The Effects of Simultaneous Dual Focus Lenses on Refractive Development in Infant Monkeys

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Submitted: February 26, 2014
Accepted: October 2, 2014

Citation: Arumugam B, Hung L-F, To C-H, Holden B, Smith EL III. The effects of simultaneous dual focus lenses on refractive development in infant monkeys. *Invest Ophthalmol Vis Sci*. 2014;55:7423-7432. DOI:10.1167/iov.14-14250

PURPOSE. We investigated the effects of two simultaneously imposed, competing focal planes on refractive development in monkeys.

METHODS. Starting at 3 weeks of age and continuing until 150 ± 4 days of age, rhesus monkeys were reared with binocular dual-focus spectacle lenses. The treatment lenses had central 2-mm zones of zero power and concentric annular zones with alternating powers of +3.0 diopter [D] and plano (pL or 0 D) ($n = 7$; +3D/pL) or -3.0 D and plano ($n = 7$; -3D/pL). Retinoscopy, keratometry, and A-scan ultrasonography were performed every 2 weeks throughout the treatment period. For comparison purposes data were obtained from monkeys reared with full field (FF) +3.0 ($n = 4$) or -3.0 D ($n = 5$) lenses over both eyes and 33 control animals reared with unrestricted vision.

RESULTS. The +3 D/pL lenses slowed eye growth resulting in hyperopic refractive errors that were similar to those produced by FF+3 D lenses (+3 D/pL = +5.25 D, FF +3 D = +4.63 D; $P = 0.32$), but significantly more hyperopic than those observed in control monkeys (+2.50 D, $P = 0.0001$). One -3 D/pL monkey developed compensating axial myopia; however, in the other -3 D/pL monkeys refractive development was dominated by the zero-powered portions of the treatment lenses. The refractive errors for the -3 D/pL monkeys were more hyperopic than those in the FF -3 D monkeys (-3 D/pL = +3.13 D, FF -3D = -1.69 D; $P = 0.01$), but similar to those in control animals ($P = 0.15$).

CONCLUSIONS. In the monkeys treated with dual-focus lenses, refractive development was dominated by the more anterior (i.e., relatively myopic) image plane. The results indicate that imposing relative myopic defocus over a large proportion of the retina is an effective means for slowing ocular growth.

Keywords: emmetropization, myopia, hyperopia, Fresnel lenses, refractive error, eye growth

A large body of animal research has demonstrated that ocular growth and refractive development are actively regulated by optical defocus associated with the eye's effective refractive status.^{1,2} For example, making the eyes of young animals artificially myopic with positive lenses or hyperopic with negative lenses produces compensating changes in vitreous chamber growth rates that can, within certain operational limits, eliminate the imposed refractive errors.³⁻¹¹ The basic operating characteristics of the vision-dependent mechanisms that mediate the normal emmetropization process and these lens compensating effects appear to be qualitatively similar in all species that have been studied in a systematic fashion. In this respect, it is important to note that when humans are exposed to comparable viewing conditions, their eyes exhibit qualitatively similar changes in refractive error.^{12,13} For instance, in response to the interocular imbalance in effective refractive errors produced by monovision correction strategies, children develop compensating anisometropias.¹² The pattern of results observed in humans and laboratory animals indicates that optical manipulations of the eye's effective refractive state could be used to control refractive development. In particular,

these results indicate that optically imposed myopic defocus could be used to reduce the progression of myopia, which has reached epidemic proportions in many parts of East Asia¹⁴⁻¹⁶ and is increasing in prevalence in the United States¹⁷ and other non-Asian countries.¹⁸

To design the optimal optical treatment strategy for refractive errors, it is important to understand the functional operating characteristics of the vision-dependent mechanisms that control ocular growth. For instance, in normal environments, particularly indoors, the eye can experience multiple levels of myopic and hyperopic defocus across the field that can change dramatically over time.¹⁹ The manner in which these visual signals, which compete to increase and decrease axial growth, are integrated over time and across the retina determine the overall direction of refractive development and is a fundamental operational property of the mechanisms responsible for emmetropization. In this respect, when competing visual signals are presented sequentially, the signals that decrease axial growth rates appear to be more potent or weighed more heavily than signals that normally increase growth. For example, in chickens,²⁰⁻²⁶ tree shrews,^{27,28} and

monkeys,^{29,30} brief periods of unrestricted vision or myopic defocus can prevent the axial myopia caused by much longer daily periods of form deprivation or hyperopic defocus. And when chickens experience imposed myopic and hyperopic defocus successively their eyes preferentially compensate for the myopic defocus, even when the period of hyperopic defocus is five times longer than that for myopic defocus.^{24,26} The nonlinear manner in which the eye integrates visual growth signals over time reduces the likelihood that intermittent exposures to hyperopic defocus would produce axial myopia (i.e., the temporal summation properties of emmetropization function as a safeguard to reduce the probability that the eye will become myopic).

Myopic and hyperopic defocus can occur simultaneously for superimposed objects in a three dimensional (3D) scene and when the eye is corrected with certain multifocal lenses. Observations in chickens³¹ and guinea pigs³² reared with dual-focus spectacle lenses that produce two distinct image planes simultaneously across the entire visual field suggest that the emmetropization mechanism identifies both focal planes and directs refractive development toward either the average imposed defocus³² or to a refractive state slightly more hyperopic than the average.³¹ Results obtained from marmosets reared with dual-focus contact lenses on one eye³³ were somewhat in agreement with the observations in chickens.³³ Specifically, marmoset eyes exposed to competing myopic and hyperopic defocus (± 5 diopters [D]) were slightly more hyperopic than their fellow control eyes. However, there were large intersubject differences within the treated group, the interocular differences in vitreous chamber growth rates in the treated marmosets were not different from those in animals reared with unrestricted vision; and in the majority of treated marmosets, both the treated and control eyes developed absolute myopic refractive errors, possibly reflecting optical side effects of contact lens wear.

In contrast, the end point for emmetropization under conditions of competing defocus appears to be different in macaque monkeys. For example, when infant rhesus monkeys are reared with optically imposed astigmatism, emmetropization preferentially targets one of the two line foci, usually the most myopic image shell, not the circle of least confusion.³⁴ While methodological issues may have contributed to these apparent interspecies differences (e.g., the lens powers employed in many studies were large, certainly well outside the range of powers that would be employed in a clinical setting), it is important to determine how the primate eye responds to competing simultaneous spherical defocus and the basic parameters that govern the response to competing defocus because the results have significant clinical implications. In particular, it may be possible to impose simultaneous myopic defocus across a large part of the visual field to reduce myopia progression without significantly reducing foveal image quality.¹ In this respect, certain "simultaneous" bifocal contact lenses have some of the desired optical effects and preliminary trials suggest that these lenses can reduce myopia progression.^{35–37} The purpose of this study was to determine how the optical imposition of two different focal planes across the entire visual field affected refractive development in infant monkeys.

MATERIALS AND METHODS

Subjects

The primary subjects were 14 infant rhesus monkeys (*Macaca mulatta*) that were obtained at 2 to 3 weeks of age and housed in our primate nursery that was maintained on a 12-hour light/

dark cycle (average illuminance = 350 lux).³⁸ At approximately 3 weeks of age (24 ± 3 days) the infants were randomly allocated to one of two dual-focus lens treatment groups. The back vertex powers of the treatment lenses, which were worn over both eyes, were +3 D and plano (pL or 0 D) (+3 D/pL group, $n = 7$) or -3 D and plano (-3 D/pL group, $n = 7$). The dual-focus spectacle lenses used in this study, which were based on Fresnel principles, were qualitatively similar in design to lenses developed by Tse et al.³¹ and employed in previous studies in chickens³¹ and guinea pigs.³² The optical zone diameters of the lenses were 22 mm. The lenses had a central zone of zero power that was 2 mm in diameter, which was surrounded by alternating concentric annular zones that had different posterior surface radii of curvature that produced the two focal powers. The width of each annulus was 0.4 mm; there was a 0.005-mm transition zone between the alternating adjacent power zones.

The dual-focus lenses imposed two distinct image planes over a large part of the visual field. The treatment lenses were held at a vertex distance of 11 mm, which provided monocular fields of view of approximately 85°. Because the central zero-power zones (2 mm) were smaller than the entrance pupil diameters of the infant monkeys (average pupil diameter = 3.3 ± 0.3 mm), all parts of the visual field were affected by both power zones of the treatment lenses^{39,40} (i.e., images were formed at two distinct planes at the fovea and across the entire central 85° of the retina), which would reduce central visual acuity. For healthy human observers, the superimposed images produced when viewing through the optical centers of the treatment lenses decreased central visual acuity by four to five letters on a high contrast logMAR chart. In addition, because the relatively narrow widths of the annular power zones were also smaller than the eye's entrance pupil, both power zones contributed to the retinal image regardless of eye movements or the direction of gaze. In the case of the +3 D/pL lenses, one image plane corresponded to the eye's natural refractive state and the other plane was effectively 3.1 D more myopic. For the -3 D/pL lenses, the powered portions of the treatment lenses produced an image plane that was 2.9 D more hyperopic than the eye's natural refractive state. The magnitude of the imposed deviations from the eye's natural refractive state were well within the range of optically imposed refractive errors that normally produce compensating axial growth in infant monkeys.⁹

Nine additional monkeys were reared with either full field (FF) +3 D ($n = 4$) or -3 D ($n = 5$) treatment lenses over both eyes; these two groups of monkeys served as positive controls. The onset and duration of lens wear was similar to that for the monkeys reared with the dual-focus lenses. Data were also available from previous studies for 33 additional control animals (designated "control" animals).^{9,38,41–44} Twenty-nine of these control animals were reared with unrestricted vision and four control monkeys were reared wearing helmets that held zero-powered spectacles in front of both eyes. Although the control animals were studied at different times over a period of several years, the experimental methods were identical to those employed for the animals in the dual focus treatment groups. The details of the nursery care for our infant monkeys have been described previously.⁹

We selected to employ binocular, rather than monocular, treatment lenses to avoid the potential confounding interocular effects that have frequently been observed during monocular treatment regimens,^{5,9,30,43,45–48} to reduce potential interocular differences in image quality and their potential amblyopio-genic effects,⁴⁹ and to ensure that the fixation and accommodative behavior of our animals were determined by eyes viewing through the dual focus lenses. This last point is critical because the manner in which animals accommodate

through the dual-focus lenses determines the effective sign and nature of defocus experienced by the eye. In this respect, the accommodative behavior of our monkeys wearing dual-focus lenses appeared to be similar to that exhibited by children viewing through dual-focus lenses.³⁵ In particular at ages near the start of lens wear, eccentric photorefractive showed that neither of the dual-focus lenses altered the monkeys' accommodative behavior for either distant (2 m) or near (30 cm) fixation targets. Specifically, the retinoscopy reflex was the same when the animals viewed a given fixation target with or without the dual-focus lens in place. For instance, the +3 D/pL animals still accommodated normally when viewing the near fixation target (i.e., they did not use the +3 D components of the treatment lenses as a near add). As a consequence, the +3 D/pL monkeys experienced 3 D of relative myopic defocus at near. On the other hand, the -3 D/pL monkeys experienced 3 D of relative hyperopic defocus both for distance and near vision when wearing the treatment lenses. However, over the course of the treatment period, changes in refractive error and viewing behavior probably resulted in some variability in the pattern of imposed defocus.

Ocular Biometry

The initial refractive and biometric measurements were obtained at the start of the lens-rearing period; subsequently measurements were made every 2 weeks until 150 ± 4 (average $\pm$ SD) days of age for the dual focus subject groups and up to 129 ± 11 days of age for the monkeys treated with the full-field single powered lenses. The details for measuring each eye's refractive status, corneal power, and axial dimensions have been described previously.^{5,9} In brief, to obtain these measurements, 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 cycloplegia was induced by the instillation one drop of 1% tropicamide 25 and 20 minutes prior to performing the measurements. The refractive state of each eye was measured independently by two experienced investigators using a streak retinoscope and averaged.⁵⁰ An eye's refractive error was defined as the spherical-equivalent, spectacle-plane refractive correction (95% limits of agreement = ± 0.60 D).³⁴ The anterior radius of curvature of the cornea was measured using a hand-held keratometer (Alcon Auto-keratometer; Alcon, Inc., St. Louis, MO, USA) or a corneal video topographer when the corneal power exceeded the measurement range of the keratometer (EyeSys 2000; EyeSys Vision, Inc., Houston, TX, USA). Three readings were taken from the hand-held keratometer and were averaged to calculate the central corneal power using an assumed refractive index of 1.3375 (95% limits of agreement = $+0.49$ to -0.37 D for mean corneal power).⁵¹ Ocular dimensions were measured by A-scan ultrasonography using a 13-MHz transducer (Image 2000; Mentor, Norwell, MA, USA); 10 separate measurements were averaged (95% limits of agreement = ± 0.05 mm).^{9,44}

All of 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 Animal Statement for the Use of Animals in Ophthalmic and Vision Research and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Statistical Methods

Most of the statistical analyses were performed using Minitab software (Release 16.2.4; Minitab, Inc., State College, PA, USA). Nonparametric Mann-Whitney *U* tests were used to compare

the median refractive errors between subject groups. Two-sample *t*-tests were used to compare differences in vitreous chamber depth between groups. Paired student *t*-tests and one way ANOVAs were employed to examine the interocular and between group differences, respectively, at the start of treatment. Linear regression and Pearson's correlation analyses were performed to characterize the relationship between refractive error and vitreous chamber depth. Mixed design, repeated measures ANOVAs (Super ANOVA; Abacus Concepts, Inc., Berkeley, CA, USA) were used to examine the differences in refractive errors or vitreous chamber depths between the lens treatment groups as a function of age.

RESULTS

At the beginning of the treatment period, the refractive errors in the right and left eyes were moderately hyperopic (mean $\pm$ SD for all subject groups: OD = $+4.27 \pm 1.32$ D; OS = $+4.19 \pm 1.30$ D) and well matched in each subject group ($t = 0.20$ – 1.21 ; $P = 0.27$ – 0.85). There were also no significant interocular differences in the average corneal powers, anterior chamber depths, lens thicknesses, or vitreous chamber depths in any of the subject groups ($t = -2.32$ – 2.03 ; $P = 0.06$ to 0.72). Moreover, the average refractive errors (right eye range = $+3.25 \pm 1.12$ D to $+4.70 \pm 1.00$ D; ANOVA: $F = 1.40$, $P = 0.27$) and average vitreous chamber depths were similar across subject groups (right eye range = 8.35 ± 0.19 mm to 8.64 ± 0.30 mm; $F = 1.47$, $P = 0.25$, respectively). However, shortly after the onset of lens wear many of the monkeys wearing the dual focus lenses exhibited clear departures from the pattern of emmetropization observed in control monkeys.

Figure 1 illustrates the spherical-equivalent refractive corrections plotted as a function of age for the right (filled symbols) and left eyes (open symbols) of the 7 +3 D/pL monkeys (panels A–G). Individual control monkeys are represented by the thin gray lines in each plot. In contrast to the control monkeys, which typically exhibited systematic reductions in hyperopia during the early phase of emmetropization, the +3 D/pL monkeys showed either little or no change in refractive errors or systematic increases in hyperopia. Over the course of the treatment period, the changes in refractive error for the right eyes, which with one exception were very similar to those for the left eyes (MKY 514, Fig. 1G), varied from $+0.5$ D to $+2.0$ D of relative hyperopia. The hyperopic shifts were most obvious in the animals that had relatively low hyperopic errors at the start of the treatment period (e.g., panel A). The general pattern of refractive development was, however, very similar in all of the individual monkeys and well described by the longitudinal mean data ($\pm$ SD) shown in Figure 1H. At ages corresponding to the end of the lens-rearing period, the median refractive errors for the +3 D/pL monkeys were stable and significantly more hyperopic than those for the control monkeys (right eyes: $+5.25$ D vs. $+2.50$ D, $P = 0.0001$). The average change in refractive error over the treatment period for the +3 D/pL group was also significantly different from that for control monkeys (right eye change: $+0.92 \pm 0.58$ D vs. -1.52 ± 1.91 D, $t = 6.06$, $P = 0.007$).

As shown in Figure 2, which shows longitudinal vitreous chamber depth plotted for individual monkeys, the hyperopic shifts in the +3 D/pL monkeys were primarily caused by relative reductions in vitreous chamber elongation rates. At baseline, the average vitreous chamber depth for the +3 D/pL animals was smaller than that for the control animals (right eyes: 8.35 ± 0.19 mm vs. 8.64 ± 0.30 mm; $F = 1.47$, $P = 0.25$), however, the key point was that the age-related increases in vitreous chamber depth were smaller in the +3 D/pL animals than in the controls. At the end of the lens rearing period, the vitreous chamber

FIGURE 1. Spherical-equivalent, spectacle-plane refractive corrections plotted as a function of age for the right (filled symbols) and left eyes (open symbols) of individual +3 D/pL monkeys (A–G). The average ($\pm$ SD) refractive errors for all of the +3 D/pL monkeys are shown in (H). The gray lines in each plot represent data for the right eyes of the 33 control monkeys.

depths for four of the +3 D/pL monkeys were below the range of vitreous chamber depths observed in the control monkeys and the average vitreous chamber depth (Fig. 2H) was significantly shallower than that in the control animals (treated versus control right eyes: 9.31 ± 0.34 mm vs. 9.82 ± 0.30 mm, $t = -3.90$, $P = 0.0004$). In addition, the age-related increases in the vitreous chamber depth were significantly smaller in the +3 D/pL animals compared with the control monkeys (right eye

change: +3 D/pL, 0.96 ± 0.21 mm versus controls, 1.18 ± 0.33 mm, $t = -2.20$, $P = 0.04$). However, there were no significant differences between the control and +3 D/pL monkeys in corneal power or the axial dimensions of the anterior chamber or crystalline lens (treated versus control right eyes: 55.37 ± 0.98 D vs. 55.68 ± 1.71 D; 3.10 ± 0.10 mm vs. 3.05 ± 0.30 mm; 3.66 ± 0.14 mm vs. 3.62 ± 0.21 mm, respectively, $t = -0.46$ – 0.46 , $P = 0.65$ – 0.70).

FIGURE 2. Vitreous chamber depths for the right (filled symbols) and left eyes (open symbols) of individual +3 D/pL monkeys plotted as a function of age (A–G). The average vitreous chamber depths for all of the +3 D/pL monkeys are shown in (H). See Figure 1 for details.

FIGURE 3. Spherical-equivalent, spectacle-plane refractive corrections plotted as a function of age for the right (filled symbols) and left eyes (open symbols) of individual -3 D/pL monkeys (A–G). The average ($\pm$ SD) refractive errors for all of the -3 D/pL monkeys are shown in (H). See Figure 1 for details.

As in the $+3$ D/pL monkeys, the refractive errors for the left and right eyes of the -3 D/pL animals were generally well matched throughout the treatment period. However, in contrast to the $+3$ D/pL monkeys, there was more intersubject variability in the pattern of refractive development in the -3 D/pL group (Fig. 3). In particular, three of the -3 D/pL monkeys exhibited normal emmetropization (panels A–C); these animals showed gradual reductions in hyperopia during the lens-rearing period and the refractive errors for these animals were always well within the range of refractive errors for age-matched control animals. Three monkeys (panels D–F) showed small reductions in hyperopia (panels D, E) or relatively little change in refractive error, maintaining moderate degrees of hyperopia throughout the observation period (panel F). And interestingly one of the -3 D/pL monkey (Fig. 3G) developed absolute myopic refractive errors that toward the end of the rearing period stabilized at levels that were approximately 3 D more myopic than age-matched control animals. The average data (Fig. 3H) indicate that as a group the -3 D/pL animals exhibited relatively normal refractive development. At the end of the treatment period, the median refractive error for these lens-reared monkeys was not significantly different from that for the age-matched controls (right eyes: $+3.13$ D vs. $+2.50$ D, $P = 0.15$). There were also no significant differences in the changes in refractive error over the course of the treatment period between the -3 D/pL group and the control monkeys (right eye change: -1.77 ± 1.46 D vs. -1.52 ± 1.91 D, $t = -0.38$, $P = 0.71$). However, it is important to note that the variability of the refractive error data for the -3 D/pL monkeys (as reflected in the SDs in Fig. 3H) systematically increased with time during the treatment period compared with control animals (baseline versus end of treatment SD: -3 D/pL = 1.00 D vs. 1.76 D; controls = 1.75 D vs. 1.06 D; $F = 3.99$, $P = 0.02$). In contrast the between subject variability in refraction for the $+3$ D/pL monkeys decreased by a small, but nonsignificant amount during the lens-rearing period (Fig. 1H, baseline versus end of treatment SD: 1.66 D vs. 1.25 D, $F = 0.68$, $P = 0.73$). However, the increase in variability in the -3 D/pL group primarily

reflects the myopic changes in monkey 511. If the data for monkey 511 are removed from the analysis, the group variability also decreases with time.

The different patterns of refractive development within the -3 D/pL subject group reflected the differences in vitreous chamber growth between individual monkeys. As illustrated in Figure 4E, the -3 D/pL monkey (MKY 509) that maintained the highest degrees of hyperopia during the treatment period exhibited the slowest vitreous chamber growth rate. On the other hand, the animal that developed compensating myopia (MKY 511, Fig. 4G) showed much faster than normal vitreous chamber elongation rates. For the other five -3 D/pL monkeys (Figs. 4A–E) their longitudinal vitreous chamber data fell within the range for control animals. The average vitreous chamber depths for the -3 D/pL group was very comparable to those for control monkeys at baseline and throughout the lens-rearing period (Fig. 4H). At the end of the lens-rearing period, the average vitreous chamber depth was not statistically different from that for the control monkeys (treated versus control right eyes: 9.90 ± 0.60 mm vs. 9.82 ± 0.30 mm, $t = 0.50$, $P = 0.62$). The average vitreous chamber growth between baseline and the end of treatment in the -3 D/pL monkeys was also similar to that in the controls (right eye change: -3 D/pL, 1.28 ± 0.35 mm versus controls, 1.18 ± 0.33 mm; $t = 0.71$, $P = 0.50$). In addition, there were no significant differences between the control and -3 D/pL monkeys in corneal power or the axial dimensions of the anterior chamber or crystalline lens (treated versus control right eyes: 55.43 ± 1.50 D vs. 55.68 ± 1.71 D; 3.05 ± 0.16 mm vs. 3.05 ± 0.30 mm; 3.71 ± 0.04 mm vs. 3.62 ± 0.21 mm, respectively, $t = -0.36$ – 1.15 , $P = 0.26$ – 0.99). However, as noted for the average refractive error data for the -3 D/pL animals, the intersubject variability in vitreous chamber depth increased during the treatment period.

Figure 5 compares refractive development for the right eyes between subject groups. Specifically, panels A and B compare the course of refractive development between individual animals reared with the dual focus lenses (filled symbols) and those reared with $+3$ D and -3 D single vision lenses (open

FIGURE 4. Vitreous chamber depths for the right (*filled symbols*) and left eyes (*open symbols*) of individual -3 D/pL monkeys plotted as a function of age (A–G). The average vitreous chamber depths for all of the -3 D/pL monkeys are shown in (H). See Figure 1 for details.

symbols). In each plot, the shaded areas demarcate the 10th to 90th percentile ranges for the control monkeys. At the start of the treatment period, all but one of the monkeys treated with either $+3$ D/pL or $+3$ D FF lenses had refractive errors that fell within the 10 to 90% limits for control monkeys (Fig. 5A). However, over the course of the treatment period all of the positive lens-reared monkeys developed refractive errors that were more hyperopic than 90% of the age-matched controls. The key point is that throughout the treatment period the data for the $+3$ D/pL animals overlapped the data for monkeys reared with $+3$ D FF treatment lenses and at the end of treatment period, the median ($+5.25$ D vs. $+4.63$ D, $P = 0.32$) and average refractive errors (large symbols to the right in Fig. 5A) for the $+3$ D/pL monkeys were similar to those for the monkeys reared with $+3$ D FF lenses. As illustrated in Figure

5B, refractive development was very different in the animals reared with the -3 D/pL and -3 D FF lenses. With one exception, the -3 D FF animals developed compensating myopic refractive errors. One of the -3 D/pL monkeys exhibited a myopic refractive trajectory very similar to that observed in the majority of animals reared with -3 D FF lenses. However, the other six -3 D/pL monkeys maintained varying degrees of hyperopia throughout the treatment period. As a consequence, at the end of the treatment period the median refractive error for the -3 D/pL group was significantly more hyperopic than that for the -3 D FF monkeys ($+3.13$ D vs. -1.69 D, $P = 0.01$).

Figure 5C compares the average longitudinal refractive errors between the two dual focus treatment groups. The data for the two groups overlapped after 2 weeks of lens wear.

FIGURE 5. (A) Refractive errors for the right eyes plotted as a function of age for individual lens-reared monkeys in the FF $+3$ D (*open symbols*) and $+3$ D/pL (*filled symbols*) groups. (B) Refractive errors for the right eyes plotted as a function of age for individual lens-reared monkeys in the FF -3 D (*open symbols*) and -3 D/pL (*filled symbols*) groups. The *large symbols* to the right in (A, B) represent the averages $\pm$ SD for the lens-reared monkeys at the end of the treatment period. (C) The average ($\pm$ SD) refractive errors for all of the $+3$ D/pL lens (*filled symbols*) and -3 D/pL lens-reared monkeys (*open symbols*) plotted as a function of age. The shaded areas in each plot show the 10th to 90th percentile range of ametropias for the 33 control monkeys.

FIGURE 6. Refractive errors are plotted as a function of vitreous chamber depth for individual right eyes. The filled and open diamonds represent data from +3 D/pL and -3 D/pL lens-reared monkeys, respectively. The solid line is the best fitting regression line. The small gray circles represent data from control monkeys.

Thereafter, the +3 D/pL group systematically developed relative hyperopic refractive errors while the -3 D/pL monkeys on average exhibited essentially normal emmetropization with refractive errors within the 10th to 90th percentile range for control animals. A repeated measures ANOVA showed significant differences between the two groups of monkeys as a function of age during the lens treatment period ($F = 12.24$, $P = 0.0001$).

For the two dual focus subject groups, absolute refractive error was significantly correlated with vitreous chamber depth (Fig. 6, right eyes: $r^2 = 0.72$, $P < 0.0001$). However, corneal power, anterior chamber depth, and lens thickness were not correlated with refractive status at the end of the treatment period ($r^2 = 0.03$ – 0.22 ; $P = 0.08$ – 0.56).

DISCUSSION

The main findings of this study were (1) that the animals that were reared with +3 D/pL lenses consistently developed hyperopic errors that selectively compensated for the +3 D powered components of the treatment lenses, and (2) that, on average, refractive development in the animals that wore the -3 D/pL lenses was dominated by the zero power components of the treatment lenses. Several observations support the argument that the animals in the +3 D/pL group actively and effectively compensated for the positive power components of the dual focus lenses. In particular, the median refractive error for the +3 D/pL group was +2.75 D more hyperopic than that for the control monkeys and very similar to that for monkeys reared with +3 D single-vision lenses. For the -3 D/pL group, the median refractive error was not different from that for control animals, but it was significantly more hyperopic than that for monkeys reared with -3 D single-vision lenses, supporting the idea that emmetropization targeted the image plane associated with the zero power components of -3 D/pL-treatment lenses. Emmetropization in the one obvious outlier in the -3 D/pL group also appeared to target one of the two image planes. However, in this case, the myopic refractive changes observed in MKY 511 (Fig. 5B) were very comparable to those of the majority of animals reared with -3 D single-vision lenses, indicating that in this animal emmetropization targeted the image plane produced by the -3 D power zones of

the dual-focus lenses. The key point is that for both treatment groups, when the vision-dependent mechanisms that regulate ocular growth were presented with two, approximately equally distinct, focal planes, refractive development was in the great majority of cases directed toward the more myopic/less hyperopic focal plane (i.e., the more anterior foci).

Like the dual-focus lenses employed in this study, cylinder lenses also produce two competing simultaneous image planes. In this respect, the patterns of refractive development observed previously in infant monkeys reared with an optically imposed astigmatism³⁴ were similar to those observed in the monkeys reared with dual focus lenses. Specifically, when infant monkeys were reared wearing cylinder lenses that had orthogonal principal meridian refracting powers of +1.5 D and -1.5 D, emmetropization was preferentially directed to one of the two image planes defined by the astigmatic line foci, not to the circle of least confusion. Moreover, a greater number of cylinder-reared monkeys developed relative hyperopic refractive errors (i.e., corresponding to the focal plane for the +1.5-D meridian) rather than relative myopic refractive errors. Analysis of the theoretical 3D point spread function obtained in model eyes with imposed astigmatic errors indicated that when wearing cylinder lenses, ocular growth was directed to the image planes that had the highest effective retinal image contrast across spatial frequencies and orientations (i.e., the image planes associated with the principal line foci).³⁴ With dual focus lenses, the highest effective image contrast would occur at the two secondary focal points associated the lenses' two power zones. The dioptric midpoint between these focal points would, in a manner analogous to the circle of least confusion in an astigmatic system, have image contrasts below that found at the two focal points, but relatively higher than that at most points in the 3D point spread function. Thus, as in cylinder-reared monkeys, the emmetropization process in monkeys reared with dual focus lenses appeared to target the image planes with the highest effective retinal contrast. However, the image quality at either of the focal points produced in an eye wearing a dual focus lens would obviously be reduced in comparison to that when viewing through a comparably powered single vision lens. It seems likely that the resulting increase in the eye's depth of focus associated with wearing dual focus lenses contributed to the higher variability in end-point refractive errors observed in both treated groups in comparison to control animals. There was, however, no evidence that the overall reduction in retinal image quality imposed by the dual focus lenses produced axial myopia in a manner similar to form deprivation.^{47,52} On the contrary, most of the monkeys reared with dual focus lenses exhibited relative hyperopic refractive errors.

Why does the emmetropization process preferentially target the more anterior focal point when the eye is viewing through a dual focus lens? Emmetropization appears to be regulated by mechanisms that are sensitive to the sign of defocus.^{3-7,9,11,53} However, dual-focus lenses complicate refractive development because both convergent and divergent rays are associated with both focal planes produced by a dual focus lens (i.e., both positive and negative defocus signals bracket both focal points and to a lesser degree the dioptric midpoint between the two foci). In this respect, a series of studies have demonstrated that myopic defocus appears to have a stronger influence on ocular growth than hyperopic defocus.^{25,26} For example, in animals that experience sequential periods of hyperopic versus myopic defocus, refractive development is usually biased in the hyperopic direction (i.e., toward the more anterior focal plane).^{24-26,28} Given the dominance of myopic defocus, it is reasonable to argue that with dual focus lenses any axial growth or viewing conditions that displaced the more anterior focal plane in front of the retina would result in strong visual

FIGURE 7. Comparisons of the effects of dual focus, Fresnel-like lenses (50:50 area ratios) on refractive error development in macaques (present study), chicks,³¹ marmosets,³³ and guinea pigs.³² The left scale indicates the relative percentage change in ametropias at the end of treatment. For binocularly treated animals (present study), the ametropias for the right eyes are represented relative to that for control animals. For monocularly treated animals (all other studies), the ametropias for the treated eyes are expressed relative to that of the fellow eye. Values of 0% and 100% indicate complete compensation for the most hyperopic and myopic image planes, respectively. Values of 50% indicate that the animals compensated for the average power of the dual focus treatment lenses.

signals to slow or stop axial elongation. Consequently, the more anterior focal plane would be a strong and effective end point for emmetropization, as illustrated by our data. In one -3 D/pl monkey, refractive development was not stopped at the more anterior focal point, possibly as a result of the general reduction in image quality produced by the dual focus lenses. However, emmetropization was effectively halted in this animal at the more posterior focal point, supporting the idea that each focal plane produced by dual focus lenses can serve as an end point for emmetropization. Regardless of the exact reason that the anterior focal plane is the most common target for emmetropization, this bias in the functional operating characteristics of the vision-dependent mechanisms that regulate refractive development has value from an evolutionary perspective because it reduces the likelihood that an animal will become myopic.

Between Study Comparisons of the Effects of Dual-Focus Lenses

Fresnel-like lenses have also been employed to study the effects of simultaneously imposed, competing defocus image planes on refractive development in chickens,³¹ marmosets,³³ and guinea pigs.³² Figure 7, which shows the relative ametropias of animals reared with dual-focus lenses expressed as a percentage of the dioptric interval between the competing power zones of the treatment lenses, compares the results from previous studies with those obtained in this study with infant macaques. For each study, data are shown for Fresnel lenses in which each of the two power zones made up approximately equal areas across the surfaces of the treatment lenses.

As observed in this study, there was no indication in any of the previous studies that the reduction in retinal image quality associated with dual-focus lenses promoted the development

of form deprivation myopia. Moreover, refractive development did not selectively target the more hyperopic focal plane in any study. In guinea pigs, emmetropization appeared to be directed toward the average focal plane for the two power zones of the dual focus lenses. In marmosets, and more so in chickens, refractive development was biased toward the more positive powered lens component, but in both cases refractive development fell well short of complete compensation for the more myopic focal plane. It has been suggested that the results from these dual-focus experiments indicate that the vision-dependent mechanisms that regulate refractive development identify the effective sign and magnitude of defocus associated with each focal plane^{31,33} and average these signals either in a more or less linear manner in guinea pigs or in a manner that preferentially weights the image plane associated with the more positive powered component of the treatment lenses.

In contrast to these previous studies, infant monkeys exhibited essentially complete compensation for the most myopic focal plane. From an evolutionary perspective, it could be argued that mechanisms that regulate refractive development should target the most myopic focal plane versus an average of the different focal planes that are viewed. In this respect, it seems unlikely that the differences represented in Figure 7 represent qualitative differences between species in the nature of the mechanisms that regulate emmetropization or the general viewing behavior of animals. On the other hand, there are a number of methodological issues that may have reduced the likelihood of obtaining more complete compensation for the most myopic focal plane in previous studies. For example, in each of the previous studies the dual-focus lenses were worn monocularly and the fellow eye's refractive error was used as a reference. In this respect, the interocular effects that have been documented in many experiments employing monocular visual manipulations may have influenced the fellow eye's refraction,^{5,9,30,43,45-48} which was used as the reference for treatment effects. We specifically employed a binocular treatment strategy to avoid this potential issue. In addition, in some of the previous studies, the powers employed in the dual-focus lenses may have biased refractive development toward the more hyperopic focal point. For example, in guinea pigs, the dioptric interval between the two power components of the dual-focus lenses exceeded the operating range of the emmetropization process determined using single-vision lenses.⁴ In addition, positive single-vision lenses that had powers similar to the positive component in the dual-focus lenses actually resulted in absolute myopic refractive errors in guinea pigs over a similar treatment period.⁴ In marmosets positive single-vision lenses that had the same positive power as that in the most positive component of the dual-focus lenses produced much smaller changes in refractive error than negative single vision lenses of the same absolute power (i.e., negative and positive single-vision lenses of the same powers as the components in the dual focus lenses did not produce equal magnitude changes in refractive development).³³ Moreover, in both guinea pigs and marmosets, plano control lenses appeared to produce relative myopic refractive shifts.^{4,54} In this respect, whatever caused these myopic shifts in the control eyes could have limited the compensating hyperopic shifts in the treated eyes.

Clinical Implications for Slowing Myopia Progression

The results from this study as well as those from the previous animal studies of dual-focus lenses support the idea that distance vision correcting lenses that simultaneously impose relative myopic defocus over all or a substantial portion of the

visual field can be effective in reducing myopia progression in children.^{1,35-37} A recent clinical trial compared myopia progression in children wearing single-vision soft contact lenses with myopia progression in children wearing experimental dual-focus, soft contact lenses that employed Fresnel concepts to correct the eye's distance refractive error, while simultaneously imposing +2.5 D of relative myopic defocus.³⁶ In comparison to the control lenses, the dual focus contact lenses significantly reduced myopia progression by 25% over a 2-year treatment period. These treatment effects were dependent on the average daily duration of lens wear with children wearing the experimental lenses for at least 5 hours per day exhibiting on average a 46% reduction in myopia progression. The treatment effects increased to nearly 60% in the children who wore the dual-focus lenses for at least 7 hours a day. It is likely that other methodological variables will affect the antimyopia effects of dual-focus lenses. For example as suggested by the comparisons in Figure 7, the exact power of the treatment zones relative to the effective operating range of the emmetropization process will probably influence efficacy.

When extrapolating data from infant monkeys to human juveniles, it is important to note that large absolute hyperopic shifts are possible in very young animals because it is possible to slow ocular growth while the cornea and crystalline lens, which are relatively unaffected by optically imposed defocus, are still rapidly decreasing in refracting power. We expect that similar results would be obtained in human infants. However, in juveniles, at ages when myopia typically first develops, the cornea is essentially adult-like in terms of total refracting power and age-related changes in the power of the crystalline lens are small and slow. As a result, optical treatment strategies that stop or slow axial growth in juveniles can stop or reduce myopia progression, but are unlikely to produce large hyperopic shifts in refraction.

As a potential treatment strategy, dual-focus lenses have some disadvantages. In particular, because both power zones of these Fresnel concept lenses typically cover the entrance pupil, the myopic defocus imposed by the treatment zones will degrade the foveal image. This can, depending on a variety of lens parameters, reduce the best-corrected central vision relative to traditional single vision lenses. Moreover, it could be argued that the associated reductions in image quality could possibly promote axial myopia in a manner similar to form deprivation, which has been shown to be a graded phenomenon.⁴⁷ However, as discussed above, the results of animal studies involving four different species provided no indication that the resulting reduction in image contrast associated with dual-focus lenses were myopiagenic. In fact the opposite was true, specifically that simultaneously imposed myopic defocus slowed axial growth.

Acknowledgments

Supported by NIH Grants EY03611 and EY07551 and funds from the Vision Cooperative Research Centre and the University of Houston Foundation.

Disclosure: **B. Arumugam**, None; **L.-F. Hung**, None; **C.-H. To**, P; **B. Holden**, P; **E.L. Smith III**, P

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