Vision-Dependent Changes in the Choroidal Thickness of Macaque Monkeys

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PURPOSE. To determine whether changes in the eye’s effective refractive state produce changes in the thickness of the choroid in infant monkeys.

METHODS. Normal developmental changes in choroidal thickness were studied in 10 normal rhesus monkeys. Hyperopia or myopia was induced by rearing 26 infant monkeys with either spectacle or diffuser lenses secured in front of one or both eyes. The treatment lenses were worn continuously beginning at approximately 3 weeks of age for an average of 120 days. Refractive status and ocular axial dimensions, including choroidal thickness, were measured by retinoscopy and high-frequency A-scan ultrasonography, respectively.

RESULTS. Three lines of evidence indicate that the normal increase in choroidal thickness that occurs during early maturation can be altered by the eye’s refractive state. First, in monkeys experiencing form deprivation or those in the process of compensating for imposed optical errors, choroidal thickness and refractive error were significantly correlated with eyes developing myopia having thinner choroids than those developing hyperopia. Second, the choroids in eyes recovering from binocularly induced myopia increased in thickness at a faster rate than the choroids in recovering hyperopic eyes. Third, monkeys recovering from induced anisometropias showed interocular alterations in choroidal thickness that were always in the appropriate direction to compensate for the anisometropia. These changes in choroidal thickness, which were on the order of 50 μm, occurred quickly and preceded significant changes in overall eye size.

CONCLUSIONS. Changes in the eye’s effective refractive state produce rapid compensating changes in choroidal thickness. Although these choroidal changes are small relative to the eye’s refractive error, they may play an important role in the visual regulation of axial growth associated with emmetropization. (Invest Ophthalmol Vis Sci. 2000;41:1259–1269)

During early development, the eye’s optical and axial components grow in a highly coordinated manner so that a near emmetropic refractive state is achieved and maintained in the eye.1–7 Evidence from a diverse range of animal species indicates that visual feedback, specifically the optical defocus associated with the eye’s effective refractive state, modulates early ocular growth in a manner that eliminates refractive error.8–10 These vision-dependent corrections in the eye’s refractive state come about primarily through alterations in the axial elongation rate of the vitreous chamber. In the young chick’s eye, changes in two ocular components, axial length of the eye and thickness of the choroid, underlie these compensating changes in vitreous chamber depth.11,12 In particular, the myopic changes that occur in response to chronic hyperopic defocus come about as a result of a decrease in the thickness of the choroid, together with an increase in overall eye length.

The increase in overall eye length is mediated primarily by changes in the sclera. Both the choroidal and scleral changes move the retina back toward the eye’s secondary focal point. Conversely, in response to chronic myopic defocus, the thickness of the choroid increases, and there is a reduction in the rate of overall eye elongation. These changes contribute to a forward displacement of the retina toward the eye’s image plane and a relative hyperopic shift in refractive error. Recent ultrasonographic data obtained from the tree shrew showed that the combined thickness of the retina, choroid, and sclera is altered during the recovery from form-deprivation myopia, which suggests that the choroids in mammals may also be influenced by visual feedback.13,14

Refractive error dependent variations in choroidal thickness have been observed in adult humans. Specifically, highly myopic eyes, particularly those with posterior staphylomas, have thinner than normal choroids.14 However, these differences are not in the appropriate direction to compensate for the eye’s refractive error and may reflect degenerative changes produced by mechanical factors associated with a substantial increase in overall eye size. In contrast, the choroidal thickness changes observed in young chicks are dynamic and appear to represent an active early step in the eye’s emmetropizing response to refractive error. The choroidal thickness changes in the chick occur in a matter of hours after an imposed change in refractive error and precede and possibly mediate the alterations of scleral growth that lead to overall changes in eye length.11,15 Although infant monkeys, like young chicks, rap-
ily compensate for optically imposed changes in refractive state, it is not known whether the choroid contributes to the visually mediated changes in vitreous chamber depth that underlie these emmetropizing responses. Because the choroid may play a fundamental role in emmetropization in primates, the purpose of this experiment was to determine whether choroidal thickness is influenced by the eye's effective refractive state in infant macaque monkeys. Similar experiments conducted in infant marmosets are described in an accompanying article.

**Materials and Methods**

**Subjects**

Thirty-six infant rhesus monkeys (Macaca mulatta) were used as subjects. The infants were obtained at 1 to 3 weeks of age and were hand-reared in our primate nursery, which was maintained on a 12-hour light–12-hour dark lighting cycle. All the rearing and experimental procedures were 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.

The normal maturational changes in choroidal thickness and the normal interocular variations in choroidal thickness were determined for 10 normal monkeys that were reared with unrestricted vision. The effects of visual experience on choroidal thickness were investigated in 26 infants that were used in previous studies on the effects of either optically imposed refractive errors or form deprivation on the emmetropization process. Starting at 2 to 4 weeks of age, the visual experiences of the experimental subjects were manipulated using spectacle lenses. To optically simulate either myopic or hyperopic errors, spherical ophthalmic lenses, which ranged in power between $-6$ and $+12$ D, were secured in front of one or both eyes using a light-weight helmet. For the animals that were reared with anisometropic lenses ($n = 4$), an alternating monocular occlusion strategy was used to ensure that the animals actively fixated with each eye for half the daily lighting cycle. Lens power was increased in a sequential manner during the treatment period for all the infants treated with anisometropic lenses and for 10 of the 15 infants treated with binocular, equal-powered lenses. These increases in treatment lens powers were made to maintain a chronic stimulus for compensating ocular growth. Monocular form deprivation was imposed with plano diffuser spectacles in five infants, one of which was only available for testing during the lens rearing period. Control data for the helmet rearing procedures were obtained from two monkeys reared with zero-powered lenses over both eyes. For all treatment groups, the lenses were worn continuously for periods ranging between 12 and 23 weeks (mean, 120 ± 17 days).

**Optical and Biometric Measurements**

The general procedures used to assess refractive development have been described in detail previously. To make the necessary measurements, the animals were anesthetized with ketamine hydrochloride (20 mg/kg) and acepromazine maleate (0.2 mg/kg). Cycloplegia was induced with 1% tropicamide. Refractive status, which is specified as the spherical-equivalent spectacle-plane refractive correction, was assessed by retinoscopy at the onset of the lens rearing period and typically every 2 to 4 weeks thereafter. The eye's axial dimensions were measured by A-scan ultrasonography. Vitreous chamber depths were obtained throughout the treatment period using a commercially available ultrasound system with a 7-MHz transducer (Mentor Image 2000; Mentor O & O, Norwell, MA). The thickness of the choroid was measured using a high-frequency A-scan system similar to that described by Wallman et al. With this system, the echoes recorded using a focused, 30-MHz polymer transducer (model 176599; Panametrics, Waltham, MA) were digitized at 100 MHz (model 8100 A/D board; Sonix, Springfield, VA). The transducer was coupled to the eye using a closed, water-filled interface. A three-axis positioner that was mounted on a slit lamp base was used to align the transducer to simultaneously maximize the echoes from the major optical components and the retinal–choroidal complex. Eight to 10 separate scans were recorded and stored in a computer for off-line analysis.

Characteristic A-scan traces obtained with the 30-MHz ultrasound system are shown in Figure 1. The expanded echoes from the retinal–choroidal–scleral complex show four distinct clusters of echoes. As illustrated by the close similarities between the individual waveforms in Figures 1A and 1B, the general echo pattern was very consistent within and between measurement sessions. Previous work in the chicken suggests that the first cluster of echoes, which was typically the most complex cluster, was produced by the retina and that the second and third major peaks marked the inner and outer limits of the choroid. Ultrasound traces obtained after serial dissection of the retinal–choroidal complex in two enucleated eyes confirmed this interpretation. The cornea, iris, and lens were removed from the eyes, and the top trace in Figure 1C, which includes the major peaks for the retina, choroid, and inner sclera, was recorded with the transducer immersed in the vitreous. As shown in the middle trace, the first peak disappeared when the neural retina was removed. The peak labeled 2 was lost after the removal of the pigment epithelium and the choroid. Based on these observations, peak 1 represents the vitreal-retinal interface; peak 2 is produced by the interface associated with the pigment epithelium, Bruch’s membrane, and the choroidal capillary complex; and peak 3 represents the border between the outer choroid and inner sclera.

We took the distance between the second and third major clusters of echoes as our measure of choroidal thickness. Specifically, the inner and outer borders of the choroid were considered to correspond to the apaxes of the largest amplitude peaks within the second and third echo clusters, respectively. Typically, these echo clusters consisted of three peaks, with the central peak in each having the largest amplitude (e.g., as marked by asterisks in the day 68 trace in Fig. 1B). In instances in which there were no clear amplitude differences between the peaks within a cluster, the appropriate peak was selected based on waveform comparisons, with the traces obtained in the immediately preceding and/or following measurement sessions (e.g., day 188 and day 307 traces, Fig. 1B). The choroidal thickness values presented in this article represent the means for the 8 to 10 individual traces obtained in a given measurement session. Within each measurement session, there was very good agreement between the 8 to 10 choroidal thickness measures obtained for a given eye. For example, for the 110 measurement sessions for the right eyes of normal...
monkeys, the average SD for within-session measurements was less than 2 μm.

The A-scan system that was used to measure choroidal thickness was not available at the start of the study, so that we have limited data on the initial effects of our rearing strategies on choroidal thickness. Moreover, because of the large inter-subject differences in choroidal thickness observed in normal animals, we have concentrated our analysis on the changes that occurred after sudden changes in the eye’s effective refractive status and interocular differences in choroidal thickness. In particular, we have focused on the choroidal changes that were associated with removing the treatment lenses at the end of the rearing period.

Analysis of Longitudinal Data

To determine whether there were any systematic changes in choroidal thickness during normal development or during the recovery period after our special rearing procedures, it was assumed that all the monkeys in a given experimental group were identical subjects and that the pattern of choroidal changes was the same for all subjects in a given group. We thought that this was a reasonable assumption, because the ages of the animals in all the experimental groups were very similar; all the animals received the same general postnatal care and were housed in the same vivarium; within a given experimental group the rearing procedures and/or the resultant refractive-error changes were very consistent between subjects; and within a given group inspection of longitudinal data confirmed that the general pattern of choroidal changes were similar in individual monkeys.

With these assumptions, the choroidal thickness measures for every monkey in a given subject group were regarded as repeated measures on a single subject, and the data for all monkeys in a given group were combined. To smooth the longitudinal data, a moving-average procedure with a moving-average length of three consecutive measures was applied to the resultant time series.\(^2^3\) A linear trend model was applied to the normal changes in choroidal thickness during early maturation (Fig. 2A) and to those that occurred in the experimental subjects immediately after the end of the treatment period (see
emmetropization are complete).17,18 Most dramatic refractive error changes associated with early particularly after approximately 50 days of age (i.e., after the slope of the regression line provides a reasonable description of the changes in thickness over time for individual monkeys, especially after 50 days. The results of the linear regression (dashed lines) indicated that choroidal thickness increased gradually throughout our observation period (17.3 μm/100 days, $r^2 = 0.23$, $P < 0.0001$). Inspection of Figure 2A confirms that the slope of the regression line provides a reasonable description of the changes in thickness over time for individual monkeys, particularly after approximately 50 days of age (i.e., after the most dramatic refractive error changes associated with early emmetropization are complete).17,18

Although choroidal thickness varied considerably from one individual to the next, the choroids in the two eyes of a given individual were generally well matched (Fig. 2B). The mean interocular difference for the normal and plano control monkeys was $-0.8 \pm 14.3$ μm (right eye minus left eye). The average absolute difference between the two eyes was $12.0 \pm 7.7$ μm. There were no systematic changes in the magnitude of the interocular differences in choroidal thickness as a function of age ($r^2 = 0.0$, $P = 0.84$).

**Monkeys with Experimentally Induced Refractive Errors**

Three observations suggest that the thickness of the choroid in the developing monkey is influenced by the eye’s refractive status. First, after a long period of lens wear choroidal thickness varied systematically with refractive error. Second, after binocular negative or positive lenses were removed, the choroid thickened or thinned, respectively. Third, after lens removal, monkeys in which anisometropia had developed during the treatment period showed interocular differences in choroidal thickening that were in the appropriate direction to compensate for the anisometropia.

**End-of-Treatment Refractive Error Versus Choroidal Thickness.** Figure 3A summarizes for all the binocularly treated infants the thickness of the choroids at the end of the treatment period. Choroidal thickness and refractive error were significantly correlated ($5.1$ μm/D, $r^2 = 0.42$, $P = 0.009$): Eyes shifting in the hyperopic direction while wearing positive lenses (i.e., eyes experiencing myopic defocus, open symbols) showed thicker choroids than eyes shifting in the myopic direction in response to wearing negative lenses (i.e., eyes experiencing hyperopic defocus, filled symbols). Similarly, in infant monkeys in which anisometropia developed as a result of our experimental rearing procedures (Fig. 3B), choroidal thickness was positively correlated with the refractive errors measured at the end of the treatment period ($2.7$ μm/D, $r^2 = 0.27$, $P = 0.03$). Moreover, interocular comparisons of choroidal thickness and refractive error in these anisometropic monkeys showed that the choroids in the eyes shifting in the myopic direction (e.g., eyes viewing through diffuser lenses) were significantly thinner than the choroids of the more hyperopic fellow eyes (Wilcoxon signed rank test, $P = 0.03$). As can be seen in Figure 3B, which compares the choroidal thickness and refractive errors for the two eyes of individual anisometropic monkeys, the relationship between choroidal thickness and refractive error was very consistent. In eight of the nine anisometropic monkeys, the more hyperopic eyes had thicker choroids. The only anisometropic monkeys that failed to show this pattern had myopia in both eyes and both eyes had relatively thin choroids.

**RESULTS**

**Normal and Control Infant Monkeys**

In Figure 2A, choroidal thickness is plotted as a function of age for the left eyes of individual normal infants (filled symbols) and control infants (open symbols) reared with zero-powered lenses over both eyes (open symbols). For clarity the male and female subjects were plotted separately. The results of the linear regression (dashed lines) indicated that choroidal thickness increased gradually throughout our observation period (17.3 μm/100 days, $r^2 = 0.23$, $P < 0.0001$). Inspection of Figure 2A confirms that the slope of the regression line provides a reasonable description of the changes in thickness over time for individual monkeys, particularly after approximately 50 days of age (i.e., after the most dramatic refractive error changes associated with early emmetropization are complete).17,18

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Figs. 6A, 6B, and 10). In each case, the autocorrelations of the detrended data residuals were small. Because the residuals were essentially uncorrelated, we used linear regression to obtain $r^2$ values and significance levels for each data set.24

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FIGURE 3. Choroidal thickness plotted as a function of the spherical equivalent refractive correction for (A) the right eyes of individual monkeys treated with binocular, equal-powered negative (filled symbols) or positive lenses (open symbols) and (B) both eyes of individual infants reared with monocular diffuser lenses (circles) and anisometropic treatment lenses (squares). The solid lines in (B) connect the data for the two eyes of a given monkey. For each diffuser-reared monkey, the filled and open symbols represent the deprived and nontreated eyes, respectively. For each anisometropic-lens–reared monkey, the open symbol represents the eye treated with the more positive spectacle lens. In both plots, all the data were obtained at the end of the treatment period, and the daubed lines represent the best-fitting regression lines.

Recovery from Binocular Refractive Errors. After removal of the binocular, equal-powered lenses, the choroids of monkeys treated with negative lenses thickened more rapidly than did those of monkeys treated with positive lenses.

Within certain operational limits, the course of emmetropization in both eyes of infant monkeys can be predictably manipulated by changing the eye’s effective focus with binocular equal-powered lenses. As illustrated in Figure 4, which shows data for representative subjects that were reared with negative-powered lenses in front of both eyes, negative lenses exaggerated the normal decrease in hyperopia during early emmetropization, resulting in myopia. On the contrary, positive lenses slowed the normal decrease in hyperopia and, in some cases, caused growth in the hyperopic direction (Fig. 5). After the treatment lenses were removed, all the binocularly treated animals experienced sudden and significant changes in their eyes’ effective focus. For example when the negative lenses were removed, the monkeys that had compensated for the negative lenses experienced for the first time a substantial degree of myopic defocus. Conversely, removing the positive treatment lenses resulted in a reversal of the sign of defocus from optically imposed myopia to a significant degree of uncorrected hyperopia.

A comparison of the data for the individual subjects in Figures 4 and 5 indicates that after lens removal the choroids of the negative-lens–treated infants increased in thickness at a faster rate than the choroids of the monkeys treated with positive lenses. This difference is supported statistically by the pooled data from the 15 infants reared with binocular equal-powered lenses. Figure 6 summarizes the changes in choroidal thickness that occurred after lens removal. Figures 6A and 6B illustrate the average change in choroidal thickness for the negative- and positive-lens–treated infants, respectively, plotted as a function of days with zero representing the end of the treatment period. Choroidal thickness was significantly correlated with the length of the recovery period for both the positive- ($r^2 = 0.23, P < 0.0001$) and negative-lens–reared monkeys ($r^2 = 0.38, P < 0.0001$). The slope of the regression line for the animals treated with negative lenses was significantly steeper than the slope of the function for positive-lens–treated infants ($P = 0.02$).

As illustrated in Figures 6C and 6D, there was a trend for the negative- and positive-lens–reared infants to exhibit different rates of choroidal thickening than the normal and plano control monkeys. During approximately the first 50 days of the recovery period, the slopes of the individual regression lines for all six infants treated with negative lenses were steeper than the average function for the normal/control subjects. In contrast, seven of the nine positive-lens–reared monkeys exhibited slower than normal choroidal thickening rates during the recovery period. A Mann–Whitney test confirmed that the mean increase in choroidal thickness for the negative-lens–treated infants after approximately 50 days of recovery was significantly greater than that for the positive-lens–reared in-
Recovery from Experimentally Induced Anisometropia. As shown, interocular comparisons provide a very sensitive index of visually induced alterations in eye growth. Consequently, we believe that the strongest evidence that visual feedback associated with the eye’s refractive state influences choroidal thickness comes from monkeys with experimentally induced anisometropia produced by either monocular form deprivation or anisometropic spectacle lenses. After the removal of the treatment lenses, these animals demonstrated rapid and dramatic interocular alterations in choroidal thickness that were always in the appropriate direction to compensate for the effective interocular differences in refractive error.

As illustrated by the data from the three representative monkeys in Figure 7, monocular form deprivation created by unilateral diffuser lenses produced relative myopia in the treated eyes. In all the diffuser-reared infants, the myopia was associated with a substantial relative increase in the vitreous chamber depth of the deprived eye.21 Figure 8 shows that infants reared with different powered lenses in front of each eye frequently developed compensating anisometropia, which was also due primarily to an interocular difference in vitreous chamber depth.17 For both of these subject groups, the more myopic eyes showed relative increases in choroidal thickness after lens removal or, in the case of MKY KO, after a reduction in lens power (Fig. 8, bottom). On the contrary, the eyes that experienced hyperopic defocus exhibited a relative reduction in choroidal thickness.

The similarities in the choroidal responses for the diffuser- and anisometropic-lens–reared monkeys are apparent in Figure 9, which shows the mean interocular differences in choroidal thickness plotted as a function of age, where zero indicates the onset of the recovery period. (Note that unlike in the other three anisometropic monkeys, the lens powers for MKY KO (bottom plot in Fig. 8) were reduced during the treatment period. Consequently the data for MKY KO are not included in Figure 9 and will be addressed separately.) At the end of the treatment period, the choroids in the more myopic eyes were thinner than those in their fellow eyes. These interocular choroidal differences, −25 ± 9 μm for the diffuser monkeys and −24 ± 4 μm for the anisometropic monkeys, were well outside the range of average interocular differences observed in the normal and plano control monkeys. However, within 7 days of restoration of unrestricted vision, the choroids in the more myopic eyes exhibited a dramatic relative increase in thickness. At the first measurement in the recovery period, the myopic choroids in the diffuser monkeys had increased in relative thickness by an average of 46 μm and were 23 ± 9 μm thicker than the choroids in their fellow nontreated eyes. Similarly, the myopic choroids in the anisometropic-lens–reared monkeys exhibited a 33-μm increase in thickness within 1 week and by 4 weeks after lens removal were 32 ± 13 μm thicker than those in the more hyperopic eyes. The bottom panels in Figure 9 show that in both the diffuser- and anisometropic-lens–reared monkeys these changes in choroidal thick-
ness occurred in the absence of substantial changes in overall eye size. During this same period the average changes in eye size, reflected by the interocular differences in vitreous chamber depth, were minor.

To increase statistical power, the data for the diffuser and anisometropic-lens–reared monkeys shown in Figure 9 were combined. The relative interocular changes in choroidal thickness that occurred in these experimental animals during the first 50 days of the recovery period are compared with those for the normal and plano control monkeys in Figure 10. During a comparable age period (i.e., from approximately 140 to 190 days of age), the normal subjects exhibited no systematic interocular changes in choroidal thickness (\( P < 0.33 \)). However during the first 50 days of the recovery period, the choroids in the more myopic eyes of the anisometropic monkeys demonstrated a significant relative increase in choroidal thickness in comparison with their fellow eyes (\( P < 0.001 \)). The difference in the slopes of the regression lines for the normal and anisometropic monkeys is highly significant (\( P < 0.002 \)).

This difference in slopes can be attributed in part to the fact that the direction of change was the same in every anisometric subject: In each case the choroid in the more myopic eye increased in thickness. Furthermore, the magnitude of the interocular changes was also much larger in the anisometric monkeys (Mann–Whitney test, \( P < 0.05 \)). For example, using as a reference the interocular difference in choroidal thickness that existed at the start of the recovery period, the greatest change in the interocular balance observed during the next 50 days in any of the normal and plano control monkeys was 35 \( \mu \text{m} \). In this instance, the right eye of this normal monkey was initially measured to be 10 \( \mu \text{m} \) thicker than the left eye choroid. At the next measurement session, the right eye choroid was 25 \( \mu \text{m} \) thinner than that in the left eye—that is, the interocular balance changed 35 \( \mu \text{m} \). In comparison, during the first 50 days of the recovery period, five of the seven anisometropic subjects showed changes of at least 50 \( \mu \text{m} \), with the largest change being 102 \( \mu \text{m} \).

**Observations in Individual Animals.** Many of the changes in choroidal thickness that have been described (for example, those that occurred after lens removal), were in the direction opposite the one that would be predicted if choroidal thickness were determined simply by overall eye size. Instead, it appears that the thickness of the choroid is determined by the eye’s effective ametropia. Several observations in individual animals, although there were not sufficient numbers to support statistical analysis, provided additional support for this idea.

During the recovery period, the refractive errors of many animals changed slowly but systematically, in a manner that would eliminate the experimentally induced ametropia. These refractive alterations were mediated primarily by overall ...

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**FIGURE 7.** Monocular form deprivation. Refractive error (left) and choroidal thickness (right; mean \( \pm \) SD) plotted as a function of age for three representative animals reared with diffuser lenses over one eye. The fellow eye viewed through clear, zero-powered lenses. The filled and open symbols represent the treated and nontreated eyes, respectively. The filled horizontal bars in each plot indicate the lens rearing period.

**FIGURE 8.** Refractive error (left) and choroidal thickness (right; mean \( \pm \) SD) plotted as a function of age for three representative monkeys reared with anisometropic treatment lenses and alternating monocular occlusion. The filled and open symbols represent eyes treated with negative and positive lenses, respectively. The filled horizontal bars designate the lens rearing period. For MKYs KIR (top) and ELI (middle) the lens powers that were used at the time that the first choroidal thickness measurements were obtained were 0.0 D and \( +2.0 \) D (KIR) and \( +17.5 \) D and \( +21.5 \) D (ELI), respectively. No subsequent changes in lens power were made for these two monkeys for the remainder of the treatment period. For MKY KO (bottom) the different lens powers that were used during the treatment period are shown in the right plot. The refractive error data have been replotted from Smith and Hung.17
changes in eye size. The long-term status of the choroid appeared to be different in monkeys that showed complete or near-complete recovery versus those animals that had not yet fully recovered. For example, in the monkeys that showed recovery from form-deprivation myopia (e.g., form-deprived MKY NE, Fig. 7, bottom), the interocular differences in choroidal thickness essentially disappeared as the refractive imbalance was eliminated. Conversely, form-deprived animals that had not fully recovered maintained interocular differences in choroidal thickness. For example, the previously deprived eyes of MKY JAS and MKY LAR were still myopic at the end of the observation period, and these eyes maintained thicker choroids than their fellow nontreated eyes throughout the observation period.

For one of the infants reared with anisometropic lenses (MKY KO, Fig. 8, bottom), the powers of the lenses were increased and then decreased during the treatment period. For the other three anisometropic infants, lens power was constant during the period when the ultrasonographic data were collected.) The data for this animal show compensating changes in choroidal thickness that are time locked to changes in treatment lens power. Increases in positive lens power for the right eye (open symbols) or decreases in negative lens power for the left eye (filled symbols), manipulations that produced relative myopic defocus, were both associated with increases in choroidal thickness. Changes in lens power that produced relative hyperopic defocus, an increase in negative power for the left eye or a decrease in positive power for the right eye, resulted in reductions in choroidal thickness.

**DISCUSSION**

During the first 9 to 10 months of a monkey’s life, a period that is equivalent to the rapid infantile phase of ocular growth in human infants, choroidal thickness increases at a slow but steady rate. Early during this period, the eyes of most normal monkeys also reach and then maintain the ideal refractive state, a low degree of hyperopia. The absence of a clear relationship between choroidal thickness and refractive error in normal/control monkeys suggests that these ideal ametropias have relatively little influence on choroidal thickness. The slow increase in choroidal thickness throughout early development presumably reflects normal maturation. Obviously, the increase cannot be accounted for by stretching as a result of normal ocular elongation. Measures of choroidal thickness in adult subjects (Hung L-F, unpublished data, 1999) suggest that the monkey choroid continues to increase in thickness until approximately 1.5 years, approximately the age at which axial growth normally begins to asymptote.

The main result of this study is that during this early period of monkey ocular development, choroidal thickness is
highly sensitive to abnormal refractive errors and optical defocus. Our most compelling evidence comes from the observation that an abrupt change in the eye’s effective refractive status causes rapid alterations in choroidal thickness, which, under a variety of rearing conditions, are consistently in the appropriate direction to reduce the eye’s ametropia. Experimental manipulations that impose myopic defocus (e.g., putting on a positive lens or removing a diffuser from an eye with form-deprivation myopia) produce a rapid and in some cases a dramatic increase in choroidal thickness. In contrast, manipulations that cause the eye to suddenly experience hyperopic defocus decrease choroidal thickness and reduce the normal rate of choroidal thickening. These observations arguably provide the strongest evidence to date that the primate eye, like the chicken eye, can identify the sign of optical defocus or at vide the strongest evidence to date that the primate eye, like the chick, is highly sensitive to abnormal refractive errors and optical defocus. Our most compelling evidence comes from the observation that an abrupt change in the eye’s effective refractive status causes rapid alterations in choroidal thickness. However, there are, however, substantial quantitative differences in the vision-dependent changes in choroidal thickness between chicks and monkeys. The largest choroidal thickness changes in the monkey were on the order of 40 to 50 μm, which for a typical infant would produce less than a 0.50-D change in refractive error. These thickness changes are comparable in magnitude with those observed in tree shrews and marmosets but are much smaller than in the chick, in which the choroidal thickness changes encompass a range of approximately 400 μm and can alter the eye’s refractive error by almost 10 D. Although the lower dioptric contribution of the choroid in monkeys can be attributed in small part to the fact that infant monkeys have larger eyes than young chicks, this interspecies difference appears primarily to reflect differences in the anatomy of the choroid. In the chick, vision-dependent changes in choroidal thickness reflect size changes in the conspicuous lacunae that are concentrated in the suprachoroidal space. These lacunae and smaller vessels in the choriocapillaris, which appear to be lymphatic vessels, dilate in response to myopic defocus, presumably as a result of fluid accumulation. Choroidal thinning is associated with compres-
sion of these vessels. The monkey choroid also contains lymphatic capillaries, and the suprachoroid is organized into flat sinuslike spaces that appear to be analogous to the large lymphatic lacunae in the chicken’s eye.31–33 However, these lymphatic structures occupy a smaller proportion of the choroid in the monkey and may cause the choroid to be thinner in monkeys (approximately 170 µm at age 3 months) than in chicks (approximately 250 µm at age 5 days).12 Moreover, the suprachoroid of monkeys is organized into a reticulum by interdigitating laminae that stain positively for smooth muscle α-actin.33 This regular architecture and its likely contractile nature could limit the degree to which the choroid in monkeys can thicken.

The way in which the eye’s refractive state influences choroidal thickness is not understood. That local choroidal expansion occurs in the chick during the recovery from form deprivation that is restricted to only a portion of the retina11 suggests that visual information is communicated to the adjacent choroid from localized retinal mechanisms.34 These choroidal changes could be mediated through local molecular and/or neural actions. Changes in choroidal retinoic acid synthesis,35 ion36 and protein concentrations,37 proteoglycan synthesis,11,15 and/or blood flow38,39 during and after form deprivation may provide the osmotic drive for fluid accumulation. Histologic observations suggest that during the recovery from form-deprivation myopia there is a massive movement of fluid across the retina into the choroid27 and an increase in active fluid transfer within the choroidal lymphatic system.40 In addition, both the chick and primate choroids contain nonvascular contractile cells,33,41,42 and it has been suggested recently that in primates intrinsic choroidal ganglia could mediate some local choroidal responses through innervation to smooth muscle cells.53 However, because disrupting information flow through the optic nerve prevents choroidal thinning in response to hyperopic defocus,12 extracellular factors may also influence vision-dependent changes in choroidal thickness.11,12 The central nervous system is known to innervate the choroid from a variety of sources.43

Regardless of how visual experience influences choroidal thickness, it appears that as in the chick, changes in choroidal thickness are intimately involved in the visual regulation of refractive development in monkeys. That choroidal thickness is modulated by visual experience in such diverse species as the chicken,11,12 tree shrew,13 marmoset,20 and monkey suggests that the same phenomenon may occur in humans. We propose that, at least early in life, choroidal thickness in humans is also influenced by factors associated with the eye’s effective refractive state. If this proves to be the case, the choroid may participate in the regulation of the refractive state of the human eye.

References


