Acuity and Contrast Sensitivity in Monkeys After Neonatal Intraocular Lens Implantation With and Without Parttime Occlusion of the Fellow Eye

Ronald G. Boothe,†‡ Tracyann M. Louden,* and Scott R. Lambert*‡*

Purpose. The authors used a monkey model to evaluate intraocular lenses (IOLs) for the treatment of infantile cataract in humans. Specifically, they sought to assess the effectiveness of IOLs, with and without occlusion therapy, in preventing amblyopia.

Methods. A diffuser contact lens was placed on one eye each of 11 neonatal monkeys to simulate an infantile cataract. A unilateral lensectomy, combined with the implantation of an IOL, was performed on the same eye 1 to 2 weeks after birth. Clear contact lenses were used to adjust the optical correction of the pseudophakic eyes to a near point, and opaque lenses were used to maintain daily parttime (70%) occlusion of the fellow eyes of half the subjects. Behavioral methods were used to assess grating acuity, optotype acuity (Landolt C), and contrast sensitivity.

Results. In five of the animals, complications that developed in the eye with the implant were severe enough to interfere with visual function. The authors present only behavioral outcomes obtained before or in the absence of surgical complications. In monkeys that underwent daily 70% occlusion, grating acuity in the pseudophakic eyes eventually matured to normal adult levels. Grating acuity was significantly poorer in animals with no occlusion therapy. Even in animals with normal grating acuity, assessments of optotype acuity revealed amblyopic deficits; contrast sensitivity was impaired as well at middle and low spatial frequencies.

Conclusions. The current study demonstrates that if there are no complications secondary to surgery, normal grating acuity can be obtained in neonatal monkey eyes that undergo IOL implantation, optical correction of the pseudophakic eye to a near point, and 70% occlusion of the fellow eye. However, these good outcomes for grating acuity cannot be attained without occlusion therapy. In addition, optotype acuity and sensitivity to contrast always are impaired. Invest Ophthalmol Vis Sci. 1996;37:1520–1531.

Treatment for unilateral infantile cataract in human babies poses a significant clinical challenge. After an initial report of success in maintaining some visual function after neonatal surgery,[1] numerous studies have been conducted to evaluate the effectiveness of treatments that involve some combination of early surgery to remove the cataract, optical correction of the induced aphakia with contact lenses, and occlusion therapy of the fellow eye.[2–19] Infants in these studies sometimes have been reported to attain normal or near normal visual function in both eyes as a result of these treatments,[2,20–23] but most children treated with these methods nevertheless have amblyopia in the aphakic eye.[24–27]

Three potential reasons for poor prognosis include aniseikonia,[28] poor compliance with contact lens wear,[12–18,24] and poor compliance with occlusion therapy of the fellow eye.[27] The first two of these amblyogenic factors can be eliminated or minimized by using an intraocular lens (IOL) implant.[29–31] However, there are potential drawbacks to using IOLs in infants, including complications from the surgical procedure or from implanting an IOL while the eye is still growing. An evaluation of risks and benefits associated with this form of treatment is needed to evaluate its potential for use in human infants.

Macaque monkeys provide a good animal model with which to address questions about human amblyo-

*From the *Division of Visual Science, Yerkes Regional Primate Research Center, and the Departments of †Psychology and ‡Ophthalmology, Emory University, Atlanta, Georgia.*

Supported by National Institutes of Health grant EY08544 and by National Center for Research Resources grant RR00165 to the Yerkes Regional Primate Research Center.

Submitted for publication August 3, 1995; revised March 7, 1996; accepted March 11, 1996.

Proprietary interest category: N.

Reprint requests: Ronald G. Boothe, Division of Visual Science, Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322.

Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8

TABLE 1. Rearing History of Experimental Subjects

Subject Identifier	*Age at Surgery (weeks)*	*Age Lens Wear Stopped (weeks)*	*Actual Amount Daily Occlusion (%)*	*Actual OD Lens Wear (%)*	*Behavioral Assessment*
RWF3	1.9	*	*	*	*
RFG3	2.0	36	74	97	PL
RUK3	1.9	44	73	99	PL
RAG3	1.9	58	64	88	PL OP CS LR
RDK3	2.1	71	69	93	PL OP CS LR
RGN3	1.7	43	71	98	PL OP CS LR
RBH3	2.0	57	0	97	PL OP
RHK3	2.1	71	0	99	PL OP
RNH3	2.1	56	0	97	PL
RVF3	1.4	67	0	98	PL OP
RZF3	2.0	51	0	87	PL

OD = right eye; PL = preferential looking measures of grating acuity; OP = operant measures of grating acuity; CS = operant measures of contrast sensitivity; LR = operant measures of Landolt acuity.

* Monkey RWF3 was dropped from the behavioral study because of complications from the intraocular lens implant before any results were obtained.

pia.[25,26,32] As part of a larger project, our laboratory is using this model to evaluate monofocal and multifocal IOLs as a means of correcting infantile aphakia optically[33] and of comparing these treatments to more traditional contact lens treatments.[34] In a previous report[33] based on behavioral assessments of some of these animals at early ages, we concluded that occlusion therapy may not be as important after IOL implantation as it is for contact lens treatments of infantile aphakia. In the current article, we present more extensive behavioral measurements of monkeys wearing monofocal IOLs, including additional numbers of animals and assessments at older ages of grating acuity, optotype acuity, and contrast sensitivity. Half the animals in the current study underwent daily 70% occlusion therapy of the fellow eye, and the other half did not.

METHODS

Subjects

Eleven rhesus monkeys (*Macaca mulatta*) were assigned to the experimental treatment groups evaluated in the current study. The animal identifier codes are listed in Table 1, as is information about each monkey's experimental history. Complications that developed secondary to surgery (e.g., glaucoma and haptic breakage; see ref. 35 for more details) were considered serious enough to interfere with vision before completion of all the behavioral assessments in five animals. However, our primary purpose in this study was to assess the effectiveness of our treatments in preventing amblyopia under conditions in which the surgery itself was successful. Thus, we include here only behavioral data obtained before detection of eye complications. Eye complications developed before any behavioral testing could be completed for monkey RWF3. Monkeys RFG3, RUK3, RNH3, and RZF3 were evaluated with preferential looking methods at early ages but developed eye complications that precluded further behavioral testing before the completion of operant training and testing. The remainder of the animals completed at least one final assessment of grating acuity using operant testing methods. Performance of the experimentally treated animals was compared to that of a group of 32 normal control monkeys ranging in age from 1 week to adulthood. Experimental monkeys RBH3 and RHK3 also underwent preliminary testing for contrast sensitivity, but because they did not respond to <50% contrast for any spatial frequency in their pseudophakic eyes, more detailed testing was not attempted. Experimental monkeys RAG3, RDK3, and RGN3, all of which exhibited excellent outcomes on the measures of grating acuity, subsequently underwent additional operant testing of optotype acuity and contrast sensitivity, as did one additional normal control.

All procedures were performed in strict compliance with ARVO and NIH guidelines on the use of animals in research, and the protocols were reviewed and approved by the Institutional Animal Care and Use Committee at Emory University.

Procedures

A diffuser contact lens was placed on one eye within a few hours of birth to simulate a mild infantile cataract. The effect of this diffuser lens on vision, as assessed by placing the lens on the eye of a normal human observer, is to reduce contrast at all spatial frequencies by approximately 1 log unit.[36] Lensectomy, posterior capsulotomy, and IOL implantation were performed on the same eye 1.4 to 2.1 weeks

later (see Table 1) under sterile conditions while the animal was deeply anesthetized. The IOLs were polymethylmethacrylate, polyacrylamide surface-modified lenses with a power of 30 D (P327 UV; Storz Intraocular Lens, St. Louis, MO). Examinations that included biomicroscopy, retinoscopy, keratometry, A-scan ultrasonography, tonometry, and ophthalmoscopy were performed at regular intervals before and after surgery.

After surgery, the infants were fitted with extended wear contact lenses to achieve a near-point correction (3 to 5 D overcorrection). The rationale for this optical correction was that it allowed clear vision for items at near range within the monkey's cage. Power of the correction was adjusted at regular intervals (typically, every 1 to 2 weeks) to compensate for changes in refractive error with age. In half the animals, the fellow eye wore an opaque occluder lens for 6 hours each day to achieve occlusion during 70% of the daytime hours while lights in the animal quarters remained on. Contact lens wear was monitored every 2 hours during daytime hours, and missing lenses were replaced immediately. Information about actual compliance for each animal is presented in Table 1. More detailed descriptions of our methods for manufacturing custom contact lenses for use in infant monkeys and for monitoring compliance are provided elsewhere.[37,38]

Two methods were used to track acuity development, depending on the age of the animal. At early ages, we used preferential looking methods[39] in conjunction with Teller Acuity Cards (Vistech Consultants, Dayton, OH). Stimuli shown on the Teller Acuity Cards are vertical square wave gratings. Grating on each card has a different stripe width (varying in octave steps). The preferential looking procedure estimates grating acuity, defined as the finest stripe width that elicits preferential looking behavior. More detailed descriptions of our specific preferential looking procedures, along with some preliminary results obtained from these animals at early ages, are described in more detail elsewhere.[33] We specify grating acuity in units of logMAR, which are the logarithms of the angle (in minutes of arc subtended at the eye) of a single stripe of the grating.

When they were approximately 1 year of age, we trained and tested the animals behaviorally with operant methods.[32,40] The monkey sat in a primate restraining chair or was free roaming in a cage with a face mask mounted on one wall. Two bars were positioned so that they could be manipulated easily by the left and right hands of the monkey. The monkey was trained to view a display on a video monitor and to pull the left bar when a pattern was displayed on the left side of the monitor or to pull the right bar when the pattern was displayed on the right side. Monkeys were rewarded with a fruit-flavored primate pellet (PJ Noyes, Lancaster, NH) for each correct response, and incorrect responses resulted in a time-out period of 10 to 30 seconds, during which the display was turned off.

The pattern displayed during operant assessments of grating acuity consisted of a vertical square wave grating (vertical dark and bright stripes of equal width). The width of the grating displayed on the screen was 18 cm, and the left and right edges of the screen were vignetted to minimize edge artifacts. Testing was typically conducted at a viewing distance of 400 cm, but the viewing distance was reduced to as close as 40 cm for animals with amblyopia performing poorly at longer distances. The width of the stripes was varied from trial to trial according to a two-step staircase rule[41]: After each miss, the stripes were made wider on the next trial, and after every second consecutive correct trial, the stripes were made narrower. The purpose of this staircase tracking procedure was to move the animal's performance toward the vicinity of its acuity threshold.[41] Mean luminance of the display was 20 cd/m^2, and the contrast between the dark and bright stripes at the highest spatial frequencies used for testing was approximately 80%.

The pattern displayed on the video monitor during operant assessments of contrast sensitivity was a vertical spatial sinewave grating (the luminance was modulated sinusoidally along the horizontal axis of the screen). Mean luminance, width, and vignetting of the edges of the display were the same as during measurement of grating acuity. Viewing distance and optical correction also were the same as used for the final assessment of grating acuity. Spatial frequency remained constant across trials within a given session, but the contrast between dark and bright stripes was varied within the range from 0% to 50%, from trial to trial, according to a two-step staircase rule[41,42] to determine contrast threshold. These contrast threshold measurements were then repeated, across sessions, at four to five separate spatial frequencies, separated by octave steps that spanned the range between approximately 1 cyc/deg and the high frequency cutoff of the eye tested. The spatial frequencies were presented in a counterbalanced order. These procedures allowed us to determine the basic shapes of the overall contrast sensitivity functions in which contrast sensitivity (reciprocal of contrast threshold) was plotted as a function of spatial frequency.

A standard Landolt C ring stimulus[43] was displayed on the video monitor during operant assessments of optotype acuity. Viewing distance and optical correction were the same as those used for the final assessment of grating acuity. A ratio of 5:1:1 was maintained between the outer diameter of the ring, the width of the ring, and the width of the gap. The subject was trained to pull the bar corresponding to the position of the gap, which was presented on either

the left or right side of the ring according to a random sequence. The width of the gap was adjusted from trial to trial based on a two-step staircase rule,[41,42] and Landolt acuity was specified in logMAR units of the width of the gap. Luminance of the ring was 40 cd/m^2, and its contrast with the surrounding screen on the video monitor was 80%.

Monocular viewing was achieved by placing an occluder contact lens on one eye. A clear contact lens was used to provide an optical correction to the test eye. During preferential looking tests at young ages, the power of this correction was chosen based on retinoscopy, taking into account the distance of the animal from the Teller Acuity cards. Retinoscopy provided an initial estimate of the optical correction used during operant testing. This initial value was then fine-tuned by measuring the animal's acuity repeatedly while it looked through a series of lenses until the lens power was found that produced best acuity. The operant results for grating acuity, contrast sensitivity, and Landolt acuity were obtained with the optimum lens, as established by these procedures, in place.

All our results, whether obtained with preferential looking or with operant methods, are in the form of psychometric function in which the percentage of correct trials is tabulated as a function of the parameter manipulated (logMAR units for grating acuity and optotype acuity measurements; log contrast for measuring contrast sensitivity). After qualitative evaluation to determine that performance was near 100% on easy conditions and near chance (50%) on difficult conditions, we applied statistical probit analysis[42,44] to each data set to obtain an estimate of threshold.

The longitudinal time course of acuity development was tracked in each animal starting the week after surgery and continuing for the first several months after birth. We attempted to obtain an acuity value every 1 to 2 weeks for each eye of each animal, but scheduling constraints precluded completion of testing of all eyes of all animals during each 2-week period. Results from all completed data sets are presented below in Figures 1 and 2. To make comparisons across groups of animals, we grouped the logMAR acuity values obtained from each individual infant into octave age bins centered around 2 (1.4 to 2.8), 4 (2.8 to 5.6), 8 (5.6 to 11.3), 16 (11.3 to 22.6), and 32 (22.6 to 45.2) weeks of age. As a first-order approximation, these logarithmic age bins group data so that each successive bin reflects a similar magnitude of improvement in acuity.[40] Within each age bin, we first calculated the mean of the logMAR values for each individual subject, and then calculated the mean and standard deviation for the group of subjects that contributed a value to that bin. Thus, no individual subject contributed more than one value to any single age bin, but individual subjects did contribute to more than one age bin.

RESULTS

The development of grating acuity with age is plotted for each eye of five monkeys that underwent 70% occlusion (Fig. 1), as well as for five monkeys that did not undergo occlusion (Fig. 2). The filled symbols in these figures show data from pseudophakic eyes, and the open symbols depict the fellow eyes. Triangles show data obtained with preferential looking, and circles show data obtained with operant methods. The asterisks are mean values from normal control animals previously obtained in our laboratory using the same methods. The confidence interval within which 95% of normal eyes were expected to fall is demarcated by the dashed lines, which provide a standard of reference for the data sets from the experimental animals.

Examination of Figures 1 and 2 reveals that acuity values of both eyes of the experimental animals tended to be poorer than normal during the initial postsurgery period. This is apparent from the fact that the initial acuity values for both eyes measured at the youngest ages tend to fall near the border of or outside the normal range, in the direction of poorer than normal. This initial poor performance probably reflects a general behavioral disruption in the immediate period after surgery. At intermediate ages until approximately 6 months of age, grating acuity in the fellow eyes of all animals appears to develop normally, with most values falling within the range of normal development. However, acuities in the pseudophakic eyes usually lag behind in their development during this period. This is demonstrated by within-animal comparisons of the pairs of acuity values from pseudophakic and fellow eyes obtained at similar ages (Figs. 1, 2).

In three monkeys from each group, grating acuity results were confirmed with operant methods at an older age, when it was expected that acuity should be approaching normal adult levels of about 0 logMAR (20/20 Snellen equivalent). In the three animals that underwent occlusion therapy (RAG3, RDK3, RGN3), the operant acuities obtained from each eye were near the expected normal adult values. The operant tests for each eye were repeated at two separate ages for monkeys RDK3 and RGN3. Operant results for animals that received no occlusion therapy reveal that acuities for the fellow eyes were within (RHK3, RVF3) or near (RBH3) the normal range, whereas acuities for pseudophakic eyes were substantially poorer than normal.

The differences between the two groups of animals are summarized in Figure 3. Figure 3A shows mean grating acuity values within each age bin for the animals that received 70% occlusion, and Figure 3B shows the same results for animals that did not undergo occlusion therapy. Error bars above or below the preferential looking results show the magnitude of standard errors of the mean taken across individual

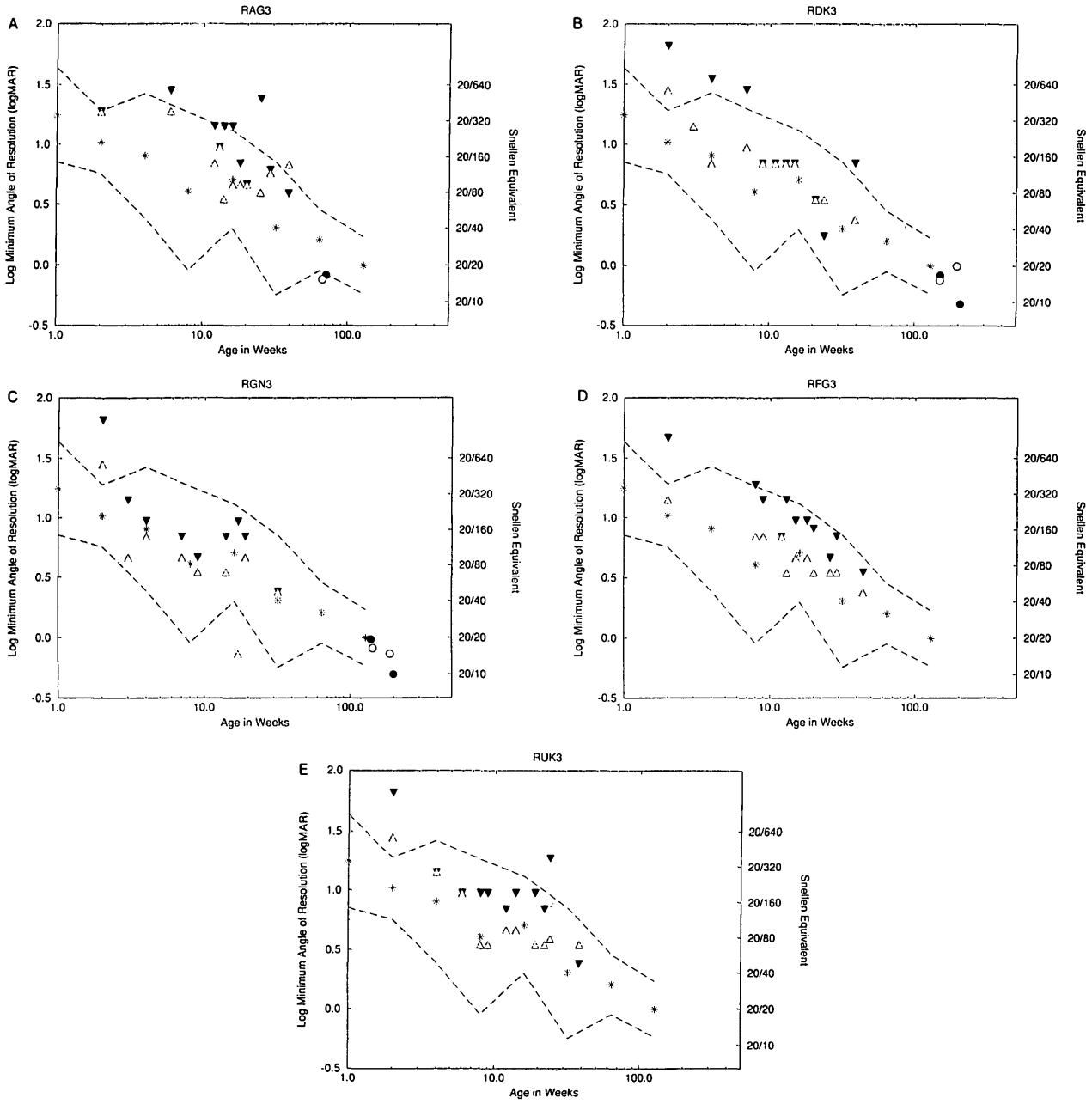

FIGURE 1. Grating acuity as a function of age for each eye of the five experimental monkeys that received an intraocular lens implant and subsequently underwent 70% occlusion therapy. Monkey RAG3 (**A**), RDK3 (**B**), RGN3 (**C**), RFG3 (**D**), and RUK3 (**E**). Triangles represent assessments with preferential looking; circles represent assessments with operant methods; open symbols represent fellow eyes; filled symbols represent pseudophakic eyes; asterisks and dashed lines show the mean acuities obtained from a group of normal infant monkeys obtained in our laboratory with the same methods and the range of acuity values within which 95% of normal eyes are expected to fall. The scale to the left designates acuity in logMAR units of the minimum grating stripe width that can be resolved. The scale at the right designates Snellen equivalent values. Normal adult monkeys are expected to have acuities the same as normal adult humans, in the vicinity of 0 logMAR (20/20 Snellen equivalent).

animals. Standard error bars are not shown for the operant results because these are based on only one or two animals for each data point. Acuity developed to normal by 1 year of age in both eyes of the group of animals that had occlusion therapy (Fig. 3A). However, in the group of animals that did not undergo occlusion therapy, grating acuity in the pseudophakic eyes lagged increasingly behind so that an amblyopia was clearly present at ages older than 6 months. To confirm that this difference between the two groups

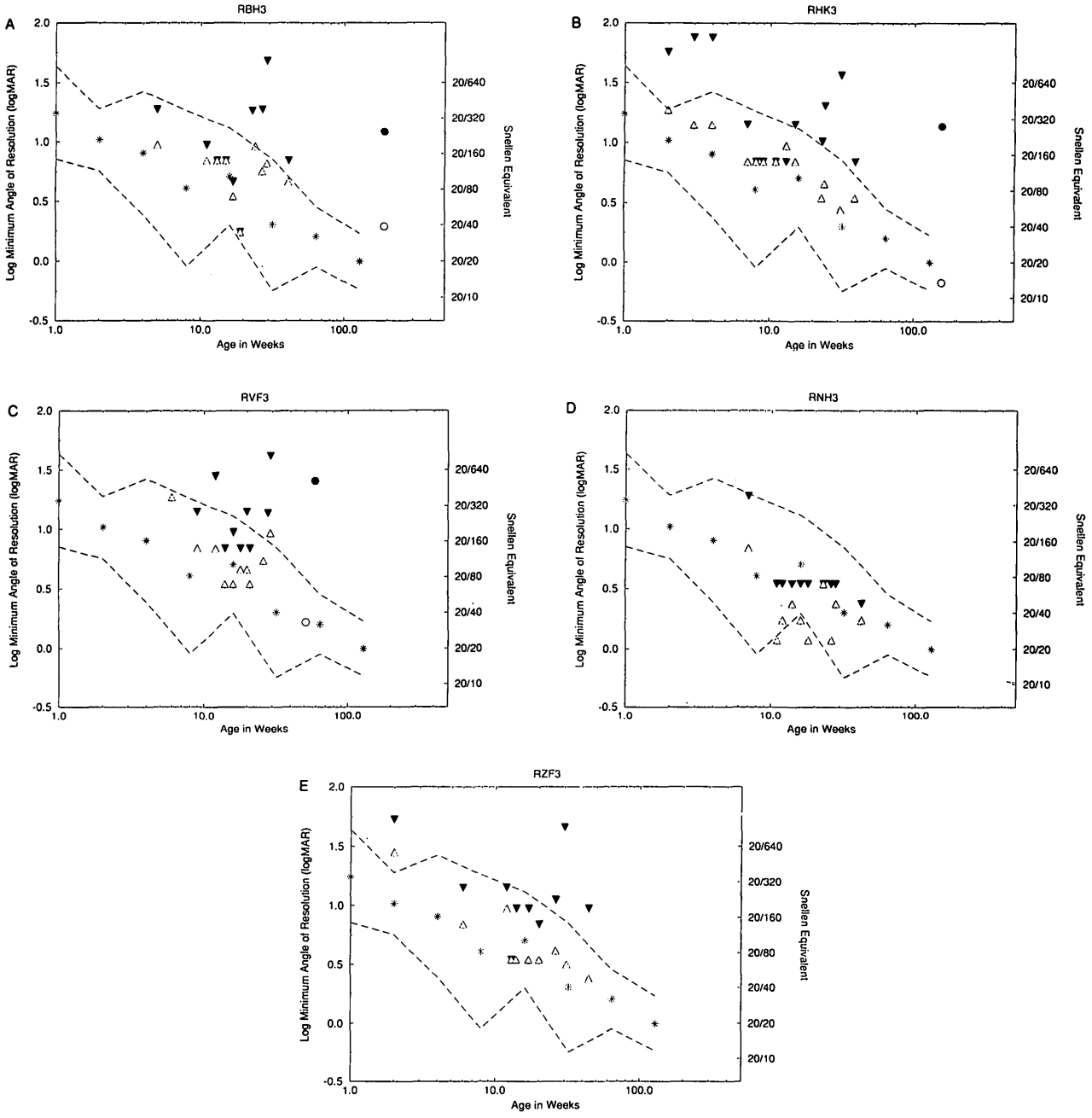

FIGURE 2. Grating acuity as a function of age for the five experimental monkeys that received an intraocular lens implant but no occlusion therapy. Monkey RBH3 (**A**), RHK3 (**B**), RVF3 (**C**), RNH3 (**D**), and RZF3 (**E**). Triangles represent assessments with preferential looking; circles represent assessments with operant methods; open symbols represent fellow eyes; filled symbols represent pseudophakic eyes; asterisks and dashed lines show the mean acuities obtained from a group of normal infant monkeys obtained in our laboratory with the same methods and the range of acuity values within which 95% of normal eyes are expected to fall. The scale to the left designates acuity in logMAR units of the minimum grating stripe width that can be resolved. The scale at the right designates Snellen equivalent values. Normal adult monkeys are expected to have acuities the same as normal adult humans, in the vicinity of 0 logMAR (20/20 Snellen equivalent).

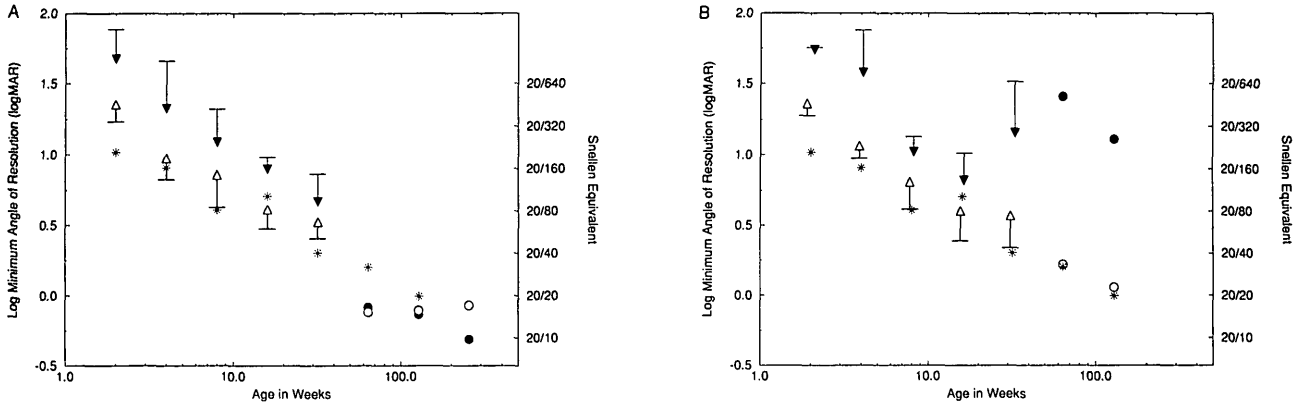

FIGURE 3. Results from the individual animals shown in Figures 1 and 2 were grouped into age bins and averaged across monkeys to facilitate a comparison across the two treatment groups. (**A**) Mean acuity values within each age bin for the group that underwent occlusion therapy. (**B**) Mean acuity values in the group that did not undergo occlusion therapy. Open symbols designate fellow eyes, and filled symbols pseudophakic eyes. Asterisk shows the mean acuities obtained from a group of normal infant monkeys obtained in our laboratory with the same methods. Triangles show results obtained with preferential looking methods, and the error bars demarcate 1 SEM calculated across monkeys. For clarity of viewing, only the positive error bars are shown for the pseudophakic eyes, and only the negative bars are shown for the fellow eyes. Circles show operant results that were grouped into age bins, but error bars are not shown because only one or two animals contributed to the operant values shown in each age bin.

was statistically significant, we calculated the amount of amblyopia present for each animal in the 32-week age bin by subtracting the logMAR value of the pseudophakic eye from its fellow eye. A Student's *t*-test on these acuity difference scores confirms a significant difference between the two groups at 32 weeks of age ($t = 3.4$; $df = 8$; $P < 0.01$).

Additional operant assessments of visual function were conducted on three of the monkeys that received occlusion therapy and had normal grating acuities in both eyes (RAG3, RDK3, and RGN3). We show the contrast sensitivity results from these animals, as well as those from a normal control animal tested under the same conditions in Figure 4. The contrast sensitivity functions for the fellow eyes (left eye in the case of the normal control animal) are plotted with the open squares. They all exhibit the characteristic form expected for normal adult humans and monkeys, with peak sensitivity values near 100 at middle spatial frequencies and a progressive decline in sensitivity at higher and lower frequencies. In a normal animal, it is expected that the high frequency cutoff value (the spatial frequency at which the high frequency portion of the contrast sensitivity function intersects with the baseline) should be similar to grating acuity, and our results appear generally consistent with this expected relationship. We demonstrate this by plotting on the same graph the grating acuity values for the fellow eyes (open circles) and connecting the symbol of the highest spatial frequency that was tested for contrast sensitivity with the acuity value (dashed line).

The contrast sensitivity results from the pseudophakic eyes (right eye in normal controls) are shown by the filled squares in Figure 4. The pseudophakic eyes exhibit reduced contrast sensitivity across the entire range of spatial frequencies tested. The slopes of the high frequency falloffs are shallow in these eyes, with the result that the extrapolated high-frequency cutoffs of some animals extend into the normal range. This accounts for the otherwise seemingly paradoxical finding of normal or near normal grating acuities in these same eyes, illustrated by the filled circles, even though contrast sensitivity is poor at low and middle frequencies. A potential explanation for this unusual shape of the contrast sensitivity function is presented in the Discussion.

The same animals that were tested for contrast sensitivity also completed assessments on an optotype (Landolt ring) acuity task, and these results are shown in Figure 5. Normal control monkey RLE2 exhibits an optotype acuity of approximately 20/30 Snellen equivalent in one eye and 20/40 in the other. These values are slightly poorer than the 20/20 usually reported for normal human adults (see Discussion). Landolt acuity values for the fellow eyes of two of the experimental monkeys, RAG3 and RGN3, are similar to those of the normal control, although the value for the third animal, RDK3, is poorer by approximately a factor of 2. We have no explanation for the poorer-than-expected results from the fellow eye of RDK3. The pseudophakic eyes of all three monkeys were poorer than normal (Fig. 5). Monkey RAG3 achieved the best performance with a Snellen equivalent acuity of approximately 20/60. The pseudophakic eyes of

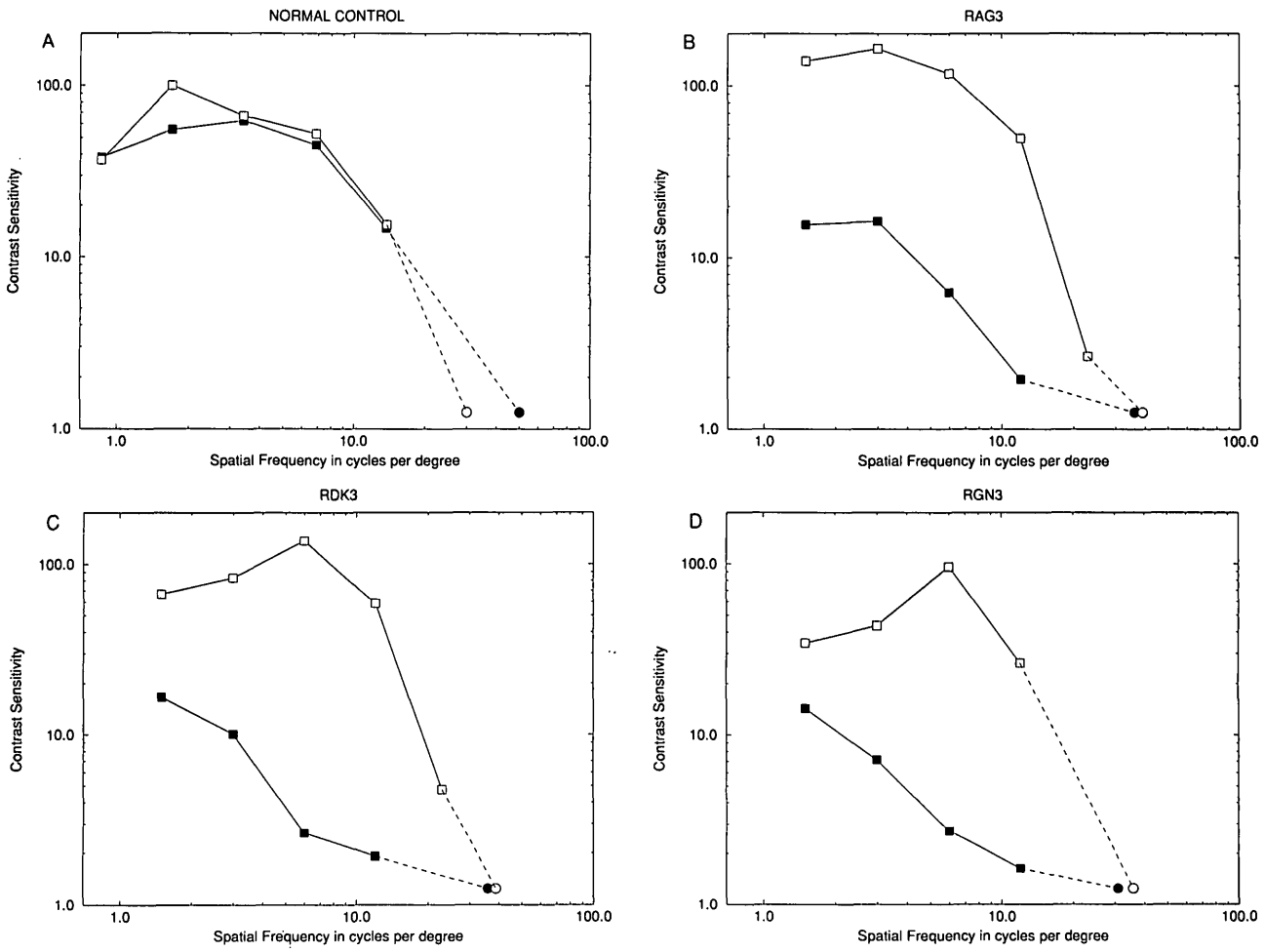

FIGURE 4. Contrast sensitivity results for a normal control monkey and three experimental monkeys that underwent occlusion therapy are shown by the squares. For comparison, grating acuity is plotted on the same graph with circles. Open symbols represent the left eye of the normal control monkey and the fellow eye of experimental monkeys. Filled symbols represent the right eye of the normal control monkey and the pseudophakic eyes of experimental monkeys. Contrast sensitivity data points are connected by solid lines to illustrate the overall shape of the contrast sensitivity function. Dashed lines connect contrast sensitivity and grating acuity results.

both RDK3 and RGN3 were more severely amblyopic, falling in the range near 20/160 Snellen equivalent.

DISCUSSION

We have established in previous studies of monkeys that unilateral infantile aphakia, if left untreated, results in severe deficits in grating acuity in the affected eye.[34] The results of our current study demonstrate that implantation of a monofocal IOL into the aphakic eye of a neonatal monkey, coupled with 70% daily occlusion therapy of the fellow eye, allows grating acuity to mature to levels that are normal or near normal. Thus, this study has established that there is a substantial benefit, in terms of improved visual function, derived from this form of treatment.

In an earlier report of some of these same animals tested at younger ages,[33] we suggested that occlusion therapy may not be as important for preventing amblyopia in pseudophakic eyes as it is for aphakic eyes given contact lenses. Based on our current results obtained over a wider age range and including additional animals, we now conclude that occlusion therapy is important in preventing amblyopia in pseudophakic and in aphakic eyes.

Even in animals that underwent occlusion therapy and developed normal grating acuity, optotype acuity was deficient, and detection of low-contrast stimuli was poor across all spatial frequencies. Thus, our results in monkeys indicate that it is probably not realistic to expect IOL implant treatment, without further refinement, to result in completely normal development of pattern perception in humans.

There are risks associated with IOL treatment that

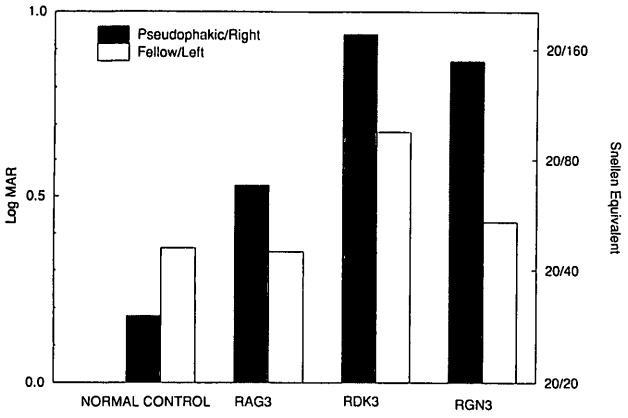

FIGURE 5. Optotype (Landolt C) acuity values are shown for the right and left eyes of normal control monkey RLE2 and the pseudophakic and fellow eyes of experimental monkeys RAG3, RDK3, and RGN3 that underwent occlusion therapy. The scale to the left designates acuity in logMAR units of the width of the gap in the Landolt C acuity that can be resolved. The scale at the right designates Snellen equivalent values.

must be taken into account when evaluating its potential use on human infants. For example, complications such as glaucoma and broken haptics have occurred in some of our monkeys receiving these treatments.[35] We are continuing to follow these animals for a longer-term assessment of the frequency and severity of complications that occur after implantation of an IOL into a growing eye.

Monkeys develop approximately four times faster than humans. The state of visual development of a monkey expressed in weeks is roughly comparable to that of a human infant whose age is expressed in months.[25,26,32] This weeks-to-months rule of thumb allows one to extrapolate the results obtained from monkeys at specific ages to humans. Using this extrapolation, our results are most directly relevant to human infants with a mild congenital cataract or an infantile cataract that develops within the first few days after birth, an IOL implant is performed at about 2 months, and daily occlusion of about 70% is then continued for the first 3 to 6 years (see Table 1).

The fact that there are usually no losses in contrast sensitivity reported after IOL implantation in human adults[45] leads us to conclude that the poor contrast sensitivity found in our monkeys was caused by amblyopia and not by some optical deficiency of the IOL itself. We are not aware of any previous studies of contrast sensitivity in human children treated with IOLs for infantile cataracts. Deficits in contrast sensitivity have been reported in aphakic children treated with contact lenses and varying amounts of patching therapy.[46] Normal contrast sensitivity has been reported in some human infants who underwent surgery within the first 6 weeks of birth, which was followed by contact lens correction and patching.[22] None of our pseudophakic monkeys in the parttime occlusion group had surgery at a comparable early age (within 1.5 weeks based on the weeks-to-months rule). Thus, it is possible that we would have obtained normal contrast sensitivity in our monkeys receiving 70% occlusion if we had performed the surgery on these animals at an earlier age.

It is difficult to make an a priori prediction about the amblyopic deficits that should be present after an infantile cataract. The visual deprivation that is experienced involves some combination of pattern deprivation at early ages because of the cataract, followed by more mild anisometropia at older ages.[25] Previous studies of contrast sensitivity in persons with mild anisometropic amblyopia usually have reported deficits primarily at high spatial frequencies, whereas amblyopia resulting from more severe pattern deprivation affects a wide range of spatial frequencies.[25] The contrast sensitivity deficits seen in the pseudophakic eyes do not fall into either of these two patterns. Sensitivity is poorer than normal at middle and low spatial frequencies, but the extrapolated high-frequency cutoffs extend to acuities near 20/20 Snellen. Furthermore, the slopes of the high-frequency falloff portions of the contrast sensitivity functions are unusually shallow. A similar unusual shape for the contrast sensitivity function has been reported when peripheral vision is tested in normal human observers under conditions of optimal focus.[47] The explanation for this finding in humans involves spatial aliasing because of undersampling of the retinal image.[47] We did not monitor fixation in our monkeys. Thus, one possible explanation for our findings is that our monkeys used peripheral vision for the contrast sensitivity task when viewing with their pseudophakic eyes. However, this does not seem plausible because our display consisted of an extended grating. A more likely explanation is that a primary component of the amblyopic deficit in our pseudophakic eyes involves undersampling, as has been proposed and modeled by previous investigators.[48,49]

The fellow eyes in our experimental monkeys appeared indistinguishable from normal eyes in terms of grating acuity and contrast sensitivity. However, they performed somewhat poorer than we expected on Landolt acuity. This issue is complicated by the fact that we tested only one normal control monkey on this task, and our control animal also performed slightly more poorly than expected. One possible reason for the poorer-than-expected performance of the normal control animal is that the luminance of the ring on our video display is only 40 cd/m^2, and maximum contrast is only 80%. Landolt acuities for humans are typically tested at approximately 80 cd/m^2 and with greater than 90% contrast.[43] However, three normal human observers viewed the same visual dis-

play as the monkeys, and each achieved Landolt acuities of 0 logMAR.

Another possible explanation for the poorer-than-expected Landolt acuities was that all our monkeys, experimental as well as normal control, had extensive experience on tasks involving grating acuity and contrast sensitivity before they were tested on Landolt acuity. Accurate fixation is not critical on these former tasks because the stimuli are extended gratings. The animals simply have to direct fixation to some portion of the display. However, in the Landolt acuity task, good performance depends on accurate fixation of the regions of the display where the gap can occur. Because of constraints involving the pixel size of our display, we had to test the animals at a viewing distance of 400 cm to measure acuities in the range of 0 logMAR. The outer diameter of our Landolt ring under these conditions was approximately 5.5 cm, which makes accurate fixation especially critical for good performance. Thus, the slightly poorer-than-expected performance of our normal control animal may have just reflected the fact that it received insufficient training on the Landolt task to overcome behavioral strategies that developed during extensive training and testing on grating tasks in which fixation was not as critical. Similarly, this factor may have contributed, at least partially, to the poor performance of the experimental animals.

However, even if we take the range of the results from the two eyes of our normal control animal as the expected level of performance on the Landolt ring task when trained and tested under the conditions used in our laboratory, there is still at least a suggestion of a small deficit for the fellow eye of monkey RGN3 and a moderate deficit for the fellow eye of RDK3. A previous study of human children treated for infantile cataracts also reported subtle deficits in the fellow eyes.[50(but see also 22)]

Our Landolt ring acuity results demonstrate that even in the experimental animals that underwent occlusion therapy and were able to detect the presence of high spatial frequency gratings with their pseudophakic eyes, there are impairments in the ability to discriminate optotypes. Based on results of previous studies in humans, this finding is not surprising. A common finding with children with aphakia is that visual function, as assessed at early ages with preferential looking studies of grating acuity, appears relatively good, but it appears relatively worse as assessed with optotypes at older ages.[7,10,23,27] Our assessments of grating acuity, with a combination of preferential looking and operant methods, demonstrate that the essential difference has more to do with the visual stimuli used (gratings or optotypes) than with the method of testing (preferential looking versus some other response measure). A similar conclusion, that optotype acuity is more sensitive than grating acuity for detecting amblyopia in children, has been reached based on previous studies of children with amblyopia.[23,51]

Studies of infants treated for congenital or infantile cataracts have reported exceedingly good visual outcomes for individual infants who underwent various treatments.[2-23] However, one must be cautious about whether the best outcome achieved in one subject can be used as a predictor of the expected outcomes of all subjects undergoing a given treatment.[24-26] Our laboratory has conducted studies on a large number of neonatal monkeys that received various treatments involving contact lenses or IOLs, and we have sometimes obtained good outcomes in individual monkeys following a variety of treatments. Note, for example, that our monkey RNH3 in the current study obtained near normal grating acuity in the pseudophakic eye, as assessed with preferential looking, even though the fellow eye of this animal was not patched. None of the other animals in this treatment group had such a good outcome, and we have no explanation for it. However, taken as a group, monkeys in our study that were treated with IOLs and 70% daily patching of the fellow eye and that had no serious postsurgical complications achieved the best outcomes we have seen to date in terms of grating acuities. For example, they have better grating acuity as a group than monkeys reared with similar amounts of occlusion and contact lens correction of the aphakic eye to a near point.[52] The caveat is that we have not observed the same high incidence of postsurgical complications with contact lens treatments as we have after IOL implantation.[35]

The good grating acuity results we have obtained for monkeys in the current study encourage us to continue further studies, in which we manipulate various treatment parameters (e.g., multifocal IOLs and other schedules of occlusion) to find a treatment protocol that leads to better contrast sensitivity and optotype acuity. Experiments are in progress to evaluate several other treatment groups. If the IOL treatment protocols can be fine-tuned for optimal outcome, it appears that IOL implantation might afford excellent visual outcomes in children treated for congenital and infantile cataracts. The biggest obstacles to applying this form of treatment to humans continue to be the incidence of postsurgical complications[35] and the unknown potential risks of wearing an IOL for a lifetime.

Key Words

contrast sensitivity, deprivation amblyopia, intraocular lens implant, monkey model, pseudophakia

Acknowledgments

The authors thank Mrs. Jean Torbit for her assistance in the preparation of the manuscript, as well as the veterinarians and staff of the Yerkes Regional Primate Research Center for their expert assistance with care of the animals used in

this project. They also thank three anonymous reviewers for their very helpful comments to revise this manuscript.

References

1. Frey T, Friendly D, Wyatt D. Re-evaluation of monocular cataracts in children. *Am J Ophthalmol.* 1973;76: 381–388.
2. Beller R, Hoyt CS, Marg E, Odom JV. Good visual function after neonatal surgery for congenital monocular cataracts. *Am J Ophthalmol.* 1981;91:559–565.
3. Pratt-Johnson J, Tillson G. Visual results in congenital cataract surgery performed under the age of 1 year. *Can J Ophthalmol.* 1981;16:19–21.
4. Rogers GL, Tischler CL, Tson BH, Hertle RW, Fellows RR. Visual acuities in infants with congenital cataracts operated on prior to 6 months of age. *Arch Ophthalmol.* 1981;99:999–1003.
5. Jacobson SG, Mohindra I, Held R. Development of visual acuity in infants with congenital cataracts. *Br J Ophthalmol.* 1981;65:727–735.
6. Burns EC, Jones RB. Long term management of congenital cataracts. *Arch Dis Child.* 1985;60:322–325.
7. Birch EE, Stager DR, Wright, WW. Grating acuity development after early surgery for congenital unilateral cataract. *Arch Ophthalmol.* 1986;104:1783–1787.
8. Catalano RA, Simon JW, Jenkins PL, Kandel GL. Preferential looking as a guide for amblyopia therapy in monocular infantile cataracts. *J Pediatr Ophthalmol Strabismus.* 1987;24:56–63.
9. Robb RM, Mayer DL, Moore DB. Results of early treatment of unilateral congenital cataracts. *J Pediatr Ophthalmol Strabismus.* 1987;24:178–181.
10. Birch EE, Stager DR. Prevalence of good visual acuity following surgery for congenital unilateral cataract. *Arch Ophthalmol.* 1988;106:40–43.
11. Levin AV, Edmonds SA, Nelson LB, Calhoun JH, Harley RD. Extended wear contact lenses for the treatment of pediatric aphakia. *Ophthalmology.* 1988;95: 1107–1113.
12. Maurer D, Lewis TL, Brent HP. The effects of deprivation on human visual development: Studies of children treated for cataracts. In: Morrison FJ, Lord C, Keating DP, eds. *Applied Developmental Psychology: Psychological Development in Infancy.* Vol. 3. San Diego: Academic Press; 1989:139–227.
13. Amaya LG, Speedwell L, Taylor D. Contact lenses for infant aphakia. *Br J Ophthalmol.* 1990;74:150–154.
14. Drummond GT, Scott WE, Keech RV. Management of monocular congenital cataracts. *Arch Ophthalmol.* 1989;107:45–51.
15. Cheng KP, Hiles DA, Biglan AW, Pettapiece MC. Visual results after early surgical treatment of unilateral congenital cataracts. *Ophthalmology.* 1991;98:903–910.
16. Lorenz B, Worle J. Visual results in congenital cataract with the use of contact lenses. *Graefe's Arch Clin Exp Ophthalmol.* 1991;229:123–132.
17. Wright KW, Christensen LE, Noguchi BA. Results of late surgery for presumed congenital cataracts. *Am J Ophthalmol.* 1992;114:409–415.
18. Neumann D, Weissman BA, Isenberg SJ, Rosenbaum AL, Bateman JB. The effectiveness of daily wear contact lenses for the correction of infantile aphakia. *Arch Ophthalmol.* 1993;111:927–930.
19. McCulloch DL, Skarf B. Pattern reversal visual evoked potentials following early treatment of unilateral, congenital cataract. *Arch Ophthalmol.* 1994;112:510–518.
20. Wright KW, Matsumoto E, Edelman PM. Binocular fusion and stereopsis associated with early surgery for monocular congenital cataracts. *Arch Ophthalmol.* 1992;110:1607–1609.
21. Gregg FM, Parks MM. Stereopsis after congenital monocular cataract extraction. *Am J Ophthalmol.* 1992;114:314–317.
22. Birch EE, Swanson WH, Stager DR, Woody M, Everett M. Outcome after very early treatment of dense congenital unilateral cataract. *Invest Ophthalmol Vis Sci.* 1993;34:3687–3699.
23. Maurer D, Lewis TL. Visual outcomes after infantile cataract. In: Simons K, ed. *Early Visual Development: Normal and Abnormal.* New York: Oxford University Press; 1993:454–484.
24. Lloyd IC, Goss-Sampson M, Jeffrey BG, Kriss A, Russell-Eggitt I, Taylor D. Neonatal cataract: Aetiology, pathogenesis and management. *Eye.* 1992;6:184–196.
25. Boothe R. Amblyopia. In: Albert DM, Jakobiec FA, eds. *Principles and Practice of Ophthalmology: Basic Sciences.* Vol. 6. Philadelphia: WB Saunders; 1993:663–682.
26. Lambert SR, Boothe RG. Amblyopia: Basic and clinical science perspectives. In: Mets MB, Greenwald MJ, Magoon EH, eds. *Focal Points.* Vol. 12. San Francisco: American Academy of Ophthalmology; 1994:1–12.
27. Lewis TL, Maurer D, Brent HP. Development of grating acuity in children treated for unilateral or bilateral congenital cataract. *Invest Ophthalmol Vis Sci.* 1995;36:2080–2095.
28. Enoch J, Hamer R. Image size correction of the unilateral aphakic infant. *Ophthalmic Paediatr Genet.* 1983;2: 153–165.
29. Burke JP, Willshaw HE, Young JDH. Intraocular lens implants for uniocular cataracts in childhood. *Br J Ophthalmol.* 1989;73:860–864.
30. Dahan E, Salmenson BD. Pseudophakia in children: Precautions, technique, and feasibility. *J Cataract Refract Surg.* 1990;16:75–82.
31. Markham RH, Bloom PA, Chandna A, Newcomb EH. Results of intraocular lens implantation in paediatric aphakia. *Eye.* 1992;6:493–498.
32. Boothe RG. Experimentally induced and naturally occurring monkey models of human amblyopia. In: Berkley MA, Stebbens WC, eds. *Comparative Perception.* Vol. 1. *Basic Mechanisms.* New York: John Wiley; 1990:461–486.
33. Lambert SR, Fernandes A, Drews-Botsch C, Boothe RG. Multifocal versus monofocal correction of neonatal monocular aphakia. *J Pediatr Ophthalmol Strabismus.* 1994;30:195–201.
34. O'Dell C, Gammon JA, Fernandes A, Wilson J, Boothe RG. Development of acuity in a primate model of human infantile unilateral aphakia. *Invest Ophthalmol Vis Sci.* 1989;30:2068–2074.
35. Lambert SR, Fernandes A, Grossniklaus H, Drews-Botsch C, Eggers H, Boothe RG. Neonatal lensec-

tomy and intraocular lens implantation: Effects on rhesus monkey. *Invest Ophthalmol Vis Sci.* 1995;36: 300–310.
36. Bradley DV, Fernandes A, Tigges M, Boothe RG. Diffuser contact lenses retard axial elongation in infant rhesus monkeys. *Vision Res.* 1996;36:509–514.
37. Gammon JA, Boothe RG, Chandler C, Tigges M, Wilson J. Extended-wear contact lenses for vision studies in monkeys. *Invest Ophthalmol Vis Sci.* 1985;26:1636–1639.
38. Fernandes A, Tigges M, Tigges J, Gammon J, Chandler C. Management of extended-wear contact lenses in infant rhesus monkeys. *Behav Res Methods Instr Comput.* 1988;20:11–17.
39. Teller DY. The forced-choice preferential looking procedure: A psychophysical technique for use with human infants. *Infant Behav Dev.* 1979;2:135–153.
40. Boothe RG, Kiorpes L, Williams R, Teller D. Operant measurements of contrast sensitivity in infant macaque monkeys during normal development. *Vision Res.* 1988;28:387–396.
41. Levitt H. Transformed up-down methods in psychoacoustics. *J Acoust Soc Am.* 1970;33:467–476.
42. Treutwein B. Adaptive psychophysical procedures. *Vision Res.* 1995;35:2503–2522.
43. Working Group 39. Recommended standard procedures for the clinical measurement and specification of visual acuity. *Adv Ophthalmol.* 1980;41:103–148.
44. Finney DJ. *Probit Analysis.* 3rd ed. New York: Cambridge University Press; 1971.
45. Rubin GS, Adamsons IA, Stark WJ. Comparison of acuity, contrast sensitivity, and disability glare before and after cataract surgery. *Arch Ophthalmol.* 1993; 111:56–61.
46. Tytla ME, Maurer D, Lewis TL, Brent HP. Contrast sensitivity in children treated for congenital cataract. *Clin Vision Sci.* 1988;2:251–264.
47. Thibos LN, Still DL, Bradley A. Characterization of spatial aliasing and contrast sensitivity in peripheral vision. *Vision Res.* 1996;36:249–258.
48. Levi DM, Klein SA, Yap YL. Positional uncertainty in peripheral and amblyopic vision. *Vision Res.* 1987; 27:581–597.
49. Wilson HH. Model of peripheral and amblyopic hyperacuity. *Vision Res.* 1991;31:967–982.
50. Lewis TL, Maurer D, Tytla ME, Bowering ER, Brent HP. Vision in the 'good' eye of children treated for unilateral congenital cataract. *Ophthalmology.* 1992;99:1013–1017.
51. Mayer DL, Fulton AB, Rodier D. Grating and recognition acuities of pediatric patients. *Ophthalmology.* 1984;91:947–953.
52. Boothe RG, Lambert S, Bradley D, Brown R, Morris M, Louden T. Visual function following treatment for unilateral infantile cataract: Operant assessments of acuity in a monkey model. ARVO Abstracts. *Invest Ophthalmol Vis Sci.* 1994;35:2201.