements over time. P100 peak latency is affected by non-pathophysiologic parameters such as pattern size, pattern contrast, pattern mean luminance, refractive error, poor fixation, and miosis.

Flash VEPs are much more variable across subjects than pattern responses but show little interocular asymmetry (Fig. 6.7b). They may be useful in patients who are unable or unwilling to cooperate for pattern VEPs, and when optical factors such as media opacities prevent

the valid use of pattern stimuli. The visual evoked potential to flash stimulation consists of a series of negative and positive waves. The earliest detectable response has a peak latency of approximately 30 msec poststimulus, and components are recordable with peak latencies of up to 300 msec. Peaks are designated as negative and positive in a numerical sequence. This nomenclature is recommended to automatically differentiate the flash VEP from the pattern reversal VEP. For the flash VEP, the most robust components are the N2 and P2 peaks. Measurements of P2 amplitude should be made from the positive P2 peak at around 120 msec to the preceding N2 negative peak at around 90 msec.

VEPs should be recorded when the infant or child is in an attentive behavioral state.³⁵ Direct interaction with the child can help maintain attention and fixation, and two testers are beneficial, one to work with the child and the other to control data acquisition. The order of stimulus presentation also should be flexible and selected to ensure that responses most critical to the diagnostic question are obtained within an individual child's attention span. Binocular pattern stimulation, which facilitates attention and fixation, may be useful to evaluate overall visual function (Fig. 6.8). Monocular testing to at least one stimulus is desirable to assess the function of each eye. It is particularly important to obtain

replicate responses from children to assure that the response measured is a reliable signal and not an artifact.³⁶ As for adults, additional channels of recording may be important for diagnosis of chiasmal and postchiasmal dysfunction.³⁷ When pattern VEPs cannot be reliably recorded, flash testing, which is less dependent upon cooperation, can usually be achieved. Pattern-reversal VEPs recorded from patients with nystagmus or unstable fixation should be interpreted with caution. Pattern-onset/offset stimuli can be helpful in gaining attention of children and are usually more robust in cases of nystagmus, but the waveform components change with age. We have been able to use the Sweep VEP as a consistent measure of visual function, both cross-sectionally and longitudinally in patients with nystagmus.³⁸ The reader is referred to multiple excellent texts regarding the VEP consequences of diseases of the postchiasmal, prechiasmal, chiasmal, and retinal systems in infancy and childhood. Table 6.3 summarizes specialized VEP tests.

6.2.2 Electroretinography

Electroretinography (ERG) evaluation of children with nystagmus has both diagnostic and prognostic value. In patients with nystagmus and a normal clinical examination alone, a true diagnosis of infantile nystagmus syndrome (INS) without associated sensory system deficits

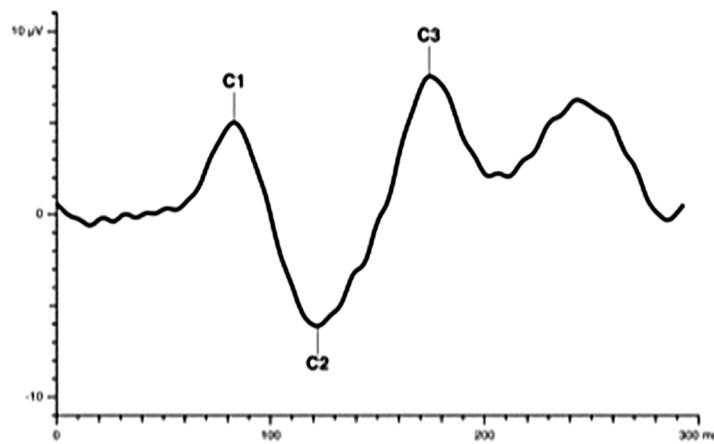


FIGURE 6.8 Normal appearance of positive and negative waves of a normal pattern visual evoked potential response.

Table 6.3 Specialized Visual Evoked Potential (VEP) Testing

Specialized VEP Types (not covered by ISCEV*)
1. Steady-state VEP
2. Sweep VEP
3. Motion VEP
4. Chromatic (color) VEP
5. Binocular (dichoptic) VEP
6. Stereo-elicited VEP
7. Multichannel VEP
8. Hemifield VEP
9. Multifocal VEP
10. Multifrequency VEP
11. LED Goggle VEP

*ISCEV, international society for clinical evaluation of vision

cannot be inferred. In a large study of Ganzfeld ERGs recorded from 105 consecutive patients clinically believed to have “idiopathic” INS, retinal disease associated with INS was diagnosed in 59 patients (56%).³⁹ Other visual system diseases associated with nystagmus in infancy include Leber’s amaurosis, delayed visual maturation, albinism, optic nerve hypoplasia, achromatopsia, and X-linked congenital stationary night blindness. ERGs have been shown to help in distinguishing between these conditions.³⁵

The global or full-field ERG is a mass electrical response of the retina to photic stimulation and is used worldwide to assess the status of the retina in eye diseases in human patients and in laboratory animals used as models of retinal disease (Fig. 6.9). The basic method of recording the electrical response known as the global or full-field ERG is by stimulating the eye with a bright light source such as a flash produced by a strobe lamp. The intense flash of light elicits a biphasic waveform recordable at the cornea. The two components that are most often measured are the a- and b-waves. The a-wave is the first large negative component, followed by the b-wave, which is corneal positive and usually larger in amplitude. The amplitude from the baseline to the negative trough of the a-wave, the amplitude of the b-wave measured from the trough of the a-wave to the following peak of the b-wave, the time from flash onset to the trough of the a-wave, and the time from flash onset to the peak of the b-wave are the most common measures. These times, reflecting peak latency, are referred to as “implicit times.” The a-wave, sometimes called the “late receptor potential,” reflects the general physiological health of the photo-receptors in the outer retina. In contrast, the b-wave reflects the health of the inner layers of the retina, including the “on” bipolar cells and the Muller cells. Two other waveforms that are

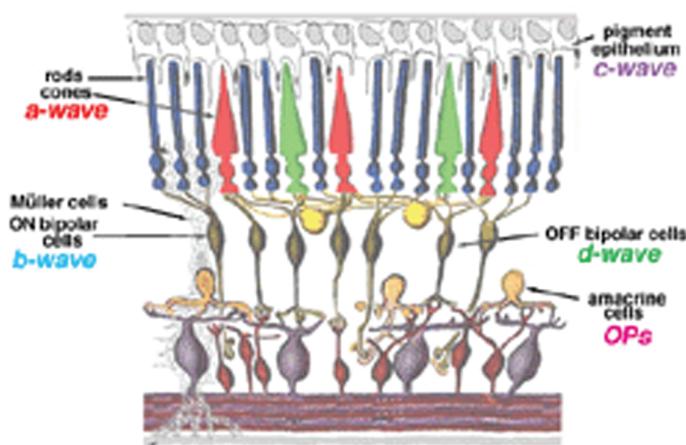


FIGURE 6.9 Diagrammatic representation of electroretinographic (ERG) activity in the retina. Color photography of retinal layer anatomy with labeled areas responsible for ERG waveform components.



FIGURE 6.10 Photograph of actual setup for intraoperative examination under anesthesia and electroretinography.

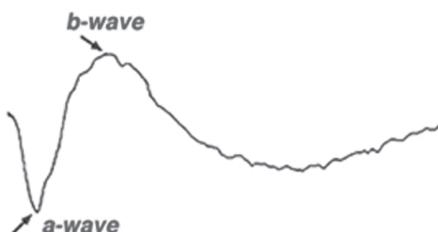
sometimes recorded for clinical purposes are the c-wave originating in the pigment epithelium and the d-wave indicating activity of the “off” bipolar cells. There are also wavelets that occur on the rising phase of the b-wave known as oscillatory potentials, thought to reflect activity in amacrine cells.

The ERG of a normal full-term infant looks similar to a mature ERG.⁴⁰ The ERG attains peak amplitude in adolescence and slowly declines in amplitude throughout life. The ERG can be recorded several ways. The pupil is usually dilated. There are a number of corneal ERG electrodes that are in common use. Some are speculum structures that hold the eye open and have a contact lens with a wire ring that “floats” on the cornea supported by a small spring. Some versions use carbon, wire, or gold foil to record electrical activity. There are also cotton wick electrodes. There are yet other simpler ERG recording devices using gold Mylar tape that can be inserted between the lower lid and sclera/cornea. Most electrodes are monopolar, that is, they are referred to another electrode site, most commonly on the forehead. There are also several methods of stimulating the eye. Most laboratories use a Ganzfeld (globe) with a chin rest and fixation points. The Ganzfeld allows the best control of background illumination and

stimulus flash intensity. Either strobe lamp or Ganzfeld methods of flash presentation can be used to record the ERG following a single flash or to average responses to several flashes with the aid of a computer.

Infants up to about 6 months years of age can usually be tested without sedation by the parent holding them bundled in a blanket. Most of our ERG testing is performed as part of a more extensive exam under anesthesia (Fig. 6.10). Anesthesia affects the ERG varying with type and depth of anesthesia. Some anesthetics can attenuate b-wave amplitude as much as 50%. Light levels of anesthesia have little effect, and most anesthetics do not usually affect a-waves or implicit times.

Most disorders of the retina are detected by an attenuation of amplitude. Implicit times of both a- and b-waves are also affected in some conditions (Fig. 6.11). We usually dark-adapt the patient for a set time of 30 minutes, then attach electrodes using dim red illumination. We record the ERG using single, scotopic white flashes. We then turn on moderately high background illumination for about 10 minutes and record ERGs using 30 Hertz flicker and bright white flashes. The reader is referred to multiple excellent texts regarding the ERG consequences of diseases of the retina, retinal



The basic waveform of the ERG

FIGURE 6.11 Appearance of positive and negative waves from a normal electroretinogram.

pigment epithelium, and optic nerve in infancy and childhood.

6.2.3 Optical Coherence Tomography

Optical coherence tomography (OCT) is analogous to ultrasound except that near-infrared light waves instead of acoustic waves are used to measure distances of specific structures. OCT depends on optical ranging; in other words, shining a beam of light onto the object, then recording the echo time delay of light measure distances. Since the velocity of light is so high, it is not possible to directly measure the echo time delay of reflections; therefore, a technique known as low-coherence

interferometry compares reflected light from the eye to that reflected from a reference path of known length. Different internal structures produce different time delays, and scanning the incident optical beam can generate cross-sectional images of the structures. These two-dimensional scans are then displayed in a color scale where “warm” colors (red to white) represent areas of high optical reflectivity, and “cool” colors (blue to black) represent areas of low reflectivity (Fig. 6.12). The commercially available OCT machines were originally developed by a team of bioengineers and physicians at the Massachusetts Institute of Technology in Boston, MA. The original machine was brought to market in 1995 (OCT-1) and revised in 2001 to be more user- and patient-friendly (OCT-2). The 2002 release of the OCT-3 enabled *in vivo* imaging of the posterior segment at resolutions of <10 µm. With the advent of spectral domain OCT (SD-OCT, Cirrus OCT; Carl Zeiss Meditec, Dublin, CA), high-resolution three-dimensional macular imaging is possible at greater than 50 times the speed of time domain OCT (TD-OCT), thereby offering new hope for imaging. The current technology thus permits excellent resolution and has been used to help diagnose and guide treatment for macular edema, macular and lamellar holes, epiretinal

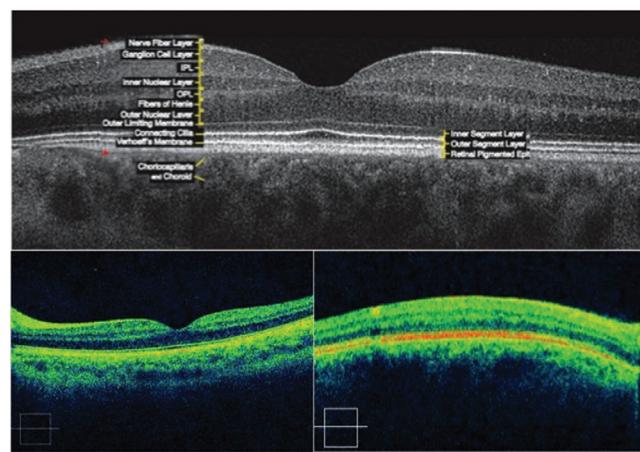


FIGURE 6.12 Results of ultra high definition spectral domain optical coherence tomography (OCT). showing individual retinal and subretinal anatomy (A–C). Bottom two photos are from a patient with infantile nystagmus syndrome.

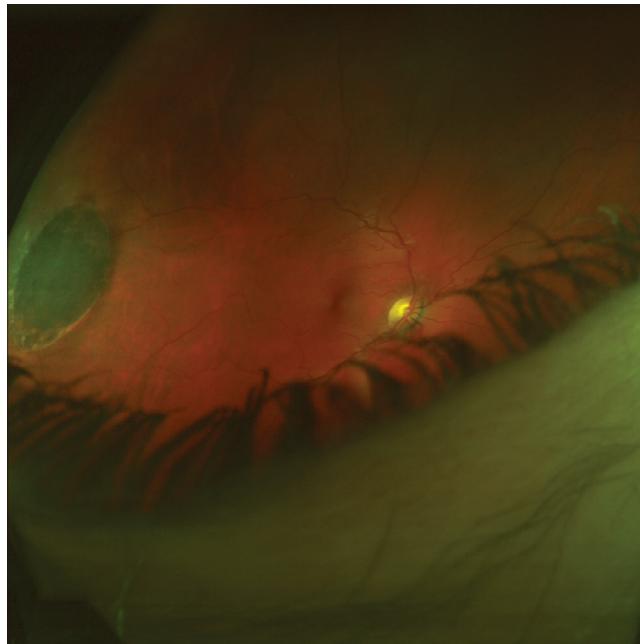


FIGURE 6.13 Example using Optos wide-field fundus camera photography showing a large pigmented lesion of the peripheral retina.

membranes and pseudoholes, central serous chorioretinopathy, age-related macular degeneration, glaucoma, and optic disc lesions.

Evaluation of the retina in patients with nystagmus can occasionally be difficult because of the constant motion of the eye. Eye motion has impeded the implementation of TD-OCT for diagnostic purposes in the nystagmus

population. In addition to eye motion, compromised vision and the shortened attention span of children often compound the challenge of quality TD-OCT macular image acquisition.

The new SD-OCT has allowed a more reliable study of patients with nystagmus.⁴¹ Its use for macular imaging has been reported in patients with albinism and nystagmus. It has



FIGURE 6.14 A stereo image of the optic nerves in a patient with oculocutaneous albinism and nystagmus showing optic nerve and peripapillary dysplasia, hypopigmentation, and normal vasculature.



FIGURE 6.15 A standard 30-degree fundus photograph of a patient with oculocutaneous albinism and nystagmus showing optic nerve dysplasia/hypoplasia, macular/foveal dysplasia, severe hypopigmentation, and vascular anomalies.

demonstrated several features in this population, including the persistence of an abnormal, reflective nerve fiber layer band; persistence of multiple inner retinal layers; loss of the normal thickened photoreceptor nerve layer; and increased reflectivity of the choroid due to decreased pigmentation.^{41,42} Chong et al. hypothesized that the most external retinal layers, specifically the external limiting membrane, photoreceptor inner segment layer, and photoreceptor outer segment layer, appeared normal.⁴² These foveal morphologic findings echo the description by Marmor et al. of an absent foveal pit, or fovea plana, and agree with histopathological studies and less detailed TD-OCT reported findings of either absent or rudimentary foveal pits in oculocutaneous albinism.⁴³ Our observations of the retinal morphology in the nystagmus population reveal that all cases of clinical foveal hypoplasia demonstrate a persistence of the outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, and nerve fiber layer. Our results agree with the description by Chong et al. of the involved retinal layers responsible for the lack of foveal differentiation in albinism.^{41,42}

Protocols, similar to the TruTrak eye-tracking software available on the Spectralis SD-OCT (Heidelberg Engineering, Vista, CA), are currently under way to align images with scanning

laser ophthalmoscope fundus landmarks, such as blood vessels, to remove eye motion artifact caused by microsaccades. Applying this software to the extreme case of eye motion, nystagmus, and incorporating it into a technology that is already available to clinicians would be an exciting and powerful application of the SD-OCT. Because the nystagmus population can also fall victim to common ocular diseases, such as diabetes, glaucoma, and macular degeneration, the use of SD-OCT, especially with software that may reduce eye motion and help recover three-dimensional spatial integrity, would be an important diagnostic and management tool.

6.2.4 Fundus Photography

Fundus photography in patients with nystagmus can be a very important adjunct in their clinical evaluation and follow-up. In those patients in whom retinal or optic nerve diseases are suspected, photography may be indispensable in assisting with diagnosis and prognosis of associated afferent system diseases.⁴⁴ There are multiple methods of obtaining photographs (Figs. 6.13, 6.14, and 6.15). The use of stereo photos, narrow-angle, high-magnification, and wide-angle, low-magnification techniques can be combined to obtain the best views of the macula/fovea, optic nerve head, and peripheral retina. In patients too young to cooperate for photography while awake, there are multiple types of handheld and portable intraocular cameras that can be used as part of an examination under anesthesia. (Some of the more popular cameras include TOPCON® Medical systems fundus camera [Paramus, NJ], Optos P200® instrument [Optos Plc, Fife, Scotland], NIDEK NM- 200D® [Nidek, Gamagori, 30-degree field], KOWA GENESIS D® [Tokyo, Japan], and RETCAM II® [Clarity Medical Systems, Pleasanton, CA]).

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Every truth passes through three stages before it is recognized. In the first it is ridiculed, in the second it is opposed, in the third it is regarded as self-evident.

—Arthur Schopenhauer (1788–1868)

THE NEW treatments discussed in this chapter result from the past half-century of eye-movement-based research (summarized in Chapters 2–5) into the different types of nystagmus found in infancy; that research forms the foundation for the various “clinical pearls” that have also emerged from studying ocular motor data from patients exhibiting nystagmus.

7.1 MEDICAL

There are a number of signs and symptoms due to nystagmus that are amenable to treatment. The first and most obvious is *decreased vision* (“central visual acuity,” “gaze-angle” acuity, near acuity). Correction of significant refractive errors in children with nystagmus is the single most powerful therapeutic intervention for improving vision and visual function in these patients. Refractive etiologies of decreased “vision” include either one or a combination of conditions, for example, myopia, hyperopia, astigmatism, and anisometropia.^{1–3} These refractive conditions can contribute significantly to already impaired vision in patients with other “organic” etiologies of decreased vision, for example, amblyopia, optic nerve and/or retinal disease, oscillopsia, and the oscillation itself. The second is *anomalous head posturing* (AHP). The etiology of the AHP includes a “gaze-null” due to infantile nystagmus syndrome (INS) or acquired nystagmus (e.g., chin-down in downbeat nystagmus), an “aDDuction null” due to FMNS (FMNS, manifest strabismus with the preferred eye fixing in aDDuction), convergence damping or purposive esotropia

(“nystagmus blockage”) due to INS, and a periodically changing head posture due to asymmetric, (a)periodic, alternating nystagmus (APAN).⁴ The prevalence of AHP in 37 patients with strabismus and nystagmus was INS in 23 (62%); FMNS in 12 (32%) and incomitant strabismus and SN were each in 1 patient (3% each).⁵ The third is *oscillopsia*, which is usually due to either acquired nystagmus or a change in the sensory/motor status of the patient with INS (e.g., “decompensated” strabismus, a change in the gaze null angle or decreasing acuity).⁶ Other less common associated signs and symptoms include hypoaccommodation (can be associated with acquired nystagmus and/or INS) and photophobia (INS associated with the congenital cone dystrophy’s and albinism).² General treatment medical and surgical indications and guidelines are outlined in Tables 7.1^{7–20} and 7.2 (some for investigational use only).

Nonsurgical treatment of involuntary ocular oscillations has been part of therapeutic interventions for as long as humans have suffered from their symptoms. Older treatments include iodide, bromides, atropine, and quinine.²¹ Knowledge of the pathogenesis of a form of nystagmus should suggest the treatment. It is essential to carefully evaluate patients before and during therapy for abnormal eye movements. In the case of new treatments, it is best to carry out prospective, controlled, masked trials. Careful measurements of binocular and monocular visual acuity using validated, age-appropriate acuity testing methods and systematic eye-movement examination and recordings are essential.

Table 7.1 Medical Treatment of Nystagmus

NYSTAGMUS TYPE	TREATMENTS
Infantile nystagmus syndrome	Fresnell prisms, orthoptics, gabapentin, baclofen, biofeedback, acupuncture
Acquired pendular nystagmus	Fresnell prisms, orthoptics, gabapentin, baclofen, clonazepam, cannabis, alcohol, carbamazepine, 5-hydroxytryptophan, scopolamine, memantine, botox, trihexyphenidyl, cannabis, alcohol as part of the syndrome of oculopalatal tremor (“myoclonus”): gabapentin, valproate, trihexyphenidyl
Peripheral vestibular	Positional exercises, heta-histidine, cinnarizine, acetazolamide, diphenhydramine, promethazine, prochlorperazine, ondansetron
Downbeat	3,4 Diaminopyridine, clonazepam, gabapentin, clonazepam, baclofen, trihexyphenidyl, acetazolamide (associated with episodic ataxia type II), baclofen, clonazepam, gabapentin
Upbeat	Baclofen, botox
Periodic alternating	Baclofen, clonazepam, alcohol, gabapentin
Seesaw	Baclofen, propanolol, clonazepam, methylphenidate
Saccadic intrusions/oscillations	Carbamazepine, propanolol, timolol (topical)
Superior oblique myokymia	Corticosteroids, propanolol, clonazepam, baclofen, clonazepam, gabapentin, intravenous immunoglobulin, plasma exchange
Opsoclonus	Carbamazepine
Ocular motor neuromyotonia	Prism, orthoptics
Voluntary ocular flutter	Prism, orthoptics
Chronic internuclear ophthalmoplegia	Prism, orthoptics

7.1.1 Optical

The timely, accurate, and consistent correction of ametropia in patients with nystagmus is the single best method of improving vision and visual function. The use of telescopes, magnification, and other low-vision aids are valuable refractive adjuncts that can be used situationally in nystagmus patients with and without associated sensory system deficits.²² Some US states allow the use of telescopes to obtain a limited driver's license.

A different approach to the treatment of acquired nystagmus has been the use of an optical system that stabilizes images on the retina.^{23,24} This system consists of a high-plus

spectacle lens worn in combination with a high-minus contact lens (see Fig. 7.1). The system is designed on the principle that stabilization of images on the retina could be achieved if the power of the spectacle lens focused the primary image close to the center of rotation of the eye. However, such images are then defocused, and a contact lens is required to extend the clear image back onto the retina. Since the contact lens moves with the eye, it does not negate the effect of retinal image stabilization produced by the spectacle lens. With such a system, it is possible to achieve up to about 90% stabilization of images upon the retina. However, there are several limitations to the system. One is that it

Table 7.2 Summary of Nystagmus Intervention

NYSTAGMUS	TREATMENTS	RESULTS	MECHANISMS
Infantile nystagmus syndrome	Eye-muscle surgery Contact lenses Prisms Memantine Gabapentin Biofeedback Acupuncture Spectacles	Improvement in acuity, head turn, contrast sensitivity, gaze-dependent vision, nystagmus foveation, width of null zone, recognition time	Afferent interruption Mechanical null-zone repositioning Central nervous system areas affected by medications
Periodic alternating nystagmus	Baclofen Eye-muscle surgery Gabapentin	Improvement in rhythm, foveation, head movements, head posture, acuity	Central nervous system GABA agonist Null point movement Afference interruption
Downbeat nystagmus	3,4-Diaminopyridine Eye-muscle surgery (chin-down posture) Botulinum A injection	Improved oscillopsia, acuity, head posture	Restores inhibition of upward drift through K ⁺ blockade Muscle paresis Null-zone shift
Upbeat nystagmus	3,4-Diaminopyridine Eye-muscle surgery (chin-up posture) Botulinum A injection	Improved oscillopsia, acuity, head posture	Restores inhibition of upward drift through K ⁺ blockade Muscle paresis Null-zone shift
Acquired pendular nystagmus	Gabapentin Memantine Eye-muscle surgery Servomechanical	Improved acuity, nystagmus, oscillopsia	NMDA receptor inhibition Glutamate antagonism Image stabilization
Fusion maldevelopment nystagmus syndrome	Prisms Spectacles Eye-muscle surgery Botulinum A injection	Improved binocular acuity, head posture, nystagmus	Fusion promotion Afference interruption Muscle paresis
Oculopalatal tremor	Vertical rectus tenotomy	Decreased oscillopsia	Afference interruption

inhibits eye movements (including the vestibulo-ocular reflex and vergence) and thus is useful only when the patient is stationary and is viewing monocularly. Another is that with the highest power components (contact lens of -58.00 diopters and spectacle lens of +32.00 diopters), the field of view is limited. The latter degrades visual function and is one of the key problems in

INS due to sharp null zones. Some patients with ataxia or tremor (such as those with multiple sclerosis) have difficulty inserting the contact lens. However, initial problems posed by rigid polymethyl methacrylate contact lenses can be overcome by using gas-permeable or even soft contact lenses. Most patients do not need the highest power components for oscillopsia to be

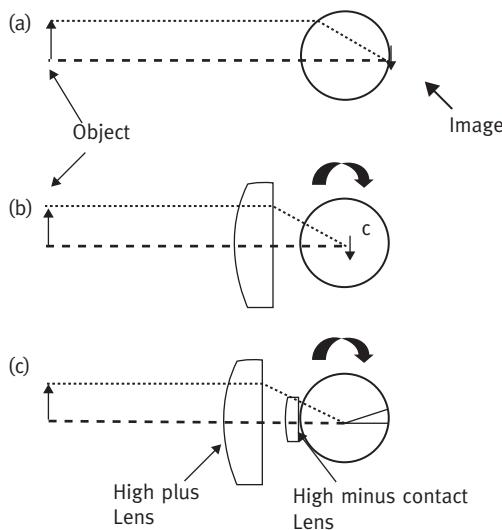


FIGURE 7.1 Optical method of retinal image stabilization using a high-power biconvex (+) field lens and a high-power concave (-) lens to stabilize a distance image in the center of rotation of the eye and subsequently move it posteriorly on the retina. (a) Normal inverted projection of an object. (b) The field lens refocuses the inverted image at the center of the globe where it is stable despite eye motion. (c) The contact lens refocuses the stable image on the retina.

abolished or vision to be improved. In selected patients the device may prove useful for limited periods of time, for example, if the patient wishes to watch a television program. It is not a useful therapy in INS.

A more recent innovation has been to use an electronic circuit to distinguish between the nystagmus oscillations and normal eye movements.⁹ This approach is most applicable in patients with pendular nystagmus. Eye movements are measured using an infrared sensor and, after filtering, fed to a phase-locked loop that generates a signal similar to the nystagmus but is insensitive to other eye movements, such as saccades. This electronic signal is then used to rotate Risley prisms, through which the patient views the environment. When the Risley prisms rotate in synchrony with the patient's nystagmus, they negate the visual effects of the ocular oscillations. Improvement and miniaturization

of a prototype device may eventually lead to a spectacle-mounted device that selectively cancels out the visual effects of pathological nystagmus.

7.1.1.1 VERSION PRISMS

The use of prism treatment is dependent on whether the AHP is caused by a “gaze null” associated with INS or acquired nystagmus or an “adduction null” associated with FMNS.^{25–28} Version prisms move objects in the visual field to the null position (see Fig. 7.2). Thus, objects in primary position may be viewed without an AHP. Unfortunately, version prisms are usually not feasible due to the large gaze angles needed to minimize the nystagmus which require prohibitive amount of prism correction in the spectacle plane; that is, a 20° gaze null requires ~50 prism diopters spectacles.^{26,27} Thus, only Fresnell type press-on prisms can straighten the head. Since acuity is often decreased with the use of Fresnell and large amounts of “ground-in” prism, this method is rarely used for treatment. Nonetheless, this is useful for measuring the AHP in terms of “prism diopters.” The prism diopter measurement can then be used as a guide for surgical treatment. It is our experience and that of others that patients who use a consistent, eccentric null zone to improve their vision and visual function benefit from having their nystagmus improved and null zone broadened, deepened, and moved within 5° of primary position, regardless of how much of the time they adopt a head posture. The use of “time spent posturing” is not a valid clinical indicator of the need for treatment. Many patients *do not* posture most of the time because they *cannot* posture most of the time, and, if they could, they would. The neck and facial muscles prohibit constant use of an eccentric head posture.²⁹ Also, older patients diminish the time they use an AHP because of social pressures.

7.1.1.2 VERGENCE PRISMS

If the patient has congenital nystagmus, fusion, and “damps” with convergence, the distance

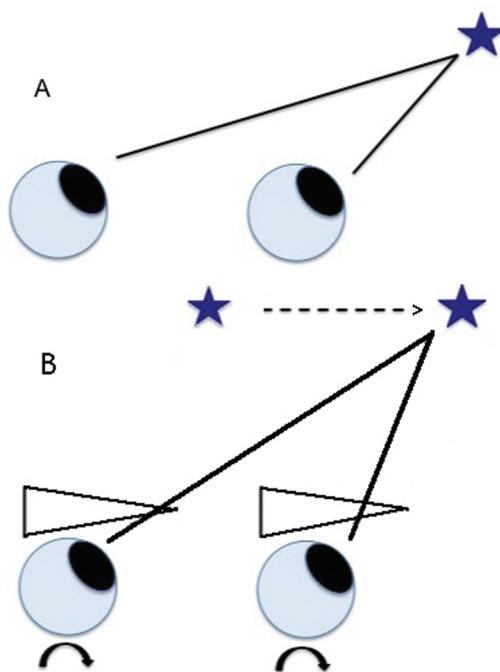


FIGURE 7.2 Use of bilateral prism with conjugate direction of base and apex to improve a head posture associated with an eccentric gaze nystagmus “null” position. (A) Right eccentric gaze null position. (B) Base-out prism over left eye and base-in prism over right eye (i.e., base-right prisms) to move primary position objects to the preferred null position.

acuity may benefit dramatically from the use of base-out prism spectacles (Fig. 7.3).^{26,27,30} These “convergence prisms” provide the optical approach for patients with infantile or acquired nystagmus whose nystagmus dampens when they view a near target. A useful starting point is 7.00-diopter base-out prism over each eye with best refraction combined with -0.50 to -1.00 diopter spheres to compensate for the vergence-induced accommodation (although the additional correction may not be needed in presbyopic individuals). Note that although additional vergence will usually further damp and improve INS waveforms, the total of 14 diopters we use for distance viewing allows for the vergence reserve needed for near viewing. It is fortunate that eyeglass frame designs are now smaller. These reduced eye-size spectacles with the combination of new high-index “plastic” lenses decrease weight,

edge, and central lens thickness, thereby minimizing their weight and associated optical aberrations. The written prescription usually contains the words “small eye size” and “high index lenses” to assist both the optical dispenser and the patient. If the patient does respond to the prisms in the office (“fast prism adaptation”), he or she will also respond to a bimedial rectus recession surgical procedure. This procedure may be an alternative to prism spectacles in patients who have no other significant refractive error (see surgical treatments in Section 7.2).

7.1.1.3 CONTACT LENSES

From 1973 to 1987, 210 contact lenses were fitted in 112 patients with nystagmus and a refraction anomaly. In 79%, it was possible to correct myopia or a myopic or mixed form of astigmatism.

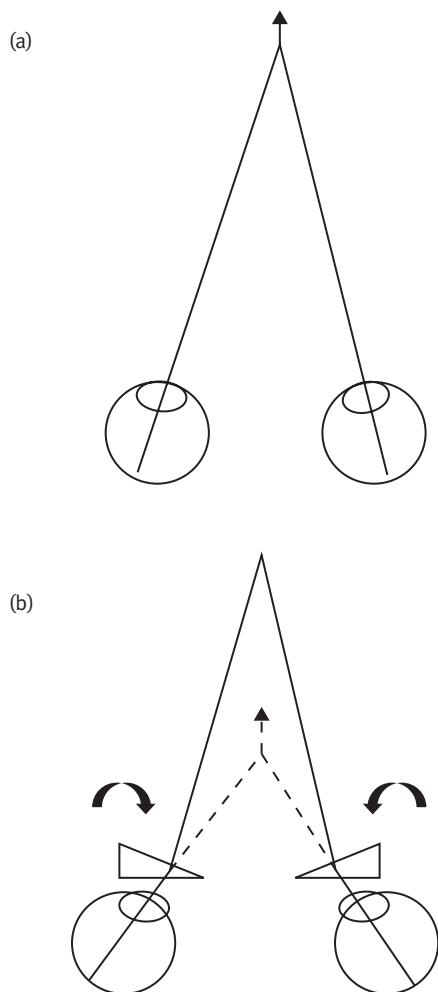


FIGURE 7.3 Use of base-out prisms to stimulate convergence and “damp” nystagmus. (a) Prior to placement of base-out prism in front of each eye. (b) Induced fusional convergence due to base-out prism.

The visual acuity improved significantly and the intensity of the nystagmus was reduced. The hard lenses were well tolerated in all patients. In a short report, patients with INS had two evaluations separated by at least 1 week (one with spectacles, one with contact lenses), including visual acuity, contrast sensitivity, oscillopsia scale, quality of life questionnaire (NEI VFQ-25), and eye-movement recording with an infrared tracking system.³¹ All patients subjectively preferred contact lenses to spectacles; some saying

they could “see better.” Their contrast sensitivity and VFQ-25 scores were improved with contact lenses compared with spectacles alone. Several parameters of nystagmus, uncorrelated to acuity (e.g., frequency, amplitude, and peak slow-phase velocity) showed no change in two patients, worsening in one patient and improvement in one patient. The authors suggested that some of the clinical improvement may result from a better optical correction of their refractive error with contact lenses than with spectacles rather than due to INS damping as had been previously demonstrated.³² However, one patient who used spectacles plus planar contact lenses also showed improvement—contradicting their speculation. No eye-movement data were presented to allow evaluation of the actual nystagmus waveform changes nor were the patients prescreened to determine which might benefit from the exteroceptive input produced by the contact lenses; patients with well-developed foveation periods (i.e., high eXpanded Nystagmus Acuity Function [NAFX] values) cannot show much improvement with any therapy. Also, the only nystagmus parameter correlated to acuity that was measured (foveation time) was defined by fixed position and velocity criteria rather than the idiosyncratic criteria dictated by the wide range of INS waveforms in patients; the latter is used in calculating the NAFX. Finally, the single most important factor in improving visual function, widening of the gaze-angle range with high acuity, was not measured. Other studies, using eye-movement data and the NAFX, demonstrated that soft contact lenses improved INS waveforms over a broad range of gaze angles and compared favorably with other therapies.^{33–35}

A special contact lens with a centrally tinted area (absorption 80%) that is slightly greater in diameter than the pupil under daylight conditions can correct ametropia and reduce light exposure and dazzle in a cosmetically much better way.² Tinted spectacle or contact lenses may be useful in relieving photophobia associated with a number of cone disorders, including achromatopsia. In addition to decreasing light sensitivity, tinted lenses have been reported to improve visual acuity, decrease the size of central scotomata, enlarge peripheral visual field,

and enhance visibility of long wavelength stimuli in bright illumination.³⁶

7.1.1.4 CORRECTION OF AMETROPIA / ANISOMETROPIA

In a report by Egorova, significant ametropia was diagnosed in 98.9% of 670 school children with varied ocular pathology.³⁷ Myopia was detected in 48.9%, hyperopia in 50.0%, astigmatism in 97.8%; in 38.6%, it exceeded 2.0 diopters, which was mainly encountered at the retinopathy of prematurely newborns, albinism, and congenital myopia. Anisometropia exceeded 2.0 diopters in 21.8% of cases; with highest anisometropia more frequent in patients with retinopathy of prematurity, infantile myopia, and aphakia. Nystagmus was present in 46.4% of children. The spectacle vision correction was found to be effective in improving vision and visual function in 94.8% of patients.

In adults and older children, a subjective refraction is the foundation for any type of refractive therapy. All “refractionists” develop their own method in this regard, and each of their idiosyncrasies assists them with rapid and accurate subjective refraction. Our method is the following. Try to “ignore” the oscillation and start with the distance retinoscopy in a phoropter (in those patients without an AHP) or trial frame (in those patients who have a significant AHP). The next step is to do binocular refraction. This goes against the classic teaching for subjective refraction, but it is *the most important step* in evaluating these patients because many (over 50%) will have significant changes in their nystagmus under complete monocular conditions (often decreasing their best possible acuity). The best way to do this is to fog the eye that is not being refracted with only enough extra plus to decrease the vision in that eye by 1–3 lines. Many patients with coincidental strabismus (about 50% of the childhood nystagmus population) can fix well enough with one eye at a time, and be subjectively aware of this, so no fogging is necessary. Now your usual routine for subjective refraction can be accomplished.

Once subjective refraction is completed, two other optical maneuvers can be performed.

If the patient has INS and is orthophoric, add 7 diopters of base-out prism in front of each eye with an additional -1.00 sphere (for the coincidental vergence-induced accommodation) to test the effect of “convergence damping” on acuity at distance. The improvements in acuity, nystagmus intensity, and AHP obtained by this maneuver can be quite impressive in this subset of INS patients without strabismus. The second maneuver is to add prisms to correct the strabismic deviation. If this assists with sensory fusion or any binocular cooperation, the patient’s nystagmus is often reduced, potentially improving acuity and/or other visual functions. Binocular visual acuity is tested before and after these maneuvers, demonstrating whether they are effective. If they are, they can be incorporated in a treatment approach.

All nystagmus patients should also be evaluated with an objective refraction procedure. In children and many adults, a complete cycloplegic refraction (e.g., 40 minutes after 1% cyclogyl, 50–60 minutes after 1% atropine) provides additional and important data for treatment decisions. In many adult patients with nystagmus from childhood, there are uncorrected (and now “latent”) refractive errors. The error is usually mixed astigmatism or hyperopia and is not discovered with subjective refraction. Start again with the retinoscopic findings and, if the patient is verbal, do binocular refraction for distance, as described earlier. In patients whose refraction is different under cycloplegia, record both subjective and objective refraction for decision making regarding spectacle prescription. In patients who are not verbal, observation of changes in nystagmus, AHP, or strabismus after trying the two prism maneuvers mentioned earlier can assist with deciding their effectiveness. Although there are no “universal” rules for amount of correction, the following general approaches have been successful in our experience with these patients. The full cycloplegic and anisometropic correction is usually prescribed in children up to about 10 years of age. Many adults may not be able to tolerate their cycloplegic refraction, and they should be given the most they can tolerate during subjective refraction (see aforementioned technique). In addition, these patients should

be brought back to the office about 4–6 weeks later to try to “push” more of the “latent refractive error” subjectively. Even some adult patients will respond over time with increased acuity and acceptance of large amounts of hyperopia, astigmatism, and anisometropic refractive errors.

7.1.1.5 INTRAOCULAR LENSES

Implantation of prosthetic iris devices (intraocular lenses) appears to be useful in the management of patients with nystagmus and iris deficiency secondary to albinism or aniridia.^{38–42} Although a long way from being considered standard of care in patients with nystagmus and iris defects, as a whole, this method of treatment may become acceptable for those who have additional ocular morbidity such as severe ametropia or iris defects.

7.1.1.6 REFRACTIVE SURGERY

Patients with nystagmus have had successful refractive surgery to correct their refractive error using a variety of laser systems.^{43–47} These reports suggest that laser refractive surgery may be safely and accurately performed in patients with INS. The BSCVA may improve in certain patients postoperatively. By using the Intralase femtosecond laser and an active tracking system with or without mechanical fixation, laser refractive surgery may be safely and accurately performed in selected cases of nystagmus. A large prospective trial aimed at safety and efficacy needs to be performed to confirm that the device is safe and suitable for patients with INS.

7.1.2 Pharmacological

Nystagmus caused by peripheral vestibular imbalance usually resolves spontaneously over the course of a few days because of central adaptive mechanisms. Drug treatments play only a minor role, mainly to control attendant vertigo and nausea. Drugs with antihistamine, anticholinergic, and phenothiazine properties remain the most popular approach to symptom management.¹⁸ In vestibular neuritis, recovery of the peripheral vestibular function can be improved

by oral corticosteroids; in Meniere disease, there is first evidence that high-dose, long-term administration of betahistine reduces attack frequency; carbamazepine or oxcarbamazepine is the treatment of first choice in vestibular paroxysmia, a disorder mainly caused by neurovascular cross-compression.⁴⁸

Clonazepam is reported to reduce downbeat nystagmus (DBN) from a variety of causes.⁴⁹ The GABA agonist baclofen is reported to reduce DBN and associated oscillopsia.⁵⁰ The anticholinergic drug scopolamine reduces DBN when given intravenously, but oral anticholinergic agents such as trihexyphenidyl produce only a modest improvement, which is offset by substantial side effects.⁵¹ A new approach to the treatment of DBN arose out of the seminal observation that nystagmus occurring in episodic ataxia type 2 responds to acetazolamide; this disorder is now known to be a calcium channelopathy.⁴⁸ Strupp et al. showed that 10 of 17 patients with DBN showed a decrease of more than 50% in their nystagmus 30 minutes after ingesting 20 mg of 3,4-diaminopyridine (DAP).⁵² This medication was generally well tolerated, although it is known to induce seizures in some subjects. In a study of 10 patients with spinocerebellar atrophy, Tsumeniet et al. found that DAP may be effective on DBN and oscillopsia, although it was not proved to be effective on other symptoms of ataxia in these patients.⁵³

Upbeat nystagmus (UBN) is occasionally suppressed by clonazepam, but it often resolves spontaneously over a few months.²⁰ Glauser et al. showed that UBN can be reduced DAP causing relief from distressing oscillopsia, and impaired upward smooth pursuit.⁵⁴ Baclofen also reduces nystagmus slow-phase velocity and distressing oscillopsia in patients with UBN.⁵⁵ The response to baclofen appears to be a GABA-B-ergic effect with augmentation of the physiological inhibitory influence of the vestibulo-cerebellum on the vestibular nuclei with subsequent inhibitory effect on the velocity storage mechanism.

Adaptive mechanisms that attempt to hold velocity storage in check cause an oscillating vestibular imbalance, manifest as periodic alternating nystagmus (PAN). Baclofen is effective treatment in most cases of acquired and some

cases of infantile PAN.^{4,56} Individual patients with seesaw nystagmus (SSN) have been reported to benefit from gabapentin, clonazepam, or alcohol.⁵⁷

The most effective treatments for acquired pendular nystagmus (APN) in association with disorders of central myelin are gabapentin and memantine.²⁰ Other drugs with presumed GABAergic effects, such as clonazepam and valproate, also help some patients. Isoniazid has also been studied as treatment for APN in three patients with multiple sclerosis, and reduced nystagmus and relieved oscillopsia in two.⁵⁸ Of 15 patients with APN studied in a double-blind comparison with baclofen, visual acuity improved with gabapentin, but not with baclofen.¹¹ Memantine is a relatively new drug specially developed for use in moderate-to-severe dementia.⁵⁹ It is an uncompetitive N-methyl-D-aspartate receptor antagonist and reduces glutamatergic excitotoxicity. It has recently received approval from the US Food and Drug Administration for treatment of Alzheimer disease. Memantine has been in use in Germany for over 20 years, and it is known to be a safe and well-tolerated drug. Multiple studies have confirmed that APN, especially associated with multiple sclerosis, have shown a good response to oral memantine, with reduced nystagmus and improved vision and decreased visual symptoms.²⁰ Alcohol has been reported to variably suppress many forms of involuntary ocular oscillations, including APN.⁶⁰ Smoking cannabis has been reported to suppress both APN and INS but formal evaluations of this potential therapy are difficult to accomplish.^{61,62}

Although therapy with gabapentin, carbamazepine, 5-hydroxytryptophan, and scopolamine have been useful in selected patients with ocular palatal myoclonus, most do not respond to drug treatment.²⁰

In patients with saccadic oscillations, improvement in reading performance may be improved if they are suppressed using methylphenidate.⁶³ Several benzodiazepines (diazepam, clonazepam) and the barbiturate phenobarbital are reportedly effective in abolishing high-amplitude square-wave jerks and macrosaccadic oscillations.⁶⁴ Symptomatic treatment of the saccadic oscillations is unsatisfactory, although

propranolol, verapamil, clonazepam, and gabapentin have been reported to suppress them in individual patients.⁶⁴

Recovery of opsoclonus associated with brainstem encephalitis may be speeded by intravenous immunoglobulin.¹⁰ In opsoclonus associated with cancer, treatment of the tumor itself often does not ameliorate the neurological syndrome. Carbamazepine may prove effective treatment for ocular motor neuromyotonia.⁶⁵

Superior oblique myokymia spontaneously resolves in some patients and others are not sufficiently bothered by their symptoms that they request treatment. Individual patients have responded to carbamazepine, baclofen, *b*-adrenergic blocking agents, or gabapentin given systemically or topically.^{66,67} Patients who do not respond to drug therapy, who develop side effects from the drugs, or who do not wish to take drugs for their condition may experience complete relief of symptoms after extraocular muscle surgery.

7.1.3 Botulinum

An approach to treatment of nystagmus that has gained some popularity is injection of botulinum toxin into either the extraocular muscles or the retrobulbar space.⁶⁸ Using both techniques, Ruben et al. reported improvement of vision in most of their 12 patients with a variety of diagnoses.⁶⁹ The major side effect was ptosis. However, eye movements were not systematically measured and compared before and after injection. Repka et al. also described improvement of vision following retrobulbar injection of botulinum toxin in six patients and documented the effects on eye movements.⁷⁰ The main reservation expressed by these authors was the temporary nature of the treatment and the necessity for repeated injections. In other studies, nystagmus was abolished or reduced in the treated eye for about 2–3 months, but no patient was pleased with the results because of ptosis, diplopia, increase of nystagmus in the noninjected eye, or filamentary keratitis. The profound side effect of a poor to absent vestibulo-ocular reflex as a result of the injection contribute a new, and often overwhelming, visual

symptom to these patients often precluding repeat injections.

7.2 EYE-MUSCLE SURGERY

There is quantitative data that if the slow foveation periods occurring during each beat of nystagmus can be lengthened or increased by the patient or by therapeutic interventions (i.e., medicines, surgery, contact lenses, acupuncture, biofeedback) some of a patient's visual functions may be increased.^{71,72} In Anderson's second edition textbook printed in 1959, *Ocular Vertical Deviations and the Treatment of Nystagmus*, he states; "It has been found that such operation not only may greatly lessen torticollis, but may also improve vision by lessening the nystagmus itself."⁷³ The idea that eye-muscle surgery has visual system beneficial effects beyond the "mechanical" repositioning of the muscles or globe is a novel concept, initially predicted after post-Kestenbaum eye-movement data analysis,^{74,75} but only successfully demonstrated after years of careful analysis of patients, their eye-movement measurements of nystagmus, and hypothesis-driven animal and human trials.^{74,76–84}

7.2.1 General Principles

The first step, before considering therapies, was the establishment of definitive, differential diagnostic criteria for INS and other forms of nystagmus.⁸⁵ Here, accurate ocular motor recordings quickly demonstrated that they were both essential and invaluable. The key waveform characteristics that are pathognomonic for INS became easily distinguishable. No longer is "nystagmus" an acceptable diagnosis. Eye-movement recordings were to eventually be used to identify many different types of nystagmus and saccadic intrusions and oscillations (see Chapter 5, Tables 5.1 and 5.6). An integral part of waveform descriptions was identification of the portions of each cycle during which the image of the target was on the fovea (foveation periods) during fixation^{71,86} as well as during smooth pursuit^{87,88} and vestibulo-ocular movements.⁸⁹ Documentation of these important characteristics of INS 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 waveform characteristic(s); that is the primary outcome measure.

Although two medical goals of INS therapy may be reconstructive and visual acuity improvements, they are *not* the primary outcome measures.⁹⁰ Because measured visual acuity is the result of several variables (e.g., stress, afferent deficits, head position, eye position) whose relation to the INS (or FMNS) waveform is idiosyncratic, it is not always a good measure of real-world visual function.^{91,92} INS amplitude is the characteristic most directly related to cosmetic appearance; however, amplitude is not a good predictor of acuity or other visual function. A therapy that reduces amplitude may not improve acuity, and one that does improve acuity may not reduce amplitude. The waveform characteristics related to overall visual function 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.⁹³ It predicts best possible visual acuity.

The indications for eye-muscle surgery in any patient with nystagmus result from a thorough history, clinical evaluation, and special testing. Special testing may include neuroimaging, serological (blood, urine, spinal fluid) testing, electrophysiology (eye-movement recordings, electroretinography, visual evoked responses, dark adaptation), photography, and angiography. Once it has been determined that the ocular motor abnormality cannot be treated or improved as part of coincidental therapy of an underlying systemic condition, eye-muscle surgery can be considered. There is a two-fold purpose of eye-muscle surgery in patients with nystagmus. One is to center the preferred position of the eye(s) (and, therefore, the head), and the other is to improve the oscillation's beat-to-beat characteristics. There is a high association of strabismus and nystagmus, often allowing the surgeon to treat both at the same time.⁵ The two conditions often affect each other; improving

the strabismus may favorably affect the nystagmus and vice versa. The presence of an AHP may be present in both the infantile and acquired forms of nystagmus and, in both, surgery serves to position gaze (or the eyes) in the straight-ahead position.

Clinical Pearl: When performing simultaneous nystagmus and strabismus surgery, the procedure is determined by a combination of moving the eccentric null (straightening the head) using the preferred eye and correcting the remaining strabismus using the nonpreferred eye.

The idea that there is “neurological” benefit to surgery on the extraocular muscles has a long history.^{74,78} The postulation and clinical trials of a new surgical therapy for INS 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 and studying the eye movements of achiasmic Belgian sheep-dogs with INS and SSN.⁸⁰ In an early study of INS surgery (circa 1977), a profound change was noted in the shape of the nystagmus intensity versus gaze angle function. After Anderson-Kestenbaum surgery, in addition to the expected shift of this plot toward primary position, the breadth of the null region increased and the overall nystagmus intensity decreased.⁷⁴ It was reasoned that there were two independent effects of this surgery due to different mechanisms. The expected null shift toward primary position was mechanical due to the effective rotation of the globe opposite 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 removal (resection) and movement (recessions) of the muscle was the accompanying incision at its insertion (tenotomy) and reattachment, it was hypothesized that the tenotomy and reattachment alone was responsible for the favorable INS changes.⁷⁵ Initially, the procedure was simply called the tenotomy procedure, despite its description that accurately described

reattaching each muscle at its original point of insertion. Unfortunately, some took the procedure’s name “tenotomy” literally. Therefore, to avoid both misunderstanding and problematic surgeries, it is now referred to as the tenotomy and reattachment (T&R) procedure.

It was to take 20 years before access and testing of this hypothesis on an animal model of naturally exhibiting the pathognomonic INS waveforms occurred. In 1991, Dell’Osso was contacted by Robert W. Williams of the University of Tennessee, Memphis who provided videos of the horizontal nystagmus of several achiasmic Belgian sheep-dogs, asking whether they resembled human INS. LFD was struck by the similarity of the head posturing of the dogs and children with INS and arranged to document the waveforms to establish the diagnosis. The videos also revealed an SSN. In 1992, horizontal INS waveforms and vertical-torsional SSN was documented in the dogs.^{94–96} This was the first time nystagmus waveforms (i.e., the horizontal components) were recorded from an animal that had the characteristics of human INS, including foveating and braking saccades. In subsequent recordings, it was verified that all achiasmic dogs had both INS and SSN, including a dog with hemichiasma.^{94–96}

The animal model for INS 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. The hypothetical T&R procedure was first performed by Hertle (Dell’Osso assisted) 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 T&R procedure was performed on the four vertical recti and four obliques.⁹⁷ The first stage tested the efficacy of T&R on horizontal INS, and the second, on SSN. The results were immediately obvious; there was a profound damping of the horizontal INS over a broad range of gaze angles (stage 1) and the SSN was abolished (stage 2).⁹⁷ Eye-movement recordings over the next 7 months verified the profound and persistent nystagmus damping. The dog also exhibited immediate behavioral improvements that supported the prediction that the INS damping would increase his acuity.⁹⁷

As a result of the T&R hypothesis, based on analysis of human eye-movement data after Anderson-Kestenbaum procedures, and demonstration that T&R damped the INS in a canine model of human INS, a clinical trial of this procedure under the support of the National Eye Institute was performed.^{91,92} Pre- and post-T&R eye movement data were recorded at the Laboratory of Sensorimotor Research, NEI. The data were masked and analyzed by a separate expert ocular motor scientist at the Daroff-Dell'Osso Ocular Motility Laboratory. The first phase included 10 adults and the second, 5 children. After the data from up to 6 weeks after tenotomy for the first five adult subjects were analyzed, they were unmasked to determine whether phase 2 could be started. Preliminary results of these data showed improved NAFX scores and improved visual function. The NAFX values for all patients improved (average improvement was 48%).^{91,92}

The T&R procedure was tested on two monkeys said to have “congenital nystagmus” with mixed results.⁹⁸ However, closer examination of the eye-movement data revealed the monkeys had FMN and NOT nystagmus (see Chapters 2 and 3); they did not have IN. Thus far, no case of INS in monkeys has been confirmed by eye-movement data. However, multiple studies of the T&R procedure have demonstrated positive waveform and therapeutic results in confirmed cases of INS in dogs (achiasmic Belgian sheep-dogs and Briards with Leber congenital amaurosis) and hundreds of human patients with either INS or acquired nystagmus.^{82,91,92,97,99–103}

Insight into the physiology of this response has renewed the interest of the ocular motor basic-science community regarding ocular motor proprioception and its role in both involuntary ocular oscillations and normal ocular motor control.^{57,104} The tendino-scleral area of the global portion of the extraocular muscle where surgery is carried out is now called its “enthesis.” Recently identified and studied enthesial neurons by Hertle et al. and Buttner-Ennever et al. have shown them to have proprioceptive anatomy and physiology.^{105,106} They probably provide feedback that assists with alignment and stabilization of the eyes. These

structures are probably related to afferent central nervous system input, and disruption of them during surgery might influence postoperative outcome. Using rabies toxin as an anatomic tracer, it has been possible to show that an afferent group of ocular motor neurons (distinct from the classic oculomotor, trochlear, and abducens nuclei, and surrounding each of them) innervates these enthesial fibers.^{107–109}

The role of sensory receptors in eye muscles is not well understood, but there is physiological and clinical evidence for the presence of proprioceptive signals in many areas of the central nervous system. It is unclear which structures generate these sensory signals and which central neural pathways are involved. Three different types of receptors are associated with eye muscles: (1) muscle spindles, (2) palisade endings, and (3) Golgi tendon organs, but their occurrence varies widely between species.¹⁰⁸ A review of their organization shows that each receptor is mainly confined to a morphologically separate layer of the eye muscle. The palisade endings, which are unique to eye muscles, are associated with the global layer; and they have been found in all mammals studied so far.^{110,111} Their function is unknown. The muscle spindles, if they are present in a species, lie in the orbital layer, or at its junction to the global layer. Golgi tendon organs appear to be unique to sheep and goats, and so on. They lie in an outer distal marginal layer of the eye muscle, called the “peripheral patch layer” in sheep. The specific association between palisade endings and the multiply innervated type of muscle fibers of the global layer has led to the hypothesis that together they may act as a sensory receptor and provide a source of central proprioceptive signals.

Thus, eye-muscle surgery may improve the nystagmus waveform, and vision/visual function in some patients, by altering a proprioceptive feedback pathway that normally calibrates the ocular motor system. It has been repeatedly shown since the late 1990s that surgical disruption of the enthesis (and associated enthesial neuroanatomy) in patients with INS results in long-standing beneficial effects on nystagmus and visual function. The neurophysiological hypothesis for the “improvement”

in the nystagmus is that there is a reduction of small-signal gain of the ocular motor plant by interfering with enthesial, neural proprioceptive tension control.¹¹² Enthesial nerve signals from palisade-type non-twitch fibers are likely involved in modulating the gain of sensory feedback from the eye muscles analogous to the gamma-efferent loop that controls the gain of proprioceptive feedback in skeletal muscles. Neuropeptides, neurotransmitters, and membrane transport mechanisms may play an important role in the neurochemical functioning of these enthesial endings' membrane potential as it does in other sensory systems. Plasticity in the central ocular motor system may be modulated as a result of the peripheral "trauma" to the enthesial area. This posttraumatic plasticity facilitates enthesial neuronal feedback to central ocular motor areas continuing to enhance the developmentally disturbed circuit, resulting in the improved ocular oscillation of INS.

7.2.2 Classification

The type of operation used for nystagmus has not been systematically classified until recently. In 1953, Anderson and Kestenbaum independently suggested that an abnormal head posture related to nystagmus could be alleviated by surgery.^{73,113} In the following year Goto made similar suggestions.¹¹⁴ Anderson's proposal was for recession of the pair of yoke rectus muscles whose action was in the direction of the face turn. Goto suggested resection of the yoke antagonist muscles, and Kestenbaum favored surgery on all four horizontal recti muscles, although he also suggested the two eyes should have sequential surgery. It is the Kestenbaum strategy, with modifications, that is most commonly performed today, and his name tends to be attached to this surgical approach to nystagmus. A logical extension of these procedures was applied by Dermot Pierse of England in 1959.⁷⁶ He described two patients with nystagmus with the head held backward for maximum vision. He weakened both depressors (inferior rectus and superior obliques).

Many authors subsequently have published their results with similar operations.^{74,77,78,115–122}

Relevant studies of INS surgery^{74,91,92,97,123–134} are summarized in Table 7.3. Our approach to eye-muscle surgery in patients with nystagmus developed as a result of a need to improve multiple preoperative ocular motor and/or visual system abnormalities in this patient population. These include, but may be limited to, nystagmus, anomalous head posturing, strabismus, deficient acuity, stereopsis, motion processing, gaze dependent vision, and visual reaction time. The nine-operation system^{122,135} presented in Table 7.4 (see also Chapter 2, Section 2.4.3) allows the clinician to maximize surgical intervention in those patients in whom the *primary indication* for eye-muscle surgery is INS using one procedure with easily applicable clinical indications.

A few observations can be made as a result of using and analyzing this system. Most patients with the infantile forms of nystagmus (91%) have strabismus and/or an anomalous head posture and will benefit from some removal or repositioning of the extraocular muscles or tendons and not *only* horizontal rectus tenotomy with reattachment.^{122,136} The largest populations of patients have a combination of a head posture (horizontal or vertical) and/or strabismus. There is also a large population of patients who benefit from surgical intervention for a chin-up and chin-down head posture.^{122,136} In a study of 224 patients with INS, Abadi et al. found that 73% had spatial nulls within $1 \pm 10^\circ$ of the primary position, although 69% employed a compensatory head posture.¹³⁷ They found that patients with eccentric null zones at or beyond 20° always adopted a head posture. Head shaking was found in 27% and horizontal tropias were found in 62.4%. There is some evidence that the presence of a vertical head posture with INS is more commonly associated with diagnosable diseases of the prechiasmatic visual system, that is, albinism, optic nerve hypoplasia, and retinal dystrophy.^{2,4,136,138} It may be that clinicians have either not recognized these vertical null positions or there is less experience with their treatment; either way, those patients with a chin-down or chin-up posture should be eligible for surgical treatment in the same way, and for the same reason, as those with horizontal head postures.

Table 7.3 Summary of Interventional Treatment Trials for Infantile Nystagmus Syndrome

AUTHORS	YEAR	TYPE OF STUDY	SURGICAL AND PHARMACOLOGICAL TREATMENTS	OUTCOMES
Dell'Osso, Flynn	1979	Case series (N = 3)	Kestenbaum surgery for horizontal AHP	Null shift and broadening, VA \square in all cases
Carruthers	1995	Case series (N = 4)	Botox	VA \uparrow in 3/4
Gradstein, Reinecke, Wizov	1997	Case series (N = 9) Congenital PAN	Three prior Kestenbaum procedures, five recessions of horizontal recti, one had Baclofen	Kestenbaum: VA unchanged Rec.: AHP & VA \uparrow in all cases Baclofen: unsuccessful
Dell'Osso, Hertle, Williams, et al.	1999	Case study (N = 1), Canine	Severed and reattached the tendons of the extraocular muscles	Immediate and persistent visible, behavioral, and EOG effects
Graf, Droutras,	2000	Case series (N = 34)	Kestenbaum surgery for horizontal AHP	Long-term dose/response effect of 1.5°/mm
Kaufmann Lee, Lee, Kim, et al.	2000	Case series (N = 63)	Mod. Kestenbaum surgery (AHP), varying degrees, follow up > 5 m	Mean preop AHP 32° Mean postop AHP 5°
Graf	2002	Case series (N = 78)	Kestenbaum (N = 31) Artificial divergence (N = 27) Combined (N = 20)	AHP \downarrow from 30° to 10° AHP \downarrow from 30° to 5° AHP \downarrow from 30° to 7° \uparrow foveation broadened null zone
Hertle, Maybodi, Mellow, et al.	2002	Case study (N = 1)	Antianorexic drug (diethylpropionate)	VA 20/70 to 20/50
Alio, Chipont, Mulet, et al.	2003	Case series (N = 42)	Extensive recessions of the four horizontal rectus muscles	AHP \downarrow in all cases 21% \uparrow by 0.2 logMAR Consecutive XT three cases
Hertle, Dell'Osso, et al.	2003	Case series (N = 10)* one excluded from NAFX analysis	Tenotomy of all four horizontal recti with reattachment at original insertion Followed-up after 1 yr+	Mean foveation times \uparrow in 9/9 VA \uparrow in 5/10 NEI-VFQ-25 \uparrow in 9/10

(continued)

Table 7.3 (Continued)

AUTHORS	YEAR	TYPE OF STUDY	PHARMACOLOGICAL TREATMENTS	SURGICAL AND OUTCOMES
Kose, Egrilmez, Uretmen, et al.	2003	Case series (N = 12)	Retroequatorial recession of all four horizontal recti. Follow-up ranged 6–26 months	Intensity ↓ sig in all patients. VA ↑ in 10/12 Improvements
Cao, Xin, Wang, et al.	2004	Case series (N = 21)	Parks shift of neutral zone	Nystagmus ↓ VA ↑ 2–5 lines AHP ↓ in all cases
Erbagci, Gungor, Bekir	2004	Case series (N = 7)	Large recessions of four horizontal recti	VA ↑ in 5/7, (5/5) AHP & (5/7) intensity ↓
Hertle, Dell'Osso, Fitz Gibbon	2004	Case series (N = 5)	Tenotomy of all four horizontal recti with reattachment at original insertion	1 yr postop, 2/3 had persistent significant ↑ in NAFX and foveation times VA ↑ in 4/5
Hertle, Annninger, Yang, et al.	2004	Case series (N = 15)	Various surgery on all four horizontal recti	VA ↑ ≥ 0.1 LogMAR in 14/15 AHP ↓ Nystagmus ↓
Oleszczynska-Prost	2004	Case series (N = 32)	Botox	Amplitude ↓ in 29%–50% VA ↑ in all cases HT ↑

Table 7.4 Nystagmus Operation Classification System (Based on 100 Patients)**Operation 1—Eccentric Horizontal Null Position Alone (22%)***Indication*

Measurable or clinically observable eccentric gaze null with head posture in opposite direction

Preparation

Rule out aperiodic or periodic infantile subtype; no changing posture over 10 minutes of observation

Technique

- A. Recess lateral rectus 10.0 mm in the abducted eye + medial rectus 7.0 mm in the adducted eye with tenotomy and reattachment of the other horizontal recti for turns up to 20°
- B. Recess lateral rectus 10.0 mm on the abducted eye + medial rectus 7.0 mm on the adducted eye 10.0 mm and resect the medial rectus 7.0 mm on the abducted eye + resect the lateral rectus 11.0 mm on the adducted eye for head turns greater than 20°

Operation 2—Chin-Down Head Posture (+/- Strabismus) (16%)*Indication*

Chin-down head posture alone, nystagmus changes intensity in downgaze

Preparation

Rule out aperiodic or periodic infantile subtype, no changing posture over 10 minutes of observation

Technique

Bilateral inferior oblique myectomy plus bilateral superior rectus 5.0 mm recessions + recess or resect one horizontal rectus on each eye for strabismus

Operation 3—Strabismus Alone (15%)*Indication*

Nystagmus and horizontal strabismus with no head posture

Preparation

Treat refractive errors

Technique

Recess/resect on all four horizontal recti for the total deviation or bilateral recess for the total deviation plus tenotomy and reattachment on the remaining two horizontal recti

Operation 4—Head Posture + Strabismus (10%)*Indication*

Head posture plus strabismus

Preparation

Rule out aperiodic or periodic infantile subtype or esotropia with fusion maldevelopment and adduction damping, that is, no changing posture over 10 minutes of observation; determine fixing eye (eye driving the head posture)

Technique

Straighten the head with prism correction over the fixing eye, neutralize the resulting strabismic deviation with prism over the nonfixing (deviated) eye; perform bilateral recess/resect on each eye's respective measured prism correction or bilateral recess plus tenotomy and reattachment on the remaining two horizontal recti

(continued)

Table 7.4 (Continued)**Operation 5—Chin-Up Head Posture (+/- Strabismus) (10%)***Indication*

Chin-up head posture alone, nystagmus increased intensity in upgaze

Preparation

Rule out aperiodic or periodic infantile subtype; no changing posture over 10 minutes of observation

Technique

Bilateral superior oblique 5.0 mm tenectomy nasal to the superior rectus plus bilateral inferior rectus 5.0 mm recessions + recess or resect one horizontal recti on each eye for strabismus

Operation 6—Nystagmus Alone (About 7%–15% of Infantile Nystagmus Syndrome Population) (9%)*Indication*

Infantile nystagmus syndrome with or without periodicity and *NO* strabismus, static anomalous head posture, or fusion with convergence damping

Preparation

Rule out strabismus, static head posture, or convergence damping

Technique

Bilateral horizontal recti tenotomy and reattachment

Operation 7—Multiplanar Head Posture (+/- Strabismus) (7%)*Indication*

Combination chin-up/down and face turn

Preparation

Rule out aperiodic or periodic infantile subtype or esotropia with fusion maldevelopment and adduction damping, that is, no changing head posture over 10 minutes of observation

Technique

Three muscles each eye; combine respective oblique plus vertical recti (above) for chin-up/down with 9.0–10.0 mm recess of lateral rectus of abducting eye and 7.0–8.0 mm recess of medial rectus of adducting eye for face turn or recess or resect one horizontal rectus on each eye for strabismus with no face turn

Operation 8—Convergence Damping (Artificial Divergence) (6%)*Indication*

Binocular function (stereopsis) with measurable improvement or observable convergence damping

Preparation

Prism adapt with 7 BO each eye, not Fresnell

Technique

Bilateral medial rectus recess 3.0 mm +/- bilateral lateral rectus tenotomy and reattachment

Operation 9—Torsional Head Posture Alone (5%)*Indication*

Torsional head posture alone

Preparation

Rule out aperiodic or periodic infantile subtype; no changing head posture over 10 minutes of observation

Technique

Horizontal transposition of vertical recti one full tendon width (hint: take the vertical recti off, move the eyes in the direction of the head posture, reattach the vertical recti), that is, right head tilt, RSrec nasal, RIrec temporal, LSrec temporal, LIrec nasal

Strabismus surgeons are reluctant to operate on the obliques without some obvious oblique dysfunction due to the potential of creating cyclovertical motor and sensory complications. Unfortunately, nystagmus surgeons are often required to operate on extraocular muscles without obvious dysfunction, including the obliques. This is especially true for chin-up and chin-down postures. The reason that we have preferred bilateral oblique and recti operation for chin-up and chin-down postures is that this combination will prevent secondary alphabet and cyclotorsional deviations more than combined vertical rectus recession and resection procedures. The key to surgical success in this group of patients is attention to detail with equal oblique and recti surgery on each eye. The only consequence of surgery is usually a 15%–20% comitant, limitation of vertical gaze with some lid retraction.

In our experience most patients (80%–85%) with INS will have, in addition to their oscillation, either a clinically significant head posture, strabismus, or vergence damping alone or in some combination. These facts require that the surgical approach to treatment incorporate all the patient's findings. Thus, the rationale for

classification of surgical procedures into nine separate but related types was necessary. Twenty percent had operation 1 (eccentric horizontal head position alone), 15% had operation 2 (chin-down head posture +/- strabismus), 12% had operation 3 (strabismus alone), 12% had operation 4 (horizontal head posture + strabismus), 10% had operation 5 (chin-up head posture +/- strabismus), 11% had operation 6 (nystagmus alone, no head posture, vergence damping or strabismus), 8% had operation 7 (multiplanar head posture +/- strabismus), 8% had operation 8 (induced convergence alone), and 4% had operation 9 (torsional head posture alone). Each of the nine individual methods used to approach surgery on the extraocular muscles of both eyes is diagrammed in the figures of Appendix C.

The average changes in the visual acuities of the patients undergoing each of the nine operations are shown in Figure 7.4. As can be seen from those circled, patients with the poorest preoperative acuities received the most improvement, as was predicted by the NAFX versus percent improvement curve shown in Chapter 2, Figure 2.26. Because measured acuities reflect both sensory and motor deficits and posttherapy visual acuity

AVERAGE ACUITY COMPARISON PRE VS. POSTOP – ALL 9 OPERATIONS

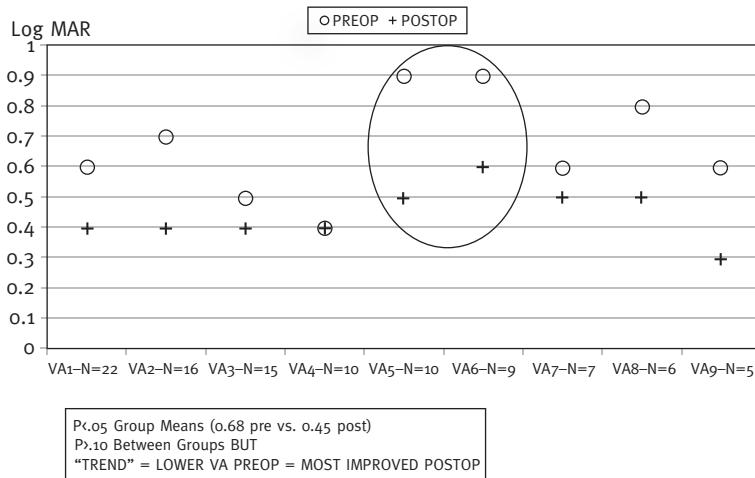


FIGURE 7.4 In 100 patients followed prospectively before and after eye-muscle surgery for infantile nystagmus, the group comparison showed best-binocular acuity significantly improved after surgery. Circled groups showed greatest improvements (see discussion in Section 7.2.2). The logMAR values shown reflect the negative of the logarithm of the decimal acuity.

is not a direct measure of that therapy, relative improvements cannot be used to compare the results of the different operations; only NAFX values can do that accurately. However, the longest foveation domain (LFD) measure translates directly into the range of gaze angles with the highest acuity, regardless of whether there are associated sensory deficits. Thus, the prediction of percent increase in LFD (also shown in Chapter 2, Fig. 2.26) is the actual percent broadening of the highest acuity range of gaze angles.

To better appreciate the implications of the NAFX and LFD plots in Chapter 2 and just how much broadening, shifting, and raising the NAFX peak improves the patient's overall visual function, Figures 7.5 and 7.7–7.9 were constructed to illustrate the difference between the gaze angles with maximal, albeit perhaps still poor, acuity that further degrades at gaze angles lateral to the NAFX peak. This type of illustration does not represent the *perceived* visual world; that perception is of uniform clarity (limited by peak visual acuity) just as normals perceive uniform clarity despite reduced acuity of targets lateral to the fovea. Instead, it illustrates the patient's profound acuity degradation at different gaze angles away from the peak gaze angle while the head is held in primary position.

In Figure 7.5 the gaze-dependent acuity of a patient with a narrow, lateral (leftward) null (sharp, lateral NAFX peak) appears with the head in primary position (top panel). To see objects/persons in primary position clearly, the head must be moved to the right (middle panel), and to see clearly in right gaze, the head must be moved further to the right (bottom panel). This is both stressful and time consuming in real-world situations and is why broadening the LFD is a prime goal in INS therapy; even normal acuity (20/20) would not alleviate the visual function deficit of a narrow range of gaze angles with that high acuity. This has historically been unappreciated or underappreciated by both physicians and family members and is why multiple visual acuity measurements must be made for all INS patients, before and after therapy.

There are two schools of thought regarding the actual amounts of resection and recession

one should perform to achieve a given amount of eye rotation in the Kestenbaum procedure. Flynn favored making equal amounts of recession and resection to place the eyes in a position equal to but in the opposite direction of the null angle. Values taken from the published curve⁷⁴ are shown in Table 7.5 (see Chapter 2, Fig. 2.30 for curve). Parks favored unequal amounts based on the difference in muscle strengths between the medial and lateral rectus muscles (see Table 7.6). Significantly, both methods have been used with success in INS surgeries. Although the values shown in the figures in Appendix C reflect the Parks approach, the advantage of the Flynn approach is that it retains homeostasis as much as possible. The reported success in INS treatment using several different formulae to determine the amounts of recession and resection needed suggested that the actual amounts were not as important as doing the surgery. The demonstration that the T&R portion of these surgeries was responsible for broadening the range of gaze angles with the patient's highest acuity provides an explanation for patient satisfaction and claims of being able to "see better" despite different amounts of globe rotation, and even when no improvement in peak acuity was measured.

Clinical Pearl: Determination of the amounts of recession and resection needed to rotate the eyes using bilateral recession and resection of the horizontal recti (A-K procedure) may be best accomplished by dividing the total amount of surgery (indicated by the curve given in Dell'Osso and Flynn 1979) in two and applying those equal amounts to the two antagonist muscles.

The issue of the timing of nystagmus surgery, with or without an associated AHP, is not settled.^{139,140} It is our opinion that early surgery (under 24 months of age) for INS may result in a more profound effect on the nystagmus and associated visual system development than later surgery (after 5–7 years of age);³ this is especially true for those INS patients with associated visual sensory deficits. We usually wait until the children are on their feet (about 10–14 months

Patient with a Narrow, Lateral Low-Acuity Visual Field



Patient with a Narrow, Lateral Low-Acuity Visual Field



Patient with a Narrow, Lateral Low-Acuity Visual Field



FIGURE 7.5 Illustrations of the clarity of portions of the visual field in an infantile nystagmus syndrome (INS) patient with a narrow, lateral, null (sharp, lateral eXpanded nystagmus acuity function [NAFX] peak) and how gaze angle (+) affects an INS patient's view of the world and the necessary head (H) shifts to maintain the same gaze angle and effectively move that lateral acuity peak across the visual field in order to see each portion clearly.

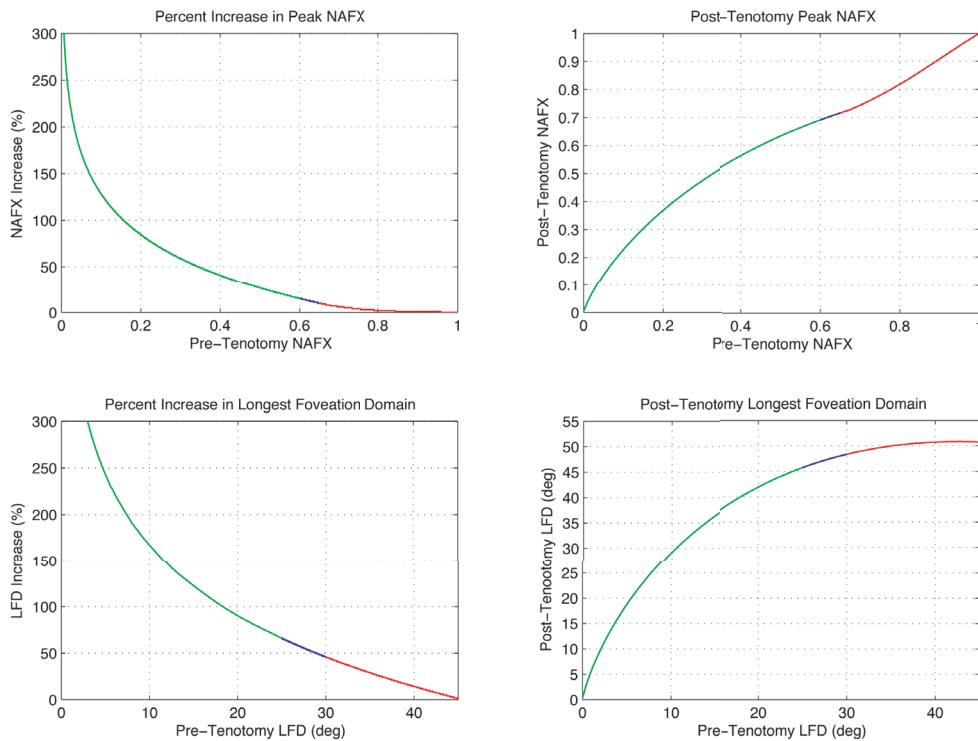


FIGURE 7.6 Plots of pre-tenotomy and reattachment (T&R) eXpanded nystagmus acuity function (NAFX) peak versus percent increase (top left panel) or post-T&R NAFX (top right panel) and pre-T&R longest foveation domain (LFD) versus percent increase (bottom left panel) or post-T&R LFD (bottom right panel). Colors of each curve illustrate the areas where excellent (green), good (blue), and poor (red) improvement will result.

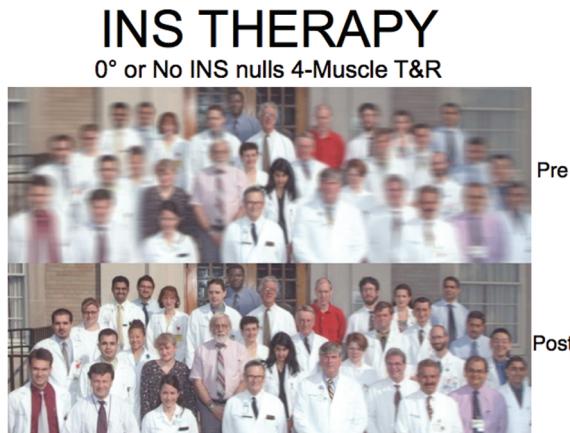


FIGURE 7.7 Illustrations of the clarity of portions of the visual field in an infantile nystagmus syndrome patient with a narrow, central, null (sharp, central eXpanded nystagmus acuity function [NAFX] peak) before and after tenotomy and reattachment (T&R) surgery. As noted, this procedure can also be used in cases where there are no nulls.

Table 7.5 Nystagmus Operation—Modified Bilateral Horizontal Recess/Resect

LEFT NULL ANGLE RIGHT FACE TURN	LEFT EYE		RIGHT EYE	
	(RECESS LR)	(RESECT MR)	(RECESS MR)	(RESECT LR)
Flynn (for <10°, four-muscle T&R)	10°	<1 mm	<1 mm	<1 mm
	15°	2.5 mm	2.5 mm	2.5 mm
	20°	6.5 mm	6.5 mm	6.5 mm
	30°	8.5 mm	8.5 mm	8.5 mm
	45°	9.5 mm	9 mm	9.5 mm
	50°	10.5 mm	10 mm	10.5 mm

LR, lateral rectus; MR, medial rectus; T&R, tenotomy and reattachment.

of age) unless there is an associated infantile strabismus that requires surgery. Early eye-muscle surgery for eye-movement disorders is not a new idea. The results of Birch et al. suggest that early surgical alignment in those patients with infantile esotropia is associated with better stereopsis and higher prevalence of fusion without adverse motor outcomes, because early surgery minimizes the *duration* of misalignment, not because alignment is achieved during an early critical period of visual maturation.^{141–143} Drover found in a comparison clinical trial that following surgery a comparison group of patients showed rapid development and possessed motor skills comparable to those of normal children, suggesting that early surgery is beneficial to both visual and motor development.¹⁴³ Early surgery for infantile esotropia promotes the

development of cortical visual motion processing, whereas later surgery is associated with abnormal mVEPs. Shirabe et al. concluded that early surgery in infantile esotropia is beneficial to achieve binocular visual function, but it was necessary to confirm a stable angle of deviation with accurate preoperative evaluation.¹⁴⁴ In the final report of the early versus late infantile strabismus surgery study, a controlled, prospective, multicenter study children operated early had better gross stereopsis at age 6 as compared to children operated late.¹⁴⁵ Human and animal studies conducted largely during the last 25 years support both the clinical insights that early ocular motor treatment is preferred. Although there are data suggesting improved results in early eye-muscle surgery (under 24 months of age) for nystagmus, the total picture is not clear.

Table 7.6 Nystagmus Operation—Traditional Bilateral Horizontal Recess/Resect

LEFT NULL ANGLE RIGHT FACE TURN	LEFT EYE		RIGHT EYE	
	(RECESS LR)	(RESECT MR)	(RECESS MR)	(RESECT LR)
Classic	<20°	7 mm	6 mm	5 mm
Parks	30°	9 mm	8 mm	6.5 mm
(+) 40%	45°	10 mm	8.5 mm	7 mm
(+) 60%	50°	11 mm	9.5 mm	8 mm
				12.5 mm

LR, lateral rectus; MR, medial rectus.

7.2.3 Preoperative Evaluation

7.2.3.1 VISUAL ACUITY

Valid measurement of visual acuity is best performed with refraction in place both binocularly and monocularly using one of three methods: the Teller Acuity Card (TAC) or Lea Symbols procedure in preverbal children, the amblyopia treatment study (ATS) ETDRS chart protocol (≥ 7 years of age), or the ATS single, surrounded, HOTV optotype protocol (< 7 years of age).^{146,147} Measurements are obtained in the patient's null position determined by the use of clinical evaluation, head posture measuring system +/- eye-movement recordings. Due to the patient's nystagmus, visual acuity is tested with the TAC's held vertically so that the gratings are horizontally oriented.¹⁴⁸ It is important to note that the ocular motor oscillation of INS is almost uniformly horizontal, with horizontal intensity changes seen even in those patients with torsional and vertical head postures, thus allowing the testing of acuity with vertically held TAC valid for all these patients.

7.2.3.2 OCULAR MOTOR AND STANDARD CLINICAL EVALUATIONS

Ocular motor examination includes a determination of heterophoria/tropia at distance (3–6 m) and near (33 cm) in all diagnostic positions of gaze. Sensory adaptations such as suppression, anomalous retinal correspondence, and varied levels of fusion should be determined in standard fashion. Cycloplegic refraction, tonometry, and examination of the anterior and posterior segments should be performed on all patients. Fundus photographs, electroretinography, and visual evoked potential testing are performed when retinal and/or optic nerve pathology are clinically suspected. Evaluation of the ocular motor oscillations includes measurement of any anomalous head posture and changes in the oscillation in primary position, at near, and in diagnostic positions of gaze under monocular and binocular conditions.

7.2.3.3 STRABISMUS

Because of the prevalence of strabismus in patients with INS, the type, amount, and comitance of

the strabismus should be measured as part of the clinical exam. However, our analysis of thousands of eye-movement records revealed that often the strabismus is time varying as well as gaze-angle dependent. This has provided further importance for the use of such data. By observing shifts in the alignments of the foveation periods from each eye with the target position, the fixating eye can be identified along with the amount and stability of the strabismus angle.

As has been stated previously, both the nystagmus surgery and any necessary strabismus surgery should be performed in the same procedure. For instance, if an INS patient had an NAFX peak (nystagmus "null") 20° to the right and a 19° left-eye esotropia when looking 20° to the right, the total leftward surgical shift (recession plus resection) of each eye for the nystagmus portion of the procedure, determined from Chapter 2, Figure 2.30, would be 11 mm (i.e., RLR: 5.5 mm recession; RMR: 5.5 mm resection; LMR: 5.5 mm recession; LLR: 5.5 mm resection). The strabismus portion would require 9.8 mm total to rotate the deviated left eye to the left. Thus, the combined surgery would be RLR: 5.5 mm recession; RMR: 5.5 mm resection; LMR: $5.5 + 4.9 = 10.4$ mm recession; LLR: $5.5 + 4.9 = 10.4$ mm resection. If, on the other hand, the patient had a 15° left-eye exotropia, the combined surgery would be RLR: 5.5 mm recession; RMR: 5.5 mm resection; LMR: $5.5 - 4.9 = 0.6$ mm recession; LLR: $5.5 - 4.9 = 0.6$ mm resection. In this case, doing the indicated recession and resection of the right eye and simply performing a T&R procedure on the LMR and LLR would yield approximately the same results. If the patient alternated the fixating eye, the total strabismus correction could be split between the appropriate muscles of each eye (i.e., add 4.9 mm to the recessions of the RLR and LMR for the esotropic example or subtract 4.9 mm from the recessions of the RLR and LMR for the exotropic example). The broadening effects of the built-in T&Rs will overcome small deviations from the calculated numbers.

7.2.3.4 EYE-MOVEMENT RECORDINGS

The horizontal and vertical eye-movement recordings are most easily accomplished using

an IR reflection method or digital video eye-movement system (see Appendix A). Key to both accurate, repeatable diagnosis and waveform and NAFX analysis of the fixating eye is accurate calibration of each eye individually while the other is occluded. As described earlier, it is also necessary for accurate, time-variable strabismus analysis. While the careful use of the clinical exam, history, and clinical motility tests can help identify some types of nystagmus; only eye-movement data can reliably do so for all types.

One of the newest and most important uses of eye-movement data analysis (using the NAFX) is its unique ability to differentiate the two components (sensory and motor) of measured visual acuity. When one measures visual acuity in an INS patient, the resultant value is due to *both* the sensory and motor deficits. However, the percentage of each is unknown and that means that the potential for improvement is also unknown. All current therapies for INS are aimed at improving the INS waveform, which would then improve acuity, both peak and gaze-angle acuity. However, one cannot predict how much improvement in measured acuity is possible knowing only its measured value. In one patient, that value might be totally dependent on a sensory deficit (i.e., when the INS waveform was of the highest quality). In another patient with the same measured acuity, it could be totally due to a poor INS waveform. In the first case, no improvement is possible with any known INS therapy; in the second case, a high percentage improvement is possible, depending on the NAFX value. In most cases, there are both sensory and motor deficits compromising visual acuity, and significant improvement in visual function is possible despite the sensory deficit. The methodology available to estimate the therapeutic improvement possible regardless of the relative percentages of sensory and motor deficits is discussed in Section 7.5.

7.2.3.5 HEAD-POSTURE MEASUREMENTS (“NULL ZONES”)

Head posturing due to INS and not other central nervous system or vestibular abnormalities

is confirmed by history, complete ophthalmic evaluation, and eye-movement recordings showing INS that changed in intensity commensurate with head posturing or eye positioning. It should be noted here that in patients with INS, an AHP is not the “abnormality” that needs to be treated. An AHP is an adaptive strategy that is deliberately employed in the service of improved visual function; it is not a primary abnormality. If it were, surgery on the neck muscles would be in order, not on the EOM. Also, an AHP is under the direct control of the patient and is, therefore, neither an accurate nor repeatable measure of the real problem (or, especially postoperatively, of the “success” of a surgical procedure)—the position of the INS waveforms with the most well-developed foveation periods is. The most precise method to determine the amount of EOM surgery needed to reposition the gaze angle with the best foveation is through the use of data from eye-movement recordings (e.g., NAFX function) plotted over all gaze angles. Correction of the primary problem (i.e., the lateral position of the NAFX peak) and broadening the NAFX peak will automatically negate the need for the patient to adopt an AHP postoperatively. Thus, accurate treatment of the primary abnormality removes the secondary symptom of an AHP and prevents the subsequent development of structural abnormalities in the neck. If neither NAFX analysis (the best method) nor visual acuities at different gaze angles (an acceptable clinical method) are available, measuring head position will yield an approximate value upon which to base EOM surgery. Measurement of the patient’s head position using one of a number of head-posture measurement systems is best accomplished with refraction in place during threshold visual acuity testing at distance and near.¹⁴⁹ Head-posture testing should be repeated at multiple intervals over a continuous 15-minute time frame to help rule out APAN.

There is a strong caveat to using direct AHP measurements (no matter how accurately the measurement is accomplished) in either determining the amount of surgery necessary or assessing the results of that surgery. Because the AHP is both variable and under the direct

control of the patient, it is *inherently unreliable and subject to bias*, postoperatively. This is especially problematic with children who “know” that the purpose of the surgery was to “straighten their head” and that their parents had spent a lot of money to do so. It is not surprising to hear, in cases of insufficient surgical rotation of the eyes, that immediately postoperatively the patient’s AHP was gone but months later it had “reappeared” at an intermediate position. The myth of the reappearing null angle is just that, a myth based on unreliable data. All accurate eye-movement data confirm that the surgical rotation to center an eccentric null is permanent (i.e., remains unchanged many years later) whether initially done correctly or undercorrected. However, there are three reasons that an AHP may “reappear”: (1) there is a surgical undercorrection; (2) a previous nondominant (and clinically “silent”) multiplanar eccentric null position becomes clinically relevant (e.g., a “new” vertical AHP after treatment of a horizontal AHP); and (3) a new strabismus develops, prompting a change in the INS compensation mechanism.

7.2.3.6 LABORATORY AND SPECIAL TESTS

Those patients in whom systemic diseases or associated ophthalmic abnormalities are suspected as a result of a thorough history and clinical evaluation may need serology, urine analysis, neuroimaging, genetic testing, neurological and ophthalmological electrophysiology, and consultation by other specialists.

7.2.4 Results

7.2.4.1 VISUAL ACUITY

Multiple examples of level II- and III-based evidence suggest eye-muscle surgery improves nystagmus and visual function in patients with INS.^{79,84,92,97,102,122,128,136,150–153} Vision, if used as a secondary outcome measure when reporting effects of eye-muscle surgery must be explicit and measured at multiple gaze angles straddling the angle of best acuity. The steps necessary to refract patients with nystagmus are summarized in Table 7.7,^{154,155} and the various signs and symptoms of nystagmus amenable to refractive treatment are listed in Table 7.8.

Table 7.7 Refraction Steps in Patients with Nystagmus

STEPS IN REFRACTION OF PATIENTS WITH NYSTAGMUS

1. Acuity Measurement
 - a. PEDIG—ATS and ETDRS Protocols
 - b. Measure binocularly
 - c. Allow patients with anomalous head position to assume that position
2. Perform Subjective Refraction
 - a. Begin with retinoscopy obtained at distance (phoropter or trial lenses)
 - b. Do binocular refraction
 - c. Fog nontested eye with enough plus to decrease acuity by 1–3 lines
 - d. Perform routine subjective refraction (e.g., sphere, cylinder, etc.)
 - e. Repeat procedure on opposite eye
 - f. With best refraction in place, add up to 7 prism diopter base-out (if patient has fusion) with additional 0.75 to 1.00 sphere to check for “convergence damping”
 - g. Check binocular acuity again (with AHP, if present)
3. Perform Objective Refraction
 - a. Forty minutes after 1% cyclogyl or 60 minutes after 1% atropine
 - b. Start with retinoscopic findings in both eyes
 - c. Repeat steps C–F above (if patient is able)
 - d. Record differences in subjective and objective refraction

Table 7.8 Refractive Treatment in Patients with Nystagmus

SIGNS AND SYMPTOMS OF NYSTAGMUS AMENABLE TO REFRACTIVE TREATMENT		
SIGN	SYMPTOM	ETIOLOGY
Decreased vision		Myopia Hyperopia Astigmatism Anisometropia Amblyopia
Anomalous head posture		INS null or vestibular gaze damping FMNS adduction damping NBS INS convergence damping
Oscillopsia		“Acquired” nystagmus INS change (motor or sensory status)
Photophobia		Retinal dystrophies Albinism
Hypoaccommodation		Unknown

INS, infantile nystagmus syndrome; FMNS, fusion maldevelopment nystagmus syndrome; NBS, nystagmus blockage syndrome

There are at least five psychophysical measures of acuity (e.g., detection, recognition, resolution, hyperacuity, and localization). Variables reported pre- and postoperatively in patients with INS include optotype and gaze-dependent acuity, contrast sensitivity, motion detection, null-zone characteristics, visual recognition time, subjective visual function, and electrophysiological characteristics. In 138 patients from multiple studies who had their null zone optotype best-corrected binocular vision tested within 1 week and 4 to 6 weeks after eye-muscle surgery for INS grouped mean data showed a significant improvement ($p < .05$) and, overall, 75% improved 1–3 lines and 15% 3 lines or

greater. Eye-movement recordings also show that surgical intervention increases the prevalence of favorable nystagmus waveforms. Even if the nystagmus were completely eliminated, the integrity of the afferent system (optic nerve, retina, brain disease) and the age-related timing of surgery may limit the acuity potential in any specific patient with INS.

As a result of eye-muscle surgery improving their beat-to-beat nystagmus, these patients receive more useful vision per unit time and, as a function of gaze, recognize objects faster, have less head movement and better motion and contrast sensitivity; thus, they “function” better. The common clinical misperception is that eye-muscle surgery only serves to either centralize the INS null position or reposition the eye(s) in the orbit.¹⁵⁶ In fact, what happens in patients with INS is a broadening and deepening of the null zone (more importantly, a broadening and raising of the NAFX peak). In a more scientifically sound representation of this phenomenon, this area is labeled “visual function space,” a three-dimensional representation of visual function. Data accumulated over the last 30 years show that many afferent and efferent visual system measures improve as a result of eye-muscle surgery on INS patients, regardless of the indication (eccentric null, vergence damping, strabismus, or nystagmus alone), suggesting that neurovisual changes take place as a result of the surgical procedure itself, unrelated to moving or removing some of the extraocular muscle.⁷⁵ The current hypothesis is that surgical interference with peripheral extraocular muscle/tendon, “enthesisal” proprioceptive nerve endings influence central ocular motor pathways, resulting in an improved INS oscillation. In a recent study of 100 patients with INS the average group multiple aspects of ocular motor as well as visual sensory system function improved significantly after surgery.¹²²

7.2.4.2 STRABISMUS

The occurrence of strabismus with nystagmus, especially in infancy and childhood, is very common, with reported incidence of 20%–75%.^{122,157–161} In a report of 100 patients

undergoing eye-muscle surgery for INS, there was a significant improvement in the strabismic deviation of the 71 patients with associated strabismus.¹²² In patients with FMNS and strabismus, surgery of the eyes decreases the nystagmus intensity and may also improve binocular visual acuity.¹⁶² Properly combined nystagmus and strabismus surgeries should both improve INS waveforms (i.e., breadth and height of the NAFX peak) and reduce or eliminate the strabismus (i.e., alignment of the two eyes).

7.2.4.3 EYE-MOVEMENT RECORDINGS

Postoperative eye-movement recordings have always demonstrated the expected INS waveform improvements that were based on the preoperative recordings. Recordings made years later also confirmed the stationary nature of these therapeutic improvements. Usually plots of the post-operative NAFX values taken at different gaze angles are compared to those made preoperatively. From such comparisons, improvements in peak NAFX and LFD can be made. Broadening of the LFD is the most important therapeutic improvement to overall visual function and raising the peak NAFX translates directly into higher best-corrected visual acuity, regardless of whether there is an associated sensory deficit.

7.2.4.4 HEAD-POSTURE MEASUREMENTS

Although the most accurate method of determining how to use eye-muscle surgery to improve an AHP due to INS is the use of eye-movement recordings (as mentioned earlier), there is over 50 years of reported information on the use of other methods of evaluation and treatment. It is worthwhile to briefly review some of this data. The extent of the head posture is usually dictated by the velocity distribution of the nystagmus slow phase, beat direction, and the neutral zone, suggesting that the surgical management of a head posture has been based on the relocation of the minimum intensity zone to the primary gaze position.¹⁶³ In a larger study, the net change in 38 patients after surgery of their head turn was 33.4°.¹⁶⁴

Excellent results were reported in another 38 patients with a horizontal head turn, and five with a vertical abnormal head posture who underwent horizontal nystagmus surgery.¹¹⁹ Kraft et al. reported a success rate of 78.3% of 23 INS patients having surgery for an AHP.¹⁶⁵ Roberts et al. reported in 7 patients and Hertle et al. in 24 patients that rectus and oblique surgery were effective surgical management of vertical plane torticollis.¹⁶⁶ Lee et al. reported that 56 out of 63 patients (89%) achieved a straight head position or a residual face turn of 10° or less after bilateral recession and resection for INS and an AHP.¹²⁶ Graf reported in 78 patients with an AHP, aged 3 to 68 years, that the AHP was reduced to 10° or less in 69 patients after one procedure.¹²⁷ Chang et al. reported that in the follow-up of an average 33 months, 45 out of 51 patients (88.2%) who underwent eye-muscle surgery for an AHP resulted in an AHP less than 10°.¹⁶⁷ Surgery on the extraocular muscles in 19 patients aged less than 2 years with INS resulted in a significant improvement in those who had an AHP.³

In 53 patients who had eye-muscle surgery with a diagnosis of infantile periodic alternating nystagmus and a dynamic “null” position, their PAN cycle, null period, and variability, duration, and eccentricity of their AHP improved significantly after eye-muscle surgery.¹⁶⁸ In another report in 70 patients with INS who had eye-muscle surgery and an AHP, the average change in posture improved significantly for all directions (horizontal, vertical, and torsional).¹²² These and multiple other reports since 1959 confirm that extraocular muscle surgery in the treatment of AHPs associated with nystagmus is a safe and effective therapy. Had the primary outcome measure been the NAFX peak (determined from eye-movement data), the results could have been better and should have been less variable (i.e., would have better reflected the actual improvements).

7.2.5 Complications

Fortunately for those patients who undergo eye-muscle surgery, the overall incidence of surgical complications is low (<3%–5%).^{169,170} Confusions

involving incorrect procedures and patients can occur despite the Universal Protocol.

Unsatisfactory eye alignment (5%–20%) after surgery is the most common undesirable effect after surgery, but it should not be considered a “complication” in the true sense of the word, due to the generally unpredictable number of neurological and physiological factors that contribute toward “perfect” ocular alignment in the first place. Despite careful preoperative measurements and utilization of common surgical dosage tables, a certain percentage of patients will have new deviations or be overcorrected or undercorrected after surgery.¹⁷¹ A change in the refraction (<5%) can occur, especially if two muscles are operated in the same eye. For example, operating on two horizontal muscles can induce a small with-the-rule astigmatism. This change is typically temporary and resolves after a few months.⁸⁴ Diplopia (<5%) can occur, particularly in adult patients who are overcorrected. Patients younger than age 10 years typically can suppress the deviated eye, but older patients may not have suppression or, if suppression is present preoperatively, may not be able to shift the suppression scotoma to cover an overcorrection.¹⁷² During surgery, scleral penetration or perforation (< 9%) can occur from an inadvertent deep pass of the suture needle or during dissection to isolate and disinsert the muscle tendon. The risk increases during a reoperation or on an eye with high myopia. In most cases, the penetration/perforation does not create a problem other than a chorioretinal scar, but in some cases can trigger endophthalmitis, vitreous hemorrhage, or retinal detachment.¹⁷⁰

Postoperative infection (<1%) can occur, usually within the first week after surgery. Most infections occur around the initial surgical incision into the conjunctiva. Rarely, infections can penetrate deeper into the orbit with proptosis, eyelid swelling, chemosis, and erythema. As mentioned earlier, sometimes endophthalmitis can develop, either with or without a scleral perforation.¹⁷⁰ Allergic reactions (<1%) can occur in response to either the suture material or postoperative medications. A foreign body granuloma (<1%) can develop, usually a few weeks after surgery. The granuloma typically

presents at the suture site as a localized, elevated, hyperemic mass that is less than 1 cm in diameter. A conjunctival or Tenon’s inclusion cyst (<1%) can present days to years after surgery.¹⁷⁰ Conjunctival scarring can be a persistent problem after surgery. Instead of returning to the typical translucent white appearance, the conjunctiva can remain bulky and hyperemic. Orbital tissue adherence (<1%) is usually seen after in conjunction with excessive bleeding into the orbital tissues or after infection. The orbital tissues and/or muscles produce a fibro-fatty scar that is adherent to the muscle and globe leading to a restrictive strabismus. A dellen (<1%) can occur on either the cornea or sclera when thickened bulbar conjunctiva (either from scarring, hemorrhage, or swelling) prevents adequate and even lubrication of the ocular surface.¹⁷³

Anterior segment ischemia (ASI) (very rare) occurs when strabismus surgery creates impaired blood flow to the anterior segment.¹⁷⁴ Most of the blood supply to the anterior segment flows through the ciliary arteries within the four rectus muscles. Simultaneous surgery on three rectus muscles in the same eye, or two rectus muscles in a patient with compromised blood flow from vascular disease are high-risk situations. Typical findings in ASI include iritis, corneal edema, folds in Descemet’s membrane, and, if severe, anterior segment necrosis and phthisis of the operated eye can occur. Eyelid malpositions (<5%) occur after eye-muscle surgery, most often on the vertical recti. The eyelid retractors, particularly in the lower eyelid, are adherent to the intermuscular septum and fascial tissue around the vertical rectus muscles. This connection creates a shift in eyelid position during standard recession or resection surgery of the vertical rectus muscles. A lost or slipped muscle occurs (very rare) when the muscle slips free of the sutures or surgical instruments during or after surgery.

Other rare complications that can lead to disruption in vision include macular edema, burns, corneal erosion, diplopia, disruption of fusion, dragged-fovea diplopia syndrome, and induced intraocular inflammation. Anesthetic complications include malignant hyperthermia, too little anesthesia, globe penetration/perforation,

orbital hemorrhage, and nausea and vomiting; very rarely, asystole may occur as part of the oculocardiac reflex.¹⁷⁰

7.3 OTHER

7.3.1 Biofeedback

Biofeedback has also been reported to help some patients with congenital nystagmus.^{175–177} Auditory feedback of eye position and eye motion was given to each subject to aid in controlling the abnormal eye movement. Less than 1 hour was needed for all the subjects to learn to use the auditory information. Reductions in eye-movement amplitude ranged from 41% to 73%. Sensory functions like visual acuity and contrast sensitivity also improved under the auditory feedback condition. Auditory feedback of eye position in these patients was thought to have potential usefulness in improving INS. In a related study using biofeedback, multiple subjects could voluntarily suppress nystagmus and prolong foveation time. A damping of the nystagmus amplitude, intensity, and frequency was observed. On the average the intensity decreased by about 40%, and the foveation time was prolonged by about 190%. After completion of the training all the patients reported a subjective improvement in their vision when suppressing their nystagmus.¹⁷⁸ Sharma et al. studied 10 patients with INS without null position who underwent six sessions (twice a week for 3 weeks) of auditory biofeedback.¹⁷⁷ All patients could reduce the nystagmus during the treatment sessions. Mean amplitude (degrees) and intensity of nystagmus were reduced. Simultaneous eye-movement recording shows significant reduction of nystagmus amplitude and intensity because of auditory biofeedback only during the treatment sessions; also, any objective effect on visual acuity and contrast sensitivity was noted only during the therapy. The role of these treatments in clinical practice has yet to be demonstrated.

7.3.2 Acupuncture

The treatment of INS using acupuncture has been around for decades.¹⁷⁹ In one study, six

patients with INS received a series of treatments consisting of two needles inserted into each sternocleidomastoid, stimulated by tapping gently every 5 minutes, for 20 minutes per session.¹⁸⁰ Their eye movements were recorded using scleral search coils and changes in their INS waveforms analyzed at each point in the treatment. Changes in the stability and duration of foveation periods were examined. In four of the six patients, improved foveation was recorded at the commencement of treatment; three maintained this response throughout the treatment period and after the needles were removed. In two, the INS waveform itself was modified. Although not practical at the present time the acupuncture study suggests that afferent stimulation to the neck and face stimulate projections to the reticular formation and vestibular nucleus and may alter the behavior of the pathophysiological mechanism underlying INS.⁷⁵ In the future this information may support a pharmacological method to access these pathways other than direct dermal stimulation.

7.3.3 Cutaneous Stimulation

Cutaneous afferent stimulation (rubbing, vibration, or electricity) of the forehead or neck damps INS in some individuals. Discussions regarding possible mechanisms for the INS damping produced by contact lenses led to the hypothesis that excitation of the ophthalmic division of the trigeminal nerve by cutaneous stimulation above one eye could affect the oscillation of INS.¹⁸¹ The stimulation resulted in a 50% diminution of the INS amplitude. This led to studies of afferent stimulation using vibration and electrical stimuli of the forehead and the neck. Damping of INS is not necessary for improved acuity; lengthening foveation periods and reducing their position variation are the most important effects of therapy for functional vision improvement; however, amplitude reduction does result in cosmetic improvement.

7.3.4 Gene-Transfer Therapy

As part of a larger study of gene-transfer therapy in RPE65-deficient canines, we completed

a study to determine whether their nystagmus can be used as a motor indicator of restored retinal function.^{101,103} Treated and untreated canines were comfortably suspended in a custom-built sling and encouraged to fixate on distant targets at gaze angles varying between $+/-15^\circ$ horizontally and $+/-10^\circ$ vertically. Ocular motility recordings were made, using two distinct methods: infrared reflection and high-speed video. The resultant recordings from three untreated, four treated, and three pre- and posttreatment dogs were analyzed for using the NAFX.^{101,103} During fixation, the untreated dogs exhibited large-amplitude, classic INS waveforms, including pendular and jerk in both the horizontal and vertical planes, which prevented them from keeping the targets within the area centralis (the region of highest receptor density, spanning $+/-3^\circ$ horizontally by $+/-1.5^\circ$ vertically, analogous to the fovea). Some untreated dogs also had small-amplitude ($0.5^\circ-1^\circ$), high-frequency (6–9 Hz) oscillations. Under the same conditions, successfully treated canines no longer exhibited clinically detectable INS. Their IN was converted to waveforms with very low amplitudes that yielded higher NAFX values and allowed target images to remain well within the area centralis. In this animal model, gene-transfer therapy that successfully restored retinal function also reduced the accompanying INS to such a great extent that it was not clinically detectable approximately 90% of the time in many of the dogs.^{101,103} Two research groups, one in Philadelphia (Maguire et al.) another in London, England (Bainbridge et al.), recently tested RPE65 replacement in two human trials with a total of six LCA patients.^{182–184} Remarkably, visual improvements were documented by ETDRS visual acuity measurements, pupillometry, nystagmus-frequency reduction, visual field measures, perimetry, and an obstacle course. There were no local or systemic side effects, or improvements in ERG measures.

In 1982, Cross et al. reported on a case of acquired periodic alternating nystagmus (PAN) that appeared following bilateral vitreous hemorrhages and which cleared after vitrectomy.¹⁸⁵ Jay et al. reported a case of acquired PAN in a 60-year-old man with cataracts that

disappeared clinically after removing one of the cataracts and replacing it with an intraocular lens.¹⁸⁶ Finally, Rabiah et al. reported that the nystagmus (presumably INS) in 40% of children with congenital cataracts was reduced or clinically eliminated after cataract surgery.¹⁸⁷ These reports, plus our findings that gene therapy to alleviate canine LCA also resulted in the clinical elimination of INS, provide strong evidence that, unlike the visual system, the ocular motor system has no “sensitive” period after which deficits cannot be corrected. It appears that the necessity to constantly maintain accurate and precise calibration of the ocular motor subsystems throughout life also allows recalibration when deficient visual input is improved. Thus, future INS therapies that ameliorate or eliminate an associated visual sensory deficit rather than the present therapies that are either peripheral (e.g., surgery or topical drugs applied to the extraocular muscles) or central (e.g., systemic drugs) may have substantial therapeutic benefits to visual function.

7.3.5 Mind-Body Stress Reduction: Mindfulness Meditation Techniques

Half of the adults in the United States use complementary and alternative medicine with mind-body therapy being the most commonly used form. Mindfulness-based stress reduction (MBSR) has been used with patients with a variety of conditions.^{188,189} Randomized controlled clinical trials and seven uncontrolled clinical trials reported positive results, including improvements in mood, sleep quality, and reductions in stress.¹⁹⁰ From a clinical viewpoint, MBSR has shown efficacy for many psychiatric and physical conditions and also for healthy subjects. Mindfulness-based cognitive therapy (MBCT) is mainly efficacious in reducing relapses of depression in patients with three or more episodes. Zen meditation significantly reduces blood pressure and Vipassana meditation shows efficacy in reducing alcohol and substance abuse in prisoners.¹⁹¹ Despite encouraging findings, several limitations affect current studies. Neurology patients, including those with nystagmus, often turn to their physicians

for insight into the effectiveness of the therapies and resources to integrate them into their care. Mind-body therapy application to general pain, back and neck pain, carpal tunnel syndrome, headaches, fibromyalgia, multiple sclerosis, epilepsy, muscular dysfunction, stroke, aging, Parkinson disease, stroke, migraine headache, and attention-deficit/hyperactivity disorder are several conditions where there is evidence for mind-body therapies.¹⁸⁸ Mind-body therapies for other neurology applications have limited evidence, due mostly to small clinical trials and inadequate control groups.¹⁹¹ The potential application of MBSR in the treatment of nystagmus is an opportunity yet to be explored.

7.3.6 Occupational and Vision Therapy

In addition to those medical and surgical therapies discussed earlier, optical aids, vision therapy, and low-vision rehabilitation are available to nystagmus patients to improve visual functioning.¹⁹² These therapies improve visual function in patients with INS by promoting binocularity, enhancing image quality and stabilization, building vergence and accommodation, and providing novel orientation and mobility techniques to overcome a visually challenging environment.¹⁹³ Vision therapy has been practiced since the late 1800s to assist with binocular function. The goal of vision therapy for treating nystagmus is to try to increase foveation time and promote binocularity. Handheld magnifiers, credit-card style, full 8.5x11 magnifier pages, globes, and magnifying rulers may be useful to many patients.

Handheld mini telescopes are useful for spotting things far away, as are bioptics, which are tiny telescopes mounted on the top of glasses. Closed-circuit TVs can be portable or permanent; these systems have large screens that will greatly magnify a page from a book or a cricket from the back yard. Computer software such as *ZoomText* (or similar software) and accessibility features in Windows and Macintosh computers can magnify what is shown on the computer screen. Screen-reading software such as *JAWS* will assist with interpretation of text displayed on the computer screen.¹⁹⁴

7.3.7 Educational Assistance

The rate at which visual impairments occur in individuals under the age of 18 years is 12.2 per 1000. Severe visual impairments (legally or totally blind) occur at a rate of .06 per 1000.¹⁹⁵ Globally, more than 171 million people are visually impaired, of whom 134 million people had low vision and 37 million were blind. Worldwide for each blind person, an average of 3.4 people have low vision, with country and regional variation ranging from 2.4 to 5.5. Visual impairment is unequally distributed across age groups. More than 82% of all people who are blind are 50 years of age and older, although they represent only 19% of the world's population. Childhood blindness is estimated at 1.4 million blind below age 15 years. Available studies consistently indicate that in every region of the world, and at all ages, females have a significantly higher risk of being visually impaired than males.¹⁹⁶

Children and youth with low vision have unique educational needs. Research documents that these students often require direct instruction by a teacher for students with visual impairments in areas that are not typically addressed for other students. All students who meet the criteria for visual impairment within their state should have a document that addresses their individual needs. This document, called an individualized education plan (IEP), is used to place a child in the most appropriate educational setting. A thorough assessment for students with visual impairments is the key in creating an adequate IEP. And the assessment process is an essential component in developing appropriate goals and objectives for the student. Parents may learn that their child has vision impairment much earlier than do parents of children with other disabilities. Children with visual impairments should be assessed early in order to benefit from early intervention programs, when applicable. Students with visual impairments may need additional help with special equipment and modifications in the regular curriculum to emphasize listening skills, communication, orientation and mobility, vocation/career

options, and daily living skills. Students who have visual impairments combined with other types of disabilities have a greater need for an interdisciplinary approach and may require greater emphasis on self-care and daily living skills.¹⁹⁷

Information for parents of school children with nystagmus is available through many resources both online and via eye care societies; particularly useful societies are the American Nystagmus Network (<http://www.nystagmus.org/entry.html>) and the England Nystagmus Network (<http://www.nystagmusnet.org/>). The student should be encouraged to explain his or her visual needs; however, continual and undue attention to these should be avoided. Allow books/objects to be held close to the eyes, the head tilted, and any other body posture adopted if this enhances vision. Provide the students with their own book/worksheet. Sharing is impossible. Enlarging material will often help, although good contrast may suffice. Wall displays for reference should be placed at eye level and where the student can stand close. Ask the student where he or she would prefer to sit. It is often facing and near to the board; students should not sit to one side. He or she should be offered positions close to demonstrations during activities. Store visual aids so that the student has easy access and can use them when he or she judges that they will be helpful. Allow the use of prescribed tinted glasses, cap, hat, or eyeshade to reduce the effects of glare. Read aloud when writing on the board; describe diagrams. Allow sufficient time to complete tasks and to examine materials/objects. Good (though not necessarily bright) lighting is essential. The light should be behind the student and directed onto the object being viewed. Matte surfaces for walls, boards, and paper prevent light reflection and glare. Use strong color contrast between letters/figures/lines and background. These should be well spaced. To keep track of where the pupil is up to when reading, a piece of dark card may be used or he or she can track with a finger. Exercise books with matte paper, different colors, and line spacing should be made available.

7.4 ASSESSING THERAPEUTIC OUTCOMES (POST-THERAPY)

7.4.1 Direct Outcome Measures (eXpanded Nystagmus Acuity Function, Longest Foveation Domain, and Target Acquisition Time)

In assessing outcome measures for any therapy, it is important to differentiate between a desired medical outcome that may, or may not, be directly related to the actual changes brought about by that therapy, and those actual changes (i.e., the *direct outcome measures*). An example would be the outcome measure for strabismus surgery. While the restoration of binocularly is a highly desirable medical outcome, it does not directly result from aligning the two eyes and, therefore, should not be used as an outcome measure for the success or failure of the strabismus surgery. In acquired nystagmus with oscillopsia, the diminution or elimination of the perception of world motion is a highly desirable medical outcome; it does not directly result from damping the nystagmus and, therefore, should not be used as an outcome measure for the success or failure of the nystagmus surgery, which may have damped the nystagmus, as anticipated. Similarly, in nystagmus surgery (specifically INS surgery), while improved peak acuity is also a highly desirable medical outcome, it does not directly result from extraocular muscle surgery and, therefore, should not be used as an outcome measure for the success or failure of the nystagmus surgery.

The only direct changes that can be brought about by nystagmus surgery are those that can be measured from ocular motor data (i.e., changes in INS waveforms that may improve visual function). The direct ocular motor outcome measures that affect visual function are as follows: the peak NAFX value, the LFD value, and the Lt (target acquisition time) value. The peak NAFX improvement translates directly into improved acuity, the LFD improvement translates directly into the widening of the range of gaze angles with the highest acuity, and the Lt improvement translates directly into shortened target acquisition time.

7.4.1.1 POST-TENOTOMY AND REATTACHMENT

We assessed the therapeutic effects of the T&R procedure by measuring the posttherapy peak NAFX, LFD, and Lt values and comparing them to their respective pretherapy values; improvements were expressed as percentages.^{3,4,82,83,91,92,99,100,102,136,168} As Figure 7.6 (top left and right panels) shows, for low pre-T&R peak NAFX values, improvement is greatest and for high pre-T&R peak NAFX values, improvement is least. The same applies for the LFD improvements, as is shown in Figure 7.6 (bottom left and right panels). These improvements are in the motor component of visual function and are independent of any associated sensory deficits and were also independent of age. As Figure 7.7 illustrates, the T&R procedure allows clearer vision over a broader range of gaze angles.

It has been hypothesized that adding an extra suture or two to each tendon in the T&R procedure (augmented T&R) might result in an even greater diminution of the small-signal gain of the extraocular muscles.¹⁹⁸ If that were found to be true, a further hypothesis was advanced that the four-muscle T&R might be replaced by simply placing several sutures in the tendons of each extraocular muscle (or manipulating them mechanically, pharmacologically, or

cryogenically) without performing any tenotomies (augmented tendon suture—*sans* tenotomy). Some data have begun to be collected to test this hypothesis.

7.4.1.2 POST-CONVERGENCE/BIMEDIAL RECTUS RECESSIONS

Our research found that, for those binocular INS patients whose IN damped with convergence, the improvements in peak NAFX and LFD were greater than for gaze-angle peaks.²⁸ The visual function improvements of convergence induced by either base-out prisms or the bilateral medial rectus muscle recession procedure are illustrated in Figure 7.8.

7.4.1.3 POST-KESTENBAUM OR ANDERSON PLUS TENOTOMY AND REATTACHMENT

The beneficial effects of surgery of the extraocular muscles was first demonstrated by eye-movement data analysis of patients who underwent the four-muscle Kestenbaum procedure.^{74,78} These included translation of the eccentric null to primary position, improvement of the null, and broadening of the null. The latter gave rise to the hypothesis that led to the T&R procedure.⁷⁵

Patient with a Narrow, Central Low-Acuity Visual Field

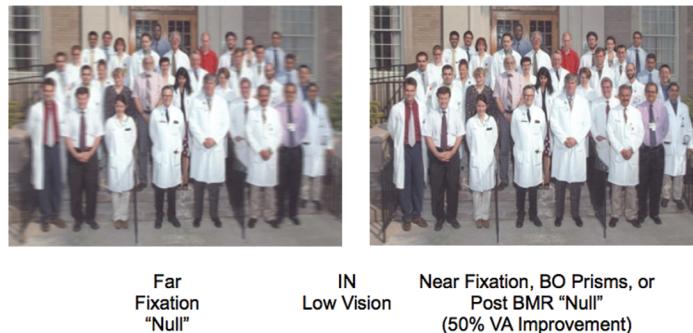


FIGURE 7.8 Illustrations of the clarity of portions of the visual field in an infantile nystagmus syndrome (INS) patient with a narrow, central, null (sharp, central eXpanded nystagmus acuity function [NAFX] peak) before and after either base-out prisms or bimedial recession surgery to broaden and shift the central acuity peak.

Figure 7.9 illustrates the multiple therapeutic benefits of the four-muscle Kestenbaum procedure for these patients. The top left panel shows the preoperative acuity field. The top right panel illustrates the expected shift in clear vision to primary and, prior to the Dell'Osso and Flynn study,⁷⁴ the absence of appreciable improvements in visual function. However, the bottom panel illustrates the actual visual function benefits measured after the Kestenbaum surgery. Not only has the angle of clear vision been shifted but also improved and, most important, broadened.

7.4.1.4 SOFT CONTACT LENSES

Studies of the therapeutic effects of soft contact lenses on INS revealed some increases in peak NAFX and significant broadening of the LFD.^{32,33} Thus, contact lenses would have the same broadening effect on the range of gaze angles with highest acuity as the T&R or convergence therapies illustrated in Figures 7.7 and 7.8.

7.4.1.5 SYSTEMIC ACETAZOLAMIDE AND TOPICAL BRINZOLAMIDE

Our most recent research has been into the therapeutic effects of either systemic acetazolamide or topical brinzolamide (i.e., eye drops) on INS.^{34,35} Both produced both higher NAFX and LFD values and would, therefore, also result in the types of improvements illustrated in Figures 7.7 and 7.8 (see also Chapter 2, Fig. 2.26). As Figure 7.10 shows, the brinzolamide eye drops improved the peak NAFX more than contact lenses and produced the same improvement in the LFD. The possible use of topical drugs, in the form of eye drops, to treat INS is a new area of research whose outcomes are yet to be determined.

7.4.2 Indirect/Clinical Outcome Measures

Improvement in those direct-outcome characteristics of IN is reflected in clinical improvements in visual function such as high-spatial frequency discrimination (e.g., visual acuity),

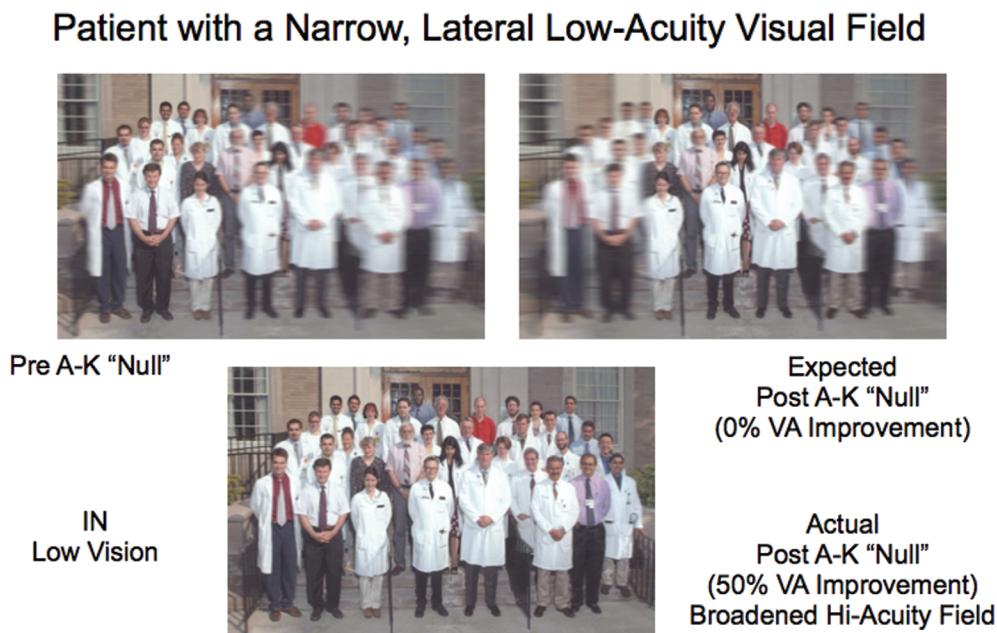


FIGURE 7.9 Illustrations of the clarity of portions of the visual field in an infantile nystagmus syndrome patient with a narrow, lateral, null (sharp, lateral eXpanded nystagmus acuity function [NAFX] peak) before and after Kestenbaum surgery to broaden and shift the lateral acuity peak to primary position. Also shown is the expected effect of shifting the lateral acuity peak with no other improvements.

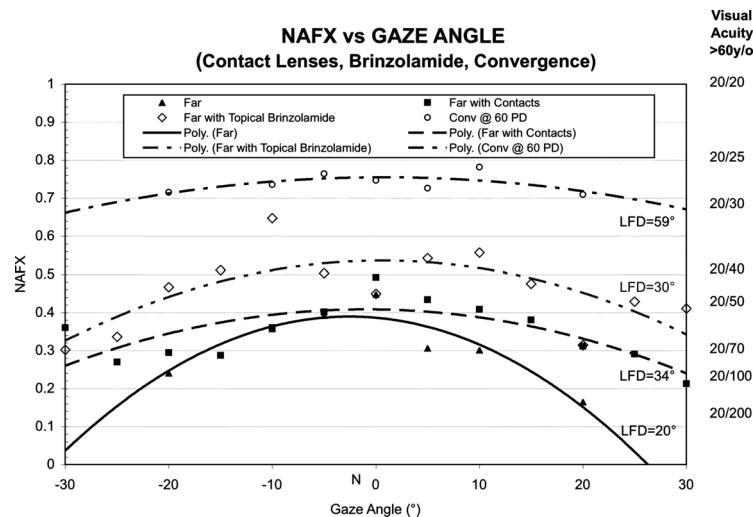


FIGURE 7.10 Plots of % eXpanded nystagmus acuity function (NAFX) improvement versus gaze angle for contact lenses, topical brinzolamide, and convergence showing the large increases resulting from all treatments at lateral gaze angles. The longest foveation domain (LFD) values for each curve are shown.

broader range of gaze angles where acuity is near peak values, and faster target acquisition and recognition. These direct outcome measures are reflected in therapeutic improvements in peak visual acuity and broadening of the gaze-angle range of high acuity.

7.4.2.1 VISUAL ACUITY AT DIFFERENT GAZE ANGLES

Visual acuity measurements taken at five or more gaze angles can be used to determine the most effective therapy and as an outcome measure (especially the LFD) if eye-movement recordings are unavailable. In cases with no associated sensory deficits, the NAFX values translate directly into best-corrected visual acuities. In cases with associated sensory deficits, the actual measured visual acuities would be less than predicted by the NAFX values. However, the percent improvements in NAFX values would be equally reflected in measured acuities. The percent improvements in LFD values would be directly translated into ranges of gaze angles with improved acuities for both patient populations.

It is important to understand that plots of NAFX versus gaze angle demonstrate the drastic decrements in visual acuity lateral to the NAFX peak, wherever it is located. Thus, even in cases

where only the LFD is broadened (i.e., little or no increase in peak NAFX), large improvements in visual acuity across the field of gaze result and thereby improve visual function leading to patient satisfaction. The large improvements in acuity for three different therapies are illustrated in Figure 7.11. Regardless of whether peak acuity (at primary position) is increased, each increases acuity by large amounts at lateral gaze angles. Such increases result in overall increases in visual function that can be documented by pre- and posttherapy acuity measurements at different gaze angles.

7.5 ESTIMATING THERAPEUTIC OUTCOMES (PRE-THERAPY)

7.5.1 Direct Outcome Measures (eXpanded Nystagmus Acuity Function, Longest Foveation Domain, and Target Acquisition Time)

When pretherapy values of the NAFX function are low or medium, posttherapy values are higher. They also remain near peak values at gaze angles lateral to the peak (LFD or peak broadening). Also, the long pretherapy latencies before target acquisition are shortened after therapy. These direct outcome measures, unlike measured acuities, are measures of the motor components of

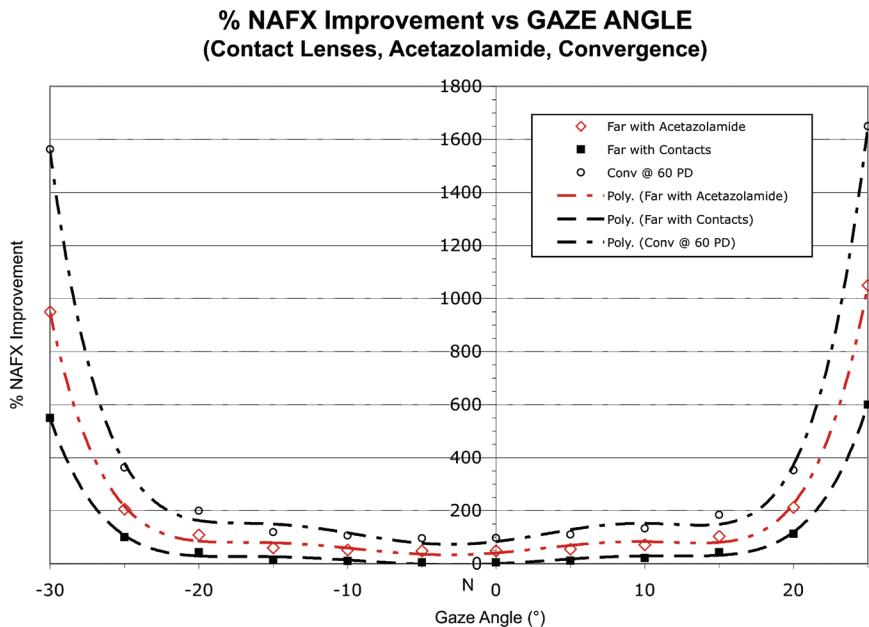


FIGURE 7.11 Plots of % eXpanded nystagmus acuity function (NAFX) improvement versus gaze angle for contact lenses, systemic acetazolamide, and convergence showing the large increases resulting from all treatments at lateral gaze angles.

visual acuity. Because of that, they can be used to provide per-therapy estimates of percent improvements in measured peak acuities and range of gaze angles with high acuity. These estimations are not dependent on the presence, absence, or severity of associated sensory deficits. For the first time, it became possible not only to determine the most appropriate therapy for individual INS patients and have a direct measure of that therapy but also be able to use pretherapy data to estimate the improvements that would result from the therapy. Such estimates provide the physician and patient with realistic expectations and also are useful in determining the efficacy of the therapy.

7.5.1.1 TENOTOMY AND REATTACHMENT (INFANTILE NYSTAGMUS SYNDROME WITHOUT AFFERENT VISUAL DEFICITS)

For INS patients with no afferent deficits, the NAFX values measured from eye-movement data are correlated with the patient's best-corrected visual acuity.¹⁸¹ Thus, both the pre- and post-therapy values have visual acuity equivalents, and specific measured increases in the NAFX result

in the same increases in visual acuity. The curves shown in Figure 7.6 were plotted from the results of evaluating the T&R procedure in patients from several studies.¹⁰⁰ It then became possible to use those curves to estimate both NAFX and LFD improvements before application of the therapy.

The following example illustrates how both the improvements in peak NAFX and LFD can be estimated for an 8-year-old INS patient who has no associated afferent deficits and a measured pre-T&R NAFX peak of 0.30. Using either of the curves in Figure 7.12, the 0.30 value is located on the x-axis and the corresponding estimated improvement (0.48 or 60%) is read off the y-axis. Then using the curve in Figure 7.13, the pre-T&R point is plotted (filled circle at: calculated pre-NAFX = 0.30, measured preacuity = 20/70); allowing for measurement errors, that point should lie on or near the age-dependent NAFX versus acuity line. The estimated post-T&R value is then plotted on the NAFX versus acuity line (open circle) and estimated best-corrected visual acuity read from the y-axis, here 20/40. Note that if it is known that the patient has no afferent

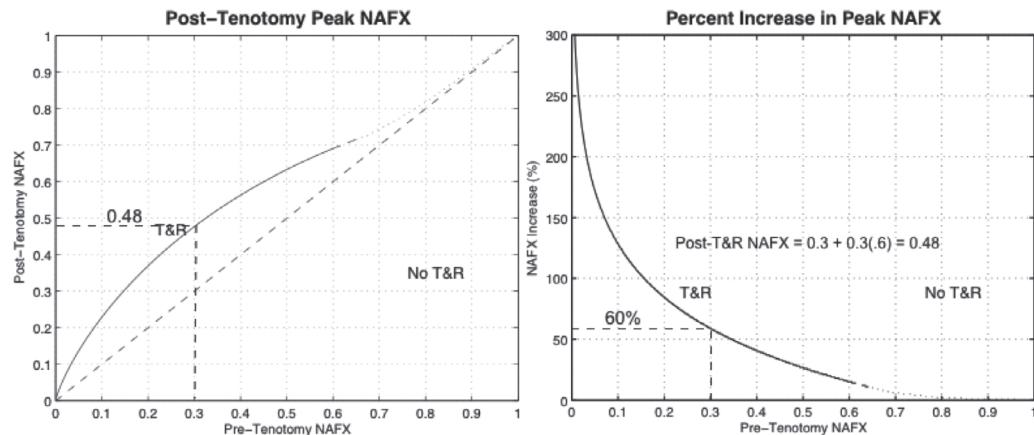


FIGURE 7.12 Plots of estimated improvements in eXpanded nystagmus acuity function (NAFX) (left panel) or NAFX percentage (right panel) versus pre- tenotomy and reattachment (T&R) value. Example shows the improvements for a pre-T&R value of 0.30.

sensory deficits and eye-movement data to calculate the NAFX are not available, measured pre-T&R visual acuity, expressed as a decimal, may be used with the curves in Figure 7.12 to obtain the estimated improvements in visual acuity, *but only in such cases*. For patients outside this age range, conversion between NAFX value and visual acuity is obtained from lines of the age-appropriate slope (for printable graphs

needed to estimate NAFX, and LFD therapeutic improvements, see Appendix D, Figs. D.6 and D.7). To calculate the estimated improvements in the LFD value, the curves in Figure 7.14 are used. The pre-T&R value (for this example, 15°) is located on the x-axis and the corresponding estimated improvement (>31° or >110%) is read off the y-axis. Worksheets useful in making these estimations are shown

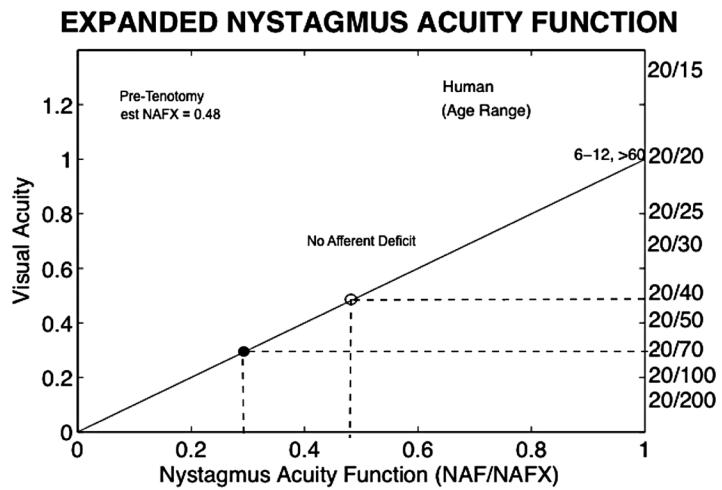


FIGURE 7.13 Plot of visual acuity versus eXpanded nystagmus acuity function (NAFX) for an infantile nystagmus syndrome patient (age range 6–12 years or >60 years) with no afferent visual sensory deficits. Shown are the pre-tenotomy and reattachment (T&R) (solid circle) and estimated post-T&R (open circle) values and their respective best-corrected visual acuity values.

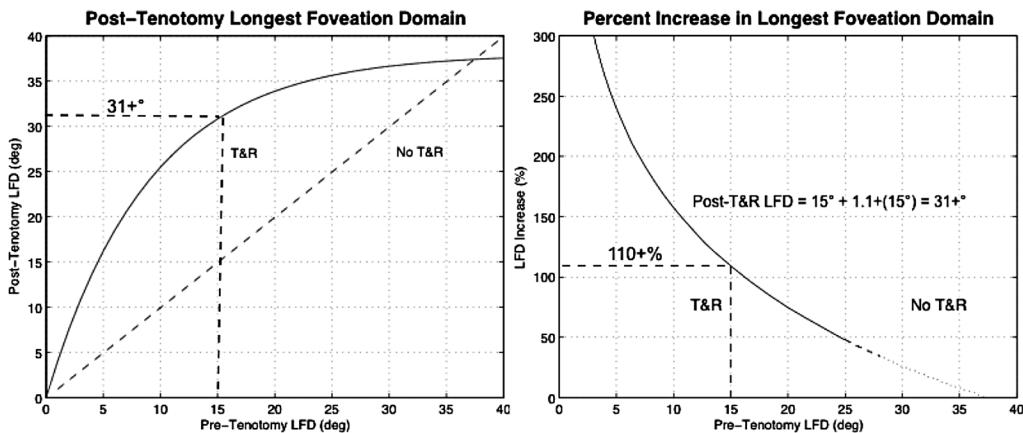


FIGURE 7.14 Plots of estimated improvements in LFD (left panel) or LFD percentage (right panel) versus pre-tenotomy and reattachment (T&R) value. Example shows the improvements for a pre-T&R value of 15°.

in Appendix D and may be copied and printed from Appendix F.3.

7.5.1.2 TENOTOMY AND REATTACHMENT (INFANTILE NYSTAGMUS SYNDROME WITH AFFERENT VISUAL DEFICITS)

Many INS patients also have associated afferent sensory deficits. Fortunately, because the NAFX and LFD measures are only dependent on the motor components of visual function, the aforementioned method may be modified to also estimate the measured improvements of the T&R procedure in this larger subset of INS patients.

To estimate the improvement in peak NAFX, the same steps outlined earlier for INS patients with no afferent visual sensory deficits are followed using Figure 7.12. Let us assume that instead of 20/70, the pre-T&R measured acuity is 20/200. As in the example for INS with no associated visual sensory deficits, the pre- and post-T&R points are plotted as follows. First, plot the pre-T&R point (obtained from Fig. 7.12) at the measured previsual acuity point (filled circle at: calculated pre-NAFX = 0.30, measured preacuity = 20/200), as is shown in Figure 7.15; due to the sensory deficit, it should lie well below the age-determined NAFX versus acuity line. Then, plot a line through that point that is parallel to the age-specific NAFX versus acuity line.

Finally, plot and the estimated post-T&R point on the new line (open circle) and read off the estimated visual acuity (here, 20/70). Note that in this example, the sensory deficit alone (i.e., no IN and NAFX = 1.0) would have only reduced visual acuity to 20/25, the bulk of the acuity deficit being attributable to the INS waveform. In other cases the situation could well be reversed with a higher NAFX and equally low, or lower, measured pre-T&R acuity. To calculate the estimated improvements in the LFD value, the pre-T&R value (for this example, 15°) is located on the x-axis in Figure 7.14 and the corresponding estimated improvement (>31° or >110%) is read off the y-axis. Note that the LFD improvement is calculated in exactly the same way regardless of the presence or absence of afferent visual sensory deficits and that the percent improvements in both NAFX and LFD are also independent of such deficits.

7.5.1.3 PRISMS/BIMEDIAL RECTUS RECESSIONS

Research has shown that, in binocular (i.e., no strabismus) INS patients whose IN damps with convergence, the therapeutic improvements resulting from convergence are greater than from using the gaze angle with peak NAFX (i.e., the “null”).²⁸ Thus, for this subset of patients

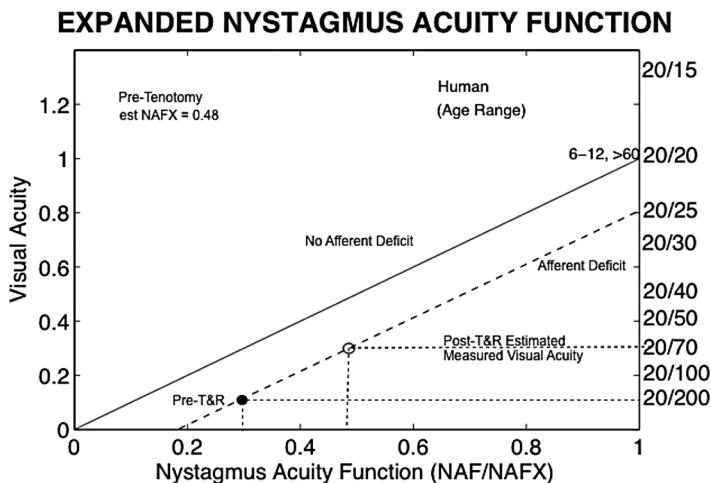


FIGURE 7.15 Plot of visual acuity versus eXpanded nystagmus acuity function (NAFX) for an infantile nystagmus syndrome patient (age range 6–12 years, or >60 years) with an afferent visual sensory deficit. Shown are the pre-tenotomy and reattachment (T&R) (solid circle) and estimated post-T&R (open circle) values and their respective best-corrected visual acuity values.

either base-out prisms or a bimedial rectus recession operation is indicated. The estimated null broadening and increase in peak NAFX should exceed those values determined from the T&R estimation curves of Figure 7.6.

7.5.1.4 SOFT CONTACT LENSES

Research has shown that, in INS patients whose IN damps with soft contact lenses, the therapeutic improvements resulting from their use are similar to those from the T&R procedure.^{32,33} Thus, for this subset of patients, the estimated null broadening should equal and the increase in peak NAFX might be less than those values determined from the T&R estimation curves of Figure 7.6.

7.5.2 Indirect/Clinical Outcome Measures

Although it is obvious that accurate and repeatable diagnoses, identification of appropriate therapeutic options, measurements of direct outcome measures, and estimation of therapeutic improvements can only be made using eye-movement data, they are not always available. As mentioned earlier, if one is absolutely sure that

a patient has no afferent visual sensory deficits associated with his or her INS, the direct relationship between the waveform quality measure, NAFX, and visual acuity can be used in both the estimation of the post-T&R therapeutic improvement and measuring that post-T&R improvement. However, when such afferent deficits are present, both become problematic because the proportion of measured acuity attributable to either the afferent deficit or the INS waveform is unknown.

7.5.2.1 VISUAL ACUITY AT DIFFERENT GAZE ANGLES

Measuring visual acuity at different gaze angles does provide a method to estimate the LFD improvement in all INS patients (as the above examples show) and the peak NAFX in some. At one end of the spectrum, where the measured visual acuity is high, one can presume the INS waveform component is paramount and substitute age-determined NAFX values for visual acuity measurements. At the other end, where visual acuity is very poor and the INS appears to be slight, one can presume that afferent visual sensory deficits are paramount; as Figure 7.6 shows, the probability for therapeutic improvement

as a result of INS therapy is low in such cases. That does not mean that all, or even most, cases of afferent visual sensory deficits plus INS will not be helped by INS therapy; many cases exist where the INS waveform plays a substantial part in poor measured acuity.

In summary, it had been almost two decades since the first four-muscle T&R surgery for INS was successfully performed on an affected canine. During that time, clinicians have reluctantly (with speeds almost below motion-perception threshold) transitioned from the second to the final stage of Schopenhauer's three stages of truth recognition (see epigraph).

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8

SUMMARY AND CONCLUSIONS

One of the most important functions in science is to reward those who disprove our most closely held beliefs.

—Carl Sagan (1934–1996)

IN THIS text, we have presented a synopsis of the past 50 years of our and many others' ocular motor research relevant to the diagnosis and treatment of infants, children, and adults with infantile nystagmus syndrome (INS) and other benign types of nystagmus of infancy. Analogous to the assessment of afferent visual system function with the use of the electroretinogram (retinal level) and visual evoked potential (prechiasmal and postchiasmal levels), definitive diagnostic ocular motility criteria have now been established for *all* types of nystagmus appearing in infancy. The purely clinical signs of these types of nystagmus, albeit indispensable, are often ambiguous and reliance on them for final diagnosis and treatment without quantitative motility data will continue to cause diagnostic errors that may be compounded by poor or inaccurate choices for therapeutic intervention. In many cases, *both* afferent and efferent visual function can be improved by the correct therapy applied in a timely manner. Unfortunately, only in selected centers of ophthalmological or neuro-ophthalmological research are ocular motility recordings now routinely available as part of the evaluation of nystagmus patients. Decades ago, cardiologists realized that they could not rely solely on their fingers and ears to accurately diagnose complex disorders of cardiac function. Clinical observation alone is no longer a valid or reliable way to evaluate ocular motor disorders.

To paraphrase the magician, “the (patient’s) eye is quicker than the (physician’s) eye.”

Recently discovered peripheral afferent neuroanatomy with its central ocular motor connections may be the mechanism by which peripheral disruptions initiate central changes. Plasticity following peripheral nerve transection has been demonstrated throughout the neuroaxis in animal models of nerve injury. Human brain imaging studies have corroborated the findings from animal models with the identification of altered functional magnetic resonance imaging activation maps due to spinal cord injury, amputation, toe-to-thumb transfer, and in patients with carpal tunnel syndrome. There is functional plasticity in several cortical areas following upper limb peripheral nerve transection and surgical repair. Until recently, most neuroscientists believed that the adult brain is hard-wired and largely incapable of reorganization. The only areas of the brain where some reorganization might occur would be those involved in learning and skill acquisition. However, over the past two decades, it has been conclusively established that even primary sensory areas of the brain are capable of reorganization in response to injuries or changes in patterns of peripheral stimulation. The mechanisms that facilitate functional plasticity are thought to include the immediate unmasking of preexisting projections from adjacent cortical and subcortical levels, and long-term sprouting of

axons at multiple levels of the neuroaxis, including the primary somatosensory cortex. There is accumulating evidence that EOM proprioceptive afferent signals are not only available to ocular motor and visual control structures, but they influence the processing of information in these structures and may be involved in modifying visuomotor behavior after eye-muscle surgery as well as oral and topical medications.

The patient's complete diagnosis must include the *motility* diagnosis in addition to the *afferent-system* diagnosis, as must the therapeutic plan. No longer can visual scientists or clinicians ignore the complex interrelationship of the developing visual afferent and visual motor systems and, as a consequence, need to evaluate *both* if there is a developmental disorder in *either*. Most, if not all, of the technologies for evaluation of the afferent visual system are feasible for clinical use. This includes behavioral testing of acuity in infants, visual evoked responses, electroretinography, color, contrast sensitivity, and visual field testing. There is now also important information to be obtained from optical coherence tomography. The complex combination of structural and developmental visual sensory and visual motor abnormalities in infants and children with nystagmus results in varied and multiple effects on visual system functioning; these include decreased spatial acuity, contrast sensitivity, color, motion perception, dark adaptation, functional visual field/space, visual recognition time, and a high incidence of ametropia, binocular dysfunction, and amblyopia. There may be a form of amblyopia unique to the developing visual system of eyes in constant motion we have labeled "motion amblyopia," the complete visual consequences of which are yet to be described. The importance of how treating the developing system affects both the afferent and efferent systems was shown in an animal model of developmental retinal disease, with associated infantile nystagmus, when, after treating the sensory system with gene-transfer therapy, the ocular motor system was also improved. The addition of eye-movement recordings in the clinical setting to augment tests of the afferent visual sensory system is now a clinical necessity. Also, best-corrected binocular visual acuity must be

measured in at least five gaze angles to document the sharpness of the off-peak, pretherapy decrement of visual acuity and its broadening after therapy; therein lies the most important measure of improved visual function. Also, a broader range of highest acuity will diminish the need for an anomalous head position and make up for slight errors in surgical corrections. After therapy, peak acuity may not improve significantly and nystagmus amplitude or frequency may not decline; the latter factors affect cosmesis but are not tightly correlated to visual function.

The strides made in the understanding, diagnoses, analyses, and treatment of the nystagmus found in infants and children began in the 1960s and are based on accurate eye-movement data and application of the control-system approach to understanding the relevant ocular motor system mechanisms. In the ensuing five decades, the key observations and hypotheses that followed were as follows: (1) the recognition that IN does not cause the eyes to oscillate across the target (as the medical texts claimed) but rather they move *away from* and *back to* the target with each cycle; (2) as the eyes approach the target, they *slow down* and *Maintain foveation* for an extended period of time; (3) the resulting foveation periods can be very *accurate* from one cycle to the next despite variations in the nystagmus waveforms and direction; (4) the IN waveform characteristics that determine visual acuity are the *duration* of the foveation periods and their *position and velocity variations*—all other portions of the IN waveform are essentially noncontributory; (5) there are a range of secondary therapeutic benefits to extraocular muscle surgery for INS—*broadening* the range of gaze angles with highest acuity and improving visual recognition time; (6) in INS patients with neither gaze-angle or convergence "nulls," simply performing a *Tenotomy and reattachment* (T&R) of each of the four horizontal rectus muscles duplicates the *broadening* benefits and *improves visual function* significantly; (7) a *mathematical function* applied to eye-movement data that was based on only the statistics of *foveation periods* (e.g., the *eXpanded Nystagmus Acuity Function*—NAFX) provides a measure of the

motor component (independent of the sensory component) of best-corrected visual acuity; (8) eye-movement data provide the most accurate and unbiased (i.e., not under the patient's control, as is anomalous head position) method of determining the amount of surgical correction necessary; (9) when the NAFX is combined with measured, best-corrected visual acuity, it provides, for the first time, a pretherapeutic estimate of the amount of visual function improvement that would result from the proposed therapy; and (10) the use of computer modeling to encapsulate top-down hypotheses, in the form of behavioral ocular motor system models, is of paramount importance in understanding the underlying mechanisms of different types of nystagmus present in infancy and in predicting the effects of therapy on target acquisition time for stationary and moving targets. Additionally, the development and use of the "Eyeballs 3D" program to illustrate in real time the motion of the eyes and the waveforms producing that motion has been of immense pedagogical value, both to us and to others.

This body of ocular motor research into INS has resulted in new approaches to its diagnosis and therapy. They are presented in Chapters 5–7 and include clinical guidelines to examination and diagnosis as well as the development of surgical techniques (e.g., the nine operations) and other therapies (e.g., contact lenses or base-out prisms) based on our eye-movement findings. The net result is a level of accuracy and predictability that supercedes past practices, which were based on clinical examination alone and mistaken premises; the net results are greater improvement for more patients and a higher degree of patient satisfaction.

As pointed out in Chapter 2, the roots of the word *nystagmus* are Greek, which may partially explain the extensive mythology that had been built up around this eye sign (see Appendix B, Section B.5). Early in our research, the absence of accurate, quantitative eye-movement data was recognized as the main reason for the misstatements of fact and contradictions present in the literature as well as the simplistic presumptions regarding the possible causes and underlying mechanisms of the different types of nystagmus

appearing in infancy. Unfortunately, the Greek origin of the word may also be related to the "tragedy" that still exists today—the failure to adequately treat patients and improve their visual function despite the proven therapies presented in this volume. This failure on the part of the medical community has relegated many children and adults with INS to a second-class life, unable to realize their full potential, professionally or personally. Fortunately for future patients, the overwhelming amount and veracity of the data gathered and analyzed in the twentieth century are slowly bringing the field of pediatric vision care out of the nineteenth and into the twenty-first century, where diagnosis, therapy, and measured outcomes are data driven.

We have striven to cite all relevant, scientifically sound research in the various chapters and hope that those studies cited (and the citations that each contain) have not left many we unintentionally omitted. The serious student of INS should also read the many excellent papers emanating from the laboratories of Richard Abadi and Harold Bedell; there is a wealth of relevant psychophysics in that literature. Unfortunately, because of the persistence of the ophthalmic mythology surrounding nystagmus, the literature (past and present) contains many studies that are not of the same quality of those we cited. As pointed out in Chapter 2, many of them have been reviewed as part of six literature reviews of nystagmus and saccadic intrusions and oscillations published during 1980–1991 and were not included in this volume. Finally, a small number of papers have made it into the literature despite the false and plagiarized material they contained, and the unethical behavior of some of their authors. That is an unfortunate and irreversible pollution of the literature. To cite such papers would denigrate the honest, objective science that comprises the majority of research in this area; therefore, they were not cited herein.

In Appendix A, we have provided eye-movement recording methodology, analysis methodology, calibration techniques; in Appendix B, clinical examination forms, clinical pearls, and ophthalmological myths and facts; in Appendix C, illustrative cases and treatment; and in

Appendix D, diagnosis and treatment flowcharts and graphs useful for INS analysis. On Companion Website, we provided in Appendix E, "Eyeballs 3D," canine, and patient videos and in Appendix F, OMLAB reports, patient handouts, physician/scientist worksheets, analysis software, and modeling software.

In the final analysis, we must answer this question, "Can nystagmus patients be diagnosed

and treated without eye-movement data?" The answer is, "Yes, but not always *correctly* or *optimally and only with variable or unpredictable outcomes*." Difficult, and some not-so-difficult, cases require eye-movement data to avoid problematic outcomes; the less difficult cases will also benefit from the more accurate and repeatable diagnoses and predictable, measurable therapeutic improvements based on eye-movement data.

EPILOGUE

Science is unlike democracy; a good hypothesis neither requires nor becomes more accurate by scientific consensus. In fact, many of the most scientifically far-reaching hypotheses suffered both the skepticism and hostility of contemporary scientists.

—Louis F. Dell’Osso (1941)

THE SCIENTIFIC research that is the basis for this book and for the diagnostic and therapeutic advances that resulted has been both our driving force and source of great personal satisfaction. There is little that compares with the exhilaration of making new discoveries, of being the only person who knows of them (albeit, until publication of the findings), or of making the critical connections that transform new knowledge into successful therapeutic applications. However, the essay that follows, submitted by a prospective medical student whose visual function is limited by both albinism and infantile nystagmus syndrome, provides an elegant painting for which our work is but a frame.

Freshman Applicant Prompt 2
Tell us about a personal quality, talent, accomplishment, contribution, or experience that is important to you. What about this quality or accomplishment makes you proud, and how does it relate to the person you are?

BEHIND THESE BLUE EYES

I HATE first impressions. When people first meet me, they stare bewilderingly into my blue eyes, not able keep up with the rapid movement of my nystagmus, automatically writing me off as handicapped, blind, and useless. Having been born with Albinism, and been labeled as legally

blind, people see my eyes as genetic mutations. If that is so, this mutation has proven to be the best life lesson.

Throughout my life, it has always been my goal to turn my disability into an ability. Whether it be through playing varsity basketball for seven years, maintaining above average grades, or disproving the stereotype that “albinos” are anti-social, by surrounding myself with an endless group of friends and by holding countless leadership roles, through student council, public speaking, and mentor programs.

“Just wear your glasses and adapt,” is the typical response I would receive when I would seek help from my eye doctors. I’ve been adapting my entire life in order to survive in this world that was made for perfect sight—Charles Darwin would be proud. But, as independent as I have worked so hard to become, I was still not happy with having to hide my wandering eyes.

“I want to be a doctor.” Whenever people hear what my dream career is their faces cringe with doubt. I don’t blame them. I am very aware that becoming a doctor is a very challenging task for anyone, but for someone who’s visually impaired, it’s nearly impossible. Despite the doubt others may have, I have no second thoughts. If anything, I think this is one aspect of my life in which my disability can benefit me. Doctors can prescribe medicines and perform procedures that can alleviate the short-term

pain of patients that have been diagnosed with an illness that will affect the rest of their life. But as for the long-term pain, how many doctors can give advice on how to put a disability on the back burner and live their lives to the fullest, all based on personal experience?

If there is anything I take pride in, it is my ability to overcome obstacles. I am looking forward to spending the rest of my life helping others, physically and mentally, to overcome their illnesses, but in order to do this, I must first have 100% confidence in myself. I need to be able to look the world in the eyes and make a good first impression.

So I took the initiative, and did some research. I spent months looking for my “confidence booster.” I was referred to Dr. David Granet, an ophthalmologist from UC San Diego. He offered me a life changing surgery that would dramatically decrease my nystagmus and increase my vision. With this new source of hope, I confronted my parents and doctors about the surgery. Before I knew it, I was at UCSD, lying on the operating table, a place where most people feel anxiety and fear; I felt only hopeful anticipation of waking up to a more lucid world, free of

the piercing stares that have made first impressions so unbearable. This was the boost I was looking for. Today, my nystagmus has decreased to the point where I can actually feel comfortable enough to look you in the eyes and give my first genuine impression.

My name is Kaila Uniacke; look me in the eyes and you may see a girl with a disability. Take a closer look, and you will see that behind these blue eyes, lies anything but. I am a student, not just of textbooks, but of life, a lifelong learner, taking each of my life lessons to heart. I live not to cover up my flaws, but to express myself, to stand out, to make a difference. If you could see the world through my eyes, you would realize that I may not have sight, but I know I have vision; the vision to take pride in everything I do, whether I succeed or fail, whether my dreams come true or fall short. I will always be proud of who I am, imperfections and all. I am a girl with many passions in life: a passion for laughter, a passion for medicine, a passion to continually prove to the world that my disability has not won.

—It's nice to meet you.

APPENDIX A

EYE-MOVEMENT RECORDING SYSTEMS AND CRITERIA

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THE STUDY of ocular motor mechanisms (normal or abnormal) for the diagnosis and treatment of ocular motor disorders requires accurate recording of eye movements. This includes a reliable, easy-to-use recording system; accurate *monocular* calibration and linearization paradigms; and, in subjects with nystagmus or other ocular motor oscillations, knowledge of the foveation portions of the eye-movement waveforms. We describe the historical development of eye-movement recording systems, the advantages and disadvantages of those commonly used today, the requirements for accurate calibration of those systems, and the use of eye-movement recordings in basic research, including clinical settings.

Despite the fact that human hearing is inferior to that of the owl, and the human sense of smell is far poorer than a dog's, our visual acuity is excelled by few other species. However, if we processed our entire visual field simultaneously at our maximal resolution, we would need so many optic nerve fibers to carry visual information back to the brain that there would be room for little else. Evolution has solved this problem by making the resolution of the retina—the light-sensitive neural layer of the

eye—inhomogeneous. Visual acuity in the central 1° of the visual field is maximal, but it falls off rapidly as one moves toward the periphery. What keeps us from ever being aware of this is the nearly incessant motion of our eyes, controlled by the interconnected control systems that direct our gaze to an object of interest and keep it fixated in the face of target and body movement. Massive processing in the visual areas of the brain integrates the discontinuous flow of visual images along with efference copy of motor commands to the extraocular muscles, into the clear, stable perception of the world experienced by both normals and those with some ocular motor oscillations.

What follows are descriptions of the more common eye-movement recording technologies used in the past and present. Technical descriptions, engineering, and physics of these and other methods will not be discussed in this volume (see also Abel and Dell'Osso¹). Rather, emphasis will be on the abilities of different types of systems and the calibration requirements to provide accurate eye-movement data in both the basic and clinical research settings.

Historically, the instrumentation for recording all types of eye movements was used

originally to record vestibular nystagmus. Purkinje noted eye movements by visual observation in 1825 and E. Darwin by palpations of the eyes in 1794.² Studies of eye movements by visual observation were described by Javal in 1879.³ The experimenter stood behind the subject and observed the movement of the eyes in a mirror. Specially designed optical instruments were used to magnify the mirrored images that then could be studied in detail. More accurate descriptions, based on the observation of afterimages, were also made at the end of the eighteenth century. Using this method, Wells described the slow and fast phases of vestibular nystagmus.⁴ The occurrence of saccades during reading was first reported by Javal and Lamare, who used a rubber tube connected to the conjunctiva and both ears.³ With this device, each eye movement caused a sound that was heard. Hering used a similar acoustic device in combination with the technique of afterimages.⁵

The earliest mechanical methods of recording eye movements were proposed by Raehlmann in 1878, who used one end of a lever attached to the globe and with the other end of the lever, recorded the transmitted eye motions, on a moving smoked drum (Fig. A.1).^{2–4,6,7} The lever technique was modified by Gradenigo in 1909, by Buys and Coppez in 1909, and Ohm in 1914. In their studies, one polished end of the lever touched the anesthetized cornea, while the other end of the moving lever made the record on a moving paper

tape or “kymograph”⁸ (Fig. A.2). The technique further improved when small cups resembling contact lenses were attached to the cornea. In 1899, Orschansky fixed a small mirror to the cup on the eye and used a beam of light to project the reflected eye movements onto a screen.^{9,10} The method of recording eye movement by reflected light was further advanced with the use of special contact lenses. Unfortunately, this method could injure the eye and was too heavy to measure the large accelerations occurring during saccades. To overcome this problem, Javal recorded the reflection of a light beam from a little mirror attached to the conjunctiva, a method that was not successfully applied before von Romberg and Ohm used it to measure ocular torsion. This technique was, however, still too invasive.¹¹

Photographic analysis of nystagmus was introduced by Dodge and Cline in 1901 and

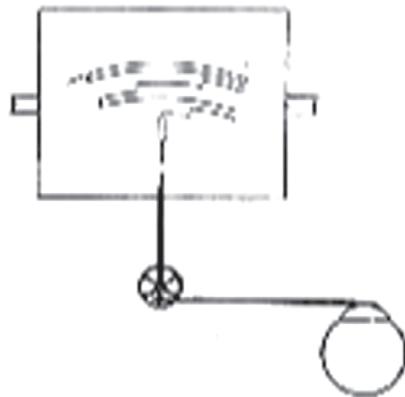


FIGURE A.1 Lever device to document horizontal eye movements during reading.

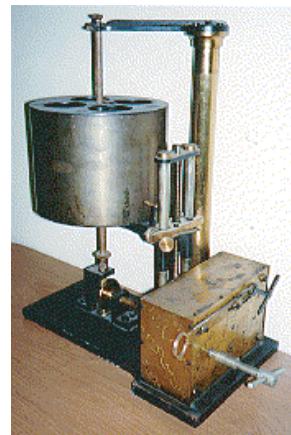


FIGURE A.2 Model of Kymograph of the type used to record eye movements. Time recordings of physiological phenomena became possible when a galvanometer's needle was put into contact with a loop of paper coated with a thin layer of smoke black and stretched over a metal drum. A precise mechanical clockwork allows the drum to be rotated at a calibrated speed, and the movements of the galvanometer's pen scratch out the smoke black, leaving a record of amplitude as a function of time. Mechanical phenomena, such as eye movements, could be recorded along time, by rigging levers, axes, membranes, springs, and strings. The time axis was calibrated and measured by using electromagnetic tuning forks attached to inscribing pens.

1903.³ In 1913 Coppez used early cinematography. Electrical recording of eye movements was first reported by Schott in 1922 by modifying electrocardiography.¹² Schott and Meyers measured electrical potentials with skin electrodes attached near the eye.¹² Mowrer et al. discovered that the electrical potential is primarily caused by the electrical dipole between cornea and retina, which moves with the eye. This technique has been the basis of modern electroneystagmography (ENG) or electrooculography (EOG)¹³ (Fig. A.3). The eyes are the origin of a steady electric potential field, which can also be detected in total darkness and if the eyes are closed. The electric signal that can be derived using two pairs of contact electrodes placed on the skin around each eye with a ground or reference electrode placed on the forehead. Jung applied this method to record horizontal and vertical components of the eye position simultaneously¹⁴ (Fig. A.4). Previously, recording techniques had been restricted to one movement direction only. Moreover, the EOG allows recording of eye movements while the eyes are closed, of particular interest for sleep research.

Noncontact optical methods are currently the most popular. The use of infrared light reflected (IR) from the eye, which is sensed by specially designed optical sensors remains common. A voltage is generated from the difference in reflection between the sclera and iris as the eye moves and is the basic output to extract eye

rotation information (Fig. A.5). These IR devices measure the intensity of these reflections by photosensitive elements placed at different locations in front the eye. The first system was developed by Torok et al.¹⁵

Video-based eye trackers typically use one or multiple Purkinje images and the center of the pupil as features to track eye movement over time. These optical methods, particularly those based on video recording, are now widely used and are favored for eye-movement analysis. They are especially useful in infants and children, being noninvasive and inexpensive (Fig. A.6). These so-called double Purkinje image (DPI) eye trackers reach high resolution, accuracy, and bandwidth. The high accuracy of the DPI eye tracker during steady fixation is due to the fact that it uses the angular differences between light reflections that are insensitive to small translations between the eye and the tracker. Videooculography (VOG), defined as the use of these methods for dynamic measure of eye movements, became feasible with the rapid development computer-based automatic image processing. This progress is mainly reflected in the frame rates being processed online and in the robustness and the accuracy of the marker detection algorithms. Both improve with the increase in computational power. Since the measurement of two-dimensional gaze direction in VOG is primarily based on the localization of the pupil, the two-dimensional VOG

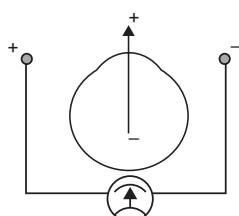


FIGURE A.3 The eye acts as a dipole in which the anterior pole is positive and the posterior pole is negative (arrow). The cornea (relative positive charge) approaches one canthal electrode while moving away from the other canthal electrode to which the retina moves near (relative negative charge), resulting in recordable changes in the potentials between the two electrodes.



FIGURE A.4 Electrode placement for contact oculography. Pairs of electrodes are placed to the left and right and top and bottom of each eye. If the eye is moved from the center position toward one electrode, this electrode “sees” the positive side (the cornea) and the opposite electrode “sees” the negative side (the retina). Consequently, a potential difference occurs between the electrodes.

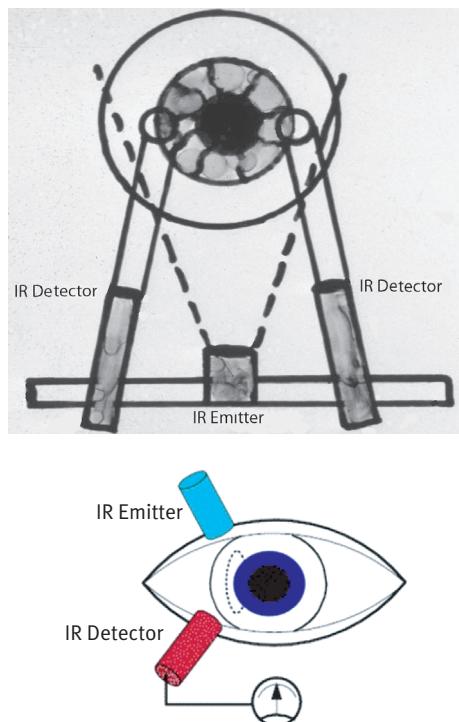


FIGURE A.5 Principle of infrared-reflectance (IR), eye-movement recording. A voltage is generated as the eye moves in front of an infrared detector due to the difference in reflectance between the sclera and iris as the eye moves. This signal from the detector as a result of the measured difference in reflectance is amplified and filtered to produce the eye-movement recording. Standard push-pull-connected detectors (top panel) and single detector (bottom panel).

works reliably in head-mounted systems and with stabilized head positions. To compute the three-dimensional eye position, the orientation of the iris signature can be used. This signature must be scanned along a circular path close to the limbus, in order to be insensitive to changes of the pupil diameter. Direct polar cross-correlation of the iris signature at the actual eye position with that of a reference position can be used to measure ocular torsion. This works well while gaze is pointing straight ahead, but geometric distortions of the iris occurring at eccentric gaze positions lead to large errors.

None of the recording methods mentioned thus far are able to quantify horizontal, vertical,



FIGURE A.6 Remote video-based, eye-movement recording system. This method is based on tracking of the position of eye-fixed markers in a two-dimensional image.

and torsional eye movements simultaneously. Vertical and horizontal movement components could be quantified by the EOG, IR, or the DPI tracker, but these devices cannot measure ocular torsion. Von Romberg and Ohm measured pure ocular torsion in primary position with their mirror system.¹⁶ By the nineteenth century, the technique of afterimages had provided important findings about ocular torsion during fixation. This field of research became of increasing interest when the magnetic search-coil technique, developed by Robinson and Collewijn et al., was extended by Collewijn et al. and Kasper and Hess to cover three-dimensional movements.^{17,18} The method is based on the voltages induced in coils by two or three orthogonal, rapidly alternating magnetic fields. The coils are embedded in a soft silicone annulus that adheres elastically to the eyeball. One coil is sufficient to measure gaze direction (Fig. A.7). Two coils with different orientations must be molded in the annulus to measure gaze direction and ocular torsion simultaneously. The search-coil method combines high spatial and temporal resolution and is so far the most precise method for measuring ocular torsion.

Like other methods based on contact lenses, the search-coil technique has the main disadvantage of being invasive (Fig. A.8). Therefore, considerable effort was made to evaluate the

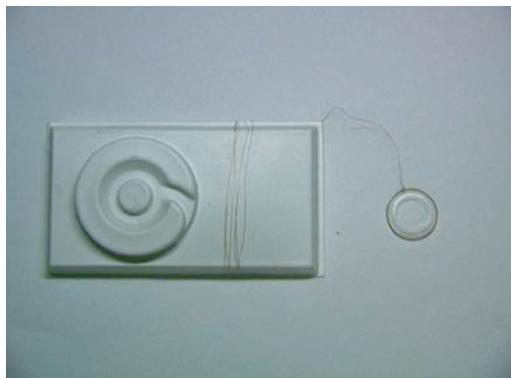


FIGURE A.7 Scleral search coil. The coils are embedded in a soft silicone annulus that adheres elastically to the eyeball.



FIGURE A.8 Scleral search coil. The silicone annulus rests on the eye at the corneo-scleral limbus on the conjunctiva similar to the older “scleral” contact lenses.

three-dimensional eye position on the basis of photographic images of the eye. All photographic methods are based on the detection and localization of eye-fixed markers (pupil, limbus, iris signatures, episcleral blood vessels) in image coordinates. The eye position with respect to the head can be computed from these image coordinates if the camera is firmly attached to the head. Otherwise, head-fixed markers can be used to compensate for relative translations between head and camera. Howard and Evans described a method for computing three-dimensional angular eye positions from the image coordinates of the markers.¹⁹

A.1 RECORDING METHODS

A.1.1 Contact Electrooculography

The simplest method for measuring human eye movements is based on the feature that the human eye is an electrical dipole. The axis of this dipole and the optical axis of the human eye are roughly collinear. The retina is more negative than the cornea. The potential difference of about 0.4–1.0 millivolts results from the electrical activity of photoreceptors and neurons in the retina. Changes of this potential induced by sudden light stimulus have been used for decades to monitor the electrical activity of the retina (electroretinogram [ERG]). However, the EOG measures the eye dipole as it rotates. This causes

small differences between the electrical potential at the skin surface next to the eye depending on eye position. A rightward eye movement will increase the surface potential at the temporal canthus and decrease it at the nasal canthus of the right eye (Fig. A.4). The potential differences can be measured with a contact electrode configuration. The voltages are usually referenced to a third electrode that is generally placed at the forehead or one of the mastoid processes or on the earlobe.^{2,20–22} To simultaneously record vertical eye movements, two additional electrodes must be placed below and above the eye. Vertical EOG signals are less reliable than horizontal signals due to lid artifacts.

The resolution of both horizontal and vertical EOG signals is limited by electromagnetic field noise in the environment, thermal noise generated by the input resistance of the amplifier and the contact resistance of the skin electrodes, and capacitive noise due to electrical activity of muscles and neurons.^{2,20–22} To lower the contact resistance, the skin should be cleaned with alcohol. Electrodes should be made of relatively nonpolarizable material such as silver-silver chloride or gold and applied with a conductive paste. Subjects should be instructed to avoid any movements except eye movements. Changes of the dark adaptation level induce slow drifts of the corneo-retinal potential that are superimposed

on the EOG signal. Since both the EOG and ERG measure the corneo-retinal potential, the standards of ERG recordings are also recommended for EOG recordings. The spatial resolution of EOG is $\sim 1^\circ$, temporal resolution ~ 40 Hz, vertical recording is confounded by blink artifact, noise is 1° or more, setup is slow, calibration is needed, and cost is $\sim \$500.00$.

A.1.2 Infrared Reflection

These devices measure the differences in intensity of infrared light reflected from across the surface of the eye at a fixed location from the eye.^{2,23–26} Light intensity is measured with photo diodes that have a high temporal resolution (Figs. A.9 and A.10). The distance between eye and photoreceptors is in the range of 24 mm. At such small distances, the differences in the intensity between the different photodiodes depend mainly on the position of iris and pupil, which reflect less light than the surrounding sclera. IR devices are very sensitive to relative translations of the photodiodes and the eye because they do not evaluate the angle, but only the intensity of the reflection. For an eye radius of 1.25 cm, a translational error of 1 mm will lead to an eye-position error of almost 5° . The system must therefore be firmly attached to the head. IR devices have a much lower noise level than EOG, but they suffer from eyelid artifacts that critically depend on the position of the photodiodes. These lid artifacts may increase dramatically if



FIGURE A.10 Infrared reflectance eye-movement recording system embedded in a goggle system specially designed for use in infants.

the device is not properly adjusted in front of the eye. Lid artifacts are more pronounced for vertical than for horizontal eye movements. Moreover, the position of the photodiodes is also critical for the system linearity. Due to these features, optimal adjustment of the device requires that the experimenter carefully controls the eye-position signal of the IR device and compares it with the eye movements (Figs. A.11 and A.12). The spatial resolution is $\sim 0.1^\circ$, temporal resolution is 100–500 Hz, and vertical recording is confounded by blink artifact and the intrinsic difficulty in distinguishing lid movement from eye movement. Setup is fast but calibration is necessary. Linearity is a problem with nonlinearity occurring at 15° – 20° and cost is moderate, $\sim \$4000$.



FIGURE A.9 Infrared reflectance eye movement recording system embedded in a goggle system. This shows the combination of vertical and horizontal detectors for each eye.



FIGURE A.11 Children positioned in head and chin rest with infrared goggles in place and a viewing stimulus screen for accurate calibration (side view).



FIGURE A.12 Children positioned in head and chin rest with infrared goggles in place and a viewing stimulus screen for accurate calibration (front view).



FIGURE A.13 Three-foot scleral search-coil, magnetic field system with dichoptic stimuli apparatus (monocular stimulus screens and mirrors). Around the head of the subject an alternating horizontal and vertical magnetic field (spatially and temporally in quadrature) is generated and consequently an alternating voltage will be induced in the scleral contact lens with embedded coil.

IR systems are second only to EOG in their range of applications. Because they can resolve fine detail with low noise, they are excellent for conditions where subtle features of the eye movement are important. IR systems were the key to the accurate analyses of saccadic trajectories and the analysis of small corrective saccades within nystagmus waveforms. Also, being non-invasive, they provided a major advantage for the study of patients and children.

A.1.3 Scleral Search Coil

The scleral search-coil system measures the voltages in one or two coils induced by two or three rapidly oscillating magnetic fields^{2,17,18,27–31} (Fig. A.13). The coils are molded in a soft contact annulus that is attached to the eyeball. Three pairs of large coils, mounted in a cubic frame, generate the magnetic fields. The subject's head is positioned at its center. The field coils should be large, because the homogeneity of the magnetic field is crucial for the precision of the measurement. With pairs of square-shaped coils, arranged in a cubic configuration, the inhomogeneity inside of a central test cube stays below 5% when the edge length of the test cube approaches one-fifth of the edge length of the field coil. This means that when using field coils with an edge length of 1.5 m, subjects should not move by more than 7 cm.

The voltage induced by one of the magnetic fields in the scleral search coil is proportional to the projection of the coil vector (defined as the vector orthogonal to the effective coil plane) onto the magnetic field vector. Thus, the three voltages induced by three orthogonal magnetic fields form the vector components of the coil vector expressed in field coordinates. A dual search coil for recording three-dimensional eye orientation provides six voltages, corresponding to the two three-dimensional coil vectors of the directional and the torsional coil (Fig. A.14). Methods to compute the three-dimensional eye orientations from these six signals are then

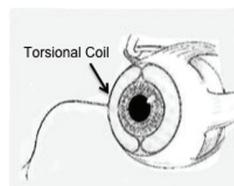


FIGURE A.14 Torsional coil on eye. The principle of the scleral search-coil technique is based upon the magnetic induction of a small coil embedded in a flexible ring of silicone rubber, which adheres to the limbus of the human eye concentric with the cornea.

employed. Search-coil recordings require a calibration procedure that is often based on multiple alignments to targets at various positions. The calibration parameters are computed by minimizing the errors between the calibrated gaze vector and target vectors.^{2,17,18,27–31} Systems with three magnetic fields can be objectively calibrated, that is, their calibration does not rely on accurate fixation of targets at different positions, as most other recording techniques. Only a single fixation target is needed in order to determine the orientation of the coil with respect to the eye. Another important advantage of three-field systems over two-field systems is that the orientation of the coil vector can be determined without knowledge of the actual inductance of the scleral search coil. This is because changes in inductance will have the same proportional effect on all three voltages and can easily be eliminated by normalization.^{2,17,18,27–31}

With the search-coil technique, the inherent system noise of horizontal and vertical eye position has been estimated to be on the order of 0.5 min of arc (0.0083°). The system resolution is a very important parameter; it determines the smallest eye movement that can be detected. However, to compare the metrics of eye movements between different subjects or with a stimulus-defined requirement the accuracy is more important than the system noise. The system accuracy of search coils depends mainly on the quality of the calibration. Due to its large signal-to-noise ratio and reliability, the search-coil technique has been the generally accepted reference standard for eye movement recordings for 30 years. However, the disadvantages, connected with the invasiveness of the method, have also been recognized. The search coil not only measures eye movements but also affects them. Some authors have found that saccades last longer (by about 8%) and become slower (by about 5%) when subjects wear search coils in both eyes than when they do not.^{32,33} It was also shown that the eye torsion, when evaluated with the search coil, depends on the orientation of exit point of the connecting line from the search coil and, with the nasal exiting orientation of a commercial eye coil (Skalar), ocular torsion depended more on eye elevation than

with a modified exit point that minimized the contact between wire and eyelids. Other disadvantages of the scleral search coil are that wearing the coil may lead to drying, and temporal deformations of the cornea, and reduced visual acuity in the eye with the search coil. Therefore, the manufacturer of the search coil limits wearing time to 30 minutes.

The coil spatial resolution is ~0.01°; temporal resolution is at least 1000 Hz. Vertical and torsional recordings are also possible and linearity is good, although setup is slow and calibration is needed. A reasonable coil system can be bought for about \$15,000; each eye coil costs about \$100. A typical eye coil lasts for two subjects. There is a small risk of a corneal abrasion from the contact lens. The estimate of the risk is about 1/400 subjects. There is also a small risk of transmitting very serious diseases if the lab reuses lens between patients. Certain biologic agents (prions—such as found in “Mad Cow”) are very difficult to kill. This risk can be avoided if the lab simply uses a new scleral contact lens rather than “recycling” them. Only about 30 minutes of continuous recording is usually possible at one setting. Eye-coil systems are usually research tools. To use an eye-coil system subjects must sign a consent form because of the risk of corneal abrasion. This technology is certainly the most expensive of all, because of the cost of the eye coils.

A.1.4 High-Speed Video Oculography

Video-based, eye-movement recordings have become more and more popular because of the rapid progress made in electronic data processing.^{21,24,34–39} High-speed video oculography (VOG) has become affordable, the robustness of the algorithms improved, and the range of applications expanded (Fig. A.15). Nowadays, commercial companies produce VOG devices that can be used in a functional magnetic resonance imaging scanner (MeyeTrack^R, SMI^R, Berlin, Germany). Most fundamental VOG techniques are based on tracking of the position of eye-fixed markers in a two-dimensional image. These positions have to be expressed in head-fixed coordinates. Since head-fixed markers are difficult to obtain with high precision, one

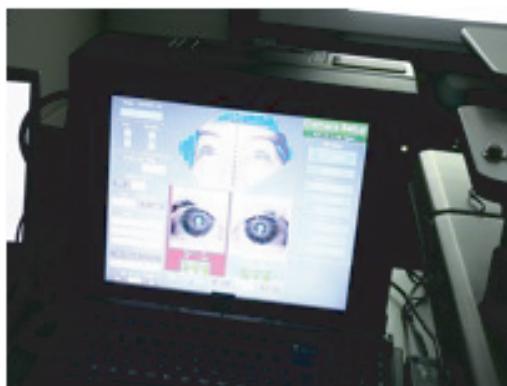


FIGURE A.15 Video-based, eye-movement system showing programming computer interface displaying calibration parameters and actual pupil location within the camera system.

strategy of VOG systems is to attach the video camera as firmly as possible to the head. As long as the system is not compensated for relative translation between camera and head, the accuracy of VOG has a problem very similar to that of IR. A translation of 1 mm will result in an error of about 5°. Head-fixed devices cause a problem under head free conditions, because the stability of the head mount is not sufficient. Because of this problem, actual VOG systems can make highly accurate measurements of eye position, only as long as the head is stable in space.

A VOG method of compensating for head translation uses the relative position of the corneal reflex of an infrared LED (Eyelink II^R, SR Research, Osgoode, Canada) (Fig. A.16). One difficulty with this method is that using the corneal reflection adds more noise. For eye movements

of about 12°–15° the reflection reaches the edge of the cornea and can no longer be used for compensation. Moreover, this approach relies on the topography of the cornea, which varies between subjects. Therefore, it seems to be useful when compensating for large translations, but it may be unable to provide very high accuracy. Since the pupil position is detected and evaluated in image coordinates, the nonlinearity of the VOG (in contrast to IR) systems is well defined by the geometry of the image projection. With parallel projection, the angular eccentricity of the eye can be approximated by the inverse sinus of the ratio of the eccentricity of the pupil center and the eye radius, both expressed in image coordinates. The main aim of the VOG calibration is therefore to determine the location of the center of rotation of the eye and the radius of the eyeball. The resolution of the two-dimensional VOG defined by the standard deviation of system noise measured with an artificial eye is about 0.01°. The VOG of two-dimensional measurements of ocular torsion also reach accuracy values that are similar to those of coil measurements. The spatial resolution is 1 part in 1024 and now with high-speed cameras, temporal resolution is as high as 1000 Hz. VOG can record vertical and torsion movements.^{21,24,34–39} Setup is rapid and calibration may be less difficult. Goggles effectively black out vision, so maintaining a “light-tight” lab is not crucial; this may be important in some applications and for some systems. Systems cost from \$18,000 to \$50,000.

As Figure A.17 illustrates, in addition to the study of humans with nystagmus, we have used both IR and video systems successfully to study canine eye movements in both normal dogs and those with nystagmus. The dog on the left was an achiasmic Belgian sheepdog with infantile and seesaw nystagmus; the dog on the right was a Briard with Leber congenital amaurosis; and the dog at the bottom was a normal Brittany, highly trained for upland bird hunting.

Eizenman and his students have developed new algorithms for video-based systems that may make patient-cooperative calibration unnecessary.^{40,41,42} This promises to be a major improvement in the ability to obtain accurate eye-movement data from infants and uncooperative

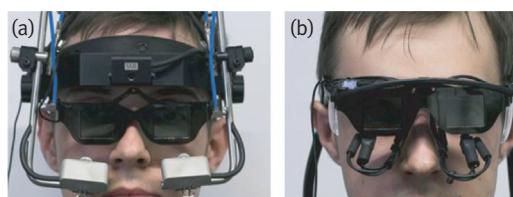


FIGURE A.16 Head-mounted eye trackers: (a) SMI EyeLink I and (b) Arrington Research ViewPoint PC-60 BS007. The shutter-glasses have been attached to the head-mount and the cameras are recording the eyes from below.

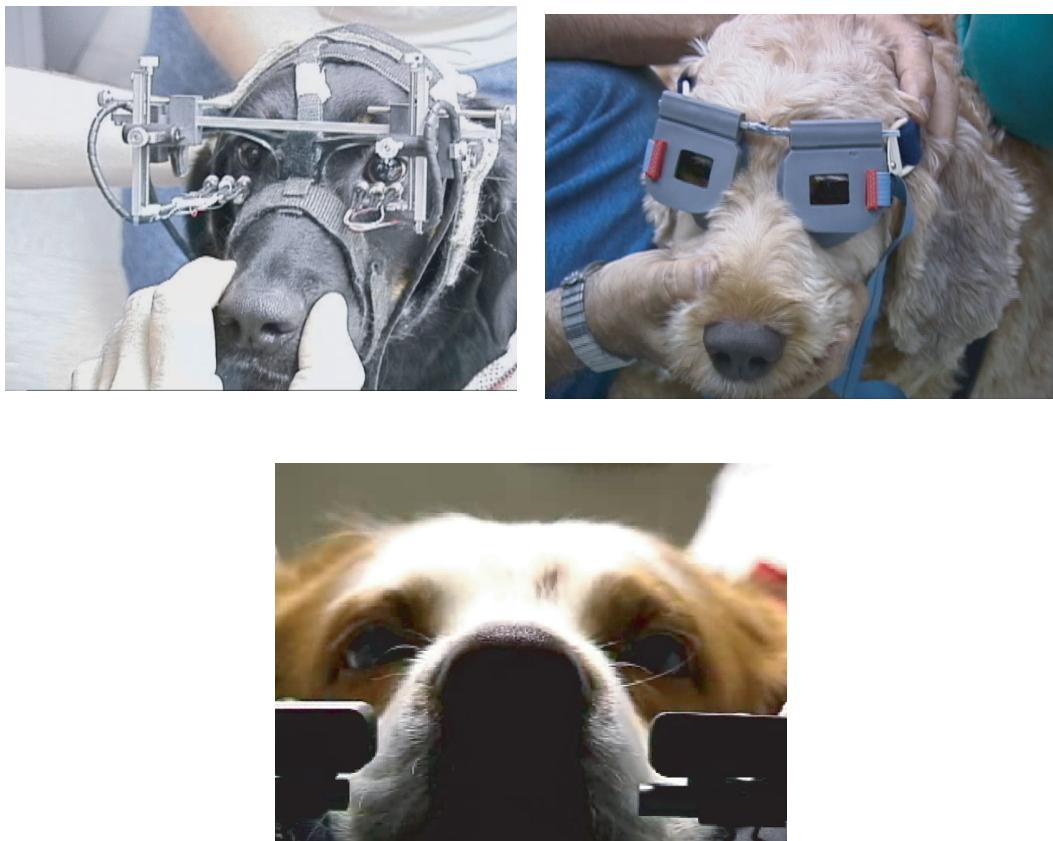


FIGURE A.17 Use of infrared (eyeglass-frame type, top left panel and goggle type, top right panel) and high-speed digital video (bottom panel) systems to study canine eye movements.

children in the clinic. Its accuracy in patients with nystagmus is yet to be tested.

A.2 RESEARCH CRITERIA

At present, IR, search-coil, and digital video systems meet the criteria for accurate eye-movement data. Each has its own set of advantages and limitations, and a well-equipped laboratory usually has several of the systems available that can be tailored to each study. In all systems, accurate, monocular calibration and zeroing is a necessity.

A.3 CLINICAL CRITERIA

In the clinic or clinical laboratory, IR, search-coil, and digital video systems have also been used, but the search-coil system is usually too

invasive for studying most patients and children. Accurate differential diagnoses of nystagmus and detection of fixating-eye changes due to strabismus require accurate, monocular calibration and zeroing.

A.4 CALIBRATION TECHNIQUES

A.4.1 Adults and Children

For both adults and children each eye must be calibrated at several target positions while the other eye is occluded; for search coils, each eye must be zeroed while the other is occluded (each eye coil will have been precalibrated on a protractor jig before inserting it into the eye). The calibration and zeroing values can then be used post hoc on the data collected to ensure accuracy and linearity.

A.4.1.1 INFANTILE NYSTAGMUS

For infantile nystagmus syndrome (INS) patients, monocular calibration allows analysis of the fixating eye for foveation quality and detection of microstrabismus, both static and time varying. Application of foveation-quality formulae like the NAFX require that the data being analyzed come from the fixating eye only; data from a deviated eye would be meaningless in the determination of best-possible acuity.

A.4.1.2 FUSION MALDEVELOPMENT NYSTAGMUS

For fusion maldevelopment nystagmus (FMNS) patients, monocular calibration is necessary for the same reasons as for INS patients. In these patients, switching from one fixating eye to the other varies with both gaze angle and time; without an accurate method of determining which eye is fixating at any particular instant, analysis would become hopelessly confounded.

A.4.2 Infants

For infants with either INS or FMNS, the difficulties in calibration may, in some cases, preclude acquiring accurate data. This is usually a problem in children between the ages of 2 to 4 years old who may be uncooperative. For this group, a non-invasive, self-calibrating system would be invaluable (see earlier discussion of recently developed software algorithms that may solve this problem).

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APPENDIX B

CLINICAL EXAMINATION

- | | |
|--|---|
| B.1 GENERAL CLINICAL EXAMINATION
FORM 272 | B.4 CLINICAL PEARLS 277 |
| B.2 STRABISMUS EXAMINATION
FORM 276 | B.5 OPHTHALMOLOGICAL MYTHS AND
FACTS 279 |
| B.3 NYSTAGMUS EXAMINATION
FORM 277 | |

B.1 GENERAL CLINICAL EXAMINATION FORM

Outpatient Pediatric Ophthalmology Medical Record

New Annual Follow up Urgent Consult

Referring Physician: Unknown _____ PCP: Unknown _____

Chief Complaint: _____ Time Patient in Office: _____

HPI: (Location, Duration, Frequency, Severity, Associated Sign and Symptoms, Modifying Factors)

Ocular HX: (Mark X if positive HX, -- if no HX)

- Cataracts
- Glaucoma
- Strabismus
- Visual Delay
- Retinopathy of Prematurity
- Amblyopia
- Nystagmus
- Retinal Disease
- Corneal Disease
- Refractive Error
- Other _____

PMH: (Mark X if positive HX, -- if no HX)

- Diabetes
- Arthritis
- Cancer
- Thyroid
- Cerebral Palsy
- Autism
- Hearing Deficit
- Hydrocephalus
- Craniofacial Disease
- Childhood Heart Condition
- Other _____

Review of Systems: (Normal mark X; Abnormal mark numerically the give description below) Medications: None (Mark X if none) Allergies: None (Mark X if none)

<u>Constitutional</u> (fever, wt loss/gain)	<u>Gastrointestinal</u> (diarrhea, constipation)
<u>Neurological</u> (seizures, headache)	<u>EENT</u> (infections, blurriness, deafness)
<u>Musculoskeletal</u> (weakness, pain)	<u>Endocrine</u> (diabetic, thyroid)
<u>Hematologic</u> (sickle cell, clotting)	<u>Respiratory</u> (cough, SOB)
<u>Cardiovascular</u> (palpitation, angina)	<u>Genitourinary</u> (frequency, stones)
<u>Psychiatric</u> (depression, bipolar)	<u>Integumentary</u> (rashes, lesions)

Description: _____

Family HX: (Mark X if positive HX & note patient relation, --if no HX)

- Retinal Detachment _____
- Glaucoma _____
- Lazy Eye _____
- Diabetes _____
- Childhood Cataracts _____
- Nystagmus _____
- Thyroid _____
- Cancer _____
- Other _____

Social HX: (Mark X if positive HX, -- if no HX)

- Substance Use _____
- Sexual Activity _____
- Grade Level _____
- Guardian – Relation _____
- Sports _____
- Other _____

**Outpatient Pediatric Ophthalmology
Medical Record**

Exam: (Mark X if Positive)

Appropriate for age Developmentally Delayed Cooperative Uncooperative Unresponsive/Sleeping

Stereopsis:

Worth 4 Dot:

Color:

Visual Field:

Near Point of Convergence:

Near Point of Accommodation:

Fusional Amplitude:

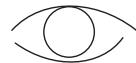
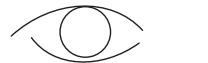
Accommodative Amplitude:

Exophthalmometry:

Direct Ophthalmoscopy:

Dynamic Retinoscopy:

	External: (Mark X if Normal)
	Head Posture
	Head/Face
	Brows
	Lids
	Lashes
	Lacrimal System
	Levator Function
	Margin Reflex Distance



Glasses / Near Vision / Motility: <div style="text-align: center; margin-bottom: 10px;"> Glasses Distance No Glasses </div> <div style="text-align: center; margin-bottom: 10px;"> Glasses IOP / @ _____ </div> <div style="text-align: center; margin-bottom: 10px;"> Glasses/ Bifocal / No Glasses </div> <div style="text-align: center; margin-bottom: 10px;"> Pupils / OU Vision - Glasses / No Glasses </div> <div style="text-align: center; margin-bottom: 10px;"> HOTV Snellen Animal Single Crowd Line </div>	Distance Vision / Glasses / No Glasses	OU Vision - Glasses / No Glasses
Nystagmus: (Mark X if positive) <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="width: 45%;"> <input type="checkbox"/> Jerk R in R / L <input type="checkbox"/> Jerk L in R / L <input type="checkbox"/> Pendular <input type="checkbox"/> Rotatory <input type="checkbox"/> Latent/ Manifest Latent <input type="checkbox"/> Seesaw </div> <div style="width: 45%;"> <input type="checkbox"/> Jerk Up in Up / Down <input type="checkbox"/> Jerk Down in Up / Down <input type="checkbox"/> Decreases with Convergence <input type="checkbox"/> Head Oscillation <input type="checkbox"/> Iris Transillumination <input type="checkbox"/> Null Position _____ </div> </div>		
Fixation Preference OD / OS		
Fixation Preference OD / OS		
Versions/Ductions: <input type="checkbox"/> Full (Mark X if normal) <div style="text-align: center; margin-top: 10px;"> Glasses Bifocal No Glasses </div> <div style="text-align: center; margin-top: 10px;"> Diagram: <div style="border: 1px solid black; width: 100px; height: 100px; margin: auto;"></div> </div>		

**Outpatient Pediatric Ophthalmology
Medical Record**

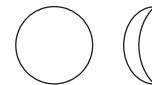
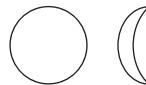
Refraction / Retinoscopy / Keratometry			Diagnostic Medications Given:	
Keratometry /			Time: _____ (Mark X if used)	
			<input type="checkbox"/> Mydriacyl 1% OD / OS	
			<input type="checkbox"/> Cyclogyl 1% OD / OS	
			<input type="checkbox"/> Phenylephrine 2.5% OD / OS	
			<input type="checkbox"/> Fluress 0.25% OD / OS	
			<input type="checkbox"/> Tetracaine 0.5% OD / OS	
			<input type="checkbox"/> Cyclogyl 2% OD / OS	
			<input type="checkbox"/> Pilocarpine 1% OD / OS	
			<input type="checkbox"/> Goniosoft 2.5% OD / OS	
			<input type="checkbox"/> Pilocarpine 2% OD / OS	
			<input type="checkbox"/> Atropine 1% OD / OS	
			Administered By: <hr style="border: 0.5px solid black; margin-bottom: 5px;"/> (Signature)	
AutoRef /	Vision /	OU -		
MRef /	Vision /	OU -		
CRef /	Vision /	OU -		
CRet /	Vision /	OU -		

Slit Lamp Exam: (Mark X if normal for each eye listed)

OD

OS

- | | |
|--|--------------------------|
| <input type="checkbox"/> Lids & Lashes | <input type="checkbox"/> |
| <input type="checkbox"/> Conjunctiva | <input type="checkbox"/> |
| <input type="checkbox"/> Cornea | <input type="checkbox"/> |
| <input type="checkbox"/> ANT Chamber | <input type="checkbox"/> |
| <input type="checkbox"/> Iris | <input type="checkbox"/> |
| <input type="checkbox"/> Lens | <input type="checkbox"/> |

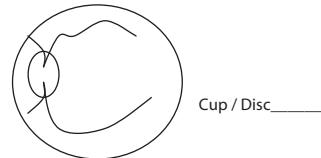
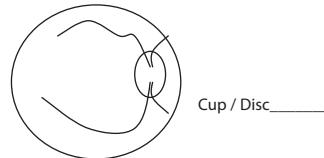


Fundus Exam: (Mark X if normal for each eye listed)

OD

OS

- | | |
|---|--------------------------|
| <input type="checkbox"/> Vitreous | <input type="checkbox"/> |
| <input type="checkbox"/> Optic Nerve | <input type="checkbox"/> |
| <input type="checkbox"/> Vessels | <input type="checkbox"/> |
| <input type="checkbox"/> Macula/Fovea | <input type="checkbox"/> |
| <input type="checkbox"/> Periph. Retina | <input type="checkbox"/> |



Outpatient Pediatric Ophthalmology
Medical Record

Impression/Diagnosis:	Plan/Treatment:
Follow Up: _____ Eyeglasses Given: <input type="checkbox"/> AutoRef <input type="checkbox"/> CRef <input type="checkbox"/> CRet <input type="checkbox"/> MRef Sphere Cylinder Axis Add/Prism OD: _____ + _____ X _____ OS: _____ + _____ X _____	

Orders:

<input type="checkbox"/> Fundus Photos Optic Nerve Macula EUA	<input type="checkbox"/> Optical Coherence Tomography RNFL Macula Optic Nerve
<input type="checkbox"/> Humphrey Visual Fields 24 -2 30 -2 Peripheral Screen	<input type="checkbox"/> Electroretinography Standard EUA
<input type="checkbox"/> Visual Evoked Potentials Swee p Flash Pattern	<input type="checkbox"/> CT-Scan <input type="checkbox"/> MRI contrast without contrast 1mm 5 mm
<input type="checkbox"/> Color D-15	<input type="checkbox"/> Preferential Looking Tests
<input type="checkbox"/> Sensorimotor Examination	<input type="checkbox"/> Eye Movement Recording
<input type="checkbox"/> A-Scan	<input type="checkbox"/> B-Scan

Letter: (Mark X for all that apply)

 Dictated to Referring Physician cc: _____

Signatures:

Technician _____

Resident _____

Physician _____

B.2 STRABISMUS EXAMINATION FORM

Pediatric Ophthalmology
Outpatient Medical Record

SENSORIMOTOR EXAM

INDICATIONS:

- | | | | | |
|---------------------------------------|------------------------------------|--|--|-----------------------------------|
| <input type="checkbox"/> STRABISMUS | <input type="checkbox"/> HEADACHES | <input type="checkbox"/> PUPIL ABNORMALITY | <input type="checkbox"/> ABNORMAL HEAD POSTURE | <input type="checkbox"/> DIPLOPIA |
| <input type="checkbox"/> NYSTAGMUS | <input type="checkbox"/> PTOSIS | | <input type="checkbox"/> TORTICOLLIS | |
| <input type="checkbox"/> OTHER: _____ | | | | |

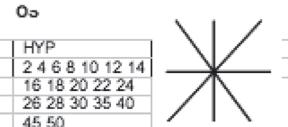
PROCEDURE:

- Prism and Alternate Cover
 Krimsky.

Hirschberg
 Other: _____

		OD		
		ESO-EXO		
		5 10 15 20 25		
		30 35 40 45 50		
		ESO-EXO	ESO-EXO	ESO-EXO
		5 10 15 20 25	5 10 15 20 25	5 10 15 20 25
		30 35 40 45 50	30 35 40 45 50	30 35 40 45 50
		ESO-EXO		
		5 10 15 20 25		
		30 35 40 45 50		

CC SC D N



HYP	HYP	HYP
2 4 6 8 10 12 14	2 4 6 8 10 12 14	2 4 6 8 10 12 14
16 18 20 22 24	16 18 20 22 24	16 18 20 22 24
26 28 30 35 40	26 28 30 35 40	26 28 30 35 40
45 50	45 50	45 50

Saccades _____ Pursuit _____ VOR _____

F D _____ F G _____

DISTANCE NEAR

Convergence Amplitude
Divergence Amplitude
Accommod Amplitude
Anomalous Head Posture
Ocular Oscillations

NO CHANGE LEFT, RIGHT, UP AND DOWN GAZE

HYP	HYP
2 4 6 8 10 12	2 4 6 8 10 12
16 18 20 22 24	16 18 20 22 24
26 28 30 35 40	26 28 30 35 40
45 50	45 50

HEAD TILT RIGHT HEAD TILT LEFT

STEREO _____ NATP

RELIABILITY GOOD POOR

INTERPRETATION:

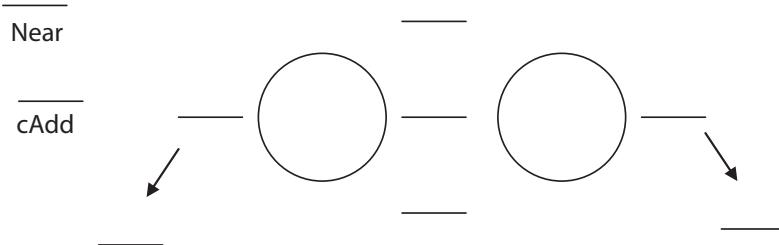
- | | |
|---|---|
| <input type="checkbox"/> NO RESTRICTIVE OR PARALYTIC STRABISMUS | <input type="checkbox"/> MEASUREMENT CONSISTENT WITH 4 TH CN PALSY |
| <input type="checkbox"/> NO A OR V PATTERN PRESENT | <input type="checkbox"/> MEAUREMENT CONSISTENT WITH 6 TH CN PALSY |
| <input type="checkbox"/> V PATTERN PRESENT | <input type="checkbox"/> MEASUREMENT CONSISTENT WITH DUANE'S SYNDROME |
| <input type="checkbox"/> A PATTERN PRESENT | <input type="checkbox"/> MEASUREMENT CONSISTENT WITH BROWN'S SYNDROME |
| <input type="checkbox"/> MEASUREMENT CONSISTENT WITH 3 RD CN PALSY | <input type="checkbox"/> DOUBLE ELEVATOR PALSY |
| <input type="checkbox"/> CN/LN/MLN | <input type="checkbox"/> OTHER: _____ |
| <input type="checkbox"/> AN | |

PHYSICIAN SIGNATURE: _____

B.3 NYSTAGMUS EXAMINATION FORM

.3 NYSTAGMUS EXAMINATION FORM

OCULAR MOTILITY CHART



W-4-Dot Dist _____ Near _____ Stereo _____

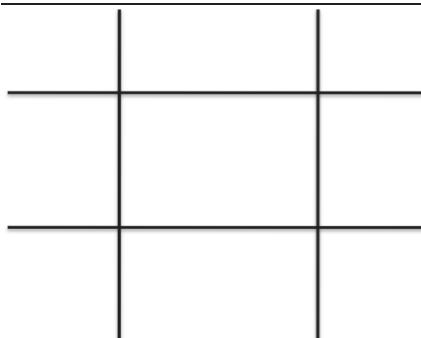
Saccades _____ Pursuit _____ VOR _____

Forced Ductions _____

Forced Generations _____

	DIST ANCE	NEAR
Convergence Amplitude	_____	_____
Divergence Amplitude	_____	_____
Torsion	_____	_____
Accommod Amplitude	_____	_____
Anomalous Head Posture	_____	_____

Ocular Oscillations Characteristics:	YES	NO
---	-----	----



B.4 CLINICAL PEARLS

Following are the clinical pearls presented throughout this volume along with the chapter and section in which they appeared.

Chapter 2

2.1.2.6

Clinical Pearl: Based on the research of the past 50 years, the INS in all patients is directly caused by

instability in smooth pursuit damping plus a variable amount of tonic imbalance in the visual-vestibular system. Thus, INS is a motor oscillation with known motor causes, making the adjective “motor” (e.g., motor nystagmus or congenital motor nystagmus) redundant. Similarly, the terms “sensory” and “idiopathic” are both incorrect and misleading. None of these terms should be used in describing INS.

2.1.3.1

Clinical Pearl: Patients with INS and two static (or multiple) head postures should be examined for a latent component, FMNS or APAN.

2.1.4.1

Clinical Pearl: Occlude the nonpreferred eye and examine the preferred eye with the head straight and gaze in primary position over at least 5–7 minutes. A regular or irregular changing oscillation intensity and/or direction indicates APAN.

2.1.4.1

Clinical Pearl: Patients with INS whose measured visual acuity changes from one office visit to the next may have short periods when the nystagmus stops and acuity peaks; this is an exaggerated form of APAN.

2.1.5

Clinical Pearl: Patients who (taking advantage of their null) move their heads word to word across the line while reading (even those with high acuity) may have INS with a narrow range of gaze angles where their acuity is highest.

2.1.6

Clinical Pearl: Patients with INS whose near visual acuity is greater than distant may have INS that damps with convergence.

2.1.8

Clinical Pearl: Point out the head tremor to the patient. If it stops, the nystagmus is that of INS; if it persists, both are more likely acquired.

2.4

Clinical Pearl: INS therapy is not contraindicated in patients with associated visual sensory deficits; in fact, these patients have the greatest chances for significant (i.e., life-changing) improvements in their visual function.

2.4.2.2

Clinical Pearl: Contact lenses are not contraindicated in INS and can provide better acuity than spectacles in patients whose nystagmus damps with afferent stimulation. Plano soft contact lenses can be used if no refractive correction is required. Four advantages of contacts in the INS patient are better optical quality, improvement in nystagmus saccade, move with eye to utilize eccentric gaze null, and ability to decrease light sensitivity/interference via tinting or painting.

Chapter 3

3.2.3

Clinical Pearl: To distinguish between benign (non-neurologically threatening), infantile, primary-position, jerk nystagmus, and that which is neurologically threatening, first verify that there is no periodic alternation in direction and then perform bilateral, sequential, cover-uncover testing. If the cover test causes a reversal in the nystagmus direction consistent with FMNS, the nystagmus is benign (FMNS or INS with a latent component). If not, attempt to rule out INS (by history, clinical signs [see Table 2.1], and waveforms).

3.2.3

Clinical Pearl: If the results of an alternate-cover test indicate a benign, infantile, primary-position, jerk nystagmus (i.e., it causes a reversal in the nystagmus direction consistent with FMNS or INS with a latent component), perform the test again but in far adduction of the fixating eye (e.g., far left gaze when the left eye is occluded). If the nystagmus again reverses (i.e., becomes jerk left in left gaze with left eye occluded), it is INS with a latent component. Repeat the test in adduction of the other eye fixating. If the nystagmus remains in the direction of the fixating eye, it may be either FMNS or INS with a large latent component.

Chapter 4

4.2.1.3

"Cultured" Clinical Pearl: Based on the observation that head nodding is compensatory in the SNS, if further research on the eye movements of the "SN-like" nystagmus associated with brain-stem gliomas demonstrates that no head nodding is exhibited by these patients, the presence of deliberate, compensatory head nodding is an indication of SNS and is benign.

Myth: Nystagmus causes the eyes to oscillate across the intended line of regard (i.e., fixation direction).

Facts: Nystagmus slow phases take the eyes away from the intended line of regard (target being fixated) and the eyes are returned by either a foveating saccade (for pendular waveforms) or a foveating fast phase (for jerk waveforms).

Myth: Extraocular muscle surgery to correct anomalous head positions does not improve the nystagmus or visual acuity.

Facts: Nystagmus surgery of the extraocular muscles to center eccentric INS "nulls" not only corrects anomalous head positions but also broadens the range of gaze angles with highest acuities, may increase the peak acuity, and shortens the target acquisition time; all of which improve visual function.

Myth: If there is no anomalous head position or no nystagmus damping with convergence, nothing can be done to improve the nystagmus.

Facts: Improvement of INS waveforms, and therefore, visual function, is possible by the tenotomy and reattachment procedure, which broadens the range of gaze angles with highest acuities, may increase the peak acuity, and shortens the target acquisition time; all of which improve visual function.

Myth: Patients with afferent visual sensory deficits and nystagmus cannot be helped by nystagmus surgery.

Facts: All INS patients can profit from the therapeutic improvements in visual function resulting from the proper extraocular muscle surgery, and those with the poorest acuities may profit the most (i.e., receive the largest percent increases in the direct outcome measures affecting visual function).

Myth: After surgery to correct anomalous head position by centering an eccentric nystagmus null, the null often returns at some intermediate lateral gaze angle.

Facts: Eye-movement data verify that adequate surgery, determined by that data, permanently repositions an eccentric INS null to primary position. However, insufficient surgery, determined by measurement of the anomalous head position, can result in the patient using the partially centered null by adopting a head turn that is less than preoperatively.

Chapter 5

5.1.1.2

Clinical Pearl: When the preferred fixating eye is kept in abduction, the nystagmus is most probably IN, not FMN. Caveat: It might still be FMN if the patient has exotropia or an angle kappa.

Chapter 7

7.2.1

Clinical Pearl: When performing simultaneous nystagmus and strabismus surgery, the procedure is determined by a combination of moving the eccentric null (straightening the head) using the preferred eye and correcting the remaining strabismus using the nonpreferred eye.

7.2.2

Clinical Pearl: Determination of the amounts of recession and resection needed to rotate the eyes using bilateral recession and resection of the horizontal recti (A-K procedure) may be best accomplished by dividing the total amount of surgery (indicated by the curve given in Dell'Osso and Flynn, 1979) in two and applying those equal amounts to the two antagonist muscles.

B.5 OPHTHALMOLOGICAL MYTHS AND FACTS

Listed next are ophthalmological myths that were prevalent in the literature and, in some cases, still taught, repeated, or even published. The factual data contradicting each are also listed.

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C.1 INFANTILE NYSTAGMUS SYNDROME

This section contains examples of optical and surgical nystagmus therapies for patients with infantile nystagmus syndrome (INS) whose characteristics determine which is the most effective therapy.

C.1.1 Gaze-Angle Null Only

The therapeutic options for an INS patient with a gaze-angle null (i.e., an eccentric eXpanded nystagmus acuity function [NAFX] peak) depend on three things: the eccentricity, the depth, and the breadth of the null, as discussed in Chapter 2. If nystagmus surgery is indicated, the amount necessary is determined by the eccentricity.

C.1.1.1 VERSION PRISMS

If the null is close to primary position (e.g., $< 5^\circ = 8.75 \text{ PD}$) and is broad (e.g., $> 25^\circ$), version prisms may be used to center it, however. At larger eccentricities, the required prism would be too great, causing both chromatic aberration and diminished acuity. At narrower breadths, a therapy that broadens the null (version prisms do not) is more suitable.

C.1.1.2 SOFT CONTACT LENSES

If the null is in primary position and is narrow, soft contact lenses may be used to improve the range of gaze angles with best-corrected visual acuity (i.e., broaden the null); they may also improve the peak acuity.

C.1.1.3 FOUR-MUSCLE RESECTION, RECESSION, AND TENOTOMY AND REATTACHMENT

If the null is at any eccentricity $>10^\circ$ and is of any breadth, the four-muscle resection and recession procedure or the two-muscle recession plus tenotomy and reattachment (T&R) of the other two muscles may be used. These nystagmus surgeries both center and broaden the null.

In the example shown in Figure C.1, the null is $>20^\circ$ to the right and the four-muscle resection and recess procedure is used.

In the example shown in Figure C.2, the null is $<20^\circ$ to the right and the two-muscle recession plus two-muscle T&R procedure is used to center and broaden the null.

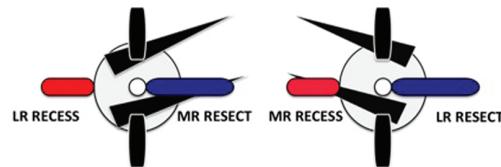
C.1.1.3.1 Fine Tuning with Prisms. It used to be thought that if the surgery to center the null was insufficient, postoperative fine-tuning with the use of version prisms could achieve the desired result. However, the use of eye-movement data (to determine the surgical rotation needed) plus documentation of the null-broadening effects of the surgery itself have precluded the need for postoperative prisms in most cases.

C.1.1.3.2 Soft Contact Lenses. Just as soft contact lenses improve INS before surgery, they can be used postoperatively in lieu of eyeglasses. The extent of further improvement has not been studied and may be idiosyncratic.

C.1.2 Convergence Null Only

The therapeutic options for an INS patient with a convergence null (i.e., an NAFX peak at

OPERATION 1—HORIZONTAL HEAD POSTURE ALONE



LEFT FACE (RIGHT GAZE NULL > 20 DEG)

OD LATERAL RECESS 9-10
OD MEDIAL RESECT 7-8
OS LATERAL RESECT 10-11
OS MEDIAL RECESS 6-7

22%



FIGURE C.1 Operation 1—Bilateral horizontal rectus recession and resection to improve a horizontal head posture and the nystagmus associated with a moderate to large horizontal eccentric-gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. LR, lateral rectus; MR, medial rectus.

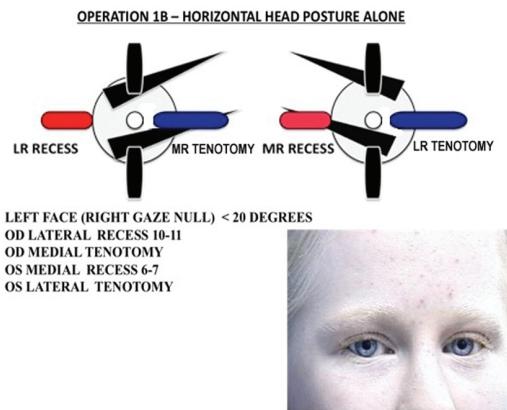


FIGURE C.2 Operation 1B—Bilateral horizontal rectus recession and tenotomy + reattachment to improve a horizontal head posture and the nystagmus associated with a small horizontal eccentric-gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. LR, lateral rectus; MR, medial rectus.

near) depend on only one thing: the absence of strabismus. Whether through the use of base-out prisms or bilateral medial rectus recessions, convergence-induced foveation improvement and null broadening is the most therapeutically beneficial method currently available. When both gaze-angle and convergence nulls are present, the latter is almost always greater.

C.1.2.1 Vergence Prisms with Negative Spheres

Although the NAFX continues to increase as the eyes converge by as much as 60 PD, the use of base-out prisms to improve the foveation quality at distance is accomplished by 7 PD base-out OU (i.e., a total of 14 PD of convergence) with the addition of -1.0 S OU to negate the vergence-induced accommodation in children and young adults. This allows for further convergence at middle-distance and near targets without loss of fusion and the resulting diplopia. At the onset of presbyopia, these added negative spheres must be removed from the prescription.

C.1.2.2 Soft Contact Lenses

Soft contact lenses can also be used to broaden the null when the base-out prisms are not in use, such as for some sports where eyeglasses would interfere, or socially if preferred by the patient.

C.1.2.3 Bimedial Recession

The bimedial recession operation is the most therapeutically powerful nystagmus surgery for INS. Originally, the addition of bilateral lateral rectus T&R to the bimedial recessions was advocated to achieve the maximal benefits of four-muscle T&R. However, research has shown that convergence alone (e.g., fixation on a near target or through the use of base-out prisms) achieves the maximal improvements in NAFX values and negates the need for the addition of the T&R of the lateral rectus muscles. This is the *only* nystagmus surgery where operating on two muscles will provide foveation improvements that are equivalent to operating on all four. Because the bimedial recession *nystagmus* surgery for binocular INS patients induces convergence, it has different therapeutic benefits than the same *strabismus* surgery for esotropic patients, where it does not induce convergence.

The patient in Figure C.3 has INS that damps with convergence and has no strabismus. The artificial divergence produced by the bimedial recessions induces the convergence necessary to improve the INS foveation quality at distance.

C.1.3 Both Gaze-Angle and Convergence Nulls

Some INS patients exhibit both gaze-angle and convergence nulls. This allows for several approaches, although one is the most effective.

C.1.3.1 Convergence > Gaze-Angle

C.1.3.1.1 Composite Prisms and Negative Spheres. It used to be thought that in cases with both types of nulls, a combination of version and vergence prisms (i.e., composite prisms) would provide the greatest improvement in foveation quality. However, research has shown that

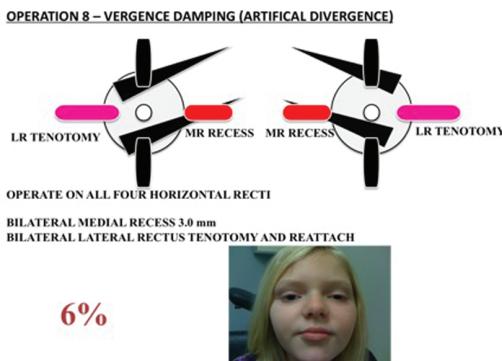


FIGURE C.3 Operation 8—Bilateral medial rectus recession with bilateral horizontal rectus tenotomy and reattachment (T&R) to induce vergence and improve the nystagmus. Subsequent research indicates that the addition of the bilateral T&R is unnecessary. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. LR, lateral rectus; MR, medial rectus.

because of the large broadening of the gaze-angle range of highest NAFX caused by the convergence, gaze angle becomes inconsequential and the need for composite prisms is negated. The negative spheres are still required for pre-presbyopic patients (e.g., children and young adults).

C.1.3.1.2 Base-Out Prisms and Negative Spheres. Because of the aforementioned findings, the same base-out prisms with negative spheres are used in these cases as in those with only convergence damping.

C.1.3.1.3 Soft Contact Lenses. As in the aforementioned cases, soft contact lenses can also be used to broaden the null when the base-out prisms are not in use.

C.1.3.1.4 Bimedial Recession. The bimedial recession nystagmus procedure described earlier is the recommended therapy for these cases.

C.1.3.2 Gaze-Angle > Convergence

There are very rare cases where eye-movement data show that the gaze-angle improvements in foveation may exceed those of convergence. For

these cases, the same therapies recommended for gaze-angle-only cases apply.

C.1.3.2.1 Version Prisms. If the null is close to primary position (e.g., $< 5^\circ = 8.75 \text{ PD}$) and is broad (e.g., $> 25^\circ$), version prisms may be used to center it. At larger eccentricities, the required prism would be too great, causing both chromatic aberration and diminished acuity. At narrower breadths, a therapy that broadens the null is more suitable.

C.1.3.2.2 Soft Contact Lenses. If the null is in primary position and is narrow, soft contact lenses may be used to improve the range of gaze angles with best-corrected visual acuity and may improve peak acuity.

C.1.3.2.3 Four-Muscle Resection, Recession, and Tenotomy and Reattachment. If the null is at any eccentricity $> 10^\circ$ and is of any breadth, the four-muscle resection and recession procedure or the two-muscle recession plus T&R of the other two muscles may be used to center and broaden the null. In these rare cases, the bimedial recession nystagmus surgery may be combined with this surgery in an attempt to maximize the foveation improvements.

C.1.4 No Nulls

There are some patients with INS who have no null or whose null is in primary position. Prior to the discovery of the beneficial effects of the four-muscle T&R nystagmus surgery, these patients had no therapy available to improve their foveation quality.

C.1.4.1 Soft Contact Lenses

As in the aforementioned cases, soft contact lenses can also be used to further damp the INS.

C.1.4.2 Four-Muscle Tenotomy and Reattachment

The patient in Figure C.4 had no INS nulls. The therapy of choice was the four-muscle T&R procedure.

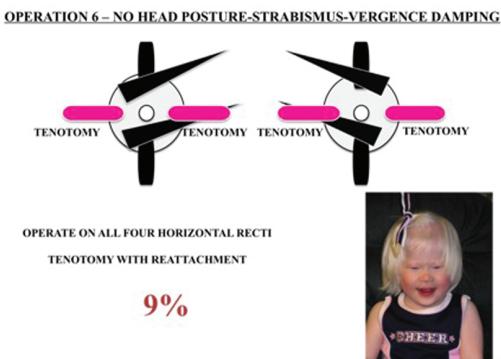


FIGURE C.4 Operation 6—Bilateral horizontal rectus tenotomy and reattachment alone to improve the nystagmus. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences.

C.1.4.2.1 Tenotomy and Reattachment with Augmented Tendon Suture. It has been hypothesized that adding a suture or two to each tendon undergoing a T&R might result in greater improvement. These additional sutures are placed in the tendons alone, not to the globe. If the data confirm this hypothesis, the augmented suture technique would be recommended.

C.1.4.2.2 Augmented Tendon Suture Procedures sans Tenotomy and Reattachment. A related hypothesis has also been advanced. Simply placing a suture or two to each tendon (again, not to the globe) without performing a T&R might also result in improvement, greater than or equal to the T&R. Again, if the data confirm this, the augmented suture technique sans T&R would be recommended; it is both simpler and safer than suturing to the globe.

C.1.4.3 Faden

The Faden procedure has not been studied using the eye-movement, data-based analysis techniques described in Chapter 2; therefore, its potential benefits as a nystagmus surgery used instead of, or in concert with, the surgeries presented in this appendix cannot be assessed at this time.

C.2 INFANTILE NYSTAGMUS PLUS STRABISMUS

C.2.1 Gaze-Angle Null Only

Many INS patients also have strabismus. Their treatment mimics those described earlier with the additional recessions or resections needed to correct the strabismus.

C.2.1.1 Four-Muscle Resection, Recession, and Tenotomy and Reattachment

Many patients have strabismus and nystagmus with an eccentric gaze null (i.e., either INS or FMNS). The operation shown in Figure C.5 corrects the strabismus and improves the nystagmus.

The INS patient in Figure C.6 had a leftward null position and an esotropia. The nystagmus plus strabismus surgical procedure employed combined the necessary recessions and resections to improve both the INS foveation quality and the ocular alignment.

C.2.2 Vertical and Torsional Nulls

Many INS patients have nulls in the vertical or torsional plane, despite the horizontal

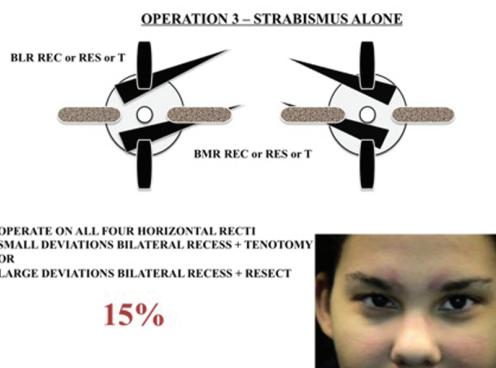


FIGURE C.5 Operation 3—Bilateral horizontal rectus (BLR) and bimedial horizontal rectus (BMR) recession (RES), resection (REC), or tenotomy (T) to improve the strabismus, anomalous head posture, and the nystagmus associated with an eccentric-gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences.

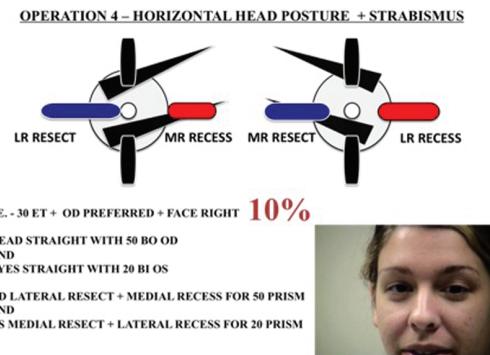


FIGURE C.6 Operation 4—Bilateral horizontal rectus recession and resection to improve the strabismus and the nystagmus associated with a primary position null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. ET, esotropia; LE, left eye; LR, lateral rectus; MR, medial rectus.

predominance of the nystagmus. The same principles embodied in nystagmus surgery of the horizontal rectus muscles must be applied to the vertical rectus and oblique muscles.

Patients like the one in the Figure C.7 have a vertical null (in upgaze) with or without

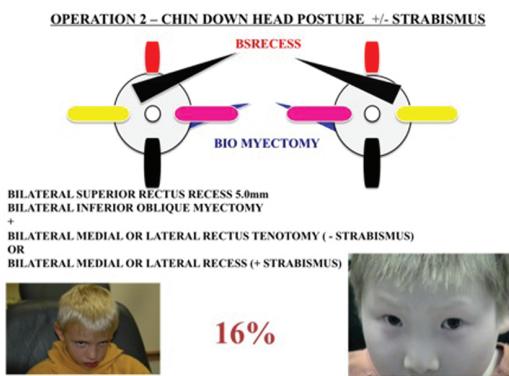


FIGURE C.7 Operation 2—Bilateral superior rectus recession and inferior oblique myectomy with bilateral single horizontal recti tenotomy with reattachment or recession to improve a chin-down head posture and the nystagmus +/- strabismus associated with a vertically upward eccentric-gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. BIO, bilateral inferior oblique; BS, bilateral superior rectus.

strabismus. A bilateral superior rectus recession and bilateral inferior oblique myectomy is used to center the vertical null plus either a bilateral medial or lateral rectus T&R (if no strabismus) or a bilateral medial or lateral rectus recession (if strabismus).

Patients like the one in Figure C.8 have a vertical null (in downgaze) with or without strabismus. The surgical procedure combines the necessary recessions and resections to improve both the INS foveation quality and eye alignment, if strabismus is present.

Patients like the one in Figure C.9 have a multiplanar null position (here, torsionally counterclockwise and to the left); they may or may not have strabismus. The surgical procedure combines the necessary nystagmus surgery to improve the INS foveation quality and addition of strabismus surgery to improve eye alignment, if strabismus is present.

Patients like the one in Figure C.10 have a torsional null position; the patient has a counterclockwise INS null. The nystagmus surgical procedure corrects the torsional null.

OPERATION 5 – CHIN UP HEAD POSTURE +/- STRABISMUS



FIGURE C.8 Operation 5—Bilateral inferior rectus recession and superior oblique tenectomy with bilateral single horizontal recti tenotomy with reattachment or recession to improve a chin-up head posture and the nystagmus +/- strabismus associated with a vertically downward eccentric-gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. BI, bilateral inferior rectus; BSO, bilateral superior oblique.

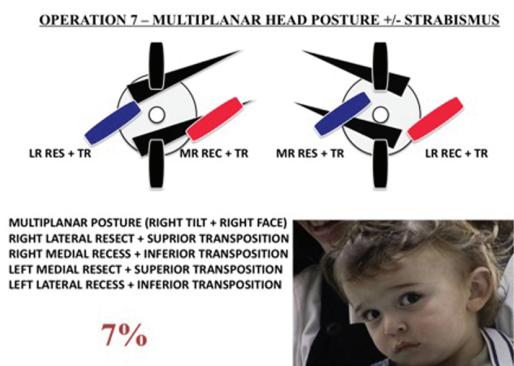


FIGURE C.9 Operation 7—Bilateral horizontal rectus muscle transposition with or without associated resection/recession to improve a multiplanar head posture, the nystagmus +/- strabismus associated with multiplanar eccentric-gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. LR, lateral rectus; MR, medial rectus; REC, resection; RES, recession; TR, transposition.

C.2.3 No Nulls

C.2.3.1 Four-Muscle Tenotomy and Reattachment and Strabismus

INS patients with no nulls plus strabismus require the four-muscle T&R nystagmus

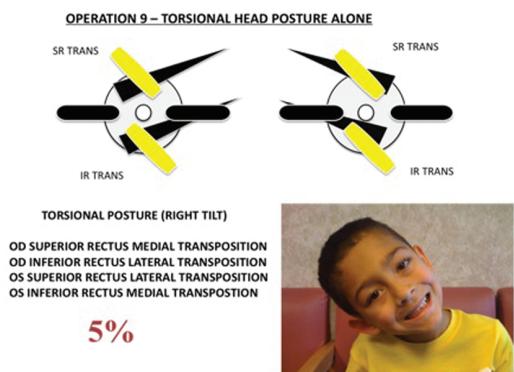


FIGURE C.10 Operation 9—Bilateral vertical rectus muscle transposition to improve a torsional/tilt head posture and the nystagmus associated with a torsional gaze null. The percentage indicates the incidence of this procedure. The operation number reflects the order of these incidences. IR, inferior rectus; SR, superior rectus; TRANS, transposition.

surgery with the addition of whatever recessions or resections are needed to correct the misalignment of the eyes.

C.3 FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

Patients with fusion maldevelopment nystagmus syndrome (FMNS) all have strabismus. Their surgical therapy will require strabismus surgery (to correct eye alignment) and may also require the T&R nystagmus surgery applied to horizontal rectus muscles not recessed or resected (to improve nystagmus foveation).

C.3.1 Unicocular Fixation

Some FMNS patients always fixate with their preferred eye, regardless of gaze angle. For them, eye-muscle surgery combines operating on the nonpreferred eye plus T&R of the remaining horizontal rectus muscles. This may produce fusion damping in addition to the nystagmus damping from the surgery itself.

C.3.2 Alternating Fixation

Some FMNS patients alternate their fixating eye, depending on gaze angle. In these cases, recessions of the two medial rectus muscles and T&R of the two lateral rectus muscles is recommended for small deviations. For exotropia, recessions of the two lateral rectus muscles and T&R of the two medial rectus muscles is recommended (again for small deviations). For large deviations, recessions and resections of all four horizontal rectus muscles sufficient to align the eyes is recommended.

C.3.3 Alexander's Law Threshold

The amount and type of eye-muscle surgery may be affected by the preoperative intensity of the Alexander's law threshold and slope (i.e., the gaze angles at which the FMN begins to increase and the rate of that increase).

C.4 NYSTAGMUS BLOCKAGE SYNDROME

Nystagmus surgery for patients with the nystagmus blockage syndrome (NBS) is determined by the characteristics of the baseline INS (i.e., null angle depth and breadth) with no purposive esotropia. The variable esotropia with either eye fixing is amenable to surgical correction, although the procedure is less well defined. The suggestions that follow apply to both types of the NBS (see Chapter 4). However, eye-movement data that could confirm the efficacy of these suggestions are lacking.

C.4.1 Bimedial Recession (Plus Tenotomy and Reattachment)

If there is good binocular function, bimedial recession will result in improved baseline foveation due to convergence.

If there is a static esotropia to which the purposive esotropia is added to improve foveation, a bimedial recession strabismus surgery to correct

the maximum esotropia plus a T&R of the two lateral rectus muscles is recommended to improve both convergence and baseline foveation.

C.4.2 Recession and Resection Plus Tenotomy and Reattachment

If the purposive esotropia added to improve foveation, and is always in one eye, a head turn toward that eye results. In these cases, recession and resection to move the adopted eccentric position to primary position plus a T&R of the horizontal rectus muscles of the other eye may improve both foveation quality and reduce/eliminate the head turn. The preferred eye drives the head.

C.4.3 Four-Muscle Tenotomy and Reattachment

If the eyes are aligned before the purposive esotropia is added to improve foveation and there is poor binocular fusion, a four-muscle T&R is recommended to improve baseline foveation.

APPENDIX D

DIAGNOSIS AND TREATMENT FLOWCHARTS

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D.1 WAVEFORM-BASED DIAGNOSES

Using eye-movement recordings, accurate, repeatable diagnoses can be made of infantile nystagmus syndrome (INS), fusion maldevelopment nystagmus syndrome (FMNS), the nystagmus blockage syndrome (NBS), the pendular nystagmus of the nucleus of the optic tract (NOT) associated with either INS or FMNS, and the spasmodic nutans syndrome (SNS). If none can be identified, the nystagmus will be either vestibular nystagmus (VN) or another type of acquired nystagmus (AN). The flowcharts in this Appendix reflect the differential diagnosis material in Chapter 5 and the therapeutic material in Chapter 7.

Using the flowchart in this chapter (Fig. D.1), eye-movement data provide the answers along each path to a nystagmus diagnosis.

D.2 THERAPEUTICALLY EXPLOITABLE WAVEFORM CHARACTERISTICS

Using eye-movement recordings, the therapeutically exploitable characteristics of INS, FMNS, NBS, the pendular nystagmus of the nucleus of the NOT associated with either INS or FMNS, and SNS may be determined.

Using the flowchart below (Fig. D.2), eye-movement data provide the answers along each path to a therapeutically appropriate therapy.

D.3 CLINICALLY BASED DIAGNOSES AND LIMITATIONS

Although it is possible to accurately diagnose and treat some cases of INS or FMNS based on clinical signs and examination alone, other cases the correct diagnosis will be problematic. Using the flowchart in Figure D.3, some diagnoses may be presumed while others remain doubtful.

Nystagmus diagnosis from clinical examination alone is highly problematic and may result in the choice of an ineffective therapy.

D.4 THERAPEUTICALLY EXPLOITABLE CLINICAL CHARACTERISTICS

Some of the INS characteristics may be determined clinically to provide an indication of the therapy best suited for a patient (see Fig. D.4).

Unlike the case when using waveform analysis, the improvements resulting from

Waveform Diagnoses

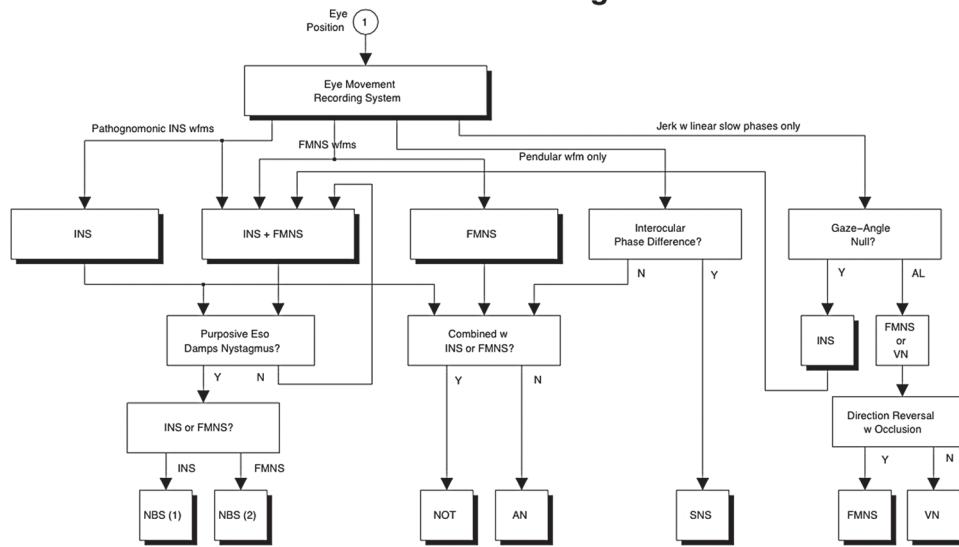


FIGURE D.1 Flowchart demonstrating how eye-movement data are used to arrive at a *repeatable, definitive* nystagmus diagnosis. AN, acquired nystagmus; FMNS, fusion maldevelopment nystagmus syndrome; INS, infantile nystagmus syndrome; NBS, nystagmus blockage syndrome; NOT, nucleus of the optic tract; SNS, the spasmus nutans syndrome; VN, vestibular nystagmus.

Therapeutically Exploitable INS Characteristics

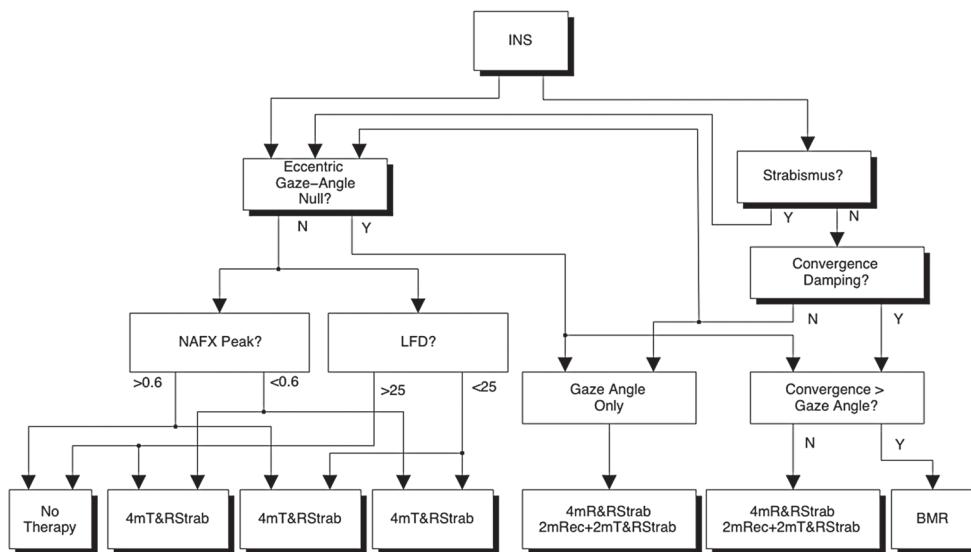


FIGURE D.2 Flowchart demonstrating how eye-movement data are used to determine therapeutically exploitable characteristics of infantile nystagmus syndrome (INS). The relevant therapies may be surgical or nonsurgical. Note that when the expanded nystagmus acuity function (NAFFX) peak is high and the longest foveation domain (LFD) is broad, their values cannot be significantly increased and, therefore, no waveform foveation improvements are possible; only under these simultaneous conditions is nystagmus therapy precluded. BMR, bimedial recession; m, muscle; Rec, recession; R&R, recess and resect; Strab, strabismus; T&R, tenotomy and reattachment.

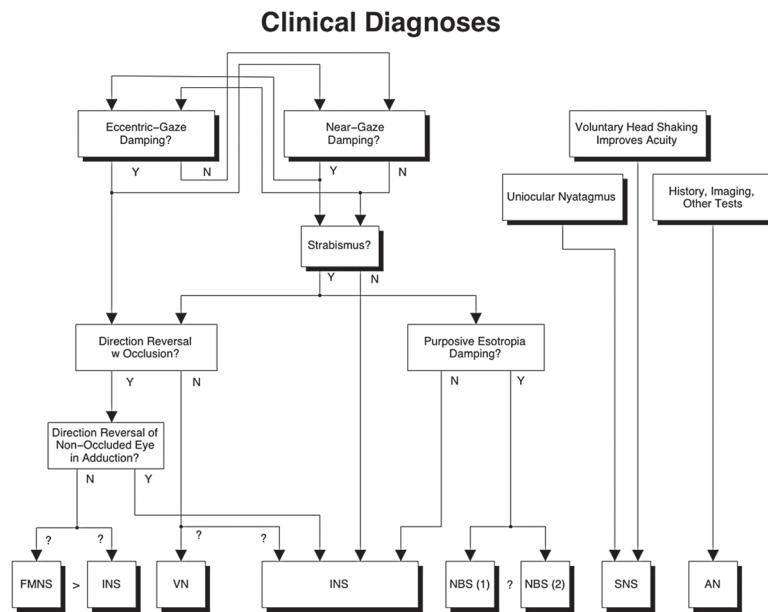


FIGURE D.3 Flowchart demonstrating how clinical observations and tests may be used to arrive at a nystagmus diagnosis. Note that, unlike when using waveform analysis, all paths do not lead to a definitive diagnosis and there is no reliable path to acquired nystagmus. AN, acquired nystagmus; FMNS, fusion maldevelopment nystagmus syndrome; INS, infantile nystagmus syndrome; NBS, nystagmus blockage syndrome; SNS, the spasmodus nutans syndrome; VN, vestibular nystagmus.

Therapeutically Exploitable Clinical Characteristics

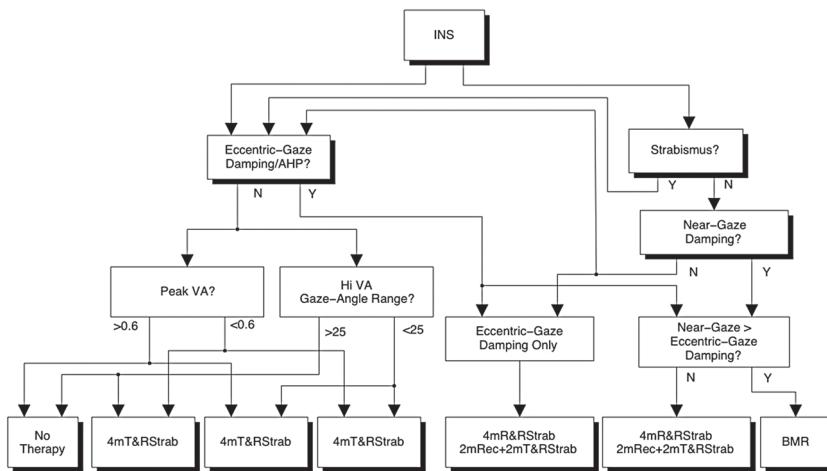


FIGURE D.4 Flowchart demonstrating how clinical observations and tests may be used to determine therapeutically exploitable characteristics of infantile nystagmus syndrome (INS). The relevant therapies may be surgical or nonsurgical. Note that when the peak is high and the range of high-visual acuity (Hi VA) gaze angles is broad, their values cannot be significantly increased and, therefore, no waveform foveation improvements are possible; only under these simultaneous conditions is nystagmus therapy precluded. BMR, bimedial recession; m, muscle; Rec, recession; R&R, recess and resect; Strab, strabismus; T&R, tenotomy and reattachment.

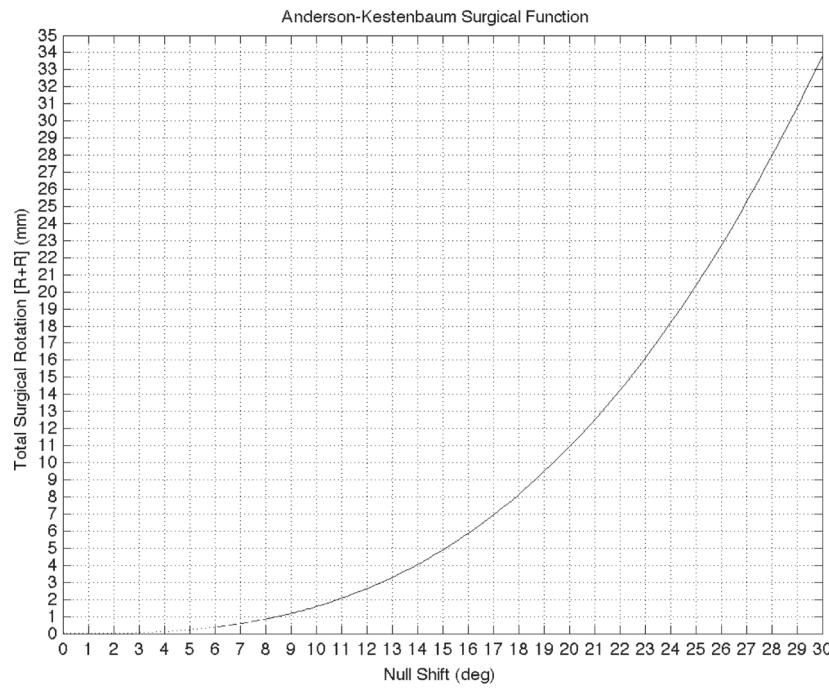


FIGURE D.5 Plot of total millimeters of extraocular muscle surgery (recession plus resection) required to achieve the required amount of null (eXpanded nystagmus acuity function [NAFX] peak) shifting in infantile nystagmus syndrome.

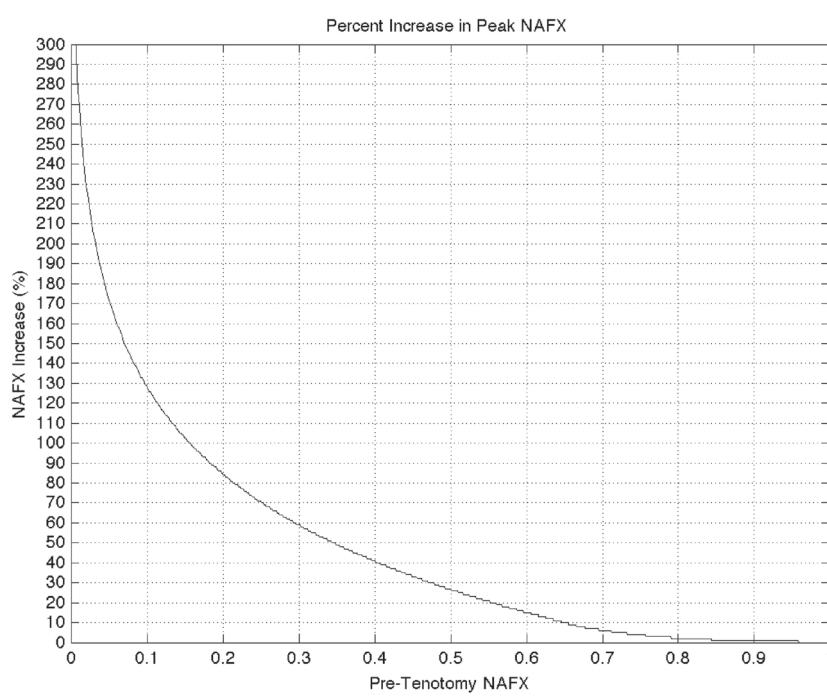


FIGURE D.6 Plot of the estimated posttherapeutic improvement in the eXpanded nystagmus acuity function (NAFX) peak based on the pretherapeutic NAFX peak value.

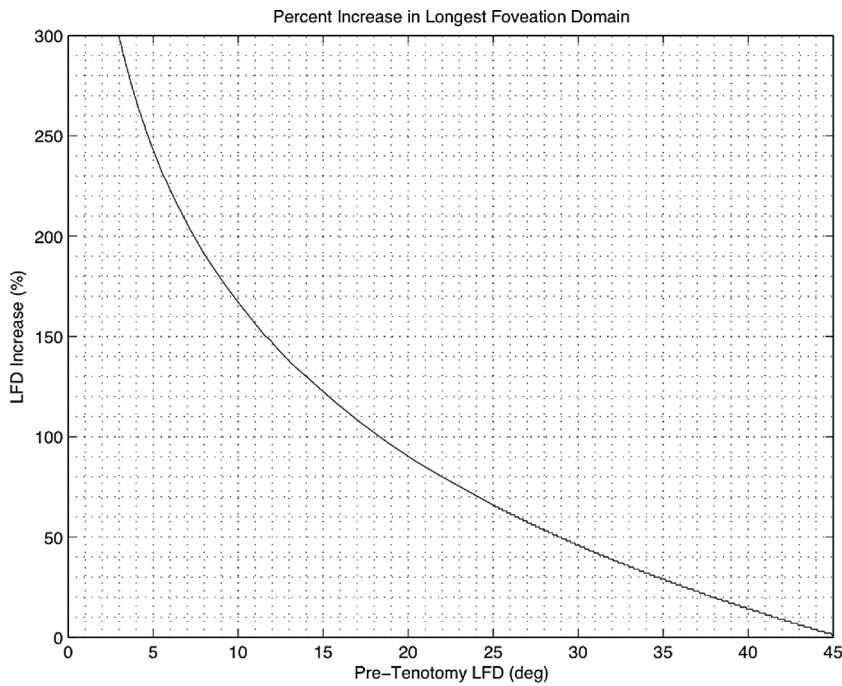


FIGURE D.7 Plot of the estimated posttherapeutic improvement in the longest foveation domain (LFD) based on the pretherapeutic LFD value.

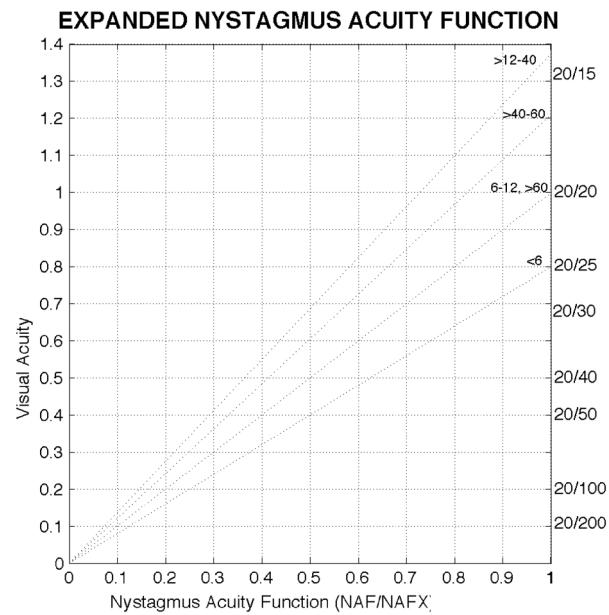


FIGURE D.8 Plot of the eXpanded nystagmus acuity function (NAFX) versus best-corrected visual acuity for patients of different ages.

the indicated therapies cannot be estimated prior to therapy because acuity measures may not be correlated with INS foveation quality alone. Therapies chosen based solely on clinical observations and tests may not provide improvements in visual function.

D.5 ANALYSIS GRAPHS

The graphs in Figures D.5 through D.8 are useful in the determination of surgical recessions

and resections, pretherapeutic estimation of therapeutic improvements, posttherapeutic measurement of therapeutic improvements, and differentiation of the motor and sensory components of visual acuity. Individual work sheets may be copied and printed from the Companion Website (Appendix F, Section F.3) or downloaded from www.omlab.org.

APPENDIX E

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THE VIDEO files in this appendix may be viewed or copied. Many were originally presented as parts of papers or posters at various scientific meetings.

E.1 “EYEBALLS 3D” EYE-MOTION AND WAVEFORM VIDEOS

This appendix contains videos made from patient data, the OMS behavioral model, and patients, canines, and other animals with nystagmus. In many of the “Eyeballs 3D” videos a yellow fixation target is superimposed on the eyeballs and the target position (usually at 0°) is shown, surrounded by the foveal area ($\pm 0.5^\circ$, shown as a dot-dashed line). In phase planes, the saccade window ($\pm 0.5^\circ$ by $\pm 4^\circ/\text{sec}$) is shown as a rectangular box. These additions help us appreciate the saccade periods in INS waveforms. Eyeballs 3D videos may be viewed individually or using E1_Eyeballs 3D.ppt (Mac users may prefer to use E1_Eyeballs 3D.key). It is best to view the videos in the continuous-loop mode (CMD-L command). These and other PowerPoint and KeyNote presentations are in their respective folders. It is best to view the videos in the continuous-loop mode (CMD-L command).

MV1 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 1 Cycle 1/20-Speed Illustrating Foveation Period

Note the flattened foveation period at 0°.

MV2 Infantile Nystagmus Syndrome (Jerk with Extended Foveation) 4 Cycles 1/3-Speed with Phase Plane

Note the flattened foveation periods at 0° immediately following the foveating leftward fast phases; all fall within the foveal area. In the phase plane, they fall within the foveation window where there is a discernable pause in the trajectory of the phase plane.

MV3 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 3 Cycles 1/2- Speed Illustrating Well-Developed Foveation

Note the accuracy of each successive foveation period.

MV4 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 3 Cycles 1/5-Speed with Phase Plane

Note the accuracy of each successive foveation period, especially in the phase plane where they overlap despite cycle-to-cycle variation throughout the rest of the cycles. Also, the pause within the foveation window is discernable.

MV5 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 1/2-Speed Three-Dimensional Motion with Subclinical Seesaw Nystagmus

This video illustrates that even in so-called horizontal IN, there is an appreciable torsional component and a hidden (subclinical) seesaw component. The red markers on the eyeballs help to appreciate the torsional motion.

MV6 Infantile Nystagmus Syndrome 1/5-Speed Subclinical Seesaw Nystagmus Motion Amplified

In this video, the horizontal and torsional motion has been turned off and the vertical has been amplified. By focusing on a spot between the eyes, the subclinical seesaw component of INS can be appreciated.

MV7 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 1/2-Speed from Ocular Motor System Model and Patient

This video demonstrates the ability of the behavioral OMS model to simulate even the most complex INS waveform (PPFs). Note the same accuracy of successive foveation periods in the model (left) as in the patient (right).

MV8 Infantile Nystagmus Syndrome (Pendular with Foveating Saccades) Step Responses Ocular Motor System Model

Behavioral OMS model simulations of INS during small (5°) and large (30°) saccades. Note the ovection accuracy within 1–3 cycles after the voluntary saccade.

MV9 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 1/2-Speed Pulse Responses Ocular Motor System Model

Behavioral OMS model simulations of INS during short (50 ms) and longer (100 ms $^\circ$) pulses. Note the normal behavior of ignoring short target pulses is duplicated despite the INS. Again note the foveation accuracy.

MV10 Infantile Nystagmus Syndrome (Pseudo Pendular with Foveating Saccades) 1/2-Speed Ocular Motor System Model Ramp and Step-Ramp Responses

Behavioral OMS model simulations of INS during ramp and step-ramp responses. Note the normal behavior of accounting for the target step in the latter response is duplicated despite the INS. Again note the foveation accuracy.

MV11 Fusion Maldevelopment Nystagmus Syndrome Gaze-Angle Effect Ocular Motor System Model

Behavioral OMS model simulations of FMNS demonstrating the small (left simulation) Alexander's law variation of the jerk-right FMN with gaze angle and the switch from a linear jerk-right nystagmus whose corrective fast phases foveate the target to a rightward saccadic pulse train whose initiating saccades defovetate the target,

allowing sustained foveation at the ends of the decelerating, corrective slow phases. In the right simulation, the large Alexander's law variation results in the rightward saccadic pulse train at 0° transforming into a jerk-right FMN in left gaze.

MV12 Fusion Maldevelopment Nystagmus Syndrome 1/2-Speed Alternate Cover Test Ocular Motor System Model

Behavioral OMS model simulations of the alternate cover test in FMNS demonstrating the changes in FMN direction as the fixating eye is changed.

MV13 Fusion Maldevelopment Nystagmus Syndrome Adducting Eye Fixation Ocular Motor System Model

Behavioral OMS model simulations of change in FMN direction and fixating eye as gaze is changed. In left and center gaze, the right eye is fixating with the left being esotropic; and in right gaze, the left eye is fixating with the right being esotropic.

MV14 Infantile Nystagmus Syndrome Damping with Rapid Convergence

Demonstration of INS damping with rapid convergence followed by an increase when distance fixation is resumed.

MV15 Infantile Nystagmus Syndrome 1/2-Speed Pre-Tenotomy and Reattachment

INS of a patient with a right esotropia before treatment with a bilateral horizontal rectus muscle T&R plus strabismus procedure. Note the large variability and failure to achieve good, repeatable foveation.

MV16 Infantile Nystagmus Syndrome 1/2-Speed Post-Tenotomy and Reattachment

INS of a patient after treatment with a bilateral horizontal muscle T&R plus strabismus

procedure. Note the improved foveation quality and better eye alignment.

MV17 Infantile Nystagmus Syndrome 1/2-Speed RPE65-Deficient Canine Pre-Gene Therapy

Multiplanar INS in an RPE65-deficient Briard dog prior to gene transfer therapy. Note both the uncontrolled nystagmus and eye drifting.

MV18 Infantile Nystagmus Syndrome 1/2-Speed RPE65-Deficient Canine Post-Gene Transfer-Therapy Scan Path

Left- and right-eye scan paths of the above RPE65-deficient Briard dog prior to gene therapy. Note that neither eye can foveate the target.

MV19 Infantile Nystagmus Syndrome 1/2-Speed RPE65-Deficient Canine Post-Gene Transfer-Therapy

Multiplanar INS in an RPE65-deficient Briard dog after gene therapy. Note both the nystagmus and eye drifting are markedly diminished (different scale from MV17).

MV20 Infantile Nystagmus Syndrome 1/2-Speed RPE65-Deficient Canine Post-Gene Transfer-Therapy Scan Path

Left- and right-eye scan paths of the above RPE65-deficient Briard dog after gene therapy. Note that both eyes continuously foveate the target.

MV21 Oscillopsia Simulation

An illustration of the perception of oscillopsia secondary to horizontal acquired nystagmus. Note that as you stare at the scene, in addition to the visual problems, there may be a sense of disequilibrium.

MV22 Unicocular Acquired Pendular Nystagmus Pre- and Post-Therapy

Note the reduction in the nystagmus (5° p-p to <1° p-p).

MV23 Infantile Nystagmus Syndrome (Alternating Jerk) Ocular Motor System Model

Behavioral OMS model simulation of alternating direction jerk INS. Note that despite the cycle-to-cycle direction changes, foveation quality is maintained.

MV24 Flutter

Typical flutter seen in neurological disease.

MV25 Flutter in a Blind Patient

High-frequency flutter recorded from a blind patient.

MV26 Psychogenic (Voluntary) Flutter

A party trick incorrectly called voluntary “nystagmus.”

MV27 Square-Wave Jerks

Typical square-wave jerks often seen in normal individuals.

MV28 Opsoclonus

Typical multivectorial opsoclonus.

KeyNote and PowerPoint Files

E.1.1 Infantile Nystagmus Syndrome Dynamic Visual Acuity

INS1_Ramp Response Bad Timing

Target motion near INS fast phase results in poor pursuit and long target-acquisition latency.

INS2_Ramp Response Good Timing

Target motion during INS slow phase results in good pursuit and shorter target-acquisition latency.

INS3_Ramp Response Poor Gain

Target motion in opposite direction in same patient results in poor pursuit and long target-acquisition latency.

INS4_Ramp Response Eye Switching

Switching the fixating eye during pursuit results in poor pursuit and long target-acquisition latency.

INS5_Ramp Response Post T&R

Post T&R, target motion near INS fast phase still results in poor pursuit and long target-acquisition latency; also there is a steady-state position error.

INS6_Water Trial

Demonstration of post-therapy ability to track and shoot a flying bird during a water trial for hunting dogs.

INS7_Hunting

Demonstration of post-therapy ability to track and shoot a flying bird during upland game hunting.

INS8_Activities

Photos of possible normal-life-style activities after INS treatment.

E.1.2 Infantile Nystagmus Syndrome Latency

L1_INS Step Response

Despite normal saccadic latency, the target acquisition time (before target foveation) in INS is longer.

L2_INS Step Response Different Timings

In INS, the target acquisition time is determined by the timing of the target step; near intrinsic INS saccades it is longer than during the slow phase.

L3_INS Step Response Preprogrammed Fast Phase

Individuals with INS respond to target steps in different ways; here a preprogrammed fast phase is elongated to reposition the eyes; it is followed by another saccade to reach the target.

E.1.3 Infantile Nystagmus Syndrome Latency Poster

Each of the following poster panels is self-explanatory.

LP1_Abstract

LP2_Latency T&R Procedure

LP3_Latency Background

LP4_Latency Questions

LP5_Latency Hypotheses
 LP6_Latency Methods 1
 LP7_Latency Methods 2
 LP8_Latency Model
 LP9_Latency Model Predictions 1
 LP10_Latency Model Predictions 2
 LP11_Latency Results 1
 LP12_Latency Results 2
 LP13_Latency Results 3
 LP14_Latency Results 4
 LP15_Latency Results 5
 LP16_Latency Results 6
 LP17_Latency Results Preprogrammed Fast Phase
 LP18_Latency Results Riding Slow Phase
 LP19_Latency Results Anticipation
 LP20_Latency Results Altered Fast Phase
 LP21_Latency Results Waveform Change
 LP22_Latency Results Hypometria
 LP23_Latency Results Riding Slow Phases
 LP24_Latency Results Direction Change
 LP25_Latency Conclusions 1
 LP26_Latency Conclusions 2
 LP27_Latency Conclusions 3

E.1.4 Infantile Nystagmus Syndrome Model Poster

Each of the following poster panels is self-explanatory.

MP1_Abstract
 MP2_INS Models
 MP3_INS Model Behavior
 MP4_INS Model Questions
 MPS_INS Model Hypotheses
 MP6_INS Model Methods
 MP7_INS Model Block Diagram
 MP8_INS Model
 MP9_INS Model AL Gain Modulation
 MP10_INS Model Internal Monitor
 MP11_INS Model Methods 2
 MP12_INS Model Alexander's Law
 MP13_INS Model Predictions Sharp AL
 MP14_INS Model Predictions Medium AL
 MP15_INS Model Predictions Broad AL
 MP16_INS Model Outputs Sharp Null
 MP17_INS Model Outputs Sharp Nulls
 MP18_INS Model Outputs Medium Nulls
 MP19_INS Model Outputs Broad Nulls

MP20_INS Model Outputs Sharp Null
 MP21_INS Model Medium NAFX Peak
 MP22_INS Model Sharp NAFX Peak
 MP23_INS Model Broad NAFX Peak
 MP24_INS Mode Results
 MP25_INS Model Conclusions

E.2 CANINE VIDEOS (PLUS OTHERS)

Canine videos may be viewed individually or using E2_Canine Videos.ppt (Mac users may prefer to use E2_Canine Videos.key). It is best to view the videos in the continuous-loop mode (CMD-L command).

CV1 Normal Brittany

Gaze changes on command with no head motion exhibited and recorded from a well-trained, Brittany upland game dog (Copper the wonder dog).

CV2 Achiasmatic Belgian Sheepdog: Pre-Tenotomy and Reattachment

The INS of an achiasmatic Belgian sheepdog before any treatment. Note both horizontal INS and SSN.

CV3 Achiasmatic Belgian Sheepdog: Post-Tenotomy and Reattachment

The INS of an achiasmatic Belgian sheepdog after a two-stage (horizontal and vertical) four-muscle T&R treatment. Note the damping of the horizontal INS and elimination of the SSN.

CV4 RPE65-Deficient Canine: Pre-Gene Transfer-Therapy Behavior

The inability of an RPE65-deficient Briard to navigate around obstacles.

CV5 RPE65-Deficient Canine: Post-Gene Transfer-Therapy Behavior

The remarkably improved ability of an RPE65-deficient Briard to navigate around obstacles after gene-therapy treatment.

CV6 RPE65-Deficient Canine: Pre-Gene Transfer-Therapy Eye Movements

Eye movements of an RPE65-deficient Briard prior to treatment. Note the multiplanar nystagmus.

CV7 RPE65-Deficient Canine: Post-Gene Transfer-Therapy Eye Movements

Eye movements of an RPE65-deficient Briard after gene-therapy treatment. Note the absence of clinically visible multiplanar nystagmus.

CV8 Cat with Infantile Nystagmus

A Siamese (albinotic) cat with INS.

CV9 Goat with Seesaw Nystagmus

A dwarf goat with SSN.

KeyNote and PowerPoint Files

E.3 PATIENT VIDEOS

Patient videos may be viewed individually together with the accompanying eye-movement figure.

PV1 Saccadic Initiation Failure

Eye-movement video and recording showing a patient with saccadic initiation failure (ocular motor apraxia). The recording illustrates severe hypometria during attempted horizontal gaze with unequal involvement of right and left eyes. The left eye shows an almost total inability to generate a saccade. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV2 Brainstem Tumor: Tonic Gaze Deviation

Eye-movement video and recording showing a patient with a brainstem tumor and involuntary tonic vertical gaze deviation. The recording

illustrates periodic fast vertical eye movements on a background of saccadic oscillations. On the figure: up, up; down, down; OD, right eye; OS, left eye; Sec, seconds.

PV3 Acquired Downbeat Nystagmus

Eye-movement video and recording showing a patient with acquired downbeat nystagmus. The recording illustrates a continuous jerk down oscillation with linear and occasional decreasing velocity slow phases, worse in lateral and down gaze. On the figure: up, up; down, down; OS, left eye; Sec, seconds.

PV4 Acquired Gaze-Evoked (Gaze-Holding Failure) Nystagmus

Eye-movement video and recording showing a patient with gaze-holding failure nystagmus. The recording illustrates horizontal, jerk oscillations with linear slow phases, increasing in intensity and changing direction from jerk right in right gaze to jerk left in left gaze and jerk right in right gaze. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV5 Acquired Unidirectional Gaze-Evoked (Gaze-Holding Failure) Nystagmus

Eye-movement video and recording showing a patient with gaze-holding failure nystagmus in left gaze and associated saccadic oscillations due to cerebellar disease. The recording illustrates horizontal, jerk oscillations with linear slow phases, increasing in intensity in left gaze with associated saccadic oscillations in primary position. On the figure: up, right; down, left; OD, right eye; Sec, seconds.

PV6 Ocular Motor Neuromyotonia of Cranial Nerve III

Eye-movement video and recording showing a patient with ocular motor neuromyotonia affecting the right medial rectus (inferior division of CN III) by “spasm” of convergence and esotropia after prolonged adduction of the right

eye (medial rectus stimulation). The recording illustrates a slow saccadic response of abducting right eye after prolonged adduction. On the figure: up, up; down, down; OD, right eye; OS, left eye; Sec, seconds.

PV7 Ocular Motor Neuromyotonia of Cranial Nerve VI

Eye-movement video and recording showing a patient with ocular motor neuromyotonia affecting the right lateral rectus (CN VI) by “spasm” of divergence and exotropia after prolonged abduction of the right eye (lateral rectus stimulation). The recording illustrates a slow saccadic response of the adducting right eye after prolonged abduction and an associated pendular nystagmus of the left eye. On the figure: up, up; down, down; OD, right eye; OS, left eye; Sec, seconds.

PV8 Infant with Opsoclonus (Ocular Flutter—“Saccadomania”)

Eye-movement video and recording showing an infant with irregular, multiplanar, conjugate, symmetric, saccadic oscillations typical of opsoclonus. The recording illustrates the typical conjugate, saccadic, and multiplanar components (broken into horizontal and vertical by the recording technique) of the oscillation. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV9 Acquired Saccadic Oscillations-1

Eye-movement video and recording showing a patient with constant, conjugate, horizontal ocular oscillations typical of saccadic oscillations. The recording illustrates constant, conjugate, back-to-back saccades both with (square-wave jerks) and without an intersaccadic interval. On the figure: up, right; down, left.

PV10 Acquired Saccadic Oscillations-2

Eye-movement video and recording showing a patient with constant, conjugate, horizontal ocular oscillations typical of macro saccadic

oscillations associated with cerebellar disease. The recording illustrates horizontal, constant, conjugate, back-to-back saccades both with an intersaccadic interval. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds; the two top traces are position and the bottom traces are velocity.

PV11 Acquired Saccadic Oscillations-3

Eye-movement video and recording showing a patient with constant, conjugate, horizontal ocular oscillations typical of saccadic oscillations associated with cerebellar disease. The recording illustrates horizontal, constant, conjugate, back-to-back saccades with an intersaccadic interval interrupting low-gain smooth pursuit. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds; the two top traces are position and the bottom traces are velocity.

PV12 Acquired Nystagmus Plus Saccadic Oscillations

Eye-movement video and recording from a patient with a brainstem tumor showing a multiplanar constant, conjugate, oscillation that is predominantly vertical. The recording illustrates both (separated by the horizontal and vertical recording channels) a vertical, upbeat jerk oscillation with linear slow phases and a constant, horizontal saccadic oscillation with an intersaccadic interval. On the figure: up, either right (horizontal trace) or up (vertical trace); down, either left (horizontal trace) or down (vertical trace); OD, right eye; OS, left eye; Sec, seconds.

PV13 Acquired Upbeat Nystagmus with Wiernecke's Encephalopathy

Eye-movement video and recording from a patient with malnutrition-induced Wiernecke's encephalopathy, upbeat nystagmus, convergence spasm, and resolving CN VI palsy. The recording from the right eye illustrates typical jerk-up nystagmus with linear and decreasing velocity slow phases, worse in upgaze. On the figure: up, up; down, down.

PV14 Acquired Vertical Pendular Nystagmus

Eye-movement video and recording from a patient with vertical, pendular nystagmus consequent to a brainstem hemorrhage and cerebrovascular accident. The recording illustrates conjugate, in-phase, pendular nystagmus that occasionally changes to upbeat with a pendular slow phase. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV15 Fusion Maldevelopment Nystagmus-1

Eye-movement video and recording from a patient with amblyopia OD and a small-angle strabismus. He has a change in both nystagmus intensity and direction with monocular cover. The recording illustrates a conjugate, variable-intensity, and changing direction (jerk in the direction of the viewing eye) oscillation with linear (nystagmus) and decreasing velocity (saccadic pulse trains) slow phases, typical of FMNS with a monocular preference. In this patient, the left eye is preferred. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV16 Fusion Maldevelopment Nystagmus-2

Eye-movement video and recording from a patient with amblyopia OS and a small-angle strabismus. She has a change in both nystagmus intensity and direction with monocular cover. The recording illustrates a conjugate, variable-intensity, and changing direction (jerk in the direction of the viewing eye) oscillation with linear (nystagmus) and decreasing velocity (saccadic pulse trains) slow phases, typical of FMNS with a monocular preference. In this patient the right eye is preferred. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV17 Down Syndrome and Infantile Nystagmus

Eye-movement video and recording showing a patient with Down syndrome and nystagmus. The

recording illustrates pendular and unequal mixed INS waveforms. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV18 Achiasma Plus Seesaw Nystagmus Plus Infantile Nystagmus

Eye-movement video and recording from a patient with achiasma showing the horizontal (faster) and vertical (slower) oscillations of INS and SSN, respectively. The recording from the vertical channel illustrates the 180° out-of-phase, slower vertical oscillation superimposed on a symmetric, smaller amplitude, jerk, INS waveform. On the figure: up (U), up; down (D), down; OD, right eye; OS, left eye; Sec, seconds.

PV19 Octogenarian with Infantile Nystagmus

Eye-movement video and recording from an 86-year-old patient with albinism and INS. The recording illustrates conjugate, jerk with extended foveation waveforms. Notice that after the 2-sec mark the nystagmus improves due to a null position in immediate left gaze. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV20 Infantile Nystagmus: Aperiodically Changing Intensity (Not Direction)

Eye-movement video and recording from a patient with strabismus and INS. The recording illustrates conjugate, pseudopendular with foveating saccades and jerk with extended foveation waveforms. The bottom trace shows how the nystagmus spontaneously changes over time while the patient remains visually stimulated and in the same mental state (aperiodicity). On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV21 Infantile Nystagmus: Aperiodically Changing Direction (Not Intensity)

Eye-movement video and recording from a patient with INS. The recording illustrates conjugate, jerk

with extended foveation waveforms. The trace shows how the nystagmus spontaneously changes direction over time while the patient remains visually stimulated and in the same mental state (aperiodicity). There is no change in eye position or spontaneous change in fixation between the eyes that would diagnose INS with a “latent component” rather than aperiodicity. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV22 Infantile Nystagmus: Unequal-1

Eye-movement video and recording from a patient with A-pattern strabismus and INS. The recording illustrates in-phase, unequal, jerk with extended foveation waveforms with the fixing eye (predominantly right eye in this segment of the recording) and saccadic oscillations in nonfixing eye (predominantly the left eye in this segment of the recording). On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV23 Infantile Nystagmus: Unequal-2

Eye-movement video and recording from a patient with INS. The recording illustrates in-phase, unequal, jerk with extended foveation waveforms. The intensity of the visually preferred left eye is obviously less than the right. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV24 Infantile Nystagmus: Unequal-3

Eye-movement video and recording from a patient with INS. The recording illustrates in-phase, unequal, jerk with extended foveation waveforms and breaking saccades. The visually preferred left eye is due to better foveation and not overall intensity as shown by analysis of foveation using the expanded nystagmus acuity function (NAFX). On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV25 Infantile Nystagmus: Jerk with Extended Foveation

Eye-movement video and recording from a patient with INS and jerk with extended

foveation waveforms. The recording illustrates pure, conjugate, jerk with extended foveation waveforms. The intensity of both eyes is equal during this 2-second data collection and the binocular acuity of this patient is 20/25. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV26 Infantile Plus Nucleus of the Optic Tract Nystagmus: Dual Jerk

Eye-movement video and recording from a patient with INS and dual-jerk waveforms. The recording illustrates pure, conjugate, dual jerk with extended foveation waveforms. The intensity of both eyes is equal during this 10-second data collection and the binocular acuity of this patient is 20/25. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV27 Infantile Nystagmus: Pre- and Postoperative

Eye-movement video and recording from a patient with INS before and after eye-muscle surgery. The 11-second recording illustrates, in-phase, INS with unequal pendular and pseudocycloid waveforms. The improvement in intensity of the nystagmus illustrated in the bottom figures illustrates what happens after surgery. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV28 Optic Nerve Dysplasia and Infantile Nystagmus: Multiplanar

Eye-movement video and recording from a patient with a large-angle exotropia, optic nerve dysplasia and INS. This 8-second recording from his preferred right eye illustrates both the horizontal (red) and vertical (yellow) components of a conjugate, jerk with extended foveation INS. The fast phases are artificially separated into right and down by the recording methodology, but the clinical appearance is an “oblique” nystagmus. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV29 Infantile Nystagmus: Jerk with Extended Foveation

Eye-movement video and recording from a patient with X-linked (FRMD7) INS jerk waveforms. The recording illustrates pure, conjugate, jerk with extended foveation waveforms. The intensity of both eyes is equal during this 9-second data collection and the binocular acuity of this patient is 20/50. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV30 Infantile Nystagmus: Unequal with a “Latent Component”

Eye-movement video and recording from a patient with INS, esotropia, high myopia, amblyopia, and a history of retinopathy of prematurity. The recording illustrates in-phase, unequal, jerk right with the right eye viewing and jerk left with the left eye viewing both with extended foveation waveforms. The intensity of the nystagmus and quality of foveation is better with the preferred right eye. On the figure: up, right; down, left; OD, right eye; OS, left eye; Deg, degrees.

PV31 Albinism and Infantile Nystagmus

Eye-movement video and recording from a patient with INS and albinism. The recording illustrates pure, conjugate, jerk with extended foveation waveforms. The intensity of both eyes is equal during this 12-second data collection and the binocular acuity of this patient is 20/60. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV32 Optic Nerve Dysplasia and Infantile Nystagmus: Multiplanar

Eye-movement video and recording from a patient with strabismus, optic nerve dysplasia, and INS. This 6-second binocular recording illustrates both the horizontal and vertical components of a conjugate, jerk, dual-jerk, and unequal pendular INS. The fast phases are artificially separated into right and down by the recording methodology, but the clinical appearance is an

“oblique” nystagmus. On the figure: up, right and up; down, left and down; OD, right eye; OS, left eye.

PV33 Albinism, Upgaze Null, and Infantile Nystagmus: Equal

Eye-movement video and recording from a patient with INS, albinism, and chin-down head posture. The recording illustrates conjugate, jerk with extended foveation waveforms. The intensity of both eyes is equal during this 7-second, upgaze data collection (his best nystagmus characteristics). On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV34 Retinal Dystrophy and Infantile Nystagmus: Multiplanar

Eye-movement video and recording from a patient with a stationary rod-cone dystrophy and INS. This 24-second binocular recording illustrates both the horizontal and vertical components of a conjugate, jerk waveform INS. The fast phases are artificially separated into right and down by the recording methodology, but the clinical appearance is a “vertical” nystagmus. On the figure: up, right and up; down, left and down; OD, right eye; OS, left eye; Sec, seconds.

PV35 Albinism and Infantile Nystagmus: Pre- and Postoperative Horizontal Null

Eye-movement video after, and recording from a patient before and after eye-muscle surgery with INS and albinism. The two recordings illustrate, conjugate, jerk, and jerk with extended foveation (plus one pseudopendular with a foveating saccade—right panel) INS waveforms. The improvement in this patient’s nystagmus intensity illustrates a marked improvement in foveation with a small decrease in frequency, giving the clinical illusion that there was no effect of the operation. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV36 Albinism and Infantile Nystagmus: Multiplanar

Eye-movement video and recording from a patient with albinism, strabismus, optic nerve dysplasia, and INS. This 15-second binocular recording illustrates both the horizontal and vertical components of a horizontally conjugate and vertically out-of-phase, unequal pendular INS. The waveforms are artificially separated into horizontal and vertical by the recording methodology, but the clinical appearance is an “elliptical” (sometimes diagonal) nystagmus (note the subclinical see-saw component). On the figure: up, right and up; down, left and down; OD, right eye; OS, left eye.

PV37 Infantile Nystagmus: Periodic Alternating

Eye-movement video and recording from a patient with pure periodic INS. Eye-movement recording performed under binocular conditions showing velocity data only from the preferred right eye over 800 seconds illustrating a typical periodic rhythm. On the figure: up, right; down, left; OU, both eyes open.

PV38 Infantile Nystagmus: Asymmetric Aperiodic Alternating

Eye-movement video and recording data of OS from patient with X-linked (FRMD7) asymmetric aperiodic alternating INS performed under binocular conditions using data from the left eye illustrating asymmetry during an aperiodic, rhythmic cycle with changes in the waveforms evident when the fast phase is to the left (pure jerk left waveform) and to the right (jerk right with extended foveation). It is easy to see how this patient has better vision and visual function during the jerk-right phase of the cycle. OS, left eye; up, right (R); down, left (L); upper trace, position; lower trace, velocity.

PV39 Albinism and Infantile Nystagmus: Pre- and Postoperative Vertical Null

Eye-movement video and recording from a patient with INS and an upgaze, eccentric null

position (chin-down head posture), before and after eye-muscle surgery. The two videos show the significant improvements in clinical head position and nystagmus prior to (a) and after (b) eye-muscle surgery. The 50-second recording illustrates, in-phase, unequal, INS with jerk waveforms. The improvement in intensity of the nystagmus illustrated in the bottom four figures illustrates what happens after surgery. On the figure: up, right; down, left; OD, right eye; OS, left eye; PRE-OP, preoperatively; POST-OP, postoperatively; Sec, seconds.

PV40 Albinism, Upgaze Null, and Infantile Nystagmus

Eye-movement video and recording from a patient with INS, exotropia, albinism, and chin-down head posture. The recording illustrates conjugate jerk and pendular waveforms. The intensity of both eyes is equal during this 7-second, upgaze data collection (his best nystagmus characteristics). On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV41 Albinism and Infantile Nystagmus

Eye-movement video and recording from a patient with INS and albinism. The recording illustrates pure, conjugate, jerk with extended foveation waveforms. The intensity of both eyes is equal during this 12-second data collection and the binocular acuity of this patient is 20/40. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV42 “Vertical” Infantile Nystagmus-1

Eye-movement video and recording from a rare patient with predominant vertical INS. The recording illustrates pure, vertical, conjugate, pendular waveforms. Complete neurological and ophthalmological investigations were otherwise normal. The intensity of both eyes is equal during this 12-second data collection and the binocular acuity of this patient is 20/50. On the figure: up, up; down, down; OD, right eye; OS, left eye; Sec, seconds.

PV43 Retinal Dystrophy and “Vertical” Infantile Nystagmus-2

Eye-movement video and recording from a rare patient with strabismus and a predominant vertical INS. The recording illustrates vertical, conjugate, jerk waveforms. The gross, vertically, dysconjugate movements of the two eyes every 5 seconds is occurring during horizontal refixation showing a changing hypertropia. Complete neurological and ophthalmological investigations showed a stationary rod-cone dystrophy. The intensity of both eyes is equal during this 50-second data collection and the binocular acuity of this patient is 20/70. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV44 Spasmus Nutans Nystagmus-1

Eye-movement video and recording from a 2-year-old patient with barely visible nystagmus that improved over the last 6 months according to maternal history. The recording illustrates dysconjugate (unequal and 180° out of phase), high-frequency (7–10 Hz) pendular waveforms. Complete neurological and ophthalmological investigations were otherwise normal. On the figure: up, right; down, left; OD, right eye; OS, left eye.

PV45 Spasmus Nutans Nystagmus-2

Eye-movement video and recording from an 8-month-old patient with a head oscillation and dysconjugate, unequal nystagmus that had been previously diagnosed as congenital nystagmus. The recording illustrates dysconjugate (unequal and 180° out of phase), high-frequency (7–10 Hz) pendular waveforms. Complete neurological and ophthalmological investigations were otherwise normal. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

PV46 Voluntary Ocular Flutter

Eye-movement video and recording from a 10-year-old patient with an intermittent, high-frequency, small-amplitude, dysconjugate,

voluntary, familial oscillation. The recording illustrates dysconjugate (unequal and out of phase), high-frequency (7–10 Hz) flutter waveforms. Complete neurological and ophthalmological investigations were otherwise normal. On the figure: up, right; down, left; OD, right eye; OS, left eye; Sec, seconds.

E.4 HISTORICAL

E.4.1 Demonstration of Bias and Bias Shift in Infantile Nystagmus Waveforms

The first definitive evidence (1972) supporting the hypothesis that those with INS oscillate away from and back to the target came from a fundus film that was made while the subject was fixating the low-level laser aiming spot in a laser photocoagulation apparatus. The fovea could be seen oscillating to one side of the spot and then shifting to the other. In the same year, the first eye-movement data confirmation was made that both eyes of a person with INS oscillate to one side of the target, coming to rest on the target and thereby allowing good visual acuity. Figure E.4.1 shows the two eyes oscillating to the right of the target at 10° right gaze and then (at arrow) simultaneously shifting to the left. Subsequent eye-movement data confirmed that the same applied for all nontransient INS waveforms.

E.4.2 Demonstration That Cutaneous Stimulation Damps Infantile Nystagmus

It was first demonstrated in 1994 that cutaneous stimulation could damp INS via exteroceptive signals from the ophthalmic division of the trigeminal nerve. In Video E.4.2, note the damping of the INS during stimulation of the forehead and its reappearance after stimulation ceased.

E.4.3 First Canine Eye-Movement Recording

Canine eye-movement recordings were first made in 1993 at the University of Tennessee,

on an achiasmatic Belgian sheepdog, by L. F. Dell’Osso and J. B. Jacobs. Figure E.4.3a shows a dog calmly suspended in a sling while having his eye movements recorded by an infrared method. Figure E.4.3b shows several methods (infrared, top two; and digital video, bottom) of recording canine eye movements. Figure E.4.3c shows a dog calmly suspended in a sling while having his eye movements recorded by a digital video method. Figure E.4.3d shows an achiasmatic Belgian sheepdog with INS and the dramatic difference in the dog’s demeanor after

T&R procedures were performed on all of his extraocular muscles.

E.4.4 First Tenotomy and Reattachment Surgery for Infantile Nystagmus

Performed in 1997 on an achiasmatic Belgian sheepdog, by R. W. Hertle and assisted by L. F. Dell’Osso—believed to be the first time a person with INS assisted in a surgery for INS (see Figs. E.4.4a and E.4.4b).

APPENDIX F

ONLINE ACCESS

- F.1 OMLAB REPORTS 309
 - F.1.1 #011105 Recording and Calibrating the Eye Movements of Nystagmus Subjects 310
 - F.1.2 #111005 Using the NAFX for Eye-Movement Fixation Data Analysis and Display 310
 - F.1.3 #111905 Nystagmus Therapies: Types, Sites, and Measures 310
 - F.1.4 #090506 Original Ocular Motor Analysis of the First Human with Achiasma: Documentation of Work Done in 1994 310
 - F.1.5 #123007 The Benefits of Extraocular Muscle Surgery in INS 310
 - F.1.6 #030509 How Someone “Sees” the World and How to Clinically Assess Therapeutic Improvements in Visual Function 310
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THE REPORT, figure, and video files in this appendix may be copied, viewed, or printed. Many of the Omlab Reports, Patient Handouts, Physician Worksheets, and Software were originally made available at <http://www.omlab.org>.

F.1 OMLAB REPORTS

Both PDF and HTML forms of the OMLAB reports described below may be found in the F.1 OMLAB REPORTS folder.

F.1.1 #011105 Recording and Calibrating the Eye Movements of Nystagmus Subjects

OMLAB Report #011105 describes the methods used to obtain accurately calibrated eye-movement data in subjects with ocular oscillations.

F.1.2 #111005 Using the NAFX for Eye-Movement Fixation Data Analysis and Display

OMLAB Report #111005 describes the proper use of the NAFX software to assess the foveation quality of nystagmus waveforms.

F.1.4 #090506 Original Ocular Motor Analysis of the First Human with Achiasma: Documentation of Work Done in 1994

OMLAB Report #090506 presents the first ocular motor analysis of a human with achiasma.

F.1.5 #123007 The Benefits of Extraocular Muscle Surgery in INS

OMLAB Report #123007 describes the often-unappreciated beneficial effects of extraocular muscle surgery in patients with INS.

F.1.6 #030509 How Someone “Sees” the World and How to Clinically Assess Therapeutic Improvements in Visual Function

OMLAB Report #030509 presents a visual picture of how the world appears to a person with INS and the methods to assess therapeutic improvements.

F.2 PATIENT HANDOUTS

Both PDF and HTML forms of the patient handouts described below may be found in the F.2 PATIENT HANDOUTS folder. They are written in lay terms so that they may be easily understood by patients.

F.2.1 INS Information

Handout F.2.1 answers common general questions that INS patients or their parents may have.

F.2.2 INS Treatments

Handout F.2.2 answers more specific questions (including those about surgery and strabismus) that INS patients or their parents may have.

F.2.3 Tenotomy and Reattachment

Handout F.2.3 provides illustrations of the world seen through the eyes of someone with INS and helps both INS patients and their parents to better appreciate the types of visual function limitations produced by INS; a similar post-T&R illustration demonstrates the type of improvement possible. In addition, several common questions regarding the T&R procedure are answered.

F.2.4 INS and Acuity

Handout F.2.4 answers common questions that about INS waveforms and their relation to visual acuity that patients or their parents may have.

F.2.5 INS Miscellaneous

Handout F.2.5 answers additional questions that INS patients or their parents may have.

F.3 PHYSICIAN/RESEARCH SCIENTIST WORKSHEETS

Both PDF and HTML forms of the patient handouts described below may be found in the F.3 PHYSICIAN RESEARCH SCIENTIST HANDOUTS folder.

F.3.1 Recession and Resection Surgical Calculation

Figure F.3.1 is a plot of the required null shift versus the total surgical rotation required; that

is, the sum of the amounts of recession and resection required in each eye.

F.3.2 Estimating Improvement in Peak NAFX

Figure F.3.2 is a plot of the pre-T&R NAFX versus the estimated post-T&R percent increase in peak NAFX.

F.3.3 Estimating Improvement in LFD

Figure F.3.4 is a plot of the pre-T&R LFD versus the estimated post-T&R percent increase in LFD.

F.3.4 NAFX versus Visual Acuity (Motor and Sensory Components)

Figure F.3.4 contains plots of the pre-T&R LFD versus visual acuity for several age groups. By choosing the proper line based on the patient's age, one can use this plot to make a pre-T&R estimate of the post-T&R improvement in visual acuity for both INS patients with and without associated visual sensory deficits.

F.4 CLINICAL EXAMINATION FORMS

Both PDF and HTML forms of the patient handouts described below may be found in the F.4 CLINICAL EXAMINATION FORMS folder.

F.4.1 General Clinical Examination Form

Forms F.4.1.1–F.4.1.4 are general ophthalmological examination forms.

F.4.2 Strabismus Examination Form

Form F.4.2 is a strabismus examination form.

F.4.3 Nystagmus Examination Form

Form F.4.3 is a nystagmus examination form.

F.5 ANALYSIS SOFTWARE

Both PDF and HTML forms of the patient handouts described below may be found in the F.5 ANALYSIS SOFTWARE folder.

F.5.1 OMtools

The OMtools folder and its subfolders and files should be placed in the MATLAB folder along with the proper paths. These files contain the software we developed during 20 years of ocular motor research and evaluation of INS.

F.5.2 OMS Model GUI User Guide

The PDF in the F.5.2 OMS USER GUIDE 1.5 folder explains the use of this GUI with current versions of the behavioral ocular motor system model and outlines how additional GUI functions may be included in the model and the GUI.

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