The Effects of the Relative Strength of Simultaneous Competing Defocus Signals on Emmetropization in Infant Rhesus Monkeys

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Purpose. We investigated how the relative surface area devoted to the more positive-powered component in dual-focus lenses influences emmetropization in rhesus monkeys.

Methods. From 3 to 21 weeks of age, macaques were reared with binocular dual-focus spectacles. The treatment lenses had central 2-mm zones of zero-power and concentric annular zones that had alternating powers of either +3.0 diopters (D) and 0 D (+3 D/pL) or −3.0 D and 0 D (−3 D/pL). The relative widths of the powered and plano zones varied from 50:50 to 18:82 between treatment groups. Refractive status, corneal curvature, and axial dimensions were assessed biweekly throughout the lens-rearing period. Comparison data were obtained from monkeys reared with binocular full-field single-vision lenses (FF+3D, n = 6; FF−3D, n = 10) and from 35 normal controls.

Results. The median refractive errors for all of the +3 D/pL lens groups were similar to that for the FF+3D group (+4.63 D versus +4.31 D to +5.25 D; P = 0.18–0.96), but significantly more hyperopic than that for controls (+2.44 D; P = 0.0002–0.003). In the −3 D/pL monkeys, refractive development was dominated by the zero-powered portions of the treatment lenses; the −3 D/pL animals (+2.94 D to +3.13 D) were more hyperopic than the FF−3D monkeys (−0.78 D; P = 0.004–0.006), but similar to controls (+2.44 D; P = 0.14–0.22).

Conclusions. The results demonstrate that even when the more positive-powered zones make up only one-fifth of a dual-focus lens' surface area, refractive development is still dominated by relative myopic defocus. Overall, the results emphasize that myopic defocus distributed across the visual field evokes strong signals to slow eye growth in primates.

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

Myopia has reached epidemic proportions in many parts of East Asia[1–5] and it appears that the prevalence of myopia is rapidly increasing in the United States[6] and other non-Asian countries.[7–9] Moreover, in recent decades, the onset of myopia has shifted to younger ages,[10] which has ultimately led to an increased prevalence of high degrees of myopia.[1,11] This increase in highly myopic eyes, which has been dramatic in many countries,[1,11,12] is a significant economic burden[13–15] and a major public health concern because of the associated sight-threatening conditions of myopic macular degeneration, retinal detachment, cataract, and glaucoma.[16–20] Unfortunately, it has been estimated that the retinal complications due to myopia will increase dramatically over the next few decades as the prevalence and degree of myopia continues to increase and as the population around the world ages.[9,21] In this respect, treatment strategies that could effectively reduce myopia progression and/or delay the onset of myopia could have substantial therapeutic benefit.[22–24]

Fortunately, research conducted on laboratory animals has provided the scientific foundation for potential optical treatment strategies to reduce the burden of myopia. Specifically, in a wide variety of animal species it has been demonstrated that ocular growth and refractive development are regulated by visual feedback associated with the eye's effective refractive state, in essence optical defocus.[25–32] Most importantly, optically imposed myopic defocus has been shown to consistently slow ocular growth and produce hyperopic shifts during emmetropization in young animals.[32–35] This pattern of results indicates that optical correction strategies that produce myopic defocus in children should be effective in reducing myopia progression. In this respect, recent clinical trials have shown that a variety of lens designs that correct distance vision while simultaneously imposing relative myopic defocus over a large part of the retina[22] can produce clinically meaningful reductions in myopia progression in children.[36–41]

In particular, traditional multifocal spectacles[42–44] and aspheric spectacle lenses that were designed to produce relative myopic defocus primarily in the periphery[36] have been shown to reduce myopia progression in children, with Franklin-style bifocals, which typically impose myopic defocus over a

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larger area of the retina, being the most effective in reducing progression rates.[45] In general, contact lenses strategies have had greater success in reducing myopia progression in children and, primarily because the optical effects of these correction strategies are located closer to the eye's principal plane and are relatively unaffected by head or eye movements, contact lenses offer a number of practical advantages. Four basic types of contact lens designs, corneal reshaping therapy (CRT) or orthokeratology,[46–48] aspheric peripheral plus lenses,[37] simultaneous bifocals,[38,41] and extended depth of field lenses (Bakaraju RC, et al. *IOVS* 2015;56:ARVO E-Abstract 1728), have been shown to be effective in reducing myopia progression. Corneal reshaping therapy uses specially designed contact lenses that are worn overnight to reduce central corneal power to correct distance vision. The therapeutic effects obtained with CRT are thought to come about because the effective increase in positive power in the peripheral cornea produces relative myopic defocus.[49–51] Aspheric contact lenses in which the relative positive power of the lenses increases with distance from the optical center reduce peripheral hyperopia while maintaining relatively unrestricted central foveal vision.[37] Bifocal and dual-focus contact lenses usually have concentric, alternating power zones that simultaneously produce two image planes, one correcting the eye's distance refractive error and the other imposing relative myopic defocus over the entire visual field, including the fovea.[38,41] Extended depth-of-field lenses (Bakaraju RC, et al. *IOVS* 2015;56:ARVO E-Abstract 1728) use combinations of high-order monochromatic aberrations to effectively create multiple image planes of good optical quality that are relatively myopic in comparison with the eye's distance refractive correction and affect both central and peripheral imagery.

A common feature of all of these correcting strategies is that they produce spatially superimposed, simultaneous competing image planes across all or a large proportion of the retina. Understanding how these simultaneous, but competing, visual signals are integrated is a critical operational characteristic of the mechanisms that regulate ocular growth and refractive development and is important for optimizing these optical treatment strategies. For example, in many cases, the competing images are superimposed on the central retina, which can compromise central visual acuity. In this respect, it may be possible to reduce the saliency of the imposed myopic defocus so that the treatment strategy maintains myopia control without significantly compromising central vision.

Experiments in a variety of animal species have demonstrated that when young animals are reared wearing dual-focus lenses (typically Fresnel-like lens designs) in which the competing optical zones make up approximately equal proportions of the treatment lens' surface area, refractive development is usually dominated by the more-myopic/least-hyperopic image plane.[52–55] It appears that, as observed in experiments in which competing signals were presented to the eye sequentially, visual signals that normally slow ocular growth are more effective in influencing refractive development.[56–61] This suggests that it may be possible to reduce the surface area of a dual-focus lens devoted to the more positive-powered component, which would reduce the degrading effects of superimposed defocus on visual performance, possibly without reducing the ability of the imposed defocus to slow myopia progression.

In chickens[52] and guinea pigs,[54] the ability of the more positive-powered components of a dual-focus lens to control refractive development is influenced by the relative surface areas of the treatment lenses that are devoted to the two power zones, in essence the relative amount of light contributing to each image plane. Specifically, decreasing the surface area of a dual-focus lens that is devoted to the more positive-powered lens component shifts refractive development in favor of the more negative-powered lens component.[52,54] Knowing how much lens area must be devoted to the more positive-powered component to maintain control of refractive development is key to improving overall vision through dual-focus–type treatment lenses. Therefore, the purpose of this study was to investigate how the relative strengths of simultaneous, competing defocus signals produced by dual-focus lenses influence refractive development in infant monkeys.

Materials and Methods

Subjects

Data are presented for 24 infant rhesus monkeys (*Macaca mulatta*) that were reared with dual-focus, Fresnel spectacle lenses over both eyes. The dual-focus lenses were qualitatively similar in design to those described by Tse et al.[52] in their previous study involving chickens. In particular, all of the dual-focus lenses had a 2-mm diameter central zone of zero power (i.e., plano power) that was surrounded by alternating concentric annular power zones of +3 diopters (D) and plano (+3 D/pL lenses) or −3D and plano (−3 D/pL lenses). We previously reported that refractive development in monkeys that were reared with dual-focus lenses in which the alternating annular power zones had equal 0.4-mm widths (i.e., 50:50 area ratios for the two power zones) was dominated by the power zones producing the more anterior focal point.[55] To investigate the relative strengths of the competing defocus signals produced by these dual-focus lenses, we varied the relative sizes of the annular zones associated with the two powers. Specifically, we held the widths of the more-positive/less-negative power zone constant at 0.4 mm and increased the widths of the less-positive/more-negative–powered zones. For the +3 D/pL lenses, the widths of the +3 D zones were held constant while the widths of the plano zones were increased to 0.8, 1.2, or 1.8 mm, resulting in approximate surface area ratios between the +3 D and plano zones of 33:67, 25:75, and 18:82 (see Fig. 1). For the −3 D/pL lenses, we investigated the effects of increasing the widths of the −3 D power zones to 0.8 mm, resulting in a surface area ratio of 67:33. In all lenses, the transition between the two power zones was maintained at 0.005 mm. A minimum of six animals were included in each dual-focus lens group.

Varying the surface area ratios for the two power zones of the dual-focus lenses altered the proportion of light contributing to the resulting two focal planes and, thus, the relative saliency of the two image planes. It is important to note that these changes in the power zone dimensions did not alter the dioptric positions of the two competing image planes nor did they alter the area of the visual field that experienced competing defocus signals. In this respect, it was critical that neither the central plano zone nor the combined widths of the two power zones exceeded the diameter of the eye's entrance pupil. For the lenses used in this study, the central plano zone (2 mm) and the largest combined widths of the annular power zones (2.2 mm in 18:82 +3 D/pL lenses) were smaller than the average pupil size of our normal infant monkeys (3.3 ± 0.3 mm). This ensured that regardless of the direction of gaze, rays of light passing through both of the power zones contributed to retinal image formation (i.e., competing image planes were maintained).

The optical zones of the dual-focus lenses were 22 mm in diameter and the lenses were held at a vertex distance of 11 mm using specially designed goggles.[31] As a consequence, the treatment lenses produced two distinct image planes across the entire 85 degrees of the central retina. In the case of the +3

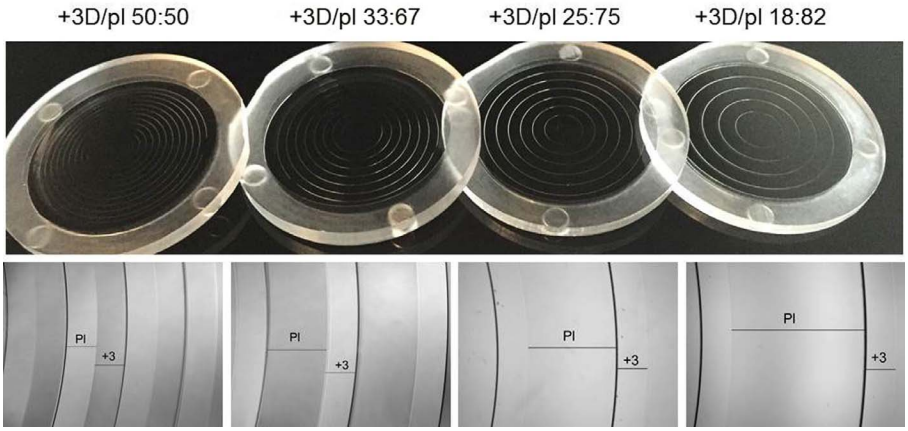

Figure 1. Photographic images of the +3 D/pL dual-focus lenses (*top*) and a magnified view of the annular power zones for the 50:50, 33:67, 25:75, and 18:82 power ratio lenses (*bottom*). The width of the +3 D annular zones was 0.4 mm for all lenses; the widths of the zero-powered zones varied from 0.4 to 1.8 mm.

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 refractive errors imposed via spherical treatment lenses that normally produce compensating axial growth in infant monkeys.[31] Moreover, we specifically concentrated our efforts on the effects of the +3 D/pL lenses because the competing defocus signals produced by these lenses are qualitatively and quantitatively similar to those produced by many optical treatment strategies that are currently being used in attempts to slow the progression of myopia in children. In addition, we chose to use binocular treatment lenses to more closely mimic clinical conditions and to ensure that the fixation and accommodative behavior of our monkeys were determined by eyes experiencing competing defocus signals.

Comparison data were obtained from 16 monkeys that were reared with binocular, full-field (FF), single-vision lenses that had refracting powers of +3 D (FF+3D; $n = 6$) or −3 D (FF−3D; $n = 10$). Some of the data from these animals have been published previously.[30,31,55,62] The onset and duration of lens wear for all of the FF monkeys were similar to those for the dual-focus lens groups. Control data were also obtained in previous studies from another 35 monkeys that were reared with unrestricted vision.[31,63–66] Although the data from these animals were collected over a period of years, the rearing and biometric measurement methods were identical to those used with the animals reared with the dual-focus lenses.

All of the animals were obtained at 2 to 3 weeks of age and housed in our primate nursery that was maintained on a 12-hour light/12-hour dark cycle (average illuminance = 350 lux). The lens-rearing procedures were initiated at approximately 3 weeks of age (24 ± 3 days) when the infants were randomly assigned to subject groups. In all subject groups, the treatment lenses were worn continuously until approximately 21 weeks of age (151 ± 4 days). The details of the nursery care have been described previously.[31]

Ocular Biometry

The procedural details for measuring the eye's refractive status, corneal power, and axial dimensions have been described previously.[30,31] Briefly, 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 of 1 to 2 drops of 1% tropicamide 25 and 20 minutes before obtaining the measurements. The refractive state of each eye was measured independently by two experienced investigators using a streak retinoscope and averaged.[67] An eye's refractive error was defined as the spherical-equivalent, spectacle-plane refractive correction (95% limits of agreement = ± 0.60 D).[68] 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).[69] 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 = ± 0.05mm).[31,65] The initial biometric measures were obtained at ages corresponding to the start of lens wear and were performed every 2 weeks throughout the observation period.

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 and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Statistical Methods

The statistical analyses were performed using Minitab software (Release 16.2.4; Minitab, Inc., State College, PA, USA). Nonparametric Mann-Whitney tests were used to compare the median refractive errors between subject groups. Two-sample *t*-tests were also used to compare differences in the average refractive errors and vitreous chamber depths between groups. Paired Student's *t*-tests and 1-way ANOVAs were used to examine the interocular and between-group differences at ages corresponding to the start of lens wear, respectively. Linear regression analyses were performed to characterize the relationship between refractive error and the ratio between

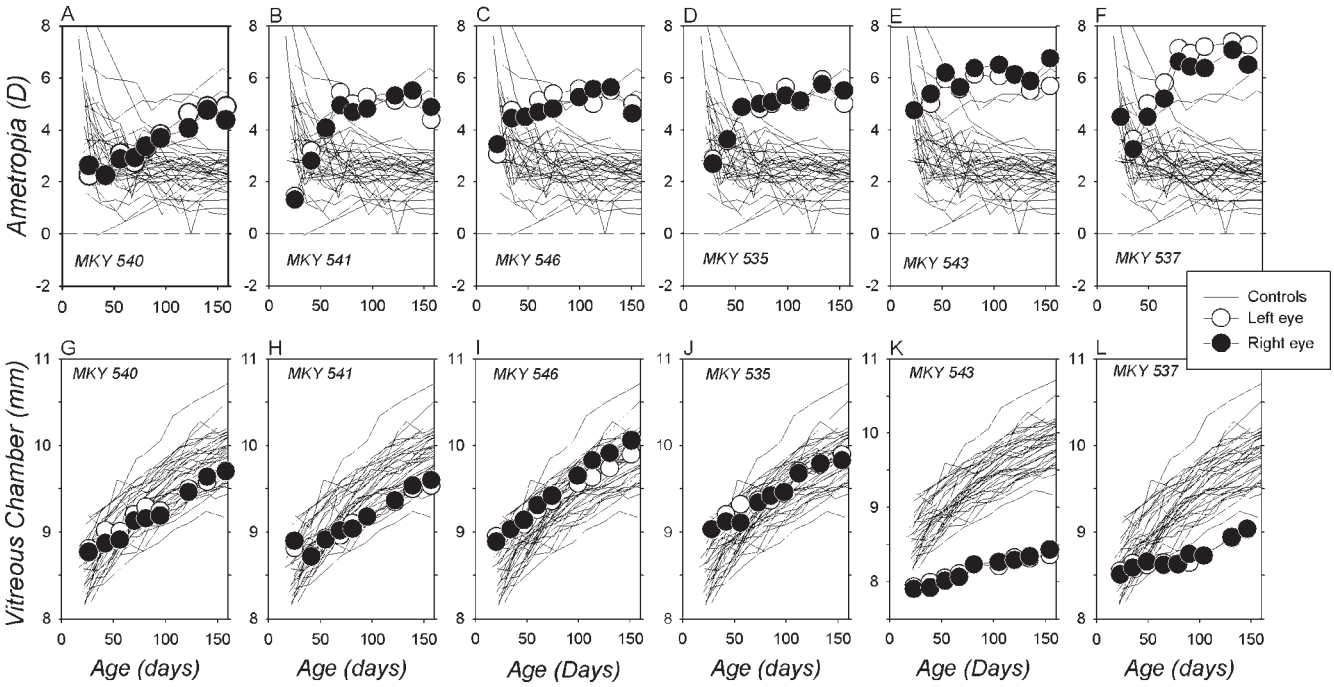

Figure 2. Spherical-equivalent, spectacle-plane refractive corrections (*top*) and vitreous chamber depths (*bottom*) plotted as a function of age for the right (*filled symbols*) and left eyes (*open symbols*) for individual +3 D/pL 33:67 lens-reared monkeys. The *thin gray lines* in each plot represent data for the right eyes of the 35 control monkeys. The plots for treated subjects are arranged from left to right according to the maximum degree of hyperopia observed during the treatment period.

axial length and corneal radius. 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 various lens treatment groups as a function of age.

Results

At ages corresponding to the onset of lens wear, the average infant in each subject group was moderately hyperopic (average for all subjects: OD = +4.06 ± 1.92 D; OS = +4.09 ± 1.91 D) and there were no between-group differences in refractive error ($F = 0.59$, $P = 0.79$) or vitreous chamber depth ($F = 2.00$, $P = 0.06$). In addition, there were no significant interocular differences in refractive error, corneal power, or axial dimensions in any of the subject groups ($t = -2.32$ to 1.21, $P = 0.06$–0.98).

Figures 2, 3, and 4 illustrate the spherical-equivalent, spectacle-plane refractive corrections (top rows) and vitreous chamber depths (bottom rows) plotted as a function of age for the right (filled symbols) and left eyes (open symbols) for individual +3 D/pL monkeys in the 33:67, 25:75, and 18:82 area ratio groups, respectively. Comparable figures for the +3 D/pL monkeys in the 50:50 area ratio group can be found in our previous publication.[55] Within the +3 D/pL 33:67 subject group, the results were very consistent (Fig. 2). At the onset of lens wear, all six infants exhibited refractive errors that were well within the range of ametropias for age-matched normal control monkeys (thin lines); however, in contrast to control monkeys that usually showed systematic reductions in the initial degree of hyperopia over the course of emmetropization, with time all six treated monkeys showed absolute hyperopic shifts in refractive error that were associated with slower than normal rates of vitreous chamber elongation. As the surface area devoted to the zero-powered lens component was increased, the between-subject variability in the pattern of refractive development increased. For example, in the +3 D/pL 25:75 group, five of the six infants maintained approximately the same degree of hyperopia throughout the lens-rearing period (Figs. 3B, 3E) or showed increases in the degree of hyperopia (Figs. 3C, 3D, 3F). In contrast, one monkey in the +3 D/pL 25:75 group (Fig. 3A) appeared to exhibit normal emmetropization. In the +3 D/pL 18:82 group, three infants exhibited systematic increases in axial hyperopia (Figs. 4D–F). One animal appeared to undergo normal emmetropization (Fig. 4A) and interestingly, two infants showed initial hyperopic shifts that appeared to reflect compensation for the +3 D power component, but approximately midway through the rearing period these animals showed relative myopic shifts down to normal degrees of hyperopia (Figs. 4B, 4C). For these animals, it appears that the target for emmetropization changed from the +3 D to the plano image plane during the course of lens wear.

With three exceptions, refractive-error development was similar in the left and right eyes of animals reared with the +3 D/pL lenses throughout the lens-rearing period. Monkeys MKY571 and MKY576 (Figs. 3A, 3F) developed obvious anisometropias early in the treatment period that were maintained throughout the observation period. Monkey 575 (Fig. 3B) developed a transient anisometropia. Initially, the left eye of MKY 575 (Fig. 3B) appeared to be targeting the more anterior focal plane, whereas its right eye appeared to be targeting the more posterior focal plane. However, at approximately 75 days of age, the left eye showed reductions in hyperopia that eliminated the anisometropia. As a consequence, at the end of the lens-rearing period, 16 of 18 +3 D/pL exhibited anisometropias of less than 1.0 D and interocular comparisons indicated that there were no statistically significant differences between the right and left eyes of the +3 D/pL animals in refractive error, corneal power, or any axial dimension ($t = -0.18$ to 0.65, $P = 0.53$–1.0). Therefore,

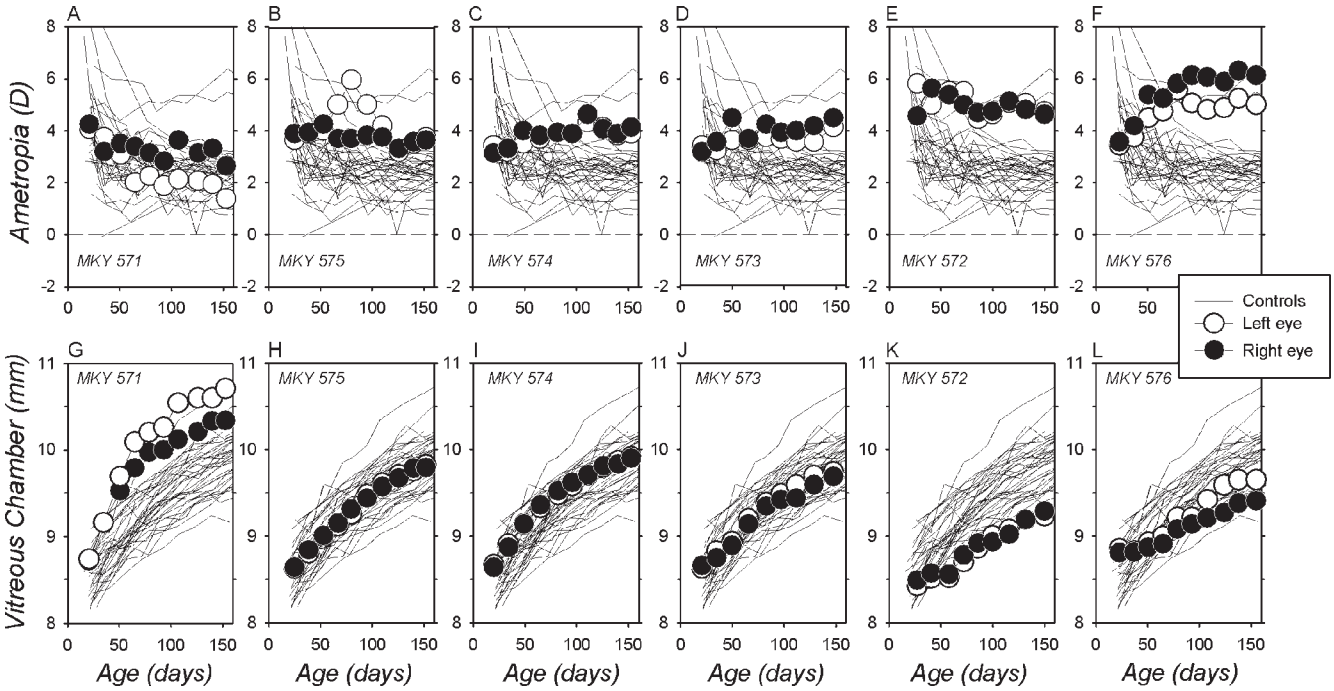

Figure 3. Spherical-equivalent, spectacle-plane refractive corrections (*top*) and vitreous chamber depths (*bottom*) plotted as a function of age for the right (*filled symbols*) and left eyes (*open symbols*) for individual +3 D/pL 25:75 lens-reared monkeys. See Figure 2 for details.

quantitative analyses were conducted using only the right eye data.

Figure 5 compares refractive development in the +3 D/pL groups, including the 50:50 ratio group from our previous study,[55] with that in the monkeys reared with FF+3D lenses (A) and the normal control monkeys (the shaded area in each plot shows the 10% to 90% range of ametropias in normal monkeys). Despite the intersubject variability in some of the +3 D/pL groups, at the end of the lens-rearing period, the median refractive errors for all of the +3 D/pL groups were significantly more hyperopic than those of control monkeys (treated versus control right eyes: +3 D/pL 50:50, +5.25 D versus +2.44 D, $P = 0.0002$; 33:67, +5.19 D, $P = 0.0004$; 25:75, +4.31 D, $P = 0.002$; 18:82, +4.28 D, $P = 0.003$). Even if the two monkeys that were more hyperopic than 90% of the normal monkeys at the beginning of the lens-rearing period in the +3

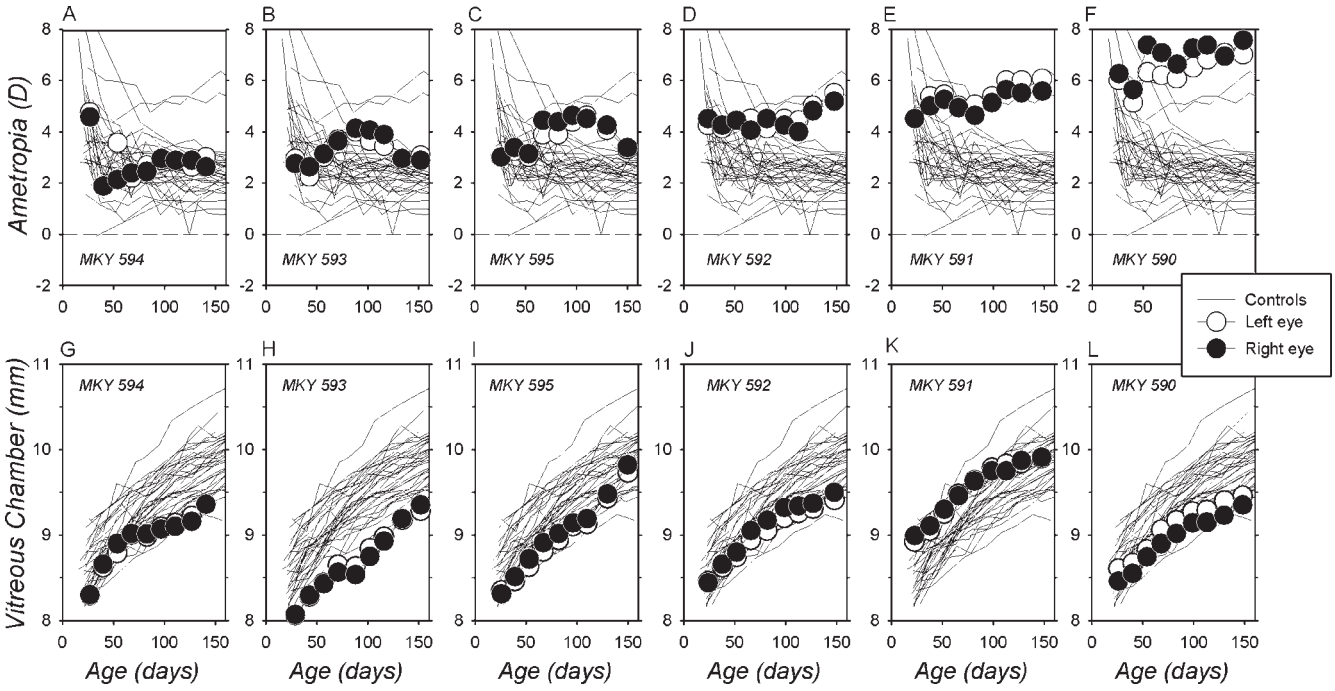

Figure 4. Spherical-equivalent, spectacle-plane refractive corrections (*top*) and vitreous chamber depths (*bottom*) plotted as a function of age for the right (*filled symbols*) and left eyes (*open symbols*) for individual +3 D/pL 18:82 lens-reared monkeys. See Figure 2 for details.

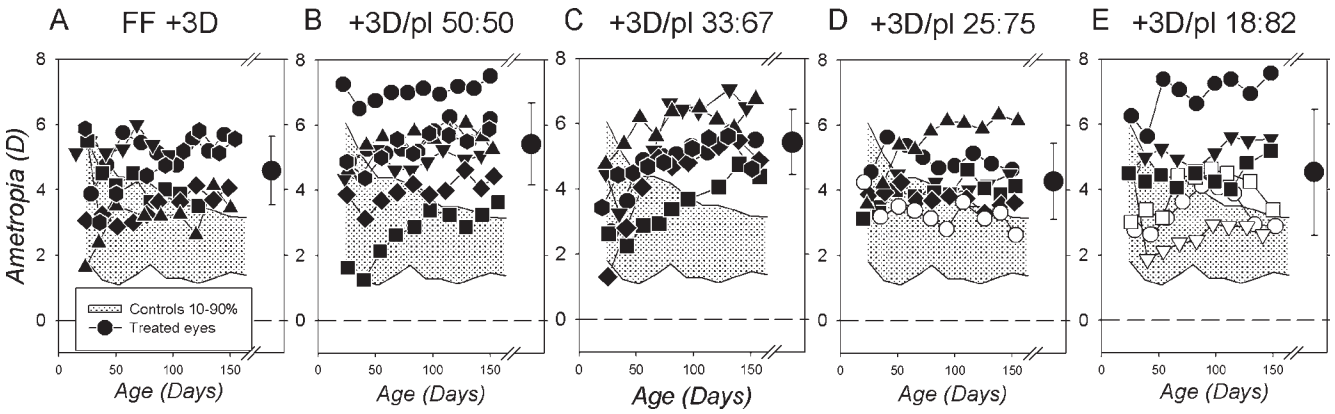

Figure 5. Refractive errors for the right eyes plotted as a function of age for all of the individual lens-reared monkeys in the FF+3D, +3 D/pL 50:50, 33:67, 25:75, and 18:82 subject groups (**A–E**). The *large symbols to the right* in each panel represent the averages (±SD) for the lens-reared monkeys at the end of the treatment period. The *shaded areas in each plot* show the 10th to 90th percentile range of ametropias for the 35 control monkeys. The *filled* and *open symbols* represent animals that appeared to compensate for the anterior and posterior focal planes, respectively.

D/pL 50:50 and 18:82 groups were removed from the analysis, there were still significant differences in the median refractive errors compared with controls for these two subject groups ($P = 0.0006$ and $P = 0.02$, respectively). In addition, the average changes in refractive error that took place during the treatment period for all of the +3 D/pL groups were also significantly more hyperopic than that for age-matched normal control monkeys (final – initial refractive corrections for treated versus control monkeys: 50:50, +0.92 ± 0.58 D versus −1.53 ± 1.84 D, $P = 0.0001$; 33:67, +2.21 ± 0.84 D, $P = 0.0001$; 25:75, +0.51 ± 1.44 D, $P = 0.01$; 18:82, +0.27 ± 1.17 D, $P = 0.03$). However, at the end of the treatment period, there were no significant differences between any of the +3D/pL groups and the FF+3D monkeys in either the median (FF+3D median = +4.63 D, $P = 0.22$–0.94) or average refractive errors (FF+3D = +4.58 ± 1.04 D versus +3D/pL 50:50 = +5.42 ± 1.26 D, $P = 0.22$; 33:67 = +5.44 ± 0.99 D, $P = 0.18$; 25:75 = +4.27 ± 1.16 D, $P = 0.64$; 18:82 = +4.53 ± 1.92 D, $P = 0.96$). Moreover, there were also no significant differences in either the median ($P = 0.08$ to 1.00) or average refractive errors ($P = 0.10$–0.98) between the +3 D/pL dual-focus groups.

The relative hyperopic ametropias observed in the +3 D/pL subjects were axial in nature. Inspection of the longitudinal vitreous chamber growth curves for the individual treated animals that developed the higher degrees of hyperopia in each ratio group (i.e., the right of center plots in Figs. 2–4) reveals that these animals exhibited slower than normal vitreous chamber elongation rates. For the animals in +3 D/pL 33:67 group (i.e., the group that showed the most consistent hyperopic shifts), the average age-related increase in vitreous chamber depth during the treatment period was significantly smaller than that observed in control monkeys (0.78 ± 0.25 mm versus 1.21 ± 0.34 mm, $P = 0.006$) and at the end of the lens-rearing period, the average vitreous chamber depth was significantly shallower than that in age-matched control animals (9.44 ± 0.60 mm versus 9.83 ± 0.32 mm, $P = 0.02$). The average age-related increases in vitreous chamber depth in the 25:75 (1.07 ± 0.36 mm, $P = 0.43$) and the 18:82 +3 D/pL groups (1.12 ± 0.24 mm, $P = 0.44$) were smaller, but not significantly smaller, than those in normal monkeys. The end of treatment differences in the average vitreous chamber depths between the control and treated animals reached borderline significance for the 18:82 monkeys (9.55 ± 0.25 mm, $P = 0.05$), but not for the 25:75 subject group (9.74 ± 0.28 mm, $P = 0.52$). There were no significant differences between any of the +3 D/pL treatment groups and age-matched control monkeys in the end-of-treatment corneal powers (treated versus control right eyes: 54.82 ± 1.46 D to 55.37 ± 0.98 D versus 55.74 ± 1.68 D, $P = 0.21$–0.62), anterior chamber depths (3.03 ± 0.17 mm to 3.12 ± 0.16 mm versus 3.06 ± 0.30 mm, $P = 0.55$–0.93), or crystalline lens thicknesses (3.65 ± 0.18 mm to 3.71 ± 0.11 mm versus 3.63 ± 0.22 mm, $P = 0.22$–0.87).

The longitudinal refractive error and vitreous chamber depths of the monkeys reared with the −3 D/pL 67:33 treatment lenses are illustrated in Figure 6. Subject MKY 536 (Fig. 6A) developed relative myopic errors that at the end of the treatment period fell outside the normal range. In contrast, the other five monkeys exhibited relatively normal emmetropization profiles (i.e., their refractive errors were within the normal range throughout the treatment period; Figs. 6B, 6C) or they developed moderate hyperopic errors that were slightly more hyperopic than most age-matched normal monkeys.

In Figure 7, refractive development for the right eyes of the −3 D/pL 67:33 animals is compared with that for monkeys reared with FF–3D lenses, −3 D/pL 50:50 monkeys, and normal control monkeys. The patterns of refractive development in the −3 D/pL 50:50 and 67:33 groups were similar. One animal in each group appeared to compensate for the −3 D power component of the treatment lenses; their final refractive errors were more myopic than 90% of the normal monkeys. However, at the end of the treatment period, the median refractive errors for the 50:50 (+3.13 D) and 67:33 area ratio groups (+2.94 D) were similar ($P = 0.94$) and not significantly different from that for the normal control monkeys (+2.44 D, $P = 0.14$–0.22). The average changes in refractive error that took place during the treatment period for the 50:50 (−1.77 ± 1.46 D) and 67:33 −3 D/pL treatment groups (−0.72 ± 1.76 D) were also similar to that observed in the normal control monkeys (ametropia = −1.53 ± 1.84 D, $P = 0.33$–0.72). Similarly, at the end of treatment period, the average refractive errors in the 50:50 (+2.93 ± 1.76 D) and 67:33 (+2.80 ± 1.45 D) lens-reared monkeys were not significantly different from that in the normal controls (+2.48 ± 1.06 D, $P = 0.54$–0.63). In addition, the average changes in vitreous chamber depth for the −3 D/pL monkeys (50:50 = 1.28 ± 0.35; 67:33 = 1.36 ± 0.45 mm) were comparable to those observed in the normal monkeys (1.21 ± 0.34 mm, $P = 0.48$–0.63) and at the end of the treatment period there were no significant differences in the average vitreous chamber depths between the 50:50 (9.89 ± 0.60 mm) and 67:33 −3 D/pL groups (9.61 ± 0.36 mm) and the normal monkeys (9.83 ± 0.32 mm; $P = 0.21$–0.79). There were also no significant differences in the end-of-treatment corneal powers (treated versus control right eyes: 55.43 ± 1.45 D to 56.33 ±

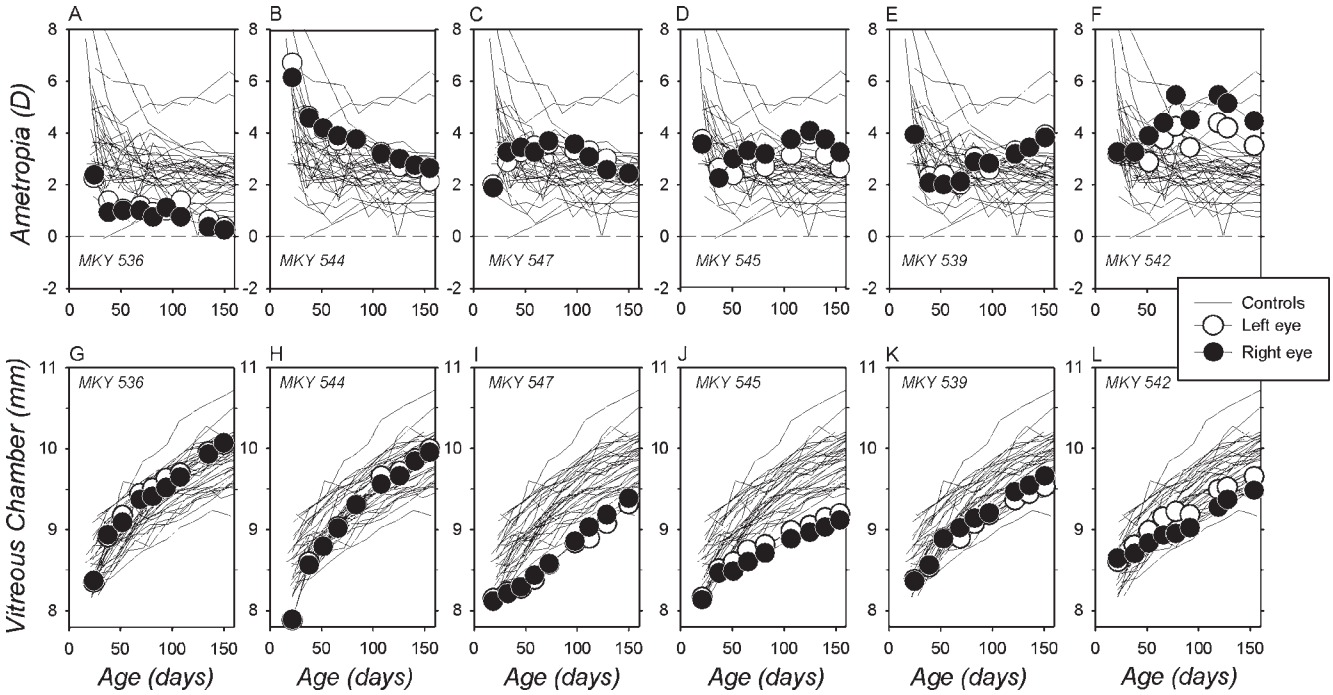

Figure 6. Spherical-equivalent, spectacle-plane refractive corrections (*top*) and vitreous chamber depths (*bottom*) plotted as a function of age for the right (*filled symbols*) and left eyes (*open symbols*) individual −3 D/pL 67:33 lens-reared monkeys. See Figure 2 for details.

1.09 D versus 55.74 ± 1.68 D, $P = 0.29$–0.63), anterior chamber depths (3.04 ± 0.12 mm to 3.05 ± 0.16 mm versus 3.06 ± 0.30 mm, $P = 0.72$–0.92), or crystalline lens thicknesses (3.65 ± 0.17 mm to 3.71 ± 0.04 mm versus 3.63 ± 0.22 mm, $P = 0.06$–0.83) between the −3 D/pL dual-focus groups and age-matched controls.

On the other hand, refractive development for most animals in the −3 D/pL 50:50 and 67:33 groups was different from that observed in the monkeys reared with FF–3D lenses. Whereas 9 of the 10 FF–3D monkeys developed ametropias that were more myopic than 90% of the normal control monkeys, only 2 of the 12 −3 D/pL monkeys exhibited evidence of compensating myopia. At the end of the treatment period, the median and average refractive errors for the monkeys in the 50:50 (+3.13 D and +2.93 ± 1.76 D) and 67:33 −3 D/pL groups (+2.94 D and +2.80 ± 1.45 D) were significantly more hyperopic than those for the monkeys reared with FF–3D lenses (–0.78 D and –0.34 ± 1.67 D, $P = 0.002$–0.006).

The axial nature of the refractive errors that were produced by the dual-focus lenses is emphasized in Figure 8, in which the end-of-treatment ametropias are plotted as a function of the ratio of axial length and the corneal radius of curvature (AL/CR ratio) for individual animals. Because corneal power was unaffected by our rearing strategies, using the AL/CR ratio provides a more valid indication of the contribution of axial changes to the eye's final ametropia. In essence, the AL/CR ratio reduces the variance between animals due to differences in absolute corneal power. There was a strong negative correlation between the final ametropia and the AL/CR ratio ($P = 0.0001$) demonstrating that the relative hyperopia observed in most animals reared with dual-focus lenses was associated with shorter axial lengths.

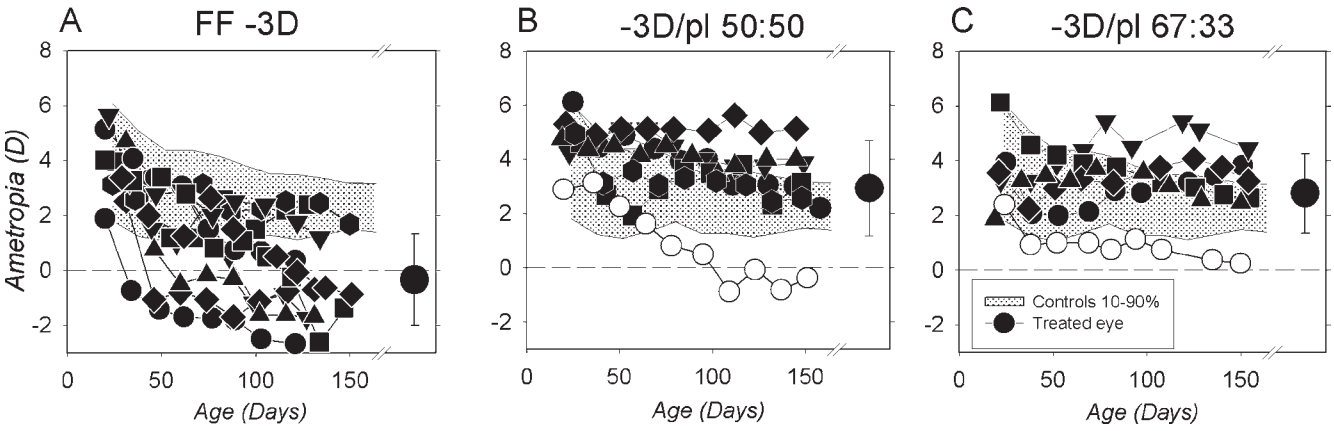

Figure 7. Refractive errors for the right eyes plotted as a function of age for all of the individual lens-reared monkeys in the FF–3D, −3 D/pL 50:50 and 67:33 subject groups (**A**–**C**). The *large symbols to the right* in each panel represent the averages (±SD) for the lens-reared monkeys at the end of the treatment period. See Figure 5 for details. In (**B**) and (**C**), the *filled and open symbols* represent animals that appeared to compensate for the anterior and posterior focal planes, respectively.

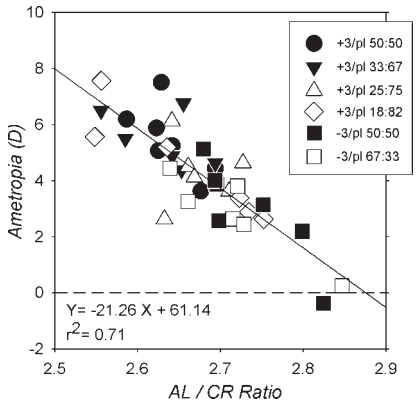

Figure 8. Refractive errors are plotted as a function of the AL/CR for the right eyes of all the monkeys treated with dual-focus lenses. The *circles*, *down triangles*, *up triangles*, *diamonds*, and *filled* and *open squares* represent data for the monkeys treated with the +3 D/pL 50:50, 33:67, 25:75, 18:82, −3 D/pL 50:50, and 67:33 lenses, respectively. The *solid line* is the best-fitting regression line.

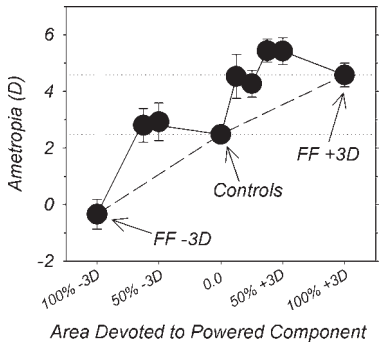

Figure 9. The average ametropias (±SEM) plotted as a function of the percentage of surface areas that was devoted to the powered portions of the treatment lenses. The control monkeys reared with unrestricted vision are represented at the 0 point on the abscissa. The monkeys reared with the FF−3D and FF+3D single-vision lenses are represented at the "100% −3 D" and "100% +3 D" positions, respectively. The dual-focus groups are positioned according to the proportion of lens surface areas devoted to the −3 D and +3 D power zones.

Discussion

The main finding from this study was that when infant monkeys experience competing defocus signals, ocular growth and refractive development were typically directed toward the more anterior focal plane, even when the saliency of the more posterior focal plane was much greater than that for the more anterior focal plane. This conclusion is supported by the fact that at the end of the lens-rearing period the median and mean refractive errors in all of the +3 D/pL lens groups were statistically similar to those for monkeys reared with FF+3D lenses and significantly more hyperopic than the refractive errors of control monkeys reared with unrestricted vision. Similarly, the end-of-treatment refractions for both of the −3 D/pL lens groups corresponded statistically to the more anterior focal plane and were significantly more hyperopic than the ametropias in monkeys reared with FF−3D lenses. This pattern of results emphasizes that relative myopic defocus produces a very strong signal to reduce ocular growth. In this respect, previous experiments in chickens and monkeys have demonstrated that myopic defocus has a greater effect on refractive development than an equivalent amount of hyperopic defocus when the competing signals are interleaved and presented successively over time.[57,61]

Previous studies involving chickens,[52] marmosets,[53] and guinea pigs[54] investigated the effects of optically imposed simultaneous competing defocus on refractive development and in some respects the results are similar to those obtained in this study. In marmosets reared with monocular dual-focus contact lenses (+5/−5 D with approximately equal area ratios), the treated eyes became relatively more hyperopic than their fellow eyes, and the degree of hyperopia was equivalent to that produced by +5 D single-vision contact lenses. Thus, as in this study, refractive development was dominated by the anterior focal plane; however, the degree of hyperopia that the young marmosets developed did not completely compensate for the magnitude of the imposed myopic defocus.[53] Chickens reared with dual-focus spectacle lenses in which each of the two power zones made up equal surface areas also demonstrated a hyperopic bias during refractive development (i.e., the imposed myopic defocus appeared to dominate refractive development). However, the degree of hyperopia was always lower than that produced by a positive-powered single-vision lens that had the same power as the positive component of the dual-focus lenses.[52]

In chickens and guinea pigs, altering the surface area ratios of the constituent components of dual-focus lenses produced different patterns of results than those we observed in monkeys. In particular, in chickens, as the relative surface area of the more positive-powered component of the dual-focus lenses was reduced, the average refractive errors became increasingly biased toward the more negative-powered component.[52] In other words, refractive development was increasingly biased toward the more posterior focal plane; however, the degree of myopia was always less than that produced by single-vision lenses of the same negative power. In guinea pigs reared with dual-focus lenses that had equal surface areas devoted to the two power zones, refractive development appeared to be directed to the dioptric midpoint between the imposed focal planes. When the areal balance between the two power zones was altered, refractive development appeared to be directed to the weighted average of the two powers.[54] The results in chickens and guinea pigs suggest that the emmetropization process integrates the sign and magnitude of competing defocus signals. In guinea pigs, it appears that refractive development is directed to the focal plane associated with the linear average of the two power zones in a dual-focus lens and that alterations in the surface area ratio between the two power zones shifts the target image plane by a proportional amount. In chickens, the weighting of the competing defocus signals also varies with the area ratio for the two power zones, but in a nonlinear manner. In contrast, there was no compelling evidence for a comparable averaging process in monkeys.

In Figure 9, the average (±SEM) refractive errors obtained at an age equivalent to the end of the lens-rearing period are plotted as a function of the percentage of the surface area that was devoted to the powered portion of the treatment lenses. The control monkeys reared with unrestricted vision are represented at the 0 point on the abscissa. The monkeys reared with −3 D and +3 D single-vision lenses are represented at the "100% −3 D" and "100% +3 D" positions, respectively. The dual-focus lens groups are positioned according to the proportion of lens surface area devoted to the −3 D and +3 D power zones. If monkeys integrated the competing defocus signals in a simple linear manner, as observed in guinea pigs,[54] the dual-focus data should have fallen along the dashed lines that connected the data points for the control monkeys and the monkeys treated with single-vision lenses. Instead, however, the ametropias for all of the dual-focus groups were clustered in two groups around

the dotted lines, which represent the expected refractive errors for zero and +3 D single-vision lenses.

Examining the data for individual animals reared with dual-focus lenses also emphasizes that emmetropization always appeared to be directed toward one of the two focal planes associated with the treatment lenses. For example, in animals reared with −3 D/pL lenses, one subject in each power ratio group failed to maintain relative hyperopic errors associated with the zero-powered lens component. In both cases, the refractive errors of these animals stabilized during the lens-rearing period at relative myopic levels that were near the mean for monkeys reared with −3 D single-vision lenses. And although the average ametropia for the +3 D 18:82 lens group was comparable to the hyperopic refractive errors produced by +3 D single-vision lenses, inspection of Figure 4 suggests that there are two distinct response types in this subject group. Specifically, at the end of the treatment period, the animals illustrated in Figures 4A through 4C exhibited refractive errors that were comparable to those of the control monkeys, suggesting that for these three monkeys, emmetropization was directed toward the more posterior focal point. It is interesting that for subjects MKY 593 and MKY 595 (Figs. 4B, 4C), early refractive development shifted in a hyperopic direction, as if emmetropization was being directed toward the more anterior focal plane. However, approximately midway through the rearing period, presumably because of the reduced strength of the myopic defocus signal, emmetropization for these two monkeys was subsequently redirected to the more salient posterior focal plane. McFadden et al.[54] also observed somewhat similar intergroup variations in guinea pigs. Even though the average ametropia exhibited by guinea pigs reared with dual-focus lenses appeared to correspond to the dioptric midpoint of the two power zones, they observed that two of the nine guinea pigs in each dual-focus lens groups (+5/−5 50:50 and 40:60) developed hyperopic ametropias that were comparable to those normally produced by equivalent positive-powered single-vision lenses (i.e., emmetropization appeared to be directed toward the more anterior focal plane in these four animals).

In this respect, some of the apparent differences between species may reflect basic methodological issues. It is important to note that the power components of the dual-focus lenses that we used in this study were lower than those used in all of the previous studies.[52–54] We specifically used relatively low powers (+3 D or −3 D) because these powers imposed refractive errors that were well within the operational range of the emmetropization process,[31] which may have resulted in the more consistent evidence for growth toward one of the two image planes that we observed in monkeys.

The alterations in refractive errors produced by the dual-focus lenses, like those produced by single-vision lenses in infant monkeys,[31] were associated with alterations in vitreous chamber depth. There were no indications that corneal power or any other axial component was affected by the competing defocus signal (note that we did not assess choroidal thickness). The axial nature of the refractive errors induced in monkeys by dual-focus lenses was qualitatively similar to that observed in marmosets,[53] guinea pigs,[54] and chickens[52] reared with dual-focus lenses.

Clinical Implications

The results from recent clinical trials indicate that optical correction strategies that simultaneously impose relative myopic defocus over a large proportion of the visual field (e.g., multifocal contact lenses and orthokeratology) are effective in slowing the progression of myopia in children. In the trial most relevant to this investigation, dual-focus, soft contact lenses that used Fresnel concepts (Defocus Incorporated Soft Contact lenses, "DISC" lenses) were shown to significantly reduce myopia progression relative to single-vision lenses.[41] Specifically, these treatment lenses consisted of a small central correction zone surrounded by alternating concentric power zones that either corrected the eye's distance refractive error or induced +2.50 D of relative myopic defocus. Equal surface areas were devoted to the alternating power zones (i.e., these lenses were analogous to the 50:50 +3 D/pL lenses used in this study). If our results from monkeys can be extrapolated to children, the pattern of results that we obtained using dual-focus lenses with different surface area ratios suggests that it should be possible to reduce the area of the DISC lenses (or of any concentric bifocal lenses) devoted to imposing relative myopic defocus without reducing the ability of the lenses to reduce myopia progression. In infant monkeys, the more anterior focal plane consistently dominated refractive development even when the plano zones were twice or three times as large as the positive-powered treatment zones (i.e., the 33:67 and 25:75 +3 D/pL lenses).

If treatment efficacy is not significantly affected, reducing the surface areas of multifocal treatment lenses that are devoted to producing relative myopic defocus would have several potential benefits. The most direct benefit would be an overall improvement in distance vision. For example, the DISC lenses used in clinical trials,[41] like many traditional simultaneous bifocal contact lenses, reduced the best-corrected distance visual acuity, particularly for acuities measured with low-contrast targets.[70] Decreasing the saliency of the myopic focal plane would improve overall image quality for distance vision. A potential indirect benefit would be an increase in the average daily wearing time. It seems reasonable to suppose that patients are likely to wear lenses that provide better-quality vision for longer periods each day. This is potentially important because the percentage reduction in myopic progression produced by DISC lenses increased significantly with the average daily wearing time.[41]

As discussed above, there was little evidence that the mechanisms regulating ocular growth in our monkeys integrated or averaged the defocus signals produced by dual-focus lenses. The fact that refractive development consistently targeted either the anterior, and in a few cases the posterior focal planes, but not the weighted average of the two focal planes, also has implications for optical treatment strategies. This pattern of results suggests that as long as the imposed myopic defocus reaches a given strength that you will get maximal treatment effects for that individual. If the strength of the myopic defocus signal, which in dual-focus lenses is likely to be dependent on the magnitude of defocus and the area of the lens surface devoted to the more positive-powered component, does not reach this critical threshold, then there will be little or no treatment effects. In other words, the treatment effects are not likely to be graded, but rather our results suggest that they will follow an all-or-none scenario. In this respect, to optimize dual-focus–like treatment lenses, it will be necessary to know the critical area ratio that is sufficient for the anterior focal plane to dominate eye growth, which is likely to depend on the "add" power of these treatment lenses.

It is reasonable to argue that multifocal lenses will have their maximum benefit if children do not use the "add" for near vision and in this respect there is some evidence that suggests that children do not take advantage of the add power in multifocal contact lenses to reduce accommodative efforts during near viewing.[38,41] As a consequence, the more positive-powered zones of these lenses consistently produce myopic defocus at all viewing distances, which is presumably the signal that is critical for slowing myopia progression. However, if children do use the add for near vision, then their eyes would experience hyperopic defocus during near work, which in

laboratory animals is a strong stimulus for ocular growth.[25–28,30,31] However, in our animals reared with −3 D/pL lenses, which presumably produced some hyperopic defocus at all viewing distances, refractive development was still dominated by the more anterior focal plane even when the negative power zones were twice as large as the plano power zones. These results indicate that regardless of a child's near-viewing strategy, it is unlikely that multifocal treatment lenses that included positive add components would produce an effective signal to stimulate ocular growth.

The results of this study add to the large and growing body of evidence, from both laboratory animals[32–35] and human trials,[36–41] that myopic defocus can slow axial growth. In particular, the results from this study show that even relatively weak myopic defocus signals that are distributed across a large proportion of the visual field are effective in slowing axial growth. A logical implication of these results is that either simply leaving myopic eyes uncorrected or prescribing spectacles for myopic eyes that do not fully correct the distance manifest ametropia would produce myopic defocus, at least during distance viewing, and potentially slow myopia progression. Unfortunately, relatively little is known about the course of myopia when an individual is uncorrected or when the myopic correction is not worn on a full-time basis. The effects of partial wearing schedules (e.g., wearing myopic corrections for distance viewing only)[71] or simply not correcting the eye (Li L, et al. *IOVS* 2013;54:E-Abstract 5718) have been investigated in prospective studies. Although there was no evidence that either strategy altered myopia progression, these studies were confounded by low degrees of compliance. For example, only 10 of the 32 individuals randomized into the uncorrected subject group in the Li et al. study (Li L, et al. *IOVS* 2013;54:E-Abstract 5718) were compliant; the other "uncorrected" subjects either dropped out or wore spectacles, citing blurred vision as the reason. In a retrospective analysis of lens-wearing habits, Ong et al.[72] reported that myopic individuals categorized as nonwearers showed marginally slower rates of progression than full-time lens wearers. However, these comparisons were compromised by low subject numbers (only five nonwearers) and by significant age differences between the two groups. Nevertheless, eye care practitioners do encounter children with moderate degrees of previously undetected myopia, suggesting that the myopia in these individuals had progressed even though the child was uncorrected.

More recent studies have investigated the effects of undercorrecting strategies, which are more amenable to human investigation than simply not correcting myopic errors. Interestingly, there was no evidence that undercorrecting myopia reduced myopia progression[73,74] and there were indications that in comparison with full-correction spectacles, undercorrection strategies may have actually increased myopia progression.[75,76] Why do uncorrected and undercorrected eyes continue to exhibit myopia progression? Although it has been suggested that it is not valid to apply the results from animal studies to humans[73] and that the vision-dependent mechanisms that regulate ocular growth in myopic children may not be able to accurately detect the sign of defocus,[75] there are a number of other possibilities. For example, it seems more likely that undercorrection strategies do not reduce myopic progression because the degree of myopic defocus is relatively small (e.g., −0.50 to −0.75 D), largely restricted to the central retina, and occurs only for distant fixation distances. The potential therapeutic effects of undercorrection strategies are restricted to the central retina because myopic eyes typically exhibit substantial amounts of relative peripheral hyperopia (at least in the horizontal meridian)[77–79] and traditional negative spectacle lenses induce additional amounts of relative peripheral hyperopia[80,81] (i.e., undercorrection strategies do not produce myopic defocus over a very large area of the retina, particularly during near work). This idea is supported by the fact that the effectiveness of optical strategies to slow myopia appears to be related to the amount of the retina that is potentially influenced by imposed myopic defocus.[22] Similarly, uncorrected eyes would experience myopic defocus only during distance viewing and would be likely to experience peripheral hyperopic defocus during near viewing. However, it is also possible that failure to fully correct myopic errors alters the fixation and viewing behaviors of children in ways that allow them to avoid experiencing myopic defocus and/or in ways that normally promote myopia progression. For instance, to avoid blurred vision, uncorrected and undercorrected children may spend more time performing near work,[82,83] more time indoors in environments that frequently produce large amounts of hyperopic defocus,[84] and less time outdoors.[85] As a consequence, based on the available data, it seems prudent to ensure that myopic eyes are fully corrected for distance vision using correcting strategies that also impose relative myopic defocus across a large part of the visual field without significantly compromising central vision.

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