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## Peripheral Vision Can Influence Eye Growth and Refractive Development in Infant Monkeys

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### Abstract

**PURPOSE**—Given the prominence of central vision in humans, it has been assumed that visual signals from the fovea dominate emmetropization. The purpose of this study was to examine the impact of peripheral vision on emmetropization.

**METHODS**—Bilateral, peripheral form deprivation was produced in 12 infant monkeys by rearing them with diffusers that had either 4- or 8-mm apertures centered on the pupils of each eye, to allow 24° or 37° of unrestricted central vision, respectively. At the end of the lens-rearing period, an argon laser was used to ablate the fovea in one eye of each of seven monkeys. Subsequently, all the animals were allowed unrestricted vision. Refractive error and axial dimensions were measured along the pupillary axis by retinoscopy and A-scan ultrasonography, respectively. Control data were obtained from 21 normal monkeys and 3 infants reared with binocular plano lenses.

**RESULTS**—Nine of the 12 treated monkeys had refractive errors that fell outside the 10th- and 90th-percentile limits for the age-matched control subjects, and the average refractive error for the treated animals was more variable and significantly less hyperopic/more myopic ( $+0.03 \pm 2.39$  D vs.  $+2.39 \pm 0.92$  D). The refractive changes were symmetric in the two eyes of a given animal and axial in nature. After lens removal, all the treated monkeys recovered from the induced refractive errors. No interocular differences in the recovery process were observed in the animals with monocular foveal lesions.

**CONCLUSIONS**—On the one hand, the peripheral retina can contribute to emmetropizing responses and to ametropias produced by an abnormal visual experience. On the other hand, unrestricted central vision is not sufficient to ensure normal refractive development, and the fovea is not essential for emmetropizing responses.

Early in life, the two eyes of infants normally grow in a highly coordinated manner toward the ideal refractive state, a process called emmetropization.<sup>1–3</sup> Evidence from many different species indicates that emmetropization is an active process that is regulated by visual feedback associated with the eye's effective refractive state. For example, making the eyes of young animals artificially myopic with positive lenses or hyperopic with negative lenses produces compensating ocular growth that can, within certain operational limits, eliminate the imposed refractive error (chickens,<sup>4–8</sup> tree shrews [Siegwart JT, et al. *IOVS* 1993;34:ARVO Abstract 1208],<sup>9,10</sup> marmosets,<sup>11</sup> and rhesus monkeys<sup>12,13</sup>). Given the agreement between such diverse species and the many similarities in the course of emmetropization between these

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animals and humans, in particular between monkeys and humans,<sup>12,14,15</sup> it is likely that ocular growth in humans is also regulated by visual feedback. The fact that form deprivation produces axial myopia in children,<sup>16-19</sup> as it does in many species,<sup>1</sup> reinforces the idea that visual experience regulates human refractive development and can play a significant role in the genesis of common refractive errors. Therefore, it seems reasonable to expect that lens-induced alterations in the eye's effective refractive state would predictably alter human refractive development and potentially provide an effective treatment regimen for refractive errors. However, to date the most applicable data from studies in infants<sup>20,21</sup> and children<sup>22,23</sup> are equivocal. Only recently has it been shown that multifocal lenses have a small but statistically significant effect on reducing myopic progression in children.<sup>24-26</sup>

Because imposed defocus has such a robust effect on refractive development in many species, including monkeys, why would apparently similar manipulations fail to alter refractive development in humans? The fact that vision in primates is heterogeneous across the visual field may have contributed to this failure. Because spatial vision is most acute in the fovea, almost all studies of the effects of vision on human refractive development have concentrated on the optical state at the fovea, ignoring the effects of peripheral vision.<sup>27</sup>

However, several lines of evidence suggest that peripheral vision can influence refractive development. First, peripheral retinal mechanisms are sensitive to moderately high spatial frequencies and to the effects of optical defocus. Although resolution acuity declines dramatically with eccentricity, detection acuity remains high at substantial eccentricities and is strongly influenced by optical defocus.<sup>28,29</sup> For example, at 20° eccentricities, grating detection acuity is between 12 and 20 cyc/deg (four times better than resolution acuity) and 1.0 D of defocus can reduce peripheral detection acuity by approximately 50%.<sup>29</sup> In this respect, detection acuity probably provides a better estimate of the spatial characteristics of the mechanisms that mediate emmetropization than resolution acuity because the emmetropization process is not orientation sensitive.<sup>30</sup> Regardless, high visual acuity is not an absolute requirement for emmetropization, because there is ample evidence that emmetropization operates very effectively in animals with much lower visual acuities than humans (e.g., tree shrews have grating acuities of ~2 cyc/deg<sup>31</sup>). Second, studies in birds<sup>32-34</sup> and tree shrews<sup>35</sup> have demonstrated that eye growth is regulated by local retinal mechanisms that integrate visual signals over spatially restricted areas across the retina and that alterations in peripheral vision can have a significant impact on eye shape and potentially on axial length for the central retina.

It is not known whether similar local retinal mechanisms exist in primates; however, several observations suggest that peripheral vision can influence human refractive development. For example, peripheral laser photocoagulation therapy for retinopathy of prematurity<sup>36,37</sup> and retinal diseases that primarily affect the peripheral retina and spare central vision<sup>19,38</sup> are often associated with significant refractive errors. It is also well known that spherical-equivalent refractive errors in the periphery can often be very different from those measured at the fovea<sup>39,40</sup> and that the magnitudes of these peripheral refractive errors are often sufficient to degrade peripheral visual performance.<sup>28,29</sup> More important, several observations support the idea that these peripheral refractive errors can alter foveal refractive development in humans.<sup>41-43</sup> For example, among adult emmetropes and hyperopes in pilot training, those that exhibited peripheral hyperopia in both the sagittal and tangential meridians, optical conditions known to promote axial elongation in animals, were three times more likely to exhibit adult-onset myopia than those who showed myopic peripheral refractions in at least one meridian.<sup>43</sup> Although these observations in humans do not establish causality, they suggest that peripheral factors can influence foveal refractive development.

The purpose of this study was to determine whether it is possible that peripheral retinal mechanisms participate in the visual regulation of eye growth and refractive development at the fovea in primates. Specifically, we examined whether selectively form depriving the peripheral retina would alter foveal refractive development in infant monkeys and whether an intact fovea is essential for emmetropizing responses.

## MATERIALS AND METHODS

### Subjects

Data are presented for 36 infant rhesus monkeys (*Macaca mulatta*). The animals were obtained at 1 to 3 weeks of age and housed in our primate nursery, which was maintained on a 12-hour light–dark lighting cycle. The details of the nursery care of our infant monkeys have been described previously.<sup>12</sup> After the initial biometry measurements at approximately 3 weeks of age, the monkeys were randomly assigned to either the control group ( $n = 24$ ) or the peripheral form-deprivation group ( $n = 12$ ). All the rearing and experimental procedures were reviewed and 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.

The control group consisted of 21 infant monkeys that were reared with normal unrestricted vision, and three monkeys that were reared wearing lightweight helmets that held zero-power spectacle lenses in front of both eyes. The goggles consisted of a molded urethane face shield that was secured to the head with adjustable straps. During the treatment period, which extended from 3 to 18 to 20 weeks of age, the helmets were worn continuously. The lens wells provided monocular and binocular fields of view in the horizontal plane of 80° and 62°, respectively, and an 87° vertical field. The plano-lens–reared monkeys served as control subjects for our helmet rearing procedures and the resultant restrictions in visual field. Refractive data for 16 of the normal monkeys and the three plano-lens–reared monkeys have been reported.<sup>12,30,44</sup>

We used two strategies to examine the impact of peripheral vision on eye growth and refractive development. First, to investigate the effects of selectively depriving the periphery of form vision, 12 infant monkeys were reared from 3 to 16 to 18 weeks of age wearing binocular diffuser spectacle lenses that had either 4- or 8-mm apertures ( $n = 6$  in both groups) centered on the pupils of each eye. The diffusers were made of frosted plastic and dramatically reduced form vision without substantially reducing the amount of light reaching the eye. The apertures provided a total field of potentially clear central vision of approximately 24° or 37° (assuming a 14-mm vertex distance and a 3.0-mm entrance pupil located 2.7 mm from the cornea). The fields of full illumination through the 4- and 8-mm apertures (i.e., the projection of the entrance pupil through the aperture<sup>45</sup>) were 3.4° and 16.7°, respectively. The apertures allowed binocular convergence of the pupillary axes for viewing distances as short as 22 and 10 cm, respectively (interpupillary distance, 22 mm; centers of rotation, 8.4 mm from the cornea). We used form deprivation as a stimulus for altered ocular growth, because form depriving the entire eye of infant monkeys consistently produces dramatic increases in axial growth and myopia.<sup>46,47</sup> Moreover, in contrast to optically imposed defocus where it could be argued that the stimulus for altered growth would vary with eccentricity (e.g., potentially as a function of detection acuity), the diffusers virtually eliminated form vision, and thus the stimulus for altered growth was presumably at its maximum across the peripheral retina.

Although foveal vision was potentially degraded when the infant’s eyes were not aligned with the diffuser apertures, we believe that the refractive changes described later in the article came about as a result of peripheral form deprivation. First, the diffusers were worn over both eyes, and thus it was always to the animal’s advantage to fixate through the apertures (i.e., the animals were motivated to view through the apertures). Second, the infants rapidly adapted to the

diffusers. We visually inspected the fit of the helmet and diffusers every 2 hours during the daily light cycle and periodically video recorded the animal's viewing behavior. Throughout the rearing period, the animals consistently fixated through the centers of the diffuser apertures. Third, even if foveal vision was occasionally degraded, the nonlinear temporal integration properties of the emmetropization process would make it unlikely that brief episodes of foveal image degradation would produce myopia.<sup>48–51</sup>

Our second experimental strategy took advantage of the fact that many of our peripherally form-deprived monkeys developed anomalous central refractive errors. It has been consistently demonstrated that animals recover from induced refractive errors when the visual stimulus for abnormal growth is eliminated and the animals are allowed unrestricted vision<sup>52–54</sup> and that, at least in chickens, this recovery is a vision-dependent emmetropizing response.<sup>55</sup> Therefore, in these second experiments, we assessed the ability of our peripherally form-deprived monkeys to recover from their induced ametropia and whether an intact fovea was essential for recovery (i.e., is it possible that the periphery mediates emmetropizing responses?).

To isolate the contribution of the periphery to this recovery process, an argon laser was used to photocoagulate the fovea of one eye in each of seven experimental monkeys. The laser procedures, which were performed at the onset of the recovery period, ablated the central 5° to 6° of the retina, essentially eliminating all the fovea and part of the perifovea. The goal was to eliminate the part of the retina that normally supports fine spatial resolution. The laser-treated monkeys were selected specifically because they had relatively large refractive errors as a result of the period of peripheral form deprivation. To make the foveal ablations, the monkeys were anesthetized (intramuscular injection: ketamine hydrochloride, 15–20 mg/kg, and acepromazine maleate, 0.15–0.2 mg/kg; topical: 1–2 drops of 0.5% tetracaine hydrochloride) and the laser was delivered to the eye with a slit lamp. The argon laser was operated in the blue-green mode and had a nominal spot size of 500 μm. The laser power was varied between 100 and 250 mW and presented in 50-ms pulses. The foveal burns were overlapped to ensure complete photoablation of the fovea. The argon laser was ideal for these experiments, because the amount of choroidal damage is generally minimal,<sup>56</sup> and histologic examination of burns made using this protocol has confirmed that the entire outer retina is destroyed.<sup>57</sup>

Periodic observations revealed that in all the experimental animals the first Purkinje images were symmetrically positioned in the pupil of each eye. Although we cannot rule out the possibility that some of the monkeys had microtropia, none of the animals exhibited overt strabismus.

### Ocular Biometry

Each eye's refractive status and axial dimensions along the pupillary axis were measured at the start of lens wear and then every 2 to 4 weeks throughout the treatment and subsequent recovery periods, by methods that have been described in detail.<sup>12</sup> To make these measurements, the monkeys were anesthetized as for laser treatment and subjected to cycloplegia (1% tropicamide). The refractive status of each eye, both the spherical and cylindrical components, were measured independently by two experienced investigators with a streak retinoscope and averaged.<sup>58</sup> An eye's refractive error was defined as the mean spherical equivalent, spectacle plane refractive correction. The eye's axial dimensions were measured by A-scan ultrasonography implemented with a 7-MHz transducer (Image 2000; Mentor, Norwell, MA). Ten separate measurements were averaged, and the intraocular distances were calculated with a weighted average velocity of 1550 m/s.

## Statistical Analysis

Two-sample *t*-tests and Mann-Whitney tests were used to compare the means and medians for treated and control monkeys. Paired *t*-tests were used to examine interocular differences and for before–after comparisons in individual animals. The relationship between the refractive error and vitreous chamber depth was determined with Pearson’s correlation analysis. All the analyses were executed on computer (Minitab software, ver. 12.21; Minitab, Inc., State College, PA).

## RESULTS

At the onset of the lens-rearing period, the eyes of the experimental and control monkeys were, on average, moderately hyperopic, and there were no between-group differences in refractive error or vitreous chamber depth (two-sample *t*-test,  $P = 0.59$  for refractive error;  $P = 0.62$  for vitreous chamber depth), nor were there any systematic interocular refractive error differences in either the experimental or control groups (paired *t*-test;  $P > 0.14$ ). Over time, the two eyes of each control monkey grew in a coordinated manner toward a low degree of hyperopia, the ideal optical state for young monkeys.<sup>12,14,15</sup> This emmetropization process was very successful so that by 4 to 5 months of age 90% of the control monkeys had refractive errors between +1.13 and +3.68 D of hyperopia (Fig. 1).

If unrestricted central vision was sufficient to mediate emmetropization, peripheral form deprivation should have no effect on refractive development. However, peripheral form deprivation consistently disrupted the emmetropization process. As illustrated in Figure 1, shortly after the onset of peripheral form deprivation, three of the six animals that wore diffusers with 4-mm apertures and four of the six animals viewing through 8-mm apertures exhibited relative myopic errors that were outside the range of refractive errors exhibited by the control animals. The refractive changes were symmetric in the two eyes of a given animal (mean interocular difference: right eye–left eye =  $-0.06 \pm 0.57$  D, paired *t*-test,  $P = 0.31$ ; also see Figs. 3, 4, 5) and the animals that wore the diffusers with the smaller central apertures exhibited slightly larger amounts of myopia (average =  $-0.44$  D more myopia), although these differences were not significant (two-sample *t*-test,  $P = 0.76$ ). At the end of the lens-rearing period, the experimental monkeys as a group exhibited a much broader than normal range of refractive errors, with 9 of the 12 treated monkeys showing refractive errors that fell outside the 10th and 90th percentile limits for the age-matched control animals (Fig. 1, right). Although 1 of these treated monkeys was more hyperopic than normal, 8 of these 9 treated animals exhibited relative myopic errors and the refractive errors in all 12 of the treated monkeys were significantly less hyperopic/more myopic than those of the control monkeys (mean =  $+0.03 \pm 2.39$  D vs.  $+2.39 \pm 0.92$  D; two-sample *t*-test,  $P = 0.006$ ; median =  $+0.38$  D vs.  $+2.35$  D, Mann-Whitney test,  $P = 0.003$ ). It is not known why the one animal became relatively hyperopic, whereas most of the treated animals became myopic. There was nothing notable in the history of this animal that could explain the difference. However, it has been reported that form deprivation of the entire retina also produces hyperopia in a small proportion of infant monkeys.<sup>47,59,60</sup>

The relative myopic errors came about because peripheral form deprivation accelerated the eye’s axial elongation rate (Fig. 2). At the end of the lens-rearing period, four of the treated monkeys had vitreous chambers that were longer than those of any of the control animals and the refractive errors for all the treated monkeys were inversely correlated with vitreous chamber depth ( $r^2 = 0.61$ ,  $P = 0.003$ ). The mean and median vitreous chamber depths in the treated monkeys were longer than those for control animals; but, primarily due to the variability in the treatment groups, these differences were not significant (mean = 10.01 mm vs. 9.73 mm, two-sample *t*-test,  $P = 0.16$ ; median = 10.07 mm vs. 9.74 mm, Mann-Whitney test,  $P = 0.08$ ). However, in the eight treated monkeys that exhibited relative myopic refractive errors that fell

outside the 10th- and 90th-percentile limits of the control animals, the vitreous chambers were significantly longer than normal (mean =  $10.23 \pm 0.57$  mm vs.  $9.73 \pm 0.26$  mm, two-sample *t*-test,  $P = 0.05$ ; median = 10.22 mm vs. 9.74 mm, Mann-Whitney test,  $P = 0.008$ ).

As previously observed in monkeys with axial myopia produced by form deprivation of the entire retina,<sup>53</sup> the experimental monkeys were capable of recovering from the induced refractive errors. For example, at the end of the diffuser-rearing period, monkey LEI exhibited approximately  $-2.0$  D of myopia in each eye (Fig. 3, top). However, after lens removal and the restoration of unrestricted vision, there was a decrease in the rate of axial growth, and the refractive errors of both eyes subsequently shifted in a systematic and coordinated manner back toward the normal range.

If the fovea played a dominant role in this recovery process, one would expect that foveal ablation would delay and/or decrease the effectiveness of the recovery in the treated eye. However, on the contrary, the recovery process was unaffected by the foveal ablations, regardless of whether relative hyperopic or myopic refractive errors had developed in the treated animals during the lens-rearing period. For example, during the lens-rearing period, monkey MIT (Fig. 4, left) exhibited faster than normal axial growth rates and a substantial degree of myopia in each eye. In contrast, monkey LAU exhibited slower than normal axial growth rates during the lens-rearing period and became relatively hyperopic (Fig. 4, right). Regardless, after the onset of unrestricted vision and the photoablation of the fovea in one eye, there were clear changes in the vitreous chamber elongation rates in both eyes (a decrease in monkey MIT and an increase in monkey LAU) and both eyes of each of these monkeys showed more normal refractive errors. The key finding was that the recovery process was very similar in the intact and laser-treated eyes.

The similarity of the recovery process in the intact and laser-treated eyes is emphasized in Figure 5, which shows longitudinal, interocular differences in refractive error for all seven of the lens-reared monkeys that had foveal ablations in one eye. At the onset of the recovery period, several of the monkeys (e.g., monkeys MIT and NOL) exhibited anisometropia that was slightly outside the control range; however, in each case, the degree of anisometropia decreased with time. For the other laser-treated monkeys, there were no systematic differences between the two eyes throughout the recovery period. Instead, the observed anisometropias in the laser-treated monkeys were typically within the range of anisometropias observed in control monkeys. Consequently, at 300 days of age, when the recovery process was complete, there was not a significant difference in the refractive errors of the laser-treated and fellow nontreated eyes ( $+0.80 \pm 0.71$  D vs.  $+0.79 \pm 0.76$  D; paired *t*-test,  $P = 0.91$ ). Moreover, the average degree of anisometropia manifested by the laser-treated monkeys ( $0.29 \pm 0.24$  D) was comparable to that exhibited by the experimental monkeys with intact eyes ( $0.14 \pm 0.17$  D; two-sample *t*-test,  $P = 0.24$ ) and the age-equivalent control monkeys ( $0.18 \pm 0.22$  D; two-sample *t*-test,  $P = 0.33$ ).

## DISCUSSION

Our main findings were that peripheral form deprivation can produce axial myopia at the fovea, even in the presence of potentially clear images in the central retina and that an intact fovea is not essential for the recovery from experimentally induced refractive errors. The overall pattern of results suggest that the status of peripheral retinal images can play a role in determining whether one has an abnormal refractive error and that degradation of peripheral image quality may contribute to the genesis of common refractive errors like juvenile-onset myopia. Moreover, the fact that the foveal ablations did not interfere with the recovery from the induced refractive errors suggests that the periphery can contribute to emmetropization, at least in the absence of a functioning fovea. Although it is possible that aspects of this recovery were mediated by nonvisual homeostatic processes that are, for example, sensitive to the overall size

of the eye,<sup>61</sup> previous work in chickens has shown that recovery from induced refractive errors is regulated by optical defocus and is probably mediated by the same vision-dependent mechanisms that regulate the emmetropization process.<sup>55</sup> Assuming that the recovery from form deprivation is vision dependent in monkeys, our results suggest that the peripheral retina can regulate vision-dependent emmetropizing responses and that a functioning fovea is not essential for visually regulated eye growth.

How does peripheral image quality affect foveal refractive development? One possibility is that growth signals are integrated over small restricted retinal regions<sup>33,62</sup> and that peripheral image quality influences local ocular growth in a manner that affects the overall axial length of the globe. For example, an increase in central axial length could occur if peripheral form deprivation produced an overall expansion of the posterior globe. However, many other ocular shapes are possible, depending on how isotropic the locally induced scleral changes are. For example, it is conceivable that peripheral form deprivation promotes the axial elongation of the peripheral globe, possibly resulting in a more prolate shape and myopia at the fovea.<sup>63</sup> Another possibility is that vision-dependent growth signals are pooled across large areas of the retina. Because the fovea constitutes a small geographic area, the absolute number of retinal neurons in the fovea is lower than that in the much larger periphery.<sup>62</sup> Consequently, growth signals from the periphery may overshadow contradictory signals from the fovea and dominate overall axial growth. It is also possible that critical elements in the signal cascade that regulates ocular growth are preferentially distributed in the periphery or that critical features of the cascade vary with eccentricity in a manner that favors the periphery. Eccentricity-dependent variations in these mechanisms could also selectively alter the shape of the eye. In this respect, it is interesting that myopic eyes are typically more prolate in shape than emmetropic eyes, whereas hyperopic eyes are more oblate.<sup>27,64,65</sup>

Regardless, the fact that peripheral vision can influence eye growth has important implications for the role of vision in the genesis of refractive errors in children. In particular, it emphasizes that the optical state at the fovea may not accurately reflect the overall balance of the visual signals that influence eye growth. Instead, as several investigators have suggested, it seems likely that off-axis variations in refractive error or image quality could dominate refractive development.<sup>27,42,43,62</sup> For example, it has been reported that individuals whose eyes are relatively more hyperopic in the periphery, presumably because of the geometry of the eye's optical surfaces and/or the shape of the posterior globe, are more prone to development of myopia at the fovea than individuals who manifest relative myopic refractive errors in the periphery.<sup>44</sup> Given that experimentally imposed hyperopic defocus promotes axial myopia in many animals,<sup>7,9,66,67</sup> including monkeys,<sup>11,12</sup> it is reasonable to speculate that hyperopic defocus in the periphery, like peripheral form deprivation in our monkeys, promotes axial myopia in humans. This scenario could explain, at least in part, why myopic individuals have more hyperopic off-axis refractive errors on average than do nonmyopes.<sup>27,68</sup> Moreover, the fact that peripheral refractive errors can be quite large and are not typically eliminated by optical corrections for the fovea may explain why myopia frequently progresses over time regardless of how the eyes' central refractive errors are corrected.<sup>22</sup> In any case, it seems likely that peripheral vision should be taken into account in efforts to determine the role that vision plays in the development of anomalous refractive errors.

Our results also suggest that peripheral image quality should be considered when designing treatment strategies for myopia or hyperopia. All previous optical treatment regimens have focused on manipulating image quality at the fovea and have been largely ineffective. However, given the influence of the peripheral retina, correcting peripheral optical errors or imposing specific peripheral refractive errors may be a more effective means of controlling eye growth.<sup>62</sup> For example, it may be possible to slow the progression of myopia in children by prescribing lenses that correct central refractive errors and at the same time increase the curvature of field

of the image plane, thus either correcting for any peripheral hyperopia or actually imposing myopic defocus in the periphery. Both clear vision and myopic defocus are strong stimuli for reducing axial growth.<sup>12,69</sup> Similarly, prescribing lenses that impose relative hyperopic defocus in the periphery could be effective in promoting axial elongation in short, hyperopic eyes.

There are several advantages associated with treatment strategies centered on manipulating peripheral image quality. First, central vision would be unencumbered, since it is possible to manipulate peripheral refractive errors while correcting central refractive errors. Moreover, the desired growth stimulus would be relatively constant over time, a potentially critical factor, given the nonlinear temporal integration properties of the vision-dependent mechanisms that regulate ocular growth.<sup>48,50,51</sup> Although further research is needed to determine whether selective manipulation of the periphery would be effective in children, it is clear that treatment strategies that ignore the impact of peripheral image quality on ocular growth are less likely to be successful.

## References

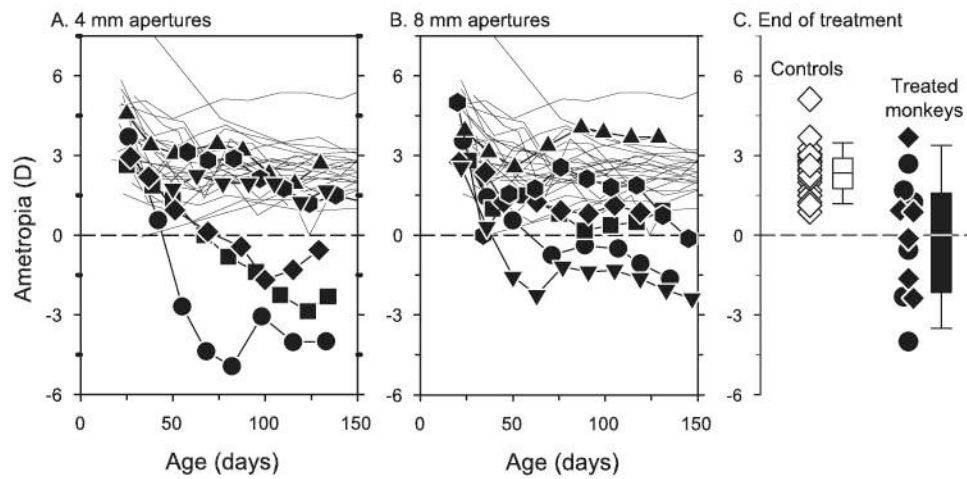
1. Smith, EL, III. Environmentally induced refractive errors in animals. In: Rosenfield, M.; Gilmartin, B., editors. *Myopia and Nearwork*. Oxford, UK: Butterworth-Heinemann; 1998. p. 57-90.
2. Norton TT. Animal models of myopia: learning how vision controls the size of the eye. *Inst Lab Anim Res J* 1999;40:59–77.
3. Wildsoet CF. Active emmetropization: evidence for its existence and ramifications for clinical practice. *Ophthalmic Physiol Opt* 1997;17:279–290. [PubMed: 9390372]
4. Irving EL, Callender MG, Sivak JG. Inducing myopia, hyperopia, and astigmatism in chicks. *Optom Vis Sci* 1991;68:364–368. [PubMed: 1852398]
5. Irving EL, Sivak JG, Callender MG. Refractive plasticity of the developing chick eye. *Ophthalmic Physiol Opt* 1992;12:448–456. [PubMed: 1293533]
6. Schaeffel F, Howland H. Properties of the feedback loops controlling eye growth and refractive state in the chicken. *Vision Res* 1991;31:717–734. [PubMed: 1843772]
7. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res* 1988;28:639–657. [PubMed: 3195068]
8. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Res* 1995;35:1175–1194. [PubMed: 7610579]
9. Shaikh AW, Siegwart JT, Norton TT. Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optom Vis Sci* 1999;76:308–315. [PubMed: 10375247]
10. Siegwart JT, Norton TT. Regulation of the mechanical properties of tree shrew sclera by the visual environment. *Vision Res* 1999;39:387–407. [PubMed: 10326144]
11. Graham B, Judge SJ. The effects of spectacle wear in infancy on eye growth and refractive error in the marmoset (*Callithrix jacchus*). *Vision Res* 1999;39:189–206. [PubMed: 10326130]
12. Smith EL III, Hung L-F. The role of optical defocus in regulating refractive development in infant monkeys. *Vision Res* 1999;39:1415–1435. [PubMed: 10343811]
13. Hung L-F, Crawford MLJ, Smith EL III. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med* 1995;1:761–765. [PubMed: 7585177]
14. Bradley DV, Fernandes A, Lynn M, Tigges M, Boothe RG. Emmetropization in the rhesus monkey (*Macaca mulatta*): birth to young adulthood. *Invest Ophthalmol Vis Sci* 1999;40:214–229. [PubMed: 9888446]
15. Kiely PM, Crewther SG, Nathan J, Brennan NA, Efron N, Madigan M. A comparison of ocular development of the cynomolgus monkey and man. *Clin Vis Sci* 1987;1:269–280.
16. Rabin J, Van Sluyters RC, Malach R. Emmetropization: a vision-dependent phenomenon. *Invest Ophthalmol Vis Sci* 1981;20:561–564. [PubMed: 7216673]
17. Robb RM. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. *Am J Ophthalmol* 1977;83:52–58. [PubMed: 835667]



18. O'Leary DJ, Millodot M. Eyelid closure causes myopia in humans. *Experientia* 1979;35:1478–1479. [PubMed: 510490]
19. Nathan J, Kiely PM, Crewther SG, Crewther DP. Disease-associated image degradation and spherical refractive errors in children. *Am J Optom Physiol Opt* 1985;62:680–688. [PubMed: 4073201]
20. Ingram RM, Arnold PE, Dally S, Lucas J. Emmetropization, squint, and reduced visual acuity after treatment. *Br J Ophthalmol* 1991;75:414–416. [PubMed: 1854694]
21. Atkinson J, Braddick O, Bobier B, et al. Two infant vision screening programmes: prediction and prevention of strabismus and amblyopia from photo- and videorefractive screening. *Eye* 1996;10:189–198. [PubMed: 8776448]
22. Chung K, Mohidin N, O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res* 2002;42:2555–2559. [PubMed: 12445849]
23. Goss DA. Overcorrection as a means of slowing myopic progression. *Am J Optom Physiol Opt* 1984;61:85–93. [PubMed: 6703013]
24. Fulk GW, Cyert LA, Parker DE. A randomized trial of the effect of single-vision vs. bifocal lenses on myopia progression in children with esophoria. *Optom Vis Sci* 2000;77:395–401. [PubMed: 10966065]
25. Edwards M, Li R, Lam C, Lew J, Yu B. The Hong Kong progressive lens myopia control study: study design and main findings. *Invest Ophthalmol Vis Sci* 2002;43:2852–2858. [PubMed: 12202502]
26. Gwiazda J, Hyman L, Hussein M, et al. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci* 2003;44:1492–1500. [PubMed: 12657584]
27. Stone RA, Flitcroft DI. Ocular shape and myopia. *Ann Acad Med Singapore* 2004;33:7–15. [PubMed: 15008555]
28. Artal P, Derrington AM, Colombo E. Refraction aliasing, and the absence of motion reversals in peripheral vision. *Vision Res* 1995;35:939–947. [PubMed: 7762151]
29. Wang Y-Z, Thibos LN, Bradley A. Effects of refractive error on detection acuity and resolution acuity in peripheral vision. *Invest Ophthalmol Vis Sci* 1997;38:2134–2143. [PubMed: 9331277]
30. Kee, C-s; Hung, L-F.; Qiao-Grider, Y.; Roorda, A.; Smith, EL, III. Effects of optically imposed astigmatism on emmetropization in infant monkeys. *Invest Ophthalmol Vis Sci* 2004;45:1647–1659. [PubMed: 15161822]
31. Petry HM, Fox R, Casagrande VA. Spatial contrast sensitivity of the tree shrew. *Vision Res* 1984;24:1037–1042. [PubMed: 6506467]
32. Hodos W, Erichsen J. Lower-field myopia in birds: an adaptation that keeps the ground in focus. *Vision Res* 1990;30:653–657. [PubMed: 2378058]
33. Wallman J, Gottlieb MD, Rajaram V, Fugate-Wentzek L. Local retinal regions control local eye growth and myopia. *Science* 1987;237:73–77. [PubMed: 3603011]
34. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res* 1997;37:659–668. [PubMed: 9156210]
35. Norton TT, Siegwart JT. Animal models of emmetropization: matching axial length to the focal plane. *J Am Optom Assoc* 1995;66:405–414. [PubMed: 7560727]
36. Knight-Nanan DM, O'Keefe M. Refractive outcome in eyes with retinopathy of prematurity treated with cryotherapy or diode laser: 3 year follow up. *Br J Ophthalmol* 1996;80:998–1001. [PubMed: 8976729]
37. Connolly BP, Ng EY, McNamara JA, Regillo CD, Vander JF, Tasman W. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: part 2, refractive outcome. *Ophthalmology* 2002;109:936–941. [PubMed: 11986101]
38. Sieving PA, Fishman GA. Refractive errors of retinitis pigmentosa patients. *Br J Ophthalmol* 1978;62:163–167. [PubMed: 638108]
39. Ferree CE, Rand G, Hardy C. Refraction for the peripheral field of vision. *Arch Ophthalmol* 1931;5:717–731.
40. Millodot M, Lamont A. Refraction of the periphery of the eye. *J Opt Soc Am* 1974;64:110–111. [PubMed: 4813433]

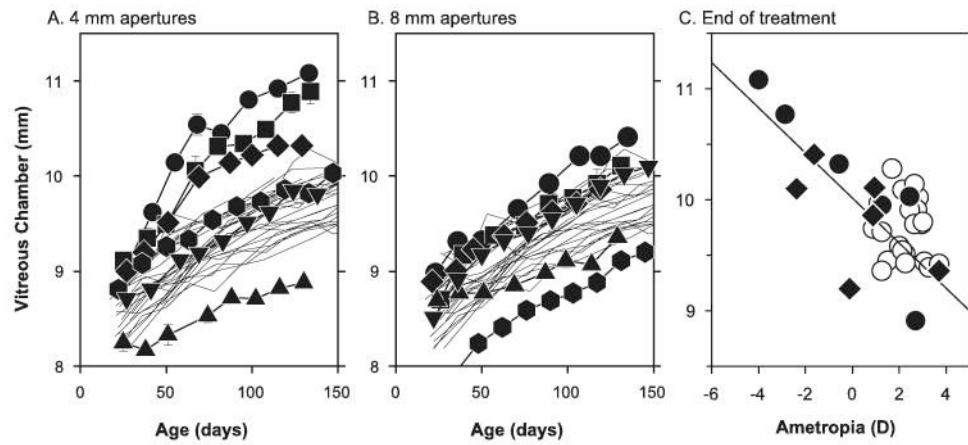
41. Mutti DO, Zadnik K, Hayes JR, Mitchell GL, Jones LA, Moeschberger ML. Axial length and ocular shape before and after the onset of myopia (Abstract). *Optom Vis Sci* 2004;12(suppl):24.
42. Schmid G. Retinal steepness vs. myopic shift in children (Abstract). *Optom Vis Sci* 2004;12(suppl):23.
43. Hoogerheide J, Rempt F, Hoogenboom WP. Acquired myopia in young pilots. *Ophthalmologica* 1971;163:209–215. [PubMed: 5127164]
44. Kee, C-s; Hung, L-F.; Qiao, Y.; Habib, A.; Smith, EL, III. Prevalence of astigmatism in infant monkeys. *Vision Res* 2002;42:1349–1359. [PubMed: 12044741]
45. Carkeet A. Field restriction and vignetting in contact lenses with opaque peripheries. *Clin Exp Optom* 1998;81:151–158. [PubMed: 12482252]
46. Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature* 1977;266:66–68. [PubMed: 402582]
47. Smith EL III, Harwerth RS, Crawford MLJ, von Noorden GK. Observations on the effects of form deprivation on the refractive status of the monkey. *Invest Ophthalmol Vis Sci* 1987;28:1236–1245. [PubMed: 3610541]
48. Napper GA, Brennan NA, Barrington M, Squires MA, Vessey GA, Vingrys A. The effect of an interrupted daily period of normal visual stimulation on form deprivation myopia in chicks. *Vision Res* 1997;37:1557–1564. [PubMed: 9231222]
49. Napper GA, Brennan NA, Barrington M, Squires M, Vessey GA, Vingrys AJ. The duration of normal visual exposure necessary to prevent form deprivation myopia in chicks. *Vision Res* 1995;35:1337–1344. [PubMed: 7610595]
50. Schmid KL, Wildsoet CF. Effects on the compensatory responses to positive and negative lenses of intermittent lens wear and ciliary nerve section in chicks. *Vision Res* 1996;36:1023–1036. [PubMed: 8736261]
51. Smith EL III, Hung L-F, Kee C-s, Qiao Y. Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Invest Ophthalmol Vis Sci* 2002;43:291–299. [PubMed: 11818369]
52. Wallman J, Adams JI. Developmental aspects of experimental myopia in chicks: susceptibility, recovery and relation to emmetropization. *Vision Res* 1987;27:1139–1163. [PubMed: 3660666]
53. Qiao-Grider Y, Hung L-F, Kee C-s, Ramamirtham R, Smith EL III. Recovery from form deprivation myopia in rhesus monkeys (*Macaca mulatta*). *Invest Ophthalmol Vis Sci* 2004;45:3361–3372. [PubMed: 15452037]
54. Siegwart JT, Norton TT. The susceptible period for deprivation-induced myopia in tree shrew. *Vision Res* 1998;38:3505–3515. [PubMed: 9893785]
55. Wildsoet CF, Schmid KL. Optical correction of form deprivation myopia inhibits refractive recovery in chick eyes with intact or sectioned optic nerves. *Vision Res* 2000;40:3273–3282. [PubMed: 11008143]
56. Geeraets WJ, Williams RC, Chan G, Ham WT, Guerry D, Schmidt FH. The relative absorption of thermal energy in retina and choroid. *Invest Ophthalmol* 1962;1:340–347. [PubMed: 13897480]
57. Chino YM, Smith EL III, Kaas JH, Sasaki Y, Cheng H. Receptive-field properties of deafferentated visual cortical neurons after topographic map reorganization in adult cats. *J Neurosci* 1995;15:2417–2433. [PubMed: 7891177]
58. Harris WF. Algebra of spherocylinders and refractive errors, and their means, variance, and standard deviation. *Am J Optom Physiol Opt* 1988;65:794–902. [PubMed: 3207150]
59. Tigges M, Tigges J, Fernandes A, Eggers HM, Gammon JA. Postnatal axial eye elongation in normal and visually deprived rhesus monkeys. *Invest Ophthalmol Vis Sci* 1990;31:1035–1046. [PubMed: 2354909]
60. Smith EL III, Hung L-F. Form-deprivation myopia in monkeys is a graded phenomenon. *Vision Res* 2000;40:371–381. [PubMed: 10820617]
61. Troilo D, Gottlieb MD, Wallman J. Visual deprivation causes myopia in chicks with optic nerve section. *Curr Eye Res* 1987;6:993–999. [PubMed: 3665562]
62. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron* 2004;43:447–468. [PubMed: 15312645]

63. Seidemann A, Schaefel F, Guirao A, Lopez-Gil N, Artal P. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A* 2002;19:2363–2373.
64. Atchison DA, Jones CE, Schmid KL, et al. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci* 2004;45:3380–3386. [PubMed: 15452039]
65. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci* 2000;41:1022–1030. [PubMed: 10752937]
66. McFadden SA, Howlett MH, Mertz JR. Retinoic acid signals the direction of ocular growth in guinea pig eye. *Vision Res* 2004;44:643–653. [PubMed: 14751549]
67. Ni J, Smith EL III. Effects of chronic optical defocus on the kitten's refractive status. *Vision Res* 1989;29:929–938. [PubMed: 2629208]
68. Millodot M. Effect of ametropia on peripheral refraction. *Am J Optom Physiol Opt* 1981;58:691–695. [PubMed: 7294139]
69. Zhu X, Winawer JA, Wallman J. Potency of myopic defocus in spectacle lens compensation. *Invest Ophthalmol Vis Sci* 2003;44:2818–2827. [PubMed: 12824218]



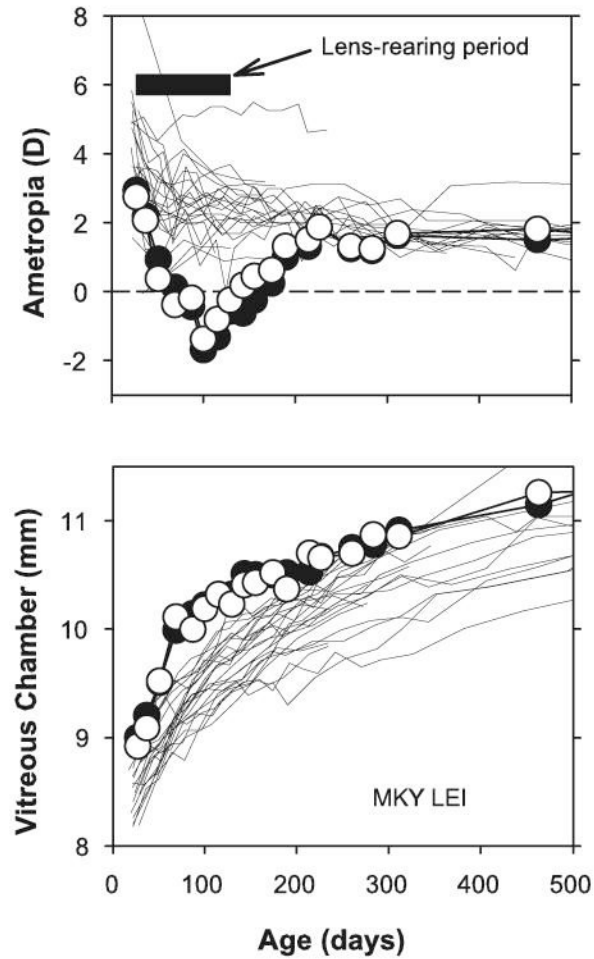
**Figure 1.**

Refractive error along the pupillary axis, specified as the spherical-equivalent, spectacle-plane refractive correction, plotted as a function of age for the right eyes of individual control animals (*lines*) and treated monkeys (*symbols*) reared with diffusers with (A) 4- and (B) 8-mm apertures. (C) Right eye refractive errors for treated ( $\bullet$ , 4-mm apertures;  $\blacklozenge$ , 8-mm apertures) and control animals ( $\circ$ ) at ages corresponding to the end of the treatment period. *Open and filled bars*: median and the 10th, 25th, 50th, and 90th percentiles for the control and treated monkeys.

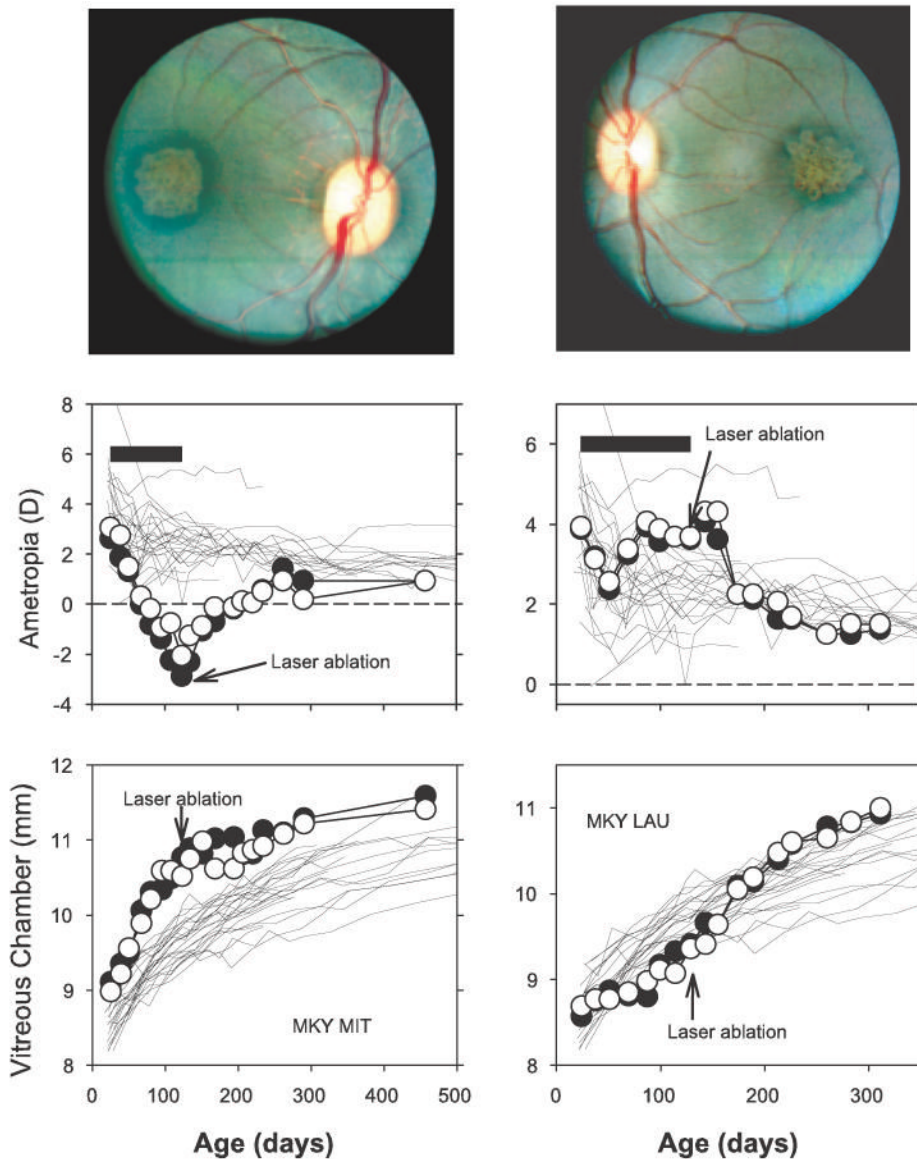


**Figure 2.**

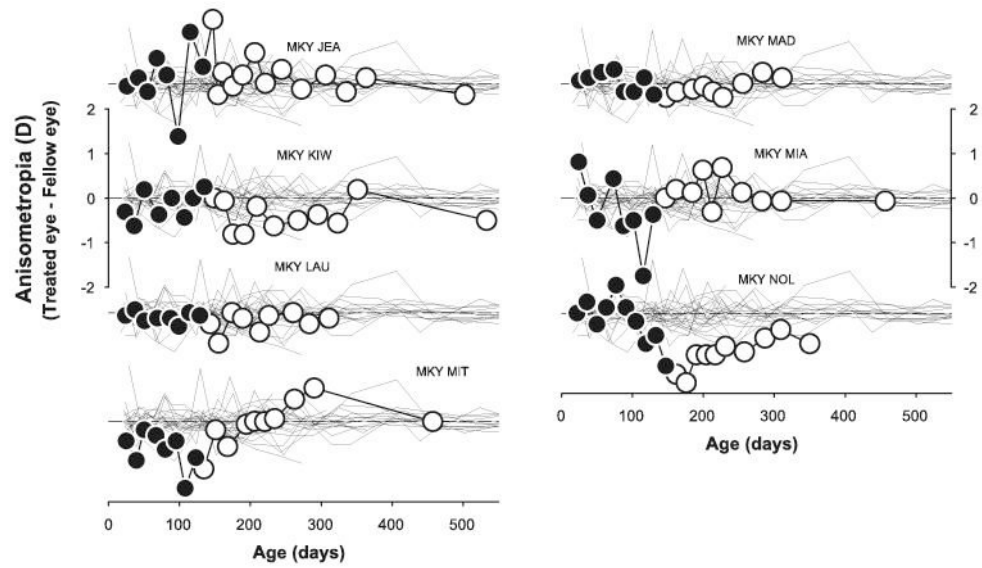
Mean  $\pm$  SD vitreous chamber depth along the pupillary axis plotted as a function of age for the right eyes of individual control animals (*lines*) and treated monkeys (*symbols*) reared with diffusers with (A) 4- and (B) 8-mm apertures. (C) Vitreous chamber depth plotted as a function of spherical-equivalent refractive error for treated ( $\bullet$ , 4-mm apertures;  $\blacklozenge$ , 8-mm apertures) and control animals ( $\circ$ ) at ages corresponding to the end of the treatment period. *Solid line*: results of the regression analysis of the data from the treated monkeys.



**Figure 3.** Recovery from experimentally induced refractive errors. Spherical equivalent, spectacle plane refractive correction (*top*) and mean vitreous chamber depth along the pupillary axis (*bottom*; the SDs were smaller than the symbol size) are plotted as a function of age in the right eyes of individual control animals (*lines*) and the right ( $\bullet$ ) and left eyes ( $\circ$ ) of a representative monkey that wore the peripheral diffusers.



**Figure 4.** Effects of foveal ablation on recovery from experimentally induced refractive errors. *Top:* retinal photographs illustrating the foveal ablations in the treated eyes. Spherical equivalent, spectacle plane refractive corrections (*middle*) and mean vitreous chamber depths along the pupillary axis (*bottom*) are plotted as a function of age, in the right eyes of individual control animals (*lines*) and the laser-treated (•) and nontreated (○) eyes of two monkeys that wore the peripheral diffusers (the SDs for the mean vitreous chamber depths were smaller than the symbol size). *Middle, filled horizontal bars:* lens-rearing periods. The laser photoablations were performed immediately after the lens-rearing period (*arrows*). Monkey LAU was selected because it was the only lens-reared monkey that was relatively hyperopic at the end of the treatment period. Monkey MIT was representative of the treated monkeys that exhibited relative myopic errors during the lens-rearing period.



**Figure 5.** Interocular differences in refractive error (laser treated eye or right eye–fellow eye) plotted as a function of age for the seven diffuser-reared monkeys that had the fovea of one eye ablated by laser photocoagulation at the end of the lens-rearing period. Data shown were obtained during (●) and (○) after the lens-rearing period. *Lines*: data from the control monkeys.