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Brief Daily Periods of Unrestricted Vision Can Prevent Form-Deprivation Amblyopia

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Abstract

PURPOSE—To characterize how the mechanisms that produce unilateral form-deprivation amblyopia integrate the effects of normal and abnormal vision over time, the effects of brief daily periods of unrestricted vision on the spatial vision losses produced by monocular form deprivation were investigated in infant monkeys.

METHODS—Beginning at 3 weeks of age, unilateral form deprivation was initiated in 18 infant monkeys by securing a diffuser spectacle lens in front of one eye and a clear plano lens in front of the fellow eye. During the treatment period (18 weeks), three infants wore the diffusers continuously. For the other experimental infants, the diffusers were removed daily and replaced with clear, zero-powered lenses for 1 ($n = 5$), 2 ($n = 6$), or 4 ($n = 4$) hours. Four infants reared with binocular zero-powered lenses and four normally reared monkeys provided control data.

RESULTS—The degree of amblyopia varied significantly with the daily duration of unrestricted vision. Continuous form deprivation caused severe amblyopia. However, 1 hour of unrestricted vision reduced the degree of amblyopia by 65%, 2 hours reduced the deficits by 90%, and 4 hours preserved near-normal spatial contrast sensitivity.

CONCLUSIONS—The severely amblyogenic effects of form deprivation in infant primates are substantially reduced by relatively short daily periods of unrestricted vision. The manner in which the mechanisms responsible for amblyopia integrate the effects of normal and abnormal vision over time promotes normal visual development and has important implications for the management of human infants with conditions that potentially cause amblyopia.

Visual experience plays an important role in both normal and abnormal visual development. Infants are born with rudimentary visual capabilities and require normal visual experience early in life to reach optimal levels of visual functioning as adults.¹ Ocular disorders such as refractive errors and media opacities that degrade the retinal image in one or both eyes can, at least during early visual development, produce amblyopia such that even when clear retinal imagery is restored, a decrease in optically corrected visual acuity remains that cannot be attributed to obvious structural or pathologic anomalies of the eye.^{2,3}

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The depth or severity of amblyopia can vary from a just-detectable decrease in visual acuity to virtual form blindness.^{4–9} In individuals without strabismus, several factors influence the degree of amblyopia produced by retinal image degradation. It is well documented that conditions that produce an interocular imbalance in retinal image quality typically result in more severe reductions in vision than conditions that affect both eyes equally^{10–16} and that the degree of amblyopia is related to the status of the patient's residual binocular vision (Movshon JA, et al. *IOVS* 2003;44:ARVO E-Abstract 3182; Bosworth RG, et al. *IOVS* 2003;44:ARVO E-Abstract 3183).¹⁷ In addition, the severity of the vision deficits in unilateral amblyopia is also influenced by factors related to the degree of retinal image degradation.^{6, 7, 18–20} Moreover, temporal factors, including the age at onset of the anisometropia or opacity,^{4, 5, 7, 21} the duration of the image degradation,^{14, 22–25} and the age at which clear vision is restored^{23, 24, 26–32} influence the severity of amblyopia produced by image degradation.

Although the effects of temporal variations in image quality during the period of abnormal visual experience have not been examined systematically, several observations suggest that the consistency of image degradation over time has a significant impact on the degree of amblyopic vision loss. For example, the lower prevalence of amblyopia in individuals with myopic anisometropia than in those with hyperopic anisometropia has generally been thought to reflect differences in the consistency of image degradation over time.^{18, 33, 34} In this respect, it could be argued that in comparison to individuals with high degrees of anisometropia, patients with lower amounts of anisometropia typically develop lower degrees of amblyopia because changes in viewing distance, gaze direction, accommodative effort, or simply increased object contrast can produce intermittent improvements in the image in the more ametropic eye, even when fixation is consistently dominated by one eye. Similarly, it is plausible that the severity of unilateral form deprivation amblyopia is generally greater than anisometropic amblyopia, in part because the image degradation produced by media opacities is typically consistent and unremitting. Experiments in monkeys support this idea. Continuous form deprivation of one eye of infant monkeys for even very short periods can produce severe amblyopia.^{21, 35, 36} However, alternating the form deprivation between the two eyes on a daily basis seriously compromises binocular vision, but allows normal monocular spatial vision to develop even when the period of alternating form deprivation is prolonged.^{37–39}

From a teleological perspective, it is reasonable to expect that intermittent periods of degraded retinal images would have little impact on spatial vision development. Because we live in a three-dimensional world, the eye normally encounters defocused images interspersed with periods of clear vision throughout the day. To ensure that vision develops normally, it makes sense that the mechanisms that regulate visual development weigh the beneficial effects of normal visual experience more heavily than the detrimental effects of abnormal visual experience. Characterizing the manner in which periods of clear and degraded retinal images are integrated over time is important because, from a clinical perspective, intermittent periods of normal vision may be sufficient to support the development of normal vision, even in the presence of a potentially amblyogenic visual anomaly.

MATERIALS AND METHODS

Subjects

Data are presented for 26 rhesus monkeys (*Macaca mulatta*). All the infants were obtained at 1 to 3 weeks of age and reared in our primate nursery, which was maintained on a 12-hour light–dark cycle. All the rearing and experimental procedures were approved by the University of Houston's Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

To characterize how the mechanisms that produce unilateral amblyopia in response to interocular imbalances in image quality integrate the effects of normal and abnormal vision over time, we determined how brief daily periods of unrestricted vision influence the development of form-deprivation amblyopia. Form deprivation imposed by diffuser lenses is the ideal amblyogenic stimulus for these experiments because the degree of image degradation cannot be improved by accommodation, changes in fixation distance, or compensating ocular growth. As a consequence, the timing and degree of image degradation can be controlled precisely. Thus, monocular form deprivation was produced in 18 infant monkeys by securing a diffuser spectacle lens in front of one eye and a clear plano lens in front of the fellow eye. The diffuser lenses, which were held in place by a lightweight helmet,⁴⁰ consisted of a plano carrier lens that was covered with a commercially available occlusion foil (Bangerter Occlusion Foils; Fresnel Prism and Lens Co., Scottsdale, AZ). The occlusion foils were the strongest diffusers that we used in our previous behavioral study on the effects of the degree of image degradation on the depth of amblyopia.⁹ Measurements of spatial contrast sensitivity obtained through the treatment lenses revealed that these diffusers reduced the contrast sensitivity of normal adult humans by over 1 log unit for grating spatial frequencies of 0.125 cyc/deg with a resulting cutoff spatial frequency near 1 cyc/deg. The lens-rearing regimen was initiated at 3 weeks of age (24.3 ± 2.8 days) and was continued for approximately 18 weeks (144 ± 17 days). At the end of the rearing period, the helmets were removed, and the animals were allowed unrestricted vision until the behavioral experiments were started. We specifically selected this rearing period, because we had previously demonstrated that continuous unilateral form deprivation during this period produced severe amblyopia in infant monkeys without interfering with interocular alignment and that, during this critical period for spatial vision development, even short durations of continuous monocular form deprivation produced severe amblyopia in infant monkeys. During the treatment period, three infants wore the diffusers continuously. For the other form-deprived monkeys, the diffuser lenses were removed each day and replaced with a clear plano lens for unitary periods of 1 ($n = 5$), 2 ($n = 6$), or 4 ($n = 4$) hours. These periods of unrestricted vision were centered near the midpoint of the normal 12-hour lights-on cycle. To control for potential effects associated with the helmet rearing procedures, four infant monkeys were reared with helmets that held clear, zero-powered lenses over both eyes. Additional control data were obtained from four normally reared infants.

The behavioral data for three of the plano-control animals and the three treated monkeys that wore the diffusers continuously have been previously reported.^{9,41} In addition, details concerning refractive development for all the animals used in this study have been described previously.^{42,43} Because the diffuser lenses altered the course of emmetropization in the treated eyes of some monkeys and because these results were potentially important for interpreting our behavioral data, aspects of our animals' refractive development are also included here.

Observations of the positions of the first Purkinje images relative to the centers of the entrance pupils indicated that all the treated animals maintained normal interocular alignment throughout the observation period.

Psychophysical Methods

When the animals were at least 18 months of age (i.e., after at least 1 year of visual experience without the treatment lenses), spatial contrast sensitivity functions were measured behaviorally for each eye. The basic apparatus and operant procedures were similar to those used in previous investigations.^{9,44,45} During the daily experimental sessions, the monkeys were seated in a primate chair inside a light-proof, sound-attenuating chamber. The primate chair was fitted with a response lever on the waist plate and a drink spout on the neck plate through which orange drink reinforcement was delivered. The animal's optimal spectacle correction, which

was determined for each eye independently using a subjective refraction procedure,⁴⁵ was held in a facemask at about a 14-mm vertex distance. For monocular viewing, the lens well for one of the eyes was occluded with an opaque disc.

The detection stimuli were vertical sinusoidal gratings that were generated using a graphics board (VSG; Cambridge Research Systems, Cambridge, UK) on a 20-in. video monitor (Nano Flexscan 9080; Eizo Nanao, Cypress, CA) that operated at a 100-Hz frame rate. The usable display subtended a visual angle of $11 \times 14^\circ$ at the 114-cm viewing distance and had a space-averaged luminance of 60 cd/m². The grating stimuli were presented as Gabor patches, which consisted of a carrier grating presented in sine phase with the center of the display. The contrast of the grating was attenuated by a two-dimensional (2-D) Gaussian envelope and declined to a value of 1/e of the maximum contrast at 4° from the Gabor's center. The number of grating cycles within the Gabor varied as a function of spatial frequency. As a result, at low spatial frequencies when a small number of grating cycles were presented, probabilistic concerns may have limited absolute sensitivity by a small amount.⁴⁶ However, for spatial frequencies above the peak of the monkey's contrast sensitivity function, the number of grating cycles exceeded the number required for optimal performance. A Pritchard spectrophotometer equipped with an automated scanning spot was used to calibrate the luminance and contrast of the display. The contrast of the grating pattern was defined as $(L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$, where $L_{\max}$ and $L_{\min}$ represent the maximum and minimum luminances of the grating, respectively.

The behavioral paradigm was a temporal-interval detection task that required the monkey to press and hold down the response lever to initiate a trial and then to release the lever within a criterion response interval (900 ms) after the presentation of the grating stimulus to score a 'hit' and to receive a juice reinforcement. The grating stimuli were presented for durations of 500 ms, with equal probability between 250 and 6000 ms after the initial lever press. Contrast detection thresholds were measured as a function of spatial frequency from 0.125 or 0.25 cyc/deg to 16 cyc/deg in 0.15-log-unit intervals. Data were collected using an adaptive decreasing contrast staircase procedure. The decision rules were based on a one-down, two-up strategy where each hit was followed by a 0.05-log-unit reduction in contrast, and two consecutive misses were followed by a 0.6-log-unit increase in contrast. The one-down, two-up strategy caused the staircase reversals to converge to a contrast where the probability of a hit was 25%, and this contrast was taken as the threshold. During a given experimental session, the staircases for 5 to 7 different spatial frequencies were simultaneously interleaved.

Contrast sensitivity functions were generated from the geometric means of a minimum of 10 threshold measurements at each spatial frequency. For descriptive purposes and to calculate an eye's grating visual acuity, each contrast sensitivity function was fit with a double exponential function ($\text{contrast sensitivity} = [ks (sf \cdot kf)^{al}] \exp(-ah \cdot sf \cdot kf)$), where sf is spatial frequency; al and ah are parameters that reflect the slopes of the low- and high-spatial frequency portions of the function, respectively; ks and kf are proportional to the peak contrast sensitivity and the optimum spatial frequency, respectively) using an iterative routine that minimized the sum of squared errors.⁴⁷

The effects of the different rearing strategies on spatial vision development were quantified primarily by interocular comparisons between the treated and nontreated eyes and by comparisons of the parameters of the exponential functions fit to the contrast sensitivity data, specifically the peak contrast sensitivities and the optimum and cutoff spatial frequencies. For a global measure of spatial vision, the area under the contrast sensitivity function plotted on log-log coordinates was calculated by integrating the exponential functions that were fit to the data between 0.2 cyc/deg and the cutoff spatial frequency.⁴⁸

RESULTS

The contrast sensitivity functions for the normal (Fig. 1) and plano-control animals (Fig. 2) were comparable in every major respect. The contrast sensitivity functions for each eye were band-pass in shape. The maximum contrast sensitivities were near 100 for midspatial frequencies between approximately 2.0 and 3.0 cyc/deg, and the extrapolated cutoff spatial frequencies were approximately 20 cyc/deg (mean $\pm$ SD: normal = 22.7 ± 3.1 versus the plano control = 19.7 ± 2.1 cyc/deg). As expected, the contrast sensitivities for the two eyes of each of the normal and plano-control monkeys were well matched. The mean interocular differences in contrast sensitivity across all spatial frequencies were 0.05 ± 0.04 and 0.06 ± 0.04 log units for the normal and plano-control monkeys, respectively. The largest interocular contrast sensitivity differences for the normal and plano-control monkeys were 0.16 and 0.15 log units, respectively. Thus, the results in Figures 1 and 2 demonstrate that our helmet rearing procedures, by themselves, did not interfere with the development of spatial vision and that interocular comparisons of contrast sensitivity potentially provide a very sensitive gauge for any treatment-related reductions in the spatial vision of the deprived eyes.

As illustrated in Figures 3 to 6, the nontreated fellow eye ($\circ$) of each diffuser-reared monkey exhibited a qualitatively normal contrast sensitivity function. There were small, but statistically significant differences between the spatial contrast sensitivities of the nontreated fellow eyes and those of the control animals. Specifically, the mean grating acuity and the mean area under the contrast sensitivity functions for the nontreated fellow eyes were slightly lower than those for the control (18.5 cyc/deg vs. 21.7 cyc/deg; two-sample *t*-test, $df = 15$, $T = -2.25$, $P = 0.04$; $2.98 \log^2$ vs. $3.31 \log^2$ $df = 18$, $T = -2.11$, $P = 0.05$). Amblyopic humans, and particularly those who experienced monocular form deprivation, also frequently exhibit mild visual deficits in their nonamblyopic fellow eyes.^{49,50} Of note, the nontreated eyes of the diffuser-reared animals that were allowed 2 and 4 hours of unrestricted vision each day tended to exhibit the lower contrast sensitivities. An ANOVA showed that the areas under the contrast sensitivity functions for the nontreated eyes of the animals in the 2- and 4-hour unrestricted vision groups were significantly lower than those for the nontreated eyes of the animals that wore the diffusers continuously ($F = 4.01$, $P = 0.03$).

Many of the treated eyes of the diffuser-reared monkeys exhibited the spatial frequency dependent losses in contrast sensitivity that are characteristic of amblyopia. As illustrated in Figure 3, continuous monocular form deprivation produced obvious and severe reductions in the spatial contrast sensitivity of the treated eyes (Fig. 3, filled symbols). All three monkeys that wore the diffusers continuously showed a 10-fold reduction in peak contrast sensitivity and cutoff spatial frequency in their treated eyes relative to either normal monkeys or their nontreated fellow eyes. However, as shown in Figures 4 to 6, the degree of amblyopia caused by form deprivation was dramatically reduced by allowing the experimental monkeys relatively short daily period of unrestricted vision.

Figure 4 shows the monocular contrast sensitivity functions for all 5 monkeys that experienced 1 hour of unrestricted vision centered within 11 hours of daily form deprivation. Within this group, the treatment effects ranged from severe amblyopia to virtually normal spatial contrast sensitivity. Two monkeys (MKY SAW and MKY QUE) showed contrast sensitivities similar to those of the monkeys reared with continuous form deprivation, with nearly 10-fold reductions from normal in peak sensitivities and cutoff spatial frequencies. At the other end of the spectrum, two monkeys in the 1-hour group (MKY NAN and MKY HAL) demonstrated normal or near normal spatial contrast sensitivities in their treated eyes. The results for the remaining monkey in this treatment group were intermediate between these two extremes. Monkey TIA exhibited very small interocular differences in contrast sensitivities for low spatial frequencies, a slightly reduced peak contrast sensitivity in the treated eye, and less than an

octave difference between the cutoff spatial frequencies for its two eyes. The dramatic effects of 1 hour of unrestricted vision per day for the monkeys in this treatment group cannot be attributed to a reduction in the cumulative number of hours of form deprivation, because the average length of the lens-rearing period was 20 days longer in this treatment group than in the group that wore the diffusers continuously. Instead, the obvious effectiveness of periodic interruptions of form deprivation emphasizes the significance of the constancy of image degradation in amblyogenesis.

Extending the length of the daily period of unrestricted vision increased the consistency and magnitude of these protective effects. Figure 5 shows the contrast sensitivity functions for the six monkeys that received 2 hours of unrestricted vision and 10 hours of form deprivation each day. Three monkeys in this group (Fig. 5, top row) showed reduced contrast sensitivity in their treated eyes over the entire range of spatial frequencies; however, the interocular reductions in peak sensitivity and cutoff spatial frequency were only about one octave. The other three monkeys in this group exhibited losses in contrast sensitivity that were confined to higher spatial frequencies and cutoff spatial frequencies that were only about an octave below those for their nontreated eyes. Four hours of unrestricted vision virtually eliminated the effects of 8 hours of severe form deprivation. Figure 6 shows that three of the four monkeys in this treatment group had identical contrast sensitivities in their two eyes, and the fourth animal (MKY TAY) had very minor interocular deficits in contrast sensitivity at only very high spatial frequencies.

Figure 7 summarizes the effects of our rearing regimen on the development of form deprivation amblyopia. At left, interocular differences in log contrast sensitivity are plotted as a function of spatial frequency for individual animals. As represented by the open symbols, the normal monkeys and the plano-control monkeys showed virtually identical right- and left-eye contrast sensitivities over the entire range of spatial frequencies tested. Treated monkeys, however, showed relative losses in the contrast sensitivity in their form-deprived eyes that increased with spatial frequency in all treatment groups. However, as the daily period of unrestricted vision was increased, the magnitude and the extent of the deficits in the spatial frequency domain decreased dramatically. It is also clear that as the period of unrestricted vision was increased, the rescue effects became more consistent within a given treatment group. To quantify the overall temporal integration properties of the mechanisms responsible for monocular form deprivation, the average interocular ratio of the area under the contrast sensitivity function for the nontreated eye and the treated eyes were plotted as a function of the duration of the daily period of unrestricted vision (Fig. 7, right). Continuous form deprivation produced approximately a ninefold reduction in the area under the contrast sensitivity function for the deprived eyes compared with the nondeprived eyes. Only 1 hour of unrestricted vision reduced the amblyogenic effect of continuous form deprivation by a factor of 3. With 2 hours of unrestricted vision, the reductions in contrast sensitivity were equivalent to approximately 10% of those produced by continuous form deprivation. The interocular contrast sensitivity ratios for the animals that wore the diffusers continuously and those in the 1- and 2-hour unrestricted vision groups were significantly higher than those for our control animals (ANOVA, $F = 13.15$, $P < 0.0001$; Tukey pair-wise comparisons, family error rate, 0.05). However, with 4 hours of unrestricted vision, the interocular contrast sensitivity function ratios were indistinguishable from those of the normal (open circle) and plano-control (open diamond) monkeys. The time constant for the exponential function fit to the data was approximately 56 minutes.

As illustrated in Figure 8, which shows the interocular differences in refractive error plotted as a function of age for each treated monkey, in many of the diffuser-reared monkeys significant refractive errors developed during the lens-rearing period, which were typically manifest as an anisometropia. Although all the animals that developed more than 1 D of anisometropia during the diffuser-rearing period recovered from these induced refractive errors after lens removal

(i.e., the anisometropia decreased to below 1 D), the interocular balance of refractive errors was not always stable thereafter. Instead, several of the treated animals developed anomalous refractive errors developed well after the end of the lens-rearing period. Three aspects of these refractive errors are of interest because they could influence the degree of permanent amblyopia. First, experimentally induced refractive errors that developed during the diffuser-rearing period could have altered the nature of the visual experience in the treated eye during the daily periods of unrestricted vision. For example, it could be argued that animals with large anisometropias would be less likely to benefit from daily periods of unrestricted vision because the treated eye would presumably be defocused during the periods of unrestricted vision. Moreover, because it takes longer to recover from large than small experimentally induced refractive errors, large experimentally induced ametropias may effectively extend the duration of the treatment period. In this respect, animals that had larger anisometropias and recovered more slowly from the experimentally induced refractive error might be expected to exhibit smaller protective effects and thus higher degrees of amblyopia. Finally, it could be argued that anisometropias that develop after the diffuser-rearing period, but within the critical period for spatial vision development, could potentially confound any protective effects provided by the periods of unrestricted vision during the diffuser-rearing period.

When the data from all the experimental animals were pooled, there was a tendency for large interocular differences in contrast sensitivity to be associated with large degrees of anisometropia at the end of the lens-rearing period (Fig. 9; ANOVA, $F = 3.16$, $P = 0.06$). However, examination of the refractive errors within a given treatment group suggests that these experimentally induced refractive errors did not have a strong influence on the degree of form-deprivation amblyopia. In particular, within a given group there was no clear relationship between the degree of anisometropia at the end of the lens-rearing period and the depth of amblyopia. For example, the monkeys that were allowed 1 hour of unrestricted vision each day (Fig. 9, filled diamonds; Fig. 8, second row) showed a six to sevenfold range in their interocular contrast sensitivity function ratios, but the range of anisometropias at the end of the lens-rearing period was quite small (+0.8 to -1.3 D). In contrast, the degree of anisometropia at the end of the lens-rearing period in the monkeys in the 2-hour group (Fig. 9, filled circles; Fig. 8, third row) varied from +0.8 to -4.4 D, but they all exhibited relatively similar interocular differences in contrast sensitivity. Thus, potential differences in the quality of the retinal image related to refractive error during the daily periods of unrestricted vision did not appear to contribute to differences in the degree of amblyopia between animals. Also, the longer recovery times associated with larger anisometropias at the end of the lens-rearing period did not appear to influence the degree of form-deprivation amblyopia. For example, in the continuous form deprivation group, MKY LIS exhibited a smaller myopic anisometropia that recovered much faster than the anisometropia in MKY JAS (Fig. 8; top row); however, MKY LIS demonstrated more severe form deprivation amblyopia. Similarly, MKY ULR in the 2-hour group (Fig. 8; row 3) exhibited faster refractive error recovery than MKY NEL, but more severe amblyopia. Finally, although a number of the treated animals had significant anisometropias that developed well after the end of the diffuser-rearing period, these anisometropias did not overshadow the effects of the period of form deprivation or the protective effects provided by the daily periods of unrestricted vision. For example, monkeys MIG (continuous group), HAL (1-hr group), XYL (2-hour group), and NIN (4-hour group), all had significant anisometropia after approximately 250 days of age. However, each of these monkeys exhibited mild contrast sensitivity deficits within their respective treatment groups.

DISCUSSION

Our main findings were that relatively brief daily periods of unrestricted vision greatly reduced the degree of amblyopia produced by otherwise constant monocular form deprivation and that the magnitude of this protective effect increased with the daily duration of unrestricted vision.

The fact that comparatively short periods of unrestricted vision counterbalanced the severely amblyogenic effects of long daily periods of form deprivation indicates that the mechanisms that are responsible for amblyopia do not weigh the effects of clear versus degraded spatial vision equally. Either the mechanisms responsible for amblyopia integrate the effects of clear versus degraded visual experience in a nonlinear fashion over time and/or the response of these mechanisms to clear vision is much stronger or persists to a greater extent beyond the exposure period than the responses to form deprivation. This bias in the effective temporal integration properties of the vision-dependent mechanisms responsible for amblyopia would help ensure the development of normal spatial vision and would greatly reduce the likelihood that transient periods of image degradation would have a lasting impact on spatial vision.

The nontreated fellow eyes of the diffuser-reared monkeys also had lower contrast sensitivities than did the eyes of normal monkeys. Similar dominant eye deficits have been observed in previous studies of animals with experimentally induced unilateral amblyopia (Kiorpes L, et al. *IOVS* 2005;46:ARVO E-Abstract 3592)^{51–53} and, more importantly, in humans with unilateral amblyopia,^{49,50} which increases the confidence associated with extrapolating our results to children. Although the reason for the reduced spatial vision in the dominant eyes is not known, it is interesting that the largest reductions in dominant eye acuity were found in the animals allowed the longest periods of unrestricted vision.

In otherwise normal infant monkeys, hyperopic anisometropias can produce unilateral amblyopia early in life.⁴⁵ Given that many of our diffuser-reared animals developed significant anisometropias, why was there little evidence that the presence of anisometropia influenced the degree of amblyopia observed in our experimental monkeys? A variety of factors may have limited the impact of these refractive errors in our form-deprived monkeys. First, our diffuser rearing strategy typically produced myopic anisometropia. Thus, as in humans with myopic anisometropias, our animals, particularly those that had not developed substantial amounts of form-deprivation amblyopia, may have alternated fixation between the two eyes based on viewing distance, which would reduce the likelihood that an anisometropia would produce amblyopia. Second, in the case of the continuously form-deprived monkeys (animals that would not be expected to alternate fixation regardless of viewing distance), any additional effects associated with the presence of anisometropia after the removal of the diffuser lenses may have been overshadowed by the severe amblyopia produced by the prior period of continuous form deprivation, particularly since these animals would not experience the optical effects of the anisometropia until approximately 5 months of age, when the effects of image degradation on spatial vision are greatly reduced.^{21,36} Similarly, the anisometric errors that developed well after the end of the diffuser rearing period may have failed to produce any obvious spatial vision alterations because the onset of these refractive errors occurred when the animals were less susceptible to amblyogenic stimuli. In addition, for the animals that received unrestricted vision during the diffuser-rearing period, it is possible that form deprivation produced alterations in cortical physiology before the onset of any experimentally induced refractive error that minimized the consequences of an anisometropia. For example, in young monkeys, form deprivation can produce significant alterations in vision and cortical physiology in as little as 2 weeks—that is, well before the onset of anisometropia in most animals. In this respect, we have previously shown that a brief period of optical strabismus, presumably by reducing the possibility for anomalous binocular competition in the visual cortex, greatly reduces the amblyogenic effects of a subsequent period of form deprivation.⁵⁴ Of interest, our recent electrophysiological investigations of the visual cortex in our experimental monkeys revealed that cortical binocular interactions were greatly reduced in all three subject groups that received unrestricted visual experience. If these cortical changes occurred before the onset of anisometropia, they may have reduced the susceptibility of our monkeys to the normal amblyogenic effects of an anisometropia.

What are the critical temporal factors for averting amblyopia from monocular form deprivation? Several observations indicate that a reduction in the absolute exposure duration over the entire period of form deprivation was not the critical factor. First, the duration of the treatment period for the monkeys that received daily periods of unrestricted vision was longer than that for the monkeys that experienced constant form deprivation. Moreover, it has been previously shown that periods of uninterrupted form deprivation as short as 2 weeks can produce severe amblyopia in infant monkeys.^{11,36} Therefore, it is unlikely that the protective effects observed in the experimental monkeys can be attributed to a decrease in the total absolute amount of anomalous visual experience. Instead, it is the nature of the daily exposure history that appears to be critical for the observed protective effects.

From our results alone, we cannot determine whether the observed protective effects were due to a decrease in the daily duration of form deprivation, an increase in the daily duration of unrestricted vision, or a combination of the two. However, it seems unlikely that a reduction in the daily duration of form deprivation from 12 hours for the monkeys that experienced continuous form deprivation to 11, 10, or even 8 hours per day would, in the absence of unrestricted visual experience, substantially reduce the degree of amblyopia. In young kittens, it has been demonstrated that a single, 4-hour period of monocular form deprivation was sufficient to initiate the shifts in the ocular dominance of cortical cells that underlie many aspects of the visual deficits associated with form-deprivation amblyopia.⁵⁵ Moreover, 4-hour daily periods of monocular form deprivation in otherwise dark-reared kittens produce dramatic shifts in cortical ocular dominance in favor of the non-deprived eye⁵⁶ and 7 hours of monocular form deprivation each day produced virtual form blindness.⁵⁷ The key point is that the duration of monocular form deprivation, although short in these kitten experiments, was long enough to cause extensive cortical reorganization. Given the similarities in the cortical alterations produced by abnormal visual experience in young kittens and monkeys, it is reasonable to expect that 8 to 12 hours of form deprivation each day would produce similar results in primates, which supports the idea that it is the absolute duration of the daily periods of unrestricted vision and/or the proportion of the daily visual cycle that includes unrestricted vision that is critical for the protective effects from form deprivation.

In our monkeys, 4 hours of unrestricted vision each day (i.e., unrestricted vision for 0.33 of the lighted daily cycle) was sufficient to eliminate interocular differences in spatial contrast sensitivity. These results are qualitatively and quantitatively similar to results obtained from monocularly form-deprived kittens by Mitchell et al.⁵⁷ In their study, monocularly form-deprived kittens were allowed 0.5-, 1-, or 2-hour periods of unrestricted binocular vision during the 7-hour light cycle each day. Figure 10 compares the degree of form deprivation amblyopia in our monocularly form-deprived monkeys (solid symbols) with cats from Mitchell et al. (open circles) plotted as a function of the duration of the daily period of unrestricted vision. The degree of amblyopia is represented by the inter-ocular differences in the minimum angle of resolution (cat and monkey) and the interocular differences in the area under the contrast sensitivity function (monkey). The dotted line, which represents the exponential function fit to the contrast sensitivity data for our experimental monkeys (from Fig. 7), adequately describes the interocular acuity differences in both monkeys and cats. Considering the differences in the maturation rates and the temporal characteristics of the critical periods of plasticity for cats^{58–61} and monkeys,^{21,35,36,62,63} this agreement is remarkable and emphasizes the similarities in the operational properties of the mechanisms responsible for amblyopia in both species. It appears that the basic operational properties of these mechanisms have been conserved across species, which suggests that the human visual system should also have quantitatively similar integration properties. These results also underscore the potential importance of the daily exposure cycle in the development of spatial vision.

The steepness of the function in Figure 10 for short periods of unrestricted vision may have contributed to the high degree of intersubject variability observed in the monkeys that received 1-hour of unrestricted vision. Because the function is very steep, small intersubject differences in innate susceptibility to form deprivation and/or small variations in effective exposure duration could make substantial differences in the degree of amblyopia. Although the onset of diffuser wear was fixed relative to birth, infant monkeys with similar gestational ages, but different conceptual ages, exhibit different visual acuities and presumably have differences in their susceptibility to anomalous visual experience.⁶⁴ In addition, even though infant monkeys older than 4 weeks are relatively active throughout the day, infant monkeys do nap. Therefore, it is possible that differences in activity patterns could have contributed to some of the variability that we observed in our 1-hour experimental group. We were aware of this potential confound and specifically observed the animals during the periods of unrestricted vision, especially when the animals were young. Although we found that our monkeys rarely slept when anyone was in the room, we cannot rule out the possibility that differences in the level of activity/alertness may have contributed to the larger intersubject variability found in the 1-hour group.

In kittens, brief periods of concordant binocular vision are more effective in preventing deprivation-induced amblyopia than similar duration periods of nonconcordant binocular vision. For example, if optical prisms are used to prevent concordant binocular vision during the daily interruptions of form deprivation, kittens still develop substantial amblyopia in their deprived eyes. In our experiments, the experimental monkeys were provided unrestricted binocular viewing during the daily interruptions in form deprivation. In many cases, it could be argued that our animals experienced concordant binocular vision. For example, all our animals maintained normal interocular alignments throughout the rearing period and the daily periods of unrestricted vision greatly reduced the degree of experimentally induced refractive errors. For example, in our 1-hour group, the average anisometropia was 0.49 ± 0.45 D during the diffuser rearing period. In this respect, studies in human subjects have shown that binocular function is largely unaffected with this magnitude of imposed optical defocus.^{65–74} Thus, as reported in kittens, concordant binocular vision during the daily periods of unrestricted vision may have played a significant role in the observed protective effects. In contrast, a number of the monkeys in our 2-hour group developed significant anisometropias, which presumably would have compromised binocular vision during the daily periods of unrestricted vision. Yet these animals exhibited substantial protective effects, which suggest that concordant binocular vision may not be essential. Further studies are presently under way to determine the role of concordant binocular vision in the protective effects provided by short daily periods of unrestricted vision.

The results from our experimental monkeys have implications for young infants that have conditions that produce amblyopia. First, our findings clearly show that to consistently produce amblyopia, monocular image degradation must be very consistent over time. Thus, our study supports the idea that hyperopic anisometropia is a greater risk for amblyopia than is myopic anisometropia, because with hyperopic anisometropia, monocular image degradation is more consistent over time. More importantly, our results suggest that the vision-dependent mechanisms that mediate normal spatial vision development in infants can function effectively with only short daily periods of normal vision. Consequently, providing brief daily periods of unrestricted vision could have substantial therapeutic value in the management of children who have conditions that lead to amblyopia.

In addition, our findings show that protection from amblyogenic image degradation can be accomplished early in the course of visual development. Our monkeys were treated up to approximately 18 weeks of age, which is equivalent to approximately 18 months in human infants.⁷⁵ Our results show that although both monkey and human infants are extremely

susceptible to the deleterious effects of image degradation during this time, the mechanisms supporting visual development are exquisitely sensitive to the protective effects of periods of unrestricted binocular vision. Early detection of conditions that can cause potentially amblyogenic image degradation, such as congenital cataract or hyperopic anisometropia, is critical for the preservation of normal vision. Our results strongly support early screening and exams by eye doctors to detect impediments to clear vision early in visual development.

Because only a few weeks of continuous form deprivation can produce severe amblyopia in infant primates,^{11,36} amelioration of the conditions that produce form deprivation as quickly as possible is undoubtedly the best option for ensuring normal visual development in human infants.^{15,23,24,32,76} However, if it is not possible to achieve permanent elimination of the cause of form deprivation immediately, temporary manipulations that provide short daily periods of unrestricted vision, such as periodically lifting a drooping eyelid, or keeping corrective lenses on a hyperopic anisometrope for even short periods during the day, may be sufficient to maintain normal visual development. The key point is that substantial beneficial effects could result from relatively short daily intervention periods.

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Figure 1.

Mean contrast sensitivity ($\pm$ SD) plotted as a function of spatial frequency for the left (○) and right (●) eyes of the four normal monkeys. The smooth lines drawn through the data represent the best-fitting exponential functions.

Figure 2.

Mean contrast sensitivity ($\pm$ SD) plotted as a function of spatial frequency for the left (○) and right (●) eyes of the four control monkeys that were reared with plano lenses in front of both eyes. The data for monkeys HT2, MIS, and AXE have been replotted from Smith et al.⁹

Figure 3.

Mean contrast sensitivity ($\pm$ SD) plotted as a function of spatial frequency for the treated ($\bullet$) and nontreated eyes ($\circ$) of the three monkeys that wore the diffuser lenses continuously. The data for these monkeys have been replotted from Smith et al.⁹

Figure 4. Mean contrast sensitivity ($\pm$ SD) plotted as a function of spatial frequency for the treated (●) and nontreated (○) eyes of the five diffuser-reared monkeys that were allowed 1 hour of unrestricted vision each day.

Figure 5. Mean contrast sensitivity ($\pm$ SD) plotted as a function of spatial frequency for the treated ($\bullet$) and nontreated ($\circ$) eyes of the six diffuser-reared monkeys that were allowed 2 hours of unrestricted vision each day.

Figure 6. Mean contrast sensitivity ($\pm$ SD) plotted as a function of spatial frequency for the treated ($\bullet$) and nontreated ($\circ$) eyes of the four diffuser-reared monkeys that were allowed 4 hours of unrestricted vision each day.

Figure 7.

Left: Interocular differences in log contrast sensitivity (nontreated eye – treated eye) plotted as a function of spatial frequency for individual control (*open symbols*) and diffuser-reared monkeys (*filled symbols*). For the normal and planolens control monkeys, the right eye was considered to be the treated eye. *Right:* Mean interocular ratios (nontreated eye/treated eye) of the area under the contrast sensitivity functions (log–log coordinates) plotted for each subject group as a function of the duration of the daily period of unrestricted vision. *Open symbols* represent both normal and control animals.

Figure 8.

Interocular differences in refractive error (treated eye refractive correction – fellow eye refractive correction) plotted as a function of age for individual experimental animals. The animals in the different treatment groups are displayed in different rows, with the *top row* showing animals that experienced continuous form deprivation. The *second, third, and fourth rows* display data for the animals in the 1-, 2-, and 4-hour treatment groups, respectively. The order of subjects in each row matches the order in Figures 3 to 6, with the degree amblyopia increasing from *left to right*. Data were obtained during (●) and after (○) the diffuser-rearing period, respectively. Data were replotted from Smith et al.⁹ and Qiao-Grider Y et al.⁴³

Figure 9.

Interocular ratios (nontreated eye/treated eye) of the area under the contrast sensitivity functions (log–log coordinates) plotted as a function of the degree of anisometropia at the end of the treatment period. (•) Monkeys that wore the diffuser lenses continuously. The remaining monkeys experienced daily periods of unrestricted vision of (◆) 1, (◊) 2, and (▼) 4 hours, respectively.

Figure 10.

Degree of form deprivation amblyopia in our monocularly form-deprived monkeys (*filled symbols*) and cats (*open symbols*) plotted as a function of the duration of the daily period of unrestricted vision. The degree of amblyopia is represented by the interocular ratio (nontreated eye/treated eye) of the minimum angle of resolution (cat MAR and monkey MAR) and the interocular ratio of the area under the contrast sensitivity function (Monkey CSF). *Dotted line*: the exponential function fit to the contrast sensitivity data for our experimental monkeys from Figure 7. Cat data are adapted from Mitchell et al.⁵⁷