DISSOCIATED HORIZONTAL DEVIATION: CLINICAL SPECTRUM, PATHOGENESIS, EVOLUTIONARY UNDERPINNINGS, DIAGNOSIS, TREATMENT, AND POTENTIAL ROLE IN THE DEVELOPMENT OF INFANTILE ESOTROPIA (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

BY Michael C. Brodsky MD

ABSTRACT

Purpose: To elucidate the pathophysiology of dissociated horizontal deviation.

Methods: The reversed fixation test was performed prospectively in 28 patients who developed consecutive exotropia following horizontal extraocular muscle surgery for infantile esotropia. All patients were assessed for the presence of adduction weakness, latent nystagmus, dissociated vertical divergence, and neurologic disease.

Results: A positive reversed fixation test, indicating the presence of dissociated horizontal deviation, was found in 14 of 28 patients (50%) with consecutive exotropia. In patients with dissociated horizontal deviation, the exodeviation was usually smaller with the nonpreferred eye fixating than with the preferred eye fixating, and smaller with the preferred eye fixating than during periods of visual inattention or under general anesthesia. Dissociated horizontal deviation correlated with the findings of dissociated vertical divergence, but not with asymmetric adduction weakness, latent nystagmus, or neurologic disease.

Conclusions: Using reversed fixation testing, dissociated horizontal deviation can be detected in 50% of patients who develop consecutive exotropia following surgery for infantile esotropia. In this setting, monocular fixation with either eye superimposes a dissociated esotonus upon a baseline exodeviation. Fixation with the nonpreferred eye usually exerts greater esotonus than fixation with the preferred eye, producing an asymmetrical exodeviation during prism and alternate cover testing. Depending on the baseline anatomical position of the eyes, this dissociated esotonus can manifest as an intermittent exodeviation or an intermittent esodeviation. This unrecognized form of ocular motor dissociation may contribute to the pathogenesis of infantile esotropia.

Trans Am Ophthalmol Soc 2007;105:272-293

INTRODUCTION

Dissociated horizontal deviation is defined as a change in horizontal ocular alignment, unrelated to accommodation, that is brought about solely by a change in the balance of visual input from the two eyes.[1] It usually manifests as a spontaneous unilateral exodeviation or an exodeviation of greater magnitude in one eye during prism and alternate cover testing (Figure 1).[2-8] Unlike in other forms of intermittent exotropia, the observed exodeviation is slow, variable, and asymmetrical in the two eyes.[2-8] In some instances, fixation with one eye evokes an esodeviation of the other eye during prism and alternate cover testing (Figure 2).[3,4,7,8]

Many reports have described dissociated horizontal deviation in patients who have been treated with strabismus surgery for infantile esotropia. These patients characteristically show dissociated signs such as latent nystagmus and dissociated vertical divergence, as well as torsional eye movements, sensorial suppression, and a positive Bielschowsky phenomenon in the horizontal plane.[3-8] These signs have led to the clinical inference that this unilateral or asymmetrical exodeviation must constitute a variable abducting component of dissociated vertical divergence.[7,9-11]

The purposes of this investigation are to:

1. Determine the prevalence of dissociated horizontal deviation in patients with consecutive exotropia
2. Examine the nature of dissociated innervation that produces unilateral or asymmetrical exodeviation
3. Determine whether the clinical expression of dissociated horizontal deviation is influenced by fixation preference
4. Elucidate the role of the reversed fixation test in diagnosing dissociated horizontal deviation
5. Define evolutionary ocular motor mechanisms that give rise to dissociated horizontal deviation
6. Consider the potential role of dissociated horizontal deviation in the pathogenesis of infantile strabismus
7. Reevaluate current treatment recommendations

HISTORICAL BACKGROUND

Tonus refers to the effects baseline innervation on musculature in the awake, alert state. Since the normal anatomic resting position of the eyes is an exodeviated position, extraocular muscle tonus plays a vital physiologic role in establishing ocular alignment.[12] Under normal conditions, binocular esotonus is superimposed upon the normal anatomic position of rest to maintain approximate binocular alignment, save for a minimal exophoria that is easily overcome by active convergence. While convergence functions to actively alter horizontal eye position, tonus effectively resets the baseline eye position (i.e., the anatomic position of rest). When binocular visual input is preempted early in life, monocular fixation generates an esotonus that gradually drives the two eyes into a "convergent" position, resulting in infantile esotropia.[12]

In the study of strabismus, the term *dissociation* has dual application. It can refer to unequal sensory visual input to the two eyes (sensory dissociation) or to the resulting inequality of the resulting ocular deviation (motor dissociation) when each eye is used for fixation.[13] In 1904, Bielschowsky first applied the term *dissociated* to binocular eye movements.[14-16] He used the term *dissociated*

From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

vertical divergence to describe the curious alternating hyperdeviation of the nonfixating eye that accompanies congenital esotropia. Although Bielschowsky confined his use of this term to a vergence movement, dissociated eye movements can comprise any ocular movements (conjugate or disconjugate) that result from a change in the relative balance of visual input from the two eyes. In this context, dissociated vertical divergence (a cyclovergence movement) and latent nystagmus (a cycloversion movement) qualify equally as dissociated eye movements, since both are driven by fluctuations in the relative balance of binocular visual input from the two eyes.

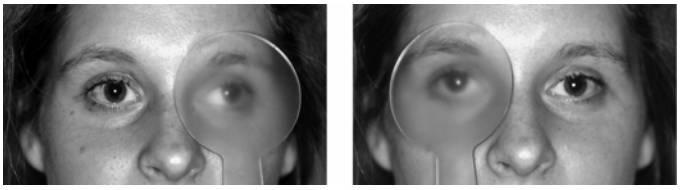

FIGURE 1

Dissociated horizontal deviation with greater exodeviation in the left eye than the right eye (courtesy of Michael Gräf, MD).

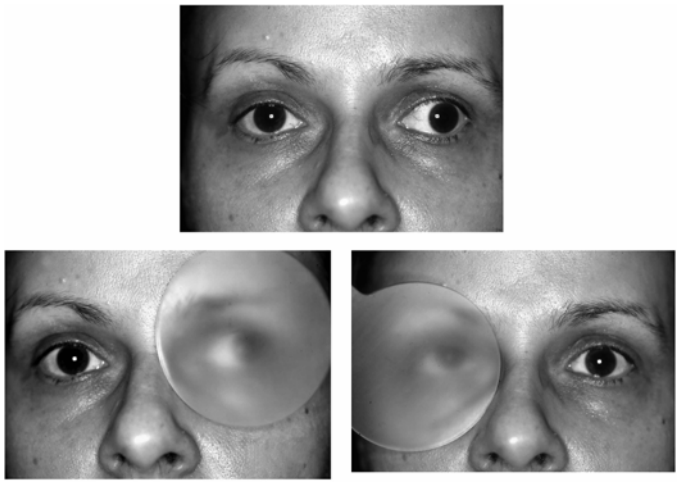

FIGURE 2

Dissociated horizontal deviation. Top, A large left exotropia is present when the patient fixates with the preferred right eye. Bottom, When fixation is switched to the nonpreferred left eye, the large left exodeviation converts to a right esodeviation with dissociated vertical deviation (courtesy of Michael Gräf, MD).

In historical terms, the concept of dissociated *horizontal* deviation is relatively new to pediatric ophthalmology. In 1976, Raab[17] described the slow unilateral abduction of the deviating eye as a horizontal variant of dissociated vertical divergence. In 1990, Spielmann[18] assigned the diagnosis of dissociated horizontal deviation to patients with infantile strabismus who manifest an intermittent *esodeviation* of one eye (Figure 3). This phenomenon can be visualized by using the Spielmann occluder, which diffuses visual input to the covered eye while providing a fairly clear visualization of the eye position to the examiner.[19] Spielmann's observation suggested that monocular fixation can *increase* esotonus in some patients with infantile strabismus. With the term applied to two seemingly disparate clinical conditions, further confusion arose when Zubcov and colleagues[20] applied the term *dissociated horizontal deviation* to a third situation, in which greater degrees of convergence are presumably used to block latent nystagmus when the poorer eye is used for fixation. In his discussion of this article, Raab[21] objected to this application of the term *dissociated horizontal deviation* to this mechanism, which he considered to be distinct from the horizontal component of dissociated vertical divergence.

Following these conflicting descriptions, a flurry of reports described dissociated horizontal deviation in patients with intermittent exodeviations that were larger in one eye or confined to one eye on prism and alternate cover testing.[2-8] In 1990, Romero-Apis and Castellanos-Bracamontes[2] described 6 patients with dissociated horizontal deviation, 3 of whom had been treated with previous strabismus surgery for infantile esotropia. In 1991, Wilson and McClatchey[3] further characterized this condition in a report of 6 patients with dissociated horizontal deviation (3 of whom had also undergone previous strabismus surgery for infantile esotropia). Affected patients manifested a slow, spontaneous, unilateral exodeviation of variable amplitude. Prism neutralization of the exodeviation produced an esodeviation of the fellow eye on alternate cover testing, confirming the dissociated nature of the exodeviation.[3] The exodeviation was often larger during periods of visual inattention. Some patients displayed a positive Bielschowsky phenomenon in the horizontal plane (Figure 4).[3]

In 1992, Romero-Apis and Castellanos-Bracamontes[4] compiled a report of 20 cases (including their initial 6 cases). In my personal communication with Dr Romero-Apis, he confirmed that 17 of these 20 patients had "primary" dissociated horizontal deviation (i.e., without previous strabismus surgery). The other 3 patients had developed consecutive exotropia after surgical treatment for infantile esotropia. This report distinguished dissociated horizontal deviation from other forms of intermittent exotropia on the basis of the coexistent dissociated vertical divergence, latent nystagmus, and sensorial suppression of one eye (even during periods of orthotropia) in the former condition (Table 1).[4] In 1993, Zabalo and associates[6] described 9 cases of dissociated horizontal deviation and confirmed the findings of a positive Bielschowsky phenomenon. These seminal reports advocated limiting surgery to a single lateral rectus muscle in the exodeviating eye (recession with or without a posterior fixation suture) for unilateral cases of dissociated horizontal

deviation. Subsequently, Wilson and colleagues[8] modified these recommendations to include bilateral lateral rectus recessions for cases of so-called bilateral dissociated horizontal deviation or for unilateral dissociated horizontal deviation combined with exotropia.

In 1994, Enke and colleagues[22] performed a retrospective review of patients treated surgically for infantile esotropia. They found dissociated horizontal deviation to be present in 22 of 484 patients, yielding a prevalence of 5%. In a subsequent retrospective study from the same group, Wheeler and associates[23] found dissociated horizontal deviation in 34 of 484 patients (7%) who had undergone surgical correction of infantile esotropia. In 1998, Olson and Scott[24] noted that dissociated horizontal deviation can accompany congenital monocular elevation deficiency. In 2001, Hunter and colleagues[25] described an infantile variant of intermittent exotropia, which they considered to be a form of infantile exotropia. It seems likely that this condition may also overlap with dissociated horizontal deviation, since 46% of patients exhibited dissociated vertical divergence.

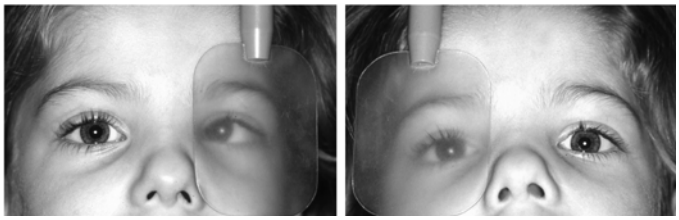

FIGURE 3

Dissociated horizontal deviation manifesting as a large unilateral intermittent esodeviation (courtesy of Michael Gräf, MD).

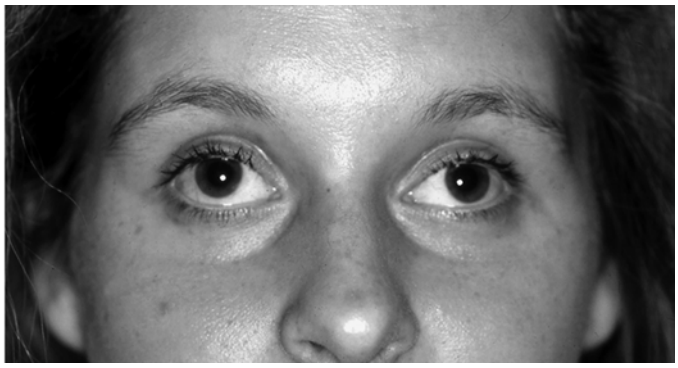

FIGURE 4

Dissociated horizontal deviation. Same patient as in Figure 1 showing bilateral exodeviation during period of visual inattention (courtesy of Michael Gräf, MD).

In 2003, Spielmann and Spielmann[26] applied the term *antinomic* strabismus (antinomy-a contradiction between two equally valid principles or between inferences correctly drawn from such principles)[27(p92)] to patients who display exotropia when one eye is fixating and esotropia when the other eye is fixating. These patients fell into 1 of 4 groups: (1) a primitive exodeviation with an excess of physiologic accommodative vergence; (2) a consecutive exodeviation due to surgical overcorrection of an accommodative esotropia; (3) an infantile exodeviation with dissociated horizontal deviation; and (4) a consecutive infantile exodeviation with dissociated horizontal deviation (corresponding most closely to our cohort).[27,28] In 2005, Gallegos-Duarte[29] found paradoxical cortical responses using digital cerebral mapping in two children with dissociated strabismus. These metabolic responses may have been the effect rather than the cause of dissociated horizontal deviation.

TABLE 1. CLINICAL SIGNS DISTINGUISHING DISSOCIATED HORIZONTAL DEVIATION FROM OTHER FORMS OF INTERMITTENT EXOTROPIA

DISSOCIATED HORIZONTAL DEVIATION	NONDISSOCIATED INTERMITTENT EXOTROPIA
1. Amplitude of exodeviation is dependent on the fixating eye (ie, asymmetrical)	1. Amplitude of exodeviation is independent of the fixating eye (ie, symmetrical)
2. Slow velocity of spontaneous exodeviation	2. Rapid velocity of spontaneous exodeviation
3. Variable amplitude of spontaneous exodeviation	3. Constant amplitude of spontaneous exodeviation
4. Positive Bielschowsky phenomenon	4. Negative Bielschowsky phenomenon
5. Associated latent nystagmus and torsional ocular rotations, prominent dissociated vertical divergence	5. No associated latent nystagmus or torsional ocular rotations, little if any dissociated vertical divergence
6. Positive reversed fixation test	6. Negative reversed fixation test

In 2007, Merriam and Kushner[30] described *antipodean* strabismus in a disparate group of older patients who had esotropia with one eye fixating and exotropia with the other eye fixating, yet lacked dissociated signs of congenital strabismus. It is unclear whether antipodean strabismus and dissociated horizontal deviation share the same pathophysiology. Buckley and Seaber[31] have noted that children with perinatal brain injury may display a *dyskinetic* strabismus, in which the position of the eyes varies between esotropia and exotropia. Given the diminished visual acuity and poor fixation responses in these children, it may be difficult to determine whether this fluctuating horizontal deviation is truly dissociated.

The major difficulty in establishing the diagnosis of dissociated horizontal deviation is that many cases of unilateral or

asymmetrical exodeviation are attributable to other conditions (Table 2).[32,33] Following strabismus surgery for infantile esotropia, a slipped, excessively recessed, or weak medial rectus muscle or a tight lateral rectus muscle can produce an exodeviation, which changes amplitude when the fixating eye is switched. [7,8,22,23] This scenario is suggested by a greater diminution of adduction in one eye, with a correspondingly larger exodeviation in the corresponding field of gaze. Because dissociated horizontal deviation is so often diagnosed in patients who develop exotropia following strabismus surgery for infantile esotropia, this diagnostic distinction is critical.

An unequal horizontal deviation simulating dissociated horizontal deviation may also be due to unequal accommodation in the two eyes.[34] When testing for dissociated horizontal deviation, the full cycloplegic refraction must be provided to prevent an unequal accommodative convergence caused by an uncorrected anisometropia.[32,33] For example, a patient with anisohyperopia (plano OD; +5.00 OS) may show 15 prism diopters (Δ) of exotropia when fixating with the right eye, and 10Δ of esotropia (secondary to accommodative convergence) when fixating with the left eye. To confirm the diagnosis of dissociated horizontal deviation, the head position, direction of gaze, fixation distance, and degree of accommodation must all remain unchanged as fixation switches from one eye to the other.[32,33]

TABLE 2. DIFFERENTIAL DIAGNOSIS OF DISSOCIATED HORIZONTAL DEVIATION

Uncorrected anisometropia
Accommodative esotropia with baseline exotropia
High AC/A ratio with baseline exotropia
Monocular accommodative paresis
Convergence substitution
Extraocular muscle weakness or restriction
Infantile nystagmus with convergence blockage
Dyskinetic strabismus
Antipodean strabismus.
Third-nerve palsy with cyclic spasm

Although dissociated horizontal deviation now has a clear clinical profile, its pathogenic mechanism remains elusive. Fundamental sensorimotor factors that dictate its asymmetry have not been systematically examined. In the discussion that follows, I will attempt to provide a unifying sensorimotor mechanism to explain dissociated horizontal deviation.

ROLE OF REVERSED FIXATION TESTING IN DIAGNOSIS OF DISSOCIATED HORIZONTAL DEVIATION

The reversed fixation test was devised by Mattheus and colleagues[35-37] as a clinical technique to visualize the dissociated component in patients with dissociated vertical divergence. The reversed fixation test must be preceded by the prism and alternate cover test, which is used to neutralize the observed hyperdeviation of one eye. The reversed fixation test is then performed by instructing the patient to continue fixating through the prism with the hyperdeviated eye, then shifting the occluder to again cover the prismatically neutralized eye. The eye without the prism is then observed for a downward refixation movement, which is said to be indicative of dissociated vertical divergence. Since a dissociated hyperdeviation will increase slowly over several seconds, the occluder must be held in front of each eye for at least 5 seconds before shifting it to the opposite eye. A paretic or restricted extraocular muscle will not produce a positive reversed fixation test (defined as the presence of any vertical movement) because the vertical deviation has already been neutralized for that position of gaze. In infantile strabismus, the reversed fixation test is particularly useful for distinguishing dissociated vertical divergence from the nondissociated vertical divergence caused by primary oblique muscle overaction.[37]

In 2001, Gräf[32,33] promulgated the reversed fixation test as the decisive diagnostic test for dissociated horizontal deviation. This test allows the examiner to visualize a dissociated component without inducing any positional change in the fixating eye. When a horizontal refixation movement is seen, the diagnosis of dissociated horizontal deviation is established[1,38] (Figures 5 and 6). The reversed fixation test provides two advantages to routine prism and alternate cover testing for the diagnosis of dissociated horizontal deviation. First, it assures that an incomitant horizontal deviation will not be misdiagnosed as dissociated. Second, it allows the examiner to identify dissociated horizontal deviation in the presence of a seemingly constant exodeviation.

Figure 5 depicts a positive reversed fixation test *in an esotropic patient* who manifests a 30Δ left esotropia in primary gaze and 40Δ right esotropia in primary gaze. For this example, we will assume that no baseline exodeviation exists and that the patient has a fixation preference for the right eye. The two eyes are depicted as viewed from above the patient. The top left figure depicts the preferred right eye fixating in primary position with 30Δ of esotropia in the left eye. The middle left figure depicts the prismatically neutralized position of the left eye in 30Δ of adduction. The lower left figure depicts the final step of the reversed fixation test, in which the cover is again shifted to the left eye, causing the preferred right eye to make a 10Δ abduction refixation saccade. The top right figure depicts the nonpreferred left eye fixating in primary position with 40Δ esotropia in the right eye. The middle right figure depicts the prismatically neutralized position of the right eye in 40Δ adduction. In this position, the right eye exerts 10Δ of esotonus, driving the left eye into 10Δ of exodeviation under the cover. The lower right figure depicts the reversed fixation test, in which the cover is shifted to the right eye, causing the nonpreferred left eye to make a 10Δ adduction refixation saccade. This example reveals

the two fundamental characteristics of the reversed fixation test: first, that the refixation movement in the final step of the reversed fixation test represents *the difference* in the amount of esotonus that is generated by monocular fixation with either eye; and second, that the direction of movement is equal and opposite in the two eyes.

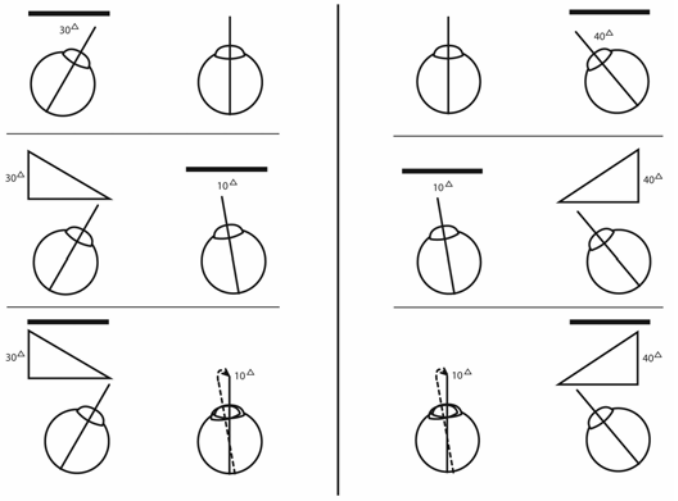

FIGURE 5

Reversed fixation test for esodeviation. The two eyes are depicted with no baseline deviation as viewed from the top of the head. Left panel: Top, The neutralized left esodeviation during right eye fixation. Middle, An esodeviation of the right eye when the left eye fixates in its prismatically neutralized position. Bottom, The reversed fixation test, which elicits an abduction refixation movement of the preferred eye. Right panel: Same sequence showing how the reversed fixation test elicits an adduction refixation movement of the nonpreferred eye.

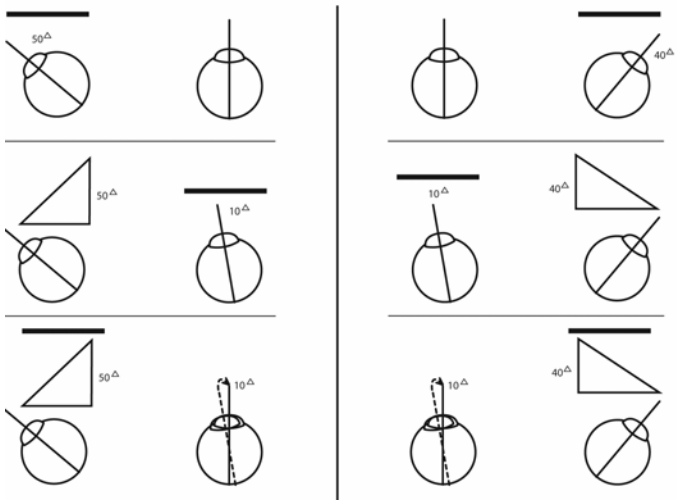

FIGURE 6

Reversed fixation test for exodeviation. The two eyes are depicted with a large baseline deviation as viewed from the top of the head. Left panel: Top, The neutralized left exodeviation during right eye fixation. Middle, An esodeviation of the right eye when the left eye fixates in its prismatically neutralized position. Bottom, The reversed fixation test, which elicits an abduction refixation movement of the preferred eye. Right panel: Same sequence showing how the reversed fixation test elicits an adduction refixation movement of the nonpreferred eye.

Figure 6 depicts a positive reversed fixation test *in an exotropic patient* who conforms to the patients included in the present study. For this example, we will assume that the patient has a consecutive exotropia that measures 50Δ when the right eye is fixating in primary position and 40Δ when the left eye is fixating in primary position. We will also assume that the patient has a fixation preference for the right eye and that the patient displays a baseline exodeviation of 80Δ under nondepolarizing paralyzing general anesthesia. The top left figure shows that when fixating in primary position with the right eye, the left eye shows 50Δ of exotropia (caused by a reduction of the 80Δ baseline exodeviation by the 30Δ esotonus exerted during fixation with the right eye). The middle left figure shows that when the left eye is neutralized in its exotropic position of 50Δ, the right eye shows a 10Δ esodeviation under the cover. This esodeviation occurs because with the left eye fixating in its exotropic position of 50Δ, the baseline exodeviation of 80Δ creates a 30Δ exotropia of the right eye, which is more than offset by the 40Δ esotonus exerted during fixation with the left eye). The bottom left figure depicts the reversed fixation test, wherein a shift of the cover to the left eye produces a 10Δ abduction movement of the right eye.

The top right figure shows the patient fixating with the nonpreferred left eye in primary position, producing 40Δ of exotropia in the nonpreferred right eye (caused by a reduction of the 80Δ baseline exodeviation by the 40Δ esotonus exerted by the left eye). The middle right figure shows that when the occluder is moved to the right eye (with the left eye neutralized in its position of 40Δ exotropia), the right eye has a 10Δ exodeviation under the cover. This exodeviation occurs because with the right eye fixating in its exotropic position of 40Δ, the baseline exodeviation of 80Δ creates a 40Δ exodeviation of the left eye, which is only partially offset by the 30Δ esotonus exerted during fixation with the right eye. The bottom right depicts the reversed fixation test, wherein a shift of the cover to the right eye produces a 10Δ adduction movement of the left eye. This example again shows that the refixation movements of the two eyes are always *equal and opposite* and that they reflect *the difference* in esotonus that is generated by monocular fixation with either eye.

The reversed fixation test is analogous to the swinging flashlight test.[39] Shining light into either eye increases iris sphincter tonus *in both eyes* because of the pupillary light reflex. But swinging the flashlight back and forth from one eye to the other will cause the pupil to dilate in an eye with an optic neuropathy. Does this mean that light increases iris dilator tonus in an eye with optic neuropathy? Of course not; it simply means that because the pupillary light reflex produces a *consensual response*, the act of swinging the flashlight back and forth produces a *weighted* response, so that the amount of sphincter tonus momentarily decreases when the

flashlight is swung from the good eye to the bad eye. The same holds true for the horizontal refixation movement that is elicited by the reversed fixation test. This movement reflects the *weighted* response of the dissociated esotonus exerted by each of the two eyes during monocular fixation. In the same way that the swinging flashlight test makes it possible to visualize an afferent pupillary defect when the speed and amplitude of pupillary contraction are similar in each eye, the reversed fixation test makes it possible to visualize the difference in the balance of esotonus that is exerted by monocular fixation with each eye. Like the swinging flashlight test, the reversed fixation test is a more sensitive clinical tool because any imbalance in monocular esotonus results in a clearly visible movement of the uncovered eye. In this way, the reversed fixation test educes the key clinical sign on which one makes the diagnosis of dissociated horizontal deviation. The small size of the refixation movement in the reversed fixation test does not mean that the amount of esotonus exerted by monocular fixation with either eye is also small. It is only the *difference in esotonus* that is exerted by monocular fixation with either eye that determines the size of the refixation movement in the reversed fixation test.

In the reversed fixation test, fixation through the neutralizing prism with the eye that exerts greater esotonus will induce an *abduction movement* of the contralateral eye, while fixation through the prism with the eye that exerts less esotonus will induce an equal adduction movement of the contralateral eye. These associated movements occur because the eye that manifests a greater degree of exotropia when the contralateral eye is fixating must also be the one that generates greater esotonus when it takes up fixation. When fixating through a prism in its more exotropic position, it will drive the contralateral eye inward past midline, both because of its more exotropic fixational position and because of the greater esotonus that it exerts. Conversely, the less exotropic eye is, by definition, the eye that generates less esotonus when it takes up fixation. When fixating through a prism in its less exotropic position, it will fail to drive the contralateral eye inward past midline, both because of its less exotropic fixation position and because of the lesser esotonus that it exerts. From this analysis, we can use our clinical examination to determine whether the preferred eye or the nonpreferred eye generates greater esotonus in patients with dissociated horizontal deviation.

METHODS

We sought to use the reversed fixation test to determine the prevalence of dissociated horizontal deviation in a cohort of patients with infantile esotropia who had developed consecutive exotropia after horizontal strabismus surgery. The word *consecutive* means "following one after the other in order, successive."[26(p279)] In historical context, the original definition of *consecutive exotropia* referred only to exotropia that *developed spontaneously* from an initial esotropia.[40,41] By contrast, the term *secondary exotropia* originally applied to the postsurgical transformation of a constant esotropia to a constant exotropia. Over the past 50 years, the definition of consecutive exotropia has been expanded to include patients who develop exotropia after surgical correction of esotropia. In this treatise, I adhere to the current usage of the term *consecutive exotropia* as an exotropia that develops postoperatively following surgical correction of an esotropia.

Between January 2003 and November 2006, Ms Katherine J. Fray, CO, and I prospectively examined 28 patients with consecutive exotropia for the presence of dissociated horizontal deviation. Since many reported cases of dissociated horizontal deviation have been described in patients with consecutive exotropia, we reasoned that some patients with consecutive exotropia may show a positive reversed fixation test even when overt clinical signs of dissociated horizontal deviation are not apparent. We also wished to assess the role of fixation with the dominant vs. the nondominant eye on the size of the horizontal deviation. Jampolsky[42] has observed that some patients with strabismus may prefer fixating with the eye that has poorer visual acuity. We therefore assigned the dominant eye as the preferred eye for fixation rather than the eye with eye with higher visual acuity.

Consecutive exotropia was diagnosed when we found a constant or intermittent exodeviation that exceeded 12Δ at distance or near, using the simultaneous prism and cover test. Once consecutive exotropia was diagnosed, we used the prism and alternate cover test to determine the size of the exodeviation with each eye fixating in primary position. We then documented the presence and direction of any horizontal refixation movement that was evoked by the reversed fixation test.[1,38] The reversed fixation test was performed during distance fixation at 6 m, and with the cycloplegic refraction in place, to eliminate any confounding effect of diminished accommodation in the nonpreferred eye.

At the inception of the study, our goal was only to determine the presence and direction of any horizontal refixation movement elicited by the reversed fixation test when the nonpreferred eye was fixating through the prism in its neutralized position. Shortly thereafter, we began performing the reversed fixation test with each eye fixating through the prism, to determine the relative effects of fixation with the preferred and nonpreferred eye upon the size and direction of the dissociated movement. We also began using prism neutralization to measure the size of the dissociated component evoked by the reversed fixation test.

We routinely recorded the presence or absence of adduction weakness, assigning a value of -½ to correspond to 90% adduction, -1 to correspond to 80% adduction, and -2 to correspond to 60% adduction**.** We documented the presence or absence of latent nystagmus and dissociated vertical divergence. Latent nystagmus was defined as a conjugate, horizontal, jerk nystagmus with a fast phase in the direction of the fixating eye, and with an amplitude that increased when the fixating eye was moved into an abducted position. Patients who exhibited a manifest form of latent nystagmus under binocular conditions were classified as having latent nystagmus. Dissociated vertical divergence was defined as an alternating hyperdeviation of the occluded eye, or a hyperdeviation of one eye without a corresponding hypodeviation of the contralateral eye. We also documented the presence or absence and characteristics of any associated neurologic disease.

We also looked for changes in the angle of the exodeviation during periods of patient inattention to determine how the exodeviation changed when fixation was suspended. In patients who were subsequently treated with additional horizontal strabismus surgery, we examined the position of the eyes under nondepolarizing paralyzing anesthesia to determine how the clinical

measurements corresponded to the baseline exodeviation of the eyes when innervational forces were suspended.

We excluded patients with congenital nystagmus with or without associated sensory visual loss to avoid the potential confounding effects of active convergence blockage. We also excluded patients in whom the reversed fixation test could not be performed because of age, short attention span, ocular or central nervous system disease causing reduced vision in one or both eyes, or dense amblyopia precluding central fixation in one or both eyes. Statistical analysis was performed using Fisher's exact test.

This study was approved by the Institutional Review Board for the University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Arkansas.

RESULTS

Fourteen of 28 patients (50%) with consecutive exotropia were found to have dissociated horizontal deviation, as demonstrated by a positive horizontal reversed fixation test (Table 3). In these patients, the measured amplitude of the final refixation movement ranged from 2 to 10Δ. In 10 of the 14 patients, the final step of the reversed fixation test showed *an abduction saccade* of the preferred eye (Table 4). In 3 of 14 patients, the final step of the reversed fixation test showed *an adduction saccade* of the preferred eye. In the remaining patient, the movement of the preferred eye was not examined in the final step of the reversed fixation test. In all 8 patients in whom it was tested, the reversed fixation test showed an adduction saccade of the nonpreferred eye. In the reversed fixation test, a significantly greater number of patients displayed abducting saccades vs. adducting saccades of the preferred eye (P = .02, Fisher's exact test).

TABLE 3. CLINICAL FINDINGS IN PATIENTS WITH CONSECUTIVE EXOTROPIA

CASE/AGE/SEX	VA*	PACT	RFT	ADDUCTION	DVD	LN	NEUROLOGIC DISEASE
1/15/M	OD 20/30 **OS 20/20**	16Δ RXT,10Δ RhT 25Δ RXT′,10Δ RhT′	-	OD -1 OS -1/2 to -1	+	-	CP, CVL, PVL
2/12/F	**OD 20/30** OS 20/25	10 Δ RXT 18Δ LXT	+	OD -1/2 OS -1/2	+	-	-
3/11/F	OD 20/200 **OS 20/125**	40Δ RXT 30Δ LXT′	-	OD -1/2 OS -1/2	-	-	CP
4/17/M	**OD 20/20** OS 20/30	30Δ RX(T), 5Δ Rh(T) 25Δ LX(T), 5Δ LH(T) 35Δ RX(T)′, 5Δ Rh(T)′ 30Δ LX(T)′, 5Δ LH(T)′	+	OD -1/2 to -1 OS -1½	+	+	ADHD
5/5/M	OD 20/20 **OS 20/20**	14Δ RX(T) 12Δ LX(T) 18Δ RX(T)′	-	OD -1/2 OS -1/2 to -1	-	-	-
6/15/F	OD <20/400 **OS 20/20**	45Δ RXT, 10Δ RhT 45Δ RX(T)′, 5Δ Rh(T)′	-	OD -1/2 OS full	-	-	-
7/10/M	OD 20/50 **OS 20/50**	30Δ RXT 30Δ LXT 40Δ RXT′ 40Δ LXT′	-	OD -1/2 OS -1/2	-	-	-
8/11/F	**OD 20/15** OS 20/20	45Δ RXT, 3Δ RhT 40Δ LXT, 3Δ LHT 50Δ RXT′, 3Δ RhT′ 45Δ LXT′, 5Δ LHT′	-	OD -1/2 OS -1/2	+	-	-
9/4/F	OD 20/20 **OS 20/20**	20Δ RX(T), 6Δ RH(T) 20Δ LX(T), 6Δ Lh(T) 12Δ RX(T)′	-	OD -1/2 OS -1/2	+	-	Seizures

TABLE 3 (continued). CLINICAL FINDINGS IN PATIENTS WITH CONSECUTIVE EXOTROPIA

CASE/AGE/SEX	VA*	PACT	RFT	ADDUCTION	DVD	LN	NEUROLOGIC DISEASE
10/4/M	**OD 20/20** OS 20/20	20Δ LX(T)	-	OD full OS full	+	-	-
11/10/F	OD 20/40 **OS 20/20**	45Δ LX(T)′ 18Δ RXT, 4Δ RHT 20Δ LXT, 3Δ LhT	+	OD -1/2 OS -1/2	+	-	CP
12/49/F	OD 20/30 **OS 20/30**	20Δ RXT′, 4Δ RHT′ 25Δ LXT′, 4Δ LhT′ 2Δ RXT, 14Δ RhT 9Δ LXT, 20Δ LHT	+	OD -1½ OS -1½	+	-	-
13/4/M	**OD 20/20** OS 20/20	20Δ RXT′, 18Δ RhT′ 10Δ RXT 16Δ LXT, 3Δ LHT	+	OD -1/2 OS -1/2	+	+	-
14/3/F	OD 20/20 **OS 20/20**	16Δ RXT′, 4Δ RhT′ 20Δ LXT′, 3Δ LHT′ 18Δ RXT, 3Δ RhT 18Δ LXT, 3Δ LHT	-	OD -1/2 OS -1/2	-	-	-
15/17/M	**OD 20/20** OS 20/20	25Δ RXT′, 3Δ RhT′ 25Δ LXT′, 3Δ LHT′ 12Δ RXT 16Δ LXT	+	OD -1/2 OS -1/2	+	-	-
16/35/F	OD 20/40 **OS 20/40**	12Δ LXT′ 18Δ RXT 12Δ LXT	+	OD -1/2 OS -1/2	+	-	-
17/8/F	**OD 20/25** OS 20/25	18Δ RX(T)′ 10Δ LX(T)′ 14Δ RXT, 3Δ RHT 14Δ LXT, 1Δ LhT	-	OD -1/2 OS -1/2	+	+	-
18/12/M	**OD 20/25** OS 20/25	3Δ RET′, 1Δ RHT′ 3Δ LET′, 3Δ LHT′ 25Δ LXT, 5Δ LhT	-	OD -1/2 to -1 OS -1/2 to -1	-	-	-
19/23/M	OD 20/40 **OS 20/20**	25Δ LXT′, 2Δ LhT′ 45Δ RXT, 5Δ RHT 40Δ LXT, 5Δ LhT	-	OD -1 OS -1	+	+	-
20/24/F	**OD 20/50** OS 20/125	60Δ RXT, 5Δ RHT′ 57Δ LXT′, 5Δ LhT′ 10Δ RET 8Δ LET	+	OD -1/2 to -1 OS -1½	+	+	ADHD
21/15/F	OD 20/60 **OS 20/40**	18Δ RXT′ 25Δ LXT′ 12Δ RXT, 16Δ RHT 5Δ LXT, 12Δ LhT 30Δ RXT′, 16Δ RHT′ 20Δ LXT′, 14Δ LhT′	+	OD -1/2 OS -1/2	+	+	IVH, hydrocephalus, seizures

TABLE 3 (continued). CLINICAL FINDINGS IN PATIENTS WITH CONSECUTIVE EXOTROPIA

CASE/AGE/SEX	VA*	PACT	RFT	ADDUCTION	DVD	LN	NEUROLOGIC DISEASE
22/19/F	OD 20/60 **OS 20/40**	16Δ RXT, 8Δ RhT 16Δ LXT, 8Δ LHT 30Δ RXT′, 5Δ RhT′	-	OD -1/2 OS -1/2	-	-	-
23/23/M	OD 20/30 **OS 20/20**	20Δ RXT, 5Δ RhT 35Δ LXT, 6Δ LHT 40Δ RXT′, 7Δ RhT′ 65Δ LXT′, 3Δ LHT′	+	OD -1.5 OS -1	+	-	Porencephalic cyst, right hemiplegia, seizures
24/23/F	**OD 20/20** OS 20/20	25Δ RXT, 12Δ RHT 20Δ LXT, 8Δ LhT 35Δ RXT′, 12Δ RHT′ 30Δ LXT′, 8Δ LhT′	+	OD -1/2 OS -1	+	-	Prematurity
25/27/F	**OD 20/25** OS 20/25	25Δ RXT 35Δ LXT	+	OD -1 OS -1	+	+	-
26/10/M	OD 20/20 **OS 20/30**	18Δ XT, 6Δ RhT 25Δ XT′, 6Δ RhT′	-	OD full OS full	-	-	-
27/13/F	**OD 20/20** OS 20/50	30Δ RXT′, 8Δ RhT′	+	OD -1/2 OS -1	-	-	-
28/7/F	OD 20/20 **OS 20/30**	16Δ RXT 16Δ LXT 8Δ RXT′	+	OD full OS -1/2	+	-	-

ADHD, attention-deficit/hyperactivity disorder; CP, cerebral palsy; CVL, cortical visual loss; DVD, dissociated vertical deviation (divergence); IVH, intraventricular hemorrhage; LET, left esotropia; LhT, left hypotropia; Lh(T), intermittent left hypotropia; LHT, left hypertropia; LH(T), intermittent left hypertropia; LN, latent nystagmus; LXT, left exotropia; LX(T), intermittent left exotropia; OD, right eye; OS, left eye; PACT, prism and alternate cover test; PVL, periventricular leukomalacia; RET, right esotropia; RFT, reversed fixation test; RHT, right hypertropia; RH(T), intermittent right hypertropia; RhT, right hypotropia; Rh(T), intermittent right hypotropia; RXT, right exotropia; RX(T), intermittent right exotropia; VA, visual acuity; + sign = present; - sign = absent.
*Bold text indicates preferred eye for fixation.

Primary position measurements of the exodeviation were unequal when the right and left eye were fixating in 12 of 14 patients (86%) with dissociated horizontal deviation and in 3 of the 8 (37.5%) patients without dissociated horizontal deviation in whom primary position fixation with both eyes was measured ($P = .05$, Fisher's exact test). Seven of 14 patients with dissociated horizontal deviation had a greater exodeviation when fixating with the preferred eye in primary position (this calculation includes case 20, who had an esodeviation at distance with a smaller esodeviation of the fixating eye). Two patients with dissociated horizontal deviation (cases 27 and 28) had the same exodeviation with either eye fixating in primary position because of a greater adduction lag in the nonpreferred eye. The remaining five patients with dissociated horizontal deviation (cases 4, 11, 12, 23, 24) had a greater exodeviation when fixating with the nonpreferred eye in primary position. Three of these 5 patients (cases 4, 23, 24) had a greater adduction lag in the nonpreferred eye, which explained the greater exodeviation when the nonpreferred eye was used for fixation. One patient (case 11) had dissociated horizontal deviation and greater exodeviation when fixating with the nonpreferred eye and showed an abduction saccade of the nonpreferred eye in the last step of the reversed fixation test, indicating that fixation with the nonpreferred eye was generating *less* esotonus. The last patient with dissociated horizontal deviation (case 12) showed an abduction saccade of the preferred eye with no asymmetry in adduction between the two eyes.

Primary position measurements of the exodeviation were measured with each eye fixating in 8 of the 14 patients without dissociated horizontal deviation. In the remaining 6 patients, primary position measurements were obtained with only the preferred eye fixating. Five of the 8 patients in whom we had obtained bilateral primary position measurements (cases 7, 9, 14, 17, 22) showed an *equal* exodeviation with each eye fixating, whereas 3 (cases 5,8,19) showed asymmetrical exodeviations. Of the 2 that showed asymmetrical exodeviations, one had a greater exodeviation with the preferred eye fixating secondary to a greater adduction lag in the nonpreferred eye (case 5), and one had a greater exodeviation with the nonpreferred eye fixating despite equal adduction movements (case 19).

We found asymmetrical adduction in 6 of 14 patients with dissociated horizontal deviation (cases 4, 20, 23, 24, 27, 28) vs. 3 of 14 patients without dissociated horizontal deviation (cases 1, 5, 6) ($P = .42$, Fisher's exact test). Seven of these 9 patients with asymmetrical adduction (cases 1, 4, 6, 20, 23, 24, 27) had stronger adduction in the preferred eye, indicating that in patients with asymmetrical adduction, the eye with greater adduction tends to be the preferred eye. The remaining patients without dissociated

horizontal deviation (cases 5 and 28) showed worse adduction in the fixating eye.

TABLE 4: CLINICAL CHARACTERISTICS OF POSITIVE REVERSED FIXATION TESTS

CASE/AGE/SEX	REVERSED FIXATION TEST*
2/12/F	**OD 9Δ abduction saccade**
	OS adduction saccade
4/17/M	**OD 6Δ abduction saccade**
	OS 4Δ adduction saccade
11/10/F	OD 4Δ abduction saccade
	OS adduction saccade
12/49/F	OD NT
	OS abduction saccade
13/4/M	**OD abduction saccade**
	OS NT
15/17/M	**OD NT**
	OS adduction saccade
16/35/F	OD 6Δ adduction saccade
	OS 10Δ abduction saccade
20/24/F	**OD 3Δ adduction saccade**
	OS No movement
21/15/F	OD 8Δ adduction saccade
	OS 2Δ abduction saccade
23/23/M	OD NT
	OS abduction saccade
24/23/F	**OD 2Δ adduction saccade**
	OS 4Δ abduction saccade
25/27/F	**OD 4Δ abduction saccade**
	OS 7Δ adduction saccade
27/13/F	**OD 8Δ abduction saccade**
	OS 4Δ adduction saccade
28/7/F	OD 4Δ adduction saccade
	OS 6 Δ abduction saccade

NT, not tested; OD, right eye; OS, left eye.
*Bold text indicates preferred eye for fixation.

Nineteen of the 28 patients (68%) had dissociated vertical divergence, and 7 of the 28 patients (25%) had latent nystagmus. The prevalence of dissociated vertical divergence was significantly higher in patients with dissociated horizontal deviation (13 of 14 = 93%) compared to those patients without dissociated horizontal deviation (6 of 14 = 43%) (P = .01, Fisher's exact test). The prevalence of latent nystagmus was not significantly higher in patients with dissociated horizontal deviation (5 of 14=36%) compared to patients without dissociated horizontal deviation (2 of 14 = 14%) (P = .38, Fisher's exact test). It was common for patients with a positive reversed fixation test to have an exodeviation that appeared to be much larger on casual inspection than it measured using prism alternate cover testing.

A history of neurologic disease was present in 6 of 14 patients (43%) with dissociated horizontal deviation and in 3 of 14 patients (21%) without dissociated horizontal deviation (P = .42, Fisher's exact test) (Table 2).

ILLUSTRATIVE CASE (CASE 25)

A 27-year-old woman was referred for treatment of a long-standing consecutive exotropia. Her eyes had crossed shortly after birth, and she had undergone bilateral strabismus surgery at 2 years of age. Postoperatively, her eyes were initially aligned but her left eye soon began drifting outward. Her exodeviation gradually became constant, but she noted no diplopia. She was the full-term product of an uncomplicated pregnancy, labor, and delivery and was neurodevelopmentally normal.

On examination, corrected visual acuity was 20/25 OU. She preferred fixation with the right eye. Both pupils reacted normally to light with no afferent pupillary defect. She had an A-pattern with 4+ superior oblique muscle overaction in the right eye and 1+ superior oblique overaction in the left eye. She had a -1 adduction lag in both eyes. Prism and alternate cover testing at 6 m disclosed 35Δ left exotropia and 18Δ of dissociated vertical divergence when fixating with the preferred right eye, and 25Δ of right exotropia and 12Δ of dissociated vertical divergence when fixating with the nonpreferred right eye. The horizontal reversed fixation testing disclosed a 4Δ abduction saccade of the right eye and 7Δ adduction saccade of the left eye. Cycloplegic refraction was -1.75 +1.25 ×

60 degrees in the right eye and -1.50 sphere in the left eye. Retinal examination disclosed mild intorsion of both eyes.

Under nondepolarizing, paralyzing, general anesthesia, each eye showed a symmetrical baseline exodeviation of 90Δ, as estimated by light deflection through prisms held over both eyes. Surgical exploration disclosed medial rectus muscles inserted 10 mm from the limbus. She was treated with bilateral medial rectus muscle advancement and bilateral superior rectus muscle recession.

Comment. This case history illustrates the prototypical clinical findings of consecutive exotropia combined with dissociated horizontal deviation. The patient has an exodeviation that is greater when she fixates with the preferred eye. The reversed fixation test showed an abduction saccade of the preferred eye and an adduction saccade of the nonpreferred eye. Since adduction was symmetrical bilaterally, the asymmetrical exodeviation cannot be attributed to an asymmetrical medial rectus weakness. The much larger baseline exodeviation under general anesthesia, together with the results of the reversed fixation test, illustrate how fixation with either eye exerts a large-amplitude esotonus, and how fixation with the nonpreferred eye exerts greater esotonus than fixation with the preferred eye.

DISCUSSION

NEW FINDINGS

Using the reversed fixation test, we found that dissociated horizontal deviation lies buried away within a consecutive exotropia in 50% of patients who have a history of infantile esotropia. By providing a novel clinical tool for distinguishing dissociated horizontal deviation from the secondary effects of asymmetrical postoperative medial rectus muscle weakness, the reversed fixation test confirms the existence of dissociated horizontal deviation as an entity *sui generis.* Furthermore, it expands the clinical spectrum of dissociated horizontal deviation to include patients with consecutive exotropia who show no difference in the measured exodeviation when each eye is used to fixate in primary position.

Our findings support the conclusion that monocular fixation generates dissociated esotonus in patients with dissociated horizontal deviation.[28,32] Several lines of evidence point to this conclusion. First, under nondepolarizing paralyzing general anesthesia, the eyes of patients with dissociated horizontal deviation display a large baseline exodeviation that far exceeds the measured exodeviation (Figure 7). Given that suspension of tonic innervation results in a large-angle exotropia, it follows that any innervational component must augment esotonus to produce a smaller intermittent exodeviation (or esodeviation) in the awake state. Second, patients with dissociated horizontal deviation tend to exhibit a larger angle of exotropia when visually inattentive.[3] Since the degree of exodeviation that is apparent with visual inattention (e.g., when the patient is asked to remember an event 24 hours ago or to solve a mathematical task) is often visibly larger than that measured when either eye is used to fixate, it follows that monocular fixation must augment esotonus.[32] Such periods of "nonfixation" may only partially unmask the baseline exodeviation that would be present under nondepolarizing paralyzing general anesthesia.

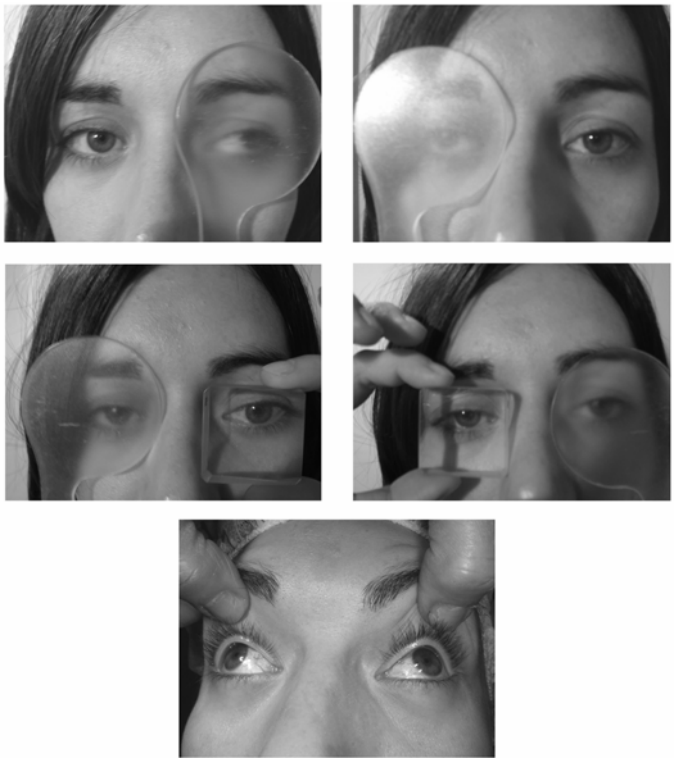

FIGURE 7

Dissociated horizontal deviation. Top, The patient shows a greater exodeviation when the preferred right eye is used for fixation. Middle left, A small esodeviation of the right eye after the left exodeviation has been prismatically neutralized. Middle right, A small exodeviation of the left eye after the right exodeviation has been prismatically neutralized. The refixation movement in the final step of the reversed fixation test will therefore consist of a small abduction saccade in the preferred right eye and a small adduction saccade in the nonpreferred left eye. Bottom, Patient under nondepolarizing paralyzing anesthesia showing large baseline bilateral exodeviation (courtesy of Susana Gamio, MD).

Finally, dissociated horizontal deviation does not manifest only as an intermittent exodeviation. Spielmann's seminal report of dissociated horizontal deviation in a cohort of patients with intermittent *esodeviation* of one eye demonstrates how this dissociated esodeviation can be superimposed upon any baseline horizontal position.[18] Spielmann's use of bilateral translucent occluders to equalize visual input and block fixation revealed a baseline orthoposition in the absence of sensory dissociation.[18] The fact that dissociated horizontal deviation can manifest as a dissociated *esodeviation* (when the baseline position of the eyes is straight), or a dissociated *exodeviation* (when the baseline position of the eyes is one of exodeviation), again shows that fixational innervation must augment *esotonus*.

We also found that fixation with the nonpreferred eye usually exerts greater esotonus than fixation with the preferred eye. In 10 of 14 patients with dissociated horizontal deviation, the preferred eye showed an abduction saccade in the final step of the reversed fixation test (Table 4). Previous clinical descriptions[3-8] and electro-oculographic studies[20,32] of patients with dissociated horizontal deviation have also documented a switch from exotropia to esotropia as occurring when fixation is switched to the nonpreferred eye. As discussed below, these results cannot be attributed to the effects of asymmetrical adduction, demonstrating that dissociated esotonus coexists as a distinct condition. This pathogenic mechanism explains how a patient with dissociated horizontal deviation can display an exodeviation of the nonpreferred eye and an "antinomic" esodeviation of the preferred eye.[27,28] Dissociated horizontal deviation produces the equivalent of a primary deviation during fixation with the preferred eye and a secondary deviation during fixation with the nonpreferred eye. Since dissociated horizontal deviation can be evoked in the absence of any movement of the fixating eye, however, the concept of Hering's law cannot be extrapolated to this dissociated phenomenon.

Because dissociated esotonus is made visible only by the reversed fixation test, the fundamental connection between dissociated esotonus and infantile strabismus has gone unrecognized. Our findings indicate that dissociated esotonus, dissociated vertical divergence, and latent nystagmus constitute a trilogy of dissociated ocular motor responses to unequal visual input. Primary oblique muscle overaction, while driven by similar visuo-vestibular input, does not behave as a dissociated movement, in that it does not change as a function of relative visual input to the two eyes.[43,44] Far from being uncommon, the 50% prevalence of dissociated esotonus in our cohort of patients with consecutive exotropia approximates the 40% to 90% range of estimates for dissociated vertical divergence in infantile esotropia.[45-49] This prevalence supports the original contention of Raab[17] that these two dissociated deviations are part of a single continuous spectrum.

Wilson[7] has coined the term *dissociated strabismus complex* to emphasize that the dissociated eye movements that accompany infantile strabismus can be predominantly vertical, horizontal, or torsional. This concept derives direct support from the finding of a positive Bielschowsky phenomenon in both dissociated vertical divergence and dissociated horizontal deviation. In dissociated vertical divergence, placement of darkening filters of increasing density before the fixating eye causes the hyperdeviating eye to descend progressively below midline.[3,50] Since the darkened eye maintains fixation, this change cannot be caused by a fixation shift, but results strictly from a change in the balance of luminance to the two eyes. In their seminal observations, Wilson and McClatchey[3] observed that "the outwardly drifted eye returned to and crossed the midline, to become slightly esotropic as the fixating eye received progressively less luminance. In light of our findings, one can speculate that this sensorimotor response may reflect two overlapping mechanisms. Assuming that the preferred eye was used for fixation during the test to simulate real world conditions, then shifting the balance of luminance in favor of the nonpreferred eye would be expected to induce a progressive esodeviation, since the nonpreferred eye evokes relatively greater esotonus. However, it may also be that increasing fixational effort through the dark filter with the preferred eye directly increases esotonus in the same way that inducing fixation with the nonpreferred eye does. We did not test for the Bielschowsky phenomenon as part of our protocol because Gräf[33] has reported it to be difficult to elicit and not as sensitive as reversed fixation testing for establishing the diagnosis.

The frequency of unequal exodeviations did not differ significantly in patients with and without dissociated horizontal deviation. However, the small number of patients without dissociated horizontal deviation who were measured with each eye fixating in primary position may have limited the power of this study to detect a significant difference. While a difference in the measured exodeviation with each eye fixating in primary position is usually found in patients with dissociated horizontal deviation, it is nevertheless clear that one cannot rely on this difference to establish the diagnosis of dissociated horizontal deviation. As seen in cases 27 and 28, it is possible to have dissociated horizontal deviation, as demonstrated by reversed fixation testing, even when the horizontal deviation is the same when either eye fixates in primary position. This situation occurs when the nonpreferred eye exhibits a greater medial rectus weakness secondary to the previous strabismus surgery. Because of the resulting adduction lag, greater medial rectus innervation becomes necessary to fixate with the nonpreferred eye in primary position. By itself, this "fixation duress" would produce a larger primary position exodeviation of the preferred eye. However, this effect is offset by the greater dissociated esotonus that is simultaneously exerted during fixation with the nonpreferred eye, resulting in no net difference in the measured exodeviations when each eye fixates in primary position. Cases such as these have not been recognized as examples of dissociated horizontal deviation and have not been included in previous clinical descriptions of this condition.

Conversely, 3 patients with dissociated horizontal deviation (cases 4, 23, 24) showed asymmetrical exodeviations with each eye fixating in primary position on the basis of asymmetrical adduction. In these patients, the "fixation duress" caused by diminished adduction in the nonpreferred eye appeared to override the effects of dissociated esotonus, resulting in a larger exodeviation when the nonpreferred eye was used for fixation. These examples illustrate how asymmetry of exodeviation in the primary position is neither necessary nor sufficient to establish the diagnosis of dissociated horizontal deviation, making the horizontal reversed fixation test is the critical diagnostic test for this condition.[1,38]

Regardless of the presence or absence of dissociated horizontal deviation, we found that 7 of the 9 patients (cases 1, 4, 6, 20, 23,

24 27) with asymmetrical adduction preferred fixation with the eye that showed stronger adduction. Since a greater adduction lag in the nonpreferred eye generates a larger exotropia of the *preferred* eye, while dissociated horizontal deviation is usually associated with a greater exotropia of the *nonpreferred* eye, it follows that the effects of asymmetrical adduction must be distinct from those of dissociated horizontal deviation.

From these observations we can begin to construct a sensorimotor profile for the common exotropic form of dissociated horizontal deviation. This patient can spontaneously fluctuate between 4 sensorimotor states: (1) a large bilateral exodeviation that manifests during periods of inattention and nonfixation; (2) a smaller exodeviation that manifests when the preferred eye fixates; (3) an even smaller exodeviation, orthoposition, or esodeviation that manifests when the nonpreferred eye fixates; and (4) approximate ocular alignment during binocular periods when peripheral fusion is exerted. The slow velocity of the exodeviation is explained by the "braking" effect of dissociated esotonus, while its variable amplitude probably reflects momentary fluctuations in fixational effort and depth of suppression.

A corollary clinical sign of dissociated horizontal deviation was the visible discrepancy between the cosmetic exotropia and the measured exotropia (Figures 1 and 4). It was common to find patients with dissociated horizontal deviation who intermittently manifested a large bilateral exodeviation during periods of visual inattention, while displaying measurements within the monofixation range during prism and alternate cover testing. In our experience, the finding of a *simultaneous bilateral* exotropia is a distinguishing clinical sign of dissociated horizontal deviation (Figure 4). For reasons that are unclear, we have not observed this sign in patients with other forms of intermittent exotropia.

Our study demonstrated some intrinsic characteristics of the horizontal reversed fixation test that have profound implications for understanding dissociated horizontal deviation. Our previous model of the reversed fixation test assumed that the observed movement reflected the full amount of monocular esotonus exerted by the eye behind the prism.[1] Because the size of the final refixation movement is generally small, this model would predict that dissociated esotonus produces a relatively small change in horizontal alignment. By mathematically modeling the reversed fixation test with each eye fixating (Figures 5 and 6), we found that the observed refixation movement of each eye approximates the difference in the esotonus exerted by monocular fixation with each eye. The present study modeled the effects of bilateral nonsimultaneous esotonus on the reversed fixation test. When comparing the eye position under nondepolarizing paralyzing general anesthesia with the clinical measurements (Figure 7), it becomes clear that this small difference occurs amidst enormous amplitudes of esotonus that are generated during fixation by either eye. As discussed below, this conclusion has intriguing implications for the potential role of dissociated esotonus in the pathogenesis of infantile esotropia.

The expected result of the reversed fixation test should be an abduction saccade in the eye that generates less esotonus and an equal adduction saccade in the eye that generates greater esotonus. This intrinsic characteristic of the reversed fixation test allows us to subtract out the effect of asymmetrical adduction weakness and deduce that fixation with the preferred eye usually generates less esotonus than fixation with the nonpreferred eye. As seen in Table 4, the amplitude of these opposing movements may differ slightly, probably owing to the effects of fixational effort and intermittent suppression. Since it is the difference in esotonus exerted by monocular fixation with either eye that dictates the size of the movement for each eye, this model also predicts that one should never see a refixation movement in the final step of the reversed fixation test in only one eye. In fact, we observed a unilateral refixation movement in a patient (case 20) who had undergone large recessions of both horizontal muscles in the nonpreferred eye. In this patient, we assume that the appropriate neural signal for the dissociated movement was executed but that previous surgical weakening of both horizontal rectus muscles had eradicated the expected refixation movement in the observed eye. Thus, the effects of previous strabismus surgery can rarely produce a positive reversed fixation test in only one eye.

Our finding that the reversed fixation test generates a refixation movement in both eyes should not be taken to imply that dissociated esotonus is necessarily generated by monocular fixation with either eye. If dissociated esotonus were evoked by fixation with only one eye, a difference in the dissociated esotonus exerted by monocular fixation with either eye would still exist, resulting in a refixation movement of similar amplitude in both eyes. However, a large degree of dissociated esotonus exerted by only one eye would create *a large difference in esotonus* exerted by monocular fixation with either eye and produce a correspondingly large refixation movement in the reversed fixation test. In our study, only small refixation movements (≤10Δ) were observed. This logic suggests that dissociated horizontal deviation, like other dissociated eye movements, is probably evoked to some degree by fixation with either eye. However, Spielmann's observation[18] that some patients exhibit intermittent esodeviation in just one eye leaves this issue open to question.

RELATIONSHIP TO OTHER DISSOCIATED DEVIATIONS

Previous investigations of patients with infantile esotropia have found latent nystagmus in 25% to 52% and dissociated vertical divergence in 40% to 90% of cases.[45-48] It is not known how these observed frequencies vary with age, previous surgical realignment, or the development of consecutive exotropia. The present study found latent nystagmus in 7 of 28 patients (25%), and dissociated vertical divergence in 19 of 28 patients (68%) with consecutive exotropia. In our patients with consecutive exotropia, the prevalence of dissociated horizontal deviation fell between that of latent nystagmus and dissociated vertical divergence. Dissociated horizontal deviation correlated significantly with dissociated vertical divergence but not with latent nystagmus, reinforcing the prevailing notion that dissociated horizontal deviation is a variable component of dissociated vertical divergence.

In several respects, however, dissociated horizontal deviation may be phenomenologically more similar to latent nystagmus. As discussed in the next section, the common evolutionary underpinnings of latent nystagmus and dissociated horizontal deviation may correspond respectively to the version and vergence components of a visually guided turning movement in lateral-eyed animals (i.e.,

both may represent primitive ocular motor responses to horizontal head rotation).[43,51] Using scleral search coil recordings, Guyton and associates[52] documented the coexistence of dissociated esotonus in patients with dissociated vertical divergence, and postulated that dissociated vertical divergence existed solely for the purpose of damping latent nystagmus. In light of our findings, it now seems probable that any horizontal damping of latent nystagmus is an epiphenomenon of the dissociated esotonus that characterizes dissociated horizontal deviation, rather than the result of an elaborate compensatory adaptation to improve visual acuity in latent nystagmus.[31,51] Our findings support Gräf's interpretation that the secondary effect of dissociated horizontal deviation can be to diminish the horizontal component of latent nystagmus.[32] This secondary damping may have contributed to the lack of correlation between dissociated horizontal deviation and latent nystagmus in our study. The other indication of greater mechanistic overlap of dissociated horizontal deviation with latent nystagmus lies in the fact that dissociated esotonus and latent nystagmus both increase to a greater degree when the nonpreferred eye is used for fixation, whereas dissociated vertical divergence is generally larger when the preferred eye is used for fixation, as has long been recognized in cases of unilateral amblyopia.

The association of dissociated esotonus with consecutive exotropia casts doubt on the Zubcov theory[20] that dissociated horizontal deviation results from asymmetric convergence damping of latent nystagmus, by showing that this esodeviation is an epiphenomenon of unequal visual input. As first noted in 1966, by Adelstein and Cüppers, [53] patients with congenital nystagmus can sometimes utilize active convergence to "block" the nystagmus and improve visual acuity. These sustained convergence efforts and the resulting hypertonicity of the medial rectus muscles can rarely lead to a secondary constant esotropia.[53-55] Subsequent electro-oculographic studies by Dell'Osso and colleagues[56] showed that true convergence blockage occurs by 1 of 2 mechanisms. The first mechanism is seen in binocular patients with congenital nystagmus who generate large tonic convergence movements to diminish their congenital nystagmus. The second occurs in binocular patients with congenital nystagmus who generate large tonic convergence movements, which converts the congenital nystagmus to a low-amplitude manifest latent nystagmus.[57] In both groups, the nystagmus intensity is proportional to the angle of the deviation, and the active convergence blockage serves to improve visual acuity. In neither group is latent nystagmus present at the beginning of the active convergence movement, suggesting that latent nystagmus is not an inciting factor for active convergence blockage.

In light of these findings, it is easy to see how the dissociated esotonus that can accompany monocular fixation in these patients has been misconstrued as an active convergence blockage mechanism in latent nystagmus. This conflation of two distinct physiologic mechanisms has led to authoritative statements such as "Infants with high-velocity, latent nystagmus (greater than 1.5 degrees/sec) often have large, variable angles of esotropia. They may superimpose bouts of convergence upon a baseline of esotropia. The convergence dampens [*sic*] the nystagmus velocity and improves visual acuity."[56] Many patients with infantile esotropia and the manifest form of latent nystagmus have undoubtedly been misdiagnosed as having esotropia secondary to active convergence blockage of congenital nystagmus with secondary esotropia.[54] Many authorities have emphasized the importance of distinguishing between the coexistence of infantile esotropia with latent nystagmus, and the active blockage of congenital nystagmus by convergence.[54,56,58,59] Recognition of dissociated esotonus as a distinct physiological process provides an alternative explanation for this phenomenon in patients with latent nystagmus. In summary, the "convergence" that has been noted to accompany latent nystagmus is synonymous with dissociated esotonus. The pieces of the puzzle are coming together.

EVOLUTIONARY UNDERPINNINGS

Dissociated horizontal deviation has its origins in the primitive visual reflexes that utilize binocular visual input to modulate ocular motor and postural tonus in lower animals.[44] In afoveate lateral-eyed animals, primitive subcortical luminance and motion reflexes are modulated globally by peripheral retina. In foveate animals, these peripheral visual reflexes are suppressed as fixation and visual contour come to play an increasing role.[50] As evolution proceeds, cortical reflexes are grafted onto peripheral subcortical mechanisms to coactivate these primitive visual reflexes.[60] Concurrently, primitive reflexes which were originally *adapted* for optimal function in afoveate animals become *exapted* to the foveate system wherein visual form and contour and fixation play the predominant role.[61]

Although lateral-eyed animals lack single binocular vision, each eye receives constant visual input, resulting in a dissociated form of simultaneous binocular vision that is recapitulated in the humans with infantile strabismus.[43] Unequal visual input to the two laterally placed eyes elicits a series of *visuo-vestibular reflexes*. Within the central vestibular system, visual input is summated with labyrinthine input to establish central vestibular tonus, providing the baseline innervational output to the postural and extraocular muscles.[43]

In humans with infantile strabismus, the sensory dissociation resulting from binocular misalignment evokes a similar physiologic response as would a change in the balance of binocular visual input in the lateral-eyed animal.[43] Following surgical realignment of the eyes, fluctuating cortical suppression of one or both eyes can reactivate these visuo-vestibular reflexes to produce dissociated vertical divergence, latent nystagmus, and primary oblique muscle overaction.[43] Although we clinically deconstruct primitive eye movements in humans, these overlapping signs may simply represent different planar manifestations of a single central vestibular disturbance in 3-dimensional space.[43]

Dissociated vertical divergence in humans recapitulates the *dorsal light reflex* in fish and insects, utilizing relative binocular luminance as a sensory stimulus to modulate eye and body position.[50] This visuo-vestibular reflex causes fish and insects to tilt spontaneously toward an overhead light that is shined from one side, providing an accessory mechanism for the animal to use binocular visual input to maintain vertical orientation independent of labyrinthine input.[50] Since the sky serves as a space-stable hemispheric light source, luminance input to the two laterally-placed eyes is equal when the animal is positioned vertically.[62] Unequal luminance input to the two eyes is therefore interpreted as body tilt (with the eye with greater luminance input misdirected toward the

sky), necessitating a postural readjustment and a vertical divergence of the eyes.[50,62] This visual reflex also operates in the pitch plane to produce a conjugate torsion of the laterally-placed eyes toward a light source that is shined overhead from the front or the back of the animal.[44] Reactivation of these primitive visual reflexes in humans with infantile strabismus appears to manifest as dissociated vertical divergence (in the roll plane) and primary oblique muscle overaction (in the pitch plane).[43,44,50]

During body rotation, the final vestibulo-ocular response consists of a *labyrinthine* component (which induces equal movement of the eyes) and an *optokinetic* component (which allows the nasally moving visual field to dictate the movement of both eyes).[51,62-65] Lateral-eyed animals display a striking *nasotemporal asymmetry* to optokinetic targets, wherein nasally moving rotations of the visual world generate much stronger optokinetic responses than temporally moving rotations.[51,63-65] Optokinetic nystagmus is a general gaze-stabilizing system that complements the vestibulo-ocular system.[51,64] During a turning movement of the head or body, it is primarily the nasally-directed optokinetic rotation of the visual world (as seen by the leading eye) that directs the optokinetic response of both eyes.[51,64] Monocular nasotemporal asymmetry may be an adaptation that preferentially generates the necessary optokinetic response to stabilize the near visual world on the side to which the animal is turning. During forward translation, the minimal retinal sensitivity to full-field temporal optokinetic rotation also prevents both eyes from rotating posteriorly out of the oncoming frontal field of vision.[51,63-65] These mechanisms provide anticipatory ocular stabilization for navigation, assuring that the animal can see where it is going.

In lateral-eyed animals, horizontal nasotemporal optokinetic responses are greater in the nasally stimulated eye than in the temporally stimulated eye, resulting in a small degree of *convergence* of the two eyes. In rabbits, nasal-to-temporal optokinetic movement evokes a brisk optokinetic response, with an associated convergence of the eyes that is caused by greater slow-phase movement of the stimulated eye.[65] In goldfish, active turning movements elicit repetitive saccadic convergence movements that are punctuated by optokinetic/vestibular counterrotations that place the eyes in a convergent position in the direction of the turn.[66] These unequal ocular rotations produce an anticipatory convergence movement which serves to position the eyes so that at the completion of rotation, the visual world into which the animal is navigating can be viewed through a thin area of binocular overlap in the median plane.

Monocular nasotemporal asymmetry is retained in normal human infants during the first 6 months of life, but this primitive visual motion bias persists indefinitely when infantile strabismus has produced early sensory dissociation.[63,67] Since latent nystagmus is characterized by a conjugate rotation of both eyes that is always nasalward for the fixating eye, it has been proposed that asymmetrical horizontal optokinetic nystagmus in lateral-eyed animals may be the evolutionary analog of latent nystagmus in humans with infantile strabismus.[63,67,68] As discussed below, the anticipatory convergence induced by nasal optokinetic rotation may be the evolutionary forerunner of dissociated horizontal deviation.

In humans with infantile strabismus, primitive afoveate luminance reflexes are still retained, as evidenced by the presence of a positive *Bielschowsky phenomenon*.[3,50] In dissociated horizontal deviation, the increasing esodeviation that is evoked by the placement of progressively darker lenses before the fixating eye demonstrates that peripheral retinal mechanisms subserving luminance continue to function independently of newer central fixational mechanisms. Thus, dissociated horizontal deviation is not purely a foveal function but also a function of peripheral visual input to the two eyes.

ETIOLOGIC IMPLICATIONS

The discrepancy between the size of the large baseline exodeviation observed under general anesthesia, and the much smaller exodeviation (or antinomic esodeviation) measured during prism alternate cover testing, demonstrates that large degrees of dissociated esotonus must be generated by monocular fixation in patients with dissociated horizontal deviation. The amplitudes of dissociated esotonus must far exceed those of dissociated vertical divergence. Yet the small refixation movement evoked by the reversed fixation test (indicative of the difference in esotonus exerted by monocular fixation with either eye) demonstrates that the amplitudes of esotonus exerted by each of the two eyes must also be fairly similar. These findings have intriguing implications for the pathogenesis of infantile esotropia, which displays a large-angle, symmetrical esodeviation.

Since dissociated deviations almost uniquely accompany infantile strabismus, could infantile esotropia arise from dissociated esotonus? Our results suggest that dissociated esotonus could indeed by responsible for the development of infantile esotropia. Several investigators have noted that shining a light into one eye of an infant induces an adduction movement of the illuminated eye (although there remains controversy as to whether this movement is an adduction movement, a version movement, or a combination of the two; and whether it is modulated by nasal or temporal hemiretinal input).[60,69,70]

Contrary to the antiquated stereotype of "congenital" esotropia as a large-angle deviation that is present at birth, most cases of "congenital" esotropia are now recognized to be acquired (i.e., "infantile").[71,72] The eyes do not simply snap in to their final esotropic position in this condition. Nascent infantile esotropia is an intermittent, variable deviation before 12 weeks of age that either resolves or gradually becomes constant after building in intensity to a large, fixed angle of horizontal misalignment.[71,72] Ing[73] has noted that 50% of patients with infantile esotropia show an increase in the measured angle between the time of first examination and the date of surgery. Clearly, unequal visual input in infancy must produce a gradual and progressive increase in the angle of esotropia. The fact that this esodeviation appears during the early period when stereopsis is developing, but before macular anatomy has matured sufficiently to provide high resolution acuity,[74] suggests that it is actively driven primary by an imbalance in peripheral visual input.

Guyton[75] has invoked *vergence adaptation* and *muscle length adaptation* to explain how a small innervational bias (such as the convergence produced by increased accommodative effort in the presbyopic patient) can build slowly over time into a large constant deviation. Vergence adaptation refers to the learned tonus levels that normally operate to maintain a baseline ocular alignment and

thereby minimize retinal image disparity. According to Guyton, vergence adaptation can allow primitive motor biases to gradually amplify and create strabismic deviations under pathological conditions.[75] Muscle length adaptation refers to the ensuing shortening of extraocular muscles due to loss of sarcomeres that results from perturbations in the normal physiologic effects of vergence adaptation. Our results predict that dissociated esotonus may become the sensorimotor substrate for vergence adaptation. The innervational effects of primitive tonus mechanisms may be especially powerful before the onset of fusional control, allowing primitive visual reflexes to be fully operative in early infancy.[43] Any factor that disrupts binocularity can augment dissociated esotonus, leading over time to a tonic esodeviation that gradually becomes constant. Although this process can ultimately lead to loss of sarcomeres and secondary shortening of the medial rectus muscles, the fact that the eyes straighten almost completely under general anesthesia[75-80] suggests that this mechanical effect plays a minor role in the pathogenesis of infantile esotropia. In this way, the large-angle crossing of the eyes that we recognize as infantile esotropia could represent the final stage of dissociated esotonus. As in many other forms of ocular misalignment, the constant esodeviation that develops over time may eventually obscure the pathogenesis.

Since infantile esotropia seems to be driven by abnormal tonus, dissociated binocular vision in infancy must augment esotonus to gradually alter the baseline position of the eyes to a *convergent* position. Early monocular visual loss is known to generate esotonus and reproduce the same constellation of dissociated eye movements that accompany infantile esotropia.[79] Patients with unilateral congenital cataract often develop large-angle esotropia, latent nystagmus, dissociated vertical divergence, and a head turn to fixate in adduction with the preferred eye.[79] By contrast, early infantile esotropia is often characterized by fairly symmetrical vision in the two eyes, but with alternating suppression of the nonfixating eye. So perhaps dissociated horizontal deviation is not an epiphenomenon of infantile esotropia, but a "footprint in the snow" of the horizontal tonus imbalance that is actually responsible for its inception.

Regarding the pathogenesis of infantile esotropia, Jampolsky[42,70] has emphasized the mechanistic importance of distinguishing between *convergence* as an active binocular function and *esotonus* as a passive innervational output that is centrally driven by greater visual input to one eye. The importance of this distinction lies in understanding that convergence implies a deviation from baseline under normal conditions of sensory input, whereas estonus implies a return to baseline under altered conditions of sensory input. The distinction between convergence (the effect) and esotonus (the cause) lies at the heart of understanding infantile esotropia. Nevertheless, there remains the unfortunate tendency in the strabismus literature to conflate esotonus of the eyes *as a position* with convergence of the eyes *as an active function*.

Recent clinical evidence casts further light on this critical distinction. Horwood and colleagues have recently shown that normal infants display fleeting, large-angle convergent eye movements during the first 2 months of life, *which are predictive of normal ocular alignment*.[81] Furthermore, the prevalence of infantile esotropia tends to increase over the period when the excessive convergence eye movements of infancy are disappearing in normal infants.[82] This time course challenges the dubious assumption that infantile esotropia results from excessive convergence output. A recent haploscopic photorefraction study of infants between the ages of 0 and 12 months found that ocular misalignments in children younger than 4 months of age appear to be unrelated to accommodation and occur more frequently when the infants are viewing monocularly and unable to use binocular fusional mechanisms.[82] The absence of correlation between accommodative behavior and early infantile misalignment also rules out accommodative convergence as a causative factor.[82]

A combination of diagnostic and semantic limitations has nevertheless led to the logical fallacy that excessive output of the convergence system (as we classically define it) must underlie infantile esotropia. Since the eyes in infantile esotropia are clearly "convergent," what is needed is a new category of convergence to encompass the transient and long-term changes in binocular alignment (both vertical and horizontal) that are uniquely generated in infancy by unequal visual input. The primitive visual reflexes that modulate extraocular muscle tonus rely on subcortical binocular pathways that are *unidirectional*, drawing the eyes into a more convergent horizontal position and into a more divergent vertical position relative to their baseline position. The category *visuo-vestibular tonus vergence* most accurately encompasses the unique, multidimensional, stereotypical, reflex extraocular muscle tonus imbalance that ensues when unequal binocular visual input disrupts the development of normal cortical binocular control mechanisms.

Dissociated horizontal deviation disentangles these mechanisms by demonstrating that dissociated esotonus can be superimposed upon an existing exodeviation without regard to fusion, accommodation, disparity, or proximity. The reversed fixation test educes the momentary change in dissociated esotonus brought about by a fixation shift, without inducing any positional change in the fixating eye. Dissociated horizontal deviation tells us that there exists a primitive tonus system, independent of active convergence, that can operate under conditions of unequal visual input to reset eye position to a new baseline "convergent" position.

IMPLICATIONS FOR CLINICAL STRABISMUS MEASUREMENT

Dissociated horizontal deviation comprises 2 fundamental layers of dissociation. Not only is there a level of dissociation between the degree of exotropia when each eye is fixating monocularly in primary position, but there exists a second level of dissociation between the exotropic position of the eyes under conditions of inattention and monocular fixation with the preferred eye under conditions of attention. The reversed fixation test reveals to us the first level of dissociation, whereas the larger exotropia under conditions of general anesthesia discloses the second level of dissociation. Neither level of dissociation contributes directly to the observed differences between Krimsky and prism and alternate cover testing, since monocular fixation is a prerequisite for both of these tests.[83,84]

The existence of dissociated horizontal deviation demonstrates the "Heisenberg uncertainty principle" of infantile strabismus measurement. This principle of quantum physics states that an observer cannot simultaneously know the wavelength and momentum of a particle within a wave packet.[85] In a more general sense, this principle predicts that the act of measuring a given parameter within

a system will influence the resulting measurement. In clinical strabismus measurement, one cannot measure the deviation without controlling fixation, but the act of inducing fixation changes the measurement. During prism and alternate cover testing, the exodeviation can only be measured (horizontal strabismus measurements can only be obtained with one eye fixating), so it is important to remember that the act of monocular fixation can augment esotonus and thereby alter the manifest deviation. The inescapable conundrum seems to be that even though monocular fixation changes the horizontal deviation you are trying to measure, you cannot measure the horizontal deviation unless one eye is fixating.

The existence of dissociated esotonus introduces an important and unappreciated confounding variable into the clinical measurement of infantile strabismus. This dissociated component potentially corrupts any clinical measurement that is obtained when either eye is fixating. Clinically, this confounding variable produces a visible discrepancy between the large baseline exodeviation that is unmasked during periods of nonfixation, and the smaller exodeviation (or antinomic esodeviation) that is measured during monocular fixation.[3]

The consecutive exotropia in our patients usually developed in the setting of a decompensated monofixation syndrome. Although Parks[86] considered monofixation syndrome following strabismus surgery to represent a stable sensorimotor situation, Kushner and associates[87] noted that exotropia within the monofixation range provides less stable sensorimotor outcome than orthotropia or esotropia. Such patients often exhibit a small esodeviation on simultaneous prism cover testing (a measurement based on binocular viewing conditions) and a larger esodeviation on prism alternate cover testing (a measurement based on monocular viewing conditions).[86,88]

Acquired monofixation syndrome is considered to be the rule after "successful" strabismus surgery for infantile esotropia. Since peripheral fusion maintains some degree of ocular alignment in the absence of central fusion, postoperative measurements must be obtained with simultaneous prism and cover testing to avoid disrupting peripheral fusion and inducing an artifactual large esodeviation. It is therefore worth asking whether the effects of dissociated esotonus could also explain the horizontal disparity between phoria and tropia that characterizes monofixation syndrome. In our experience, patients with stable monofixation syndrome do not exhibit a positive reversed fixation test. It seems likely that the presence of long-standing peripheral fusion must somehow suppress or override the clinical expression of dissociated esotonus in the monofixation syndrome (as it seems to do in normal humans).

NOSOLOGIC CONSIDERATIONS

The term *intermittent exotropia* is currently applied both descriptively (an application that would include dissociated horizontal deviation) and diagnostically (an application that would exclude it). By its very nature, however, intermittent exotropia is ultimately a descriptive term, although it comprises many different conditions that have different diagnostic implications. As such, the intermittent exodeviation that manifests in patients with dissociated horizontal deviation should be considered as a distinct form of intermittent exotropia with its own unique pathophysiology (just as the intermittent esodeviation of one eye caused by dissociated esotonus is a unique form of intermittent esotropia).

Many clinical reports have applied the hybrid term "intermittent exotropia/dissociated horizontal deviation," acknowledging some diagnostic ambiguity between the 2 conditions and implying that these conditions often coexist.[3-8] So what are the innervational substrates for these distinct but overlapping categories of intermittent exotropia? The common forms of intermittent exotropia, characterized by a distance exodeviation exceeding the near exodeviation, are believed to result from intermittent binocular fusional control of a baseline exodeviation.[76,89,90] Although Burian believed intermittent exotropia to be caused by an active divergence mechanism,[91] independent studies have found that exotropic patients are approximately 30Δ more exotropic when deeply anesthetized than in the awake state,[79,80] suggesting that intermittent exotropia actually results from intermittent fusional control of a large baseline exodeviation.

When consecutive exotropia is associated with dissociated horizontal deviation, fixation with the better eye superimposes dissociated esotonus on the baseline exodeviation that is induced by strabismus surgery to produce a variable intermittent exodeviation. The difference between intermittent exotropia and dissociated horizontal deviation lies simply in the presence of binocular fusion (which behaves as an all-or-nothing phenomenon in intermittent exotropia) and dissociated esotonus in dissociated horizontal deviation, which functions as an open-loop process without reference to ultimate binocular alignment. Because fixation with the nonpreferred eye exerts greater esotonus during prism and alternate cover testing, the baseline exodeviation can be unilateral, asymmetrical, or antinomic. A more mechanistic designation for this baseline exodeviation associated with dissociated horizontal deviation would be consecutive *exotropia/dissociated esotonus* for postoperative cases, and *primary or secondary exotropia/dissociated esotonus* for virgin cases.

But in recognizing that dissociated horizontal deviation and intermittent exotropia can coexist, are we implicitly recognizing that intermittent exotropia and infantile esotropia can also coexist? At first glance, it is difficult to imagine how these how these 2 diametrical forms of horizontal misalignment would not be mutually exclusive, especially since they occupy 2 opposite ends of a clinical and developmental spectrum. In contradistinction to infantile esotropia, intermittent exotropia usually manifests later in childhood and is notable for the absence of dissociative signs (although small degrees of dissociated vertical divergence can be detected).[92]

Our findings suggest that the exotropic form of dissociated horizontal deviation uniquely embodies the coexistence of the mechanical exodeviating forces that give rise to intermittent exotropia, and the dissociated esotonus that gives rise to infantile esotropia. The common denominator for all conditions that encompass the exotropic form of dissociated horizontal deviation is a

baseline exodeviation in combination with dissociated esotonus. For these 2 conditions to coexist, it is only necessary for the ocular misalignment to have its onset in early infancy. This developmental mechanism explains the co-occurrence of dissociated eye movements with the constant[93,94] and intermittent[25] forms of infantile exotropia, as well as with primary dissociated horizontal deviation.[4] All of these conditions share a common pathophysiology, wherein dissociated esotonus is superimposed upon a baseline exodeviation to produce an intermittent exodeviation that varies in size depending on which eye is used for fixation. In some cases, fixation with the nonpreferred eye exerts sufficient esotonus to override the baseline exodeviation and produce an esotropia. In other cases, some degree of binocular fusion is also present, producing the clinical picture of combined intermittent exotropia and dissociated horizontal deviation. In classifying these disorders pathogenetically, it is critically important to distinguish sensorimotor factors from the different forms of ocular misalignment that they ultimately produce. Dissociated horizontal deviation shows us that these 2 conditions can coexist in the same patient, and that it is only the resultant horizontal deviations and not the underlying conditions that are diametrically opposed.

THERAPEUTIC IMPLICATIONS

Initial treatment recommendations reflected the clinical conceptualization of dissociated horizontal deviation as a unilateral form of intermittent exotropia.[3-8] Early reports advocated limiting surgery to the lateral rectus muscle in the exodeviating eye (recession with or without a posterior fixation suture) for patients manifesting a predominantly unilateral intermittent exotropia, while reserving bilateral lateral rectus muscle recession for cases of so-called bilateral dissociated horizontal deviation or unilateral dissociated horizontal deviation combined with exotropia.[3-8] Thus, if an intermittent exotropia of 25Δ is normally treated with bilateral lateral rectus muscle recessions of 6 mm OU, a dissociated horizontal deviation producing intermittent exotropia in only the left eye would be treated with a left lateral rectus muscle recession of 6 mm.

More recently, Bock and colleagues[95] advocated a combined recess/resect procedure in which the lateral rectus muscle of the exodeviated eye was resected and resutured to the globe in a recessed position to treat dissociated horizontal deviation. This procedure had been developed by Scott[96] to produce a similar effect to the original posterior fixation suture described by Cüppers.[97] This approach was premised on the common misconception that dissociated horizontal deviation either causes or contributes to the lateral incomitance that is observed in some patients following bilateral medial rectus muscle recession. It now appears that the (often delayed) onset of consecutive exotropia is influenced by at least 6 components that are coexpressed to varying degrees: (1) a baseline exodeviation consequent to previous strabismus surgery; (2) the mitigating effects of dissociated esotonus during periods of monocular fixation; (3) normal age-related diminution in binocular convergence in early childhood; (4) relative fragility of peripheral fusion in maintaining large amplitudes of binocular convergence; (5) fixation duress consequent to surgical weakening of the medial rectus muscles; and (6) lateral rectus muscle contracture. While this recess-resect procedure may indeed reduce lateral incomitance caused by medial rectus weakness and secondary lateral rectus muscle tightness, it does not directly treat the dissociated horizontal deviation. Recognizing the fundamental mechanism of dissociated horizontal deviation, Spielmann and Spielmann[27,28] have advocated bilateral lateral rectus recession to treat the baseline exodeviation, in combination with bilateral posterior fixation sutures placed on the medial rectus muscles to treat the dissociated esotonus that is evoked by monocular fixation. Given the coexistence of a baseline exodeviation and increased esotonus, this procedure is mechanistically tailored to the consecutive exotropia/dissociated esodeviation that characterizes dissociated horizontal deviation. However, placement of posterior fixation sutures within the previously recessed medial rectus muscles can be technically difficult.

In reviewing the current treatment approaches for dissociated horizontal deviation, a troubling paradox arises. While bilateral lateral rectus recessions are the common treatment for intermittent exotropia (which usually shows greater exodeviation at distance), they are notoriously ineffective in treating consecutive exotropia (which usually shows greater exodeviation at near).[90] Because postoperative weakness of the medial rectus muscles underlies consecutive exotropia, most surgeons now advocate advancements of one or both medial rectus muscles back to the original insertions for the treatment for this condition.[89,90] But for the exotropic variant of dissociated horizontal deviation (i.e., consecutive exotropia with dissociated esotonus), the prescribed treatment is *unilateral* lateral rectus recession.[3-8] So we go from a situation where bilateral lateral rectus recession *is not enough* to one where it *is too much*. Something is wrong.

The recommendation for unilateral lateral recession originally arose from the notion that dissociated horizontal deviation is essentially a unilateral form of intermittent exotropia. It was undoubtedly reinforced by the fact that the measured angle of dissociated horizontal deviation is generally smaller than that of intermittent exotropia, due to the effects of dissociated esotonus. It was further bolstered by the observation that the preferred eye can become esotropic when the nonpreferred eye is used for fixation. All of these factors led to fears of surgical overcorrection with bilateral surgery. Finally, this treatment approach "self-validated" because unilateral lateral rectus recession produces postoperative measurements indicative of horizontal alignment. Postoperative measurements are routinely obtained with prism and alternate cover testing when the stronger eye is being used for fixation.

But in patients with the exotropic form of dissociated horizontal deviation, dissociated esotonus is actively exerted while the horizontal deviation is being measured, so that the clinical measurement that is obtained effectively masks the residual undercorrection of the baseline exodeviation. If these patients always maintained monocular fixation with the good eye, monocular lateral rectus recession would indeed be satisfactory. Following unilateral lateral rectus recession, patients with dissociated horizontal deviation often complain that one or both eyes continue to drift when they are fatigued or daydreaming. In our experience, unilateral lateral rectus recession produces the illusion that horizontal alignment has been restored during prism and alternate cover testing (which is generally obtained with the preferred eye fixating) while the patient often continues to manifest a troublesome exotropia under

conditions of visual inattention.

Contrary to these recommendations, our treatment strategy has consisted of patching or pharmacologic occlusion of the preferred eye to minimize amblyopia and suppression in the nonpreferred eye, followed by strabismus surgery with the goal of eliminating the baseline exodeviation. We generally treat the combination of consecutive exotropia and dissociated horizontal deviation with bilateral medial rectus advancements (when the near deviation is greater and/or there is adduction lag with lateral incomitance) or large bilateral lateral rectus recessions (when the distance deviation is greater). This approach allows peripheral fusion to once again override the effects of dissociated esotonus. In our experience, once horizontal ocular alignment and binocularity are restored, peripheral fusion suppresses the clinical expression of dissociated esotonus.

LIMITATIONS

This study should be viewed in light of its inherent limitations. First, it is possible that some associations went undetected because of the small sample size. For example, primary position measurements were not always obtained during fixation with each eye, which may have caused the study to miss an association between dissociated horizontal deviation and unequal exodeviations when fixating with each eye in primary position. An association between dissociated horizontal deviation and latent nystagmus could have also gone undetected. Second, the large exodeviation of the eyes under nondepolarizing paralyzing general anesthesia was observed but not measured. The existence of dissociated esotonus would predict a greater difference between the measured and paralyzed eye positions in patients with dissociated horizontal deviation than in those without dissociated horizontal deviation. Third, eye movement recordings were not obtained to measure the exodeviation during periods of binocular occlusion or visual inattention. Eye movement recordings may have shown whether the increase in exodeviation with visual inattention is dependent upon the presence of dissociated horizontal deviation. They may have also disclosed subclinical latent nystagmus in some patients. Finally, treatment results for dissociated horizontal deviation were not examined in this study.

SUMMARY

1. Dissociated horizontal deviation is present in 50% of patients who develop consecutive exotropia following surgical correction of infantile esotropia.
2. The common clinical presentation of dissociated horizontal deviation as an intermittent exodeviation of one eye results from the superimposition of a *dissociated esotonus* upon *a baseline exodeviation*. This mechanism explains how the same dissociated movement can manifest as a unilateral esotropia, a unilateral exotropia, or an antinomic deviation.
3. In dissociated horizontal deviation, fixation with the nonpreferred eye usually exerts a greater degree of esotonus than fixation with the preferred eye.
4. In patients with consecutive exotropia, dissociated horizontal deviation need not be accompanied by unequal exodeviations in primary position. Therefore, a positive reversed fixation test is both necessary and sufficient to confirm the diagnosis of dissociated horizontal deviation.
5. Dissociated horizontal deviation may produce a visible discrepancy between a large baseline exodeviation during periods of visual inattention and the smaller measured exodeviation during periods of monocular fixation.
6. The clinical designation of intermittent exotropia/dissociated esotonus for primary cases, and consecutive *exotropia/dissociated esotonus* for cases following surgical treatment of infantile esotropia, provides an accurate mechanistic description for these conditions.
7. The reversed fixation test proves that changes in dissociated esotonus can result directly from a shift in fixation from one eye to the other. This observation casts doubt on the notion that asymmetrical convergence-blockage of latent nystagmus underlies dissociated horizontal deviation and shows how unequal damping of latent nystagmus can be an epiphenomenon of dissociated esotonus.
8. Dissociated horizontal deviation is rarely problematic when stable peripheral fusion is operative. Thus, any surgical procedure that effectively restores binocular horizontal alignment in the patient who is awake and alert (together with nonsurgical treatment of associated amblyopia) should effectively suppress its clinical expression.
9. Dissociated horizontal deviation uniquely embodies the coexistence of mechanical exodeviating forces that give rise to intermittent exotropia and the dissociated esotonus that may give rise to infantile esotropia.
10. Dissociated esotonus may provide a mechanistic link to the pathogenesis of infantile esotropia.

ACKNOWLEDGMENTS

Funding/Support: This study was supported in part by a grant from Research to Prevent Blindness, Inc.

Financial Disclosures: None.

Other Acknowledgments: Katherine J. Fray, CO, contributed enormously to the preparation of this thesis. Michael Graf, MD, Susana Gamio, MD, Edward Raab, MD, Malcolm Ing, MD, and Burton Kushner, MD, reviewed this thesis and provided numerous insightful comments. Michael Graf, MD, and Susana Gamio, MD, provided the excellent clinical photographs depicting dissociated horizontal deviation. Paula K. Roberson, PhD, graciously and expeditiously performed the statistical analysis.

REFERENCES

1. Brodsky MC, Gräf MH, Kommerell G. The reversed fixation test. A diagnostic test for dissociated horizontal deviation. *Arch Ophthalmol* 2005;123:1083-1087.
2. Romero-Apis D, Castellanos-Bracamontes A. Desviacion horizontal disociada (DHD). *Rev Mex Oftalmol* 1990;64:169-173.
3. Wilson ME, McClatchey SK. Dissociated horizontal deviation. *J Pediatr Ophthalmol Strabismus* 1991;28:90-95.
4. Romero-Apis D, Castellanos-Bracamontes A. Dissociated horizontal deviation: clinical findings and surgical results in 20 patients. *Binoc Vis Q* 1992;7:173-178.
5. Quintana-Pali L. Desviacion horizontal disociada. *Bol Oftalmol Hosp de la Luz* 1990;42:91-94.
6. Zabalo S, Girett C, Domínguez D, Ciancia A. Exotropia intermitente con desviación vertical discodiada. *Arch Oftalmol B Aires* 1993;68:11-20.
7. Wilson ME. The dissociated strabismus complex. *Binocul Vis Strabismus Q* 1993;8:45-46.
8. Wilson ME, Hutchinson AK, Saunders RA. Outcomes from surgical treatment for dissociated horizontal deviation. *J AAPOS 2000*;4:94-101.
9. Santiago AP, Rosenbaum AL. Dissociated vertical deviation. In: *Clinical Strabismus Management. Principles and Surgical Management.* Philadelphia: WB Saunders; 1999:245-246.
10. Prieto-Díaz J, Suza-Dias C. *Strabismus*. 4th ed. Boston: Butterworth-Heinemann; 2000: 216-218.
11. Von Noorden GK. *Binocular Vision and Ocular Motility: Theory and Management of Strabismus.* 5th ed. St Louis: Mosby; 1996:367-368.
12. To cross or not to cross? *Proceedings of the Smith-Kettlewell Ocular Motor Tonus Symposium.* Tiberon, CA, June 2-4, 2006, pp 2-4.
13. Lyle TK. *Worth and Chavasse's Squint. The Binocular Reflexes and Treatment of Strabismus*. Philadelphia: Blakiston; 1950:40-41.
14. Bielschowsky A. Über die Genese einseitiger Vertikalbewegungen der Augen. *Z Augenheilkd* 1904;12:545-557.
15. Bielschowsky A. Die einseitigen und gegensinnigen ("dissoziierten") Vertikalbewegungen der Augen. *Albrecht Von Graefes Arch Ophthalmol* 1930;125:493-553.
16. Bielschowsky A. Disturbances of the vertical motor muscles of the eye. *Arch Ophthalmol* 1938;20:175-200.
17. Raab EL. Dissociated vertical deviation in combined motor anomalies. In: Fells P, ed. *Proceedings of the Second Congress of the International Strabismological Association*. Marseilles: Diffusion Générale de Librairie; 1976:189-193.
18. Spielmann A. Déséquilibres verticaux et torsionnels dans le strabisme précoce. *Bull Soc Ophtalmol Fr* 1990;4:373-384.
19. Spielmann A. A translucent occluder for studying eye position under unilateral or bilateral cover test. *Am Orthopt J* 1986;36:65-74.
20. Zubcov AA, Reinecke RD, Calhoun JH. Asymmetric horizontal tropias, DVD, and manifest latent nystagmus. An explanation of dissociated horizontal deviation. *J Pediatr Ophthalmol Strabismus* 1990;27:59-64.
21. Raab EL. Discussion: Asymmetric horizontal tropias, DVD, and manifest latent nystagmus. *J Pediatr Ophthalmol Strabismus* 1990;27:65.
22. Enke ES, Stewart SA, Scott WE, Wheeler DT. The prevalence of dissociated vertical deviation in congenital esotropia. *Am Orthopt J* 1994;44:109-111.
23. Wheeler DT, Enke ES, Scott WE. Surgical management of dissociated horizontal deviation associated with congenital esotropia. *Binocul Vis Strabismus Q* 1996;11:256-262.
24. Olson RJ, Scott WE. Dissociative phenomena in congenital monocular elevation deficiency. *J AAPOS* 1998;2:72-78.
25. Hunter DG, Kelly JB, Ellis FJ. Long-term outcome of uncomplicated infantile exotropia. *J AAPOS* 2001;5:352-356.
26. Spielmann AC, Spielmann A. Antinomic deviations: esodeviation associated with exodeviation. In: Faber TJ, ed. *Transactions 28th Meeting European Strabismological Association, Bergen, Norway, June 2003*. London: Taylor and Francis; 2004:173-176.
27. *Webster's Ninth New Collegiate Dictionary*. Springfield, MA: Merriam-Webster Inc; 1988.
28. Spielmann AC, Spielmann A. Antinomic horizontal deviations: esodeviation associated with exodeviation. Clinical features and surgery. *J Fr Ophtalmol* 2005;28:481-488.
29. Gallegos-Duarte M: Paradoxical cortical response during the intermittent photo stimulation in the dissociated strabismus. *Cir Cir* 2005;73:161-165.
30. Merriam S, Kushner BJ. Mechanisms causing antipodean strabismus. *J AAPOS* 2007;11:249-253.
31. Buckley E, Seaber JH. Dyskinetic strabismus as a sign of cerebral palsy. *Am J Ophthalmol* 1981;91:652-657.
32. Gräf M. Dissociated horizontal deviations (DHD): terminology, diagnosis and etiology. In: Faber TJ ed. *Transactions: 27th Meeting, European Strabismological Association, Florence, Italy, June 2001*. Lisse, The Netherlands: Swets & Zeitlinger; 2001:105-108.
33. Gräf M. Dissociated horizontal deviations (DHD): terminology and causes. *Klin Monatsbl Augenheilkd* 2001;218:401-405.
34. Gräf M, Becker R, Kloss S: Dissoziierte Naheinstellungstrias mit akkommodativem Konvergenzexzess. *Ophthalmologe* 2004;101:1017-1019.
35. Mattheus S, Deberitz I, Kommerell G. Differentialdiagnose zwischen inkomitierendem und dissoziiertem Schielen. *Arbeitskreis Schielbehandlung Berufsverband der Augenärzte Deutschlands* 1978;10:135-137.

36. Kommerell G, Mattheus S. Reversed fixation test (RFT), a new tool for the diagnosis of dissociated vertical deviation. In: Reinecke RD, ed. *Strabismus II*. Orlando, FL: Grune & Stratton; 1984:721-728.
37. Mattheus S, Kommerell G. Reversed fixation test as a means to differentiate between dissociated and nondissociated strabismus. *Strabismus* 1996;4:3-9.
38. Apatachioae ID, Barar A, Vintila G, Apatachioae C. Dissociation horizontal deviation—a diagnostic problem in strabismus. *Oftalmologia* 2006;50:63-69.
39. Levatin P: Pupillary escape in disease of the retina or optic nerve. *Arch Ophthalmol* 1959;62:768-779.
40. Manley DR. Strabismus: Clinical presentations in surgical procedures. In: Harley RD, ed. *Pediatric Ophthalmology.* Philadelphia: WB Saunders; 1975:237-241.
41. Hurtt J, Rasicovici A, Windsor CE. *Comprehensive Review of Orthoptics and Ocular Motility; Theory, Therapy, and Surgery.* St Louis: CV Mosby; 1972:71.
42. Jampolsky A. Ocular divergence mechanisms. *Trans Am Acad Ophthalmol* 1970;68:808.
43. Brodsky MC. Visuo-vestibular eye movements. Infantile strabismus in three dimensions. *Arch Ophthalmol* 2005;123:837-842.
44. Brodsky MC, Donahue SP. Primary oblique muscle overaction. The brain throws a wild pitch. *Arch Ophthalmol* 2001;119:1307-1314.
45. Lang J. Der kongenitale oder frühkindliche Strabismus. *Ophthalmologica* 1967;154:201-208.
46. Parks MM. Surgical treatment of congenital esotropia. *Trans Am Acad Ophthalmol Otolaryngol* 1972;76:1465-1478.
47. Helveston EM. Dissociated horizontal deviation: a clinical and laboratory study. *Trans Am Ophthalmol Soc* 1981;78:734-779.
48. Noorden von GK. A reassessment of infantile esotropia (XLIV Edward Jackson Memorial Lecture). *Am J Ophthalmol* 1988;1:1.
49. Robb RM, Rodier DW. The variable clinical characteristics and course of early infantile esotropia. *J Pediatr Ophthlamol Strabismus* 1987;24:276-281.
50. Brodsky MC. Dissociated vertical divergence. A righting reflex gone wrong. *Arch Ophthalmol* 1999;117:1216-1222.
51. Miles FA. The sensing of rotational and translational optic flow by the primate optokinetic system. In: Miles FA, Wallman J, eds. *Visual Motion and Its Role in Stabilization of Gaze.* Amsterdam, The Netherlands: Elsevier Science; 1993:393-403.
52. Guyton DL, Cheeseman EW, Ellis FJ, et al. Dissociated vertical deviation: an exaggerated normal eye movement used to damp cyclovertical latent nystagmus. *Trans Am Ophthalmol Soc* 1998;96:389-429.
53. Adelstein FE, Cüppers C. Zum Problem der echten und der scheinbaren Abducenslähmung (das sogenannte "Blockierungssyndrome") in Augenmuskellähmungen, Büch. *Augenarzt* 1966;46:271.
54. Kommerell G. Nystgagmusoperationen zur Korrektur verschiedener Kopfzwangshaltungen. *Klin Monatsbl Augenheilkd* 1974;164:172.
55. von Noorden GK, Munoz M, Wong SY. Compensatory mechanisms in congenital nystagmus. *Am J Ophthalmol* 1987;104:387-397.
56. Dell'Osso LD, Ellenberger CJ, Abel LA, et al. The nystagmus blockage syndrome: congenital nystagmus, manifest latent nystagmus, or both. *Invest Ophthalmol Vis Sci* 1983;24:1580-1587.
57. Tychsen L. Infantile esotropia: current neurophysiologic concepts. In: Rosenbaum AL, Santiago AP, eds. *Clinical Strabismus Management. Principles and Surgical Techniques.* Philadelphia: WB Saunders; 1999:117-138.
58. Spielmann A. Les soi-disant syndromes de blocage: adduction, ésodéviation et elevation dans les strabismus précoces. *Ophtalmologie* 1988;2:1-4.
59. von Noorden GK. *Binocular Vision and Ocular Motility. Theory and Management of Strabismus.* 5th ed. St Louis: CV Mosby; 1996:488.
60. Keiner GBJ. *New Viewpoints on the Origin of Squint; A Clinical and Statistical Study of Its Nature, Cause, and Therapy*. The Hague: Nijhoff; 1951:61-75.
61. Brodsky MC. Do you really need your oblique muscles? Adaptations and exaptations. *Arch Ophthalmol* 2002;120:820-828.
62. Brodsky MC. Dissociated vertical divergence: perceptual correlates of the human dorsal light reflex. *Arch Ophthalmol* 2002;120:1174-1178.
63. Brodsky MC. Latent nystagmus: vestibular nystagmus with a twist. *Arch Ophthalmol* 2004;122:202-209.
64. Wallman J. Subcortical optokinetic mechanisms. In: Miles FA, Wallman J, eds. *Visual Motion and Its Role in Stabilization of Gaze.* Amsterdam, The Netherlands: Elsevier Science; 1993:321-342.
65. Collewijn H. *The Oculomotor System of the Rabbit and Its Plasticity.* Berlin: Springer-Verlag; 1981:49-74.
66. Easter SS, Johns PR, Henckenlively D. Horizontal compensatory eye movements in goldfish (*Carassius auratus*). *J Comp Physiol* 1974;92:23-35.
67. Braddick O. Where is the naso-temporal asymmetry? *Curr Biol* 1996;6:250-253.
68. Kommerell G. Beziehungen zwischen Strabismus und Nystagmus. In: Kommerell G, ed. *Augenbewegungsstörungen, Neurophysiologie und Klinik: Symposion der Deutschen Ophthalmologischen Gesellschaft, Freiburg,1977*. München, Germany: Bergmann;1978:367-373.
69. Mitsui Y, Tamura O. *Strabismus and the Sensorimotor Reflex.* Tokyo: Excerpta Medica; 1986:41-67.
70. Jampolsky A. Unequal visual inputs in strabismus management: a comparison of human and animal strabismus. *Symposium on Strabismus: Transactions of the New Orleans Academy of Ophthalmology*. St Louis: CV Mosby; 1978:422-425.

71. Pediatric Eye Disease Investigator Group. The clinical spectrum of early-onset esotropia: experience of the congenital esotropia observational study. *Am J Ophthalmol* 2002;133:102-108.
72. Pediatric Eye Disease Investigator Group. Spontaneous resolution of early-onset esotropia: experience of the congenital esotropia observational study. *Am J Ophthalmol* 2002;133:109-118.
73. Ing MR. Progressive increase in the quantity of deviation in congenital esotropia. *Trans Am Ophthalmol Soc* 1994;92:117-131.
74. Fawcett SL, Wang YZ, Birch EE. The critical period for susceptibility of human stereopsis. *Invest Ophthalmol Vis Sci* 2005;46:521-525.
75. Guyton DL. Changes in strabismus over time: the roles of vergence tonus and muscle length adaptation. *Binocul Vis Strabismus Q* 2006;21:81-92.
76. Roth André, Speeg-Schatz. *Eye Muscle Surgery. Basic Data, Operative Techniques, Surgical Strategy*. Masson, Paris: Swets & Zeitlinger; 1995:283-324.
77. Jampolsky A. Strabismus and its management. In: Taylor DS, Hoyt CS, eds. *Pediatric Ophthalmology and Strabismus*. 3rd ed. London: Elsevier Saunders; 2005:1001-1010.
78. Thouvenin D, Nogue S, Fontes L, Norbert O. Strabismus after treatment of unilateral congenital cataracts. A clinical model for strabismus physiopathogenesis? In: de Faber, ed. *Transactions 28th European Strabismological Association Meeting, Bergen, Norway, 2003*. London: Taylor and Francis; 2004:147-152.
79. Apt L, Isenberg S. Eye position of strabismic patients under general anesthesia. *Am J Ophthalmol* 1977;84:574-579.
80. Romano P, Gabriel L, Bennett W, et al. Stage I intraoperative adjustment of eye muscle surgery under general anesthesia: consideration of graduated adjustment. *Graefes Arch Clin Exp Ophthalmol* 1988;226:235-240.
81. Horwood A. Too much or too little: neonatal ocular misalignment frequency can predict lateral abnormality. *Br J Ophthalmol* 2003;87:1142-1145.
82. Horwood AM, Riddell PM. Can misalignments in typical infants be used as a model for infantile esotropia? *Invest Ophthalmol Vis Sci* 2004;45:714-720.
83. Aouchiche K, Dankner SR. What's the difference? Krimsky vs alternate cover testing. *Am Orthopt J* 1988;38:148-150.
84. Choi RY, Kushner BJ. The accuracy of experienced strabismologists using the Hirschberg and Krimsky tests. *Ophthalmology* 1998;105:1301-1306.
85. Capra F. *The Tao of Physics*. Boston: Shambhala; 1999:158-159.
86. Parks MM. The monofixation syndrome. *Trans Am Acad Ophthalmol Soc* 1969;67:609-657.
87. Kushner BJ, Fisher M. Is alignment within 8 prism diopters of orthotropia a successful outcome for infantile esotropia surgery? *Arch Ophthalmol* 1996;114:176-180.
88. Jampolsky A. Esotropia and convergent fixation disparity of small degree: differential diagnosis and management. *Am J Ophthalmol* 1956;41:825-833.
89. Kushner BJ. Exotropic deviations: a functional classification and approach to treatment. *Am Orthopt J* 1988;38:81-93.
90. Kushner BJ, Morton GV. Distance/near differences in intermittent exotropia. *Arch Ophthalmol* 1998;116:478-486.
91. Burian HM. Pathophysiology of exodeviations. In: Manley DR, ed. *Symposium on Horizontal Ocular Deviations*. St Louis: CV Mosby; 1971:119-127.
92. Pritchard C. Incidence of dissociated vertical deviation in intermittent exotropia. *Am Orthopt J* 1998;48:90-93.
93. Moore S, Cohen RL. Congenital exotropia. *Am Orthopt J* 1985;35:68-70.
94. Rubin SE, Nelson LB, Wagner RS, et al. Infantile exotropia in healthy infants. *Ophthalmic Surg* 1988;19:792-794.
95. Bock CJ, Buckley EG, Freedman SF. Combined resection and recession of a single rectus muscle for the treatment of incomitant strabismus. *J AAPOS* 1999;3:263-268.
96. Scott AB. Posterior fixation: adjustable and without posterior sutures. In: Lennerstrand G, ed. *Update on Strabismus and Pediatric Ophthalmology*. Boca Raton, FL: CRC Press; 1994;339.
97. Cüppers C. The so-called "Fadenoperation" (surgical correction by well defined changes in the arc of contact). In Fells P, ed. *Second Congress of the International Strabismological Association*. Marseilles: Diffusion Générale de Librairie; 1976:395.