Protective Effects of High Ambient Lighting on the Development of Form-Deprivation Myopia in Rhesus Monkeys

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PURPOSE. Time spent outdoors reduces the likelihood that children will develop myopia, possibly because light levels are much higher outdoors than indoors. To test this hypothesis, the effects of high ambient lighting on vision-induced myopia in monkeys were determined.

METHODS. Monocular form deprivation was imposed on eight infant rhesus monkeys. Throughout the rearing period (23 ± 2 to 132 ± 8 days), auxiliary lighting increased the cage-level illuminance from normal lighting levels (15–630 lux) to ~25,000 lux for 6 hours during the middle of the daily 12-hour light cycle. Refractive development and axial dimensions were assessed by retinoscopy and ultrasonography, respectively. Comparison data were obtained in previous studies from 18 monocularly form-deprived and 32 normal monkeys reared under ordinary laboratory lighting.

RESULTS. Form deprivation produced axial myopia in 16 of 18 normal-light-reared monkeys. In contrast, only 2 of the 8 high-light-reared monkeys developed myopic anisometropias, and in 6 of these monkeys, the form-deprived eyes were more hyperopic than their fellow eyes. The treated eyes of the high-light-reared monkeys were more hyperopic than the form-deprived eyes of the normal-light-reared monkeys. In addition, both eyes of the high-light-reared monkeys were more hyperopic than those of normal monkeys.

CONCLUSIONS. High ambient lighting retards the development of form-deprivation myopia in monkeys. These results are in agreement with the hypothesis that the protective effects of outdoor activities against myopia in children are due to exposure to the higher light levels encountered outdoors. It is possible that therapeutic protection against myopia can be achieved by manipulating indoor lighting levels. (*Invest Ophthalmol Vis Sci.* 2012;53:421–428) DOI:10.1167/iov.11-8652

Soon after birth, the eyes of most infants normally grow in a highly coordinated manner toward the ideal optical state that is then maintained throughout childhood and into early adult life, a process called emmetropization. Evidence from many different species indicates that this process is actively

regulated by visual feedback associated with the eye's refractive state—in essence, optical defocus.^{1–3} For example, making the eyes of young animals artificially myopic with positive lenses or hyperopic with negative lenses produces compensating ocular growth that can, within certain operational limits, eliminate the imposed refractive error.^{4–10} However, for reasons not currently understood, a substantial and increasing proportion of the human population develop myopia during early adolescence.^{11–13} It is possible that myopia onset and progression in children are triggered by visual experience, acting through the vision-dependent biochemical cascade that normally promotes the development of the optimal refractive state or possibly the failure of this focus-dependent process to stop axial growth. In this respect, most optical treatment strategies that have been designed to prevent or reduce myopia in children are based on manipulating accommodative effort and/or the effective focus of the retinal image. The fact that some recent optical treatment strategies that impose relative myopic defocus over a large portion of the retina have been shown to produce clinically meaningful reductions in myopia progression^{14–20} has reinforced the predominant view that visual factors other than defocus do not influence refractive development.

However, the local mechanisms that mediate the effects of optical defocus on ocular growth are complex, involving many different retinal, choroidal, and scleral components.^{21–23} Although optical defocus appears to be the primary stimulus, some individual components in this signal cascade (e.g., dopaminergic amacrine cells) have been shown to be influenced by other stimulus attributes (e.g., light levels).¹ As a consequence, the operational efficiency of this defocus-driven feedback loop is potentially influenced by a variety of external factors, including other visual factors. Specifically, recent observations in humans and laboratory animals suggest that ambient light levels may also influence this vision-dependent loop and consequently refractive development. For example, individuals who spend more time outdoors have more hyperopic refractive errors and a lower prevalence of juvenile-onset myopia.^{24–27} The protective effect of time outdoors is not associated with sporting activities nor is it a substitution effect for time spent in activities that are linked to myopia (e.g., near work).^{26,28} Instead, it is the total amount of time outdoors that appears to be important. In this respect, the absolute differences in the amount of outdoor activities between myopic and nonmyopic children are relatively small; however, these behavioral differences are present up to 3 years before the onset of myopia,²⁴ which suggests that lower amounts of outdoor activities may contribute to myopia onset. Although the mechanisms underlying this protective effect are not well understood, it has been proposed that these protective effects are due to the relatively flat dioptric topographies of outdoor scenes²³ and/or to the high ambient lighting levels typically encountered outdoors,²⁹ which are often 100 times higher than indoor levels. In this

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respect, it may be significant that most human studies that have reported the protective effects of outdoor activities have been conducted in climates with substantial amounts of sunlight (e.g., Singapore and Sydney).^{26–28}

Research in chickens has provided direct evidence that high lighting levels can have a protective effect against myopigenic visual stimuli. For example, exposing young chicks to high illuminances, either from sunlight or intense laboratory lights, reduces the degree of axial myopia produced by form deprivation by 65% over a 4-day treatment period, accelerates the hyperopic compensation to positive lenses, and slows myopic compensation to negative lenses, although full compensation is still achieved by the end of a 6-day treatment period.^{29,30} In addition, the ability of a brief period of unrestricted vision to prevent form-deprivation myopia increases with increasing ambient lighting levels,²⁹ and in chicks reared with unrestricted vision, emmetropization is slowed by high light levels, leading to more hyperopic refractive errors.³¹

It is not reasonable to extrapolate the results from chickens to humans, because light levels and lighting cycles can have qualitatively different effects in primates and birds. Although there are many similarities in the vision-dependent mechanisms that regulate refractive development in birds and primates,^{1–3} there are qualitative differences. In particular, although lighting cycles can affect refractive development in monkeys,^{32,33} lighting levels and light cycles can influence refractive development in chickens via mechanisms that do not appear to operate in primates (e.g., direct pineal stimulation)³⁴ and to alter ocular growth in chickens in ways that do not occur in primates. For example, exposure to continuous light produces dramatic changes in corneal curvature in chickens,^{35,36} but it does not affect the anterior segment in monkeys.^{32,33}

Therefore, the purpose of this study was to evaluate the potential protective effects of high ambient lighting on vision-induced myopia in primates by comparing refractive development in monocularly form-deprived infant rhesus monkeys reared under normal laboratory lighting with that of those exposed to high levels of artificial light.

METHODS

Subjects

Data are presented for 58 infant rhesus monkeys (*Macaca mulatta*). The primary subject group consisted of eight animals that were reared with monocular form deprivation and were exposed daily to high artificial lighting levels. Comparison data were available from previous studies for 32 normal control animals^{6,37,38} and 18 monocularly form-deprived monkeys that were reared under ordinary laboratory lighting.^{38–40} Twenty-eight of the control animals were reared with unrestricted vision, and four control monkeys were reared wearing helmets that held 0-powered spectacles in front of both eyes. All the animals were obtained at 1 to 3 weeks of age and, after the initial biometry measurements at approximately 3 weeks of age, they were randomly assigned to their respective subject groups. Although the different subject groups were studied at different times over a period of several years, the experimental methods were identical. The details of the nursery care for our infant monkeys are described elsewhere.⁶

Monocular form deprivation was produced by fitting infant monkeys with goggles⁶ that secured a 0-powered spectacle lens over one eye and a diffuser spectacle over the treated eye. The diffusers consisted of a 0-powered carrier lens covered with a light-perception Bangerter occlusion foil (Fresnel Prism and Lens Co., Eden Prairie, MN), which resulted in dramatic reductions in retinal image contrast. Specifically, in adult humans, the diffusers reduced contrast sensitivity for 0.125-cyc/deg gratings by more than 1 log unit and virtually eliminated contrast signals for spatial frequencies above approximately 1.0

cyc/deg.⁴⁰ The diffusers did not alter the spectral composition of the retinal image and reduced light transmission by only approximately 0.1 log units.⁴¹ The goggles provided monocular and binocular fields of view in the horizontal plane of 80° and 62°, respectively, and an 87° vertical field. Except for brief periods needed for routine cleaning and maintenance, the monkeys wore the helmets continuously from 23 ± 2 to 132 ± 8 days of age. The helmets were inspected at approximately 2-hour intervals throughout the day, to ensure that the helmets fit the subjects appropriately and that the spectacle lenses were clean and free of debris that might have interfered with the desired optical effects. Since the primary goal was to determine whether high light levels can retard axial growth, form deprivation was the procedure of choice because form deprivation produces: (1) a strong, consistent myopigenic stimulus throughout the treatment period; (2) large myopic errors at normal lighting levels, making it possible to detect minor changes in myopic development^{38–40}; and (3) qualitatively similar refractive errors in humans and monkeys.⁴² Moreover, the decrease in pupil size associated with high lighting levels, which would alter the depth of field and the effects of negative lenses, does not affect the reduction in image contrast produced by diffusers. Employing monocular form deprivation also has the advantage of providing a within-animal control for other factors that could alter the effects of any treatment regimen (e.g., changes in retinal sensitivity with ambient light levels).

The housing areas for all the animals were illuminated with fluorescent tubes (F32T8/TL735, correlated color temperature = 3500 K; Philips Lighting US, Somerset, NJ) maintained on a 12-hour light/12-hour dark cycle. The fluorescent lighting provided illuminances that ranged from 15 lux (back walls of lower cages) to 630 lux (ceilings of upper cages). In addition to the fluorescent lights, the housing area for the form-deprived monkeys in the high ambient lighting group was illuminated by four, 1000-W metal halide lamps (MH1000; Plusrite, Ontario, CA) positioned above the animals' cages. The metal halide lamps had major output peaks throughout the visible spectrum, resulting in a correlated color temperature of 4200 K. The light from the lamps was filtered to eliminate wavelengths below 360 nm and was delivered indirectly to the animals' cages, resulting in illuminances that varied from 18,000 to 28,000 lux, which were well within the range of illuminances commonly encountered in outdoor settings. For reference, at noon on a clear summer day in Houston, the outdoor illuminance levels can exceed 130,000 lux and can be 15,000 to 20,000 lux in the shade of trees. The auxiliary lights were turned on for 6 hours each day during the middle of the 12-hour lights-on cycle. Additional air ducts were installed in the high-light caging area to ensure that the temperature (74° ± 10°F) and humidity (50% ± 5%) were maintained within normal limits.

Ocular Biometry

The refractive status, corneal power and axial dimensions were measured for each eye of each subject at ages corresponding to the start of diffuser lens wear and then every 2 to 4 weeks throughout the treatment period. To make these measurements, the monkeys were anesthetized (intramuscular injection: ketamine hydrochloride, 15–20 mg/kg, and acepromazine maleate, 0.15–0.2 mg/kg; topical: 1–2 drops of 0.5% tetracaine hydrochloride) and cyclopleged (1% tropicamide). The refractive status of each eye was measured independently by two experienced investigators, with a streak retinoscope, and averaged.⁶ An eye's refractive error was defined as the spherical-equivalent, spectacle-plane refractive correction (95% limits of agreement = ±0.60 D).⁴³ The anterior radius of curvature of the cornea was measured with a handheld autokeratometer (Alcon, Ltd., Fort Worth, TX), and central corneal power was calculated from the average of three readings, using an assumed refractive index of 1.3375 (95% limits of agreement = +0.49 to −0.37 D for mean corneal power).⁴⁴ The eyes' axial dimensions were measured by A-scan ultrasonography (Image 2000; Mentor, Norwell, MA); 10 separate measurements were averaged. The average intrasession SD for the critical vitreous chamber depth measures was 0.04 mm.

All the rearing and experimental procedures were reviewed and approved by the University of Houston's Institutional Animal Care and Use Committee and were in compliance with the ARVO Animal Statement and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Statistical Methods

Mann-Whitney tests were used to compare the median data between subject groups. Paired student *t*-tests were employed to examine interocular differences. The relationship between refractive error and vitreous chamber depth was determined with Pearson's correlation analysis (all analyses: Minitab software; ver. 12.21; Minitab Inc, State College, PA).

RESULTS

At ages corresponding to the start of the treatment period (3 weeks of age), the refractive errors in the right and left eyes were well matched in all animals (all subject groups combined; OD versus OS average $\pm$ SD: $+4.12 \pm 1.77$ D vs. $+4.18 \pm 1.71$ D; $t = -1.38$; $P = 0.17$), and there were no between-group differences in the median refractive errors (right eyes: $P = 0.16$ – 0.54). However, under normal room lighting, the monocular form-deprivation regimen consistently produced relative axial myopia in the treated eyes. In Figure 1, longitudinal refractive errors and vitreous chamber depths are presented for five representative animals that were selected to illustrate the range of responses found in the form-deprived monkeys reared under normal laboratory lighting. As represented by the four rightmost plots in each row, form deprivation typically accelerated vitreous chamber elongation rates and produced a concomitant myopic shift in the refractions of the treated eyes. These myopic changes were typically observed approximately 4 weeks after the onset of form deprivation and generally increased in magnitude throughout the course of the rearing period. However, as illustrated by the monkey represented in the leftmost plots, a small number of animals exhibited relative hyperopic shifts in their form-deprived eyes. In some cases, these hyperopic shifts were transient, and the animals later manifested myopia, yet, as represented in Figure 1A, these hyperopic changes persisted throughout the rearing period in 2 of the 18 form-deprived monkeys.

In contrast, as illustrated in Figure 2, only two of the eight form-deprived monkeys reared under the high-light conditions developed myopia in their treated eyes. In the case of animal MKY 443 (Fig. 2A), the treated eye showed relatively rapid myopic changes and developed a substantial degree of myopia

by the end of the treatment period. The treated eye of animal MKY 442 (Fig. 2B) exhibited refractions that were within the normal range throughout most of the diffuser-rearing period, but manifested myopia during the last 4 weeks of treatment. On the other hand, in six of the eight high-light-reared monkeys, the treated eyes exhibited initial relative hyperopic shifts in refraction that were maintained throughout the treatment period (Figs. 2C–H).

Figure 3 compares the development of anisometropia in the monocularly form-deprived monkeys reared under normal (Fig. 3A) and high (Fig. 3B) ambient lighting. Under normal laboratory lighting conditions, 16 of the 18 form-deprived monkeys developed relative myopic errors during the treatment period. There were substantial intersubject differences in the degree of anisometropia, which ranged from $+2.69$ to -10.31 D (treated eye – fellow eye), but at the end of the diffuser rearing period (i.e., ~ 133 days of age), the treated eyes were obviously more myopic than their fellow eyes ($t = -4.95$; $P < 0.0001$). The range of anisometropic errors observed in the high-light-reared monkeys was also substantial ($+3.13$ to -11.50 D); all eight of these monkeys exhibited degrees of anisometropia that were more than 2 SD away from the average degree of anisometropia observed in the control monkeys (median anisometropias, 0.125 D vs. 2.125 D; $P < 0.00001$). At the end of the treatment period, the average refractive errors for the treated and fellow eyes of all the high-light-reared monkeys were not different (treated versus fellow eye: $+4.20 \pm 5.80$ D vs. $+4.76 \pm 2.71$ D; $t = -0.31$; $P = 0.76$), primarily because of the large myopic anisometropias observed in two animals. In the other six high-light-reared monkeys, the treated eyes were more hyperopic than their fellow nondeprived eyes ($+6.89 \pm 2.63$ D vs. $+4.91 \pm 3.18$ D; $t = 6.48$, $P = 0.001$).

As illustrated in Figure 4, which shows the refractive errors for both eyes of individual subjects at ages corresponding to the end of the diffuser rearing period, the absolute refractive errors of the high-light-reared monkeys were very different from those of normal monkeys and from those of the form-deprived monkeys reared under normal laboratory light levels. In comparison to normal monkeys, the median refractive errors for both the treated ($P = 0.04$) and fellow eyes ($P = 0.002$) of the high-light-reared monkeys were more hyperopic (Table 1). Even when we excluded the data for animal MKY 448 (Fig. 2H), the monkey that exhibited unusually high hyperopic errors at the start of the rearing period, the median fellow-eye refractive error was still more hyperopic than normal ($P = 0.007$). At the end of the rearing period, the median treated-eye refractive errors for the high-light-reared monkeys were also

FIGURE 1. Spherical-equivalent refractive corrections (A–E) and vitreous chamber depths (F–J) plotted as a function of age for the treated and fellow eyes of five representative form-deprived monkeys that were reared under ordinary laboratory lighting. Thin lines: the data for the right eyes of the control monkeys. The first symbols in each plot represent the onset of the diffuser rearing period. The diffusers were worn continuously throughout the observation period.

FIGURE 2. Spherical-equivalent refractive corrections plotted as a function of age for the treated and fellow eyes of the eight form-deprived monkeys (A–H) that were reared under high ambient lighting conditions. *Thin lines:* the data for the right eyes of the control monkeys. The first symbols in each plot represent the onset of the diffuser rearing period; the diffusers were worn continuously throughout the observation period.

significantly more hyperopic than those for the form-deprived eyes of the monkeys reared under normal laboratory lighting ($P = 0.02$). In contrast, the treated-eye refractive errors for the form-deprived monkeys reared under normal lighting levels were more myopic than the eyes of normal monkeys ($P = 0.0001$); however, the fellow eyes of the form-deprived, normal-light-reared monkeys were similar to those of normal monkeys ($P = 0.33$).

In both groups of form-deprived monkeys, the treatment-induced alterations in refractive errors were associated with alterations in vitreous chamber elongation rates. Figure 5 shows the longitudinal changes in vitreous chamber depth for the treated and control eyes of the high-light-reared monkeys. Like the myopic, form-deprived monkeys that were reared under normal laboratory lighting (Fig. 1), the two high-light-reared monkeys that developed myopia exhibited faster than normal rates of vitreous chamber elongation (Figs. 5A, 5B). However, the treated eyes of most of the high-light-reared

monkeys showed more hyperopic errors and shorter vitreous chambers than their nondeprived, fellow eyes (Figs. 5C–H). As illustrated in Figure 6, there was a strong correlation between the interocular differences (IOD) in vitreous chamber depth and refractive error ($P < 0.0001$). The corneal powers of the treated eyes of the form-deprived monkeys reared under normal laboratory lighting were slightly higher than those of their fellow control eyes ($+56.55 \pm 1.40$ vs. $+56.15 \pm 1.22$; $t = 2.19$; $P = 0.04$). However, the corneal powers and anterior segment dimensions of the treated and control eyes of the high-light-reared monkeys were well matched and indistin-

FIGURE 3. Interocular differences in spherical-equivalent refractive error (treated eye refractive correction – fellow eye refractive correction) plotted as a function of age for individual form-deprived monkeys. The first and last symbols for each animal correspond to the start and the end of the treatment period, respectively. Data are shown from the monocularly form-deprived monkeys reared under (A) normal laboratory lighting or under (B) high levels of artificial lighting.

FIGURE 4. Spherical-equivalent refractive errors obtained at ages corresponding to the end of the treatment period for both eyes of individual monkeys. ($\diamond$) Normal monkeys and the fellow eyes of the form-deprived monkeys; ($\blacklozenge$) the treated eyes of the form-deprived monkeys reared under the normal and high ambient light levels.

TABLE 1. Refractive Errors and Ocular Dimensions at Ages Corresponding to the End of the Treatment Period

	Age (d)	Eye	Ametropia (D)	K (D)	AC (mm)	LT (mm)	VC (mm)
Normal monkeys, $n = 32$	131 $\pm$ 7	Right	+2.59 $\pm$ 1.03 (+2.56)	+56.06 $\pm$ 1.69 (+56.16)	3.00 $\pm$ 0.26 (3.01)	3.62 $\pm$ 0.21 (3.57)	9.71 $\pm$ 0.27 (9.71)
		Left	+2.53 $\pm$ 1.08 (+2.53)	+56.21 $\pm$ 1.75 (+56.58)	3.04 $\pm$ 0.27 (2.99)	3.62 $\pm$ 0.21 (3.58)	9.70 $\pm$ 0.29 (9.69)
Normal lights form-deprived, $n = 18$	133 $\pm$ 9	Treated	-1.30 $\pm$ 4.25 (-1.57)	+56.55 $\pm$ 1.40 (+56.36)	3.12 $\pm$ 0.29 (3.18)	3.57 $\pm$ 0.13 (3.57)	10.48 $\pm$ 0.87 (10.57)
		Fellow	+3.04 $\pm$ 1.62 (+2.88)	+56.15 $\pm$ 1.22 (+56.17)	3.11 $\pm$ 0.23 (3.14)	3.58 $\pm$ 0.12 (3.63)	9.82 $\pm$ 0.52 (9.82)
High lights form-deprived, $n = 8$	131 $\pm$ 6	Treated	+4.20 $\pm$ 5.80 (+5.69)	+55.18 $\pm$ 1.33 (+55.32)	3.07 $\pm$ 0.16 (3.10)	3.60 $\pm$ 0.18 (3.60)	9.71 $\pm$ 0.95 (9.57)
		Fellow	+4.76 $\pm$ 2.71 (+3.88)	+55.33 $\pm$ 1.24 (+55.52)	3.05 $\pm$ 0.12 (3.08)	3.63 $\pm$ 0.16 (3.63)	9.59 $\pm$ 0.63 (9.69)

The data are expressed as the mean $\pm$ SD (median). K, corneal power; AC, anterior chamber depth; LT, lens thickness; VC, vitreous chamber depth.

guishable from those found in normal monkeys ($P = 0.12$ – 0.74 ; Table 1).

DISCUSSION

The results of this study show that absolute light levels, a fundamental variable that has largely been ignored in refractive-error research involving mammals, can have a significant impact on vision-dependent ocular growth in primates. In particular, high ambient lighting can retard the development of form-deprivation myopia. In chickens, a high-light regimen very similar to that employed in this study has been shown to slow the rate of myopic compensation for negative lenses and to reduce the degree of myopia produced by 4 days of form deprivation by approximately 65%.^{29,30} Thus, these experiments also provide another example of the operational similarities between the vision-dependent mechanisms that regulate ocular growth and refractive development in diverse vertebrate species.

In comparison to the myopia retarding effects of high ambient lighting in chickens,²⁹ the protective effects observed in monkeys were quite robust. In chickens, the one study of the effects of high ambient light levels on the development of form deprivation myopia, which was only 4 days in duration, reported a 65% reduction in the degree of form-deprivation myopia.²⁹ We observed an 87% reduction in the average degree of myopic anisometropia in the high-light-reared monkeys and, in 75% of these animals, the treated eyes actually became significantly more hyperopic than their fellow eyes. Moreover, in the monkeys the protective effects of high light levels against form-deprivation myopia were maintained over a long treatment period. It is not known whether the effects of high lighting levels on form-deprivation myopia in chickens can be maintained over long periods. In negative-lens-reared chickens, high levels of artificial light similar to those in this study slowed the rate of myopic compensation, with the largest effects found after 3 to 4 days of lens wear.³⁰ However, the negative-lens-reared chickens exhibited complete myopic compensation after 6 days of lens wear (i.e., the end point for emmetropization was not altered).

Assuming that the operating properties of the ocular growth regulating mechanisms are similar in monkeys and chickens, it seems likely that high light levels would retard form-deprivation myopia in chickens over long periods and that high light would also slow the rate of negative lens compensation in monkeys, but would not prevent complete myopic compensation. If that is the case, then the results of this study indicate that, as supported by experiments in chickens,^{45–47} the phenomena of form-deprivation myopia and negative-lens-induced myopia are not identical. Whereas optically imposed defocus effectively alters the end point for the emmetropization process, form deprivation, as first noted by Schaeffel and Howland⁴⁸ represents open-loop ocular growth. By eliminating meaningful visual feedback, in particular, visual signals that normally stop growth, severe form-deprivation presumably causes the eye to revert to some intrinsically determined growth rate. The very high degree of intersubject variability observed in the degree of form-deprivation myopia (Fig. 3) may reflect individual differences in these intrinsic growth rates or individual differences in the operational properties of the feedback loop that regulates refractive development. In this respect, the protective effects of high lighting levels on form-deprivation myopia in monkeys, suggest that in the absence of a recognizable end point for emmetropization, high ambient lighting reduces this intrinsic growth rate, possibly by effectively producing a stop signal.

In addition to the treated-eye effects, the nondeprived fellow eyes of the high-light-reared monkeys were more hyper-

FIGURE 5. Vitreous chamber depth plotted as a function of age for the treated and fellow eyes of individual form-deprived monkeys that were reared under high artificial lighting (A–H). *Thin lines:* data for the right eyes of the control monkeys. The first symbols in each plot represent the onset of the diffuser rearing period.

opic than normal. This relative hyperopia was greater than the fellow-eye effects previously observed in monocularly form-deprived monkeys reared under normal laboratory lighting.⁴⁰ Although similar fellow eye effects have not been observed in form-deprived chickens reared under high-ambient lighting,²⁹ the course of emmetropization in chickens is influenced by absolute light levels.³¹ As observed in the nondeprived fellow eyes of the high-light-reared monkeys, chickens exposed on a daily diurnal basis to high artificial lighting levels (10,000 lux) are more hyperopic than those exposed to more typical indoor light levels (e.g., 500 lux).³¹ On the other hand, chickens exposed to low ambient lighting levels tend to develop enlarged eyes⁴⁹ and to manifest relative myopic errors,^{31,50} although there are inconsistencies between laboratories on the effects of low light on refractive development in chickens.⁵¹ It is possible that in our experiments reductions in pupil size produced by the high light levels (the average pupil diameter

in the high-light-reared monkeys was 1.6 mm vs. 3.8 mm in normal-light-reared monkeys) and that the concomitant increase in the eye's depth of focus altered the effective end-point for emmetropization in the nondeprived eyes. In essence, with very small pupil sizes, the retinal blur produced by low degrees of hyperopia may not have been sufficient to stimulate additional axial elongation, thus effectively stopping emmetropization at a more hyperopic error.

Why were the treated eyes of six of the high-light-reared monkeys more hyperopic than their fellow control eyes? Both eyes were exposed to the same high-light regimen, which presumably affected intrinsic growth rates in the two eyes by a similar amount. The key difference was that the natural hyperopic errors of the fellow eyes provided a potential cue for emmetropization. Although, as argued above, reductions in pupil size would decrease the effects of a given ametropic error, the fact that the fellow eyes developed a more normal degree of hyperopia in comparison to their deprived eyes indicates that the natural ametropias provided a sufficient stimulus to support partial, but incomplete, emmetropization. On the other hand, the diffuser lenses virtually eliminated meaningful signals associated with the deprived eyes' effective refractive errors. The fact that the form-deprived eyes were more hyperopic than their fellow eyes also implies that the absence of a detectable defocus signal in form-deprived eyes is not a strong de facto stimulus for enhanced axial growth.

It is reasonable to suppose that ambient lighting levels influence the efficiency or gain of the vision-dependent mechanisms that regulate refractive development. Several hypotheses have been put forward to explain how light levels could influence ocular growth. Mutti et al.^{52,53} have proposed that the protective effects against myopia of outdoor activities, in essence high light levels, are mediated by vitamin D. Specifically, they have speculated that time spent outdoors increases the amount of cutaneously derived vitamin D and that vitamin D influences refractive development possibly through interactions with retinoic acid, a presumed signal molecule in the biochemical cascade that mediates the effects of vision on ocular growth.⁵² This idea is supported by the recent observations that (1) myopes have lower circulating blood levels of vitamin D than do nonmyopes⁵³ and (2) that there are single-nucleotide polymorphisms at loci within the vitamin D recep-

FIGURE 6. Interocular differences in refractive error plotted as a function of interocular differences in vitreous chamber depth for individual animals (treated or right eye – fellow or left eye). *Solid line:* best-fitting regression line ($y = -5.71x - 0.10$; $r^2 = 0.91$).

tor region on chromosome 12 that are associated with myopia.⁵² Although it is likely that our high-light-reared monkeys had higher than normal levels of cutaneously derived vitamin D, elevated vitamin D levels may not be sufficient to retard the development of myopia. A recent study using tree shrews reported that dietary supplements of vitamin D₃ that were sufficient to elevate serum levels of 25-hydroxyvitamin D by factors ranging from 5 to 50 times normal did not affect the myopia produced by either form deprivation or negative-powered lenses (Siegwart JT, et al. *IOVS* 2011;52:ARVO E-Abstract 6298).

On the other hand, there is growing evidence that the protective effects of light on form deprivation myopia are mediated, at least in part, through the retinal dopamine system, which can be a strong inhibitor of ocular growth. Form deprivation normally reduces the synthesis and release of dopamine^{54–56} and the typical myopic changes produced by form deprivation are blocked by the administration of a variety of dopamine agonists (Schmid KL, et al. *IOVS* 2004;45:ARVO E-Abstract 1239).^{57–59} In this respect, retinal dopamine release in mammals is stimulated by light and increases with increasing light levels.⁶⁰ Most important, recent experiments in chickens have shown that dopamine antagonists block the protective effects of high light levels on form-deprivation myopia.³⁰

Regardless of how ambient light levels affect refractive development, our results are consistent with the hypothesis that the strong protective effects that outdoor activities have on myopia in children are due to exposure to the higher light levels normally encountered in outdoor environments.^{26,29,30} Although it seems likely that other factors associated with outdoor environments besides high light levels can influence refractive development, our results also provide a potential explanation for the observation that myopia progression is slower in the summer, when daylight hours are longer and there are higher light levels, than in the winter.^{61–63} However, it is important to recognize that there is still much to be learned about the exposure parameters that influence the protective effects of ambient lighting levels. In particular, it is likely that absolute intensity, temporal exposure parameters, and the spectral composition of light are critical for the protective effects observed in this study. Moreover, it will be important to determine the effects of ambient lighting levels on negative lens compensation in primates because the presence of a defocus signal may override any effects of ambient lighting levels. Nonetheless, the fact that artificial ambient lighting can retard the development of vision-dependent axial myopia raises the possibility that substantial therapeutic protection against myopia in children could be achieved by manipulating indoor lighting levels.

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