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Form-deprivation myopia in monkeys is a graded phenomenon

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Abstract

To shed light on the potential role of the phenomenon of form-deprivation myopia in normal refractive development, we investigated the degree of image degradation required to produce axial myopia in rhesus monkeys. Starting at about 3 weeks of age, diffuser spectacle lenses were employed to degrade the retinal image in one eye of 13 infant monkeys. The diffusers were worn continuously for periods ranging between 11 and 19 weeks. The effects of three different strengths of optical diffusers, which produced reductions in image contrast that ranged from about 0.5 to nearly 3 log units, were assessed by retinoscopy and A-scan ultrasonography. Control data were obtained from ten normal infants and three infants reared with clear, zero-powered lenses over both eyes. Eleven of the 13 treated infants developed form-deprivation myopia. Qualitatively similar results were obtained for the three diffuser groups, however, the degree of axial myopia varied directly with the degree of image degradation. Thus, form-deprivation myopia in monkeys is a graded phenomenon and can be triggered by a modest degree of chronic image degradation.

Keywords: Myopia; Diffuser lens; Monkey; Emmetropization; Defocus

1. Introduction

Converging evidence from a wide range of animal species indicates that visual feedback regulates early ocular growth. The primary outcome is that in a normal, unrestricted visual environment the two eyes of most individuals grow in a highly coordinated manner toward a near emmetropic refractive state (for reviews see Wallman, 1993; Norton & Siegwart, 1995; Wildsoet, 1997; Smith, 1998). However, the potential for a clear retinal image is essential for normal emmetropization. Procedures that substantially degrade the spatial characteristics of the retinal image (e.g. eyelid closure) disrupt emmetropization and consistently result in axial myopia, a phenomenon called form-deprivation myopia. Although it is possible that form-deprivation myopia is the result of the normal emmetropization process gone awry, a number of observations suggest that form-deprivation myopia and emmetropization are not mediated by identical mechanisms (e.g. Troilo & Wallman, 1991; Bartmann, Schaeffel, Hagel & Zrenner, 1994; Schaeffel, Hagel, Bartmann, Kohler & Zrenner, 1994; Schaeffel, Bartmann, Hagel & Zrenner, 1995; Wildsoet & Wallman, 1995; Schmid & Wildsoet, 1996). Knowledge of the visual conditions that trigger form-deprivation myopia is critical for understanding the relationship between emmetropization and form-deprivation myopia and for assessing the potential role of form-deprivation mechanisms in the genesis of refractive errors that occur in the absence of severely degraded retinal images.

There is currently considerable controversy concerning the visual trigger for form-deprivation myopia in monkeys. Following the initial observation of lid-suture myopia, experiments in which the vision of infant monkeys was obstructed by corneal opacification suggested that 'form-deprivation' myopia was caused by reduced image contrast (Wiesel & Raviola, 1977, 1979). However, spectacle-lens-rearing procedures that impose anisometropic errors that fall outside the effective operating range of the emmetropization process fail to consistently produce myopia, even though the resulting chronic unilateral optical defocus produces a substantial decrease in retinal image contrast (Smith & Hung, 1999). In fact, when positive- or negative-powered con-

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tact lenses are used to produce chronic optical defocus (Crewther, Nathan, Kiely, Brennan & Crewther, 1988; Smith, Hung & Harwerth, 1994; Kiorpes & Wallman, 1995) or if diffuser contact lenses are employed to significantly degrade image contrast in a manner similar to corneal opacification (O'Leary, Chung & Othman, 1992; Bradley, Fernandes, Tigges & Boothe, 1996), most monkeys develop axially hyperopic errors. Similarly, the relatively large degree of optical defocus produced by surgically removing the crystalline lens in an infant monkey eye causes a reduction, rather than an increase, in the rate of axial elongation (Wilson, Fernandes, Chandler, Tigges, Boothe & Gammon, 1987). On the other hand, black occluder contact lenses, which prevent essentially all form vision and greatly reduce retinal illumination, produce axial myopia in monkeys (Tigges, Tigges, Fernandes, Eggers & Gammon, 1990; Ivone, Tigges, Stone, Lambert & Laties, 1991). Thus, these experiments as a whole suggest that the degree of image degradation required to produce 'deprivation' myopia in primates is so high that the mechanisms that mediate this phenomenon are only triggered under relatively extreme conditions and as a result are unlikely to play a role in normal emmetropization. In contrast to the monkey, in the chicken form-deprivation myopia is not an all-or-none process, but instead, the degree of myopia is graded and correlated with the amount of image degradation (Bartmann & Schaeffel, 1994).

However, with respect to the visual trigger for form-deprivation myopia in monkeys, the results of many of these investigations may have been confounded by the use of contact lenses, particularly in studies in which the fellow control eyes were not fitted with clear, zero-powered lenses (O'Leary et al., 1992; Bradley et al., 1996). In this respect, we found that even soft, zero-powered, extended-wear contact lenses produce significant hyperopic refractive errors in young monkeys (Hung & Smith, 1996). Although we do not know why contact-lens-rearing regimens alter ocular development, the resulting hyperopic changes could potentially mask alterations produced by the mechanisms responsible for form-deprivation myopia. Apparently, with black occluder contact lenses the deprivation myopia mechanism is stimulated sufficiently to overcome this side effect of contact lens wear so that a relative myopia results. Another issue that clouds the interpretation of contact lens studies is the potentially confounding effect of occasional lens loss. Even with extremely close monitoring, contact lens loss invariably occurs with young monkeys and is particularly more common for control eyes fitted with zero-powered lenses (Kiorpes & Wallman, 1995). In the chick, very brief daily periods of clear vision (as little as 15 min) are sufficient to eliminate or greatly reduce the effect of an entire day of deprivation (Nickla, Panos, Fugate-Wentzek, Gottlieb, & Wallman, 1989; Napper, Brennan, Barrington, Squires, Vessey & Vingrys, 1995; Schmid & Wildsoet, 1996; Napper, Brennan, Barrington, Squires, Vessey & Vingrys, 1997).

Factors unrelated to retinal image quality might also prevent the results obtained from aphakic monkeys from being applicable to the phenomenon of form-deprivation. For example, even when corrective steps are taken to eliminate optical defocus, aphakic eyes still exhibit reduced axial growth rates (Lambert, Fernandes, Drews-Botsch & Tigges, 1996). It has been suggested that removing the crystalline lens may deprive the eye of some trophic factors which are needed for normal ocular growth and for form-deprivation myopia (Coulombre & Coulombre, 1964; Wilson et al., 1987).

The purpose of this investigation was to determine how much image degradation is required to produce form-deprivation myopia in primates and whether the degree of resulting myopia is related to the amount of image degradation. To avoid some of the potentially confounding issues associated with previous studies, we employed a graded series of diffuser spectacle lenses to degrade the retinal image in a repeatable and quantifiable manner.

2. Methods

2.1. Subjects

Twenty-six infant rhesus monkeys (*Macaca mulatta*) were used as subjects. The infants were obtained at 1–3 weeks of age and were hand-reared in our primate nursery that was maintained on a 12-h light/12-h dark lighting cycle. All of 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 National Institutes of Health Guide for the Care and Use of Laboratory Animals.

The course of emmetropization and the normal interocular variations in refractive error were examined in ten infant monkeys that were reared with unrestricted vision. Data for five of these normal infants were presented previously in Smith and Hung (1999). The effects of unilateral retinal image degradation were investigated in 13 monkeys. Beginning at about 3 weeks of age (24 ± 2 days), these infants were fit with a light-weight helmet that held a diffuser spectacle lens in front of the treated eye and a clear, zero-powered lens in front of the fellow eye. The diffuser consisted of a zero-powered carrier lens that was covered with a commercially available occlusion foil (Bangerter Occlusion

Foils, Fresnel Prism and Lens). These occlusion foils are available in a range of strengths that produce reliable and repeatable degrees of optical diffusion. We employed three different degrees of optical diffusion. The effects of these three diffuser lenses on the spatial vision of adult human observers are illustrated in Fig. 1. The strongest diffusers (designated 'LP' by the manufacturer), which were employed for five infants, produced dramatic reductions in contrast sensitivity, over a 1 log reduction even at the lowest spatial frequency (0.125 cycles/degree). The resulting cut-off spatial frequency for the LP diffusers was below 1 cy/deg (cycle/degree). Five infants were treated with the diffuser lenses designated '0.1'. These intermediate strength diffusers reduced contrast sensitivity by about 0.5 log units at the lowest spatial frequency and the reduction increased to slightly over 2 log units for 2 and 8 cy/deg. The weakest diffuser lenses ('0.4'), which were fitted to three infant monkeys, produced reductions in image contrast that were comparable to a mild degree of optical defocus. Contrast sensitivity was reduced in a spatial frequency dependent manner from 0.1 log units at 0.125 cy/deg to an average of 0.75 log units at 8 cy/deg. To control for potential effects associated with wearing the goggle-like helmets, three infant monkeys were reared with helmets that held zero-powered lenses over both eyes. Data for two of these plano-control animals have been previously reported (Smith & Hung, 1999). For both the plano-control and treated animals, the lenses were worn continuously for periods ranging between 11 and 19 weeks (mean duration 102 ± 14 days).

2.2. Optical and biometric measurements

Cycloplegia was induced with two drops of topically applied 1% tropicamide. The animals were anesthetized with intramuscular injections of ketamine hydrochloride (20 mg/kg) and acepromazine maleate (0.2 mg/kg) and topically instilled 0.5% tetracaine hydrochloride. Two observers using streak retinoscopes determined an eye's refractive status, which is specified as the spherical-equivalent spectacle-plane refractive correction. The refracting power of the cornea along the eye's pupillary axis was determined with a hand-held keratometer (Alcon Auto-keratometer) and a video-topographer (EysSys 2000). The eye's axial dimensions were measured by A-scan ultrasonography. An instrument with a 7 MHz transducer was employed at each measurement session. Additional measurements were obtained from some animals using a 30 MHz A-scan system. The animals were first examined at the onset of the lens-rearing regimen and typically every 2 weeks for the first year of life (for more details see Smith et al., 1994; Hung, Crawford & Smith, 1995; Smith and Hung, 1999).

3. Results

3.1. Normal and plano-control subjects

Although normal monkeys exhibit a wide range of primarily hyperopic refractive errors shortly after birth, given unrestricted visual experience both eyes of a given individual grow rapidly and in a highly coordinated

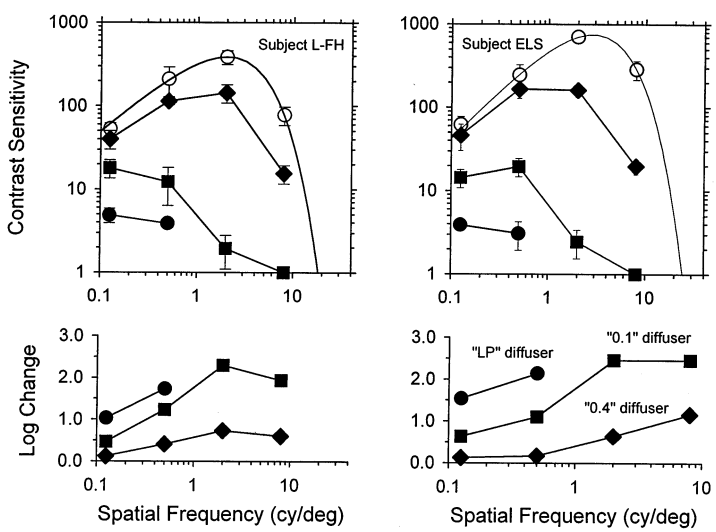

Fig. 1. Top: Mean contrast sensitivity (± 1 S.D.) plotted as a function of spatial frequency for two human observers. The open symbols were obtained with the optimum optical correction. The filled circles, squares, and diamonds were obtained while viewing through the 'LP' (strongest), '0.1' (intermediate), and '0.4' (weakest) diffuser lenses, respectively. The space-average luminance of the display was 80 cd/m^2. Contrast detection thresholds ($n = 5$ per condition) were obtained using a descending method of limits (see Smith et al. (1999) for procedural details). Bottom: Change in log contrast sensitivity produced by viewing through the three different diffuser lenses plotted as a function of spatial frequency.

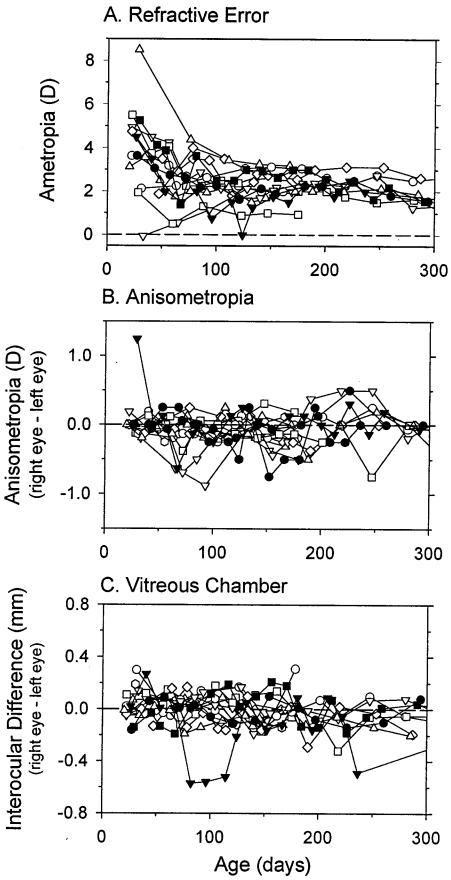

Fig. 2. The right eye, spherical-equivalent, spectacle plane refractive correction (A) degree of anisometropia (B right eye correction-left eye correction), and interocular difference in vitreous chamber depth (C, right eye-left eye) plotted as a function of age for normal infant monkeys (open symbols, $n = 10$) and control monkeys reared with zero-powered lenses over both eyes (filled symbols, $n = 3$).

manner toward a low degree of hyperopia (Fig. 2A). Refractive development for the control animals reared with zero-powered lenses over both eyes (filled symbols) was not obviously different from that for normal infants (open symbols). The refractive errors for the plano-control infants were generally clustered well within the normal data throughout the observation period. At ages corresponding to the end of the lens-rearing period for the diffuser animals (between 126 and 150 days of age), the average refractive error for the right eyes of the normal and plano-control infants was $+2.27 \pm 0.7$ D. Thereafter, their refractive errors were relatively stable until at least 300 days of age.

Significant degrees of anisometropia were rare in both normal and plano-control infants (Fig. 2B). The largest anisometropia (1.25 D) was observed in one of the plano-control infants prior to the onset of the helmet-rearing procedures. Subsequently, the degree of anisometropia never exceeded 0.87 D for any normal or plano-control infant. The mean anisometropia obtained at ages corresponding to the end of the lens rearing procedures was 0.14 ± 0.10 D and for the entire observation period was 0.20 ± 0.21 D. Likewise, the axial dimensions for the vitreous chamber were generally well matched in both eyes of both normal and plano-control infants (Fig. 2C). The largest interocular differences in vitreous chamber depth were observed in one plano-control subject during the helmet-rearing period. However, the imbalance was transient; the axial dimensions of the two eyes equalized before the end of the helmet-rearing period. The mean interocular differences in vitreous chamber were 0.10 ± 0.05 and 0.10 ± 0.10 mm for ages corresponding to the end of the typical treatment period and for the entire observation period, respectively.

3.2. Diffuser-reared subjects

By the end of the lens-rearing period, 11 of the 13 treated monkeys had developed a relative myopia in the eye viewing through the diffuser lens. In all 11 of these subjects the resulting anisometropia fell outside the range of interocular differences found in age-matched normal and plano-control monkeys. As illustrated by the data from the representative monkeys in Figs. 3–5, the overall effects of the diffuser lenses on refractive development were qualitatively similar in the three diffuser groups. Shortly after the onset of lens wear, the treated eyes typically demonstrated a relative acceleration in their vitreous chamber elongation rates and they became less hyperopic or more myopic than were their fellow non-treated eyes. In all three diffuser groups, the relative myopia in the treated eyes could be accounted for primarily by interocular differences in vitreous chamber depth. Although the myopic eyes also showed slightly steeper corneas (mean 0.39 ± 0.6 D), the interocular differences in vitreous chamber depth accounted for 89% of the variance for the interocular differences in refractive error.

Another similarity between the diffuser groups was that some animals in each group demonstrated an initial hyperopic shift in the treated eye's refractive state. Prior to the onset of diffuser induced myopia, six of the 13 treated monkeys (e.g. MKY CHI, Fig. 4; MKY HEX, Fig. 5) exhibited a transient hyperopia soon after the start of lens wear. This relative hyperopia was typically on the order of 1–2 D and in each case was associated with a relatively shorter vitreous chamber depth in the treated eye. This transient hyperopia, which can be appreciated in the interocular difference functions that are shown in Fig. 6, was short lived (2–4 weeks), typically giving way to the onset of diffuser induced myopia.

Similarities were also observed between the diffuser groups following lens removal. The accelerated vitreous chamber elongation rates in the treated eyes were generally maintained throughout the duration of diffuser

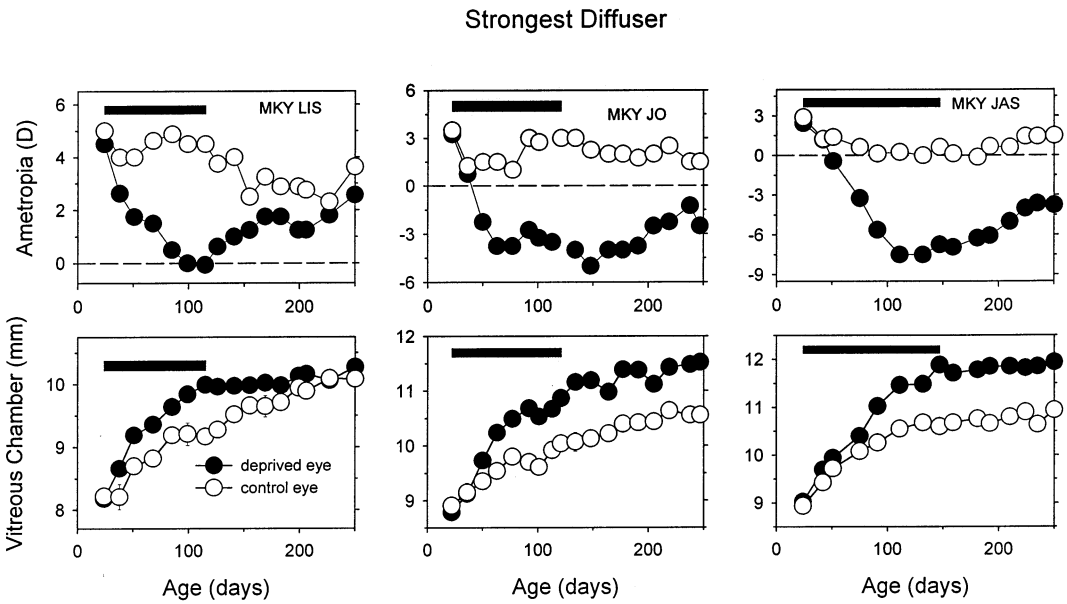

Fig. 3. Spherical-equivalent refractive error (top) and vitreous chamber depth (mean ± S.D.; bottom) plotted as a function of age for representative monkeys reared with the strongest diffuser lenses ('LP' diffusers) in front of their treated eyes (filled symbols). The fellow eyes viewed through clear zero-powered lenses (open symbols). The filled horizontal bars indicate the lens-rearing periods.

wear. However, upon restoring unrestricted vision there was an obvious reduction in the vitreous chamber growth rate in the treated eyes of most animals in each diffuser group. In contrast, the vitreous chambers of the fellow eyes continued to elongate following the onset of unrestricted vision. Since the corneas of both eyes, and presumably the crystalline lenses as well, continued to flatten there was a decrease in the degree of myopic anisometropia. In some cases the recovery was virtually complete (e.g. MKY HEX), however, most animals maintained some degree of myopic anisometropia.

For unknown reasons two of the 13 diffuser-reared monkeys, one reared with the strongest diffuser and the other reared with an intermediate diffuser, did not develop a relative myopia in their treated eyes (Fig. 7). Instead, the treated eyes of both of these monkeys developed a relative axial hyperopia shortly after the onset of lens wear. As observed in the animals that eventually became myopic, this initial hyperopic shift

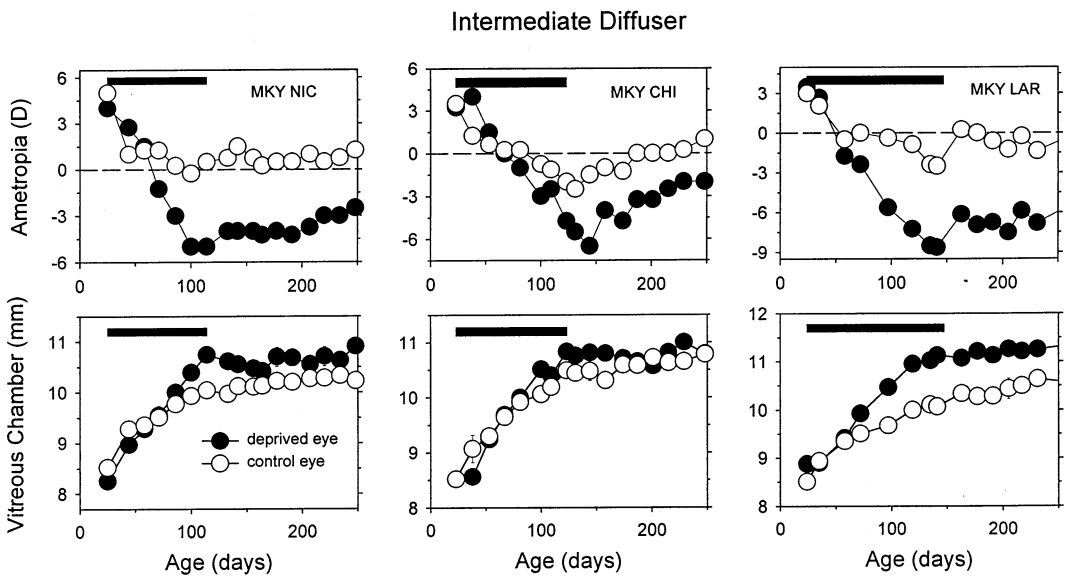

Fig. 4. Spherical-equivalent refractive error (top) and vitreous chamber depth (mean ± S.D.; bottom) plotted as a function of age for representative monkeys reared with the intermediate strength diffuser lenses ('0.1' diffusers) in front of their treated eyes (filled symbols). The fellow eyes viewed through clear zero-powered lenses (open symbols). The filled horizontal bars indicate the lens-rearing periods.

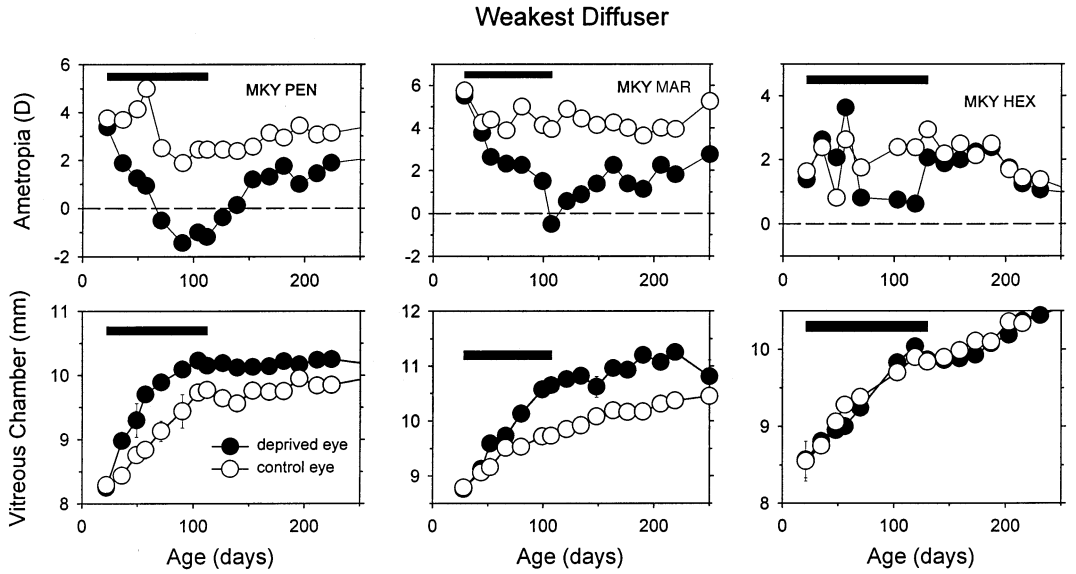

Fig. 5. Spherical-equivalent refractive error (top) and vitreous chamber depth (mean ± S.D.; bottom) plotted as a function of age for representative monkeys reared with the weakest strength diffuser lenses ('0.4' diffusers) in front of their treated eyes (filled symbols). The fellow eyes viewed through clear zero-powered lenses (open symbols). The filled horizontal bars indicate the lens-rearing periods.

was transient, however, thereafter the two eyes maintained very similar refractive errors despite the chronic degradation of retinal image contrast in the treated eyes. At the end of the treatment period the degree of anisometropia for these two infants was well within the range of anisometropias found in normal and plano-control monkeys (Fig. 8A). There was nothing unusual or unique about the rearing histories of these animals that would distinguish them from the animals that developed myopia in their treated eyes.

The magnitude of the refractive-error changes was the primary difference between the results for the different diffuser groups and was ordered according to the degree of image degradation (regression analysis, $P < 0.001$; weakest diffuser mean $= -2.98 \pm 1.9$ D, intermediate diffuser mean $= -3.5 \pm 2.53$ D, and strongest diffuser mean $= -4.69 \pm 3.8$ D). The largest anisometropias were found in infants treated with the strongest diffusers (Fig. 8A). The lowest average degree of absolute myopia was found in the treated eyes of the

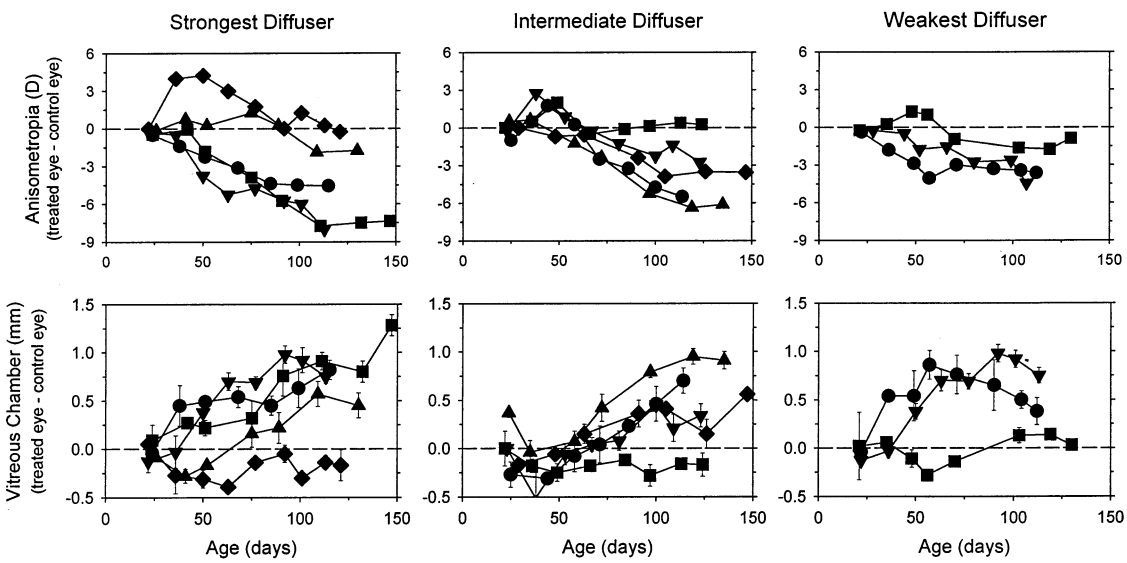

Fig. 6. Interocular differences (treated eye-control eye) in refractive error (top) and vitreous chamber depth (mean ± S.D.; bottom) plotted as function of age for all of the diffuser-reared monkeys. Data for the infants reared with the strongest, intermediate, and weakest diffuser lenses are shown in the left, middle, and right columns, respectively. A given animal is represent by the same symbol in the top and bottom plots. The first and last data points for each animal represent the start and end of the treatment period, respectively.

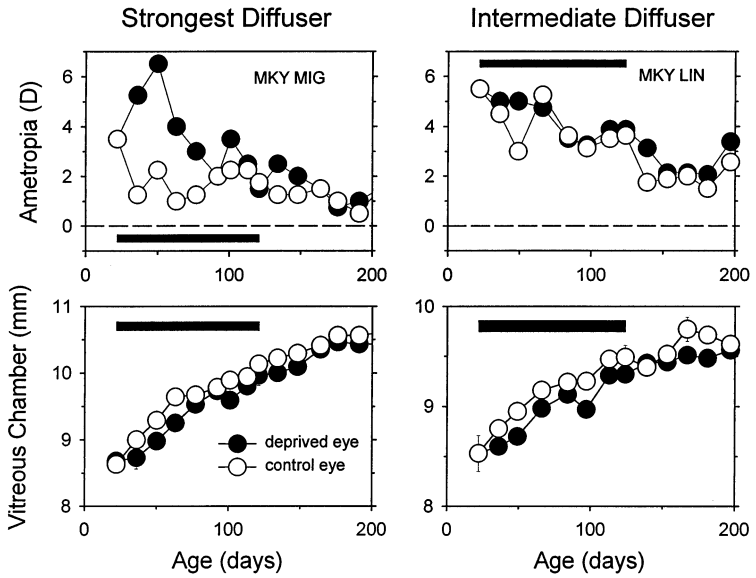

Fig. 7. Spherical-equivalent refractive error (top) and vitreous chamber depth (mean ± S.D.; bottom) plotted as a function of age for the two diffuser-reared monkeys that failed to develop myopia in their treated eyes. The treated and non-treated eyes are represented by the filled and open symbols, respectively. MKY MIG was treated with the strongest diffuser lens. MKY LIN wore the intermediate diffuser lens. The filled horizontal bars indicate the lens-rearing periods.

infants reared with the weakest diffusers (Fig. 8B). Interestingly the magnitude of the transient hyperopia that was observed in six of the treated monkeys also appears to vary with the degree of image degradation (Fig. 6).

It is not surprising that the absolute refractive errors for the treated eyes of nine of the 13 diffuser-reared monkeys were more myopic than either the left or right eyes of any of the age-matched normal and plano-control monkeys (Fig. 8B; one-way ANOVA, $P < 0.005$). It is interesting, however, that the ametropias for many of the non-treated eyes of the diffuser-reared infants, at least one animal in each diffuser group, also fell outside the range of refractive errors for the normal/control monkeys (Fig. 8B). For these non-treated eyes, the direction of the departures from the control range was not consistent. Three infants exhibited hyperopic errors in their non-treated eyes that were larger than those found in the age-matched normals/controls, whereas four of the non-treated eyes were less hyperopic or more myopic. The non-treated eyes also exhibited recovery toward more normal ametropias following removal of the diffuser lens from the fellow treated eyes. The fact that the refractive-error changes for the non-treated eyes were in some cases clearly synchronized with refractive changes in the treated eye suggest that vision-dependent factors were affecting the refractive development of both the treated and non-treated eyes.

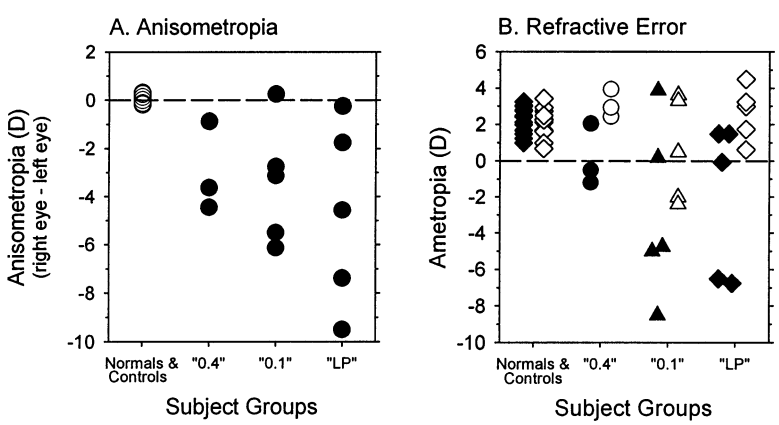

Fig. 8. (A) Interocular differences in refractive error (right or treated eye-left or control eye) for individual subjects arranged according to subject groups. The open and filled symbols represent the normal/control infants and the diffuser-reared monkeys, respectively. (B) Spherical-equivalent refractive error for the right/treated (filled symbols) and left/control eyes (open symbols) for individual subjects arranged according to subject group.

In some cases the synchronized refractive changes in the two eyes were in the same direction (e.g. MKYs CHI & LAR, Fig. 4), however, other animals showed synchronized refractive changes that were in opposite directions (e.g. MKY LIS, Fig. 3).

4. Discussion

Our main findings were that the chronic reductions in image contrast associated with optical diffusion caused axial myopia in young monkeys and that the degree of myopia varied directly with the degree of image degradation. The myopia induced by our diffuser lenses is presumably classic form-deprivation myopia. The nature of the diffuser-induced myopia in monkeys is comparable to that for the form-deprivation myopia produced by techniques like eyelid suture (Wiesel & Raviola, 1977; Raviola & Wiesel, 1985; Smith, Harwerth, Crawford & von Noorden, 1987). A key feature that is common to our rearing technique and the techniques frequently employed to produce form deprivation is that the diffuser spectacle lenses established an open-loop condition in which neither accommodation nor compensating ocular growth could improve the quality of the retinal image (Schaeffel & Howland, 1988).

In agreement with Bartmann and Schaeffel's (1994) previous findings in the chick, form-deprivation myopia in monkeys is a graded phenomenon. Evidently the degree of image degradation required to trigger deprivation myopia in monkeys is relatively low. The modest reductions in image contrast produced by our weakest diffuser lenses were sufficient to produce deprivation myopia. Since relatively small amounts of optical defocus can produce quantitatively similar reductions in image contrast, our results suggest that small amounts of chronic optical defocus could produce alterations in refractive error via the mechanisms that mediate deprivation myopia. In this respect, it appears that form-deprivation mechanisms are sensitive enough to participate in normal emmetropization and could, as others have suggested (Wallman & Adams, 1987; Bartmann & Schaeffel, 1994; Hung et al., 1995; Norton & Siegwart, 1995), play a potential beneficial role in normal development in primates.

Observations in spectacle-lens-reared monkeys suggest, however, that form deprivation may not normally be involved in primate emmetropization. For example, infants monkeys reared with 3 D of optically imposed anisometropias typically develop true anisometropias that compensate for the imposed imbalance. In contrast infants treated with anisometropic lens powers of 6 D or more do not exhibit evidence of compensating differential interocular growth. Despite experiencing high degrees of hyperopic defocus, refractive development in the fixating and non-fixating eyes of these monkeys is very similar (Hung et al., 1995; Smith & Hung, 1999). If the degree of image degradation required to trigger deprivation myopia is so low, why do moderate degrees of hyperopic optical defocus fail to consistently produce myopia? It is possible that moderate degrees of lens induced hyperopic defocus fail to produce form-deprivation myopia because the non-fixating eyes periodically receive a relatively clear image. For example, when an infant accommodates for a near target with its fixating eye, distant objects may be imaged in a relatively clear manner in the non-fixating eye with imposed hyperopic defocus. In contrast, diffuser lenses degrade the retinal image at all times. In chickens and tree shrews, very brief periods of unrestricted visual experience are sufficient to block both form deprivation and lens-induced myopia (Nickla et al., 1989; Napper et al., 1995; Schmid & Wildsoet, 1996; Napper et al., 1997; Shaikh, Siegwart & Norton, 1997). It is also possible that form-deprivation myopia and lens compensation are mediated by different mechanisms. Several observations in lens-reared monkeys suggest that the onset of amblyopia can interfere with the eye's response to optical defocus (Kiorpes & Wallman, 1995; Smith, Hung & Harwerth, 1999). However, the development of amblyopia does not preclude form-deprivation myopia. Virtually all of the diffuser-reared infants exhibited amblyopia in their treated eyes (unpublished observations). In this respect, a variety of observations in the chicken suggest that different mechanisms do in fact mediate form-deprivation myopia and the compensation for hyperopic defocus (Troilo & Wallman, 1991; Bartmann et al., 1994; Schaeffel et al., 1994; Schaeffel et al., 1995; Wildsoet & Wallman, 1995; Schmid & Wildsoet, 1996). Therefore, even though the degree of degradation required to produce form deprivation is modest and falls within the range of defocus effects that can be encountered in real-world viewing conditions, a role for form-deprivation myopia in emmetropization is still uncertain.

In many infants clear evidence for deprivation myopia was obtained after only 2 weeks of diffuser wear, i.e. at the first measurement session following the onset of the lens-rearing procedures. The onset of deprivation myopia, however, was delayed in nearly half of the diffuser-reared monkeys. It appears that in these animals, the initial response to the diffuser lenses was a reduction in vitreous chamber growth rate that resulted in a relative hyperopic shift. This transient hyperopia has not been previously found in old-world monkeys, probably because previous investigators have not examined the very early effects of form deprivation (Raviola & Wiesel, 1985; Greene & Guyton, 1986). However, Troilo and Judge (1993) have described a similar phenomenon in young marmosets following the onset of form deprivation by lid suture. After 3 weeks of depri-

vation, young marmosets consistently exhibit axial hyperopia. Subsequently, marmosets show an enlargement of the vitreous chamber and myopia, much like our infant macaques. The physiological significance of this early hyperopic shift is not known, possibly it represents an attempt to determine the sign of optical defocus. Nonetheless, it is interesting that it has not been found in non-primates. In most species, there have not been systematic investigations of the short-term effects of deprivation. However the chicken, the most common animal used in refractive error research, has been examined extensively and does not appear to show this transient hyperopic shift (Wallman & Adams, 1987; Liang, Crewther, Crewther & Barila, 1995; Nickla, Wildsoet & Wallman, 1998). A relative hyperopic shift has been observed in tree shrews following 15 days of lid suture, but this refractive change is not axial in nature. Instead the tree shrew hyperopia appears to be secondary to a mechanical flattening of the cornea (McBrien & Norton, 1992).

Although the onset of form deprivation appears to influence marmosets and rhesus monkeys in a similar fashion, these two primates appear to exhibit different responses at the end of a period of deprivation. In marmosets the process of deprivation myopia continues after the deprivation is discontinued and unrestricted vision is restored. In contrast in rhesus monkeys removing the diffuser lenses produced a dramatic reduction in axial growth rates and promoted recovery from the induced myopia. Similar recovery patterns have been observed following the termination of form deprivation in tree shrews (Siegwart & Norton, 1998) and chicks (Wallman & Adams, 1987).

Several observations indicated that the diffuser lenses influenced refractive development in the non-treated eyes, i.e. a stimulus for abnormal growth in one eye altered growth in both eyes. First, the range of refractive errors for the non-treated fellow eyes was larger than the range of ametropias observed in normal and plano-control monkeys. Although in most cases the refractive errors for the non-treated eyes were close to the normal range, in several diffuser-reared monkeys the non-treated eyes showed myopic errors of about 2 D. Myopia is very rare, essentially non-existent, in normal monkeys between 4 and 5 months of age (Kiely, Crewther, Nathan, Brennan, Efron & Madigan, 1987; Bradley, Fernandes, Lynn, Tigges & Boothe, 1999b; Smith & Hung, 1999) and none of our normal or plano-control monkeys were myopic at this age. Second, the non-treated eyes frequently exhibited refractive changes that were synchronized with removing the diffuser lens from the fellow eye. These refractive changes were typically in the direction of the average refractive error for normal infants and appear analogous to the recovery observed following lens-induced compensation in infant monkeys (Hung et al., 1995; Smith & Hung, 1999). Interocular effects from unilateral form deprivation and optical defocus have been found previously in both chickens (Sivak, Barrie & Weerheim, 1989; Wildsoet & Wallman, 1995) and monkeys (Smith et al., 1987; Hung et al., 1995; Bradley, Fernandes & Boothe, 1999a). The non-treated eye effects that we observed are not as consistent as those recently reported by Bradley et al. (1999) for monkeys reared with unilateral form deprivation. Whereas all of Bradley et al.'s monkeys exhibited relative myopia in their untreated eyes, we observed both relative hyperopic and myopic changes. Both hyperopic and myopic changes are evident in the refractive-error distribution for the non-treated eyes of monocularly lid-sutured monkeys (Smith et al., 1987). The higher prevalence of myopia found by Bradley et al. (1999) might be due to the higher degrees of image degradation produced by their black occluding contact lenses, their longer treatments periods, and/or earlier onset ages. Regardless, the refractive-error changes in the non-treated eyes support the idea that there is a central influence on refractive development in primates (Kiorpes & Wallman, 1995; Bradley et al., 1999a; Smith et al., 1999).

High inter-subject variability in the degree of myopia is a characteristic of the phenomenon of form-deprivation myopia in monkeys (von Noorden & Crawford, 1978; Thorn, Doty & Gramiak, 1982; Raviola & Wiesel, 1985; Greene & Guyton, 1986; Smith et al., 1987; Tigges et al., 1990; Bradley et al., 1999a). With techniques like eyelid suture, individual differences associated with skin pigmentation and the scarring process would be expected to result in different degrees of image degradation and thus promote inter-subject differences in the degree of myopia. The diffuser lenses that we employed in this study and the black occluder lenses used by Tigges et al. (1990) and Bradley et al. (1999) would be expected to produce a more consistent reduction in image contrast. However, even these rearing strategies yield high degrees of inter-subject variability with some monkeys showing no myopia. A more likely explanation is that this variability reflects individual differences in sensitivity to form-deprivation as Schaeffel and Howland (1988) have hypothesized for the chicken.

In contrast to the consistent myopia produced by our diffuser spectacle lenses, infant monkeys reared with diffuser contact lenses consistently developed hyperopia (O'Leary et al., 1992; Bradley et al., 1996). The degree of image degradation produced by the diffuser contact lenses in both the Bradley et al. and O'Leary et al. studies was within the range of optical diffusers that we investigated and should have been sufficient to trigger deprivation myopia. It seems likely as outlined in Section 1 that their contact-lens-rearing regimens produced changes in refractive development that overshadowed the effects of form deprivation (Hung & Smith, 1996).

When form-deprivation myopia occurs, it appears to be a robust, dramatic departure from normal development. The fact that it occurs in a very wide range of species indicates that the mechanisms involved in form-deprivation myopia are fundamental from an evolutionary point of view (Smith, 1998). However, the failure of significant reductions in image contrast, either via diffuser contact lenses or spectacle-lens-induced optical defocus, to initiate form-deprivation myopia suggests that the process of form-deprivation myopia is either easily overridden by other factors that influence ocular development or that very specific circumstances are required to maintain the process. As suggested earlier, while the absolute degree of image degradation required to produce form-deprivation myopia is low, it is possible that the degree of image degradation must be very consistent over time. It will be important to determine the temporal integration characteristics of the form deprivation process in primates in order to determine its potential role in normal development.

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