Effects of Foveal Ablation on Emmetropization and Form-Deprivation Myopia

Earl L. Smith III,1,2 Ramkumar Ramamirtham,1,2 Ying Qiao-Grider,1,2 Li-Fang Hung,1,2 Juan Huang,1,2 Chea-su Kee,1,5 David Coats,4 and Evelyn Paysse4

Purpose. Because of the prominence of central vision in primates, it has generally been assumed that signals from the fovea dominate refractive development. To test this assumption, the authors determined whether an intact fovea was essential for either normal emmetropization or the vision-induced myopic errors produced by form deprivation.

Methods. In 13 rhesus monkeys at 3 weeks of age, the fovea and most of the perifovea in one eye were ablated by laser photocoagulation. Five of these animals were subsequently allowed unrestricted vision. For the other eight monkeys with foveal ablations, a diffuser lens was secured in front of the treated eyes to produce form deprivation. Refractive development was assessed along the pupillary axis by retinoscopy, keratometry, and A-scan ultrasonography. Control data were obtained from 21 normal monkeys and three infants reared with plano lenses in front of both eyes.

Results. Foveal ablations had no apparent effect on emmetropization. Refractive errors for both eyes of the treated infants allowed unrestricted vision were within the control range throughout the observation period, and there were no systematic interocular differences in refractive error or axial length. In addition, foveal ablation did not prevent form deprivation myopia; six of the eight infants that experienced monococular form deprivation developed myopic axial anisometropias outside the control range.

Conclusions. Visual signals from the fovea are not essential for normal refractive development or the vision-induced alterations in ocular growth produced by form deprivation. Conversely, the peripheral retina, in isolation, can regulate metropizing responses and produce anomalous refractive errors in response to abnormal visual experience. These results indicate that peripheral vision should be considered when assessing the effects of visual experience on refractive development. (Invest Ophthalmol Vis Sci. 2007;48:3914–3922) DOI:10.1167/iovs.06-1264

Emmetropization is an active process that uses visual feedback to regulate eye growth in a manner that normally eliminates the refractive errors common in neonates.1–3 The mechanisms responsible for emmetropization remain active well into early adult life and probably play an important role in maintaining the optimal refractive state and the proper interocular balance of refractive errors.4–7 However, it is also likely that visual experience acting through these mechanisms contributes to the development of refractive errors in many persons.8–11

Because resolution acuity in humans is highest at the fovea, is sensitive to optical defocus, and decreases rapidly with eccentricity, it has generally been assumed that visual signals produced in the fovea dominate the emmetropization process and presumably the genesis of common refractive errors in children.12 Although this fundamental assumption is logical, it is important to note that the vision-dependent mechanisms that regulate refractive development appear to have evolved from species without foveas (e.g., fish13) and to have been maintained throughout the observation period, and there were no systematic interocular differences in refractive error or axial length. In addition, foveal ablation did not prevent form deprivation myopia; six of the eight infants that experienced monococular form deprivation developed myopic axial anisometropias outside the control range.

Visual signals from the fovea are not essential for normal refractive development or the vision-induced alterations in ocular growth produced by form deprivation. Conversely, the peripheral retina, in isolation, can regulate metropizing responses and produce anomalous refractive errors in response to abnormal visual experience. These results indicate that peripheral vision should be considered when assessing the effects of visual experience on refractive development. (Invest Ophthalmol Vis Sci. 2007;48:3914–3922) DOI:10.1167/iovs.06-1264

From the 1College of Optometry, University of Houston, Houston, Texas; the 2Vision Cooperative Research Centre, Sydney, Australia; and the 3Department of Ophthalmology, Baylor College of Medicine, Houston, Texas.

1Present affiliation: School of Optometry, The Hong Kong Polytechnic University, Hong Kong, SAR, China.

Supported by National Eye Institute Grants RO1 EY03611 and P30 EY07551; the Vision Cooperative Research Centre, Sydney, Australia; and the Greenean-Petty Professorship, UH Foundation.

Submitted for publication October 20, 2006; revised February 13, March 23, and April 23, 2007; accepted June 26, 2007.

Disclosure: E.L. Smith III, P; R. Ramamirtham, None; Y. Qiao-Grider, None; L.-F. Hung, None; J. Huang, None; C. Kee, None; D. Coats, None; E. Paysse, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked “advertisement” in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Earl L. Smith III, College of Optometry, University of Houston, 505 J Davis Armistead Building, Houston, TX 77204-2020; esmith@uh.edu.
Peripheral Control of Refractive Development

Materials and Methods

Subjects

Data are presented for 43 infant rhesus monkeys (Macaca mulatta). The animals were obtained at 1 to 3 weeks of age and were housed in our primate nursery, maintained on a 12-hour light/12-hour dark lighting cycle. All rearing and experimental procedures were reviewed and approved by the University of Houston Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

After the initial biometric measurements, which were performed when the monkeys were approximately 3 weeks of age, the monkeys were randomly assigned to either the control or the treatment group. The control group consisted of 21 infant monkeys reared with normal unrestricted vision and three monkeys reared wearing lightweight helmets that held zero-powered spectacle lenses in front of both eyes. Therefore, the purpose of this investigation was to determine whether an intact fovea is essential for normal emmetropization, a process known to be regulated by visual feedback in primates, and whether an intact fovea is essential for the development of form-deprivation myopia, a refractive error produced by anomalous visual experience.

A reduction strategy was used to assess the relative role of the fovea in refractive development. Specifically, either an argon or a frequency-doubled YAG laser was used to photocoagulate the fovea of one eye in each of 13 experimental monkeys. Laser procedures were performed immediately after the initial biometric measurements, with the intent of eliminating all the fovea and part of the perifovea. Although at 3 weeks of age the fovea in an infant monkey eye is anatomically immature and the center of the fovea cannot be identified as readily by ophtalmoscopy as in adults, the distance between the fovea and the center of the optic disc is constant during postnatal development in monkeys. Therefore, the position of the fovea was inferred using the optic disc as a reference and the pattern of the central retinal vessels, which converge to a central avascular area that will be occupied by the future fovea. However, because of a degree of uncertainty concerning the position of the center of the fovea, the sizes of the ablations were approximately 20% larger than those in our previous studies of older monkeys. Diameters of the ablation zone were approximately twice the horizontal dimension of the optic disc and corresponded to approximately the central 10°-12° of the retina. To make the foveal ablations, the monkeys were anesthetized (intramuscular injection [ketamine hydrochloride, 15-20 mg/kg; acepromazine maleate, 0.15-0.2 mg/kg] and topical instillation [1-2 drops of 0.5% tetracaine hydrochloride]), and the laser was delivered to the eye through a slit lamp or an indirect ophthalmoscope. The argon laser was operated in the blue-green mode and had a nominal spot size of 500 μm. Argon laser power was varied from 100 to 250 mW and was presented in 50-msec pulses. The frequency-doubled YAG laser was operated at 150 mW and was presented as 150-msec pulses. Foveal burns were overlapped to ensure complete photoablation of the fovea. Subsequently, ophthalmoscopy, optical coherence tomography (Stratus OCT; Carl Zeiss Meditec, Inc., Oberkochen, Germany), and fundus photography confirmed the sizes and positions of the lesions. As illustrated in the fundus photographs and the OCT retinal thickness scans for the treated and fellow eyes of two representative monkeys in Figure 1, the photoablations included all the foveas and substantial portions of the perifoveas in each animal. Sizes and positions of the ablations were similar in all 13 treated monkeys. OCT retinal thickness scans also showed that the photoablations were effective in destroying the neural retina in the treatment groups and that the effective treatment zones were substantially larger than the foveas.

Ocular Biometry

Details of our biometric measurements, which were performed every 2 to 4 weeks during the observation period, have been described elsewhere. Briefly, to perform the measurements, the animals were anesthetized (intramuscular injection [ketamine hydrochloride, 15-20 mg/kg; acepromazine maleate, 0.15-0.2 mg/kg] and topical instillation [1-2 drops of 0.5% tetracaine hydrochloride]) and cyclopleged (multiple drops of 1% tropicamide topicaly 20-30 minutes before retinoscopy). Refractive errors along the pupillary axis were determined independently by two experienced investigators using streak retinoscopy and hand-held trial lenses, averaged, and specified as spherical-equivalent, spectacle-plane refractive corrections. The 95% limits of agreement for our retinoscopy measures (spherical-equivalent refractive error) are ±0.6 D.05 Ocular axial dimensions were measured by A-scan ultrasonography implemented with either a 7-MHz (Image 2000; Mentor, Norwell, MA) or a 12-MHz transducer (OTI Scan 1000; OTI Ophthalmic Technologies, Inc., North York, ON, Canada). Intraocular distances were calculated from the average of 10 separate measurements using velocities of 1532 m/s, 1641 m/s, and 1532 m/s for the aqueous, lens, and vitreous, respectively. Corneal curvature was measured with a hand-held keratometer (Alcon Auto-Keratometer; Alcon Systems Inc., St. Louis, MO) or a videotopographer (Eyesys 2000; Eyesys Technologies Inc., Houston, TX). Both instruments provide repeatable and comparable measures of corneal curvature in infant monkeys.06
Statistical Analysis

Two-sample t-tests and Mann–Whitney U tests were used to compare the means and medians for treated and control monkeys. Paired t-tests were used to examine interocular differences in individual animals. Relationships between refractive error and vitreous chamber depth and corneal power were determined using linear regression. All analyses were executed using Minitab software (Release 12.21; Minitab Inc., State College, PA).

RESULTS

At the first measurement session, before the laser and lens-rearing procedures, no systematic interocular differences were observed in refractive error or vitreous chamber depth in the control group or in either of the two laser-treated monkey groups (paired t-test; $P = 0.20–0.99$). Moreover, the eyes of the treated and control monkeys were similar; average refractive errors for the right eyes of the control and treated monkeys were moderately hyperopic (control $[+3.78 \pm 1.75 \text{ D}]$ vs. treated $[+4.18 \pm 1.48 \text{ D}]$; two-sample t-test, $P = 0.46$), and the vitreous chamber depths for the control and treated monkeys were comparable (control $[8.64 \pm 0.31 \text{ mm}]$ vs. treated $[8.61 \pm 0.13 \text{ mm}]$; two-sample t-test, $P = 0.66$).

Monocular Foveal Ablation

If visual signals from the fovea are essential for emmetropization or play a dominant role in normal refractive development, it would be expected that eliminating the fovea would alter the efficiency, time course, or possibly the target refractive error of the emmetropization process in the treated eyes relative to control eyes. In addition, because the vision-dependent mechanisms that regulate refractive development operate in a relatively autonomous fashion in each eye, monocular foveal ablations would be expected to result in differences in the course of emmetropization between the treated eye and the fellow eye of a given experimental monkey. Figure 2 illustrates the spherical-equivalent refractive errors plotted as a function of age for the right eyes of the control monkeys (thin lines) and the treated (filled symbols) and fellow eyes (open symbols) of the monkeys that had monocular foveal ablations. At the start of the observation period, four of the five treated monkeys exhibited hyperopic errors of $+4.0 \text{ D}$ or greater. All these animals exhibited the rapid reductions in hyperopia characteristic of normal emmetropization and thereafter maintained relatively moderate degrees of hyperopia in both eyes throughout the observation period. The fifth monkey with a monocular foveal ablation exhibited comparatively low degrees of hyper-
opia at the start of the treatment period and showed relatively small subsequent changes in refractive error. The key points are that there were no systematic differences in refractive development between treated and fellow eyes and refractive errors for both eyes of the treated monkeys were well within the range of refractive errors for control animals at all ages.

Interocular differences in refractive error are plotted as a function of age in Figure 3A for the five monkeys with monocular foveal ablations and all the control animals. As illustrated in the upper plot, both eyes of each control monkey grew in a coordinated manner so that clinically significant anisometropias were rare in the normal and plano-control monkeys. During the observation period, the largest anisometropia found in a control animal measured 1.25 D, which was observed at the initial measurement session for one animal. Anisometropias larger than 0.75 D were found on only 7 of 330 occasions in the control animals, and the average anisometropia was $-0.03 \pm 0.27$ D (the right eye was considered the treated eye; paired t-test, $P = 0.24$). Although small anisometropias (e.g., 0.25–0.50 D) were relatively more common

---

**Figure 2.** Spherical-equivalent, spectacle-plane refractive corrections plotted as a function of age for individual control animals and the treated monkeys reared with monocular foveal ablations and unrestricted vision. Thin solid lines: right eyes of the control animals. Open and filled circles: control and laser-treated eyes of the experimental monkeys, respectively. Laser procedures were performed during the first measurement session at approximately 3 weeks of age.

**Figure 3.** (A) Interocular differences in refractive error (right or treated eye – left or fellow eye) plotted as a function of age for control animals (upper plot, open circles) and the treated monkeys reared with monocular foveal ablations and unrestricted vision (lower plot, filled symbols). Dashed lines: mean ± 2 SD for control animals. (B) Frequency histograms of the anisometropic errors found during the observation period for the control (upper plot) and treated (lower plot) monkeys.
In the treated monkeys (compare the upper and lower frequency distributions in Fig. 3B), none of the animals with monocular foveal ablations exhibited anisometropia that fell outside the range of anisometropias found in the control animals. During the observation period, treated eyes were on average \(-0.15 \pm 0.35 \) D less hyperopic than their fellow control eyes. Although these differences were not statistically significant (paired t-test, \( P = 0.23 \)), the reduction in retinal thickness produced by our photoablation procedures could have resulted in small myopic shifts in retinoscopy measures. Regardless, there were no indications that the degree or direction of anisometropia in the treated animals changed in a systematic manner during the observation period.

**Foveal Ablation and Form Deprivation**

If signals from the fovea were essential for the development of vision-induced refractive anomalies, it would be expected that eliminating the fovea would prevent form deprivation from altering the course of emmetropization. Specifically, in this experiment, it was expected that refractive development would be similar in the treated and fellow eyes of the animals reared with monocular foveal ablation and form deprivation. Figure 4 compares the course of refractive development during the lens-rearing period between the right eyes of the control animals and nontreated fellow eyes (open symbols) of the monkeys with monocular foveal ablations during the observation period. Laser procedures were performed during the first measurement session at approximately 3 weeks of age, immediately before the onset of form deprivation.

Regardless, there were no indications that the degree or direction of anisometropia in the treated animals changed in a systematic manner during the observation period.

**Foveal Ablation and Form Deprivation**

If signals from the fovea were essential for the development of vision-induced refractive anomalies, it would be expected that eliminating the fovea would prevent form deprivation from altering the course of emmetropization. Specifically, in this experiment, it was expected that refractive development would be similar in the treated and fellow eyes of the animals reared with monocular foveal ablation and form deprivation. Figure 4 compares the course of refractive development during the lens-rearing period between the right eyes of the control animals (thin lines) and the form-deprived (filled symbols) and nontreated fellow eyes (open symbols) of the monkeys with monocular foveal ablations.

As a group, the treated monkeys exhibited substantial variability in refractive development. At the end of the diffuser-rearing period, the range of refractive errors for the treated eyes was obviously greater than that for the control animals (-5.00 to +6.06 D vs. +0.81 to +5.50 D), and the median refractive error for the treated eyes was significantly less hyperopic or more myopic (+0.78 D vs. +2.50 D; Mann-Whitney U test; \( P = 0.05 \)). Most important, all the treated monkeys had obvious interocular differences in refractive error. By the end of the diffuser-rearing period, the treated eyes of six of the eight treated animals were more myopic or less hyperopic than their fellow eyes. Within this group, the onset and progression of form deprivation myopia was obvious in some animals (e.g., Fig. 4, lower row); however, the rate at which the relative myopia and the final degree of form-deprivation myopia emerged varied substantially among animals. Interestingly, in two treated animals, the form-deprived eyes showed relative hyperopic shifts in refractive error at the end of the rearing period (Figs. 4A, 4B). In addition, a third monkey (Fig. 4C, monkey EDE) showed an initial hyperopic shift in its treated eye, but, after approximately 50 days of form deprivation, the treated eye showed systematic reductions in the degree of hyperopia. By the end of the diffuser-rearing period, the treated eye had become more myopic than its fellow nontreated eye.

**Foveal Ablation and Form Deprivation**

If signals from the fovea were essential for the development of vision-induced refractive anomalies, it would be expected that eliminating the fovea would prevent form deprivation from altering the course of emmetropization. Specifically, in this experiment, it was expected that refractive development would be similar in the treated and fellow eyes of the animals reared with monocular foveal ablation and form deprivation. Figure 4 compares the course of refractive development during the lens-rearing period between the right eyes of the control animals (thin lines) and the form-deprived (filled symbols) and nontreated fellow eyes (open symbols) of the monkeys with monocular foveal ablations.

As a group, the treated monkeys exhibited substantial variability in refractive development. At the end of the diffuser-rearing period, the range of refractive errors for the treated eyes was obviously greater than that for the control animals (-5.00 to +6.06 D vs. +0.81 to +5.50 D), and the median refractive error for the treated eyes was significantly less hyperopic or more myopic (+0.78 D vs. +2.50 D; Mann-Whitney U test; \( P = 0.05 \)). Most important, all the treated monkeys had obvious interocular differences in refractive error. By the end of the diffuser-rearing period, the treated eyes of six of the eight treated animals were more myopic or less hyperopic than their fellow eyes. Within this group, the onset and progression of form deprivation myopia was obvious in some animals (e.g., Fig. 4, lower row); however, the rate at which the relative myopia and the final degree of form-deprivation myopia emerged varied substantially among animals. Interestingly, in two treated animals, the form-deprived eyes showed relative hyperopic shifts in refractive error at the end of the rearing period (Figs. 4A, 4B). In addition, a third monkey (Fig. 4C, monkey EDE) showed an initial hyperopic shift in its treated eye, but, after approximately 50 days of form deprivation, the treated eye showed systematic reductions in the degree of hyperopia. By the end of the diffuser-rearing period, the treated eye had become more myopic than its fellow nontreated eye.

**Foveal Ablation and Form Deprivation**

If signals from the fovea were essential for the development of vision-induced refractive anomalies, it would be expected that eliminating the fovea would prevent form deprivation from altering the course of emmetropization. Specifically, in this experiment, it was expected that refractive development would be similar in the treated and fellow eyes of the animals reared with monocular foveal ablation and form deprivation. Figure 4 compares the course of refractive development during the lens-rearing period between the right eyes of the control animals (thin lines) and the form-deprived (filled symbols) and nontreated fellow eyes (open symbols) of the monkeys with monocular foveal ablations.

As a group, the treated monkeys exhibited substantial variability in refractive development. At the end of the diffuser-rearing period, the range of refractive errors for the treated eyes was obviously greater than that for the control animals (-5.00 to +6.06 D vs. +0.81 to +5.50 D), and the median refractive error for the treated eyes was significantly less hyperopic or more myopic (+0.78 D vs. +2.50 D; Mann-Whitney U test; \( P = 0.05 \)). Most important, all the treated monkeys had obvious interocular differences in refractive error. By the end of the diffuser-rearing period, the treated eyes of six of the eight treated animals were more myopic or less hyperopic than their fellow eyes. Within this group, the onset and progression of form deprivation myopia was obvious in some animals (e.g., Fig. 4, lower row); however, the rate at which the relative myopia and the final degree of form-deprivation myopia emerged varied substantially among animals. Interestingly, in two treated animals, the form-deprived eyes showed relative hyperopic shifts in refractive error at the end of the rearing period (Figs. 4A, 4B). In addition, a third monkey (Fig. 4C, monkey EDE) showed an initial hyperopic shift in its treated eye, but, after approximately 50 days of form deprivation, the treated eye showed systematic reductions in the degree of hyperopia. By the end of the diffuser-rearing period, the treated eye had become more myopic than its fellow nontreated eye.

**Foveal Ablation and Form Deprivation**

If signals from the fovea were essential for the development of vision-induced refractive anomalies, it would be expected that eliminating the fovea would prevent form deprivation from altering the course of emmetropization. Specifically, in this experiment, it was expected that refractive development would be similar in the treated and fellow eyes of the animals reared with monocular foveal ablation and form deprivation. Figure 4 compares the course of refractive development during the lens-rearing period between the right eyes of the control animals (thin lines) and the form-deprived (filled symbols) and nontreated fellow eyes (open symbols) of the monkeys with monocular foveal ablations.

As a group, the treated monkeys exhibited substantial variability in refractive development. At the end of the diffuser-rearing period, the range of refractive errors for the treated eyes was obviously greater than that for the control animals (-5.00 to +6.06 D vs. +0.81 to +5.50 D), and the median refractive error for the treated eyes was significantly less hyperopic or more myopic (+0.78 D vs. +2.50 D; Mann-Whitney U test; \( P = 0.05 \)). Most important, all the treated monkeys had obvious interocular differences in refractive error. By the end of the diffuser-rearing period, the treated eyes of six of the eight treated animals were more myopic or less hyperopic than their fellow eyes. Within this group, the onset and progression of form deprivation myopia was obvious in some animals (e.g., Fig. 4, lower row); however, the rate at which the relative myopia and the final degree of form-deprivation myopia emerged varied substantially among animals. Interestingly, in two treated animals, the form-deprived eyes showed relative hyperopic shifts in refractive error at the end of the rearing period (Figs. 4A, 4B). In addition, a third monkey (Fig. 4C, monkey EDE) showed an initial hyperopic shift in its treated eye, but, after approximately 50 days of form deprivation, the treated eye showed systematic reductions in the degree of hyperopia. By the end of the diffuser-rearing period, the treated eye had become more myopic than its fellow nontreated eye.

**Foveal Ablation and Form Deprivation**

If signals from the fovea were essential for the development of vision-induced refractive anomalies, it would be expected that eliminating the fovea would prevent form deprivation from altering the course of emmetropization. Specifically, in this experiment, it was expected that refractive development would be similar in the treated and fellow eyes of the animals reared with monocular foveal ablation and form deprivation. Figure 4 compares the course of refractive development during the lens-rearing period between the right eyes of the control animals (thin lines) and the form-deprived (filled symbols) and nontreated fellow eyes (open symbols) of the monkeys with monocular foveal ablations.

As a group, the treated monkeys exhibited substantial variability in refractive development. At the end of the diffuser-rearing period, the range of refractive errors for the treated eyes was obviously greater than that for the control animals (-5.00 to +6.06 D vs. +0.81 to +5.50 D), and the median refractive error for the treated eyes was significantly less hyperopic or more myopic (+0.78 D vs. +2.50 D; Mann-Whitney U test; \( P = 0.05 \)). Most important, all the treated monkeys had obvious interocular differences in refractive error. By the end of the diffuser-rearing period, the treated eyes of six of the eight treated animals were more myopic or less hyperopic than their fellow eyes. Within this group, the onset and progression of form deprivation myopia was obvious in some animals (e.g., Fig. 4, lower row); however, the rate at which the relative myopia and the final degree of form-deprivation myopia emerged varied substantially among animals. Interestingly, in two treated animals, the form-deprived eyes showed relative hyperopic shifts in refractive error at the end of the rearing period (Figs. 4A, 4B). In addition, a third monkey (Fig. 4C, monkey EDE) showed an initial hyperopic shift in its treated eye, but, after approximately 50 days of form deprivation, the treated eye showed systematic reductions in the degree of hyperopia. By the end of the diffuser-rearing period, the treated eye had become more myopic than its fellow nontreated eye.
the treated monkeys reared with unrestricted vision.

function of the interocular differences in refractive error (right or treated eye reared with unrestricted vision (filled squares).

FIGURE 5. (A) Interocular differences in refractive error (right or treated eye — left or fellow eye) plotted as a function of age for control animals (open circles) and treated monkeys reared with monocular foveal ablations and form deprivation (filled symbols). The first and last symbols for each animal represent the start and end of the period of form deprivation. Dashed lines: mean ± 2 SD for the control animals. (B) Degree of anisometropia at the end of the lens-rearing period for the monocularly form-deprived animals with monocular foveal ablations (filled diamonds), monocularly form-deprived animals with intact retinas (filled hexagons), and age-matched control animals (open diamonds).

hexagons). Ranges of anisometropias in these two groups of form-deprived monkeys were similar (laser + form deprivation [+1.44 to −5.81 D] vs form deprivation only [−0.25 to −9.5 D]). In addition, though an overall shift of the results occurred for the laser-treated monkeys in the hyperopic direction, no significant differences were observed in either the mean (−1.18 ± 2.76 D vs. −5.14 ± 3.60 D; two-sample t-test, P = 0.09) or the median (−1.16 D vs. −5.97 D; Mann–Whitney U test, P = 0.11) anisometropias between these two groups of form-deprived monkeys.

In addition to the direct effects of the form deprivation on the treated eyes, it was evident that the monocular treatment regimen had altered refractive development in the fellow non-treated eyes in some animals. For example, for three animals (Figs. 4F–H), the nontreated fellow eye exhibited relative myopic errors that fell outside the normal range at some point during the treatment period. In addition, the nontreated fellow eye of monkey MAN (Fig. 4B) showed no evidence of emmetropization and by the end of the diffuser-rearing period had a refractive error of +4.63 D, which was >2 SD above the control mean. However, the mean (+2.05 ± 1.27 D vs. +2.42 ± 0.94 D; two-sample t-test, P = 0.46) and median (+1.94 D vs. 2.50 D; two-sample t-test, P = 0.25) refractive errors for the nontreated fellow eyes were not significantly different from those for the control animals.

The observed interocular differences in refractive error in the form-deprived monkeys cannot be attributed to either laser-induced or vision-induced changes in corneal power. Although at the end of the lens-rearing period there was a trend for the form-deprived eyes of the laser-treated monkeys to have slightly steeper corneas than their fellow eyes (average interocular difference, +0.33 D), these interocular differences were not significant (paired t-test, P = 0.09), and the absolute interocular differences in corneal power for the form-deprived monkeys with foveal lesions were not significantly larger than those for either the control animals (0.46 D vs. 0.25 D; two-sample t-test, P = 0.12) or the treated monkeys reared with unrestricted vision (0.46 D vs. 0.19, P = 0.07). Moreover, at the end of the diffuser-rearing period, the interocular differences in corneal power and refractive error were not significantly correlated (r² = 0.04; P = 0.25).

Anisometropias observed in the form-deprived animals with foveal ablations were primarily axial in nature. In Figures 6A and 6B, the interocular differences in vitreous chamber depth are plotted as a function of age for control animals (open circles), the treated monkeys that were reared with unrestricted visual experience (Fig. 6A, solid symbols), and the monocularly form-deprived monkeys that had foveal ablations (Fig. 6B, solid symbols). Monocular foveal ablation by itself had no apparent effect on vitreous chamber depth. No systematic interocular differences were observed in vitreous chamber depth in the treated monkeys allowed unrestricted vision (paired t-test, P = 0.71), and, with the exception of one observation, their interocular differences in vitreous chamber depth were always within 2 SD of the control mean. On the
other hand, many of the monkeys that had foveal ablations and
experienced monocular form deprivation exhibited obvious
interocular differences in vitreous chamber depth. Beginning
after approximately 1 month of form deprivation, the treated
eyes of four monkeys (FLO, FAR, JAC, FID) showed consist-
tently longer vitreous chambers than their fellow eyes, and the
interocular differences for these four animals were well outside
the control range for the remainder of the diffuser-rearing
period. On the other hand, the vitreous chamber in the treated
eye of one of the monkeys that developed a relative hyperopia
in the treated eye (monkey MAR, filled diamonds) was consist-
tently shorter than that for its fellow eye for most of the
lens-rearing period.

The observed changes in refractive error and vitreous cham-
ber depth were well correlated. Figure 6C shows the intero-
cular differences in vitreous chamber depth obtained at the
end of the diffuser-rearing period plotted as a function of the
interocular differences in refractive error for individual form-
deprived animals (filled diamonds). Data obtained at equivalent
ages are also shown for the control animals (open diamonds)
and the laser-treated monkeys reared with unrestricted vision
(filled squares). At the end of the lens-rearing period, five of
the form-deprived animals with foveal ablations exhibited inter-
ocular differences in vitreous chamber depth that fell outside
the range of interocular differences for control animals and
monkeys with monocular foveal ablations that experienced
unrestricted vision. Average interocular differences in vitreous
chamber depth for form-deprived monkeys with foveal abla-
tions (0.55 ± 0.55 mm) were significantly greater than for
age-matched control animals (0.10 ± 0.05 mm; two-sample
$t$-test, $P = 0.05$) or monkeys reared with monocular foveal
ablations (0.04 ± 0.04 mm; two-sample $t$-test, $P = 0.03$).
Regression analysis that included data from all the animal
groups showed that the interocular differences in vitreous
chamber depth were significantly correlated with the degree of
anisometropia ($P < 0.001$) and that the interocular differences
in vitreous chamber depth accounted for 81% of the variance
in the anisometropias.

**DISCUSSION**

Relative to refractive development in normal and nontreated
eyes, the course of emmetropization was not altered by foveal
ablation in the treated eyes of the infant monkeys allowed
unrestricted vision. Interpretation of these results is dependent
on the degree to which emmetropization is independent in the
two eyes. Based on the fact that monocular manipulations can
have interocular effects, it has been argued that the mecha-
nisms that regulate refractive development in the two eyes are
yoked.49-51 In fact, the nondeprived eyes of our monkeys
subjected to monocular form deprivation showed evidence of
interocular effects. The mechanisms that mediate these intero-
cular effects are not well understood. In birds, it has been
speculated that interocular effects are mediated by humoral
factors of central and ocular origin (Li T, et al. IOVS 1998;39:
ARVO Abstract 3287)46,52 and neural coupling between the
mechanisms that regulate refractive growth in the two eyes.49-52
Therefore, it could be argued that refractive develop-
ment in the treated eyes of the infant monkeys with foveal abla-
tions was guided by signals from the nontreated fellow eyes.
However, it is unclear whether similar pathways exist in pri-
mates because some of the manipulations that reveal interocu-
lar interactions in birds (e.g., continuous light exposure53) do
not have any obvious effects on emmetropization in pri-
mates,54,55 and anatomic differences between birds and pri-
mates suggest that the neural pathways likely to be involved in
any interocular neural interactions are less prominent in pri-
mates. For example, primates have 1000 times fewer centrifu-
gal fibers that project to the retina than have birds.56 Moreover,
the interocular effects in monkeys may have an optical basis. As
a result of consensual accommodation and accommodation-
convergence interactions in primates, we have previously ar-
gued that many interocular effects in monkeys could be caused
by changes in the time-averaged clarity of the retinal image in
the fellow eye as a result of manipulations of the contralateral
eye.14 In other words, the presence of interocular effects does
not necessarily imply that the mechanisms that regulate refrac-
tive development are directly yoked in the two eyes.

Conversely, strong evidence indicates that refractive devel-
opment proceeds primarily in an independent manner in the
two eyes. For example, in response to optically induced aniso-
metropia, infants of many species exhibit differential interocu-
lar growth and develop axial anisometropias that compensate
for the optically imposed errors.1-3,57 In Figure 4, the differ-
ential interocular growth produced by monocular form depre-
viation is another example of the relative independence of
refractive development in the two eyes. However, in species
with highly developed binocular vision, the nature of visual
experience in the two eyes is highly correlated. In particular,
because accommodation is yoked in the two eyes of primates
and because primates typically bifoveally fixate objects in
space, the retinal images in the two eyes are normally similar.
Consequently, refractive development, even if it is regulated
by independent mechanisms in the two eyes, normally proceeds
similarly in each eye.

Assuming that the vision-dependent mechanisms that regu-
late emmetropization are largely independent in the two eyes
of infant monkeys, results in our animals that had monocular
foveal ablations and that experienced unrestricted vision indi-
cated that visual signals from the fovea are not essential for
emmetropization. Instead the mechanisms that mediate em-
metropization can respond appropriately to optical defocus
associated with refractive error in the absence of visual signals
from the fovea. These results are in agreement with our pre-
vious finding that foveal ablation did not alter the ability of
infant monkeys to recover from experimentally induced refrac-
tive errors.27 A process mediated by optical defocus,28,29 Re-
results from both studies also imply that visual signals from the
periphery, in isolation, can be used to determine the direction
of axial growth required to eliminate refractive error and to
determine when ocular growth has eliminated that refractive
error (i.e., when emmetropia is achieved). Moreover, because
the treated and fellow eyes of these laser-treated monkeys
experienced comparable retinal images during development
given that accommodation is consensual in monkeys and that
the animals were orthotropic and had little or no anisometro-
pia), it can be argued that the emmetropization process driven
by the periphery alone can apparently operate as effectively
and efficiently as that driven by an intact eye. In other words,
in an intact eye, the overall contribution of the visual signals
from the fovea to emmetropization is probably small under
ordinary circumstances (ignoring the role of central vision in
directing accommodation).

Clinical observations in humans also suggest that the pe-
iphery can have a significant impact on emmetropization. For
example, children with retinal diseases show a larger than
normal range of refractive errors and have larger average re-
fractive errors. It is likely that these refractive errors come
about because the disease processes have interfered with the
mechanisms responsible for emmetropization. In this respect,
children who have conditions or diseases that primarily affect
the peripheral retina usually exhibit larger refractive errors
than children with eye diseases that primarily affect central
vision.11 The pattern of peripheral refractive errors may also
influence the course of refractive development in humans. For
example, young adults who are undergoing pilot training and show compound hyperopic astigmatism in the periphery are more likely to exhibit myopic shifts in central refractive error than those who exhibit myopic peripheral refractive errors.\textsuperscript{22} Similarly, children with prolate posterior segments and relative hyperopia in the periphery are more likely to develop myopia than children with oblate eyes and relative myopia in the periphery.\textsuperscript{24,58} Based on our findings in monkeys, it is reasonable to speculate that the hyperopic defocus produced by peripheral refractive errors in these children\textsuperscript{44,58} and adults,\textsuperscript{22} which would be constant over time, dominated refractive development and led to central axial myopia.

The second major finding of this study was that laser ablation of the fovea did not prevent form deprivation from altering refractive development in infant monkeys. In many respects, the refractive changes produced by form deprivation in the monkeys with foveal ablations were similar to those produced by form deprivation in intact eyes. In intact eyes and in eyes with foveal ablations, vision-induced myopia is axial in nature and caused primarily by an increase in vitreous chamber depth.\textsuperscript{34,35,39} In intact eyes and eyes with foveal ablation, substantial intersubject variability occurred in the time course and degree of myopic anisometropia produced by monocular deprivation. In both cases, form deprivation produced hyperopia in the treated eyes in a small number of animals, which in some cases was transient and eventually resulted in myopia; in other cases, the treated eye remained relatively more hyperopic than the nontreated fellow eye throughout the treatment period.\textsuperscript{14,35,36,39} Interocular effects, which are manifest as alterations in the course of emmetropization of the fellow eye, can also be seen in monocularly form-deprived monkeys with intact eyes and when the fovea in the treated eye has been ablated.\textsuperscript{14,34} Thus, in response to form deprivation, the periphery can produce the same kinds of refractive error changes that are produced in monkeys with intact eyes.

It appears that the degree of form-deprivation myopia produced in the laser-treated eyes was smaller than that produced by the same diffuser regimen in intact eyes. Although this difference was not statistically significant, it is possible that these differences represented a true quantitative difference reflecting a reduction in overall growth signals that resulted from eliminating the central retina. Given the inherently high intersubject variability in the degree of myopia produced by form deprivation in monkeys, it will take substantially larger sample sizes than those available to definitively address this issue. However, it seems reasonable to suppose that in an intact eye the signals from the fovea normally contribute to the magnitude of the eye’s response to form deprivation and that laser foveal ablation reduces the magnitude of this signal.

The pattern of results in our laser-treated, form-deprived monkeys complements our previous observation that diffuser lenses with central apertures, which produce form deprivation in the periphery but allow unrestricted foveal vision, also result in axial myopia.\textsuperscript{27} The diffuser lenses used in these previous studies were designed to produce selective peripheral form deprivation; however, the optical consequence of the treatment lenses depended on the animals’ viewing behaviors. In this respect, the animals were motivated to fixate through the apertures, and observations throughout the treatment period showed that the infants rapidly adapted to the lenses and consistently fixated through the apertures, resulting in potentially clear central vision and form deprivation in the periphery. However, it is likely that the images presented to the foveae of these monkeys were at times degraded. Given the nonlinear temporal integration properties of the emmetropization process (Vingrys AJ, et al. \textit{IOVS} 1991;32:ARVO Abstract 1203),\textsuperscript{14,35,60} it is unlikely that these brief periods of reduced central vision could have significantly contributed to the phenomenon of form-deprivation myopia. Results from the form-deprived monkeys with foveal ablations confirm our previous conclusion that selective peripheral form deprivation can produce myopia.\textsuperscript{27} Together, the results from our two studies indicate that in the absence of a visual signal from the fovea, or when conflicting visual signals exist between the fovea and the periphery, the effects of peripheral vision can dominate central refractive development.

Results of this study add to the growing body of data that indicate central/axial refractive development is influenced by image quality across the retina. Unfortunately, we know little about the spatial integration properties of the emmetropization process in primates. In particular, it will be important to learn how the signals from different parts of the eye are weighted to determine central axial elongation rates and the refractive status at the fovea and how visual experience, particularly regional variations in image quality, influence ocular shape and peripheral refractive error pattern. With respect to the development of optical treatment strategies to slow or prevent myopic progression, the results of the study reinforce the idea that peripheral vision must be taken into account to optimize any beneficial treatment effects.

**Acknowledgments**

The authors thank Ronald Harwerth and Joe Wheat for providing OCT retinal thickness scans for the treated monkeys.

**References**

44. Bradley DV, Fernandes A, Boothe RG. The refractive development of untreated eyes of rhesus monkeys varies according to the treatment received by their fellow eyes. Vision Res. 1999;39:1749–1757.
55. Smith EL III, Hung L-F, Kee C-s, Qiao-Grider Y, Ramamirtham R. Continuous ambient lighting and lens compensation in infant monkeys. Optom Vis Sci. 2003;80:574–582.