Effects of Optically Imposed Astigmatism on Emmetropization in Infant Monkeys

Chea-Su Kee, Li-Fang Hung, Ying Qiao-Grider, Austin Roorda, and Earl L. Smith III

Purpose. Although astigmatism is prevalent during early infancy, the influence of astigmatism on early refractive development is unclear. This study was undertaken to determine the effects of astigmatism on emmetropization in monkeys.

Methods. Infant rhesus monkeys ($n = 39$) were exposed to optically simulated astigmatism in one or both eyes from approximately 1 to 4 months of age. With-the-rule, against-the-rule, and oblique astigmatisms were optically simulated by appropriately orienting the principal meridians of the spherocylindrical treatment lenses (+1.50 −3.00 D × 90°, 180°, 45°, or 135°; i.e., +1.50 and −1.50 D powers in the two principal meridians). Refractive development was assessed every 2 to 3 weeks by cycloplegic retinoscopy, keratometry and corneal videotopography, and A-scan ultrasonography. Data from 19 control monkeys, including 3 animals that were reared with binocular plano lenses, were used for comparison purposes.

Results. Most of the cylinder-lens–reared monkeys, regardless of the orientation of the imposed astigmatism, showed clear signs of either hyperopic or myopic growth compared with control monkeys. The distributions of refractive error and vitreous chamber depth both showed bimodal patterns that differed from normal by amounts equivalent to the optical powers of the principal meridians of the treatment lenses. More frequently, refractive development was biased toward the eye's least-hyperopic focal plane. The refractive changes were mainly axial. After lens removal, the lens-reared monkeys recovered and as a group exhibited refractive errors and axial dimensions similar to those in control monkeys.

Conclusions. In the presence of significant amounts of astigmatism, emmetropization is directed toward one of the two focal planes associated with the astigmatic principal meridians and not the circle of least confusion. These results suggest that the mechanisms responsible for emmetropization are insensitive to stimulus orientation and the global form of the retinal image. It appears that emmetropization seeks out the image plane that contains the maximum effective contrast integrated across spatial frequency and stimulus orientation. (*Invest Ophthalmol Vis Sci.* 2004;45:1647–1659) DOI:10.1167/iovs.03-0841

As a group, neonates exhibit a large range of refractive errors, but with time, both eyes of most individuals grow in a highly coordinated fashion toward the ideal refractive state, a process called emmetropization.[1,2] Several lines of evidence indicate that the phenomenon of emmetropization is a vision-dependent process. In particular, in several animal species, optically imposing hyperopia or myopia with spectacle lenses has been shown to produce compensating changes in axial growth that eliminate the imposed spherical refractive errors (chickens,[3] tree shrews,[4] and New World [marmosets][5] and Old World [macaque] monkeys[6,7]). Thus, optical defocus can guide early ocular growth in a manner that eliminates the spherical refractive errors that are common in neonates.

However, in human infants, it is unusual for either myopia or hyperopia to exist in isolation. Instead, a high proportion of infants also exhibit significant amounts of astigmatism.[8–15] The prevalence of significant astigmatism (e.g., >1.00 D) in human infants is typically highest at approximately 10 weeks of age and then decreases with age to adult levels by school age.[8,11,16] Although astigmatism is very common during early development, the influence of astigmatism on emmetropization is unknown. The "sphericalization" that occurs during infancy does not appear to be an active vision-dependent process analogous to emmetropization, because optically imposing astigmatism on infant monkeys does not produce compensating ocular changes that eliminate the imposed astigmatic error.[17] However, it is reasonable to suppose that astigmatism could influence emmetropization in several ways.

The chronic blur associated with astigmatism could interfere with emmetropization. Even small astigmatic errors can produce functionally significant alterations in image quality[18–20] and, like the image degradation produced by form deprivation, the defocus produced by uncorrected astigmatism cannot be eliminated by accommodation or by changes in viewing distance. Therefore, the effects of astigmatism are consistent over time (i.e., chronic blur), which is an important factor in weighing the potential effects of a visual perturbation on ocular growth[4,21–23] (Kee CS, et al. *IOVS* 2002;43:ARVO E-Abstract 2925). Moreover, because the mechanisms responsible for form deprivation myopia are sensitive to small amounts of image degradation,[24,25] it is reasonable to argue that astigmatism promotes excessive axial elongation and myopia in the developing eye. This hypothesis is supported by observations in older children that indicate that astigmatic children are on average more myopic than nonastigmatic children and that the amount of astigmatism is positively correlated with the degree of myopia in children.[26]

The presence of astigmatism could, however, facilitate emmetropization. Campbell and Westheimer[27] have shown that in the absence of cues from spherical and chromatic aberration, an optically imposed astigmatism greatly improves the ability of the eye to accommodate in the appropriate direction

From the College of Optometry, University of Houston, Houston, Texas.

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Corresponding author: Chea-Su Kee, University of Houston, College of Optometry, 505 J. Davis Armistead Building, Houston, TX 77204-2020; ckee@mail.uh.edu.

in response to hyperopic versus myopic defocus. Moreover, it has also been argued that the presence of astigmatism can help the eye to focus accurately for the circle of least confusion by effectively reducing the accommodative dead zone.[28] Thus, the presence of astigmatism could enhance emmetropization by providing information on the sign of defocus and/or by improving the accuracy of accommodation or possibly the precision of the emmetropization process itself.

An equally important issue is the end point or target refractive error for emmetropization when an eye has astigmatism. In an astigmatic eye, the emmetropization process could direct axial growth to bring one of the two orthogonal focal lines or an intermediate plane, such as the circle of least confusion, into focus on the retina. The accommodative system is confronted with a similar challenge in an astigmatic eye. It is reasonable to argue that the eye should emmetropize to the circle of least confusion because this end point would yield comparable image qualities for all objects. However, because of a variety of factors, such as the eye's spherical refractive state and accommodative behavior, the magnitude of change required to bring a given image plane into focus, the predominance of specific contours in the environment, and the presence of meridional sensory anisotropies, it is difficult to predict how an astigmatic error would influence the end point for emmetropization.

A direct assessment of the effects of astigmatism on emmetropization can be obtained by examining the consequences of an imposed astigmatism on refractive development. In several studies, cylinder lenses have been used for optical imposition of astigmatic errors on developing chicks.[29–32] Although investigators in all of these studies reported that an optically imposed astigmatism altered early refractive development, there were inconsistencies between these studies concerning the end point for emmetropization. Whereas some found that the chick eye grew toward the circle of least confusion,[31] others reported that emmetropization was directed toward one of the astigmatic focal lines.[30] To date, the effects of astigmatism on emmetropization have not been systematically investigated in mammals. In several studies, researchers have reared a small number of infant cats or monkeys with imposed astigmatic errors.[33–35] However, these studies focused on the behavioral and neurophysiological consequences of early astigmatism, and little attention was devoted to potential alterations in refractive development. The purpose of this study was to characterize systematically the effects of astigmatism on emmetropization in infant macaques.

METHODS

Subjects

The subjects were 58 infant rhesus monkeys (*Macaca mulatta*). The animals were obtained at 1 to 3 weeks of age and were housed in our primate nursery, which was maintained on a 12-hour light–dark lighting cycle. After the initial biometry measurements, these monkeys were randomly assigned to either the control ($n = 19$) or the cylinder-lens–reared group ($n = 39$). All the rearing and experimental procedures, which have been described previously,[7,17] were reviewed and approved by the University of Houston's Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Visual Manipulations

Optically Imposed Astigmatism: Cylinder-Lens–Reared Group. For optical simulation of astigmatism, we used a lightweight helmet to secure spherocylindrical spectacle lenses in front of one or both eyes of infant monkeys. The principal meridians of the treatment lenses had refracting powers of +1.50 and −1.50 D, and thus the lenses altered the eye's effective astigmatism by 3.00 D without changing the eye's spherical-equivalent refractive error. The direction or axis of the optically imposed astigmatism was determined by the position of the axis of the treatment lenses. To simulate with-the-rule (WTR) astigmatism, the minus-cylinder axis of the treatment lens was oriented at 90°. Consequently, the positive- and negative-powered principal meridians were positioned at 90° and 180°, respectively. Securing a treatment lens' minus-cylinder axis at 180° imposed against-the-rule (ATR) astigmatism. Oblique astigmatism was induced by positioning the axis at either 45° or 135°.

The lens-rearing procedures were initiated at approximately 3 weeks of age (mean ± SD = 23.2 ± 3.0 days; range, 19–30 days) and the infants wore the helmets and treatment lenses continuously for an average of 109 ± 12.6 days. The rearing period, which corresponded approximately to the period between 3 and 12 months of age in human infants,[36] encompassed most of the rapid period of ocular growth when spherical treatment lenses can readily and predictably alter emmetropization in infant monkeys.[6,7] After lens removal, the monkeys were housed in our standard laboratory caging area and allowed unrestricted vision.

Several different cylinder-lens–rearing regimens were used to investigate the effects of astigmatism on emmetropization. For each of the basic lens-rearing strategies described in the following sections we studied both WTR and ATR astigmatism, and for the binocular rearing regimen we also examined the effects of oblique astigmatism. We were especially interested in comparing the effects of WTR and ATR astigmatism because observations in humans suggest that the direction of astigmatism may determine whether astigmatism disrupts emmetropization. In particular, it has been reported that infants who experience ATR astigmatism early in life are more likely to develop myopia later in childhood than infants who experience early WTR astigmatism.[37,38]

Monocular Astigmatism. Twelve infants were reared with cylinder lenses in front of one eye and a 0-power lens in front of the fellow, nontreated eye. In a given animal, the axis of the treatment lens was oriented to simulate either ATR ($n = 6$) or WTR ($n = 6$) astigmatism. Because normal infant monkeys exhibit very similar refractive errors in their eyes throughout early emmetropization, the interocular comparisons available with this rearing strategy provided a very sensitive measure of treatment-related alterations in refractive development.

Symmetrical Binocular Astigmatism. To avoid the potentially confounding interocular effects associated with monocular treatment regimens[6,39] and to ensure that the treated animals actively fixated with eyes that had imposed astigmatic errors, 19 infants were reared with cylinder lenses in front of both eyes. The axes of the treatment lenses were oriented to produce WTR ($n = 7$), ATR ($n = 6$), or oblique astigmatism ($n = 6$) in both eyes of a given infant. Because oblique astigmatism is frequently mirror symmetric in the two eyes,[40,41] the axes of the treatment lenses for the monkeys in the oblique astigmatism group were oriented at 45° and 135° for the right and left eyes, respectively.

Alternating Occlusion and Asymmetrical Monocular Astigmatism. To compare the effects of WTR and ATR astigmatism within the same subject, eight infant monkeys were treated with cylinder lenses that imposed ATR astigmatism in their right eyes and WTR astigmatism in their left eyes. To ensure that these animals actively fixated with each eye, each eye was alternately occluded with a black patch for half the daily light cycle, with the occluder being switched between the eyes midway through the light cycle.[42] Given the temporal integration properties of the mechanisms that mediate form deprivation, it is unlikely that occluding each eye for half the day significantly altered refractive development.[42,43]

Effective Astigmatic Errors. In a previous study, we documented the optical effects imposed by these cylinder lenses on the refractive states of our infant monkeys and the subsequent alterations in the effective astigmatic errors that took place during the treatment period.[17] At the start of the rearing period, our treated monkeys were

moderately hyperopic (mean = 4.36 D; median = 4.25 D; range, 1.75–7.25 D) and they had little or no refractive astigmatism (mean = 0.15 D; median = 0.13 D; range, 0.00–0.50 D). Consequently, for all but one animal, the treatment lenses essentially imposed 3.00 D of compound, hyperopic astigmatism (mean ± SD = 3.01 ± 0.17 D; range, 2.66–3.49 D), the most common form of astigmatic refractive error observed in human infants.[2,9,15,44] The only exception was a monkey that had a small amount of hyperopia and the treatment lens effectively rendered one meridian emmetropic, resulting in a simple hyperopic WTR astigmatism. During the treatment period, many of our cylinder-lens–reared monkeys showed development of significant amounts of corneal and refractive astigmatism. However, the axis of this ocular astigmatism, which was typically oblique and mirror symmetric in the two eyes, was not appropriate to compensate for the astigmatic errors imposed by the treatment lenses. There were also no significant differences in the magnitude of either refractive or corneal astigmatism in the monkeys that experienced ATR, WTR, or oblique astigmatism.[17] As a result, the degree of astigmatism that the animals experienced while viewing through the treatment lenses was not diminished over time. At the end of the treatment period, the average degree of effective astigmatism was actually slightly, but significantly, higher in comparison to that at the start of lens wear (mean ± SD = 3.51 ± 0.74 D). Only 1 of the 47 treated eyes exhibited a decrease in effective astigmatism that was larger than 0.50 D. The mismatch between the axes of the treatment lenses and the ocular astigmatism that developed in some animals resulted in a small shift in the axis of the effective astigmatism produced by viewing through the treatment lenses (median = 6.7; range, 0–23.8°). However, in no case did these small changes in effective axis fundamentally alter the directional classification of an imposed astigmatic error (i.e., infants that were treated with lenses that imposed WTR astigmatism still experienced WTR astigmatism at the end of the treatment period). The key point is that the direction and magnitude of imposed astigmatism was basically stable throughout the period of lens wear.

Unrestricted/Normal Vision: Control Group. The control group included 16 infant monkeys that were reared with normal unrestricted vision and 3 infants that were reared wearing helmets that held 0-power lenses in front of both eyes. Data on the refractive development of the normal and plano-control monkeys have been reported.[7,17]

Ocular Biometry

Each subject's refractive errors, corneal curvatures, and eyes' axial dimensions were measured at the start of lens wear and then periodically throughout the treatment and subsequent recovery periods. For 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 cycloplegled (1% tropicamide).

The eye's spectacle plane refractive corrections were measured along the pupillary axis independently by two investigators who used a streak retinoscope and hand-held trial lenses. An eye's refractive error was defined as the mean of these measurements specified in minus cylinder form. To determine the repeatability of our retinoscopy measurements, we analyzed all the spherical-equivalent refractive error data available from 10 control monkeys after 53 weeks of age, when refractive errors normally stabilize in rhesus monkeys.[36] The mean absolute difference for all pairs of consecutive readings (n = 226) was 0.24 D (95% limits of agreement = −0.60 to +0.60 D; median = −0.03 D; range, −0.81 to +0.88 D). The great majority (91.6%) of the consecutive readings were within ±0.50 D, indicating that our retinoscopy measurements were reasonably repeatable.

Corneal refracting power was determined with one of two instruments that provided repeatable and comparable measures of corneal curvature in infant monkeys.[45] In each animal, we first attempted to measure corneal radius using a hand-held keratometer that was aligned on the eye's pupillary axis (Autokeratometer; Alcon Systems, Inc., St. Louis, MO). It was assumed that the cornea's principal meridians were orthogonal, and corneal refracting power was calculated assuming a refractive index of 1.3375. The corneal powers reported for individual animals represent the average of three readings.[46] Some of the younger infants initially had corneal radii that were outside the measurement range of our hand-held keratometer. In these monkeys, corneal refracting power was assessed with a corneal video-topographer (EyeSys 2000; EyeSys Technologies Inc., Houston, TX). At least two "simulated K" readings computed for the central 3 mm of the cornea were averaged to represent the corneal refracting power.[46]

The eye's axial dimensions were measured by A-scan ultrasonography. To provide data comparable to that from our previous studies, we determined vitreous chamber depth using a system with a 7-MHz transducer (Image 2000; Mentor, Norwell, MA). Ten separate measurements were averaged, and the intraocular distances were calculated, using a weighted average velocity of 1550 m/sec. To obtain more precise measures of the anterior segment, anterior chamber depth and lens thickness were measured with a 30-MHz A-scan system that we have described in detail previously.[47]

To identify the induced astigmatic errors in infant monkeys during the lens-rearing period, we used an infrared videoretinoscope similar to that described by Schaeffel et al.[48] and a commercially available autorefractor (Power Refractor; Multichannel Systems, Reutlingen, Germany). Infrared videoretinoscopy was performed at an 82-cm working distance with the animal viewing through the astigmatic lenses (for details, see Ref. 6). Because our infrared videoretinoscope could only refract one meridian at a time, we refracted the four meridians of interest (0°, 45°, 90°, and 135°) by rotating the position of the infrared light-emitting diodes (LEDs). The direction that produced the smallest crescent in the retinoscopic reflex was taken as the meridian that was in focus. The power refractor was placed at a 1-m working distance while the monkeys were held by one of the examiners in a dimly lighted room. We chose the "complete refraction" mode and used a calibration factor for macaques that was determined by the manufacturer. The refractive status measured with this mode was then used to see which meridian was focused on the retina (within ±0.50 D). Data from both instruments indicated that the astigmatic lenses produced constant astigmatic blur for both monocularly and binocularly lens-reared monkeys (i.e., there was no evidence of astigmatic accommodation). The astigmatic error typically did not change in direction throughout an observation session (i.e., the animals consistently accommodated for the same meridian). In most cases, the monkeys showed the smallest refractive error along the least hyperopic meridian, indicating that the monkeys typically postured their accommodation for the +1.50-D meridian of the treatment lens.

Statistical Analysis

Statistical analyses were performed on computer (Minitab ver. 12.21; Minitab Inc., State College, PA). Comparisons between control and experimental groups were made by two-tailed, two-sample t-tests. Comparisons between the two eyes of individual monkeys were performed using a paired t-test. Comparisons across groups were made by one-way ANOVAs. To define the expected longitudinal changes in refractive error and vitreous chamber depth, we generated growth curves for our control monkeys by using a locally weighted regression scatterplot-smoothing algorithm (implemented with SPLUS 2000 statistical software; MathSoft, Inc., Cambridge, MA), the details of this procedure have been described elsewhere.[36]

Results

In studies of emmetropization, refractive errors are typically specified in terms of the spherical-equivalent spectacle plane refractive correction. Spherical-equivalent measures are appropriate in many respects. However, when there are significant amounts of astigmatism, the use of spherical-equivalent measures could confound attempts to assess the course of em-

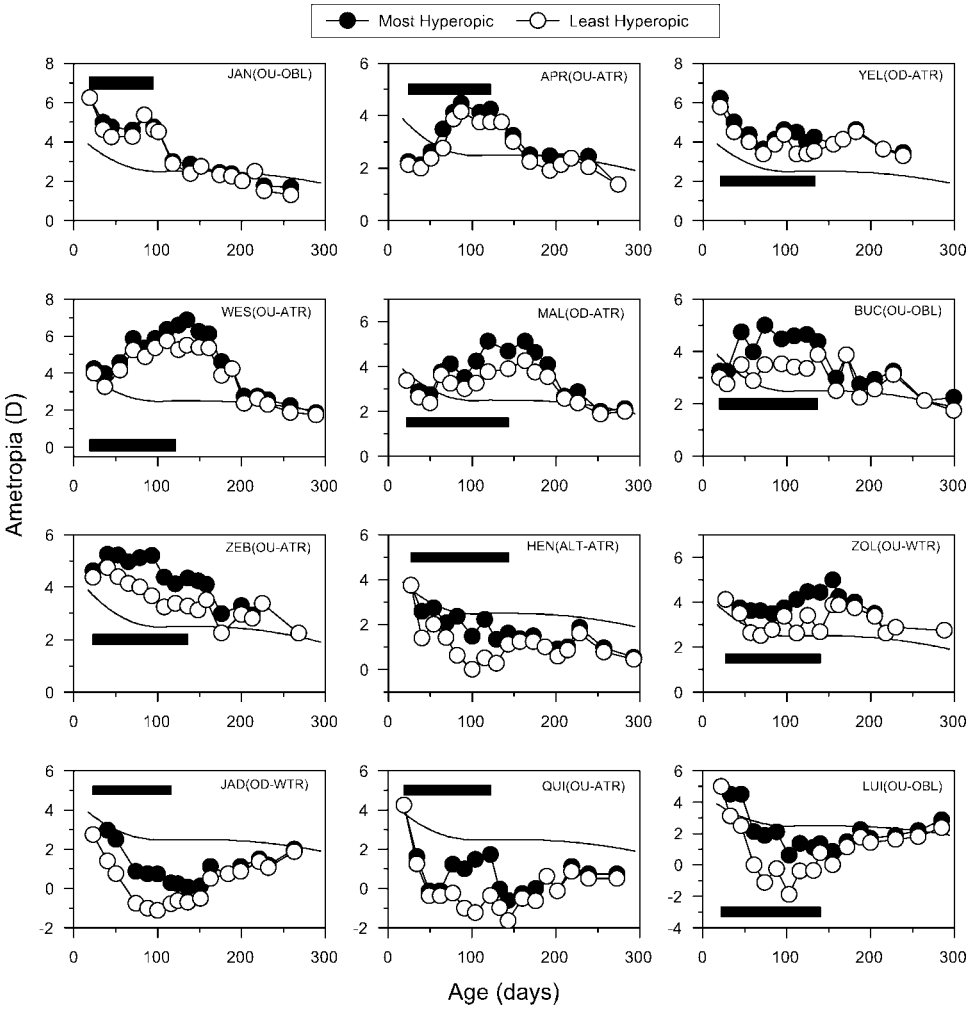

FIGURE 1. Refractive errors of the most hyperopic and the least hyperopic meridians are plotted as a function of age in 12 representative monkeys that exhibited various degrees of astigmatism during the lens-rearing period. *Solid lines without symbols*: age-dependent changes in spherical-equivalent refractive errors in the 19 control monkeys; *horizontal bars*: lens-rearing periods. The lens-rearing regimen and the orientation of the treatment lens for each monkey are indicated in parentheses beside the three-letter-name code. OD, monocular group; OU, binocular group; ALT, alternating-occlusion group; WTR, with-the-rule; ATR, against-the-rule; OBL, oblique.

metropization. Given that a significant number of our cylinder-lens–reared monkeys exhibited development of substantial astigmatic errors during the treatment period, it was important to consider whether spherical-equivalent measures were suitable for assessing emmetropization in our experimental monkeys or whether we should consider the principal meridians separately.

Figure 1 illustrates the refractive errors of the most hyperopic (filled symbols) and the least hyperopic (open symbols) principal meridians plotted as a function of age for the right or treated eyes of 12 representative cylinder-lens-reared monkeys. These monkeys were chosen because as a group they exhibited the range of astigmatic errors found in our lens-reared monkeys. The plots are arranged from top left to bottom right, according to the maximum amount of refractive astigmatism that the monkey exhibited during the treatment period (range, 0.73–2.98 D). The treatment regimen for each monkey is indicated in the parenthesis beside the three-letter animal code (OU, OD, and ALT represent the binocular, monocular, and alternating occlusion regimens, respectively). For comparison purposes, the solid line represents the age-dependent changes in the spherical-equivalent refractive errors for the 19 control monkeys determined using a locally weighted regression algorithm. Because our control monkeys exhibited little or no astigmatism,[45] spherical-equivalent measures accurately captured the course of emmetropization. As illustrated, our control animals, as a group, were moderately hyperopic at ages corresponding to the onset of the lens-rearing period. Over the next 2 to 3 months, the control animals showed a rapid and systematic decrease in hyperopia to approximately +2.50 D. The average refractive error was then relatively stable until approximately 200 days of age. Thereafter, there was a very gradual decrease in hyperopia that continued beyond our current observation period.

Most of the lens-reared monkeys showed clear departures from this normal growth pattern. In most cases, both principal meridians either showed absolute hyperopic shifts (monkeys APR, WES, MAL, and BUC) or maintained higher than normal amounts of hyperopia (monkeys JAN, YEL, ZEB, and ZOL) during the treatment period (indicated by the filled bars in each plot). A smaller number of lens-reared monkeys showed relative myopic changes in both principal meridians during the treatment period (monkeys HEN, JAD, QUI, and LUI). After the removal of the treatment lenses, both principal meridians typically exhibited very similar changes as the eyes recovered toward more normal refractive errors. The key point is that the departures from normal were clear cut, regardless of whether an eye's ametropia was specified using spherical-equivalent values or the refractive error for a given meridian. Consequently, we choose to specify refractive error using the conventional and hypothesis-neutral, spherical-equivalent notation.

Symmetrical Binocular Astigmatism

Longitudinal changes in spherical-equivalent refractive error are illustrated in Figure 2 for the right (filled symbols) and left

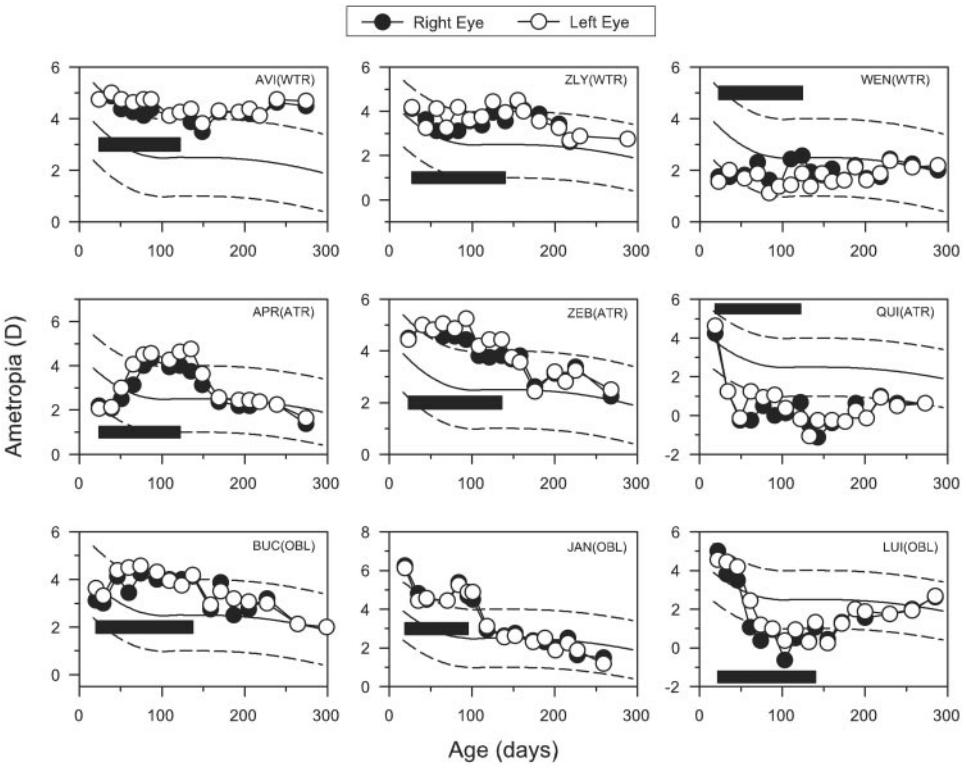

FIGURE 2. Spherical-equivalent refractive corrections for the right and left eyes are plotted as a function of age for nine representative monkeys that were treated with astigmatic lenses in front of both eyes. *Solid lines without symbols*: age-dependent changes in spherical-equivalent refractive errors in the 19 control monkeys; *dashed lines*: values that differ from these lines by ±1.50 D; *horizontal bars*: lens-rearing periods. Most of the monkeys exhibited relative hyperopic refractive errors (*left* and *middle* columns), whereas a smaller number of monkeys exhibited relative myopic refractive errors (*right* column). After lens removal, the eyes typically recovered and by approximately 9 months of age exhibited refractive errors similar to those of control monkeys. See Figure 1 for details.

(open symbols) eyes of nine representative monkeys that were reared with cylindrical lenses in front of both eyes. Each row includes data for three monkeys that experienced WTR (top), ATR (middle), or oblique (bottom) astigmatism. For comparison purposes, the solid lines without symbols represent the growth curve generated for the 19 control monkeys and the dashed lines represent values that differ by ±1.50 D from the normal growth curve. If emmetropization were directed toward the circle of least confusion, it would be expected that the data for the treated monkeys would follow the normal growth curve. However, if emmetropization was directed toward one of the focal planes associated with the astigmatic principal meridians, the refractive data should conform to one of the two dashed lines.

As represented by the monkeys in the left and middle columns of Figure 2, 13 of the 19 binocularly lens-reared monkeys exhibited ametropias that were consistently more hyperopic than normal. The generally close correspondence between the refractive errors for these animals and the dashed lines that were +1.50 D more hyperopic than the normal growth curve suggested that emmetropization was directed toward the less hyperopic astigmatic meridian (i.e., the focal plane corresponding to the positive-power meridian of the treatment lens). Five of the binocularly treated monkeys showed development of relative myopic ametropias and, as illustrated in the right column in Figure 2, the data for most of these monkeys were consistent with the idea that emmetropization was directed toward the focal plane associated with the negative-powered meridian of the treatment lens (i.e., the effectively more hyperopic meridian). Another indication that emmetropization was not generally directed toward the circle of least confusion is that many of the monkeys showed clear signs of recovery toward the normal growth curve that were synchronized with lens removal.

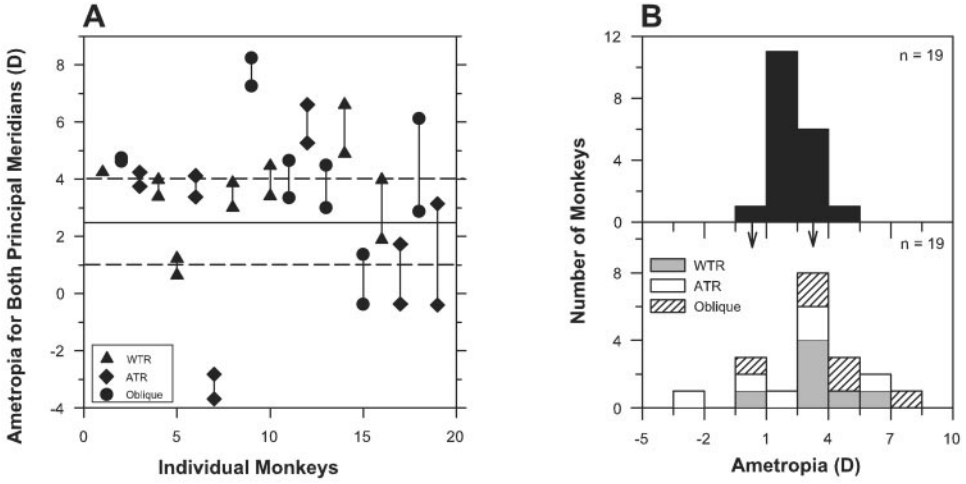

FIGURE 3. (**A**) The right-eye refractive errors for the astigmatic principal meridians of individual monkeys that were reared with cylinder lenses in front of both eyes. Data are arranged from *left to right* according to the magnitude of refractive astigmatism exhibited by individual monkeys. *Solid lines without symbols*: age-dependent changes in spherical-equivalent refractive errors in the 19 control monkeys; *dashed lines*: focal planes that differ from the mean by ±1.50 D. (**B**) The frequency distributions of spherical-equivalent refractive errors obtained at the end of the treatment period for the right eyes of the control (*top*) and binocularly treated monkeys (*bottom*). *Arrows*: values that differed from the control mean by ±1.50 D.

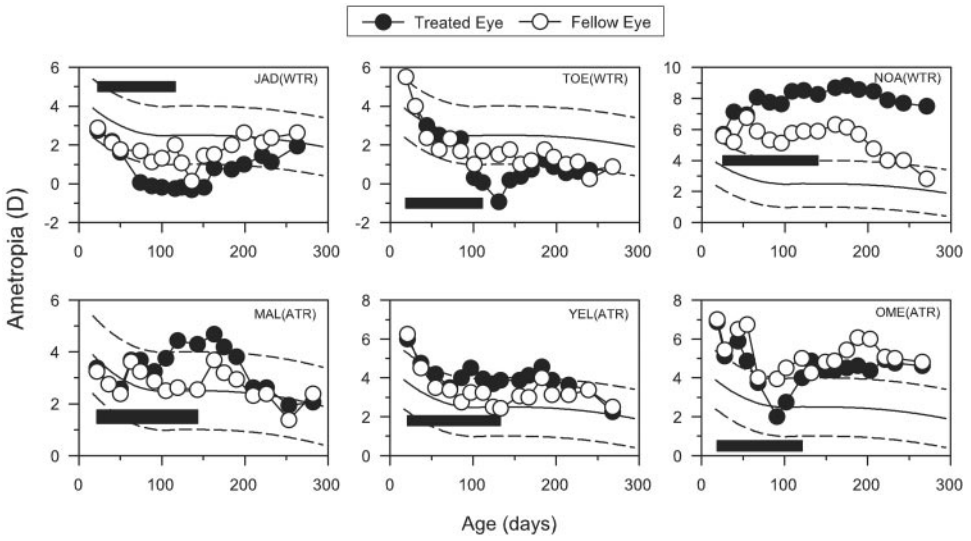

FIGURE 4. The spherical-equivalent refractive errors for the right (treated) and left eyes are plotted as a function of age in six monkeys that wore astigmatic lenses over one eye. *Solid* and *dashed lines* are as described in Figure 5.

The consistency of this pattern of results is shown in Figure 3. In Figure 3A the ametropias measured at the end of the treatment period are plotted for both principal meridians for the right eyes of individual animals (spherical-equivalent refractive errors were similar in both eyes: right = +3.24 ± 2.43 D; left = +3.44 ± 2.39 D; paired *t*-test, $P = 0.18$). The animals are arranged from left to right according to the magnitude of the astigmatism that developed in the animal during the treatment period. The solid line indicates the average ametropia for age-matched normal-control monkeys, and the dashed lines represent ±1.50 D from this mean. Thirteen of the monkeys had spherical-equivalent refractive errors that were closer to the dashed line that was +1.50 D more hyperopic compared with the average for the control monkeys. Five animals showed ametropias that were closer to the dashed line that was −1.50 D more myopic than the control average. Only one monkey (Fig. 3, number 16) had a spherical-equivalent refractive error that was closer to the average normal ametropia than either of the +1.50- or −1.50-D dashed lines. The apparent dichotomy in the group of binocularly treated monkeys can also be seen in the refractive-error frequency distribution compiled at the end of the treatment period (Fig. 3B). At the start of the treatment period, refractive errors were distributed in a near-Gaussian manner in both the control and binocularly treated monkeys (Anderson-Darling normality test, both $P > 0.53$). However, whereas the normal monkeys showed a reduction in the variance of refractive errors by the end of the treatment period, the refractive error distribution for the lens-reared monkeys became much broader and was distinguished by two peaks that were positioned ±1.50 D away from the mean refractive error of the control monkeys (marked by arrows on the abscissa). Note that only one of the binocularly lens-reared monkeys fell into the modal refractive error bin (+1.01 to +2.50 D) for control monkeys.

Monocular Astigmatism

Figure 4 illustrates the longitudinal refractive-error changes in six representative monkeys that were reared with cylinder lenses in front of one eye (WTR, top row; ATR, bottom row). If emmetropization in the treated eyes was directed toward the circle of least confusion, the monocularly lens-reared monkeys should have remained isometropic. In 11 of the 12 monocularly treated monkeys, interocular differences developed in refractive error that fell outside the range for normal-control monkeys. However, as shown in Figure 4 there was considerable variability between animals in the direction of the anisometropia. For example, whereas the treated eyes were more hyperopic than the nontreated eyes in six monkeys, the opposite was observed in five animals. In contrast, the magnitude of the anisometropia that the monocularly treated monkeys developed during the lens-rearing period was similar across the group. On average, the absolute maximum anisometropia during the treatment period was 1.54 ± 0.58 D (versus 0.19 ± 0.21 D in normal-control animals (two-sample *t*-test; $P < 0.0001$)) which matched very closely the dioptric powers of the treatment lens' principal meridians (i.e., ±1.50 D).

The correspondence between the end point for emmetropization and the refractive errors associated with the astigmatic principal meridians is emphasized in Figure 5 for the monocularly cylinder-reared monkeys. Specifically, Figure 5 compares the frequency distributions of anisometropia for control and monocularly cylinder lens-reared monkeys. The data were obtained at ages corresponding to the start (top) and end of the lens-rearing period (middle) and after 5 months of unrestricted vision after removal of the treatment lens (bottom). As illustrated in all three panels of Figure 5, the refractive errors of the two eyes of each control animal were well matched throughout the observation period. At the start of the lens-rearing period, the monocularly treated monkeys were, like normal monkeys, essentially isometropic. However, during the treatment period, the distribution of maximum anisometropic errors for the monocularly treated animals was bimodal, with two obvious peaks at ±1.5 D of anisometropia. The agreement between the degree of anisometropia and the dioptric powers for the principal meridians of the treatment lenses suggests that emmetropization in the treated eyes was typically directed toward one of the focal planes associated with the astigmatic errors produced by viewing through the cylinder lenses. The reductions in anisometropia that occurred during the recovery period in most, but not all, monocularly treated monkeys (e.g., monkey NOA, Fig. 4, top right) reinforce the idea that the treatment-induced anisometropias represented a compensating change in response to the presence of the imposed astigmatism.

Effects of the Axis of Astigmatism on Refractive Development

Figure 6A shows the refractive errors (right/treated eyes for all monkeys, except in the alternating occlusion group, in which case both eyes were included) obtained at the end of the

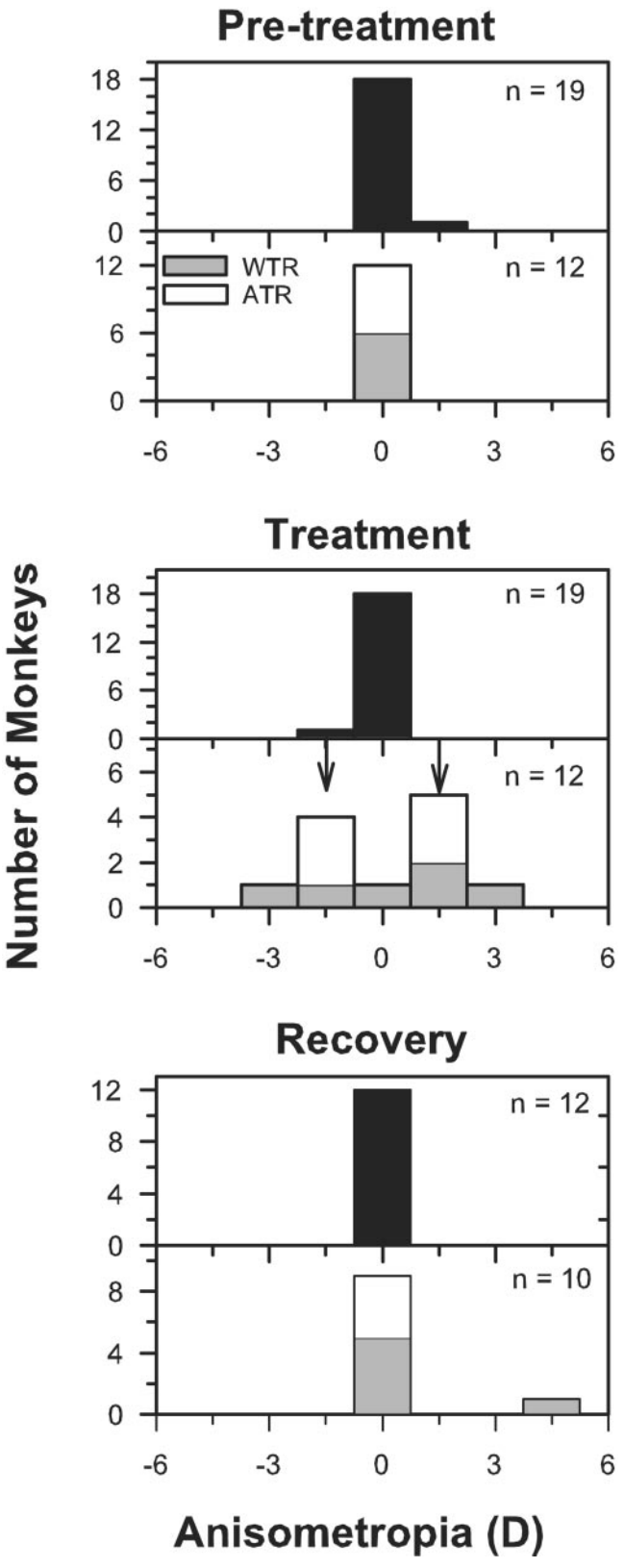

FIGURE 5. The frequency distributions of anisometropia at three different time points for the control monkeys (■) and monkeys that were reared with cylinder lenses in front of one eye. Similar anisometropic errors were found in the control and the treated eyes before treatment and after the recovery period. At the end of the treatment period, however, the distribution for the treated eyes showed two peaks on each side of the control peak. More important, these two peaks differed by 1.50 D from the control mean (marked by the *arrows*), suggesting that the treated eyes had compensated for one of the two astigmatic principal meridians.

treatment period for individual animals segregated according to the axis of the astigmatism imposed by the treatment lenses. Compared to normal-control animals, the experimental animals demonstrated a wider range of refractive errors; however, there were no significant differences in the refractive errors in eyes that experienced WTR, ATR, or oblique astigmatism (one-way ANOVA, $df = 2$, $F = 1.35$, $P = 0.27$). For all three axis orientations, the majority of monkeys were more hyperopic than the average normal monkey (61.2%, 55.0%, 83.3% for WTR, ATR, and oblique astigmatism, respectively) but some relative myopic errors were also found for each axis orientation.

For a potentially more sensitive measure of the effects of ATR versus WTR astigmatism on the direction of refractive changes we compared refractive development in the two eyes of individual animals that were reared with alternating occlusion and asymmetrical monocular astigmatism. As observed in the monocularly and binocularly cylinder-lens–reared monkeys, these animals exhibited alterations in emmetropization. Compared with normal monkeys, three of the eight animals in this group exhibited relative hyperopic errors in both eyes, and three showed relative myopic errors in both eyes. Figure 6B illustrates the interocular differences in refractive error plotted as a function of age for individual monkeys in the alternating occlusion group. Although four of the eight monkeys in this group remained essentially isometropic throughout the treatment period, four monkeys had anisometropic errors develop that were outside the normal range (thin lines) for at least part of the treatment period. At the end of the treatment period, three of these animals exhibited anisometropic errors that were ≥1.00 D, and in each case the eye with imposed ATR astigmatism was more myopic or less hyperopic than the fellow eye that experienced WTR astigmatism (indicated as negative numbers in Fig. 6B). Although there was clearly a trend for the eyes that experienced ATR to be more myopic than those that experienced WTR, the average degree of anisometropia at the end of the treatment period was not significantly different from that in the normal-control monkeys (two-sampled *t*-test, $t = -1.92$; $P = 0.10$). Similarly, interocular comparisons of the spherical-equivalent refractive errors obtained for the treated monkeys at the end of the lens-rearing period indicated that the direction of astigmatism did not significantly influence the degree of anisometropia (paired *t*-test, $t = -1.99$; $P = 0.09$).

Structural Correlates of Refractive Changes

The refractive error changes associated with form deprivation, the refractive-error compensation for positive and negative spherical lenses, and the recovery from experimentally induced refractive errors are largely mediated by alterations in axial growth rates and, in particular, vitreous chamber depth (for reviews, see Refs. 49–51). The changes in spherical-equivalent refractive error produced by optically imposed astigmatism were also due primarily to changes in vitreous chamber depth. As illustrated in Figure 7, the partial correlation coefficients for the changes in refractive error and vitreous chamber depth (obtained while keeping corneal power, anterior chamber depth, and crystalline lens thickness constant) were highly significant during both the lens-rearing (**A**) and recovery periods (**B**). In addition, changes in corneal power were negatively correlated with changes in refractive error during the treatment period ($r = -0.65$, $P = 0.003$) but not during the

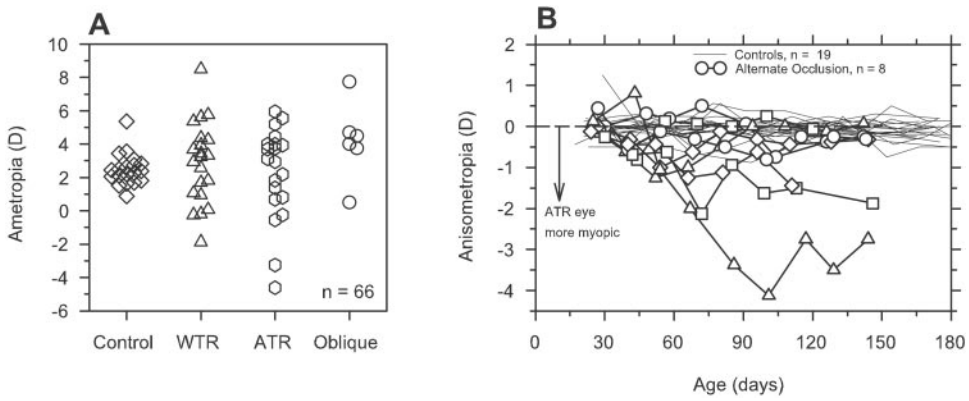

FIGURE 6. (**A**) Spherical-equivalent refractive errors for all the control and cylinder-lens–reared monkeys. (**B**) Anisometropia is plotted as a function of age in the eight monkeys that were reared using the alternating occlusion regimen. A negative value along the ordinate means that the eye that experienced ATR astigmatism was more myopic than the eye that experienced WTR astigmatism. *Thin lines*: data for the 19 control monkeys (right eye – left eye).

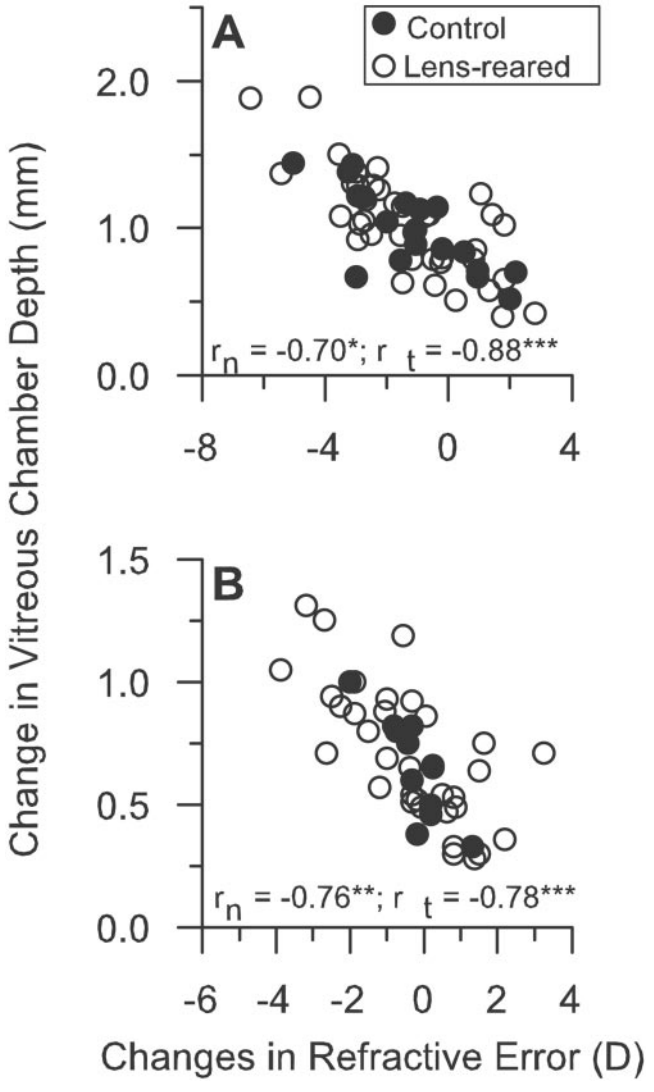

FIGURE 7. The changes of vitreous chamber depth as a function of the changes in spherical-equivalent refractive error found during (**A**) the treatment period, and (**B**) after the recovery period. In each plot, partial correlation coefficients are shown for control (r_n) and cylinder-lens-reared (r_t) monkeys (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). The refractive changes found in both the control and lens-reared monkeys were primarily due to changes in vitreous chamber depth.

recovery period ($r = -0.27$, $P = 0.274$). However, the magnitude of the corneal contribution to the experimentally induced refractive changes was relatively small. The regression equation for corneal power versus spherical equivalent refractive error obtained near the end of the treatment period indicated that corneal power contributed only 0.07 D for every 1.0 D of refractive error change. Neither anterior chamber depth nor crystalline lens thickness was correlated with the refractive error changes during either the treatment (for anterior chamber and crystalline lens, $r = -0.39$ and -0.17; all $P > 0.10$) or recovery periods (for anterior chamber and crystalline lens, $r = -0.10$ and 0.04; all $P > 0.68$).

Given that the refractive error changes were primarily axial in nature, one can make predictions about the shape of the distribution of vitreous chamber depths for the cylinder-reared monkeys. If emmetropization was directed toward the circle of least confusion the distribution should be unimodal and the peak of the function for the cylinder-lens–reared monkeys should be the same as that for normal-control monkeys. In contrast, if emmetropization was directed toward one of the two astigmatic principal meridians, the distribution should be bimodal and the two peaks should be separated by an amount equivalent to the degree of astigmatism. Figure 8A shows that at the start of the treatment period the distribution of vitreous chamber depths for all the cylinder-lens–reared monkeys was unimodal, and it compared favorably with the distribution for control monkeys (Fig. 8A, top). However, at the end of the treatment period (middle plot), the distribution of vitreous chamber depths for the treated monkeys was broader than normal, and it had two distinct peaks. It is notable that the positions of the two peaks are at vitreous chamber depths that are shorter and longer than the average vitreous chamber for control monkeys by an amount that is equivalent to ±1.50 D of defocus.[52,53] Moreover, the distribution as a whole is skewed toward shorter than normal vitreous chambers, with the larger of the two peaks representing shorter than normal vitreous chambers. At the end of the recovery period (Fig. 8A, bottom), the vitreous chamber distribution for treated monkeys was still broader than normal, but it had regained its unimodal shape. For comparison purposes, Figure 8B shows the frequency distributions of spherical-equivalent refractive errors for the same three time points. The agreement in the distributions of vitreous chamber depth and spherical-equivalent refractive error at the three time points supports the idea that the changes in refractive errors were mainly axial in nature.

DISCUSSION

Optically imposed astigmatism clearly altered ocular growth and emmetropization in our infant monkeys. Our main findings were that (1) optically imposed astigmatism increased the

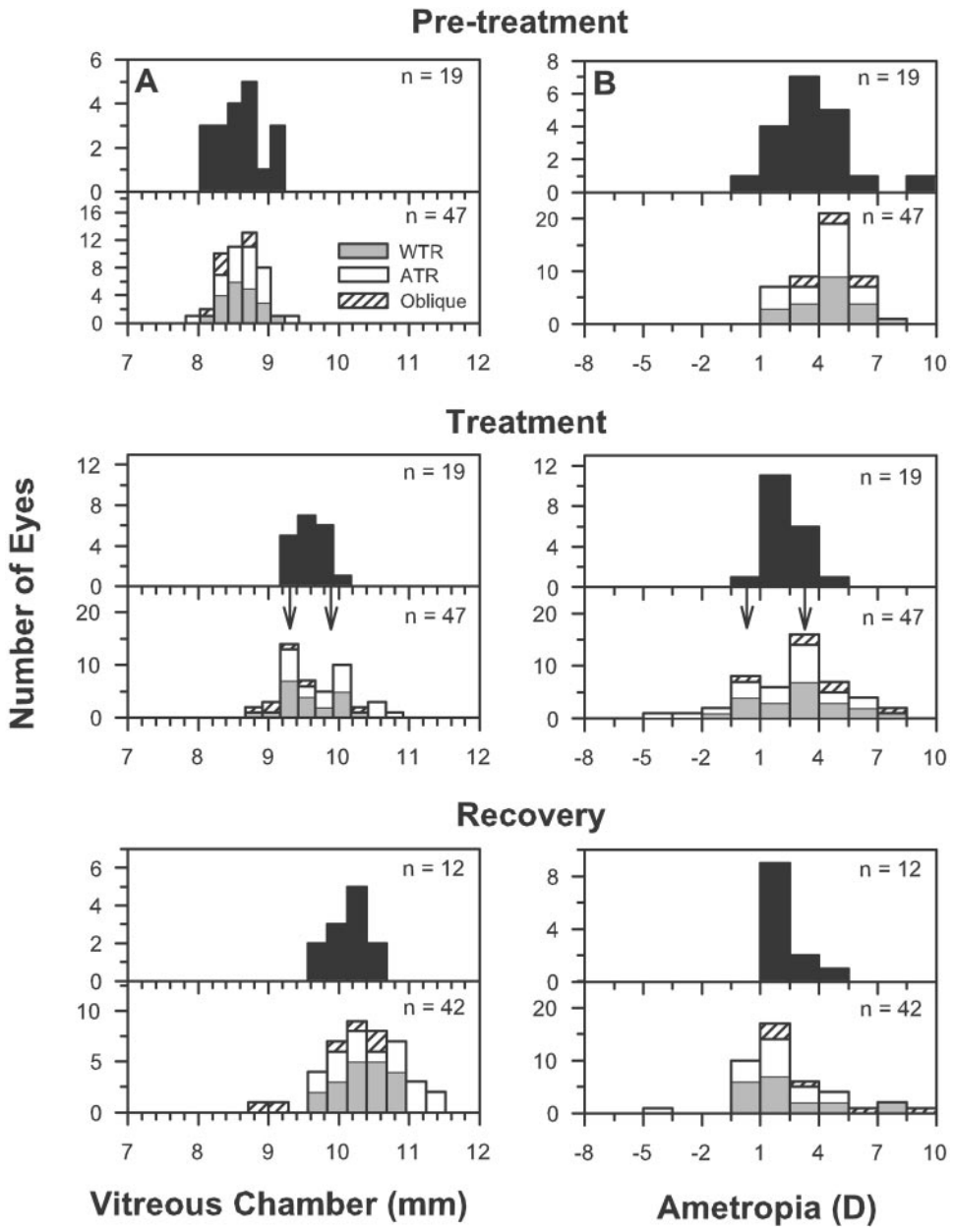

FIGURE 8. The frequency distributions of vitreous chamber depth (**A**) and spherical-equivalent refractive error (**B**) at three different time points for normal-control (■) and treated eyes. Right (treated) eyes were used in all monkeys except the alternating occlusion group, in which case both eyes were used. Similar distributions were found for normal control and treated eyes at the pretreatment and recovery periods. At the posttreatment period, two peaks were found in the treated eyes. These two peaks closely match the values equivalent to the 1.50-D difference from the control means (*arrows*). Note also that there were more shorter/hyperopic than longer/myopic eyes.

range of spherical-equivalent refractive errors exhibited by developing monkeys, (2) most of the treated animals became more hyperopic than normal, (3) the magnitude of the refractive changes observed in the cylinder-lens–reared monkeys, both myopic and hyperopic, corresponded to the refracting powers in the principal meridians of the treatment lenses, (4) the alterations in spherical-equivalent refractive error were due primarily to alterations in vitreous chamber growth and were reversible on restoration of unrestricted vision, and (5) the effects of imposed astigmatic errors on emmetropization were independent of the orientation of the imposed astigmatism.

Although it should be kept in mind that we evaluated only a limited range of possible astigmatic errors, our results call into question some of the traditional ideas concerning the effects of astigmatism on refractive development. First, we found no support for the hypothesis that the chronic image degradation associated with an uncorrected astigmatism promotes axial elongation and myopia in a manner analogous to form deprivation.[26] On the contrary, most of our treated monkeys had shorter than normal vitreous chambers and relative hyperopic refractive errors. Moreover, the myopic alterations observed in some of our cylinder-lens–reared monkeys differed from those produced by form deprivation in several ways. Whereas the degree of myopia produced by form deprivation varies substantially from subject to subject,[24,54,55] the magnitude of the myopic errors produced by our lens-rearing regimens appeared to compensate consistently for the optical defocus associated with the −1.50 D meridian of the treatment lenses. This consistency was particularly obvious in our monocularly treated monkeys (see Fig. 5). Moreover, in contrast to form deprivation, which, at least in young animals, produces progressive axial elongation throughout the period of deprivation,[24,55] the myopic errors in many of our lens-reared monkeys were relatively stable near the end of the treatment period.

We also found no support for the idea that the presence of astigmatism could facilitate emmetropization. At the end of the treatment period, our control animals as a group exhibited virtually no anisometropia and very similar absolute refractive errors. In contrast, the absolute refractive errors in our binoc-

ularly treated monkeys and the degree of anisometropia in our monocularly treated animals varied substantially compared with normal monkeys. Even when one considers that eye growth may have been directed to one of the two principal meridians of the treatment lenses, the lens-reared monkeys showed more variable refractive errors than control animals (Figs. 3, 5). There are at least two possible interpretations of these differences. It is possible that the target refractive error for emmetropization was altered in an individualized manner in the lens-reared animals. Interactions between the imposed astigmatism and the eye's aberrations may have resulted in a larger range of target refractive errors than in normal animals. So, the greater variability observed in lens-reared monkeys may not be due to a decrease in the efficiency or accuracy of the mechanisms that mediate emmetropization. However, it is also possible that the image degradation associated with the imposed astigmatism effectively decreased the signal-to-noise ratio for a given target refractive error thus resulting in less precise growth regulation.

Longitudinal studies indicate that infants and preschool children who have ATR astigmatism are more likely to develop myopia than those who have WTR astigmatism[37,38] and that the progression rates for myopia are higher in myopic children who have ATR astigmatism in comparison to those who have WTR astigmatism[56] (however, see also Ref. 57). These observations suggest that the effects of astigmatism on refractive development may depend on the direction of astigmatism and specifically that ATR astigmatism may promote the development of myopia. In our alternate occlusion group of monkeys, there was a trend for the eyes that experienced ATR astigmatism to be more myopic than their fellow eyes with imposed WTR astigmatism. However, this trend was not statistically significant, and in our larger binocular and monocular treatment groups, we did not observe any differences in refractive development for animals with imposed WTR versus those with imposed ATR astigmatism. These results suggest that the association found in humans may not reflect a causal relationship between ATR astigmatism and myopia, but instead reflect the action of some other factor that contributes to both myopia and ATR astigmatism.

It is logical to expect that when significant amounts of astigmatism are present, eye growth should be directed toward the circle of least confusion. Given that our treatment lenses had a spherical equivalent power of 0, this hypothesis predicts that axial growth and spherical refractive development, assuming that the efficiency or accuracy of the emmetropization process were not disturbed, should have been unaffected in our treated animals. Consequently, the distributions of refractive error, anisometropia, and vitreous chamber depth in our treated animals should have been comparable to those in our control animals. In particular, it would be expected that these distributions would be unimodal in shape and that the peaks of the distributions for the treated animals would be comparable to those for the control animals. However, the results in our lens-reared monkeys showed that that was clearly not the case. Simple inspection revealed the bimodal nature of the distribution of refractive errors for our binocularly treated monkeys (Fig. 3), of the distribution of anisometropias for our monocularly treated monkeys (Fig. 5), and of the distribution of vitreous chamber depths for all the treated eyes (Fig. 8). Most significantly, the two peaks in these distributions straddled the peaks of the control animal functions, and there was an obvious correspondence between the positions of these bimodal peaks and the refractive errors and axial dimensions associated with the two principal meridians of the treatment lenses. This pattern of results demonstrates that, in the presence of significant astigmatism, axial growth and refractive development are directed toward the focal planes associated with the astigmatic principal meridians and not to the circle of least confusion. This growth pattern would explain the relatively low prevalence in humans of mixed astigmatism in comparison to that for simple or compound astigmatism.[58–60] It would also explain why emmetropic individuals typically exhibit simple hyperopic astigmatism in the periphery.[61] Based on our observations, it could be argued that local emmetropization mechanisms regulate the peripheral shape of the eye so that the least hyperopic meridian associated with the eye's natural oblique astigmatism is in focus on the peripheral retina.

The fact that most of the treated eyes exhibited amounts of axial hyperopia that were in essence predicted by the meridional powers of the treatment lens indicates that when infant eyes have compound hyperopic astigmatism, emmetropization is typically directed toward the least hyperopic meridian (i.e., the anterior focal line). In this respect, emmetropization behaves in a manner that is comparable to the accommodative system. When accommodating for near objects, humans with either natural[62] (Harvey EM, et al. *IOVS* 2003;*44*:ARVO E-abstract 2727) or optically imposed[63] astigmatic errors posture their steady state accommodation for the anterior focal line and not for the circle of least confusion. It has been speculated that astigmatic eyes accommodate for the least hyperopic meridian because that strategy requires the least amount of effort to get a clear image.[62,63] Likewise, our treated monkeys appeared to accommodate for the anterior focal line while viewing through the cylindrical treatment lenses. In some respects, it is reasonable to assume that the tendency for emmetropization to be directed toward the anterior focal line reflects at least in part this inherent bias in the accommodative system. However, refractive errors and refractive development are generally measured with respect to infinity where accommodation would be less active and less likely to influence the end point for emmetropization. Consequently, it is possible that the emmetropization and accommodation processes simply share common performance properties. In this respect, it appears that for both the accommodative and emmetropization systems the retinal images at the anterior focal plane are more effective end points than the images at other positions within the interval of Sturm, including the circle of least confusion. In other words, for the emmetropization process the visual signals obtained from objects imaged at the anterior line focus are sufficient to restrain axial growth. Because this pattern of behavior occurs for all directions of astigmatism, the mechanisms responsible for emmetropization and presumably those responsible for accommodation are probably insensitive to stimulus orientation and the global form of the retinal image. This conclusion is in agreement with the idea that emmetropization is mediated in large respect by mechanisms that are located within the eye[64–66] and relies on retinal neurons with circular and probably antagonistic, center-surround receptive fields for signals related to the effective focus of the eye.

For neurons with small center-surround receptive fields, the images of a point source formed at either of the astigmatic line foci would be a reasonably effective stimulus, whereas the larger overall images at other positions within the interval of Sturm would be less effective as a consequence of antagonistic interactions from surround mechanisms. Indeed, the volume underneath the three-dimensional modulation-transfer function (3-D MTF) calculated for a monochromatic point source (550 nm) is greatest at the anterior and posterior line foci (Fig. 9). The 3-D MTF is like a conventional two-dimensional (2-D) MTF, except that it includes data for all stimulus orientations in a single 3-D plot.[67] The 3-D MTFs in Figure 9 were computed with custom software (MatLab; The MathWorks, Natick, MA).[68] First, the point-spread function (PSF) was computed considering both the wave aberrations of the eye (simple astigmatism in this case) and pupil size (3, 5, and 7 mm in

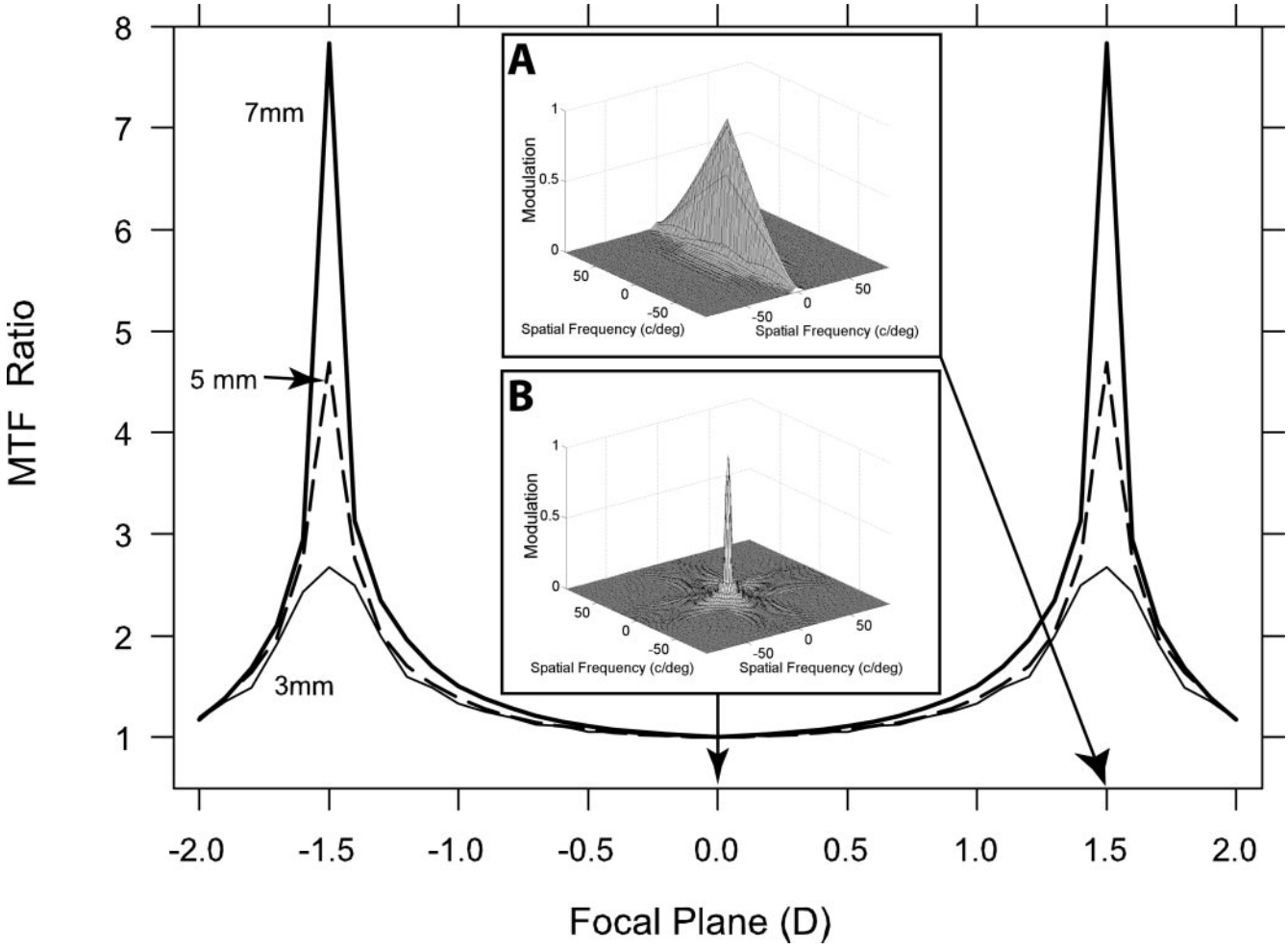

FIGURE 9. The ratio of the volume underneath the three-dimensional modulation transfer function (3-D MTF) at different focal planes compared with that at the circle of least confusion for three different pupil sizes. The 3-D MTFs were generated by custom computer programs for a 550-nm monochromatic point source being refracted through a model eye with an astigmatic refractive error analogous to those imposed by our treatment lenses (e.g, +1.50 −3.00 D × 90). *Insets*: the 3-D MTFs at the horizontal astigmatic line focus (**A**) and the circle of least confusion (**B**) for a 3-mm pupil size.

diameter). The 3-D MTF was then obtained by computing the amplitude of the Fourier transform for the PSF.[69] For Figure 9, the PSFs and their corresponding MTFs were computed at different axial planes through the astigmatic interval. As illustrated in Figure 9, the volume under the 3-D MTF at either the anterior or posterior astigmatic line foci is 2.7 to 7.8 times greater than that at the circle of least confusion for pupil sizes varying from 3 to 7 mm, respectively. It is also clear from the insets in Figure 9 that the effective spatial frequency bandwidth in the retinal image would also be greater at the anterior and posterior line foci than at the circle of least confusion. Assuming that the absolute levels of activity within retinal neurons are used to identify the target focal plane and that these activity levels reflect the effective retinal contrast integrated across spatial frequency and orientation, then eye growth should be directed toward either of the focal lines instead of the circle of least confusion.

In the presence of substantial amounts of astigmatism, why is it that most eyes emmetropized to the anterior focal line, but a substantial minority emmetropized to the posterior focal line? As stated earlier, this growth pattern could simply reflect the eye's accommodative bias toward the anterior focal line. However, this pattern of results probably comes about because infant monkeys are typically quite hyperopic. At the start of the treatment period, essentially all our monkeys exhibited compound hyperopic astigmatism (for details, see Ref. 17). Consequently, the anterior line focus would be located closest to the retina and would be the first "in-focus" plane that the eye would encounter during its normal course of elongation. Regardless of whether emmetropization involves a "grow-to-clarity" strategy or it involves mechanisms that are sensitive to the sign of defocus (with astigmatic errors positive and negative defocus signals bracket both focal lines and the circle of least confusion), the anterior focal line would represent a possible and, as reflected in our data, an effective end point for emmetropization (see also Ref. 30). However, the overall retinal image quality at the anterior focal line would be lower than the image quality at the focal point of a comparable eye that had only a spherical refractive error. It can be argued that this lower overall image quality produced by astigmatism would decrease the effectiveness of the signals generated around this focal plane to control axial growth. Consequently, this may explain the higher than normal variance of refractive errors and why axial elongation did not halt at the anterior focal line in several of our lens-reared monkeys. Of note, in most of the eyes that did not emmetropize to the anterior focal line, axial elongation continued through the circle of least confusion, but was halted at the posterior focal line. This pattern of growth

supports the idea that the anterior and posterior line foci in astigmatic eyes are more effective end points for emmetropization than the circle of least confusion.

There were several similarities between the refractive development in our cylinder-lens–reared monkeys and that in chickens reared with imposed astigmatic errors. In both chickens[29–32] (Thibos LN, et al. *IOVS* 2001;42:ARVO Abstract 324; Laskowski FH, et al. *IOVS* 1996;37:ARVO Abstract 3140) and monkeys, imposed astigmatic errors did not promote unregulated axial elongation and progressive myopia. In both species, the vision-dependent changes in spherical-equivalent refractive error were axial in nature and independent of the direction of the imposed astigmatic errors. In addition, the intersubject variability in refractive error was higher than normal in both monkeys and chickens[30–32] reared with imposed astigmatic errors. Moreover, some studies of cylinder-lens–reared chickens have found, as we did in monkeys, clear evidence that in the presence of substantial amounts of astigmatism, emmetropization is directed toward the less hyperopic, anterior focal line.[30] However, there have been inconsistencies between studies of cylinder-lens–reared chickens with respect to the end point for emmetropization[29–32] (Thibos LN, et al. *IOVS* 2001;42:ARVO Abstract 324). For example, some studies in chickens have shown hyperopic shifts in response to spherocylindrical lenses that had a spherical equivalent power of 0, suggesting partial compensation toward the less hyperopic line focus,[32] whereas in other studies, the chick eye appears to emmetropize to the circle of least confusion.[31] It is not clear why the results in chickens are inconsistent on this point.

In conclusion, irrespective of the orientation of astigmatism, in the presence of significant amounts of astigmatism, emmetropization in primates is directed toward one of the two focal planes associated with the astigmatic principal meridians. These results suggest that the mechanisms responsible for emmetropization are insensitive to stimulus orientation and the global form of the retinal image, but instead seek out the image plane that contains the maximum effective contrast integrated across spatial frequency and stimulus orientation.

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