Compensation for Experimentally Induced Hyperopic Anisometropia in Adolescent Monkeys

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Purpose. Early in life, the optical demand associated with the eye's effective refractive state regulates emmetropization in many species, including primates. However, the potential role of optical demand and/or defocus in the genesis of common refractive errors, like myopia, that normally develop much later in life is not known. The purpose of this study was to determine whether chronic optical defocus alters refractive development in monkeys at ages corresponding to when myopia typically develops in children.

Methods. A hyperopic anisometropia was produced in seven adolescent rhesus monkeys by photorefractive keratectomy (PRK) with an excimer laser. Standard treatment algorithms for correcting myopia in humans were used to selectively flatten the central cornea of one eye thereby producing relative hyperopic refractive errors in the treated eyes. The laser ablation zones were 5.0 mm in diameter and centered on the monkeys' pupils. The laser procedures were performed when the monkeys were 2 to 2.5 years old, which corresponded to onset ages between approximately 8 and 10 human years. The ocular effects of the induced anisometropia were assessed by corneal topography, retinoscopy, and A-scan ultrasonography.

Results. By approximately 30 days after PRK, the experimentally induced refractive errors had stabilized and the treated eyes were between +0.75 and +2.25 D more hyperopic than their fellow eyes. Subsequently, over the next 300 to 400 days, six of the seven monkeys showed systematic reductions in the degree of anisometropia. Although some regression in corneal power occurred, the compensating refractive changes were primarily due to relative interocular differences in vitreous chamber growth.

Conclusions. Vision-dependent mechanisms that are sensitive to refractive error are still active in adolescent primates and probably play a role in maintaining stable refractive errors in the two eyes. Consequently, conditions that result in consistent hyperopic defocus could potentially contribute to the development of juvenile onset myopia in children. (*Invest Ophthalmol Vis Sci.* 2004;45:3373–3379) DOI:10.1167/iovs.04-0226

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This study addressed the question of whether optical defocus could feasibly play a role in the genesis of common refractive errors such as juvenile-onset myopia. Early in life when the eye grows very rapidly, visual experience can have a dramatic effect on eye growth and refractive development (for reviews, see Refs. 1–4). In many species, including humans, depriving the eye of form vision during early infancy accelerates axial growth, resulting in substantial amounts of myopia.[5–10] Similarly, imposing relative hyperopic refractive errors with a negative lens produces compensating myopic growth in many species (McFadden S, et al. *IOVS* 1995;36:ARVO Abstract 3504),[11–14] including primates.[15–18] In many respects, the experimentally induced myopia in infant monkeys is similar to juvenile-onset myopia in humans. For example, in both cases the ametropias are characterized by an increase in vitreous chamber depth[15–18] and a comparatively smaller decrease in corneal radius (Qiao Y, et al. *IOVS* 2002;43:ARVO E-Abstract 2927).[2] The fact that vision-dependent mechanisms can transform a normal primate eye into a conventionally shaped myopic eye raises the possibility that the common myopic errors found in many humans are caused, at least in part, by visual experience. However, the onset of myopia in humans typically occurs after approximately 8 years of age, during a much slower phase of ocular growth.[19]

Because the effects of visual experience on the eye's refractive state decline with age,[20–22] it is possible that the "sensitive period" for refractive development ends too early for visual experience to play a role in the development of juvenile-onset myopia in children.[23] However, recent investigations in the chicken,[24] tree shrew,[22] marmoset (Troilo D, et al. *IOVS* 1999; 40:ARVO Abstract 5081), and rhesus monkey[25] have shown that form deprivation, even when it is initiated after ocular growth is nearly complete, can produce axial myopia. Thus, some degree of residual plasticity, at least to abnormal visual experience, may extend into adulthood in primates.

Although form deprivation produces myopia in adolescent monkeys, there are many gaps in our knowledge regarding vision-dependent mechanisms during the slower, juvenile phase of ocular growth. In particular, we do not know whether visual feedback associated with the eye's refractive state influences ocular growth during the stage of eye development when myopia typically emerges in children. It is critical to evaluate the effects of optical defocus, because the mechanisms that mediate form-deprivation myopia and those responsible for the compensating refractive changes in response to altered optical demands are not identical.[26–28] In this respect, evidence from tree shrews suggests that optical defocus can produce compensating myopic growth during adolescence.[14,29] However, it has been reported that adolescent rhesus monkeys with form-deprivation myopia show no signs of recovery after the restoration of unrestricted vision.[30] Although there are several possible explanations for the failure of adolescent monkeys to recover from experimentally induced myopia, one possibility is that optical defocus does not produce compensating growth in the eyes of juvenile primates. Thus, the purpose of this study was to determine whether chronic optical defocus could predictably alter refractive de-

velopment in adolescent monkeys at ages corresponding to when myopia typically develops in human children.

Materials and Methods

Subjects

Seven normal rhesus monkeys (*Macaca mulatta*) that were obtained as adolescents from a government-sponsored breeding colony were used as subjects. The animals were housed in the animal care facilities of Sun Yat-sen University of Medical Sciences, where they were maintained on a 12-hour light–dark lighting cycle. All the rearing and experimental procedures were approved by the Institutional Animal Care and Use Committees at the University of Houston and the Sun Yat-sen University of Medical Sciences and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

When the monkeys were between 2 and 2.5 years of age, hyperopic anisometropia was produced through photorefractive keratectomy (PRK). Based on comparisons of ocular growth, rhesus monkey eyes mature four times faster than human eyes.[31] Consequently, in human years, our monkeys can be considered to have been between 8 and 10 years of age, the age range when myopia frequently emerges in children.[32] The PRK procedure was performed while the animals were anesthetized (ketamine hydrochloride, 15 mg/kg intramuscular; acepromazine maleate, 0.15 mg/kg; 1% tetracaine, topical) using an excimer laser (Technolas 217; Bausch & Lomb, Tampa, FL) with flying spot and eye-tracking technologies. The ablation zone was 5.0 mm in diameter and centered on the animal's pupillary axis. The corneal epithelium was intact at the onset of the procedures, and the eyes were stabilized using forceps. The ablations were performed using the laser parameters that are normally used to correct myopia in adult humans. Our goal was to produce between 1 and 2 D of relative hyperopia in the treated eyes, which required using laser parameters that were ordinarily necessary to correct 3 to 6 D of myopia in adult humans.

Immediately after the PRK procedure, 1 drop each of 2% homatropine hydrobromide and 0.3% ofloxacin (Tarivid; Aventis Pharma Ltd., Strasbourg, Germany) was instilled together with 0.3% tobramycin and 0.1% dexamethasone ophthalmic ointment (Dobradex; Alcon Laboratories, Fort Worth, TX). Postoperative analgesia was maintained by intramuscular injections of buprenorphine (0.01 mg/kg every 8 hours), and treatment with the topical antibiotic drops (0.3% ofloxacin; four times daily) was continued until epithelialization was complete. The topical steroid (3% tobramycin and 0.1% dexamethasone) was tapered over a period of 2 weeks. Slit lamp examinations were performed daily until re-epithelialization was complete and periodically throughout the observation period, to assess corneal clarity.

Ocular Biometry

Each subject's refractive status, corneal curvatures, and eyes' axial dimensions were measured before the PRK procedure. Subsequent measures were obtained at 3, 14, and 30 days after PRK and then typically at 1-month intervals thereafter. To make these measurements, cycloplegia was induced with 3 drops of 0.5% tropicamide instilled 10 minutes apart, 45 minutes before retinoscopy was performed, and the monkeys were anesthetized with an intramuscular injection of ketamine hydrochloride (15–20 mg/kg) and acepromazine maleate (0.15–0.2 mg/kg) and the topical instillation of 0.5% tetracaine hydrochloride. Each eye's refractive status, which is specified as the spherical equivalent spectacle-plane refractive correction, was determined along the pupillary axis by two independent observers using a streak retinoscope and handheld trial lenses. Corneal topography was assessed using a handheld videotopographer (Vista; EyeSys, Houston, TX). Corneal power was calculated using a refractive index of 1.3375 and defined as the average spherical equivalent refracting power for three consecutive readings of the central corneal radius of curvature (simulated K). The eye's axial dimensions were measured by A-scan ultrasonography (AXIS-II; Quantel Medical Inc., Clermont-Ferrand, France). The 11-MHz transducer was placed in direct contact with the cornea with care being taken not to indent the cornea. The intraocular distances were determined using ultrasound velocities for the normal human eye and the reported data represent the average of 10 readings. To be considered an acceptable measure, the SEM of the 10 vitreous chamber readings had to be 8 μm or less.

Results

An intact corneal epithelium was re-established within 36 to 48 hours after surgery. Trace amounts of corneal haze were observed in some of the monkeys several days after the PRK procedure. However, these slight amounts of haze disappeared by 7 days after surgery, and thereafter the corneas remained clear throughout the observation period.

Before the PRK procedures, all the experimental subjects exhibited low refractive errors that were typical of normal adolescent monkeys. The refractive errors in the right eyes varied between −0.38 and +1.25 D, with six of the seven monkeys showing low degrees of hyperopia (average = +0.53 ± 0.49 D). The right and left eyes were also well matched. Initially, there were no significant interocular differences (paired *t*-test, $P > 0.05$) in refractive error (mean anisometropia, 0.21 ± 0.29 D), vitreous chamber depth (mean difference, 0.09 ± 0.06 mm), or corneal power (mean difference, 0.20 ± 0.19 D).

Figure 1 shows the changes in spherical equivalent refractive error, vitreous chamber depth, and corneal refracting power that took place after the PRK procedures for two selected subjects. As illustrated in the bottom panels, the PRK procedures decreased the central corneal radius, resulting in a reduction in refractive power. In most animals (e.g., monkey 063, Fig. 1, left column), the reduction in power was greatest 3 to 7 days after the laser procedures. Subsequently, corneal power typically increased by approximately 1.0 D reaching a relatively stable value by approximately 30 days after the treatment. Between 30 and 120 days after the laser procedure, the corneas in all the treated eyes were on average 1.16 ± 0.43 D (range, 0.54–1.73) flatter than those in the fellow eyes. This reduction in corneal power produced a relative hyperopic shift in the refractive errors of the treated eyes creating a hyperopic anisometropia (Fig. 1, top). The magnitude of the induced anisometropia during this same period was on average +1.50 ± 0.40 D, which was 0.34 D larger than the measured amount of laser-induced corneal flattening. Based on previous observations of monkeys with imposed anisometropia,[16] it is likely that the treated animals consistently fixated with the less hyperopic, nontreated eyes and as a consequence the treated eyes of our experimental monkeys chronically experienced an amount of hyperopic defocus equivalent to the degree of anisometropia.

The data for monkeys 063 and 038 were included in Figure 1 because, in response to the imposed anisometropia, these animals demonstrated the greatest and least amounts of compensating ocular growth, respectively. After the PRK procedure, monkey 038's treated eye exhibited approximately 3.0 D of hyperopia and was approximately 2.0 D more hyperopic than its nontreated eye, which was the largest imposed anisometropia in our treated animals. However, despite experiencing chronic monocular defocus for the remainder of the almost 600-day observation period, the vitreous chamber depths in both eyes increased slowly at the same rate and the corneas of both eyes showed small systematic reductions in power (as represented by the negative slopes of the regression lines fit to corneal power data). Consequently, the absolute refractive errors in both eyes and the degree of imposed anisometropia

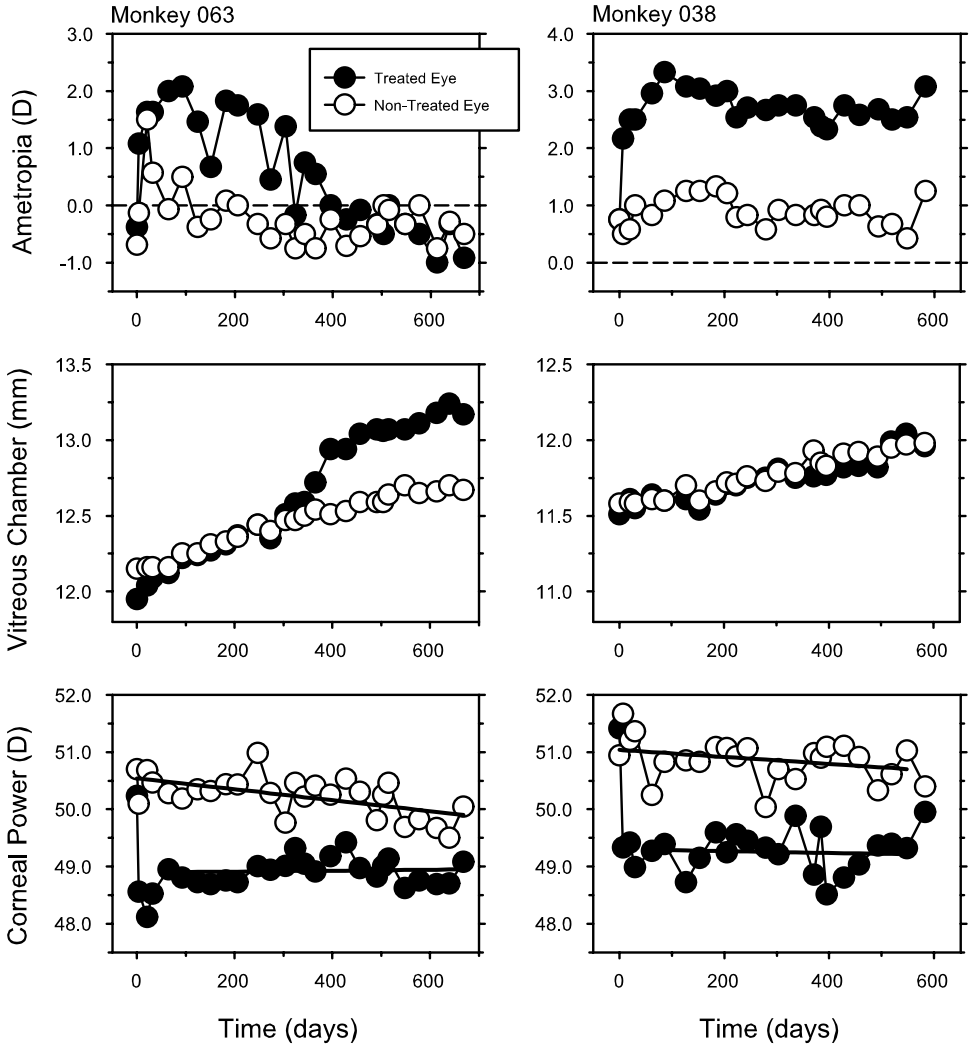

FIGURE 1. Spherical equivalent refractive error, vitreous chamber depth, and corneal refractive power plotted as a function of time in the treated and nontreated eyes of two selected animals. The 0 on the abscissa indicates when the PRK procedures were performed. Monkey 063 (*left*) exhibited clear evidence of differential interocular axial growth that compensated for the induced hyperopic anisometropia. Monkey 038 (*right*) was the only experimental animal that failed to exhibit any evidence of compensating eye growth. *Solid lines* through the treated and nontreated eyes' corneal data were determined by regression analysis of data from the time that the cornea on the treated eye appeared to stabilize and the end of the observation period.

were stable throughout the observation period (i.e., this monkey showed no evidence for compensating ocular growth.) On the other hand, monkey 063 showed clear evidence for differential interocular growth that compensated for the imposed anisometropia. The PRK procedure resulted in approximately 1.5 D of hyperopic anisometropia in monkey 063. The refractive errors in both eyes and the degree of imposed anisometropia were relatively stable from approximately 30 to 300 days after the laser treatment. However, beginning at approximately 300 days, there was a relative acceleration of the vitreous chamber growth in the treated eye and a concomitant systematic reduction in the treated eye's hyperopia. Once the balance in refractive errors between the two eyes was restored, both eyes then demonstrated similar vitreous chamber elongation rates, and the refractive error balance between the two eyes was stable for the remainder of the observation period. Although the corneal power of the treated eye was essentially stable throughout the observation period, the recovery observed in monkey 063 was facilitated in part by a small relative reduction (~0.5 D) in the corneal power of the nontreated eye.

Figure 2 illustrates the changes in the interocular differences in refractive error, vitreous chamber depth, and corneal power that took place in all the treated monkeys after the PRK procedures. To facilitate comparisons, the interocular differences in vitreous chamber depth were expressed in diopters by assuming that at the start of the experiment the optical powers of the two eyes were identical, that each eye had a single principal plane, that the distance between the retina and the principal plane was scaled to overall axial length (0.92 of the total axial length),[33] and that the refractive index of the vitreous chamber was 4/3: diopters = $[1.333/(AL \cdot 0.92)] - \{1.333/[(AL \cdot 0.92) + VC]\}$ where AL is axial length in meters and VC is interocular difference in vitreous chamber depth in meters. The diamond symbols and solid lines representing the interocular differences in corneal power were calculated by taking the difference between the linear regression functions that were fit to the corneal power data for the treated and nontreated eyes (see the bottom panels in Fig. 1). Positive values indicate that in comparison to the nontreated eye, the treated eye was more hyperopic, had a longer vitreous chamber, and/or a steeper cornea. The data for individual monkeys have been arranged according to the magnitude of the compensating refractive error changes.

Six of the seven treated monkeys showed systematic reductions in the degree of imposed anisometropia during the observation period. For several of these monkeys, as noted in Figure 1, the initial degree of imposed anisometropia was stable for the first 200 to 300 days of the recovery period. Subsequently, there were systematic decreases in the degree of anisometropia that were synchronized with somewhat abrupt relative increases in the treated eye's vitreous chamber depth (e.g., Figs. 2A, 2B, 2F). For other animals, the decrease in the degree of anisometropia was more gradual and was associated

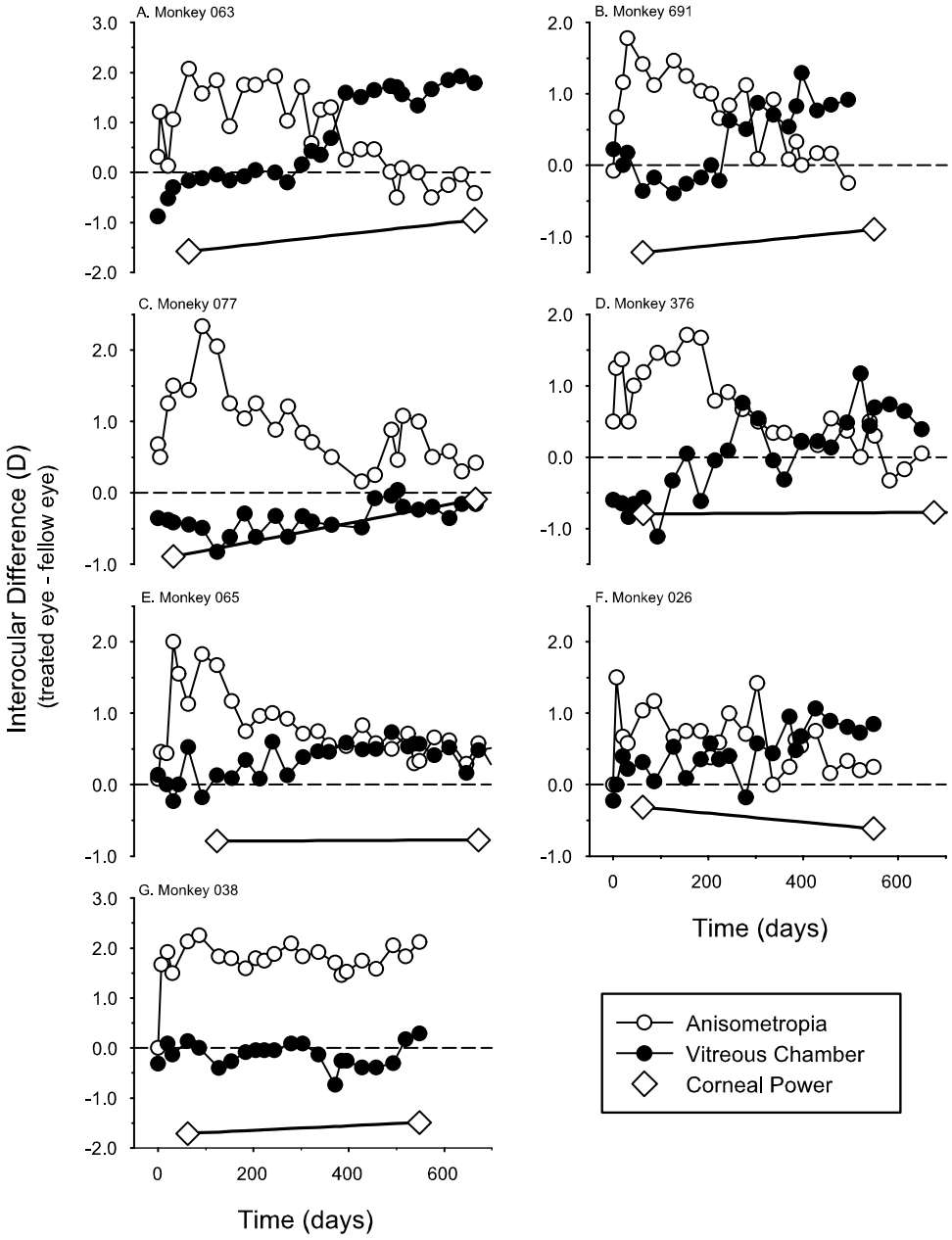

FIGURE 2. Interocular differences (treated eye minus nontreated eye) in refractive error, vitreous chamber depth expressed in diopters, and corneal power plotted as a function of age in individual animals. The dioptric equivalents for the interocular differences in vitreous chamber depth were calculated as described in the text. *Solid lines* representing the interocular differences in corneal power are the differences between the linear regression functions that were fit to the treated and nontreated eye data (Fig. 1).

with similarly gradual changes in the interocular differences in vitreous chamber depth (e.g., Figs. 2C–E). There was a high correlation between the degree of anisometropic compensation and the interocular differences in vitreous chamber depth that developed after the PRK procedure (Pearson correlation = 0.74; $P = 0.059$). In five of the six monkeys that exhibited compensating anisometropic growth (Fig. 2, subjects A–F), the changes in the interocular differences in vitreous chamber accounted for a greater amount of the compensating anisometropic changes than did the interocular changes in corneal power. The magnitude of the interocular corneal changes was larger in monkey 077 (Fig. 2C), however, the vitreous chamber alterations that occurred in this animal were appropriate to account for the remainder of the compensating anisometropic changes. As illustrated by monkey 038 (Fig. 2G), no compensating anisometropic changes were found when the axial growth rates for the two eyes were similar.

In some animals such as monkey 063 in Figure 1, it was evident that the interocular differences in vitreous chamber depth emerged as a consequence of an increase in the treated eye's growth rate. There were no obvious treatment-related departures in the growth trajectories of the nontreated eyes in any of the experimental monkeys; however, subtle decreases in the vitreous chamber growth rates of the nontreated eye cannot be ruled out and could have also contributed to the observed reductions in anisometropia.

Figure 3 compares the amount of anisometropic compensation with the initial amount of imposed anisometropia for individual monkeys, where the amount of imposed anisometropia represents the average anisometropia between 30 and 120 days after PRK, and the anisometropic compensation represents the difference between these initial amounts of imposed anisometropia and the average anisometropia for the last four measurements at the end of the observation period. In six of the seven treated monkeys, (Fig. 3, open symbols), there was a good correspondence between the initial degree of imposed anisometropia and the degree of anisometropic change that took place during the observation period. For this

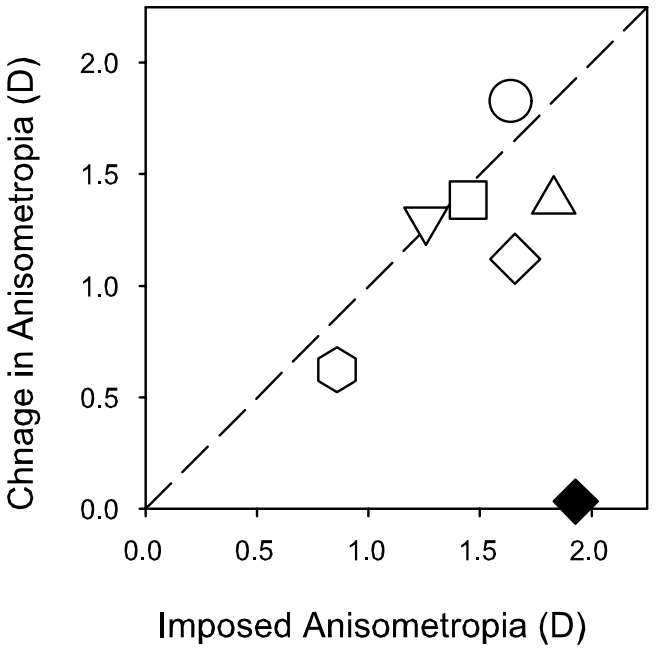

FIGURE 3. Amount of imposed hyperopic anisometropia plotted as a function of the change in anisometropia (positive values indicate a reduction in anisometropia) that occurred during the observation period in individual subjects. *Open symbols*: monkeys that showed compensating interocular growth; *filled symbol*: the animal (monkey 038) that did not show any evidence of compensating changes.

subgroup, a paired *t*-test indicated that there were no significant differences between the initial anisometropia and the amount of anisometropic compensation ($t = 1.52$, $P = 0.19$). However, as discussed earlier, one animal (monkey 038), which is represented by the filled diamond in Figure 3, was an obvious outlier. In this respect, it should be noted that in comparison to the other treated animals, monkey 038 also had the highest absolute degree of hyperopia in its treated eye after the PRK procedures and it manifested the largest initial degree of anisometropia.

DISCUSSION

Our results indicate that experimentally imposed hyperopic anisometropia can produce interocular differences in axial growth rates and refractive development in adolescent monkeys. The close correspondence between the degree of imposed anisometropia and the magnitude of the axial refractive error changes suggest that the observed refractive alterations represent compensating changes that were guided by optical defocus and regulated by visual feedback associated with the imbalance between the two eyes.

The course of emmetropization proceeds in a qualitatively similar manner in many species, including humans.[17,20,31,34–38] In rhesus monkeys, the bulk of the emmetropization process is completed by approximately 3 to 4 months of age.[17,31] Slow changes in refractive error continue over most of the first year of life, but thereafter, most monkeys maintain stable and balanced refractive errors in the two eyes well into early adult life. The results from this study contribute to the growing body of data from laboratory animals that demonstrate that vision-dependent mechanisms are active well beyond the early rapid period of ocular growth (Troilo D, et al. *IOVS* 1999;40:ARVO Abstract 5081).[22,24,25] It seems likely that these vision-dependent mechanisms are responsible for maintaining stable and balanced refractive errors in the two eyes well into adulthood.

With respect to the genesis of juvenile-onset myopia in children, these results are important because they demonstrate that optical defocus can produce axial myopia in primates at ages when myopia usually emerges in children. Consequently, this study suggests that it is feasible that visual experience, in particular hyperopic defocus, plays a significant role in the genesis of juvenile-onset myopia. Several recent clinical studies have recently demonstrated that bifocals significantly reduce the rate of progression of juvenile-onset myopia.[39–41] The anisometropic changes in our PRK-treated monkeys reinforce a hypothesis proposed in these bifocal studies that the reduction in myopic progression was achieved because the bifocals helped to eliminate hyperopic defocus during near-work tasks. However, the time course for the compensating changes observed in this study, in particular the relatively long delay between the laser procedures and the changes in ocular growth, complicates predictions in human children. In contrast to infant monkeys, in which compensating ocular changes can often be discerned within 2 weeks of the onset of an optically imposed refractive error,[16,17] the onset of the compensating changes in many of our adolescent monkeys appeared to be delayed by as much as 200 to 300 days after the treatment procedures. These delays suggest that in some adolescents, the visual stimulus for altered ocular growth must be present for some time before any predictable changes in refractive error occur. Such asynchronies, if they occur in children, would make it very difficult to identify and characterize the effects of visual experience on refractive development in children. This pattern of results suggests that extended histories of visual experience may be needed to understand the effects of visual experience on human refractive development.

Although the measured corneal and refractive changes produced by the PRK procedures were well correlated, there were systematic differences in the magnitude of the treatment effects measured by retinoscopy versus those obtained by corneal topography. In particular, shortly after the PRK procedures, the interocular differences in refractive error assessed by retinoscopy were on average 0.34 D more hyperopic than the changes predicted by our videotopography measures. Although the topography and retinoscopy data were referenced to different planes (the corneal plane for topography and an ~2-cm vertex distance for retinoscopy), the differences in effective vertex distance predicts that the measured hyperopic anisometropia would actually be approximately 0.1 D less hyperopic than that predicted by the topography measures, not more hyperopic. We believe that the most likely explanation for the observed differences between our retinoscopy and topography measures reflect the fact the corneal power measures were derived for the central cornea (an area smaller than the central 3 mm), whereas our retinoscopy measures reflect changes across a larger region of the projected pupil diameter. The corneas of infant monkeys become progressively flatter in the periphery and consequently sampling more peripheral regions could result in a relative hyperopic bias. Regardless, the consistency of the imposed hyperopic errors and the compensating refractive changes that took place in our experimental monkeys indicate that PRK is a practical method for imposing experimental refractive errors, as previously demonstrated in rabbits.[43] Although it is not readily reversible (e.g., unlike spectacle treatment lenses, the imposed changes in refractive error cannot be simply removed), PRK offers a number of advantages over methods that are commonly used to manipulate refractive error. In particular, in comparison to spectacle lens-rearing strategies, PRK does not limit the field of view, and it is feasible to employ PRK procedures in young[44] and old animals. It is also easy to manage the animals during the

treatment period, and the alterations in the animal's visual experience are virtually continuous and not subject to interruptions associated with lens losses that are inherent in some rearing regimens (e.g., contact lens-rearing regimens).

It is interesting that monkey 038, the monkey that experienced the largest imposed anisometropia, did not show any compensating changes in refractive error. Many experiments of vision-dependent refractive changes in macaque monkeys have reported clear examples of individual monkeys that for unknown reasons failed to respond in a manner consistent with most animals.[16,17,45–47] It is possible that monkey 038 is one such outlier and that the mechanisms that influence eye growth in this monkey have different operational properties in comparison to those in the average monkey. However, it is also possible that the degree of imposed anisometropia was too large to produce predictable changes. In infant monkeys, the emmetropization process appears to have a limited operating range. Imposed refractive errors that fall outside this range fail to produce predictable changes in eye growth.[17,45] Although the degree of anisometropia that monkey 038 experienced is within the range of anisometropic errors that produce predictable compensating changes in infant monkeys, it seems reasonable to expect that the effective operating range of vision-dependent mechanisms decreases with age. In this respect, studies of form-deprivation myopia in adolescent rhesus monkeys indicate the magnitude of change produced by abnormal visual experience decreases with age.[25]

There are parallels between our experimental PRK treatment strategy and some contact lens and laser surgery procedures that are currently used to correct refractive errors in individuals with presbyopia. In these "monovision" strategies, one eye is typically corrected for distance vision and the fellow eye is optically corrected for a near viewing distance.[49,50] Thus, when normally fixating a near target, the eye corrected for distance will experience hyperopic defocus. Assuming that vision-dependent mechanisms are still active at ages associated with presbyopia, the results of this study suggest that monovision strategies might result in vision-dependent alterations in a patient's normal interocular refractive-error balance. Although it has been reported that some individuals treated with a contact lens monovision strategy show treatment-related alterations in refractive error,[51] there is little evidence that PRK-induced monovision correction strategies produce refractive alterations. (However, to our knowledge there have not been any systematic studies of the stability of the anisometropic refractive errors produced by laser monovision treatment regimens.) The nonlinear manner in which the eye integrates visual signals that influence eye growth may explain the relative absence of effects in monovision. In particular, in birds,[52–54] tree shrews,[14] and macaques,[55] brief daily periods of unrestricted vision counterbalance very long daily periods of visual experience that normally promote axial myopia. Monovision patients may not experience anisometropic changes in refractive error, because they normally alternate fixation between the two eyes frequently during the day as they change viewing distance. This alternating fixation pattern would prevent either eye from experiencing defocus consistently throughout the day. In contrast, the treated eyes of our PRK monkeys were likely to be consistently defocused, regardless of the fixation distance.[16] Thus, it seems that for most individuals traditional monovision strategies would not consistently alter the interocular balance in refractive error through vision-dependent mechanisms. This question could, however, be addressed in older monkeys by using PRK technology.

References

1. Norton TT. Animal models of myopia: learning how vision controls the size of the eye. *Inst Lab Anim Res J*. 1999;40:59–77.
2. Smith III EL. Environmentally induced refractive errors in animals. In: Rosenfield M, Gilmartin B, eds. *Myopia and Nearwork*. Oxford, UK: Butterworth-Heinemann; 1998:57–90.
3. Wallman J. Retinal control of eye growth and refraction. *Prog Retin Res*. 1993;12:134–153.
4. Wildsoet CF. Active emmetropization: evidence for its existence and ramifications for clinical practice. *Ophthalmic Physiol Opt*. 1997;17:279–290.
5. O'Leary DJ, Millodot M. Eyelid closure causes myopia in humans. *Experientia*. 1979;35:1478–1479.
6. Rabin J, Van Sluyters RC, Malach R. Emmetropization: a vision-dependent phenomenon. *Invest Ophthalmol Vis Sci*. 1981;20:661–664.
7. Robb RM. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. *Am J Ophthalmol*. 1977;83:52–58.
8. Hoyt CS, Stone RD, Fromer C, Billdon FA. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am J Ophthalmol*. 1981;91:197–200.
9. Nathan J, Kiely PM, Crewther SG, Crewther DP. Disease-associated image degradation and spherical refractive errors in children. *Am J Optom Physiol Optics*. 1985;62:680–688.
10. von Noorden GK, Lewis RA. Ocular axial length in unilateral congenital cataracts and blepharoptosis. *Invest Ophthalmol Vis Sci*. 1987;28:750–752.
11. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res*. 1988;28:639–657.
12. Irving EL, Sivak JG, Callender MG. Refractive plasticity of the developing chick eye. *Ophthalmic Physiol Opt*. 1992;12:448–456.
13. Irving EL, Callender MG, Sivak JG. Inducing myopia, hyperopia, and astigmatism in chicks. *Optom Vis Sci*. 1991;68:364–368.
14. 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.
15. Graham B, Judge SJ. The effect of spectacle wear in infancy on eye growth and refractive error in the marmoset (*Callithrix jacchus*). *Vision Res*. 1999;39:189–206.
16. 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.
17. Smith EL III, Hung L-F. The role of optical defocus in regulating refractive development in infant monkeys. *Vision Res*. 1999;39:1415–1435.
18. Whatham A, Judge S. Compensatory changes in eye growth and refraction induced by daily wear of soft contact lenses in young marmosets. *Vision Res*. 2001;41:267–273.
19. Zadnik K, Mutti DO. Prevalence of myopia. In: Rosenfield M, Gilmartin B, eds. *Myopia and Nearwork*. Butterworth-Heinemann: Oxford, UK; 1998:13–30.
20. Wallman J, Adams JI. Developmental aspects of experimental myopia in chicks: susceptibility, recovery and relation to emmetropization. *Vision Res*. 1987;27:1139–1163.
21. 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.
22. Siegwart JT, Norton TT. The susceptible period for deprivation-induced myopia in tree shrew. *Vision Res*. 1998;38:3505–3515.
23. Zadnik K, Mutti DO. How applicable are animal myopia models to human juvenile onset myopia. *Vision Res*. 1995;35:1283–1288.
24. Papastergiou GI, Schmid GF, Laties AM, Pendrak K, Lin T, Stone RA. Induction of axial elongation and myopic refractive shift in one year old chickens. *Vision Res*. 1998;38:1883–1888.
25. Smith EL III, Bradley DV, Fernandes A, Boothe RG. Form deprivation myopia in adolescent monkeys. *Optom Vis Sci*. 1999;76:428–432.
26. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Res*. 1995;35:1175–1194.

27. Schaeffel F, Hagel G, Bartmann M, Kohler K, Zrenner E. 6-Hydroxydopamine does not affect lens-induced refractive errors but suppresses deprivation myopia. *Vision Res*. 1994;34:143–149.
28. Bartmann M, Schaeffel F, Hagel G, Zrenner E. Constant light affects retinal dopamine levels and blocks deprivation myopia but not lens-induced refractive errors in chickens. *Vis Neurosci*. 1994;11: 199–208.
29. Norton TT, Siegwart JT. Animal models of emmetropization: matching axial length to the focal plane. *J Am Optom Assoc*. 1995;66:405–414.
30. Raviola E, Wiesel TN. An animal model of myopia. *N Engl J Med*. 1985;312:1609–1615.
31. 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.
32. Zadnik K, Mutti DO. Incidence and distribution of refractive anomalies. In: Benjamin WJ, ed. *Borish's Clinical Refraction*. Philadelphia: WB Saunders; 1998:30–46.
33. Hughes A. The topography of vision in mammals. In: Crescitelli F, ed. *The Visual System in Vertebrates*. Springer-Verlag: Berlin; 1977:613–756.
34. Ehrlich DL, Braddick OJ, Atkinson J, et al. Infant emmetropization: longitudinal changes in refraction components from nine to twenty months of age. *Optom Vis Sci*. 1997;74:822–843.
35. Gwiazda J, Thorn F, Bauer J, Held R. Emmetropization and the progression of manifest refraction in children followed from infancy to puberty. *Clin Vis Sci*. 1993;8:337–344.
36. Ingram RM, Barr A. Changes in refraction between the ages of 1 and 3 1/2 years. *Br J Ophthalmol*. 1979;63:339–342.
37. McBrien NA, Norton TT. The development of experimental myopia and ocular component dimensions in monocularly lid-sutured tree shrews (*Tupaia belangeri*). *Vision Res*. 1992;32:843–852.
38. Troilo D, Judge SJ. Ocular development and visual deprivation myopia in the common marmoset (*Callithrix jacchus*). *Vision Res*. 1993;33:1311–1324.
39. 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.
40. 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.
41. Leung JTM, Brown B. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. *Optom Vis Sci*. 1999;76:346–354.
42. 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.
43. Bryant BR, Kampmeir J, Er H, et al. PRK-induced anisometropia in the rabbit as a model of myopia. *Graefes Arch Clin Exp Ophthalmol*. 1999;237:161–165.
44. Zhong X, Ge J, Nie H, Chen X, Huang J, Liu N. Effects of photorefractive keratectomy-induced defocus on emmetropization of infant rhesus monkeys. *Invest Ophthalmol Vis Sci*. 2004;45:3806–3811.
45. Smith EL III, Hung L-F, Harwerth RS. Developmental visual system anomalies and the limits of emmetropization. *Ophthalmic Physiol Opt*. 1999;19:90–102.
46. Smith EL III, Hung L-F. Form-deprivation myopia in monkeys is a graded phenomenon. *Vision Res*. 2000;40:371–381.
47. 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.
48. Bradley DV, Fernandes A, Tigges M, Boothe RG. Diffuser contact lenses retard axial elongation in infant rhesus monkeys. 1996;36: 509–514.
49. Gauthier CA, Holden BA, Grant T, Chong MS. Interest of presbyopes in contact lens correction and their success with monovision. *Optom Vis Sci*. 1992;69:858–862.
50. Jain S, Arora I, Azar DT. Success of monovision in presbyopes: review of the literature and potential applications to refractive surgery. *Surv Ophthalmol*. 1996;40:491–499.
51. Wick B, Westin E. Change in refractive anisometropia in presbyopic adults wearing monovision contact lens correction. *Optom Vis Sci*. 1999;76:33–39.
52. 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.
53. 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.
54. 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.
55. 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. *Ophthalmol Vis Sci*. 2002;43:291–299.