Observations on the Effects of Form Deprivation on the Refractive Status of the Monkey

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The consistency of the refractive error alterations produced by monocular form deprivation in developing monkeys and the influence of the duration and the age at the onset of deprivation on the magnitude of these alterations was investigated. Refractive error and axial length measurements are presented for a group of monkeys which had one eye sutured closed for a period exceeding 18 months beginning at various ages ranging from 26 days to 25 months. In addition, we pooled and reanalyzed refractive error and axial length data for monocularly form-deprived monkeys from previous studies. When the alterations in the deprived eye’s refractive status are specified with respect to the fellow nondeprived eye, the results are, with a few noteworthy exceptions, consistent between laboratories and individual animals. In most cases, early monocular form deprivation causes the treated eye to develop a longer axial length and to manifest a more myopic/less hyperopic refractive error than the fellow nontreated eye. The magnitude of this deprivation-induced alteration is generally dependent on the duration and the age at the onset of form deprivation. The earlier the deprivation is initiated and the longer it is maintained, the greater the degree of the relative myopia produced in the deprived eye. Invest Ophthal mol Vis Sci 28:1236-1245, 1987

Although genetic factors undoubtedly play a major role in directing ocular development, investigations involving a variety of mammalian species, including humans, have suggested that a visually dependent feedback mechanism is also involved in the regulation of eyeball growth during maturation.1-6 This vision-dependent mechanism is believed to aid in coordinating the growth of the eye’s axial and optical components so that the eye maintains an approximately emmetropic refractive condition throughout development. Presumably this regulatory mechanism monitors the quality or clarity of the retinal image and adjusts the growth of the eye accordingly, because it has been consistently demonstrated that if the potential for a clear retinal image is prevented during development, the coordinated growth of the eye is disrupted.1,2,4-8 There is, however, currently some controversy concerning the type of refractive error which is produced in young monkeys by this unregulated growth.2,7,8

Wiesel and Raviola1,4,7 have reported that form deprivation initiated early in the life of a developing monkey causes the deprived eye to become axially myopic. Their results were very consistent; virtually all of their form-deprived monkeys became myopic. Subsequently several laboratories2,8,9 reported that although neonatal lid suture did appear to disrupt the process of emmetropization, they were not able to confirm the consistent relationship between neonatal form deprivation and axial myopia. In particular, the results of von Noorden and Crawford2 are often cited as evidence that monocular form deprivation does not always cause the deprived eye to become myopic. They reported that only about half of their form-deprived eyes became myopic; the remainder exhibited hyperopic refractive errors.

To date the exact reasons for the variability in the effects of form deprivation observed between individual animals and laboratories have not been delineated. It has often been speculated that this variability may be due to differences in the lid fusion procedures employed by different laboratories2,7,10 or that it may simply be a by-product of the uncontrolled axial growth associated with form deprivation.10 It is important to determine the source of this variability, as form-deprived monkeys could potentially serve as a useful animal model in investigations of the mechanisms which regulate the emmetropization process and which when disrupted produce anomalies in the eye’s refractive status. In the present report we have pooled and reanalyzed data from previous studies.
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Table 1. Characteristics of the monkey subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age at onset*</th>
<th>Eye†</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Axial length</th>
</tr>
</thead>
<tbody>
<tr>
<td>8104</td>
<td>62 days</td>
<td>RE†</td>
<td>+2.50 – 1.25 × 180</td>
<td>+2.50 – 1.25 × 180</td>
<td>18.8 mm</td>
</tr>
<tr>
<td>8024</td>
<td>92 days</td>
<td>LE</td>
<td>+4.00 DS‡</td>
<td>+4.00 DS</td>
<td>18.2 mm</td>
</tr>
<tr>
<td>8114</td>
<td>118 days</td>
<td>RE†</td>
<td>-8.25 DS</td>
<td>-2.00 – 2.00 × 135</td>
<td>20.5 mm</td>
</tr>
<tr>
<td>8021</td>
<td>153 days</td>
<td>LE</td>
<td>+3.50 – 1.00 × 180</td>
<td>+3.50 – 1.00 × 180</td>
<td>19.6 mm</td>
</tr>
<tr>
<td>L330</td>
<td>184 days</td>
<td>RE†</td>
<td>+2.50 – 0.50 × 180</td>
<td>+2.50 – 0.50 × 180</td>
<td>18.8 mm</td>
</tr>
<tr>
<td>L332</td>
<td>242 days</td>
<td>LE</td>
<td>+5.50 – 1.00 × 180</td>
<td>+5.50 – 1.00 × 180</td>
<td>18.6 mm</td>
</tr>
<tr>
<td>L322</td>
<td>309 days</td>
<td>LE</td>
<td>+0.75 DS</td>
<td>-3.00 – 2.50 × 180</td>
<td>20.0 mm</td>
</tr>
<tr>
<td>L420</td>
<td>366 days</td>
<td>LE</td>
<td>+1.75 DS</td>
<td>+2.75 DS</td>
<td>19.0 mm</td>
</tr>
<tr>
<td>L260</td>
<td>558 days</td>
<td>LE</td>
<td>+3.25 DS</td>
<td>-1.00 – 1.50 × 135</td>
<td>19.4 mm</td>
</tr>
<tr>
<td>L244</td>
<td>770 days</td>
<td>LE</td>
<td>-8.00 DS</td>
<td>-8.00 DS</td>
<td>21.5 mm</td>
</tr>
<tr>
<td>L264</td>
<td>30 days (24 months)*</td>
<td>LE</td>
<td>-2.25 DS</td>
<td>-5.50 DS</td>
<td>20.9 mm</td>
</tr>
<tr>
<td>L266</td>
<td>26 days (24 months)*</td>
<td>LE</td>
<td>+3.75 – 1.00 × 90</td>
<td>+3.75 – 1.00 × 90</td>
<td>18.7 mm</td>
</tr>
<tr>
<td>L48§</td>
<td>30 days (60 days)*</td>
<td>LE</td>
<td>-0.50 – 1.00 × 45</td>
<td>-0.50 – 1.00 × 45</td>
<td>18.9 mm</td>
</tr>
<tr>
<td>13623§</td>
<td>33 days (14 days)*</td>
<td>LE</td>
<td>0.00 DS</td>
<td>+3.00 – 3.00 × 180</td>
<td>18.2 mm</td>
</tr>
</tbody>
</table>

† Indicates the deprived eye.
‡ DS = dioptric sphere.
§ Refractive errors previously reported in ref. 9.

* The duration of deprivation was 18 months for all subjects except for subjects L264, L266, L48, and 13623. For these subjects the duration of deprivation is given in parentheses under the age at onset.

and present new data in an attempt to identify important experimental variables. The results demonstrate that when fundamental experimental variables are taken into account, the refractive error alterations produced by long-term monocular form deprivation in developing monkeys are, with a few notable exceptions, consistent and that the discrepancies previously noted between laboratories are more apparent than real.

Materials and Methods

All of the procedures used in this investigation conform to the ARVO Resolution on the Use of Animals in Research. Twelve rhesus monkeys (Macaca mulatta) were used as subjects. Unilateral form deprivation was produced by surgically fusing the eyelids of one eye using the procedures described by von Noorden et al.11 The age at the onset of monocular form deprivation was varied from animal to animal and ranged from 26 days to 25 months of age. The duration of the form deprivation for this group of animals was in excess of 18 months for each animal (see Table 1). A brief report of some of the psycho-

physical effects of form deprivation in these animals has been presented.12

At the end of the treatment period, the palpebral fissure was re-established, the refractive status of each eye was determined by retinoscopy and with an objective infrared optometer (Bausch & Lomb Ophthalmetron, Rochester, NY), and the axial lengths were measured by A-scan ultrasonography (Sonometric DBR 310, Huntington, WV). To obtain the measurements the animals were anesthetized with ketamine hydrochloride (10 mg/kg IM) and cycloplegia was produced by the topical application of 2 drops of 1% cyclopentolate hydrochloride. The optometer was aligned on the pupillary axis and a minimum of three readings were taken for each eye. The optometer was repositioned and refocused between measurements. The optometer provided, in graphic form, an estimate of the refractive error for essentially every meridian of the eye. A basic spectacle correction was derived from the optometer readings and was subsequently refined by retinoscopy. Retinoscopy was performed with a streak retinoscope and hand-held trial lenses. For the axial length measurements, several drops of a topical anesthetic (proparacaine hydro-
chloride, 0.5%) were instilled in the eye and the ultrasound probe (10 MHz crystal) was placed in direct contact with the geometrical center of the cornea with care being taken not to indent the corneal surface. The position of the probe was adjusted to maximize the echoes from the posterior lens surface and the vitreal-retinal interface. It was assumed that the velocity of ultrasound in the monkey's eye was the same as that measured in the human eye. The distance between the crystal artifact and the echo from the vitreal-retinal interface was considered to represent the axial length of the eye and was measured to the nearest tenth of a millimeter.

The pretreatment refractive errors for some of the subjects were determined by retinoscopy at the time that form deprivation was initiated. These refractive errors are reported in Table 1, but, because these measurements were obtained for a relatively small number of monkeys, the data were not considered when the effects of form deprivation were evaluated. Nevertheless, comparisons between pre- and posttreatment refractions within this group of monkeys support the conclusions drawn below from posttreatment comparisons between deprived and nondeprived eye populations.

In order to examine the consistency of the effects of form deprivation on the monkey's refractive status and to aid in the investigation of the effects of several experimental variables on these induced refractive error alterations, we have attempted to pool all of the data for individual monocularly lid-sutured monkeys that are available in the current literature. Therefore, we have included in this paper data from previous studies by Wiesel and Raviola, von Noorden and Crawford, Harwerth et al, and Thorn et al. In addition we report axial length measurements for two monocularly lid-sutured monkeys for which refractive error data were published previously.

Results

Effects on Refractive Status

The deprivation schedule, the spectacle plane refractive errors specified in minus cylinder notation, and the axial lengths for each eye of the experimental subjects are shown in Table 1. The effects of lid suture on the monkeys' deprived eyes are illustrated in Figure 1 where the interocular differences in refractive error, expressed in diopters, are shown for each subject. The plotted values were obtained by subtracting the spherical equivalent refractive error correction for the nondeprived eye from the deprived eye's correction. Therefore, points plotted above the dashed line indicate that the deprived eye was more myopic/less hyperopic than the nondeprived eye.

For comparison purposes data previously reported from our laboratories and from the laboratories of Wiesel and Raviola have also been included in Figure 1. Only data for monkeys which were deprived during the first 2 years of life are shown. The filled symbols in the data from the study by von Noorden and Crawford represent animals which had undergone reverse-suture procedures. This reverse-suture procedure included an initial period of monocular eyelid suture that was terminated by opening the initially deprived eye and suturing closed the initially open eye. Within this population of monkeys, the durations of the deprivation periods for the first and second sutured eyes varied from animal to animal. Nevertheless, for these reverse-sutured animals the initially sutured eye was considered the "treated" eye; the eye which was subsequently closed during the reverse suturing procedures was designated as the "control" eye.

Primarily due to procedural differences, one must be cautious when pooling data between laboratories. Nevertheless the data in Figure 1 illustrate several points. First, when the refractive error alterations in the deprived eyes of the monocularly lid-sutured monkeys (open symbols) are specified with respect to the nontreated control eyes, the effects of form deprivation are consistent. With two exceptions, one animal from the study by Harwerth et al and one animal from this study, monocular lid suture always caused the deprived eye to become relatively more myopic/less hyperopic than the nontreated control eye.

A second point illustrated by Figure 1 is that the majority of the animals included in the report by von Noorden and Crawford had been reverse sutured. The inclusion of reverse-sutured animals probably contributed to the apparent discrepancies between their results and those reported by Wiesel and Raviola. One of the primary advantages of employing unilateral lid suture procedures is that the nondeprived eye provides an "in animal" control for a number of potentially critical experimental variables. Employing reverse-suture procedures confounds interocular comparisons and, as shown in Figure 1, results in a substantial degree of variability in the interocular differences in refractive error. When it is considered that the duration of deprivation was often different for the two eyes of these reverse-sutured monkeys and that with reverse-suture procedures the age at the onset of deprivation is different for the two eyes, it is not surprising that interocular comparisons of refractive errors in these animals did not yield consistent results.

Although Figure 1 demonstrates that monocular lid suture almost always causes the deprived eye to
INTEROCULAR REFRACTIVE ERROR DIFFERENCES
MONOCULARLY FORM-DEPRIVED MONKEYS

Fig. 1. Interocular spherical equivalent refractive error differences (diopters) for individual form-deprived monkeys (deprived eye correction - nondeprived eye correction). Data from three previous studies\textsuperscript{1-3} are also included. Only data for monkeys which were deprived by 2 years of age are shown. The open and filled symbols represent monocularly lid-sutured and reverse lid-sutured monkeys, respectively. With two exceptions, the data for the monocularly deprived monkeys are plotted above the dashed zero line, indicating that form deprivation caused the deprived eye to become more myopic/less hyperopic than the nondeprived eye.

become relatively more myopic than the nondeprived eye, the results plotted in Figure 2 indicate that in a number of instances the deprived eye did not develop an absolute myopia. Figure 2 illustrates refractive error frequency distributions for three different monkey populations. The histogram in panel A shows the refractive error distribution for normal macaque monkeys obtained by Young.\textsuperscript{13} This population consisted primarily of adolescent and adult macaque monkeys (\textit{Macaca mulatta} and \textit{Macaca nemestrina}); both wild and laboratory-reared animals are included in the distribution. The histograms shown in panels B and C of Figure 2 represent data for the nondeprived and deprived eyes, respectively, of monocularly lid-sutured monkeys. Again, data for monocularly deprived monkeys have been pooled from several studies.\textsuperscript{2,7,9}

The refractive error distribution for the normal monkeys in panel A demonstrates all of the essential characteristics observed in refractive error distributions for the general human population.\textsuperscript{14} The distribution is basically leptokurtic with the great majority of animals demonstrating either no refractive error or a small degree of hyperopia.

The refractive error distribution for the lid-sutured monkeys' nondeprived eyes (panel B) appears to be broader than the distribution for the normal monkeys. In particular there appears to be a higher preva-
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REFRACTIVE ERRORS (DIOPTRIC SPHERICAL EQUIVALENTS)

Fig. 2. Refractive error frequency distributions for normal and monocularly lid-sutured monkeys. The distribution for normal adult macaque monkeys (A) has been replotted from an investigation by Young.13 Data for the nondeprived (B) and deprived eyes (C) of monocularly lid-sutured monkeys from three previous studies7,9 have been combined with the data from this investigation. Only data for monkeys which were deprived by 2 years of age are shown. The data from Raviola and Wiesel's study7 were obtained from a histogram with 2-diopter bin widths (their Fig. 1). To make their data compatible with the format of the histogram illustrated above, the individual refractive errors in their histogram were sorted into 1-diopter groups centered on the nearest odd diopter. This sorting process undoubtedly contributed to the apparent absence of data for nondeprived eyes in the +2.0 diopter refractive error category (B). The distribution for the deprived eyes (C) demonstrates the range of refractive errors produced by neonatal lid suture and illustrates that some deprived eyes exhibit a hyperopic refractive error.

The prevalence of moderate degrees of hyperopia than observed in the normal population. This higher prevalence of hyperopia can be attributed, in part, to the fact that some of these animals were very young (less than 3 months of age) at the time the refractive error measurements were obtained. Although the data suggest that the refractive error distribution for the nondeprived eyes may not be entirely normal, a larger number of monocularly lid-sutured monkeys must be examined before any firm conclusions can be made concerning the status of the nondeprived eyes.

The distribution of refractive errors for the lid-sutured monkeys' deprived eyes (panel C) indicates that the majority of the deprived eyes developed an absolute myopic refractive error. However, as originally pointed out by von Noorden and Crawford,2 some of the deprived eyes clearly exhibit hyperopic refractive errors. In some, but certainly not in all cases (see subjects 8104 and 8021 in Table 1), these hyperopic refractive errors were observed in relatively young animals.

The refractive error distribution for the deprived eyes also illustrates the high degree of variability characteristic of refractive errors in lid-sutured eyes. Figures 3 and 4 demonstrate that much of this rather large range of refractive errors can be attributed primarily to basic procedural differences between animals and laboratories, specifically the age at the time of lid suture and the duration of lid suture.

Figure 3 illustrates the relationship between the age at the onset of the form deprivation and the magnitude of the interocular refractive error difference in
monocularly lid-sutured monkeys. The interocular refractive error difference in diopters (deprived eye correction – nondeprived eye correction) is plotted as a function of the subjects’ ages at the onset of deprivation. Data have been pooled from several studies, but only monkeys which were deprived for a minimum duration of 2 months are represented. With two exceptions (one animal deprived at 30 days of age in the study by Harwerth et al9 and one animal deprived at 26 days of age in this study), the data appear to follow a lawful relationship between the age at onset and the magnitude of the induced refractive error. The correlation coefficient of a linear regression analysis of the data from only the subjects which manifested a relative myopia in their deprived eyes indicates that there is a significant relationship (r = 0.65; df = 19; P < 0.01) between the log of the age at onset and the magnitude of the differences in refractive error between the deprived and control eyes. However, it must be emphasized that this conclusion only holds for subjects that developed a relative myopia in their deprived eyes.

The influence of the duration of monocular form deprivation on the magnitude of the induced refractive error is illustrated in Figure 4. The interocular differences in refractive error (deprived eye correction – control eye correction) are plotted as a function of the duration of monocular deprivation. Data are illustrated for monkeys which were form deprived before 6 weeks of age; the different symbols represent individual animals from different laboratories. Again, with the exception of the two animals noted above (the animals deprived for 22 and 24 months), the data indicate that the magnitude of the relative myopia induced in the deprived eyes increased as a function of the duration of deprivation. If the two animals which failed to develop a relative myopia in their treated eyes are excluded from the analysis, there is a significant relationship between the log of the duration of the deprivation and the magnitude of the interocular differences in refractive error (r = −0.65; df = 10; P < 0.05).

Effects on Axial Length

Form deprivation in developing monkeys has also been reported to produce alterations in the eye’s axial length.1,8,15,16 The nature of the axial length alterations produced by monocular form deprivation is illustrated in Figure 5, where the interocular differences in axial length are expressed for individual animals as the ratio of axial lengths between the deprived and nondeprived eyes. The data included in Figure 5

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**Fig. 4.** Interocular refractive error differences (diopters) for monocularly lid-sutured monkeys (deprived eye correction – nondeprived eye correction) plotted as a function of the duration of deprivation (days). Data from three previous studies1,2,3 are also shown. Only data for monkeys which were lid-sutured before 6 weeks of age are presented. The magnitude of the interocular refractive error difference increases as the duration of deprivation is increased.

**Fig. 5.** Interocular axial length ratios (deprived eye/nondeprived eye) for monocularly form-deprived monkeys. Individual data from three previous studies1,2,3 have also been included. Only animals which were deprived before 2 years of age are represented. In comparison to their nondeprived eyes, the great majority of monkeys (23 of 26 animals) exhibited longer axial lengths for their deprived eyes.
develop a longer axial length than the nondeprived control eye.

The relationship between the axial length and refractive error alterations produced by neonatal form deprivation is shown in Figure 6. The interocular refractive error differences in diopters (deprived eye - nondeprived eye) are plotted as a function of the interocular axial length ratios (deprived eye/nondeprived eye) for individual animals from two laboratories. Only animals which manifested a relative myopia or myopia in their deprived eyes are represented. The solid line was derived from a least-squares linear regression analysis of the data. The broken line represents the predicted relationship between the interocular refractive error differences and the interocular axial length ratios. The agreement between the predicted and the experimental data indicate that the deprivation-induced refractive error alterations are axial in nature.

The data demonstrate that, for this selective subset of animals, there is a significant relationship between the interocular differences in refractive error and the interocular ratios of axial length (r = 0.87; df = 15; P < 0.01). Moreover, there is good agreement between the experimental data and the predicted relationship between axial length and refractive error. Therefore, these data support the conclusion by Raviola and Wiesel that the deprivation-induced refractive error alterations shown in Figure 1 are axial in nature.

Like the alterations in refractive error described above, when the effects of form deprivation on the deprived eye's axial length are specified with respect to the nondeprived eye's axial length, the results are fairly consistent. In all but three of the animals for which data are available (23 of 26 monkeys), the axial length of the deprived eye was longer than that for the nondeprived eye. The relatively shorter axial lengths observed by Thorn et al in two of their monocularly form-deprived monkeys suggest that these animals, like the two exceptions noted above in Figure 1, had developed a relative hyperopia in their deprived eyes. However, the axial length measurements for these monkeys were obtained through their fused eyelids; their refractive errors were not measured.

Other studies in which axial length data for populations of deprived monkeys are reported (the data for individual monkeys were not available) also indicate that form deprivation results in a consistent increase in the deprived eye's axial length relative to that for nondeprived control eyes. Therefore, these results, when considered together with the individual data shown in Figure 5, indicate that monocular form deprivation almost always causes the deprived eye to develop a longer axial length than the nondeprived control eye.
from the present study) are excluded from the analysis, there is a significant correlation between the interocular axial length ratios and the age at the onset of deprivation ($r = -0.48$; df = 19; $P < 0.05$). Within the subset of our population that demonstrated a relative axial elongation in their deprived eyes, the earlier the age at the onset of deprivation, the greater the interocular difference in axial length.

The effects of the duration of deprivation on interocular axial length ratios (deprived eye/nondeprived eye) in monocularly form-deprived monkeys are shown in Figure 8. Data for monkeys which were deprived before 6 weeks of age have been pooled from three different laboratories. When all of the data are considered, the correlation between the duration of deprivation and the induced axial length anomaly is not significant ($r = -0.19$). Even when the data for the three subjects which failed to develop longer axial lengths in their deprived eyes are excluded from the analysis, the interocular axial length ratios are not significantly correlated with the duration of deprivation. In light of the significant relationship observed between the magnitude of the induced refractive error and the duration of deprivation (Fig. 4), it is somewhat surprising that an analysis of the axial length data suggests that the duration of deprivation does not influence the magnitude of the axial length alterations. However, the animal populations that provided the data for Figures 4 and 8 were not identical. In particular, Figure 8 includes axial length data from the study by Thorn et al. Since in their study the axial length measurements were obtained through the monkeys' fused eyelids, the refractive errors for these animals were not available. If the data reported by Thorn et al are also excluded from the analysis, there is a tendency for the animals which were treated for the longer durations to exhibit the larger interocular axial length ratios and the correlation between these ratios and the duration of deprivation approaches statistical significance ($r = 0.54$).

There are two reasons why the data from the paper by Thorn et al. when included in the above analysis, appear to mask the influence of the duration of deprivation on the magnitude of the induced axial length changes. First, in two of their monkeys, lid suture caused the deprived eye to become shorter than the nondeprived eye. These findings, although atypical of the population of monocularly deprived monkeys as a whole, are important because they indicate clearly that form deprivation does not always result in the development of an abnormally long axial length. Like the two animals noted in Figure 1 which failed to develop a relative myopia in their deprived eyes, there does not appear to be anything significant in the history of these two animals which would explain
why they failed to develop longer axial lengths in their deprived eyes. Second, when axial length measurements are taken through fused lids, it may not always be possible to accurately identify the position of the anterior pole of the cornea. Therefore, if the estimates of axial length included some portion of the eyelids, the measured axial lengths would be artificially long. Since the effects of form deprivation on the axial dimensions of the eye are restricted essentially to the vitreous chamber, interocular axial length differences expressed as ratios derived from axial length measurements which included some portion of the eyelids would be smaller in absolute terms than if the ratios were based on the true distance between the anterior pole of the cornea and the retina. Possibly that is why the interocular axial length ratios reported by Thorn et al are, in general, smaller than those reported by other laboratories for monkeys deprived for equivalent periods of time.

Discussion

The results demonstrate that monocular form deprivation initiated early in the life of a developing monkey disrupts the normally regulated growth of the eye. When the effects of this unregulated growth on the deprived eye's refractive status are specified with respect to that of the fellow nondeprived eye, the nature of the resulting refractive error alteration is very consistent. In almost every case (43 out of 47 cases; combined totals from this study and refs. 6–9; the group data in refs. 15 and 16 also support this consistent relationship), monocular form deprivation causes the treated eye to develop a longer axial length and/or to manifest a more myopic/less hyperopic refractive error than the nontreated eye. Furthermore, the magnitude of this relative axial myopia is dependent on the duration and the age at the onset of deprivation. However, even when the obvious experimental variables are taken into account, a small proportion of form-deprived animals fail to develop anomalous refractive errors, and in some cases these exceptions exhibit refractive error and axial length changes which indicate that form deprivation caused the treated eye to become relatively more hyperopic. At the present time these exceptions cannot be explained, but the existence of these exceptions supports the concept that multiple factors are involved in the pathogenesis of experimentally induced refractive errors.

The apparent failure of some laboratories to confirm the consistent relationship between neonatal form deprivation and induced axial myopia can be attributed in part to the difficulty of establishing appropriate controls. If relatively short periods of deprivation are employed so that the magnitude of the induced refractive anomaly is small, the normal intersubject variability of refractive errors can mask the alterations produced by form deprivation. If, for example, an animal had a moderate hyperopic refractive error prior to form deprivation, the alterations in the deprived eye's refractive status may not be sufficient to result in an absolute myopia. Normal intersubject variability in refractive errors becomes a particularly critical factor when interocular comparisons of refractive errors for a given subject are not practiced or not employed (eg, when reverse suture procedures are used) and when monkeys are employed as subjects, because usually relatively small numbers of subjects are used. The results presented in this study confirm the advantages of using unilateral form deprivation procedures which allow small treatment-related alterations to be detected by interocular comparisons between the deprived and nondeprived eyes. The most obvious advantage of employing unilateral deprivation procedures is that the nontreated eye provides an “in animal” control for a number of important and previously recognized variables that influence an animal's refractive status (eg, genetic factors, the housing environment, age, etc.).

Probably the best way to evaluate the effects of monocular form deprivation on the developing animal's refractive status would be to compare interocular refractive error differences before and after the period of form deprivation. Unfortunately, pretreatment refractive error measurements have only been reported for a small number of animals. In most investigations, including this study, it is assumed that prior to form deprivation the refractive errors for the monkey's two eyes are equal. It should be noted, however, that some of our monkeys (eg, subjects L330 and L244) exhibited a small, but significant, anisometropia prior to the onset of form deprivation. It is likely that if pre-treatment differences in refractive error were systematically taken into account, the degree of variability between animals would be further reduced and the effects of pertinent experimental variables would be more obvious.

A characteristic of the refractive error alterations produced by neonatal form deprivation is that the amount of relative myopia manifested by monkeys varies substantially from individual to individual. Since the techniques which have been most commonly used to deprive a monkey of form vision (eg, lid suture) are unrefined from an optical point of view, the associated alterations in the retinal image are difficult to accurately specify and are likely to vary to some degree from animal to animal. As a result, it has been speculated often that much of the individual variability in the magnitude of these induced refractive errors is due to inconsistencies in the nature of the anomalous visual input produced by these techniques. The results presented in Figures
3, 4, 7, and 8 indicate, however, that differences in the duration and the age at the onset of deprivation are responsible for much of the individual variability in the magnitude of the induced refractive error.

There are indications in the literature that the duration and the age at the onset of form deprivation are important experimental variables in determining the magnitude of the induced refractive error anomaly. Raviola and Wiesel\textsuperscript{7} have reported that when the lids of a monocularly lid-sutured monkey are opened, the subsequent axial growth rate of the deprived eye is identical to that of the nondeprived eye. Since the unregulated excessive axial growth was only observed when the eyes were lid-sutured, the magnitude of the resulting refractive error alterations would be dependent on the duration of the deprivation. Several laboratories\textsuperscript{1,2,3,4,7,8} have reported previously that form deprivation initiated in adolescent or mature monkeys did not cause the deprived eye to develop an anomalous refractive error. These observations suggest that a sensitive period exists for the effects of form deprivation on the monkey’s refractive status and imply that age at the onset of deprivation would influence the magnitude of the induced refractive anomaly. Sommers et al.\textsuperscript{15} however, did not observe a clear relationship between the age at the onset of form deprivation and the magnitude of the axial length alterations. The apparent discrepancy between their results and those reported in this study can most likely be attributed to differences in the range of ages considered and the number of animals analyzed. Whereas Sommers et al.\textsuperscript{15} varied the age at the onset of deprivation from 7 to 81 days, in the present study we analyzed all of the available data for monocularly deprived monkeys, which provided a range of ages between 1 day and 25 months.

It has been repeatedly demonstrated that the refractive errors produced by form deprivation are associated with alterations in the eye’s axial dimensions.\textsuperscript{1,4,7,8,15,16} The clear relationship between the interocular differences in refractive error and axial length illustrated in Figure 5 for monocularly deprived monkeys corroborates the axial nature of the induced refractive anomalies. It has been previously reported that form deprivation does not affect corneal curvature, the depth of the anterior segment, or the thickness of the lens.\textsuperscript{7} The alterations in the deprived eye’s axial dimensions appear to be limited to changes in the depth of the vitreous chamber.\textsuperscript{7,8} The close agreement between the experimental data and the predicted relationship between the refractive error and axial length alterations shown in Figure 5 supports the concept that the induced refractive errors are the result of an increase in the depth of the vitreous chamber.

By pooling data from several laboratories it has been possible to demonstrate that the refractive errors produced by form deprivation are influenced by several experimental variables. It is likely that other experimental parameters associated with form deprivation also affect the genesis of these refractive anomalies. Nevertheless, the overall consistency in the refractive anomalies reported by different laboratories indicate that these induced alterations are robust, and strengthens the use of the form-deprived monkey as a model for studying the emmetropization process and the pathogenesis of refractive errors.

Key words: myopia, form deprivation, monkey, refractive error, axial length

References