Recovery from Form-Depreivation Myopia in Rhesus Monkeys

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PURPOSE. Although many aspects of vision-dependent eye growth are qualitatively similar in many species, the failure to observe recovery from form-deprivation myopia (FDM) in higher primates represents a significant potential departure. The purpose of this investigation was to re-examine the ability of rhesus monkeys (Macaca mulatta) to recover from FDM.

METHODS. Monocular form deprivation was produced either with diffuser spectacle lenses (n = 30) or by surgical eyelid closure (n = 14). The diffuser-rearing strategies were initiated at 24 ± 3 days of age and continued for an average of 115 ± 20 days.

RESULTS. At the onset of unrestricted vision, the deprived eyes of 18 of the diffuser-reared monkeys and 12 of the lid-sutured monkeys were at least 1.00 diopters (D) more hyperopic or more myopic than their fellow eyes. The mean (diffuser = −4.06 D, lid-suture = −4.50 D) and range (diffuser = −1.0 to −10.19 D, lid-suture = −1.0 to −10.25 D) of myopic anisometropia were comparable in both treatment groups. All 18 of these diffuser-reared monkeys demonstrated recovery, with 12 animals exhibiting complete recovery. The rate of recovery, which was mediated primarily by alterations in vitreous chamber growth, the animals were allowed unrestricted vision. The ability of the animals to recover from treatment-induced refractive errors was assessed periodically by retinoscopy, keratometry, and A-scan ultrasonography. Control data were obtained from 35 normal monkeys.

CONCLUSIONS. Like many other species, young monkeys are capable of recovering from FDM. However, the potential for recovery appears to depend on whether the normal emmetropic eye growth obtained from animals can be extrapolated, at least in a qualitative sense, to humans with a relatively high degree of confidence.

However, similar experimental strategies have not always affected refractive development in a qualitatively similar manner in all animals. When inconsistencies between species can be attributed to known physiological differences between animals, they can provide substantial insight into basic aspects of emmetropization. Unexplained interspecies differences, however, signal potentially important evolutionary departures and raise concerns about generalizing animal results to humans. Consequently, identifying true interspecies differences is important, particularly when it involves animals such as monkeys, which are considered to be very close to humans. The failure of monkeys to recover from FDM when unrestricted vision is restored is one such inconsistency.

Recovery from FDM after the restoration of unrestricted vision was first observed in chicks by Wallman and Adams and represented one of the first clear indications that emmetropization was regulated by visual feedback. The ability to recover from FDM has subsequently been confirmed in chicks in several laboratories and documented in another commonly studied animal, the tree shrew. However, results in rhesus monkeys and marmosets with FDM produced by unilateral eyelid suture indicate that higher primates may not be capable of recovering from FDM.

There are several potential explanations for the failure to observe recovery in rhesus monkeys with FDM. Results in chicks indicate that the ability to recover from FDM decreases with age. In this respect, most of the results currently available for rhesus monkeys have come from animals that were
deprived for relatively long periods of time and were perhaps beyond the critical period for recovery when unrestricted vision was restored. It is also possible that lid-suture surgery, the most common method used to produce form deprivation in monkeys, produces complications, possibly optical in nature, that interfere with the eye’s ability to compensate for optical defocus after eyelid reopening. In this respect, tree shrews with FDM produced by eyelid suture fail to recover, whereas those with FDM produced by diffuser lenses do recover. The purpose of this study was to re-examine the ability of rhesus monkeys to recover from FDM. Based on promising preliminary observations in both marmosets (Troilo D, et al. IOVS 2000;41:ARVO Abstract 691; Troilo D, et al. IOVS 2002;43:ARVO E-Abstract 186) and rhesus monkeys, we concentrated our studies on relatively young rhesus monkeys that had FDM produced by wearing diffuser spectacle lenses over one eye.

Materials and Methods

Subjects

Longitudinal measures of refractive error were obtained from 44 rhesus monkeys (Macaca mulatta) that experienced monococular form deprivation. All our experimental monkeys were subjects in previous studies of either refractive or sensory development and as a group have a somewhat mixed history. A beneficial consequence of these different treatment histories is that as a group our experimental subjects exhibited a range of refractive errors from essentially emmetropia to more than −10 D of FDM.

Monocular form deprivation was imposed on experimental monkeys by either eyelid surgery or with diffuser spectacle lenses. For the majority of treated animals (n = 30), form deprivation was produced by fitting the infant monkeys with helmets that held a diffuser spectacle lens in front of one eye and a clear plano lens in front of the fellow eye. The helmet-rearing procedure, which has been described in detail in a previous study, was initiated at 24 ± 3 days of age and continued for an average of 115 ± 20 days. The amount of form deprivation varied among helmet-reared animals using either different strength diffuser lenses or by allowing the animals short periods of unrestricted vision each day during the treatment period. At the end of the treatment period, the helmets and diffusers lenses were removed, and the animals were allowed unrestricted vision.

Monocular form deprivation was produced in 14 animals by surgically closing the eyelids of one eye using the procedures described by von Noorden et al. The onset of lid closure varied between monkeys from 33 to 761 days of age in a systematic manner. Although the duration of eyelid closure ranged from 14 to 689 days, for 12 of these 14 lid-sutured monkeys, the duration of deprivation was at least 540 days. The other two lid-sutured monkeys experienced durations of 14 and 31 days, beginning at 38 and 60 days of age, respectively. At the end of the treatment period, the palpebral fissure was surgically re-established and the animals were allowed unrestricted vision.

Control data for the first 2 years of life were obtained from 17 normal monkeys that were reared with unrestricted vision. In addition, control data for the helmet-rearing procedures were obtained for three monkeys that were reared wearing helmets that held plano spectacle lenses in front of both eyes. The onset and duration of helmet wear for the plano control monkeys were equivalent to those for the diffuser-reared monkeys. Refractive-error data for the normal and the plano-lens-reared infants have been reported previously. Fifteen normal monkeys that were obtained as adolescents provided control data for the later juvenile period of refractive development.

During the recovery period, many of the treated and control monkeys were used as subjects in psychophysical studies of spatial and/or binocular vision. These experiments were initiated when the monkeys were at least 540 days of age and required the animals to perform behavioral detection tasks for approximately 2 hours each day. The details of these studies have been described previously.

Biometric Measurements

Refractive development and in particular the changes in refraction that occurred after the period of form deprivation were assessed using measurement methods that have been described in detail previously. For the helmet-reared monkeys and the young control animals, refractive error, corneal curvature, and the eye’s axial dimensions were measured at 2- to 4-week intervals throughout the observation period. To make these measurements, cycloplegia was induced with 2 drops of topically applied 1% tropicamide. The animals were anesthetized with intramuscular injections of ketamine hydrochloride (20 mg/kg) and acepromazine maleate (0.2 mg/kg) and were topically instilled 0.5% tetracaine hydrochloride. The spherical-equivalent, spectacle-plane refractive corrections were determined by retinoscopy.

The reported data represent the average from two independent observers. The mean radius of curvature of the cornea along the eye’s pupillary axis was determined with a handheld keratometer (Alcon Auto-keratometer; Alcon Systems Inc., St. Louis, MO). The eye’s axial dimensions, particularly vitreous chamber depth, were measured by A-scan ultrasonography using an instrument with a focused, 7-MHz transducer (Image 2000; Mentor, Norwell, MA). The reported axial dimensions represent the average of 10 individual readings obtained using a weighted average velocity for ultrasound of 1550 m/sec.

The general methods used to assess refractive development in the lid-sutured monkeys and the older control animals were similar to those described earlier with the following exceptions. Cycloplegia was induced with topically applied 1% cyclopentolate instead of tropicamide. No attempts were made to measure corneal curvature. Total axial length was measured with an A-scan system with a 10-MHz transducer (DBR 310; Sonometric, Huntington, WV). It was not possible, however, to obtain the dimensions of the vitreous chamber alone with this instrument. The reported axial lengths represent the mean of three to five individual readings. Of the 12 monkeys that exhibited myopic anisometropias larger than −1.0 D, the first measurements were obtained immediately after eyelid opening for six of these monkeys. For the other six lid-sutured monkeys, their initial measurements were obtained from 40 to 367 days after eyelid opening (i.e., there was a period of unrestricted vision before the first measurement). Subsequent measurements for the lid-sutured animals were made at less frequent intervals than with the diffuser-reared animals.

All the rearing and experimental procedures were approved by The University of Houston’s Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Statistical Analysis

Two-sample t-tests were used to compare the data from treated and normal monkeys. Paired student t-tests were used to examine interocular differences and for before-after comparisons in individual animals. Due to the low number of subjects, a nonparametric test (the Mann-Whitney test) was used to compare the anisometropic and axial length changes between the lid-sutured monkeys that were allowed unrestricted vision before the first measurement and those that were assessed immediately after eyelid opening. The relationship between the rate of recovery and the magnitude of the experimentally induced refractive errors was determined by nonlinear regression analysis. All the analyses were executed on computer (Minitab, rel. 12.21; Minitab Inc., State College, PA; and SPSS software, ver. 8.0; SPSS Inc., Chicago, IL).

To evaluate axial growth, a locally weighted regression scatter plot smoothing method (LOESS) was used to generate developmental curves for overall axial length and vitreous chamber growth rates in normal monkeys. LOESS is a nonparametric smoothing algorithm that allows data to be expressed in a trend without initial mathematical
RESULTS

Recovery in Diffuser-Rearmed Monkeys

The monocular form deprivation associated with our various diffuser-rearing regimens disrupted emmetropization in the deprived eyes of most of the treated animals, resulting in an interocular imbalance in refractive errors with the treated eyes typically becoming more myopic or less hyperopic than the nontreated eyes. Although monocular manipulations have been shown to alter refractive development in both the treated and nontreated eyes of infant monkeys, these interocular effects are relatively small, and consequently we considered the degree of anisometropia exhibited by the treated animals to represent the amount of FDM. At the end of the treatment period, the treated eyes of 18 of the 30 diffuser-reared monkeys were at least 1.0 D more myopic or less hyperopic than their fellow, nontreated eyes. The range of myopic anisometropias in this subgroup of treated monkeys varied from −1.0 to −10.19 D (mean = −4.06 ± 2.77 D; Fig. 1A).

As shown in Figure 1A, at least some recovery from FDM was subsequently observed in all 18 of the diffuser-reared monkeys that had ≥1.0 D of FDM at the end of the treatment period. In 12 of these 18 monkeys, the magnitude of myopic anisometropia had decreased to less than 1.0 D by the end of the observation period, which varied in duration from 126 to 1566 days. Within this group of animals, the decrease in anisometropia varied from 0.69 to 7.50 D. As illustrated by Fig. 1B, the recovery was due to a hyperopic shift in the refractive state of the treated eyes, and in some cases, a myopic shift in the refractive state of the fellow eyes. The six monkeys that had residual anisometropic errors that were greater than 1.0 D at the end of the observation period tended to be the animals that showed high amounts of FDM at the start of the recovery period. For example, four of these six monkeys had at least −5.0 D of FDM at the start of the recovery period. However, as will be shown later in this section, it is likely that more complete recovery would have been observed in these monkeys if we had increased the duration of the observation period.

The consistency and systematic nature of the recovery process are emphasized in Figures 2 and 3, which illustrate the longitudinal changes in anisometropia that occurred during the treatment (filled symbols) and recovery periods (open symbols) for the 18 diffuser-reared monkeys that developed significant amounts of FDM. Figure 2 shows individual plots for each of the 15 diffuser-reared monkeys that had less than −5.0 D of FDM. At some point during the recovery period, the anisometropia for each of these animals fell within the range of anisometropias observed in control monkeys (thin solid lines), which demonstrates how successful the recovery process was in infant monkeys. The data for the five monkeys that showed severe FDM (−5.50 to −10.19 D) are superimposed in a single plot in Figure 3. Complete recovery was observed for one of these monkeys, although it required approximately 1500 days of unrestricted vision. The other four monkeys included in Figure 3 were observed for a shorter period and showed incomplete recovery. However, considering that the recovery data for all the animals in Figure 3 appear to follow a similar time trajectory, it seems reasonable to speculate that given longer observation periods, more of these monkeys would have shown complete recovery.

Inspection of the data in Figures 2 and 3 suggests that the rate of recovery and the time required for complete recovery varied systematically with the initial degree of FDM. To quantify the rate of recovery we used a nonlinear regression analysis to fit the following logarithmic function to the anisometropia data obtained during the recovery period for each monkey: \( y = a + b \ln(x) \); where \( y \) and \( x \) represent the amount of anisometropia and the number of days since unrestricted vision was restored, respectively, and \( a \) and \( b \) represent scaling coefficients. As illustrated in Figure 4A, which shows the calculated functions for three representative animals, this log function provided a good fit \((P < 0.01)\) to the data for 16 of the 18 monkeys and an adequate fit for the remaining two animals. With a logarithmic function like this, the rate of recovery can best be described by the slope or first derivative of the logarithmic function. The first derivative of \( y = a + b \ln(x) \) (i.e., \( dy/dx \)) is \( b/x \). Therefore, \( b \) is proportional to the rate of recovery; specifically \( b \) increases as the rate of recovery gets faster. Figure 5B illustrates that the coefficient \( b \), hence the rate of recovery, was significantly correlated with the magnitude of anisometropia at the start of the recovery period \((r^2 = 0.95; P < 0.001)\). It is also clear from the first derivative of this function (\( dy/dx = b/x \)) that the rate of recovery decreased with time during the recovery process.

![Figure 1](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932925/ on 11/20/2018)
FIGURE 2. Degree of anisometropia plotted as a function of age in the 13 monkeys that exhibited between −1.00 and −5.00 D of FDM at the end of the treatment period. Data were obtained during the treatment (●) and recovery (○) periods, respectively. ○ The end of the treatment period and the restoration of unrestricted vision. Solid thin lines: data from the normal monkeys (right eye minus left eye). At some point during the recovery period, all the treated monkeys showed anisometropic errors that fell within the range of normal monkeys.
After the recovery from FDM, many of the diffuser-reared animals represented in Figure 2 subsequently maintained the resulting isometropia over very long observation periods (e.g., monkeys TIA, NEL, and LIS). However, it is interesting that some animals did not remain isometropic after the initial recovery from FDM. For example, in monkey QUI, after it recovered from approximately $-3.0$ D of FDM, a relative hyperopia developed in the originally form-deprived eye. In contrast, monkey MAR’s deprived eye became relatively myopic again after a successful recovery from $-4.40$ D of FDM. However, as shown in Figure 5, many of the 12 diffuser-reared monkeys in which less than 1.0 D of FDM developed during the treatment period also failed to maintain isometropia throughout the observation period (e.g., monkeys SAW, NIN, and MIG). Thus, the initial degree of FDM does not appear to influence the long-term stability of the balance of refractive errors between the two eyes.

The recovery from FDM in the diffuser-reared monkeys came about primarily because there was a dramatic decrease in the vitreous chamber growth rates of the deprived eyes after removal of the diffuser lenses. However, the recovery process, and particularly the reduction in myopic anisometropia, were also influenced by alterations in the vitreous chamber growth rates in the nontreated eyes. Figure 6, which shows data for two representative monkeys, illustrates the two basic recovery patterns that we observed. After the onset of unrestricted vision, vitreous chamber growth in the deprived eyes of both monkeys virtually halted, and the deprived eyes subsequently exhibited relative hyperopic shifts in refractive error as a consequence of reductions over time in the refracting powers of the cornea and crystalline lens (Qiao Y, et al. IOVS 2000;41:ARVO Abstract 693). However, the changes in the nontreated eye’s vitreous chamber growth rate depended on the nontreated eye’s absolute refractive error. Nontreated eyes that were less hyperopic than normal (e.g., monkey JAS) showed a decrease in vitreous chamber growth and relative hyperopic shifts in refractive error after the onset of unrestricted vision. In contrast, nontreated eyes with relatively high degrees of hyperopia (e.g., monkey LIS) showed an increase in vitreous chamber growth rate and a subsequent reduction in hyperopia. Consequently, the initial growth changes in both the treated and nontreated eyes contributed to the observed changes in the degree of myopic anisometropia.

Figure 7 summarizes the changes in vitreous chamber growth rates that occurred at the onset of the recovery period for all 18 monkeys that had developed significant amounts of FDM. In 16 of these 18 treated animals, the deprived eyes (Fig. 7A) showed a reduction in vitreous chamber growth rate in response to the restoration of unrestricted vision. For most monkeys, the treated-eye growth rates during the initial recovery period were near zero, indicating a complete cessation of axial elongation. For the nontreated eyes (Fig. 7B), the changes in vitreous chamber growth rates were generally smaller and
the direction of the growth changes correlated with the non-treated eyes’ absolute refractive state ($r^2 = 0.619, P < 0.001$).

In addition to the alterations in vitreous chamber growth rate, a small, but statistically significant, part of the recovery from myopic anisometropia could be attributed to corneal changes. At the end of the treatment period, the corneas of the deprived eyes were, on average, 0.37 D steeper than those of the nontreated eyes (Fig. 8A; paired $t$-test, $P = 0.005$), which contributed in part to the myopic anisometropia observed in the 18 diffuser-reared monkeys that showed significant amounts of FDM. However, at the end of the recovery period, these interocular differences in corneal power had diminished and were no longer significant (Fig. 8B, mean difference = 0.08 D, paired $t$-test, $P = 0.425$).

**Absence of Recovery from FDM in Lid-Sutured Monkeys**

Monocular form deprivation produced by surgical eyelid closure consistently disrupted refractive development in the treated eyes, resulting in a relative myopic shift in the deprived eye’s refractive state. Twelve of the 14 lid-sutured monkeys, including the two animals that experienced the shorter periods of deprivation, demonstrated relative myopic anisometropia that was $\geq -1.0$ D and the mean and range of myopic anisometropia in this group of lid-sutured monkeys (mean = $-4.45 \pm 2.90$ D; range = $-1.00$ to $-10.25$ D) was comparable to that in the diffuser-reared monkeys described earlier (two-sample $t$-test, $P = 0.67$). Because there were no significant differences in the anisometropic changes (end of the observation period minus beginning of the observation period) that we observed in monkeys that were and were not allowed unrestricted vision before the first measurement (Mann-Whitney test, treated eye $P = 1.00$; nontreated eye $P = 0.42$), the data for all 12 monkeys were pooled. In contrast to the diffuser-reared monkeys, there was little evidence of recovery from FDM in our lid-sutured monkeys. As illustrated in Figure 9, the myopic anisometropia exhibited by these lid-sutured monkeys was well outside the range of the anisometropia observed in normal monkeys; but, more important, there was no clear indication of a systematic reduction in the degree of anisometropia over time. Despite average recovery periods that were 485 ± 192 days in length, the average decrease in anisometro-

**FIGURE 5.** Anisometropia plotted as a function of age in the 12 diffuser-reared monkeys that exhibited less than $-1.0$ D of FDM at the end of the treatment period. See Figure 3 for details.
that occurred during the observation period was only 
0.44 ± 1.54 D (range = −2.25 to +3.25 D), which was not 
significantly different from zero (Fig. 10A, one-sample t-test; 
P = 0.16).

Also contrary to expectations, both the deprived and non-
treated eyes of these lid-sutured monkeys tended to become 
more myopic during the recovery period. As shown in Figure 
10B, 8 of 12 deprived eyes and all the nontreated eyes exhib-
ited relative myopic changes in refractive error over the observation period. There was a substantial amount of variability between subjects in terms of the amount of myopic progression, but the average refractive-error changes were significantly myopic for both the deprived ($-1.27 \pm 1.98$ D, one-sample $t$-test, $P = 0.024$) and nontreated eyes ($-1.94 \pm 1.81$ D, one-sample $t$-test, $P = 0.0017$).

During the recovery period, the myopic shifts observed in both eyes of the monocularly lid-sutured monkeys were associated with increases in axial length. In Figure 11, axial length is plotted as a function of age for the right eyes of normal monkeys (thin lines) and for the deprived (Fig. 11A) and nontreated eyes (Fig. 11B) of the lid-sutured monkeys. As expected, the axial lengths of many of the deprived eyes fell outside the range of axial lengths in the normal monkeys. However, inspection of the data reveals that the slopes of the treated and nontreated eyes' functions were also steeper than normal. To quantify these increases in ocular growth, we calculated the axial growth rates by dividing the total change in axial length during the entire recovery period by the length of the recovery period. Both the deprived and nontreated eyes exhibited significantly faster than normal growth rates (two-sample $t$-test, deprived eyes, $P = 0.012$; nontreated eyes; $P = 0.006$). However, the axial growth rates for the deprived and nontreated eyes were not significantly different (paired $t$-test, $P = 0.50$), which is consistent with our observation that the
amount of myopic anisometropia found in a given animal did not change significantly during the recovery period.

**DISCUSSION**

Our main findings were that infant rhesus monkeys with axial myopia produced by image-degrading diffuser lenses consistently recovered from FDM after the onset of unrestricted vision, whereas adolescent rhesus monkeys with FDM produced by surgical eyelid closure failed to show any signs of recovery, even with prolonged postdeprivation observation periods. This pattern of results is in agreement with previous observations on the reversibility of FDM in mammals. For example, previous studies have reported that lid-sutured rhesus monkeys, tree shrews, and marmosets failed to recover from FDM after the termination of eyelid closure. However, it has been shown that tree shrews and marmosets (Troilo D, et al. IOVS 2000;41:ARVO Abstract 691; Troilo D, et al. IOVS 2002;43:ARVO E-Abstract 186), like our rhesus monkeys, are capable of recovering from FDM produced by diffuser lenses.

The ocular changes responsible for the recovery from FDM in our diffuser-reared monkeys were qualitatively similar to those observed in rhesus monkeys during the recovery from myopia induced by defocusing lenses. In both cases, the onset of unrestricted vision, which was accompanied by myopic defocus for distant targets, caused a dramatic decrease in the deprived eye’s vitreous chamber growth rate. The deprived eye’s absolute refractive state became less myopic and more hyperopic over time because of a concomitant decrease in the eye’s total refracting power. Ignoring the small additional decrease in corneal power observed in the deprived eyes (mean = 0.37 D), there were no systematic interocular differences in the corneal and lenticular changes observed in our monocular diffuser-reared animals during the recovery period (i.e., the normal reductions in corneal and lenticular refracting power were not altered by the recovery process). Thus, data from normal animals should provide an indication of the relative contributions of the crystalline lens and cornea to the recovery from myopia and an approximation of the limits to the degree of recovery that is possible. For example, from approximately 115 days of age (the average age at which unrestricted vision was restored), corneal power normally decreases in an exponential fashion by approximately 2 D over the next 500 days. Over this same period, crystalline lens power normally decreases by approximately 7 D (Qiao Y, et al. IOVS 2000;41:ARVO Abstract 693). Consequently, the eyes of 115-day-old infant monkeys have the potential to recover from approximately 9 D of axial FDM and the changes in the deprived eye’s total refracting power will be dominated by maturation changes in the crystalline lens, with decreases in corneal power playing a smaller but significant role. Whether recovery in a young monkey is complete depends in large part on the eye’s absolute axial length at the end of the period of deprivation. The potential for complete recovery is substantially reduced if a deprived eye obtains an axial length that is greater than that of a normal adult. In this respect, at the end of the treatment period the deprived eyes of our diffuser-reared monkeys were longer than those of age-matched control monkeys, but were still shorter than the eyes of normal adults, and all these treated monkeys exhibited complete recovery (Fig. 12).

The nature of the ocular changes that underlie the recovery from FDM in our diffuser-reared monkeys is also qualitatively similar to that which occurs during recovery from FDM in tree shrews and chickens. For example, in the first study to document recovery from FDM in chickens, Wallman and Adams found that unrestricted vision produces a dramatic and selective cessation of vitreous chamber growth, whereas the rest of the eye appears to continue to grow normally. Recovery is

**FIGURE 9.** The degree of anisometropia plotted as a function of age for the 12 lid-sutured monkeys that had at least −1.0 D of FDM. Thin lines: represent the data from the normal animals. Filled symbols: monkeys that were examined immediately after eyelid opening. Open symbols: monkeys that were allowed unrestricted vision after eyelid opening and before the first measurement.

**FIGURE 10.** (A) Interocular differences in spectacle-plane refractive correction (treated eye minus fellow eye) for the lid-sutured monkeys that manifest at least −1.0 D of FDM at the end of the treatment period. (B) Changes in refractive error that occurred during the recovery period. In both plots, the monkeys are arranged according to the magnitude of anisometropia at the end of the treatment period.
complete when the optical components of the eye catch up with the deprivation-induced axial elongation. Siegwart and Norton\(^{31}\) observed a similar recovery pattern in myopic tree shrews. Because of anatomic differences between the eyes of chickens, tree shrews, and monkeys, it is likely that there are differences in the relative contributions of the lens and cornea to the power changes that occur during recovery from FDM, but the general strategy appears to be the same across species.

It has been documented in monkeys\(^{28,36,49}\) and several other species\(^{30,20,35,50–52}\) that monocular form deprivation can alter the course of emmetropization in the fellow nontreated eyes resulting in atypical refractive errors in both eyes. In the present study, we found that growth changes in the nontreated eyes also contributed to the isometropization process during the recovery from FDM. Therefore, when the degree of recovery from FMD is measured by interocular differences in refractive error, refractive changes in the nontreated eye can either speed up or delay recovery, depending on the nontreated eye’s absolute refractive error. It is interesting that the nontreated eyes showed clear evidence of recovery toward more normal refractive errors after the onset of unrestricted vision in the treated eye, even though the refractive errors in many of the nontreated eyes were relatively stable for some time before the end of the treatment period. This pattern of results suggests that the stimulus for abnormal growth in the fellow nontreated eye was maintained throughout the period of form deprivation.

Although the recovery process in our diffuser-reared monkeys was very successful, the recovery was not permanent in all monkeys. Instead, the eyes of some animals overshot isometropia and subsequently hyperopic anisometropia developed, whereas in others myopic anisometropia redeveloped. The instability in the balance of refractive errors in the two eyes suggests that the early period of form deprivation may have permanently compromised the processes that normally maintain isometropia, possibly reflecting plasticity-related alterations in the visual system. In this respect, observations in both humans\(^{53–56}\) and monkeys\(^{33,36,45,57–60}\) have suggested that the presence of amblyopia may interfere with the ability of the eye to grow in a manner that would compensate for chronic optical defocus and subsequent behavioral experiments (Smith EL III, et al. IOVS 2003;44:ARVO E-Abstract 3188)\(^{45}\) demonstrated that the deprived eyes of many of our diffuser-reared monkeys were amblyopic. However, there was no clear-cut relationship between the degree of amblyopia and the long-term stability of the refractive errors in our diffuser-reared monkeys. Possibly the observed instability reflects differences in the binocular vision status of our animals. In this respect, infant monkeys with experimentally induced strabismus frequently have anisometropia that develops well after the onset of the strabismus and in the absence of amblyopia.\(^{45}\) However, because many aspects of ocular growth appear to be regulated by mechanisms within the eye itself,\(^{11,47,61–64}\) it is not clear how amblyopia and/or anomalous binocular vision, which are not believed to be associated with retinal abnormalities, would directly influence the eye’s response to optical defocus. It is possible, however, that long periods of time interocular misalignments and/or slight interocular asymmetries in accommodation associated with unilateral fixation preferences could produce chronic interocular asymmetries in retinal image quality that would result in differential interocular growth.

Given the very consistent recovery observed in our diffuser-reared monkeys, why did virtually all of our animals that were form deprived by eyelid closure fail to recover from FDM? Because there was a substantial amount of overlap in the

**FIGURE 11.** Axial length plotted as a function of age for the treated (A) and nontreated, fellow (B) eyes of the 10 lid-sutured monkeys for which longitudinal axial length data were available. *Thin lines*: right eye data from the 10 normal animals for which longitudinal axial length data were available. *Filled symbols*: monkeys that were examined immediately after eyelid opening; *open symbols*: monkeys that were allowed unrestricted vision before the first measurement after eyelid opening. There were no statistically significant differences (Mann-Whitney test, treated eye, \(P = 0.59\); nontreated eye \(P = 0.75\)) in the axial length changes between the monkeys that were measured immediately after eyelid opening and those that had some unrestricted vision before the first measurement after eyelid opening.

**FIGURE 12.** Axial length of the deprived eyes of the 18 diffuser-reared monkeys that had at least 1 D of FDM, plotted as a function of age (solid lines). The earliest point for each function represents the onset of unrestricted vision. The dashed line is the LOESS growth curve for the normal monkeys. At the end of the period of deprivation, most of these diffuser-reared monkeys had axial lengths that were longer than those in age-matched control animals but still shorter than those in normal adult monkeys.
degree of amblyopia observed in our lid-sutured and diffuser-reared monkey populations (Smith EL III et al. IOVS 2003;44: ARVO E-Abstract 3188).44 it is unlikely that differences in the degree of amblyopia limited the ability of our lid-sutured monkeys to recover. There are, however, several possible explanations. It seems likely that differences in the absolute degree of deprivation-induced axial elongation and the age of onset for unrestricted vision contributed significantly to the disparities between our diffuser-reared and lid-sutured animals. In particular, most of the lid-sutured monkeys were much older at the onset of unrestricted vision (average = 701 ± 362 days, ranging from 52-1326 days) than the diffuser-reared monkeys (average = 139 ± 20 days, ranging from 107-176 days). Although hyperopic defocus can still produce appropriate compensating refractive changes in monkeys at these ages,67 it is likely that the animals’ fixation behavior combined with the way in which recovery from myopia occurs are limiting factors in this case. If the monkeys had fixated with their originally deprived eyes, then the nontreated eyes would have experienced hyperopic defocus, which could have resulted in myopic growth in the nontreated eye and an equalization of refractive error in the two eyes. However, because the originally deprived eyes were frequently amblyopic,44,65,66 it is most likely that the non-treated, fellow eyes dominated fixation and accommodation during the recovery period and hence the originally deprived eyes would experience chronic myopic defocus. Because recovery associated with myopic defocus depends on the normal reductions in the eye’s refracting power,68 an animal’s ability to recover decreases exponentially with age and presumably ceases when the cornea and lens have reached their adult dimensions. In this respect, many of the deprived eyes of our lid-sutured monkeys had axial lengths that were outside the range of our adult control monkeys before the onset of unrestricted vision (Fig. 11). Given how eyes recover from axial myopia, the absolute axial lengths of these eyes greatly reduced the potential for recovery, regardless of the effects of the resultant myopic defocus on axial growth. However, two of the monkeys that had significant amounts of FDM were lid-sutured from 38 and 60 days of age for periods of 14 and 31 days, respectively, and were very likely to have had axial lengths that were shorter than a normal adult. It is interesting that these monkeys demonstrated −1.0- to −1.5 D increases in myopia in the treated eye during the postdeprivation observation period. The data from these two animals suggest that the age of onset of unrestricted vision and the eye’s absolute axial length may not be the only limiting factors for recovery from FDM.

In both tree shrews50,51,54,55,68 and marmosets (Troilo D et al. IOVS 2000;41:ARVO Abstract 691; Troilo D, et al. IOVS 2002;43:ARVO E-Abstract 186),8,32 equating the duration of deprivation and the age at the onset of unrestricted vision does not eliminate the disparity in the ability to recover between animals form deprived by diffuser lenses versus those deprived by surgical eyelid closure. Even when the absolute axial lengths of the treated eyes are well within the normal adult range, eyes that experience form deprivation by lid suture do not recover.8,32 Consequently, it is likely that additional factors contributed to the absence of recovery in our lid-sutured monkeys. Eyelid suture has been shown to alter corneal shape in tree shrews,50,55 and we have noted by simple inspection that, on slit lamp examination, the corneal light reflex in our previously lid-sutured monkeys was often irregular. Although we do not know how long these corneal shape changes persisted, it is plausible that early eyelid suture produces permanent alterations in corneal shape that could alter the aberrant structure of the eye in a way that results in a mild degree of image degradation. Because image degradation can produce axial myopia in adolescent monkeys69 and the mechanisms responsible for FDM are sensitive to even small reductions in image quality,55 this scenario could explain why the treated eyes of our lid-sutured monkeys failed to recover, but instead continued to exhibit faster than normal rates of axial elongation. In this respect, the progressive myopic changes found in the non-treated, fellow eyes of our lid-sutured monkeys could reflect interocular influences of abnormal visual experience similar to those observed in young animals.

In conclusion, young rhesus monkeys, like young chicks,27 tree shrews,31 and marmosets (Troilo D, et al. IOVS 2000;41: ARVO Abstract 691; Troilo D, et al. IOVS 2002;43:ARVO E-Abstract 186), can recover from the axial myopia produced by early monocular form deprivation. Although the timing of the period of form deprivation and the severity of the induced axial elongation are likely to influence the potential for recovery, it is clear that the ability to recover from FDM is a common phenomenon in young animals. This interspecies congruence enhances the likelihood that human eyes behave in a similar fashion and that human eyes also have the ability to alter their growth in response to optical defocus in a manner that eliminates refractive errors.

References

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