Emmetropization in the Rhesus Monkey (Macaca mulatta): Birth to Young Adulthood

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OBJECTIVE. To provide baseline measurements on the postnatal changes in refractive error, corneal curvature, and axial elongation of the eyes of normal monkeys. Little is known about the course of normal eye growth from birth to adolescence, particularly how refractive parameters co-vary during development. In animal models of ametropia, usually one eye is manipulated and the fellow eye serves as a control. However, given individual differences, and without baseline data, it is impossible to determine whether either eye develops normally.

METHODS. Measurements were obtained on 237 rhesus monkeys, whose ages ranged from birth to 5 years. Examinations included cycloplegic refraction by retinoscopy, keratometry measurements, and A-scan ultrasound measurements of axial length. The time course of development was evaluated using a growth curve analysis appropriate for a mixture of cross-sectional and longitudinal data.

RESULTS. At birth, all three parameters were normally distributed and only weakly correlated. Monkeys had +7.0 D (SD = 2.3 D) of hyperopia, corneal power of 58 D (SD = 1.0 D), and axial length of 13.2 mm (SD = 0.4 mm). Refractive error ranged from +0.5 D to +14.5 D, with a mean difference between the two eyes of 0.5 D. Corneal curvature ranged from 61 D to 54 D, with a mean difference between the two eyes of 0.8 D. Axial length ranged from 12.0 mm to 14.2 mm, with a mean difference between the two eyes of 0.1 mm. Although the degree of hyperopia achieved asymptote, of +2 D, shortly after 1 year of age, corneal curvature and axial length did not achieve asymptote until nearly 5 years of age. By this time, refractive error had declined by 5 D, corneal curvature had declined by 7 D, and axial length had increased by 6 mm.

CONCLUSIONS. The magnitude of the individual differences that can occur in a small sample of experimental subjects is large enough to necessitate reference to age norms derived from a large population. Our results provide a baseline for studies of normal and abnormal eye growth and ametropia in primates. Our results also led to the confirmation of a set of "rules" that have been offered as an explanation of how these three parameters interact during emmetropization. (Invest Ophthalmol Vis Sci. 1999;40:214-229)

In many vertebrate species, including primates, the neonatal eye is too short in relation to the power of its optics. As a result, in the absence of accommodation, neonates have a hyperopic refractive error such that images of a distant target are focused beyond the photoreceptor layer of the retina. Yet the normal adult eye, without accommodation, is emmetropic, with images of a distant target focused near the retina. Emmetropia is properly defined as the adult value achieved by the majority of the population, and not simply as zero refractive error. 1-4 Sorsby 5 described emmetropia in the human population as "a point in the modal range which extends from 0 to +2 D." His studies revealed that for a large sample of the human population, 75% of the refractive errors fell between 0 and +1.9 D in the young adult. His measurements showed a leptokurtic distribution, with an average of approximately 1 D of hyperopia. A leptokurtic distribution is also characteristic of young adult rhesus macaques. 2,5

Emmetropization is the process by which neonatal hyperopia is reduced. It involves the coordination of the postnatal axial elongation of the eye with the maturation of its refractive components. The precision with which the elongation of the eye is matched to the power of its optics, as found in the majority of the adult human population, suggests that genetic and experiential factors work in concert to achieve emmetropia. 6-13

Theoretical issues concerning the mechanisms involved in emmetropization have fascinated scientists for well over a
century. These issues take on increased practical importance in clinical cases in which emmetropization is not successful, and vision is impaired. A number of animal models, in a variety of species, have been designed with the goal of elucidating the mechanisms of emmetropization by disrupting this process to produce ametropias. Although such studies have shown that abnormal visual input alters postnatal eye growth, very little is known about the normal course of refractive development from birth through adolescence, from a large sample of a normal population. As a result, the mechanisms involved in emmetropization remain only partially understood.

Studies of Primate Emmetropization

Because of the close similarity in the anatomy and function of the macaque visual system to that of humans, these monkeys have long served as ideal subjects to address questions about the development of the human visual system. Although previous studies have reported certain ocular parameters of normal monkeys at various ages, for several reasons the utility of that information is limited. For example, Kiely et al. reported cross-sectional measurements of ocular parameters obtained from 30 rhesus monkeys (Macaca fascicularis) whose ages ranged from 7 to 57 weeks (n = 16), from 162 to 224 weeks (n = 7), and monkeys more than 5 years of age (n = 7). For some of these monkeys, measurements were made on only one eye of an individual because the opposite eye was fitted with an extended-wear contact lens as part of a separate study. This assumes that contact lens treatment of one eye has no effect on the growth of the fellow eye, an assumption that is now known to be suspect. Although the report provided some information concerning the refractive state in that species of macaque, the very small sample size, over such a wide age range, is not sufficient for generalization to a normal population. The primary advantage of an animal model is that it can provide a level of detail that is difficult to obtain from a human population, particularly within the first few months after birth. Furthermore, in the study by Kiely et al., although less than half of the young monkeys underwent refraction 10 minutes after the instillation of one drop of tropicamide (0.5%), the remainder had their accommodation controlled by distance fixation. Neither procedure, however, is guaranteed to relax accommodation sufficiently, particularly because measurements were obtained while the monkeys were not anesthetized.

Young and colleagues performed cycloplegic (Cyclogel 1%) refraction on more than 1000 rhesus monkeys (Macaca mulatta), and other species of macaque, while the animals were anesthetized. However, the incredibly large number of measurements reported does not possess sufficient information to elucidate the course of postnatal eye growth and emmetropization in the primate. Their studies were concerned more with the "end point" of development, and in particular the refractive status of adult monkeys. This focus may have been necessary because the actual ages of the monkeys were unknown and had to be estimated on the basis of body weight. As a result, measurements of refractive error of "adolescent" monkeys were presented on a scale that was too coarse to be illuminating concerning the course of postnatal development.

Finally, Young and his colleagues did not report measurements of axial length or corneal curvature, and, thus, his studies provide no information about how these three parameters covary during emmetropization.

In summary, there are limitations to the conclusions that can be drawn from previous studies of monkeys. Uncertainties remain about three primary sources of variation of the refractive components in a normal population. The first source of variability is the presence of individual differences from animal to animal. The second source of variability is the age of the animal, because several ocular parameters vary with age. The third source of variability is the difference between the two eyes in the same animal. A necessary step for building a unified model of emmetropization in primates is to obtain a comprehensive description of the developmental changes in several eye parameters, as a function of age, in both eyes of a normal population. Because the mechanisms that lead to emmetropization have to operate by the covariation of various eye parameters, over age, within the two eyes of the same animal, a second necessary step is to make longitudinal assessments of developmental changes in individual subjects.

At the Yerkes Regional Primate Research Center of Emory University (Atlanta, GA), we were able to collect data on a large number of eyes from normal rhesus monkeys, ranging in age from birth to young adulthood, including both cross-sectional samples of the population and longitudinal samples of selected animals. The present report describes postnatal changes in three ocular parameters: refractive error, axial elongation, and corneal curvature. On the basis of these data, we corroborate three "rules" that appear to describe how these parameters covary to achieve emmetropization in primates.

Methods

Subjects

Ocular data were collected from 237 normal rhesus monkeys (Macaca mulatta) born at the Yerkes Regional Primate Research Center of Emory University.

Longitudinal Data. Five monkeys were examined regularly starting within a few weeks after birth and continuing up to 120 weeks of age in four monkeys and up to 80 weeks of age in one monkey. During the first postnatal month, these monkeys were reared in individual acrylic plastic isolates in our nursery, and thereafter in a social group.

Cross-Sectional Data. One or more measurements were also obtained from 232 normal monkeys, ranging in age from birth to 5 years. Although the majority of monkeys underwent only one ophthalmic examination, 30 monkeys had examinations performed at more than one age. A large subset of the animals (n = 144) was made up of neonates who were examined within the first week after birth. Birth weights of all neonates were in the normal range, and their physical condition was robust enough for them to undergo anesthesia for the ophthalmic examination. In the present report, monkeys less than 1 week old are referred to as "neonates"; monkeys between 1 week and 2 years of age are referred to as "infants"; monkeys older than 2 years are referred to as "adolescents"; and monkeys more than 5 years of age are referred to as "young adults."

All protocols associated with the care and handling of the monkeys conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The Yerkes Regional Primate Research Center of Emory University is fully
OPHTHALMIC EXAMINATIONS

Animals were initially given an ophthalmologic examination to confirm that no abnormalities were present. The majority of the eye examinations were performed by the same pediatric ophthalmologist (AF). Examinations were conducted while the monkeys were under general anesthesia (ketamine/acepromazine 10 mg/90 mg ratio/ml at 0.1 ml/kg). Monkeys were in the supine position with the head immobilized by a head holder. During the examination the eyelids were held open with a speculum, and the cornea was kept irrigated with regular instillation of sterile saline. The overall examination included biomicroscopy, applanation tonometry, pupil and corneal diameter measurements, and fundus examination. Measures obtained specifically for this study included the following: cycloplegic refraction by retinoscopy (3 drops of 1% cyclopentolate and 3 drops of 2.5% phenylephrine hydrochloride at 5-minutes interval, 45 minutes before retinoscopy); axial length by A-scan ultrasonography (Sonomed); and corneal curvature based on keratometry (Bausch & Lomb). Refractive errors are reported as the spherical equivalent in diopters (D). Keratometry values are reported in diopters and are the mean of three horizontal measurements and three vertical measurements. Axial length measurements are reported in millimeters and are the mean of 10 consecutive ultrasound measurements. We did not obtain all measurements on all animals. Specific numbers of animals used for each measure are specified in the Results section.

RESULTS

REFRACTIVE ERROR

Comparison of the Neonatal to the Adolescent Eye.

There were three major changes in refractive error between the neonatal period and young adulthood. First, the average magnitude of hyperopia in the population was reduced by approximately 5 D. Second, the variability of refractive error measurements in the adolescent population (mean variance = 1.4 D) was significantly reduced, compared with the amount present at birth (mean variance = 5.6 D), F(138.46) = 4.1, P < 0.01. Third, the variability in the magnitude of the absolute values of the interocular differences during adolescence (mean variance = 0.1 D) was significantly reduced, compared with the amount present at birth (mean variance = 0.8 D), F(137.46) = 7.8, P < 0.01.

Figure 1A shows the frequency distribution of 277 measurements of refractive error from both eyes of 139 neonatal monkeys measured within the first week after birth. Refractive errors, ranging from +0.5 D to +14.5 D, were normally distributed, with a mean of +7 D and a SD of 2.3 D. Figure 1B shows a corresponding frequency distribution of 94 measurements of 46 adolescent monkeys. Refractive error measurements, ranging from −1.0 D to +6.5 D, formed a leptokurtic distribution, with a mean of +2 D and a SD of 1.2 D. The adolescent measurements were significantly different from the neonatal measurements, t(184) = 14.1, P < 0.01. The frequency distribution of the absolute values of interocular differences is illustrated in Figure 1C for neonates and in Figure 1D
for adolescents. The average interocular difference of 0.5 D in neonates was significantly reduced by ½ to 0.2 D in adults, \( t(183) = 2.2, P < 0.05 \).

**Postnatal Development.** We first determined that the average residuals of the growth curves of the left and the right eyes of monkeys in the cross-sectional group were not significantly different from each other, paired \( t(150) = 1.36, P > 0.05 \), and combined the measurements of the two eyes. We then fit a growth curve to the cross-sectional data and demonstrated that the average residuals were not significantly different from the average residuals of the longitudinal measurements from the cross-sectional growth curve, Mann-Whitney \( U = 0.7, P > 0.05 \). With this justification, the measurements obtained from the cross-sectional and longitudinal groups were combined to establish the largest possible database for an examination of postnatal development. Figure 2 shows 559 measurements of refractive error as a function of age from the combined data set. The data in Figure 2A are shown on a log scale to emphasize the changes in refractive error that occur early in development, whereas Figure 2B shows these same data on a linear scale to emphasize the refractive state later in development. The smooth line in each figure shows the best fitting growth curve. The square symbols and error bars shown in Figure 2B represent the mean and standard error values of the age bins of refractive error, which were derived separately from the growth curve analyses. A comparison of the growth curve with the age bin values across ages furnishes additional confirmation that the growth curve derived by our methods provides a good description of the refractive development from birth to young adulthood. Values for the growth curve at selected ages are listed in Table I.

As shown in Figure 2A, growth curve values during the first week were at about +7 D of hyperopia, which reflects the neonatal distribution shown in Figure 1A. As seen in Figure 2B, growth curve values beyond 2 years of age are at approximately +2 D, which reflects the adolescent distribution shown in Figure 1B. Figure 2A shows that refractive errors were somewhat stable for several days after birth; evaluation of the
Figure 2. Scatter plot of measurements of refractive error (in diopters) from birth to 5 years of age shown on a logarithmic scale (A) to illustrate changes that occur early in development and on a linear scale (B) to illustrate changes that occur later in development. The solid line shown in each figure is the growth curve generated from the cross-sectional data. The filled triangles and dotted lines in (A) show the data of the 5 monkeys that comprised the longitudinal group. The filled squares in (B) represent the mean of the age bin values, which were calculated separately from the growth curve. Error bars, ±SE.
TABLE 1. Growth Curve Values and the Absolute Interocular Differences at Selected Ages

<table>
<thead>
<tr>
<th>Postnatal Age</th>
<th>Refractive Error (D)</th>
<th>Corneal Curvature (D)</th>
<th>Axial Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y W D</td>
<td>58 ± 0.07 (0.55)</td>
<td>58 ± 0.12 (0.64)</td>
<td>13.1 ± 0.02 (0.11)</td>
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<tr>
<td>1 7 8</td>
<td>58 ± 0.16 (0.69)</td>
<td>58 ± 0.16 (0.64)</td>
<td>13.4 ± 0.02 (0.10)</td>
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<tr>
<td>2 14 21</td>
<td>58 ± 0.23 (0.74)</td>
<td>58 ± 0.19 (0.64)</td>
<td>13.7 ± 0.04 (0.09)</td>
</tr>
<tr>
<td>3 28</td>
<td>58 ± 0.16 (0.54)</td>
<td>58 ± 0.16 (0.54)</td>
<td>13.9 ± 0.05 (0.08)</td>
</tr>
<tr>
<td>4 56</td>
<td>56 ± 0.13 (0.23)</td>
<td>56 ± 0.13 (0.23)</td>
<td>14.3 ± 0.08 (0.08)</td>
</tr>
<tr>
<td>12 84</td>
<td>55 ± 0.12 (0.28)</td>
<td>55 ± 0.12 (0.28)</td>
<td>15.1 ± 0.10 (0.08)</td>
</tr>
<tr>
<td>16 112</td>
<td>54 ± 0.11 (0.36)</td>
<td>54 ± 0.11 (0.36)</td>
<td>15.6 ± 0.09 (0.08)</td>
</tr>
<tr>
<td>20 140</td>
<td>54 ± 0.12 (0.41)</td>
<td>54 ± 0.12 (0.41)</td>
<td>16.0 ± 0.07 (0.07)</td>
</tr>
<tr>
<td>24 168</td>
<td>53 ± 0.11 (0.40)</td>
<td>53 ± 0.11 (0.40)</td>
<td>16.5 ± 0.06 (0.06)</td>
</tr>
<tr>
<td>28 196</td>
<td>53 ± 0.11 (0.37)</td>
<td>53 ± 0.11 (0.37)</td>
<td>16.7 ± 0.05 (0.06)</td>
</tr>
<tr>
<td>32 224</td>
<td>53 ± 0.10 (0.39)</td>
<td>53 ± 0.10 (0.39)</td>
<td>16.8 ± 0.05 (0.06)</td>
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<tr>
<td>36 252</td>
<td>53 ± 0.09 (0.42)</td>
<td>53 ± 0.09 (0.42)</td>
<td>17.0 ± 0.05 (0.07)</td>
</tr>
<tr>
<td>40 280</td>
<td>53 ± 0.09 (0.44)</td>
<td>53 ± 0.09 (0.44)</td>
<td>17.1 ± 0.04 (0.07)</td>
</tr>
<tr>
<td>44 308</td>
<td>53 ± 0.10 (0.45)</td>
<td>53 ± 0.10 (0.45)</td>
<td>17.2 ± 0.04 (0.07)</td>
</tr>
<tr>
<td>48 336</td>
<td>53 ± 0.11 (0.46)</td>
<td>53 ± 0.11 (0.46)</td>
<td>17.4 ± 0.04 (0.07)</td>
</tr>
<tr>
<td>1 52 364</td>
<td>53 ± 0.12 (0.48)</td>
<td>53 ± 0.12 (0.48)</td>
<td>17.5 ± 0.05 (0.07)</td>
</tr>
<tr>
<td>1.5 76 532</td>
<td>53 ± 0.15 (0.49)</td>
<td>53 ± 0.15 (0.49)</td>
<td>17.9 ± 0.07 (0.07)</td>
</tr>
<tr>
<td>3 156 1092</td>
<td>52 ± 0.25 (0.52)</td>
<td>52 ± 0.25 (0.52)</td>
<td>18.6 ± 0.06 (0.06)</td>
</tr>
<tr>
<td>4 208 1456</td>
<td>52 ± 0.30 (0.61)</td>
<td>52 ± 0.30 (0.61)</td>
<td>19.1 ± 0.07 (0.06)</td>
</tr>
<tr>
<td>5 256 1792</td>
<td>51 ± 0.39</td>
<td>51 ± 0.39</td>
<td>19.5 ± 0.08 (0.06)</td>
</tr>
</tbody>
</table>

Values are means ± SE, with mean OD - OS values in parentheses.

growth curve values indicated that refractive error began a noticeable and rapid decline at approximately 10 days after birth. By 28 days, 47% of the total decline in refractive error had occurred, with a mean of +4.8 D. As seen in Figure 2B, this was followed by a somewhat slower phase of decline of the neonatal hyperopia; still, by 24 weeks 80% of the total postnatal decline had occurred, with a mean of +3.2 D. By 1 year of age, refractive development had slowed even more, by which time 95% of the total decline in the mean refractive error had occurred, with a value of +2.5 D. Finally, the growth curve showed no further changes in refractive error (+2.1 D) beyond 76 weeks. A second method of defining asymptote, namely the age at which the growth curve first fell within the statistical 95% upper limit of the growth curve at 5 years (+2.5 D), yielded the age of 53 weeks.

Figure 3 shows the mean growth curve value and its standard error generated from the absolute value of the differences in refractive error measurements between the right and the left eyes, from birth to young adulthood. Interocular differences of refractive error were variable at birth, reflecting the distribution shown in Figure 1C. Variability decreased after approximately 50 days of age, and interocular differences held steady or perhaps declined slightly until approximately 1.5 years of age. Thereafter, interocular differences in refractive error began a gradual increase, which continued into young adulthood.

Longitudinal Assessments. The dashed lines shown in Figure 2A connect measurements from the five monkeys that were measured longitudinally. Examination of the dashed lines reveals that the distribution of the growth curve fell within the range of the larger group and that, on average, the rate and magnitude of refractive development for this subset of animals were similar to that of the larger population. However, the longitudinal results also revealed an additional fact that was not appreciated from an examination of the cross-sectional data. We found that monkeys that were born with greater amounts of hyperopia appeared to exhibit a faster rate of decline than did monkeys that were born with lower amounts of hyperopia. This impression was confirmed statistically, in that there was a highly significant relationship (r = 0.99) between an individual's neonatal refractive error and how much the refractive error declined by 1.5 years, t(3) = 11, P < 0.01. These longitudinal results suggested an underlying "rule" that may be in operation during emmetropization: Regardless of the amount of neonatal hyperopia, reduce it at a rate such that, by 1.5 years of age, the young adult value of +2 D is achieved.

Corneal Curvature

Comparison of the Neonatal Eye to the Adolescent Eye. Corneal curvature was reduced by approximately 7 D during postnatal development. The variability in corneal power was not significantly increased from the neonatal period (mean variance = 1.6 D) to adolescence (mean variance = 3 D), t(108,10) = 0.6, P > 0.05. The average amount of the absolute value of the interocular difference was already very small at birth and remained small in the adolescent, t(118) = 0.8, P > 0.05.

Figure 4A shows the frequency distribution of 218 measurements of corneal curvature of both eyes of 109 neonatal monkeys. Measurements of corneal curvature, ranging from 54 D to 61 D, were normally distributed with a mean of 58 D and a SD of 1 D. Figure 4B shows the frequency distribution of 22 measurements from 11 monkeys ranging in age from adolescence to young adult; the adolescent measurements were sig-
The smooth line in each figure shows the best fitting growth curve for neonates and in Figure 4C for neonates and in Figure 4D for adolescents. The average interocular difference was 0.8 D in neonates and 0.6 D in adolescents. In addition, there was no significant difference in the amount of variability of interocular differences at birth (mean variance = 0.5 D) and the variability of the interocular differences in adolescence (mean variance = 0.4). t(108,10) = 1.4, P > 0.05.

Postnatal Development. Because we determined that the average residuals of the growth curves of the two eyes of the cross-sectional group were not significantly different from each other, paired t(92) = -0.49, P > 0.05, we combined the measurements of the left and the right eyes. Next, we verified that the average residuals of the longitudinal measurements from the growth curve of the cross-sectional group were not significantly different from the average residuals of the cross-sectional measurements, Mann-Whitney U = 1.5, P > 0.05. Then, the combined data set was used to examine the postnatal development of corneal curvature. Figure 5 shows 350 measurements of corneal curvature from the combined data set. The smooth line in each figure shows the best fitting growth curve. Also presented, in Figure 5B, are the square symbols with error bars denoting the mean and standard error values of the age bin measurements of corneal curvature, which were derived separately from the growth curve analyses. A comparison of the growth curve with the mean and standard error values of the age bin, across ages, confirms that the growth curve appears to describe well the changes that occurred from birth to young adulthood. Furthermore, in those isolated cases in which the two methods do not agree with one another, the growth curve analyses appear to be superior. It is clear, for example, that the growth curve was not unduly influenced by what we consider to be outliers, such as those measurements obtained for monkeys from 1200 to 1400 days of age. Table 1 lists the growth curve values for selected ages across postnatal development.

As shown in Figure 5A, growth curve values for corneal curvature were approximately 58 D at birth, reflecting the distribution shown in Figure 4A. As demonstrated by the range of individual values of corneal power and the mean growth curve, corneal curvature changed little over the first 3 weeks after birth. Starting at approximately 28 days of age, the cornea began to flatten, marking the beginning of a short but very rapid rate of change in the power of the cornea. As shown in Figure 5B, by approximately 24 weeks of age, the postnatal decline had slowed its rate of change, at which time corneal power had decreased to a mean value of 53 D, which is 71% of the total decline in the steepness of the cornea from birth to 5 years. Thereafter, the corneas continued to flatten, albeit at a very slow rate, and by 3 years of age, corneal power had a mean value of 52 D, which is 86% of the total decline during development. From Figure 5B it is clear that, unlike refractive error, changes in corneal curvature did not asymptote until shortly before monkeys reached young adulthood. The age marking the approach to asymptote at young adult values, defined by the age at which the growth curve first fell within the statistical 95% upper limit of the growth curve value at 5 years, was 4.5 years of age.

Figure 6 shows the growth curve generated from the absolute interocular differences in corneal power from birth to young adulthood. Interocular differences of corneal power were moderately high at birth, reflecting the distribution shown in Figure 4C. During the first part of the rapid phase of postnatal decline in corneal curvature, the differences between the two eyes also declined rapidly, reaching their lowest value at around 56 days of age. Shortly after this time, however, interocular differences began to rise once more and continued to increase into young adulthood.

Longitudinal Assessments. The dashed lines shown in Figure 5A show that the distribution of the longitudinal measurements of corneal curvature fell within the range of the larger cross-sectional group. On average, the rate and magnitude of the decline of corneal power for this subset of monkeys were similar to those of the larger population. In addition, the relative magnitude of corneal power, across individuals, was maintained over the course of early development, even as the corneas flattened. That is, there was no significant relationship between the power of the corneas at birth and how much they flattened during the first 1.5 years, r = 0.79, t(3) = 2.2, P > 0.05. This indicates that changes in corneal curvature may proceed at a relatively constant rate, regardless of the curvature of the cornea at birth; a linear regression analysis found nearly identical slopes of age versus corneal curvature (-0.2, -0.2, -0.3, -0.3, and -0.3) among monkeys. Taken together, this suggested another possible "rule" that may be operating during emmetropization: Regardless of the magnitude of corneal power at birth, maintain that shape for approximately 4 weeks, and then start to flatten at a constant rate.
Figure 4. Frequency distributions of measurements of corneal curvature (in diopters) from both eyes of neonatal (A) and adolescent (B) rhesus monkeys and the absolute values of the interocular differences (OD - OS) of neonatal (C) and adolescent (D) populations.

Axial Length

Comparison of the Neonatal Eye to the Adolescent Eye. The eye increased its axial length by approximately 6 mm between birth and young adulthood. The variability of the axial length measurements of the globe, from animal to animal, in neonates (mean variance = 0.15 mm) was significantly larger compared with that of the adolescent population (mean variance = 0.38 mm), F(131,50) = 0.4, P < 0.01. Although the average amount of the absolute values of the interocular difference in axial length was already small at birth, it was reduced significantly in the adolescent group, t(181) = 3.5, P < 0.01.

Figure 7A shows the frequency distribution of 264 measurements of the axial length of both eyes of 132 neonatal monkeys. Axial length measurements, ranging from 12.0 mm to 14.4 mm, were normally distributed, with a mean of 13.2 mm and a standard deviation of 0.4 mm. Figure 7B shows the frequency distribution of 102 measurements from 51 adolescent monkeys; the adolescent measurements were significantly different from the neonatal measurements, t(181) = −75.4, P < 0.01. Measurements of axial length of the adolescent to young adult group ranged from 17.8 mm to 20.1 mm and were normally distributed with a mean of 19 mm and a standard deviation of 0.6 mm. Frequency distributions of the absolute values of the interocular differences in axial length are shown in Figure 7C for neonates and in Figure 7D for adolescents. The average absolute value of the interocular differences was 0.12 mm for neonates and 0.06 mm for adolescents. The amount of variability of the interocular differences in measurements of axial length was reduced by ½ from birth (mean variance = 0.01 mm) to adolescence (mean variance = 0.005 mm), F(131,50) = 2.19, P < 0.01.

Postnatal Development. Because we determined that the average residuals of the growth curves of the two eyes were not significantly different from one another, paired-t(160) = 0.25, P > 0.05, we combined the measurements of the left and the right eyes. Next, it was determined that there were no significant differences between the average residuals of the
Figure 5. Scatter plot of measurements of corneal curvature (in diopters) from birth to 5 years of age shown on a logarithmic scale (A) to illustrate changes that occur early in development and on a linear scale (B) to illustrate changes that occur later in development. The solid line shown in each figure is the growth curve generated from the cross-sectional data. The filled triangles and dashed lines shown in (A) show the data of the 5 monkeys that comprised the longitudinal group. The filled squares in (B) represent the mean of the age bin values, which were calculated separately from the growth curve. Error bars, ±SE.
changes in the steepness of the cornea, axial elongation of the globe did not approach asymptote until the monkeys reached adulthood. The age at which the growth curve fell within the statistical 95% upper limit of the growth curve value obtained at 5 years of age was found to be 4.7 years.

Figure 9 shows the growth curve generated from the absolute value of the differences between the two eyes for measurements of axial length, from birth to young adulthood. Unlike the pattern of interocular differences of refractive error and corneal curvature, interocular differences of axial length were at their highest at birth. However, soon after birth the magnitude of the absolute interocular differences declined rapidly, reaching their lowest level by 120 weeks of age. From this time, interocular differences of axial length measurements remained small in young adulthood.

Longitudinal Assessments. The dashed lines shown in Figure 8A reveal the similarity of this subset of data to that of the cross-sectional population. For this subset of monkeys, it was also the case that axial elongation of the globe appeared to proceed rapidly, soon after birth. However, the longitudinal results also suggested a pattern that was not appreciated when examining the results of the larger group. That is, within this group, two monkeys at the extreme values (+9 D, +4 D) of the neonatal refractive error distribution showed very different patterns of axial elongation across the course of development. The monkey with the least amount of hyperopia had eyes that grew slower and were shorter than the eyes of the monkey with the greatest amount of hyperopia. Despite this trend, however, we could not demonstrate a statistically significant relationship between refractive error at birth and the amount of axial elongation, r = 0.11, t(3) = 0.2, P > 0.05, most likely because of our small sample size. Nevertheless, this trend in the data suggested the following “rule”: The greater the amount of hyperopic blur at birth, the faster the rate of axial elongation of the eye.

Relationships between Eye Components
To determine the extent to which these three ocular parameters were correlated during development, the results for the right eyes were separated into discrete age bins. Figure 10 shows scatter plots of the relationship between refractive error, corneal curvature, and axial length of the right eyes of neonatal monkeys. The scatter plots revealed that there was little or no relationship between any of the three ocular parameters at birth. This impression was confirmed by the analyses that yielded statistically significant, yet weak, correlations, accounting for less than 10% of the variance (r values are shown in Fig. 11). We conclude, therefore, that these three parameters are only weakly correlated at birth. So, for example, whether an eye is very short or very long at birth does not appear to put strong constraints on the amount of refractive error that is present.

These same analyses were repeated for several different age groups, and the results are summarized in Figure 11, which shows the absolute values of the Pearson r correlation coefficients, for right eyes, at each age bin. An examination of Figure 11 reveals that there were marked changes in the strength of the relationships between pairs of parameters over the course of postnatal development. Between the ages of 10 to 50 days after birth, although there was a very strong, significant correlation between measurements of corneal curvature and the axial length of the eye (r = 0.97), refractive error was not significantly correlated with either parameter. Shortly thereafter, although all three parameters were significantly and highly
correlated between the ages of 50 to 150 days, corneal curvature and axial length continued to maintain the stronger relationship ($r = -0.86$). Beyond this period, however, refractive error was no longer significantly correlated with either corneal curvature or axial length. Yet, corneal curvature and axial length remained strongly and significantly correlated with each other up to 1000 days (3 years) of age.

**DISCUSSION**

**Postnatal Eye Growth**

The present results provide normative values of refractive error and two of its primary causal components, of a large sample of rhesus monkeys ranging in age from birth to young adulthood. At birth, measurements of refractive error, corneal curvature, and axial length are highly variable, normally distributed, and weakly correlated, with relatively small or moderate absolute differences between the two eyes. Although all three parameters have distinct growth phases, the three parameters differ somewhat in terms of the time course over which these phases occur. For example, although refractive error and axial length had undergone substantial maturation within 28 days of birth, corneal curvature remained unchanged during this period. The most rapid phase of growth for all parameters occurred during the first few months after birth. During this period, the magnitude of the interocular differences, of all three parameters, declined.

By the end of the first year, refractive error, corneal curvature, and axial length had matured by 95%, 71%, and 69%, respectively, of the total amount of change observed between birth and young adulthood. Over the course of the first year, changes in corneal curvature and axial length became highly correlated a few weeks after birth, and remained so until nearly 3 years of age. However, changes in refractive error were not correlated with either parameter except for a brief period early in development. That is, between 50 and 150 days of age, the
Figure 8. Scatter plot of measurements of axial length (in millimeters) from birth to 5 years of age shown on a logarithmic scale (A) to illustrate changes that occur early in development, and on a linear scale (B) to illustrate changes that occur later in development. The solid line shown in each figure is the growth curve generated from the cross-sectional data. The filled triangles and dashed lines in (A) show the data of the 5 monkeys that comprised the longitudinal group. The filled squares in (B) represent the mean of the age bin values, which were calculated separately from the growth curve. Error bars, ±SE.
time during which all three parameters were changing rapidly, refractive error was highly correlated with both corneal curvature and axial length. After this time, however, it was not surprising that refractive error was not strongly correlated with any other parameter because refractive error begins to asymptote shortly after 1 year of age, and, thus, there was no further opportunity for it to covary. Because corneal curvature and axial length continued to change, however, they remained strongly correlated until the middle of the adolescent period.

By young adulthood, variances of refractive error and axial length had decreased, but corneal curvature had not. Although corneal curvature and axial length maintained normal distributions, refractive error measurements became more tightly clustered around their mean value. Although the size of the interocular differences remained small into young adulthood for axial length, the absolute value of the interocular differences increased progressively for refractive error and corneal curvature.

**Rules That May Apply to Emmetropization**

Our evaluation of the data of the larger cross-sectional group, and that of the smaller longitudinal group, provide support for three rules that may apply to emmetropization:

1. Regardless of the amount of neonatal hyperopia, reduce it at a rate such that, by 1.5 years of age, the young adult value of +2 D is achieved.
2. Regardless of the absolute magnitude of corneal power at birth, maintain that shape for a few weeks and then start to flatten at a constant rate.
3. The greater the amount of hyperopic blur at birth, the faster the rate of axial elongation of the eye.

Rules along these lines have been articulated either explicitly or implicitly by previous authors. Our evidence in support of rules 1 and 2 is stronger than for rule 3, which is based on the results of two monkeys and did not reach statistical significance. However, corroborating evidence consistent with rule 3 also comes from human studies, which have shown that the rate of decline of refractive error in children is significantly related to their initial refractive error.

In summary, our scenario for emmetropization is as follows. At birth, all three parameters are normally distributed and only weakly intercorrelated. Immediately after birth, the eye begins to elongate. The cornea remains in its birth state for several weeks and then begins to flatten at a steady rate. The amount of hyperopic blur drives the rate of axial elongation. The greater the hyperopia the faster the rate of decline, such that all eyes achieve +2 D by 1.5 years of age. Once emmetropia is achieved, changes in the cornea and axial length are coordinated such that even if both continue to change they change at a rate that maintains emmetropia. Of course, this
Emmetropization

Comparison to Human Studies

Emmetropia. Although the present results from rhesus monkeys bear a striking similarity to the results of emmetropization in humans, some might argue that because the end point of refractive development in monkeys is +2.1 D rather than +1 D as in humans this difference reflects less precise emmetropization in monkeys. However, this difference between humans and monkeys regarding the degree of hyperopia may be a function of the small eye artifact as theorized by Glickstein and Milloot.65 We have calculated that the magnitude of the artifact for a young adult monkey with an axial length of 19 mm would be approximately +1 D, effectively eliminating any difference in the end point of emmetropization between humans and monkeys. We conclude, therefore, that the 1 D difference in the end point of emmetropization between monkeys and humans is not significant.

Emmetropization. Regarding postnatal development from birth to young adulthood, rhesus monkeys reduce refractive error by 5 D, reduce corneal curvature by 7 D, and increase axial length by 6 mm. In comparison, humans show a decrease in refractive error of approximately 3 D, a decrease in corneal curvature of 5 D, and an increase in axial length of 7 mm from birth to adulthood. Yet, although the absolute values differ between species, the two groups are alike in many respects. For example, the shapes of their frequency distributions, for all three parameters, are identical at birth and in adulthood. In addition, both groups exhibit distinct growth phases, which are most rapid early in development and become more gradual as the refractive components reach maturity. Like rhesus monkeys, human neonates have measurements of refractive error, corneal curvature, and axial length that are highly variable and normally distributed.65,66,67,68,69 Studies in human neonates and infants, using cycloplegic retinoscopy, have shown that refractive errors can range from +1 D to +6 D, with a mean of approximately +4 D.65,66,67 Measurements of corneal curvature range from 46 D to 52 D, with a mean of approximately 48 D.67,68,69 Typically, axial length measurements in the neonate range from 15.3 mm to 17.6 mm, with a mean of approximately 16.6 mm.67,68,69 Finally, during childhood, measurements of all three parameters have shown that the two eyes are nearly identical to each other,67,68,69 and as the refractive components mature, variability between individual subjects declines.67,68,69

Humans and monkeys may differ, however, in the order in which the three parameters appear to asymptote during devel-
opment. In children, corneal curvature has been reported to be the first to plateau, somewhere between 6 months of age and 2 to 3 years of age, whereas axial elongation may typically asymptote between 12 and 14 years of age. Although there is no general agreement in the literature, refractive error may achieve asymptote at 6 years of age. Of course, it may be that this plateau is only temporary, given the change in the visual demands of children as they spend more time in school; after which time there is a tendency for refractive errors to move toward myopia. A comparison of the age at which mean visual demands of children as they spend more time in school; that this plateau is only temporary, given the change in the age for achieving emmetropia are consistent with the 1-4 (weeks to months) rule that has characterized the development of several visual functions.

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