Spatial Contrast Sensitivity Deficits in Monkeys Produced by Optically Induced Anisometropia

Earl L. Smith III,* Ronald S. Harwerth,* and M. L. J. Crawford†

An anisometropia was simulated in infant rhesus monkeys by securing a high-powered minus lens (—10 D) in front of one eye. The anisometropia rearing procedure was initiated at 30 days of age and was continued for durations of 30, 60, or 90 days. Behavioral measurements of spatial contrast sensitivity obtained when the animals were 9 months of age indicated that the monkeys treated for 30 days had equal or nearly equal contrast sensitivities and cut-off spatial frequencies in the two eyes. The 30-day monkeys also demonstrated normal binocular summation for threshold stimuli. In contrast, the monkeys treated for either 60 or 90 days showed a significant reduction in contrast sensitivity in the defocused eyes for spatial frequencies greater than 1.0 cycles/deg and failed to show an improvement in contrast sensitivity under binocular viewing conditions. The cut-off spatial frequencies obtained at moderate luminance levels for the defocused eyes of the 60- and 90-day monkeys were slightly more than 1.0 octave lower than the cut-offs for the nondeprived eyes and, like humans with anisometropic amblyopia, the deficits in the spatial resolving capacity of the defocused eyes were observed over a large range of background luminances. The results indicate that the lens-reared monkey is a promising model for anisometropic amblyopia in humans. Invest Ophthalmol Vis Sci 26:330-342, 1985

Functional amblyopia is a reduction in visual acuity that occurs in the absence of any ophthalmoscopically detectable anomalies of the eye, and in appropriate cases, is remediated by therapeutic measures. The three most common etiologies of functional amblyopia are anisometropia, strabismus, and sensory deprivation.1 Although all three of these forms of amblyopia are characterized by decreased visual acuity, recent psychophysical investigations2-7 have revealed substantial differences in the visual characteristics of humans with these three types of amblyopia. The different patterns of visual deficits observed in human amblyopes suggest that these three forms of functional amblyopia may be associated with different neural abnormalities.

Since a thorough understanding of the neural basis of amblyopia is essential for the development of optimal clinical treatment and management procedures, investigators have worked to develop animal models of amblyopia that could be used in anatomic and neurophysiologic experiments, which would be harmful to human subjects. In previous studies involving monkeys, investigators have been successful in producing a behaviorally verified amblyopia in infant macaque monkeys using a variety of early rearing strategies including experimentally induced strabismus,8-10 lid-suture10,11 (sensory deprivation), and chronic unilateral atropinization,10,12 a procedure that mimics some aspects of an anisometropia. Although monkeys subjected to these rearing procedures demonstrate deficits in visual acuity, it is not known presently how well the specific visual characteristics of these monkeys match those of human amblyopes. In general, there has been a tendency to apply the neurophysiologic results from animals with a given type of experimentally induced amblyopia to all types of human amblyopia without a knowledge of the exact nature of the visual deficits of the experimental animals. However, as indicated above, there is good psychophysical evidence that there are basic differences between the three major types of functional human amblyopia and, therefore, before the knowledge gained from neurophysiologic investigations can be interpreted properly, it is important to determine the adequacy of monkeys with specific types of experimentally induced amblyopia as models for the most prevalent forms of amblyopia in the human population.

The purpose of the present study was to produce an anisometropic amblyopia in infant rhesus monkeys.
and to characterize psychophysically the animals' spatial resolving capacity. We chose to study the effects of an anisometropia on the developing monkey's visual system because anisometropia is one of the most frequent causes of amblyopia in the human population; yet very little effort has been devoted to the development of a primate model of anisotropic amblyopia. This lack of effort can be attributed primarily to the technical difficulties associated with simulating an anisometropia. Prior to this study the two techniques used to induce an anisometropia were chronic monocular atropinization and unilateral extraction of the crystalline lens. While both of these techniques optically degrade the image in one eye, they also disrupt normal accommodative function and in the case of chronic atropinization may result in permanent changes in pupil size. In this study we isolated the effects of unilateral defocus by inducing an anisometropia optically. Psychophysical measurements of contrast sensitivity were used subsequently to investigate the monkeys' spatial resolving capacity, because with human subjects contrast detection thresholds have been useful in characterizing the amblyope's deficit in spatial vision and in elucidating differences between the three common forms of amblyopia.

Materials and Methods

Subjects

All of the procedures used in this investigation conform to the ARVO Resolution on the Use of Animals in Research. Four rhesus monkeys (Macaca mulatta) were used as experimental subjects. The monkeys were obtained when they were about 2 weeks of age and were hand-fed until they were able to feed independently. When the animals were 30 days of age, each monkey was fitted with a lightweight fiberglass and aluminum helmet which was used to secure a zero-powered lens over the animal's left eye and a -10.0 D lens in front of the right eye. The lenses were 25 mm in diameter and were fitted into the helmets so that the optical centers coincided with the geometrical centers of the lens rings. The helmets held the lenses at a vertex distance of approximately 8 mm, which provided a monocular field of view of about 109 deg (ignoring prismatic effects of the minus lenses and assuming that the eye's entrance pupil is 4 mm in diameter and located 2 mm behind the cornea). Viewing through the minus lenses optically simulated a relative hypermetropic refractive error; and since the great majority of normal rhesus monkeys, both young and old, have approximately equal refractive errors in the two eyes, the rearing procedure mimicked a naturally occurring anisometropia. Although the voluntary accommodative amplitudes of young rhesus monkeys (17–18 D) are large enough to overcome the demand associated with the -10.0 D lenses as well as the usually low degree of hyperopia observed in young monkeys, it is reasonable to suppose that the lens-reared monkeys, like kittens reared with an optically induced anisometropia, postured their accommodation for the eye viewing through the zero-powered lens. Therefore, since the power of the lens secured in front of the experimental right eye exceeded the monkey's depth of focus, it was assumed that the optically induced anisometropia resulted in a habitually defocused retinal image in the experimental eye throughout the rearing period.

Once the monkeys were fitted with the helmets, they wore the devices continuously except for brief periods of time (5–10 min) each day when it was necessary to remove the helmets for cleaning and servicing purposes. During these brief periods the monkeys' eyes were covered with a dark hood or the animals were placed in a light-tight cage. The anisometropia-rearing procedure, which was initiated at 30 days of age, was continued for durations of 30 (monkeys A and Z), 60 (monkey P), or 90 days (monkey S). At the end of the rearing period the helmets were removed and the animals were housed in a normally lighted environment.

At age 9 months the refractive status of each of the monkey's eyes was determined by retinoscopy and with an objective infrared optometer (Bausch and Lomb Ophthalmetron), axial lengths were measured by A-scan ultrasonography (Kretztechnik, 7200 MA) and the ocular media and fundi were examined with an indirect ophthalmoscope. To obtain the objective measurements, the monkeys were anesthetized with ketamine hydrochloride (10 mg/kg; IM) and 1% cyclopentolate hydrochloride was instilled topically in the eyes to induce mydriasis and to paralyze accommodation.

Once the monkeys had been trained to perform the contrast sensitivity paradigm (see below), the objective refractive error data were used as a starting point for an assessment of refractive errors using psychophysical techniques. The subjective procedure was in essence a meridional refraction. The objective of the meridional refraction was to determine the most plus or least minus lens power that yielded the lowest contrast thresholds for a relatively high spatial frequency grating at each of four grating orientations (vertical, horizontal, right oblique and left oblique). The grating spatial frequency used to determine refractive status was dependent on the subject's spatial resolving capacity. For eyes which on preliminary testing exhibited normal or near-normal visual acuity, an 8 cycles/deg grating was selected because small
amounts of optical defocus produce substantial changes in contrast sensitivity and yet the monkeys are sufficiently sensitive to this spatial frequency to allow an adequate number of trials in each descending threshold series to maintain stimulus control of the subject’s behavior. For eyes that exhibited reduced spatial resolving capacities, it was necessary to use lower spatial frequencies (e.g., for the right eyes of subjects P and S a 2 cycles/deg grating was used), which were within the animal’s resolving capacity. In all cases the lens powers were varied in 0.5-D steps. Only one lens power and grating orientation were evaluated in a daily experimental session. The mean of all of the contrast thresholds measured in a given experimental session (typically 15–30 threshold measurements were obtained in a daily session) was used to evaluate the adequacy of a given lens power. The lens powers that yielded the highest mean contrast sensitivities were used to derive the optimum spheric-cylinder correction, which was used in all the subsequent behavioral experiments. To insure optimal performance, the monkeys’ refractive errors were rechecked at 6-month intervals using the objective techniques. If a substantial change in refractive error was observed, the refractive error was refined again using subjective techniques.

### Apparatus and Procedures

After the measurements of the monkeys’ refractive errors were completed, the subjects’ spatial resolving capacities were determined behaviorally by measuring contrast detection thresholds for sinusoidal gratings. A description of the basic apparatus and the operant procedures has been reported previously.20

During the daily experimental sessions, the monkeys were placed in a standard primate chair inside a light-proof, sound-attenuating room. The primate chair was fitted with a response lever on the waist plate, and a drink spout on the neck plate through which the unconditioned reinforcer was delivered. The monkeys were deprived of all liquids for approximately 22 hr before each experiment and were reinforced with orange drink (Tang) when they performed correctly in the behavioral paradigm. A lens holder and head restraint were also attached to the chair so that the monkeys’ eyes were centered in the lens wells when their mouths were on the drink spout. Any refractive errors were corrected with the appropriate lenses at a vertex distance of about 14 mm. For monocular viewing conditions, one of the lens wells was occluded with an opaque disc. In most experiments the monkeys viewed the stimulus display with natural pupils (~4.5 mm in diameter for the 27 cd/m² display); however, in some instances artificial pupils also were secured in the lens wells to eliminate possible confounding effects associated with any uncorrected refractive error.

The detection stimuli were vertical sinusoidal grating patterns generated on a CRT display (Tektronix 608, P4 phosphor) using conventional techniques. The display screen was masked by an equal-luminance surround to subtend a visual angle of 6.8 deg at the 75-cm viewing distance. The maximum space-average luminance of the display was 27 cd/m². For the experiments designed to determine the effects of luminance on the monkeys’ spatial vision, the equal-luminance surround was turned off and lower mean luminance levels were obtained by securing neutral density filters directly to the display screen. All other stimulus parameters (timing, contrast, and spatial frequency) were under computer control. A Pritchard Spectra Photometer equipped with an automated scanning slit was used to calibrate the luminance and contrast of the display. The contrast of the grating pattern was defined as \((L_{\text{max}} - L_{\text{min}})/(L_{\text{max}} + L_{\text{min}})\), where \(L_{\text{max}}\) and \(L_{\text{min}}\) represent the maximum and minimum luminances of the pattern, respectively.

Contrast detection thresholds were determined using a modification of the reaction time paradigm developed by Stebbins22 and Harwerth and Sperling.23 Briefly, the monkeys were trained to press and hold a response lever in the presence of an auditory ready signal (8-Hz clicker). A sustained lever press initiated a foreperiod that varied randomly in duration between 0.5 and 8.0 sec. At the end of the variable foreperiod, the detection stimulus was presented for 500 msec with square-wave onset and offset characteristics. If the monkey released the lever within a 900-msec limited-hold period following the presentation of the grating pattern, it was assumed that the subject had detected the stimulus, the response was reinforced (an auditory tone following all correct responses and 0.5 ml of orange drink on a 0.5 random probability basis), and the contrast of the grating pattern was reduced 0.1 log units. To discourage the monkeys from releasing the response lever indiscriminately, anticipatory responses, lever releases that occurred within the variable duration foreperiod prior to the stimulus onset, initiated a mild punishment contingency in the form of a longer intertrial interval (12 sec versus 2 sec following other trials). Following the onset of the stimulus if the monkey failed to release the lever within the limited-hold period, it was assumed that the monkey had not detected the grating pattern, the subject was not reinforced, and the stimulus contrast was not changed. After a minimum of two consecutive misses, the contrast of the grating pattern was reset to a higher level (usually to 0.40). However, to maintain stimulus control of the animal’s
Table 1.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Duration of treatment</th>
<th>Eye</th>
<th>Refractive error</th>
<th>Axial length</th>
<th>Extrapolated cut-off spatial frequency (cycles/deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30 days</td>
<td>OD*</td>
<td>+2.50 − 1.25 × 90</td>
<td>18.6 mm</td>
<td>36.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS†</td>
<td>+3.00 − 1.00 × 90</td>
<td>18.6 mm</td>
<td>35.5</td>
</tr>
<tr>
<td>Z</td>
<td>30 days</td>
<td>OD</td>
<td>+3.00 DS</td>
<td>17.8 mm</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>+3.00 − 0.50 × 180</td>
<td>17.5 mm</td>
<td>34.7</td>
</tr>
<tr>
<td>P</td>
<td>60 days</td>
<td>OD</td>
<td>−8.00 DS</td>
<td>20.5 mm</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>−4.50 DS</td>
<td>19.0 mm</td>
<td>30.2</td>
</tr>
<tr>
<td>S</td>
<td>90 days</td>
<td>OD</td>
<td>−7.50 − 1.00 × 180</td>
<td>20.1 mm</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>−6.25 DS</td>
<td>19.4 mm</td>
<td>27.1</td>
</tr>
</tbody>
</table>

* OD = right eye.
† OS = left eye.
‡ DS = dioptic sphere.

behavior, the stimulus contrast was not increased predictably after two consecutive misses, but instead, the second and each subsequent miss had a 0.5 probability of resetting the contrast to a higher level. The stimulus contrast associated with the missed trials, which resulted in the resetting of the stimulus contrast to a higher value was defined operationally as the threshold contrast. In this respect, the behavioral paradigm is analogous to a classic descending method of limits.

Threshold contrasts were determined for different stimulus spatial frequencies ranging between 0.25 cycles/deg and 16 cycles/deg in 0.3 or 0.6 octave steps for the control eyes and over whatever range was possible for the treated eyes. In all cases the 900-msec limited-hold period was long enough to ensure that the subject's ability to respond was not limited by motor considerations but instead was dependent on their ability to detect the grating pattern. Contrast sensitivity functions (the reciprocal of the threshold contrast plotted as a function of spatial frequency) were derived from the geometric means of a minimum of 12 threshold measurements at each spatial frequency.

Results

Refractive Status, Eye Alignment, and Internal Examination

The axial lengths and the spectacle-plane refractive errors determined using the objective procedures for the right (treated) and left eyes of each monkey are shown in Table 1. The two monkeys treated for 30 days demonstrated similar axial lengths and moderate but essentially equal degrees of hyperopia in both eyes. In contrast the refractive errors for the control and defocused eyes of the 60- and 90-day monkeys were substantially different; for both animals the defocused eye was more myopic than the control eye. Ultrasonography indicated that the differences in refractive status were associated with differences in axial length. For both the 60- and 90-day anisometropic monkeys, the more myopic defocused eye had a longer axial length than the fellow control eye, and in each case the differences in refractive error could be accounted for by the differences in axial length.

An analysis of videorecordings obtained when the animals' attention was directed to a bright light source held directly above a video camera showed that for all four lens-reared monkeys the catoptric images produced by the light source were positioned, symmetrically in the pupils of the two eyes. These results suggest that the monkeys developed normal interocular alignments, however, the accuracy of this technique is limited and the possibility that the lens-reared monkeys had developed a small strabismic deviation (<4.0–5.0 deg), though not suggested, cannot be ruled out.

Ophthalmoscopy revealed that the ocular media for all of the subjects' eyes were clear and free of any opacities. Although myopic crescents were observed at the optic discs in both eyes of subjects P and S, the appearances of the fundi in all of the monkeys' eyes were also within normal limits.

Contrast Sensitivity

The contrast sensitivity functions obtained from the four lens-reared monkeys for the 27 cd/m² mean luminance are shown in Fig. 1. The open and filled symbols represent data for the control and defocused eyes, respectively. The vertical error bars indicate ±1 SD. The extrapolated high spatial frequency cut-off values determined by a least-squares, linear-regression fit to the high spatial frequency data are shown for both eyes of each subject in Table 1.

The data for all of the control eyes conform to the bandpass configuration typical of contrast sensitivity functions obtained from normally reared monkeys. Specifically, the peak contrast sensitivity occurs at approximately 2.5 cycles/deg, and there is a progres-
sive decline in sensitivity for spatial frequencies higher and lower than the peak spatial frequency. The extrapolated cut-off spatial frequencies for the control eyes of the four lens-reared monkeys varied between 27.1 and 35.5 cycles/deg. The values fall within the range of cut-off spatial frequencies we obtained previously from normal rhesus monkeys (20–45 cycles/deg) using similar psychophysical procedures but a slightly higher mean luminance (40 cd/m² vs 27 cd/m²). In addition, at every spatial frequency the contrast sensitivities for all of the control eyes fall within the 95% confidence intervals for contrast sensitivities determined previously for normal monkeys.

The effect of the induced anisometropia on the
spatial resolving capacities of the defocused eyes was dependent on the duration of the treatment. Monkey A, which was subjected to the lens-rearing procedure for 30 days, exhibited equal contrast sensitivities and grating visual acuities in the two eyes. Moreover, the contrast sensitivities and cut-off spatial frequency of Monkey A's defocused eye are within the range of values obtained for normally reared control monkeys, which suggests that the anisometropia induced during the rearing period did not produce a lasting deficit in the spatial resolving capacity of this animal's defocused eye. Monkey Z, which also was treated for 30 days, demonstrated essentially equal contrast sensitivities in the two eyes for spatial frequencies below 6.3 cycles/deg. However, for grating targets with a 6.3 cycles/deg spatial frequency or higher, the defocused eye was significantly less sensitive than the control eye. Although the cut-off spatial frequency for Monkeys Z's defocused eye (26.1 cycles/deg) falls within the range of cut-off values for normal monkeys, the 8.6 cycles/deg difference in the cut-off spatial frequencies between the control and defocused eyes exceeds the largest interocular difference in grating visual acuity (3 cycles/deg difference) that we have observed previously in normal monkeys. In this case the difference in the grating visual acuity indicates that the lens-rearing procedure caused a small but significant reduction in the spatial resolving capacity of the defocused eye. The 60- and 90-day anisometropic monkeys demonstrated obvious interocular differences in spatial resolving capacity. In comparison to the control eyes, both the 60- and 90-day monkeys showed significantly lower contrast sensitivities in the defocused eyes for all spatial frequencies greater than 1.0 cycles/deg. The cut-off spatial frequencies for the defocused eyes of monkeys P and S are more than an octave lower than the cut-offs for the control eyes and are substantially lower than the grating visual acuities of normal monkeys.

The pattern of deficits in contrast sensitivity observed in the treated eyes of three of the four lens-reared monkeys is virtually identical to the reduction in spatial resolving capacity that would be produced by optical defocus. Although we measured carefully and corrected the monkeys' refractive errors, it is necessary to rule out the potential confounding effects of an uncorrected or improperly corrected refractive error in order to evaluate properly the lens-reared monkeys as models for anisometropic amblyopia. Therefore to help identify the nature of the reduction in the treated eyes' spatial vision, contrast detection thresholds were measured with the monkeys viewing the display through an artificial pinhole pupil (1.7 mm in diameter). Figure 2 illustrates contrast sensitivity functions obtained for the control (open circles) and treated eyes (filled circles) of these three lens-reared monkeys when they viewed the display through the artificial pupil. Viewing the stimuli through the artificial pupil resulted in a general reduction in contrast sensitivity in both eyes, which can be attributed largely to a decrease in retinal illuminance. The important point to note from Figure 2 is that for a given animal the magnitude of the interocular difference in spatial resolving capacity is approximately the same as the difference observed with natural pupils. The failure to observe a normalization of the defocused eyes' contrast sensitivity with the artificial pupil indicates that the reduced spatial resolving
Fig. 3. Contrast sensitivity functions obtained for five different background luminances for the 60- and 90-day anisometropic monkeys. The appropriate luminances are indicated for each set of curves. The open and filled circles represent data for the control and defocused eyes, respectively. The standard errors were smaller than the symbols used to represent the data.
capacity observed for the treated eyes cannot be attributed to uncorrected refractive errors.

Effects of Mean Luminance

In an investigation of the effects of mean luminance on the contrast thresholds of human amblyopes, Hess, Campbell, and Zimmern demonstrated substantial differences in the behavior of strabismic and anisometropic amblyopes. They found that for a given spatial frequency the degree of strabismic amblyopia, as indicated by the ratio of contrast sensitivities between the amblyopic and nonamblyopic eyes, decreased as the mean luminance of the grating pattern was decreased. On the other hand, in humans with anisometropic amblyopia, the degree of amblyopia did not diminish with background luminance for any spatial frequency. To further evaluate the lens-reared monkey as a model for human anisometropic amblyopia, contrast thresholds were measured for the 60- and 90-day anisometropic monkeys over a 5-log-unit range of background luminances.

Figure 3 displays contrast sensitivity functions obtained from Monkeys P and S for five different background luminances, which ranged from 27 cd/m² to 0.0027 cd/m² in 1-log-unit increments. The open and filled symbols represent the mean contrast sensitivities for the control and defocused eyes, respectively. The average standard errors (0.04 log units), which were smaller than the symbols used to represent the means, were similar in magnitude for the control and defocused eyes and did not vary significantly with the background luminance. As expected, mean contrast sensitivity varied systematically with background luminance for both the control and defocused eyes. As the luminance was decreased there was a progressive reduction in contrast sensitivity, particularly for the middle and high spatial frequencies. As a result, as the luminance was decreased there was a systematic shift of the peak of the functions toward lower spatial frequencies and a decrease in the magnitude of the low spatial frequency roll-off. However, for any given spatial frequency the differences in the sensitivity of the control and treated eyes did not decrease at the lower background luminances.

To illustrate the similarity between the deficits in spatial vision demonstrated by the lens-reared monkeys and humans with anisometropic amblyopia, the sensitivity ratios for the control and treated eyes of the 60- and 90-day monkeys were plotted as a function of spatial frequency for each background luminance (Fig. 4). Also included in Fig. 4 are the average sensitivity ratios obtained by Hess et al. for the nonamblyopic and amblyopic eyes of a human anisometropic amblyope (subject NN, Snellen acuity 20/60) over a comparable range of background luminances. For any given background luminance the lens-reared monkeys, like the human anisometropic amblyope, demonstrated a deficit in the contrast sensitivity of the defocused eye, which increased in magnitude with spatial frequency. The agreement
BINOCULAR SUMMATION

A. NORMAL CONTROL

B. 30 DAY ANISOMETROPIA (A)

C. 30 DAY ANISOMETROPIA (Z)

D. 60 DAY ANISOMETROPIA (P)

E. 90 DAY ANISOMETROPE (S)

Fig. 5. Log of the ratio of contrast sensitivities for binocular and monocular viewing plotted as a function of spatial frequency for a normal rhesus monkey (A), two 30-day anisometric monkeys (B and C), the 60-day anisometric monkey (D) and the 90-day anisometric monkey (E). The dashed lines show the predicted binocular summation ratio for a human observer with normal binocular vision.27 The arrows to the right of each function indicate the mean summation ratios across all spatial frequencies. Mean luminance was 27 cd/m².

between the data for the human amblyope and 90-day anisometric monkey is qualitatively and quantitatively quite good at all luminance levels. The data for the 60-day anisometropic monkey is comparable with the human data for the 27 cd/m² luminance; however, for most spatial frequencies the relative reduction in the contrast sensitivity of the treated eye increased as the luminance decreased.

Monocular versus Binocular Contrast Sensitivity

Humans27 and monkeys10,28 with normal binocular vision exhibit higher contrast sensitivities and grating visual acuities during binocular viewing conditions than during monocular viewing conditions, a phenomenon referred to as binocular summation. In contrast human anisometric amblyopes fail to show an improvement in spatial vision during binocular viewing.29,30 To determine if the lens-reared monkeys demonstrate normal binocular summation for spatial stimuli, contrast thresholds measured under binocular viewing conditions were compared with monocular contrast thresholds.

Figure 5 shows the log of the ratio of binocular contrast sensitivity to monocular contrast sensitivity plotted as a function of spatial frequency for a normal monkey28 and for the four lens-reared monkeys. The mean monocular contrast sensitivity for the two eyes was used to compute the summation ratio for the control monkey and for the lens-reared monkeys when the sensitivities of the control and defocused eyes were equal. When there was a difference in the contrast sensitivities between the two eyes, data for the more sensitive eye were used to determine the summation ratios. A summation ratio of zero would indicate that performance under binocular viewing conditions was identical to performance under monocular viewing conditions. A ratio greater than zero would indicate that performance under binocular viewing conditions was superior to that during monocular viewing. The dashed lines represent the predicted binocular summation ratio of $\sqrt{2}$ obtained from studies of normal human observers.27 The arrows to the right of each function represent the mean sensitivity ratios across all spatial frequencies.

For the control monkey (Fig. 5A) and the anisometric monkeys treated for 30 days (Fig. 5B, C), contrast sensitivity was consistently better under binocular viewing conditions than under monocular viewing conditions. (Note, however, that for Subject Z, the monkey that exhibited a mild deficit in the treated eye at high spatial frequencies, the summation ratio is close to zero for the three highest spatial frequencies.) A comparison of the binocular and monocular viewing data across all spatial frequencies indicate that for the control monkey and the two
monkeys treated for 30 days the binocular contrast sensitivity was significantly higher than monocular contrast sensitivity (control subject, t(18) = 10.9, \( P < 0.0001 \); subject A, t(18) = 11.9, \( P < 0.0001 \); subject Z, t(18) = 8.8, \( P < 0.0001 \)). Moreover, the mean summation ratios across all spatial frequencies (arrows) for the control and 30-day monkeys are close to the values obtained for humans with normal binocular vision.\(^27\) However, both the 60- (Fig. 5D) and 90-day monkeys (Fig. 5E) failed to show an improvement in contrast sensitivity under binocular viewing conditions. Instead for these subjects performance over a wide range of spatial frequencies under binocular viewing conditions was not significantly different than performance for the control eye alone (subject P, t(8) = -1.98, \( P = 0.064 \); subject S, t(18) = -0.17, \( P = 0.39 \)). The mean summation ratios across all spatial frequencies for the 60- and 90-day lens-reared monkeys are -0.05 and -0.01, respectively, and are substantially below the summation ratios exhibited by observers with normal binocular vision (0.15).

Discussion
Refractive Status and Eye Alignment
Like many kittens reared with an optically induced anisometropia,\(^31\) the lens-reared monkeys that were treated for 60 and 90 days exhibited differences in axial length and refractive error between the control and defocused eyes. In both cases the defocused eyes had longer axial lengths and were relatively more myopic than the control eyes. Similar alterations in axial length and refractive error have been produced in younger monkeys by a variety of rearing strategies, which disrupt normal visual experience (eg, lid-suture or corneal opacification).\(^32\)\(^-\)\(^34\) However, the lens-rearing procedure used in this study differs from previously used rearing strategies in that the optically induced anisometropia resulted in a habitually defocused image without attenuating the amount of light entering the treated eye. Although the differences in the lens-reared monkeys' refractive status must be interpreted cautiously because of the small number of animals studied and because we did not measure the monkeys' refractive status prior to or immediately after the treatment procedure (refractive status was evaluated at 9 months of age), the results indicate that depriving the eye of a clear retinal image disrupts the process of emmetropization. Rabin et al\(^35\) reached a similar conclusion from an analysis of refractive error data from humans deprived of pattern vision early in life. The fact that neither of the 30-day anisometropic monkeys demonstrated any differences in the refractive errors between the control and treated eyes suggests that the effects of defocus on the process of emmetropization are dependent on the duration of the deprivation. Weisel and Raviola\(^32\) have previously observed that the effects of lid suture on refractive status appear to be related to the duration of the eyelid closure.

The estimates of interocular alignment obtained using the corneal reflex technique indicated that none of the lens-reared monkeys had developed a strabismus. Previous investigations of eye alignment in monkeys subjected to a variety of rearing strategies (eg, lid-suture, chronic atropinization, optically induced strabismus) also have failed to document the presence of a strabismus using the corneal reflex technique.\(^10\)\(^\text{-}28\) Although, the accuracy of the corneal reflex technique is limited and the possibility that the lens-reared monkeys had, in fact, developed a small interocular misalignment can not be ruled out, it is interesting to note that the effects of an optically induced anisometropia on eye alignment in monkeys are much different than the effects observed in kittens reared in a similar manner. In contrast to the normal eye alignment observed in monkeys, kittens reared with an optically induced anisometropia often develop large strabismic deviations, which are diagnosed easily with the corneal reflex technique.\(^36\)

Spatial Contrast Sensitivity
Qualitatively and quantitatively the contrast sensitivity functions for the lens-reared monkeys' control eyes compared favorably with those for normal monkeys. The values for the control eyes' contrast sensitivities and the extrapolated high spatial frequency cut-offs are similar to the corresponding values that we determined previously in normal rhesus monkeys using the same basic psychophysical procedure that was employed in this study and to those values found for normal pigtail macaque monkeys by Williams et al\(^37\) using a different behavioral paradigm. The agreement between the results for normal monkeys and the control eyes of the lens-reared monkeys indicate that the control eyes had developed normal spatial resolving capacities. Although there has not been any systematic comparison between the spatial resolving capacities of normal human eyes and the nonamblyopic eyes of humans with anisometropic amblyopia, the contrast sensitivity functions reported by Bradley and Freeman\(^38\) for normal human observers and for the nonamblyopic eyes of anisometropic amblyopes are also similar.

Three of the four lens-reared monkeys exhibited
significant reductions in the spatial resolving capacities of the defocused eyes relative to the control eyes. The data obtained when the animals viewed the display through artificial pinhole pupils indicate that the relative reductions in the treated eyes' spatial vision cannot be attributed to an uncorrected refractive error. Ophthalmoscopic examination of the treated eyes also failed to provide an explanation for the reduction in spatial vision. Therefore, the results demonstrate that the lens-rearing procedure produced an anisometropic amblyopia in the treated eyes of three of the four experimental subjects. Although the contrast sensitivity functions determined for the control and treated eyes of one of the 30-day, lens-reared monkeys (subject A) were virtually identical, it is possible that this animal also had a mild anisometropic amblyopia. For human amblyopes, it is well documented that the magnitude of the amblyopic deficit is dependent on the type of stimulus used to measure visual acuity. For example, visual acuity measurements obtained with Snellen letters are typically lower than acuity measurements obtained with sinusoidal gratings. In fact, Howell et al. have shown that some humans diagnosed as amblyopic using standard Snellen letter acuity charts demonstrate normal spatial resolving capacities when tested with grating patterns. It will be interesting to evaluate this animal's spatial vision with Snellen targets.

An indication of the adequacy of the lens-reared monkey as a model for anisometropic amblyopia can be obtained by comparing the magnitude and nature of the spatial deficit demonstrated by the lens-reared monkeys with that shown by humans with anisometropic amblyopia. Figure 4 illustrates that the largest deficits observed in this study, those for the 60- and 90-day anisometropic monkeys, are equivalent to the reduction in contrast sensitivity for a human anisometropic ambylople with a Snellen visual acuity of 20/60. The majority (≈64%) of humans with anisometropic amblyopia have Snellen visual acuities of 20/120 or better in the amblyopic eye. In this respect the lens-rearing procedure has resulted in a clinically relevant degree of amblyopia. In comparison unilateral lid-suture produces a degree of amblyopia in monkeys that greatly exceeds the degree of amblyopia observed in the majority of human amblyopes. For example, lid-suture initiated in a rhesus monkey at 30 days of age and continued for just 2 weeks reduces the deprived eye's high spatial frequency cut-off to just 0.3 cycles/deg, which can be considered equivalent to a Snellen visual acuity of about 20/2000. Since the magnitude of the visual deficit in lid-sutured monkeys in so great, caution must be exercised when extrapolating the neurophysiologic results obtained from lid-sutured monkeys to all clinical situations.

The nature of the visual deficits in the lens-reared monkeys also compares favorably with the deficits observed in human anisometropic amblyopes. First for the highest mean luminance the deficits in the lens-reared monkeys' contrast sensitivity were restricted to the middle and high spatial frequencies. In an investigation of contrast sensitivity in human anisometropic amblyopes, Bradley and Freeman demonstrated that when corrections were made for interocular magnification differences, the contrast sensitivity deficits in the ambylople eyes also were restricted to middle and high spatial frequencies; sensitivity to low spatial frequencies were the same for both the amblyopic and nonamblyopic eyes. Although two of the lens-reared monkeys exhibited substantial axial anisometrias, the refractive errors were corrected with lenses at a 14-mm vertex distance, a position close to the eye's anterior focal point, which would be expected to minimize any interocular differences in relative spectacle magnification. Therefore, like humans with anisometropic amblyopia, when interocular magnification differences are eliminated, the lens-reared monkeys show essentially equal contrast sensitivities for low spatial frequencies in the control and ambyloolic eyes. As Bradley and Freeman have discussed, the deficits observed for the ambylople eyes at the higher spatial frequencies can be accounted for by habitual defocus, a condition that would have little effect at low spatial frequencies.

A second similarity in the nature of the visual deficits in lens-reared monkeys and humans anisometropic amblyopes is illustrated in Figures 3 and 4. Hess et al. have shown that in contrast to the deficits observed in strabismic amblyopia, the spatial deficits manifested by humans with anisometropic amblyopia do not normalize at low-background luminances. The data obtained for the 60- and 90-day anisometropic monkeys over a 5-log-unit range of background luminances clearly indicate the differences in the resolving capacities of the control and treated eyes did not diminish under reduced illumination. Instead the results indicate that the lens-rearing procedure produced abnormalities in both photopic and scotopic mechanisms. Hess et al. have hypothesized that the visual abnormality in anisometropic amblyopia is primarily size specific and probably extends into peripheral retinal regions. The data from the lens-reared monkeys can be interpreted in a similar manner; however, studies of the effects of field size on the monkeys visual deficits are needed before these conclusions can be justified.
Comparisons of the contrast detection thresholds for binocular and monocular viewing conditions (Fig. 5) also reveal a similarity in the nature of the visual abnormalities in the lens-reared monkeys and human anisometropic amblyopes. Like many humans with anisometropic amblyopia, the subjects that had the larger monocular spatial deficits, failed to show binocular summation for threshold stimuli. Even at low spatial frequencies where the contrast sensitivities for the control and treated eyes were equal, the thresholds for binocular viewing were equivalent to those obtained under monocular viewing conditions. Since the subjects appeared to be orthotropic, the results indicate that the lens-rearing procedure disrupted normal binocular sensory mechanisms in the 60- and 90-day monkeys. However, both of the 30-day anisometropic monkeys, even Subject Z who showed a mild amblyopia, demonstrated superior contrast sensitivities under binocular viewing conditions for most spatial frequencies. It is well documented that many human anisometropic amblyopes with mild acuity losses often demonstrate crude stereopsis. It is possible that these subjects also will exhibit some degree of stereopsis. The binocular viewing data for Subject A and Z indicate that the 30-day treatment period was not sufficient to disrupt totally normal binocular mechanisms.

In summary, the lens-rearing procedure utilized in this study produces deficits in the monkey’s spatial vision that resemble qualitatively and quantitatively the visual deficits manifested by human anisometropic amblyopes. Therefore, these results, as a whole, demonstrate that a clinically relevant anisometropic amblyopia has been created in these lens-reared monkeys.

Key words: anisometropia, amblyopia, rhesus monkey, contrast sensitivity, psychophysics

References


