Natural Strabismus in Monkeys

Convergence Errors Assessed by Cover Test and Photographic Methods

Michael W. Quick,*† Howard M. Eggers,‡‡ and Ronald G. Boothe*†§

A standard set of clinical prism and cover tests and a recently developed photographic method were used to assess binocular alignment in ten monkeys that previously were determined to have a naturally occurring infantile strabismus. Extensive measurements of the alignment state were made for fixation attempts throughout the field of gaze. Patterns of alignment errors were examined in an attempt to compare the strabismus found in individual monkeys with common syndromes of human infantile strabismus. Two monkeys showed patterns consistent with the syndrome of essential infantile esotropia. Five monkeys had patterns consistent with accommodative esotropia. One monkey that had bilateral anterior chamber hemorrhage at birth had a constant-angle esotropia. One monkey that previously had been shown to have a large-angle esotropia during development exhibited only exophoria, and in a final monkey in which large-angle esotropia was found during development, the strabismus had resolved. These results demonstrate that naturally occurring strabismus in monkeys might be related to syndromes seen in children. In addition, they provide extensive information about other characteristics of strabismus that have not been examined previously. These include a characterization of the magnitude of the misalignment in terms of error surface plots of bias and a detailed analysis of scatter in the measurements that show coupling relationships between the two eyes. Invest Ophthalmol Vis Sci 33:2986–3004, 1992

Infantile strabismus, along with its associated sensory abnormalities such as amblyopia, is a prevalent eye disorder in humans. Questions regarding its cause and treatment methods pose a significant challenge for clinical ophthalmology.1–4 One approach to addressing these questions is to conduct studies with an appropriate animal model. Macaque monkeys provide an excellent model for studying many aspects of normal and abnormal visual development,5–8 and they have been used in several previous studies of strabismus. For example, if strabismus is created experimentally in an infant monkey (using methods that involve surgical alteration of the extraocular muscles or injection of a neurotoxin into the muscle), the animal will develop acuity and contrast sensitivity deficits that are similar to those found in human strabismic amblyopia.9–17 However, these studies are limited to answering questions about factors that arise secondarily to the (experimentally) induced strabismus and have little bearing on issues pertaining to the strabismus itself.

Recently, two other types of studies that were correlated more directly with the cause and clinical characteristics of strabismus have been conducted with monkeys. First, it was found that several kinds of visual deprivation rearing of infant monkeys can lead to strabismus.13–15 The etiologic factors and characteristics of the misalignment produced in these monkeys appears to be similar to the deprivation-induced strabismus that occurs in infants secondary to conditions such as infantile cataracts.2,3 Second, large-scale screening of infant monkeys identified a number with naturally occurring strabismus of uncertain cause.16 In previous reports, we detailed some aspects of the strabismus and amblyopia present in these monkeys.17–18 The direct clinical relevance of this naturally occurring strabismus in monkeys depends in large part on the degree to which characteristics of the strabismus in the monkeys are similar to human clinical syndromes. Our previous attempts to characterize the nature of the strabismus in monkeys were based on behavioral observations of eye movements and/or on attempts to complete clinical prism and cover tests.16,19 However, these assessments are difficult to conduct with animals, and our previous attempts were inadequate to provide a confident classification.
We recently developed a noninvasive method, based on corneal reflex photography, that allows a more complete assessment of ocular alignment in monkeys. In this report, we present the results obtained from a group of naturally strabismic monkeys using these methods in conjunction with traditional clinical assessments that include refraction and prism and cover tests. We combined these results to correlate the strabismus present in individual monkeys with specific human infantile strabismus syndromes. Then, we added information provided by the photographic method to differentiate the characteristics of the strabismus found in these monkeys further.

**Materials and Methods**

**Animals**

The animals studied in this experiment were ten macaque monkeys (*Macaca nemestrina*) that previously were found to have naturally occurring infantile strabismus. Nine of these monkeys were discovered during a screening of infants born at the University of Washington Primate Center, Seattle, Washington, and the tenth was discovered at the Yerkes Primate Center of Emory University, Atlanta, Georgia. We also tested two normal control monkeys of the same species. Ophthalmologic assessments were conducted while the animals were awake and sitting in a primate restraining chair and also while they were under anesthesia. The latter procedures included measurement of refractive error and fundus examination. Awake procedures included attempts to complete prism and cover tests to both near and distant fixation targets. All procedures were done in strict compliance with the ARVO Resolution on the Use of Animals in Research.

**Photographic Corneal Reflex Methods**

The methods used to determine convergence errors are described more extensively and validated elsewhere. These methods allowed us to obtain the same types of information as typically are obtained from prism and cover tests in human subjects. The resolution of our method allowed us to measure deviations as small as a couple of degrees; this was not appreciably worse than the results obtained by prism and cover tests. An advantage of our methods was that we were able to quantify the magnitude of misalignment from instantaneous looks by the animal at a fixation target. Momentary looks at a target are easier to obtain from monkeys than the extended cooperation that is needed to complete cover tests. With these methods, we obtained large numbers of trials even in uncooperative subjects. By presenting targets at a number of locations, we obtained a more thorough specification of the strabismus in terms of the pattern of misalignment errors throughout the field of gaze.

Each monkey was placed in a primate restraining chair and presented with a small food target (such as a raisin or a peanut) held in a forceps. The monkey was allowed to eat the food target after looking at it and being photographed. The animals did not wear any optical correction during these tests. The fixation targets were presented at 35 specific locations throughout the field of gaze. For middle gaze, 12 targets were presented at four distances from the cyclopian center (0.33, 0.50, 1.0, and 2.0 m), all falling in the horizontal plane at eye level. Three targets were presented at each distance as follows: straight ahead, 30 cm to the left, and 30 cm to the right. These target locations correspond to eccentricities of approximately 8.5° for the most distant targets and 42° for the closest targets. The 12 target locations were replicated for upper and lower gazes in a horizontal plane 30 cm above eye level, and 11 of these target locations were replicated for lower gazes in a plane 30 cm below eye level. (The 12th location in lower gaze was blocked by the camera tripod.) Our intent was to sample various target locations and our choices were constrained by the size and layout of the room where we conducted our tests.

A video camera equipped with a standard 55-mm lens and a ring flash was positioned at the straight-ahead position, 30 cm in front of the cyclopian center. The camera lens was surrounded by a large sheet of polarizing filter oriented in the film plane. This sheet extended outward from the camera approximately 50° of visual angle in all directions; therefore, most of the monkey's visual field, including all fixation target locations, was viewed through the polarizing sheet. Polarizing filters were placed in goggles worn in front of the monkey's eyes. The filter in front of each eye could be oriented crossed or uncrossed with respect to the large polarizing sheet at the camera plane. The crossed orientation blocked 98.3% transmission. This allowed for the presentation of fixation targets binocularly or to each eye separately. Regardless of which eye was viewing the fixation target, we were able to photograph and determine eye position for both eyes simultaneously. All photographs were taken with the room lights off and the fixation targets illuminated by a small flashlight. Five to ten separate fixation attempts were photographed at each fixation target location.

**Data Analysis**

Our methods for determining the state of binocular alignment on the basis of measurements of the corneal reflections in the photographs were based on an
explicit geometric model described elsewhere. The model specifies the locations of the lines of sight from the two eyes in three-dimensional space and allows us to calculate Right...Error and Lef...Error error terms. These are specified in degrees of visual angle and refer to deviations of the line of sight from the intended fixation target for the right and left eyes, respectively. Each of these error terms has two components, a horizontal component that specifies eso- and exodeviations, and a vertical component that specifies hyper- and hypodeviations.

Data analyses were designed to extract two types of information about ocular misalignment from the error terms. First, we calculated error bias (ie. the mean fixation error to a particular target averaged over several fixation attempts). Second, we calculated scatter (ie. the variance of eye position over repeated fixation attempts to the same target location). Both these error terms, bias and scatter, were calculated for each fixation target location, and we also sometimes calculated average values of these measures across particular sets of target locations. We use the terms “mean bias” and “mean scatter” to refer to these averages across more than one fixation target location and restrict the terms “bias” and “scatter” to results for a single target location.

Rationale for Classification

Our most basic assessment of each monkey was to determine any evidence of a deviation during fixation in the primary position of gaze of a near target (a few centimeters in front of the monkey) or of a distant target (approximately 1–1.5 m in front of the monkey). We sought evidence of either phoria or tropia under these two conditions during the clinical assessment. Similarly, we made this assessment from the photographic results by examining the magnitude of the error bias values at the straight-ahead distances of 33 cm (3 m-angles) and 2 m (0.5 m-angle) in middle gaze.

Next, we did a more extensive search for evidence of tropia or phoria at other target locations using these photographic methods. The magnitude of error bias was calculated at each of the 35 target locations and then displayed in terms of error surfaces. We produced these types of error surfaces for each monkey under 18 conditions corresponding to the combinations of the eye being measured (left, right, or both), the eye viewing the targets (left, right, or binocular), and the direction of the error measured (horizontal or vertical). The error surface plots for each monkey were examined for patterns of misalignment. For example, we sought error surfaces with a slope along the distance axis such that the height of the surface was greater at near than at distance as an indicator of accommodative strabismus. A more detailed description of the interpretation of various surface shapes is presented subsequently in conjunction with the results from specific animals.

In addition to examining these error surface plots, we also produced scatter plots. These scatter plots were constructed by plotting Left...Error on the horizontal axis and Right...Error on the vertical axis. We examined these scatter plots to determine whether or not the data points associated with three separate viewing conditions (left eye, right eye, or binocular) fell into separate clusters. We then attempted to summarize the position and shape of each cluster by calculating its mean position and two separate standard deviations. Horizontal standard deviation error bars represent the scatter attributed to the left eye and vertical error bars represent the scatter in the right eye.

Information about bias errors of misalignment can be gleaned by examining the positions of the clusters. In a subject with normal eye alignment, the clusters formed by left eye, right eye, and binocular viewing conditions will all be superimposed with the center of each cluster falling near the (0,0) coordinate. A tropia or phoria will appear as separate clusters where the distance between the clusters reflects the magnitude of the strabismus. Additional information about binocular alignment characteristics can be found by examining the sizes and shapes of the individual clusters. For example, large-diameter clusters indicate an increased amount of variability in alignment errors. Clusters with an elongated shape in the horizontal or vertical direction indicate that there is more variance in one eye than the other. A more detailed description of the interpretation of the positions and shapes of clusters in these scatter plots is presented subsequently in conjunction with the results from specific monkeys.

Results

Table 1 summarizes the current refractive and alignment status for all 12 monkeys in this experiment. The refractive errors were determined by retinoscopy conducted during the most recent clinical evaluations. A summary statement characterizing our assessment of the alignment state is included for each monkey. In every instance, the clinical and photographic methods correlated in regard to the basic diagnosis. However, in many cases, the photographic procedure made it possible to provide additional information regarding the convergence state that was not available from the clinical evaluation alone. The monkeys were classified into six syndromes on the basis of the characteristics of their alignment states,
Table 1. Summary of the refractive error and alignment state assessed by standard clinical prism and cover test, and by photographic “cover test” for 2 normal and 10 naturally strabismic monkeys

<table>
<thead>
<tr>
<th>Monkey</th>
<th>ID</th>
<th>Right eye</th>
<th>Left eye</th>
<th>Alignment state</th>
</tr>
</thead>
<tbody>
<tr>
<td>T24G</td>
<td>ESSENTIAL_1</td>
<td>-0.62</td>
<td>+1.0</td>
<td>17° alternating esotropia with right eye fixation preference; 7° dissociated vertical divergence.</td>
</tr>
<tr>
<td>M79434</td>
<td>ESSENTIAL_2</td>
<td>+0.50</td>
<td></td>
<td>11° alternating esotropia with right eye fixation preference; 6° dissociated vertical divergence.</td>
</tr>
<tr>
<td>T82327</td>
<td>ACCOMM_1</td>
<td>+1.75</td>
<td>+9.0</td>
<td>Alternating accommodative esotropia with right eye fixation preference; 15° at near, 5° at distance.</td>
</tr>
<tr>
<td>T83124</td>
<td>ACCOMM_2</td>
<td>+9.5</td>
<td>8.0</td>
<td>Alternating accommodative esotropia; 12° at near, 3° at distance.</td>
</tr>
<tr>
<td>T81008</td>
<td>ACCOMM_3</td>
<td>+4.5</td>
<td>5.5</td>
<td>Left eye accommodative esotropia; 14° at near, 0° at distance.</td>
</tr>
<tr>
<td>F84115</td>
<td>ACCOMM_4</td>
<td>+8.0</td>
<td></td>
<td>Alternating accommodative esotropia with “V” pattern, left eye fixation preference; 15° at near, 0° at distance.</td>
</tr>
<tr>
<td>F79139</td>
<td>ACCOMM_5</td>
<td>+13.5</td>
<td>7.0</td>
<td>Alternating accommodative esotropia with “V” pattern, deviation only in lower gaze, and right eye fixation preference; 9° at near, 0° at distance.</td>
</tr>
<tr>
<td>F82366</td>
<td>INDUCED</td>
<td>+6.75</td>
<td>-2.5</td>
<td>Alternating esotropia; 12° left eye deviation, 15° right eye deviation.</td>
</tr>
<tr>
<td>T85330</td>
<td>EXOPHOR</td>
<td>+8.5</td>
<td>8.0</td>
<td>6° exophoria.</td>
</tr>
<tr>
<td>T81345</td>
<td>RESOLVED</td>
<td>+0.50</td>
<td></td>
<td>Orthophoria.</td>
</tr>
<tr>
<td>PMH</td>
<td>NORM_1</td>
<td>0.25</td>
<td>0.0</td>
<td>Normal control; orthophoria.</td>
</tr>
<tr>
<td>PHI</td>
<td>NORM_2</td>
<td>*</td>
<td>*</td>
<td>Normal control; orthophoria.</td>
</tr>
</tbody>
</table>

* Refractive error not measured

and the mnemonic labels shown in Table 1 reflect these groupings. In the following sections, we present the detailed information that was used to arrive at this classification.

Normal Control Animals

There was no evidence of any tropia or phoria at any target location for our normal control monkey NORM_1. Across all 35 target locations, the average horizontal bias error value for this monkey was 0.14° with a 95% confidence interval extending from -0.16 to 0.43°. We illustrate a typical error surface plot from monkey NORM_1 in Figure 1. This shows horizontal Right_Error bias during monocular viewing with the left eye in middle gaze. This error surface was flat with a height near zero. All error surface plots for all viewing conditions exhibited the same pattern of results as illustrated in this figure. We repeated these measurements on a second normal control monkey, NORM_2, and the error surfaces from the two monkeys appeared indistinguishable. We confirmed this impression statistically using one-way analysis of variance to compare the performance of each monkey on each error surface. These tests did not reveal any significant differences between NORM_1 and NORM_2 on any of the error surfaces. For example, the mean horizontal Right_Error across all target locations during monocular viewing with the left eye was 0.1° for monkey NORM_1 and 0.0° for monkey NORM_2, a difference that was not statistically significant (F(1,14; df, 1.68; P > 0.05).

Scatter plots from both normal control monkeys also were examined. Data points obtained for a given target location under conditions of binocular viewing and monocular viewing with left and right eyes always were intermixed and appeared to form only a single cluster, the center of which was located near the (0,0) coordinate on the scatter plot. The standard deviations in the vertical and horizontal directions were always of similar magnitude, demonstrating that the amounts of variability in the left and right eyes were comparable. The average amount of scatter for monkey NORM_1 across all conditions tested was 1.7° (95% confidence interval, 1.6-1.9°). Indistinguishable results were obtained from monkey NORM_2, and statistical comparisons did not show significant differences (P > 0.05) between any of the scatter results obtained from NORM_1 and NORM_2.

In summary, our normal control results demonstrated that a normal monkey was able to fixate targets throughout the field of gaze with a high degree of accuracy for both eyes. Furthermore, in our comparisons of NORM_1 and NORM_2, we established that the two individual normal control monkeys did not differ significantly on any of these comparisons. In the rest of this paper, we will make similar compari-
targets. Both monkeys alternated fixation between the gaze as in the straight-ahead position. The deviation was also the same magnitude for near as for distant viewing (data not shown). The explanation for the dips becomes apparent after examination of the results shown in Figures 2C–D. Left-Error for deviations in the horizontal direction during binocular viewing in middle gaze is shown in Figure 2C, and Right-Error under the same viewing conditions is shown in Figure 2D. These two error surfaces are mirror images of each other. This pattern demonstrated cross-fixation. That is, during binocular viewing, the eye contralateral to the target always was used for fixation. For targets in the straight-ahead position, eye preference alternated, resulting in a bimodal distribution. Figures 2C–D only show the magnitude of the deviation to midline targets when the measured eye was used for fixation). Under binocular conditions, the ipsilateral eye never was used for fixation in the parts of the visual field that showed a dip under monocular viewing conditions (Fig. 2B). When the monkey was forced to fixate in these parts of the field of gaze with its ipsilateral eye (by blocking the view of the contralateral eye as was done for the results shown in Fig. 2B), the contralateral eye could not follow along because it already had approached its adducting excursion limit in the orbit. Paradoxically, this decreased the magnitude of the deviation, but this simply was due to mechanical factors involving the position of the eye in the orbit and had no significance in regard to understanding the neurologic basis of the strabismus.

Statistical tests confirmed that the pattern of horizontal errors seen in monkey ESSENTIAL_1 were
significantly different from normal. For example, the mean Left-Error magnitude for monkey ESSENTIAL_1 across all fixation target locations where the right eye was used for fixation was 16.8° (significantly different from the value of 0.1° obtained from monkey NORM_1 across the same 23 target locations; F, 2575; df, 1,44; P < 0.01). The differences between the two monkeys for Right-Error under comparable conditions were of similar magnitude (F, 2329; df, 1,44; P < 0.01). As expected, mean Left-Error measured only across those targets where the left eye was used for fixation was not significantly different from normal (F, 0.03; df, 1,44; P > 0.05). Left-Error and Right-Error results for monkey ESSENTIAL_1, across comparable conditions, were not significantly different from one another (F, 0.22; df, 1,44; P > 0.05), indicating that the error was symmetric with respect to which eye was deviating. The pattern of results for horizontal errors for monkey ESSENTIAL_2 was indistinguishable from that described for ESSENTIAL_1.

Another interesting characteristic of the strabismus in both of these monkeys became apparent when examining vertical components of the bias error. We illustrate these findings in Figure 3A. These show the vertical error in the nonfixating eye under the same conditions as illustrated previously for horizontal error in Figure 2A. In Figure 3B, we present the vertical error surface for Left-Error during monocular viewing by the right eye. The pattern of results seen in Figures 2–3 was consistent with a diagnosis of dissociated vertical divergence (DVD). During binocular viewing, a significant esodeviation of approximately 17° was present in the nonfixating eye, as already described (Fig. 2A). As illustrated in Figure 3A and confirmed by statistical tests (F, 0.05; df, 1,44; P > 0.05), there were no significant vertical deviations in the nonfixating eye. Under monocular conditions, the nonviewing eye again showed an esodeviation of approximately 17° over most of the field of gaze (Fig. 2B). However, the nonviewing eye now showed a hyperdeviation of approximately 7° (Fig. 3B) that was significantly different from normal (F, 3966; df, 1,68; P < 0.01). This pattern of results was symmetric. The right eye drifted upward similarly during monocular left eye fixation. Vertical error results from monkey ESSENTIAL_2 were indistinguishable from those just described for ESSENTIAL_1.

To assess the extent to which this pattern of vertical misalignment was similar to human DVD, we conducted a variation on the Bielschowsky test, using neutral-density filters on monkey ESSENTIAL_1. Each eye was tested individually, and the results for both are shown in Figure 4. A neutral-density filter was placed in front of one eye while the moncy was fixing a target. This filter was left in place for 4–5 sec and then was removed. We tracked the vertical position of the eye behind the neutral-density filter during
the entire period. Each covered eye drifted slowly upward for several seconds after the introduction of the filter. When the neutral-density filter was removed, the eye returned quickly to the level of the fellow fixating eye. These dynamic characteristics were similar to the pattern of DVD that occurs in humans with essential infantile strabismus.

Scatter plots also were examined in both essential infantile monkeys, and typical results are shown in Figure 5. The data shown are from monkey ESSENTIAL_2 and show deviations in the horizontal direction averaged over all 35 fixation targets. The results from monocular viewing with left and right eyes formed separate clusters (Fig. 5A). The magnitude of the separations between these clusters (approximately 11°) reflected the degree of esotropia. Furthermore, two similar clusters also were formed under binocular viewing conditions (Fig. 5B). This finding reflects the alternating nature of the tropia; each cluster represents results during fixation by a particular eye.

The clusters for monkey ESSENTIAL_2 shown in Figure 5 had elliptical shapes with the elongated axis running in either the horizontal or vertical direction. This contrasted with the clusters seen in normal monkeys that have shapes approximately circular. The magnitude of the standard deviation across the minor axis of each ellipse was nearly 1.5°. This was similar to that found in normal monkeys. The major axis standard deviations were approximately 1° larger than those seen in the normal control monkeys. Statistical tests on the results shown in Figure 5 confirmed that the minor axis standard deviations were not significantly different from our normal control in either the left (F, 2.2; df, 1,68; P > 0.05) or the right eye (F, 0.0; df, 1,68; P > 0.05), whereas the major axis standard deviations were significantly larger in both the left (F, 132; df, 1,68; P < 0.01) and the right eye (F, 137; df, 1,68; P < 0.01). We obtained the same pattern of statistically significant results from monkey ESSENTIAL_1 (results not shown).

The particular pattern of cluster shapes obtained from these monkeys revealed some interesting properties of their strabismus. First, the increased variability appeared in either one eye or the other but not in both. This was reflected by the finding that the minor axis of each ellipse always was of normal magnitude. Second, the increased variance was not always added to a particular (anatomic left or right) eye. Some ellipses had their major axes oriented vertically (indicating increased variance in the right eye), whereas others were oriented horizontally (indicating increased variance in the left eye). Furthermore, the increased variance was not related to whether the eye being used for fixation was the preferred or nonpreferred at the particular target location being tested. These monkeys cross fixate; they prefer to use the left eye when viewing targets in the right field of gaze and the right eye, in the left field of gaze. However, examination of the shapes of clusters under conditions where the monkeys were forced to fixate with
a specific eye revealed that the major axis of the ellipse sometimes was associated with the preferred eye, and other times was correlated with the nonpreferred eye. The only factor that predicted the direction of the ellipse was the eye that was being used for fixation. The eye that was fixating the target showed normal variance (regardless of whether it was left or right, or whether it was preferred or not preferred for that target location); the fellow eye always showed increased variance. Thus, our scatter results in monkeys with essential infantile esotropia demonstrated an increased variance that was added to only the nonfixating eye under both monocular and binocular viewing conditions.

**Accommodative Esotropia**

Five monkeys were classified as having some form of early-onset accommodative esotropia. The deviation was noticed first in these monkeys within the first several weeks after birth. Anesthetized ophthalmologic examinations were unremarkable except for refractive error. All these monkeys were hypermetropic by several diopters in one or both eyes (Table 1). In these monkeys also, the magnitude of their deviation, when examined by cover tests, always was estimated to be larger when viewing near targets compared with distant targets.

Several distinct patterns of error surfaces were exhibited by the monkeys in this group. In the first pattern, deviations were present at all target distances under both monocular and binocular viewing conditions, and the magnitude of the deviations increased approximately linearly with the distance measured in meter angles. Two monkeys, ACCOMM_1 and ACCOMM_2, showed this pattern. We illustrate a dataset for ACCOMM_1 in Figure 6. This monkey had a strong right eye fixation preference when tested with cover tests, but our photographic assessment demonstrated that this monkey sometimes alternated fixation spontaneously under binocular viewing conditions. In Figure 6, we display Right_Error in the horizontal direction during binocular viewing, but this was restricted to those trials in which fixation was with the left eye. The mean Right_Error for targets at a distance of 0.5 m-angle was 4.9°. This increased to 8.9° at 1 m-angle, 13.4° at 2 m-angles, and 17.8° at 3 m-angles. At any one distance, there were no significant differences ($P > 0.05$) in error magnitude between the various lateral target locations. Collapsing the results from the lateral targets at each distance to arrive at an overall mean error value at that distance revealed a significant linear relationship between error and axial distance ($r = 0.99; F = 1380; df = 1,33; P < 0.01$).
Somewhat surprisingly, measures of Left_Error during right eye fixation under binocular viewing conditions showed comparable results to Right_Error during left eye fixation, as did both Right_Error and Left_Error during monocular viewing by the fellow eye. This was unexpected because of the large anisometropia that was present and consequent larger accommodative effort required of the left eye. We discuss this issue further in the Discussion section. There were no apparent differences in the patterns of horizontal errors seen in upper, middle, and lower gaze, and no vertical errors were seen at any target locations for either monkey ACCOMM_1 or ACCOMM_2.

Bias error surfaces for monkey ACCOMM_3 are illustrated in Figure 7. Figure 7A shows Left_Error during binocular viewing for errors in the horizontal direction. This monkey had an accommodative pattern characterized by a significant linear relationship between magnitude of error and axial distance ($r$, 0.97; $F$, 486; df, 1,33; $P < 0.01$). However, the error surface pattern of this monkey differed from that of the two accommodative monkeys just described for distant targets. The results from ACCOMM_3 were not significantly different from normal ($P > 0.05$) at axial distances of either 0.5 or 1 m-angle, whereas the results from ACCOMM_1 and ACCOMM_2 were significantly different ($P < 0.01$) from normal at both of these distances. Monkey ACCOMM_3 showed horizontal errors that were significantly different from normal ($P < 0.01$) at target distances of 2 and 3 m-angles. Under binocular viewing conditions, the right eye always was used for fixation. However, when forced to fixate with the left eye under monocular conditions (Fig. 7B), the right eye showed an error surface similar to that obtained under binocular conditions. Thus, the orthonotropia at distant viewing targets could not be based solely on fusional divergence because the same results were obtained during monocular and binocular viewing conditions. Comparable patterns of horizontal errors were seen for this monkey in the upper, middle, and lower gaze, and no alignment errors in the vertical direction were seen for any targets under any viewing conditions.

The same basic accommodative pattern, ie, increased error with decreasing viewing distance, was found in monkeys ACCOMM_4 and ACCOMM_5. However, these monkeys had an additional characteristic not found in any of the accommodative monkeys just described. They had different magnitudes of error in lower, middle, and upper gazes. We illustrate this finding for ACCOMM_4 in Figure 8. This figure shows Right_Error during monocular fixation with the left eye for errors in the horizontal direction. The mean Right_Error for fixation targets at distances of 1 m-angle or beyond was 0.2°, within the range expected for a normal monkey ($P > 0.05$). At 2 m-angles, the overall mean Right_Error was 10.1°, which is significantly different from normal ($P < 0.01$). However, the error magnitude varied with the gaze angle for this monkey. The mean Right_Error at the targets located in the upper and middle fields of gaze was 8.6°. This was significantly different from the 12.9° error found in the lower field of gaze ($F$, 282; df, 1,48; $P < 0.01$). For targets presented at 3 m-angles, the error magnitude at the upper and middle fields of gaze was 13.5°, and it increased significantly to a mean of 20.7° for targets in the lower field of gaze ($F$, 544; df, 1,48; $P < 0.01$).

Monkey ACCOMM_5 showed an even more exaggerated difference across gaze angles. Representative error surfaces for this monkey are illustrated in Figure 9, which shows Left_Error in the horizontal direction during right eye fixation under binocular viewing conditions. At target distances of 2 m and for targets presented in the upper and middle fields of gaze at all distances, monkey ACCOMM_5 was indistinguishable from a normal monkey ($P > 0.05$). This finding confirmed the cover test observations in which no deviation was apparent. However, photographic results in lower gazes demonstrated that the horizontal error magnitude increased significantly to 6.3° at 2 m-angles ($F$, 167; df, 1,10; $P < 0.01$) and to 9.2° at 3 m-angle.
Fig. 8. Eye alignment bias plot for monkey ACCOMM_4 showing Right—Error during monocular viewing of the left eye, for deviations in the horizontal direction. All symbols are as described in Figure 1. The three separate plots show the results obtained in upper, middle, and lower gazes. Note that the magnitude of the deviation to near targets is larger in lower than in upper or middle gazes.

Fig. 9. Eye alignment bias plot for monkey ACCOMM_5, showing Left—Error during binocular viewing for deviations in the horizontal direction. The RP symbol designates that only trials involving right eye fixation are included in this plot. All other symbols are as described in Figure 1. The magnitude of the esotropia increases with decreasing target distance, but is present only in lower gaze.

cantly different from those present in our normal control (F, 1.33; df, 1,68; P > 0.05). Thus, under monocular right eye viewing, the scatter was normal in both eyes. The mean and standard deviations shown in the upper left hand corner of Figure 10A represent errors during left eye viewing of near targets. The magnitude of scatter for these conditions was significantly larger than found in our normal control (F, 133; df, 1,68; P < 0.01). This indicates that the magnitude of the scatter was linked to whether the anatomic right or left eye was being used for fixation. When the right eye fixated, scatter was normal for both eyes; when the left eye fixated, scatter was high for both eyes. An interesting aspect of this increased scatter was that it was not correlated with the magnitude of the tropia. This is illustrated by the standard deviations shown in the lower left corner of each graph that were obtained during distant fixation at 0.5 m-angle. At this viewing distance, monkey ACCOMM_3 does not show any misalignment. This was reflected in the finding that
the positions of the left and right eye clusters were near zero for each eye. The error bars for right eye viewing were indistinguishable from normal (F. 1.64; df, 1.68; P > 0.05); those for left eye viewing were abnormally large (F. 81.4; df, 1.68; P < 0.01).

Monkey ACCOMM_3 never alternated fixation, and therefore, the distinction between anatomic right and left eye was confounded by the functional distinction between preferred and nonpreferred eye. This issue could not be addressed in the other accommodative monkeys in which alternating fixation was present because magnitude of their scatter was normal under all viewing conditions. Additional information that bears on this issue is presented in the next section in regard to monkey INDUCED.

The relative sizes of the vertical (ie, right eye) and horizontal (ie, left eye) error bars were similar for all clusters for all accommodative monkeys, regardless of whether the clusters were abnormally large (ACCOMM_3) or normal in size (ACCOMM_1, ACCOMM_2, ACCOMM_4, and ACCOMM_5). Under conditions in which the overall scatter increased, therefore, both eyes were affected similarly. In this regard, the pattern of scatter was dissimilar to that seen in monkeys with essential infantile esotropia.

Deprivation-Induced Esotropia

Monkey INDUCED had bilateral hyphemas at birth\(^16\) and currently has a large anisometropia (Table 1) that is hyperopic in the right eye and myopic in the left. The strabismus in this monkey showed some characteristics that were different from both essential infantile and accommodative esotropias described in the previous sections. Furthermore, monkey INDUCED shares some characteristics with monkeys in which a strabismus was induced experimentally by early visual deprivation.\(^13\)

This monkey showed a fixation preference related to the anisometropia. The magnitude of the deviation, although constant for a given fixating eye, changed when the monkey alternated fixation to the opposite eye. This is demonstrated in Figures 11A–B. In Figure 11A, we plot the eye alignment error surfaces for Left_Error during binocular viewing for deviations in the horizontal direction. Figure 11B is a similar measure of Right_Error. The error surfaces in these figures shows that the right eye always was used for fixation of distant targets (1.0 m and beyond). Conversely, the left eye was used for fixation of near targets. For target fixations in which the left eye deviated, there was a significant (P < 0.01) mean error of 12.2°. For right eye deviations, the mean error magnitude was 14.9°: this also was significantly larger than that seen in a normal monkey. The differences in magnitude between mean Left_Error and mean Right_Error for monkey INDUCED were significant (F. 308; df, 1.37; P < 0.01) and consistent with the anisometropia that was present in this monkey. No differences in the shapes of the horizontal error surfaces were seen between upper, middle, and lower gaze positions; in addition, no errors in the vertical direction were seen for any target location.

The scatter in monkey INDUCED was different in an interesting way from the pattern seen in either the essential infantile or accommodative esotropic monkeys. For monkey INDUCED, the right eye was preferred for distant targets. In Figure 12A, we illustrate the results obtained when the animal viewed distant
targets. The standard deviations for right eye viewing were symmetric and normal in size. The standard deviations for the left eye were symmetric but larger than normal. These results were similar to those shown by ACCOMM_3 because fixation with the preferred eye produced normal scatter in both eyes. Fixation with the nonpreferred eye caused abnormally large scatter in both eyes (Figs. 10, 12A). However, in monkey ACCOMM_3, the right eye always was preferred; therefore, it was impossible to distinguish the anatomic right eye from the functional preferred eye. Monkey INDUCED, however, switched preference to the left eye for near targets; these results are shown in Figure 12B. Scatter was normal in size for the preferred left eye and became abnormally large for the nonpreferred right eye under these conditions. These results demonstrate that the magnitude of the scatter in monkey INDUCED was determined by functional eye preference and not by the anatomic left or right eye.

These conclusions were confirmed with statistical tests. Right eye viewing to distant targets was not significantly different from responses to the same targets by a normal control monkey (F, 0.93; df, 1,32; P > 0.05). Right eye responses to near targets showed significantly larger scatter than a normal control (F, 92; df, 1,34; P < 0.01). Significant findings of similar magnitude were found for the left eye for near and distant targets, respectively. Regardless of whether monkey INDUCED was using the preferred eye (thus producing normal scatter) or the nonpreferred eye (thus causing abnormally large scatter), the magnitude of the scatter was always the same for both eyes. In this regard, the scatter results from monkey INDUCED were similar to ACCOMM_3 and dissimilar to those in the monkeys with essential infantile esotropia.

Exophoria

Monkey EXOPHOR was discovered during a routine screening of infants at the University of Washington primate colony because he exhibited an obvious large-angle esotropia. Later, when this infant was old enough to be separated from its mother, arrangements were made to have it shipped to the Yerkes Primate Center for ophthalmologic examination and further evaluation. At that time, the esotropia ap-
peared to have resolved, and the monkey now appears orthotropic based on cover and prism tests. Anesthetized examination revealed a large hypermetropia (Table 1).

Figures 13A–B summarize the eye alignment status of monkey EXOPHOR based on the photographic assessment. Figure 13A represents Left_Error during binocular viewing for errors in the horizontal direction. As can be seen, no alignment errors were present to any fixation targets during binocular viewing. The mean Left_Error across all fixation targets was $-0.1^\circ$, a value that was not significantly different from normal ($F = 0.94; df = 1, 68; P = 0.34$). This confirmed the clinical assessment of orthotropia. However, under monocular viewing, exophoria became evident. Figure 13B shows Left_Error during viewing by the right eye. The mean amount of Left_Error exophoria was $-5.9^\circ$, a value significantly different from normal ($F = 1559; df = 1, 68; P < 0.01$). No differences were seen for upper, middle, and lower gaze. In addition, no errors in the vertical direction were seen for any target locations.

A representative scatter plot for monkey EXOPHOR is shown in Figure 14. This figure shows scatter information for one fixation target (middle gaze and straight ahead at a distance of 2 m-angles) for errors in the horizontal direction. The mean error and standard deviations are shown for left eye, right eye, and binocular viewing. The monkey's exophoria was readily apparent after examining the positions of the clusters formed by the left eye, right eye, and binocular viewing that are shown in this figure. An examination of the standard deviations revealed that the shapes of all clusters were symmetric around the horizontal and vertical axes. Statistical tests confirmed that the magnitudes of horizontal and vertical standard deviations were not significantly different ($P > 0.05$) from one another, nor from those obtained from a normal monkey.

Resolved

Monkey RESOLVED was well documented in infancy to have a large-angle alternating esotropia.$^{11,16,18}$ Both eyes had several diopters of hypermetropia during infancy. The hypermetropia now has been reduced to approximate emmetropia (Table 1), and our current assessment of alignment status by clinical prism and cover and photographic methods revealed that this monkey was orthophoric. Across all experimental conditions, the error for monkey RESOLVED was indistinguishable from normal.

Discussion

Standard clinical cover tests and a recently developed photographic procedure were used to assess the eye alignment errors in ten monkeys in which a naturally occurring strabismus had been documented at an early age. The patterns of alignment errors found in these monkeys were similar in many respects to the syndromes of infantile strabismus seen in humans.
Two monkeys showed eye alignment errors consistent with the human syndrome of essential infantile esotropia. Five monkeys had some form of early-onset accommodative esotropia. One monkey that had bilateral anterior chamber hemorrhages at birth currently had a constant-angle esotropia that may have been induced by visual deprivation. Finally, in two monkeys in which a large-angle esotropia was noticed at an early age, the alignment status was changed when we examined them. One monkey had exophoria, and in the other, the strabismus had resolved and binocular alignment was indistinguishable from that of a normal monkey.

Comparison of Monkey Results With Human Syndromes

One of the least understood syndromes of human childhood strabismus is essential infantile esotropia, also referred to as nonaccommodative infantile esotropia or by the traditional name of congenital esotropia. The onset of the esodeviation in this syndrome traditionally was thought to occur prenatally, but now, it is accepted that the deviation most typically appears 2-4 mo after birth. It is characterized by a stable large-angle deviation that is of similar magnitude at both near and distance and in all angles of gaze (ie, comitant). Alternating fixation and cross fixation also are common, and there tends to be little or no refractive error in either eye. Another distinguishing feature often present in this syndrome is DVD, an upward deviation of one eye when that eye is covered (ie, when fusion is disrupted). A nasal-temporal asymmetry in the optokinetic nystagmus response also is often present.

All our findings in monkeys ESSENTIAL_1 and ESSENTIAL_2 were consistent with this syndrome. Vision develops about fourfold faster in monkeys than in humans. Therefore, the expected age of onset for this syndrome in monkeys would be a few weeks after birth. In monkey ESSENTIAL_2, the esotropia was documented by 5 wk of age. We did no first-hand observations on monkey ESSENTIAL_1 during the first few weeks after birth, but reports from animal caretakers state that the deviation was noticed soon after birth. Both monkeys showed alternating fixation when presented with targets at near and far in primary position. Examination of the pattern of alignment errors across locations in the visual field revealed cross fixation. That is, the left eye was always the preferred eye for right gaze and vice versa. If we ignored which eye was fixating and determined only the magnitude of the deviation, it became apparent that the deviation was constant across the entire field of gaze at all distances. Neither of these monkeys had a significant refractive error. The DVD was evident in the nonviewing eye during monocular fixation. This vertical deviation occurred equally when either eye was covered and was not present under binocular viewing conditions. Finally, optokinetic nystagmus responses were evaluated for both monkeys, and each exhibited a nasal-temporal asymmetry with weaker responses occurring for motion in the temporal direction.

A second common syndrome of infantile strabismus is early-onset accommodative esotropia. A traditional view held until recently by many ophthalmologists was that early-onset forms of strabismus do not contain an accommodative component, but there now appears to be a consensus that there is a human syndrome that involves an accommodative component and onset within the first year. This syndrome is characterized by a nonparalytic esodeviation with an angle greater at near than at distance. Abnormally large hypermetropia, high accommodative convergence-to-accommodation (AC/A) ratios, or a combination of both commonly are associated with this syndrome and may be predisposing factors. In uncorrected hypermetropia, excessive accommodation necessary to bring the retinal image into focus may trigger excessive convergence by the near reflex. In high AC/A ratios, a proper accommodative response may trigger an excessive convergence response.

A pattern of results consistent with early-onset accommodative esotropia was seen in five of our naturally strabismic monkeys. All had substantially hypermetropic refractive errors, and several also were anisometropic. All these monkeys shared the common result that the magnitude of the esodeviation was greater at near than at far, but it did not differ with lateral gaze angle at a given distance. The age at which the strabismus first was detected in this group of monkeys ranged from 4-15 wk after birth. Two of these monkeys (ACCOMM_4 and ACCOMM_5) had V patterns, a characteristic frequently found in humans with early-onset, but seldom in late-onset, accommodative strabismus. Finally, several of the accommodative monkeys were tested for optokinetic nystagmus, and all had a nasal-temporal asymmetry with weaker responses occurring for motion in the temporal direction.

The pattern of convergence errors seen in three monkeys (ACCOMM_3, ACCOMM_4, and ACCOMM_5) appeared similar in some ways to the subtype sometimes referred to as accommodative strabismus of the nonrefractive type. This subtype is characterized by orthotropia at far and esotropia at near. It is associated with an abnormally large AC/A ratio that leads to overconvergence at near. However, because
all three monkeys also were known to have hypermetropic refractive error. They are more likely to reflect a mixed rather than a pure subtype. The two other monkeys (ACCOM M_1 and ACCOM M_2) had esotropia at all distances. These monkeys might be examples of a pure hypermetropia subtype or a mixed subtype that reflects both hypermetropia and an abnormal AC/A ratio. An examination of these issues will require an analysis of accommodative errors and AC/A ratios for these monkeys. We made these measurements, and the results will be presented in a subsequent paper.

Another division into subtypes that we noticed in our monkeys was based on the shape of the error surfaces along the distance axis. In three monkeys (ACCOM M_1, ACCOM M_2, and ACCOM M_5), there was a gradual ramp-like increase in the magnitude of the deviation from distant targets to near targets. In two other monkeys (ACCOM M_3 and ACCOM M_4), we found an abrupt step-like transition from a normal alignment pattern at distant targets to esotropia near fixation. This step-like transition cannot be explained by a fusional divergence amplitude because it also occurred under monocular viewing conditions. The division of these two subtypes may reflect differences in the nature of the cross coupling between the accommodative and convergence systems.82

Our accommodative monkeys sometimes showed characteristics that were unexpected based on what commonly is reported for human accommodative syndromes. In particular, we did not find significant differences in the magnitude of alignment error during left and right eye fixation, even in monkeys in which a relatively large anisometropia was present. The most dramatic example of this unexpected finding was monkey ACCOM M_1, in which the magnitudes of Left_Error and Right_Error were similar despite an anisometropia of > 5 D. We do not think this apparent discrepancy was caused by an inability of our methods to distinguish these kinds of differences because we obtained differential results from monkey INDUCED that were consistent with these expectations based on characteristics of the anisometropia.

One possible reason for these apparent discrepancies is that they may reflect a species difference between monkeys and humans. Oculomotor systems of humans and macaque monkeys are known to be similar in many respects, but they also have some significant differences.82311 Therefore, we should not necessarily expect the characteristics of monkey strabismus to be identical in every respect to those found in humans. However, monkeys may provide a good model for studying some aspects of human strabismus even though they are inappropriate for other aspects. It is only possible to determine the specific ways in which monkeys are an appropriate model by doing the kinds of detailed studies that we report in this paper.

A second possible reason, and the one we favor, for the apparent discrepancy between our monkey data and typical results seen in humans with early-onset accommodative esotropia is related to the fact that the rearing and treatment conditions in these monkeys were atypical from those in children. Our monkeys were allowed to mature to adulthood with no intervention. For this reason, the human group that would be most directly comparable would involve cases in which an early-onset accommodative esotropia was documented during infancy, the child was allowed to mature to adulthood with no intervention (ie. no anaccommodative therapy, no surgery, and no patching), and a complete ophthalmologic assessment was conducted after maturity. Our expectations of the characteristics that should be present in humans with early-onset accommodative esotropia usually are not based on empirical studies of humans who meet all these conditions. Cases of early-onset accommodative esotropia in humans frequently deteriorate into a complex mixture of accommodative and nonaccommodative esotropia for which surgery must be done to restore the alignment of the eyes to the status that prevailed before the deterioration.28 It seems plausible that the characteristics of the strabismus seen in our monkeys reflected the ultimate outcome of early-onset accommodative esotropia when the afflicted infant was not treated by clinical intervention.

Two of our monkeys that no longer had esotropia that was documented at an early age (EXOPHOR and RESOLVED) also may belong to the accommodative group. In monkey RESOLVED, the moderate amount of hypermetropia that was present during infancy resolved, and similarly, the alternating esotropia that was present earlier was no longer detectable. This monkey currently appears to be orthophoric, at least within the level of resolution of our methods. It is possible that a residual microstrabismus is still present that cannot be detected with our procedures; these are limited to detecting misalignments of a few degrees or more.21

Monkey EXOPHOR is interesting because an abnormally large hypermetropia was still present even though the esotropia was not. Because this monkey currently has exophoria, its convergence system may have compensated for the accommodative convergence influence that predisposed it toward esodeviations. We previously showed that monkeys have an extraocular muscle, the accessory lateral rectus (ALR), that is not present in humans,33 and argued that one function of this muscle is to render monkeys resistant to the development of esodeviations. This
hypothesis offers one way to explain the infrequent occurrence of esotropia in monkeys compared with humans, and it may have determined the alignment pattern in monkey EXOPHOR. We speculate that this monkey had a large ALR muscle that produced enough divergence force to overcome and compensate for the influence of the hypermetropic accommodative convergence system.

There are various pieces of evidence that led us to characterize the strabismus in monkey INDUCED as being the result of visual deprivation during development. This monkey had bilateral hemorrhages of the anterior chamber at birth. This was followed by lens opacities in both eyes that persisted for several months after birth. Subsequently, a large axial anisometropia developed that persisted to the time of our study. Thus, this type of strabismus may represent the effects of blocked or clouded visual input during an early developmental period and/or the defocus caused by anisometropia. We previously demonstrated that either of these factors are sufficient to induce a strabismus if present during an early sensitive period. The strabismus in monkey INDUCED was the same magnitude at all viewing distances. This differentiates it from that seen in our monkeys with an accommodative syndrome. Even though the strabismus was a stable-angle esotropia that involved alternating fixation, it differed in several respects from that seen in our monkeys with essential infantile esotropia. The fixation preference was based on viewing distance, was related to the anisometropia, and did not involve cross fixation. There also was no DVD pattern. This monkey first presented with an alternating exotropia at 5 wk of age, which changed to an esotropia at 12 wk of age. This pattern of esodeviations seen at early ages, changing to esodeviations at older ages, is a common characteristic seen in deprivation-induced strabismus produced experimentally in monkeys. Similarly, both esodeviations and esodeviations have been reported in human infants who develop strabismus secondary to monocular congenital cataracts. Finally, monkey INDUCED differed from the essential infantile group in terms of the pattern of fixation scatter exhibited. This topic is discussed in the following section.

**Fixation Scatter in Strabismic Monkeys**

We discovered some interesting abnormalities in fixation scatter in some of our strabismic monkeys. To our knowledge, abnormalities in scatter have not been examined previously in studies of strabismus. Our results suggest that patterns of scatter may have important implications for understanding the mechanisms underlying the various syndromes of infantile strabismus. In Figure 15, we present a functionally-based model that was consistent with our scatter results. The purpose of the model is to represent the amounts of scatter present in both the fixating and nonfixating eye and the influence of the fixating eye’s scatter on scatter in the fellow eye. All our scatter results from all monkeys were consistent with a model in which the scatter of the fixating eye was controlled by visual information available from the fixating eye. The scatter of the nonfixating eye of some strabismic monkeys, however, must be influenced by either additional or separate information. We indicate this in our model by the box labeled “double eye” processing (Fig. 15) borrowed from the terminology of Hering. This box would be assumed to receive visual input (such as disparity information) from both eyes and additional information (such as the current accommodative state). We added provisions for injecting noise into one of two particular locations in our model to explain the results seen in some of our strabismic animals. We represent this in Figure 15 by the two boxes labeled noise generator 1 and noise generator 2. Each of these noise generators has a switch that can be set to produce either normal or abnormally large noise levels. The monkeys with normal scatter in both eyes can be modeled by setting the switches on both noise generators to normal.

---

**Fig. 15.** A model to account for the different patterns of fixation scatter exhibited by the strabismic monkeys. Increased noise added at the level of the fixating eye results in an increase in scatter in both eyes. Increased noise added at a later cyclopian processing stage results in an uncoupling between the eyes that is reflected in increased fixation scatter in the nonfixating eye only.
In monkey ACCOMM_3, the right eye was always the preferred eye for fixation under binocular viewing conditions. When this eye was the fixating eye, under monocular or binocular conditions, the amount of scatter measured in both eyes was normal. When the left eye was forced to be the fixating eye, which could only be accomplished under monocular conditions, both eyes showed increased levels of scatter. That is, the fixating eye was responsible for the magnitude of the scatter. The results from this monkey can be modeled by assuming that whenever the right eye is used for fixation the noise generator 1 is set to normal; when the left eye is used for fixation, the noise generator is set to abnormal. The abnormal setting injects increased noise that is propagated through the system as increased scatter in both eyes.

The abnormal scatter in monkey INDUCED is slightly more complicated, but it can still be handled by the abnormal setting on noise generator 1. In this monkey, during binocular viewing conditions, the right eye was the preferred eye for distant targets, and the left eye was preferred for near targets. When the right eye was used for fixation under preferred conditions, both eyes showed normal scatter. The same was true for left eye fixation preference. Under monocular viewing conditions, if the right eye was forced to fixate nonpreferred targets, then both eyes showed increased scatter. The same was true for the left eye. Therefore, the decision about whether noise generator 1 is set to the normal or abnormal setting is not based on the anatomic left or right eye but is determined by whether the eye is preferred or nonpreferred under the particular viewing conditions. This places constraints on the anatomic location of the noise generator. Based on the results from ACCOMM_3, we might speculate that the noise generator 1 was operating at the level of peripheral sensory pathways or perhaps the ocular dominance columns in layer IV of the primary visual cortex. Monkey ACCOMM_3 had moderate amblyopia in the left eye, and it seems reasonable to assume that, in cases where amblyopia develops in these peripheral pathways, increased noise results. However, monkey INDUCED had approximately equal acuity in both eyes, and it appeared that the noise was being injected at a more central site where information was being processed according to the preferred or nonpreferred eye and independent of whether that functional preference corresponded to the anatomic left or right eye inputs. Noise generator 1 in our model appeared to be more closely associated in this monkey with functional concepts (such as suppression and eccentric fixation) than with peripheral amblyopia or anatomic concepts (such as ocular dominance columns).

Probably the most important finding from our scatter results was the finding that the two monkeys with essential infantile esotropia (ESSENTIAL_1 and ESSENTIAL_2) had an abnormality in scatter that could not be explained by the same noise generator used in the other types of strabismic monkeys. In monkeys with essential infantile esotropia, scatter in the fixating eye does not determine the scatter in the fellow eye. The nonfixating (in the case of binocular viewing) or nonviewing eye (in the case of monocular viewing) always showed increased scatter. Scatter for the fixating eye, however, was always normal. This was true even when the fixating eye was viewing nonpreffered targets. The only way to explain this pattern of increased scatter is to add noise at a different location. We represent this as noise generator 2 in Figure 15.

There has been speculation in the ophthalmologic literature (as far back as the beginning of this century) that the essential infantile syndrome involves a congenital defect of the fusion faculty.1,2,21-25 Our scatter results were consistent with this mechanism and amplified some of the characteristics that must be present in the fusion faculty defect. Specifically, our scatter results could be modeled as increased noise entering the box labeled “double eye processing.” The new insight revealed by the results of our study is that this increased noise, even though it can be modeled as being generated internally at a site associated with cyclopian processing, has its effect in terms of increased scatter that is different in the two eyes. The basic deficit in essential infantile esotropia thus becomes manifest as a violation of Hering’s law.35

Hypotheses about the anatomic location of noise generator 2 are speculative at this time. However, our data place some constraints. The fact that the location must involve cyclopian processing that affects only the nonfixating eye indicates that it is located centally or toward the motor output end, rather than in early stages of visual processing. Arguments have been advanced, based on functional characteristics of strabismus along with evolutionary considerations about the oculomotor neural pathways, that the primary deficit in infantile strabismus may be located in one of the brainstem pathways associated with generating a vergence signal.36 Neurons that appear to be involved in generating vergence responses have been located in the midbrain dorsal and dorsolateral to the oculomotor nucleus.37-39 Particularly intriguing is the report40 in which vergence neurons were recorded simultaneously in association with nearby oculomotor neurons. These authors found that the oculomotor neurons located near the vergence neurons were related to upward movement. Thus, a deficit in this
region might be associated with both esodeviations (vergence deficit) and upward movements of the eyes (DVD).

We found it useful to think about the effects of noise generator 2 in terms of the amount of coupling strength between the two eyes during fixation tasks. The coupling strength was reduced in essential infantile esotropia compared with normal. The occurrence of DVD in essential infantile esotropia was one way in which this uncoupling was revealed. The differences in scatter between the two eyes revealed by our measurements was another.

Current studies in which strabismus has been induced experimentally in monkeys through various kinds of postnatal manipulations all have produced infantile strabismus that is consistent with our model of an abnormal noise generator 1. It will be interesting to try to discover experimental ways of manipulating neonatal monkeys in ways that produce the kinds of deficits associated with noise generator 2, which appear to characterize essential infantile esotropia.

**Key words:** strabismus, infantile esotropia, accommodative esotropia, pediatric ophthalmology, monkey model, binocular fixation

**Acknowledgments**

The authors thank the veterinarians and staff of the Yerkes Regional Primate Research Center for their expert animal care. Portions of this project were conducted as part of the requirements for a master’s thesis by the first author. The Yerkes Regional Primate Research Center is fully accredited by the American Association for Laboratory Animal Care.

**References**


