Visual Outcome after Contact Lens and Intraocular Lens Correction of Neonatal Monocular Aphakia in Monkeys

Ronald G. Boothe,^1,2,3 Tracy Louden,^1 Akhila Aiyer,^1 Alicia Izquierdo,^1 Carey Drews,^3,4 and Scott R. Lambert^1,5

PURPOSE. A monkey model was used to evaluate intraocular lenses (IOLs) and extended-wear contact lenses (EWCLs) for the optical treatment of infantile aphakia in humans. Specifically, the relative effectiveness of EWCLs used alone and IOLs used in combination with EWCLs in preventing amblyopia was assessed.

METHODS. A total of 33 rhesus monkeys was studied in this project, 24 assigned to experimental treatment groups and 9 to normal controls. Contact lenses made from a diffusing material or dyed opaque were placed on one eye at birth to simulate an infantile cataract. A unilateral lensectomy was then performed on the same eye within 2.5 weeks after birth. In 15 monkeys this was combined with implantation of an IOL. The eyes were left aphakic in the remaining 9 animals. EWCLs were used to adjust the optical correction of both aphakic and pseudophakic eyes to a near point (3–5 D). Opaque lenses were used to maintain daily part-time (~70%) occlusion of the fellow eye. The primary outcome measure was grating acuity assessed with behavioral methods. Some animals were also assessed for acuity with sweep visually evoked potentials (VEPs) and for optotype acuity (Landolt C) with behavioral methods.

RESULTS. Two of the animals with IOLs developed complications in the eye that precluded completion of the behavioral assessment protocol. Only behavioral outcomes obtained before or in the absence of surgical complications are presented. There was a developmental delay in the maturation of grating acuity in both eyes of both treatment groups. Normal adult levels of grating acuity were eventually achieved in the group treated with IOLs combined with EWCLs. Grating acuity was significantly poorer than normal in aphakic eyes treated only with EWCLs. Comparison of the two treatment groups revealed that pseudophakic eyes treated with multifocal IOLs had significantly better grating acuity than aphakic eyes. Assessments of optotype acuity and sweep VEP acuity revealed amblyopic deficits in both pseudophakic and aphakic eyes.

CONCLUSIONS. Given an absence of serious postoperative complications, neonatal correction of aphakia with IOLs combined with EWCLs can lead to normal grating acuity in a primate model. Correction with EWCLs alone was not sufficient to produce normal grating acuity. Multifocal IOL treatments combined with EWCLs provided a significantly better outcome than EWCL methods alone. However, neither IOL nor EWCL methods were able to prevent amblyopia as evaluated using behavioral testing with optotypes or with sweep VEPs. (Invest Ophthal Clinics 2000;41: 110–119)

Worldwide, tens of thousands of infants are born each year with congenital cataracts, and their treatment continues to be a serious clinical challenge.1 Exceptionally good outcomes have been reported in individual cases,2–5 but as a group, children treated for early-onset infantile cataracts have acuities of approximately 1.0 logMAR (20/200 Snellen).6–10 It would be of obvious clinical value to determine the critical factors that are responsible for good outcomes in individual infants. Some of this information can be gleaned from the human literature,6–12 but there are limitations to what can be learned from studies of humans. Published studies of individual cases are more likely to include successes than mediocre or poor outcomes, and, in addition, it is usually difficult to determine the characteristics of the population from which the reported cases are being drawn. Even in the best designed clinical studies there are problems such as associated ocular abnormalities in addition to the infantile cataract, incomplete medical histories during the neonatal period, difficulty assuring patient follow-up, inability to directly monitor amblyopia therapy, failure to assign subjects randomly to treatment groups, an absence of untreated controls, and an inability to obtain information about underlying neuropathology.

Some of these limitations can be overcome or minimized with the use of an appropriate animal model. Parallel studies...
conduct with infant human and macaque monkeys have established close similarities in postnatal visual development, except that the monkey develops about four times faster,13,14 and there is now abundant evidence that infant monkeys provide an excellent model for various aspects of normal and abnormal visual development in humans.15,16

Our laboratory has been working for a number of years with monkey models of treatment for infantile cataracts. We have published some of the details of visual outcomes of specific treatment groups at selected ages, including an extended-wear contact lens (EWCL) model17–19 and an intraocular lens (IOL) model.20 Our best outcomes have been associated with early surgery, optical correction to a near point, and part-time occlusion of the fellow eye.

In a recent publication dealing with outcomes in animals treated with IOLs,21 we described excellent outcomes for grating acuity and suggested that IOL treatments might have some advantages over EWCL treatments due to factors such as enforced compliance with optical correction and reduced anisokonia. However, we also noted that there is an increased frequency of surgical complications in pseudophakic compared with aphakic animals.22,23 The relative benefits and disadvantages of IOL treatments compared with EWCL treatments have important implications for how human infants with unilateral aphakia should be corrected. Intraocular lenses are becoming the standard for optical treatment for children with aphakia24 and are being used increasingly at young ages.25 However, the methods used to assess visual outcome in these children are nonstandard, and it is impossible to make a direct comparison of outcomes obtained from IOL and EWCL treatments based on the available human literature.26–28

In the present report we compare acuities of monkeys treated with IOLs combined with EWCLs versus EWCLs alone, using the same methods to evaluate both groups. We performed a retrospective search of our animal database to find animals with comparable treatments, except some received IOLs and others did not.

**Methods**

**Subjects**

The 33 animals evaluated in this study were all drawn from the monkey population at the Yerkes Regional Primate Research Center and assigned pseudorandomly to treatment groups. The animals were not assigned among the specific treatment groups being evaluated in this report on a strictly random basis because these animals were reared over a number of years as part of several semi-independent projects. However, in any given year we randomly assigned infants to the various rearing conditions under way that year. All neonatal monkeys were given an ophthalmologic examination before assignment to one of these treatment groups, and infants with detectable ocular pathology were excluded.

We selected from our animal database experimental animals that met the following criteria. (1) A cataract was simulated in one eye with a contact lens starting on the day of birth. (2) A lensectomy was performed on the same eye within 2.5 weeks after birth. (3) Initial optical correction, achieved on the day of surgery by implantation of an IOL, or a few days after surgery with an EWCL in the case of aphakic eyes, was accomplished within 3 weeks after birth. (4) Compliance records confirmed that daily part-time occlusion was maintained within the range 55% to 80%. (5) Both optical correction and part-time occlusion were maintained for a duration of at least 25 weeks.

Nine aphakic and 15 pseudophakic animals met all these criteria. The behavioral tests were not all performed on some animals due to logistic scheduling constraints and the fact that some animals were also participating in other studies in addition to the behavioral assessments reported here. Some animals developed complications secondary to the surgery and detailed descriptions of these complications have been published previously.22,23 Because 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, we exclude behavioral data obtained from two animals where development of glaucoma and haptic breakage precluded completion of their testing. All other complications were treated and the animals allowed to continue in the protocol. In our results (see Table 2 below) we designate as “NT” those cases where a particular behavioral observation is not available due to simple failure to test the animal, and as “PC” the cases where postoperative complications forced us to abandon the behavioral assessment protocol.

Nine normally reared age-matched monkeys were tested with the same procedures. Four 6-month-old animals were tested for grating acuity with preferential looking methods. Five young adults were tested with operant methods for grating acuity, and 4 of these were tested additionally for optotype acuity. Two of the normal controls were also tested for grating acuity with sweep visually evoked potentials (VEPs).

All procedures were done in strict compliance with NIH guidelines and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the protocols were reviewed and approved by the Institutional Animal Care and Use Committee at Emory University.

**Procedures**

Contact lenses that are custom designed for these studies of infant monkeys are manufactured in our own contact lens laboratory.17,19 A contact lens that was made out of a diffusing material or dyed opaque was placed onto one eye of all our experimental animals within a few hours after birth to simulate an infantile cataract. This lens remained on the eye only up until the day of surgery at which time it was removed and a lensectomy performed on the same eye. In animals assigned to the IOL treatment groups, a posterior capsulotomy and anterior vitrectomy were performed at the same time. The IOLs were either one-piece polymethylmethacrylate (PMMA) lenses that provided either a multifocal correction or three-piece soft acrylic lenses that provided a multifocal correction. Additional details about the IOLs are provided elsewhere.30 All surgeries were performed under sterile conditions while the animal was deeply anesthetized. Examinations that included biomicroscopy, retinoscopy, keratometry, A-scan ultrasonography, tonometry, and ophthalmoscopy were performed before surgery and at regular intervals after surgery.

Both the aphakic and pseudophakic eye were fitted with extended-wear contact lenses. We used EWCLs to achieve a near-point correction (3.00–5.00 D of overcorrection) within a few days postoperatively. The rationale for this optical correction was that it allowed clear vision for items at a near range within the monkey’s cage. Power of the correction was ad-
justed at regular intervals (typically every 1–2 weeks) to compensate for changes in refractive error with age.

Occlusion was accomplished with opaque contact lenses. Contact lens wear was monitored every 2 hours during daylight hours and the information entered into a computerized database from which we computed actual compliance. We include in this study only animals in which the actual compliance with occlusion ended up being in the range from 55% to 80%.

Our experimental animals have been grouped into two treatment groups for purposes of the comparisons made in this study. Group 1, IOL–PO, included animals with one pseudophakic eye (IOL) corrected to a near point with an EWCL, and part-time occlusion (PO) of the fellow eye. Some of the animals in this group had multifocal and others monofocal IOLs. We used Student’s t-test to compare the following treatment conditions for these two groups of animals: (1) age at initial optical correction with IOL; (2) duration of ages when EWCL optical correction was worn; (3) duration of ages when occluder lenses were worn; (4) average daily percentage of daylight hours when contact lens optical correction remained in place on the surgical eye; and (5) average daily percentage of daylight hours when occluder was in place on fellow eye. The significance level for this initial set of comparisons was set at $\alpha < 0.05$. Results of this analysis are summarized in Table 1 and reveal that none of these treatment conditions reached statistical significance. The aphakic animals wore their lenses on average for 99% of the daylight hours, whereas the IOL animals only wore their lenses for 75.1% of the daylight hours when occluder was in place on fellow eye. The percentage of the day that the EWCL remained in place did reach statistical significance. The other four comparisons of treatment conditions were the same as used for the within-group comparisons.

Results of the comparisons between the two groups are summarized in Table 3. Duration of EWCL optical correction approached but did not reach our predetermined ($\alpha < 0.05$) level of statistical significance. Furthermore, we do not consider these differences to be biologically significant because both groups had the correction in place for approximately 1 year, which is near the end of the sensitive period in monkeys. Percentage of the day when the EWCL remained in place did reach statistical significance. The aphakic animals wore their lenses on average for 90% of the daylight hours, whereas the IOL animals only wore their lenses for 80%.

### Table 1. Comparison of Treatment Conditions for IOL Animals with Mono- and Multifocal Lenses

<table>
<thead>
<tr>
<th></th>
<th>Monofocal</th>
<th></th>
<th>Multifocal</th>
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<td>$n$</td>
<td>Mean</td>
<td>SD</td>
<td>$n$</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age optical correction with IOL started</td>
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<tr>
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<tr>
<td>% time optical correction in place</td>
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<td>97</td>
<td>5.9</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>% time occluder in place</td>
<td>5</td>
<td>68</td>
<td>2.5</td>
<td>10</td>
<td>69</td>
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### Table 2. Comparison of Treatment Conditions for Aphakic Animals where Cataract Was Simulated with an Occluder or a Diffuser

<table>
<thead>
<tr>
<th></th>
<th>Occluder</th>
<th></th>
<th>Diffuser</th>
<th></th>
<th>$P$ (t-test)</th>
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<td>Mean</td>
<td>SD</td>
<td>$n$</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Age optical correction with EWCL started</td>
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<tr>
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<td>20</td>
<td>5</td>
<td>39.2</td>
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<tr>
<td>Duration of occlusion</td>
<td>4</td>
<td>78.8</td>
<td>59</td>
<td>5</td>
<td>37.2</td>
</tr>
<tr>
<td>% time optical correction in place</td>
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<td>99.7</td>
<td>0.23</td>
<td>5</td>
<td>98.7</td>
</tr>
<tr>
<td>% time occluder in place</td>
<td>4</td>
<td>67.8</td>
<td>11</td>
<td>5</td>
<td>75.1</td>
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</table>
lenses 95%. However, we do not consider it likely that this small percentage difference put the IOL eyes at any biological disadvantage because the EWCL provides all the optical correction for the aphakic eyes, whereas it is only used to fine-tune the correction for the IOL eyes. At any rate, this concern became moot when our results (see below) revealed that all our significant differences were in the opposite direction of this potential bias. We conclude that the two groups of animals were sufficiently similar to allow a meaningful comparison between IOL and aphakic forms of treatment.

Two behavioral methods were used to assess grating acuity. We used preferential looking methods in conjunction with Teller Acuity Cards (Vistech Consultants, Dayton, OH) to test grating acuity during the first 6 to 9 months after birth. Our preferential looking methods have been described in more detail previously. In some animals the acuity in each eye was tracked with preferential looking methods every few weeks during development. We report here only the results of the final preferential looking assessment that was performed on each animal at 6 to 9 months of age.

At 1 to 3 years of age we trained and then tested many of our animals with operant behavioral methods that have been described in detail elsewhere. Briefly, each monkey was trained with a food reward to view a display on a video monitor and indicate, by pulling on levers, whether a designated visual stimulus was displayed on the left or right side of the screen. Correct responses resulted in delivery of a food or juice reward, 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). A standard Landolt C Ring stimulus was displayed for assessment of optotype acuity. Testing was typically done at a viewing distance of 400 cm, but the viewing distance was reduced to as close as 30 cm for animals with poor acuity.

In some animals we used VEPs to obtain an estimate of visual resolution as reflected in electrophysiological activity in the cortex. We used the sweep VEP method described by Norcia et al. Stimuli were vertical sinusoidal gratings with 80% contrast and undergoing contrast reversal at a rate of 7.5 Hz presented on a high-resolution video monitor. Spatial frequency of the gratings changed linearly every 0.05 seconds over a 10-second trial period. VEPs were obtained using subdermal disposable needle electrodes (Rochester Electro-Medical, Tampa, FL) placed over the occipital lobes approximately 1.0 cm above the inion and halfway between the midline and the ear. A reference electrode was placed over the vertex and a ground electrode over the right frontal lobe. Signals were amplified by 50,000, and then band-pass-filtered (1.0–100 Hz). Electroencephalographic waveforms were analyzed using Fourier transformations to obtain amplitude and phase at the stimulus frequency, and nearby frequencies were used to estimate noise levels. Six to 10 trials were averaged for each animal to arrive at an estimate of acuity.

The animals were tested with VEPs under one of two conditions: awake and trained to fixate the stimulus or under anesthesia. Previous studies in our laboratory have demonstrated that there are no essential differences in the acuity values estimated under these two conditions. While recording VEPs in the awake animal, the monkey to be tested was placed in a primate restraining chair and trained with a food reward to fixate on the center of the video monitor screen for a period of 10 seconds. Recordings while anesthetized were made using propofol (5–40 mg/kg per hour, adjusted for each individual animal under guidance of the veterinary staff at Yerkes). Animals were intubated if respiratory problems were detected. Ophthalmoscopy was used to adjust head and eye position such that the stimulus was positioned near the fovea.

Monocular testing was achieved under all test conditions by having the monkey wear an opaque contact lens in the eye that was not being tested. When testing aphakic and pseudophakic eyes, the monkey also wore an optical correction appropriate for the distance of the screen in its test eye. A cycloplegic (3 drops of 1% cyclopentolate and 2.5% phenylephrine hydrochloride separated by 5 minutes, initiated 30 minutes before test) was administered to phakic eyes when testing was done under anesthetized conditions, and the test eyes were provided with optical correction and a 3-mm diameter artificial pupil.

Statistical comparisons of outcome measures were done initially with an ANOVA to establish that a significant treatment effect was present. The significance level for this initial comparison was at \( \alpha < 0.05 \). Then, planned comparisons were carried out with a Student’s t-test. The significance level of these post hoc tests was set at \( \alpha < 0.01 \) to minimize the effects of multiple comparisons. One-sided tests were used when comparing experimental animals to normal controls, because the question of interest was whether the experimental acuities were poorer than normal. Two-sided tests were used when comparing two experimental groups, because there was no a priori expectation about the direction of any differences that might be found.

### RESULTS

#### Grating Acuity Results at Young Ages

LogMAR acuity values for the individual animals that we tested with preferential looking methods at 6 to 9 months of age are...
presented for the IOL–PO group in Table 4 and for the APHAKIA–PO group in Table 5. We performed a preanalysis before combining the animals into two treatment groups. There were no significant differences between the eyes that received multifocal or monofocal lenses within the IOL–PO group, t(13) = 0.31, P = 0.16, and these animals were combined into a single APHAKIA–PO group. However, there was a significant difference between the eyes in which a cataract was simulated with an opaque or a diffuser lens, t(6) = 0.79, P = 0.46, and these animals were combined into a single APHAKIA–PO group.

Mean values and standard errors of the mean for each eye of each of our treatment groups are illustrated in Figure 1 along with values for an age-matched normal control group. An ANOVA established that there was a significant treatment effect for the OD eyes, F(2,24) = 9.99, P = 0.0007, and for the OS eyes F(2,24) = 4.69, P = 0.019. Post hoc tests revealed that grating acuities of these two treatment groups did not differ for either the surgical eyes (IOL versus APHAKIC), t(21) = 1.41, P = 0.18, or the part-time occluded fellow eyes (PO), t(21) = 0.84, P = 0.43. However, all four groups of eyes were significantly poorer than age-matched controls: IOL eyes, t(17) = 3.54, P = 0.005; APHAKIC eyes, t(10) = 6.0, P < 0.001; IOL group PO eyes, t(17) = 2.79, P = 0.01; APHAKIC group PO eyes, t(10) = 3.57, P = 0.005. From these results we concluded that development of grating acuity lagged significantly behind normal at 6 to 9 months of age in both eyes of both experimental groups.

### Grating Acuity at Older Ages

Operant testing conducted after 1 year of age allowed us to address the question of whether the poor acuity relative to age norms at 6 to 9 months was a reflection of a permanent deficit or simply a retarded development. Tables 4 and 5 list the grating acuity results obtained from all the animals tested with operant methods. Before forming two groups, we performed a preanalysis on the results from this outcome measure. There were no differences within the aphakic animals between those in which a cataract was simulated with an opaque or a diffuser lens, t(3) = 0.63, P = 0.57, and these animals were combined into a single APHAKIA–PO group. However, there was a significant difference between the eyes that received multifocal or monofocal lenses within the IOL–PO group, t(8) = 3.05, P = 0.02. Consequently, we analyzed results for multifocal and monofocal animals separately.

The mean values and standard errors of the mean for the separated multifocal and monofocal groupings and the normal control group are shown in the histogram in Figure 2. We also show, for illustration purposes only, the combined IOL group. However, the combined group did not contribute to the statistical analyses.

An ANOVA demonstrated that there was a significant overall treatment effect for the OS eyes, F(3,16) = 4.88, P = 0.015. However, post hoc comparisons to normal controls failed to reveal any significant differences of PO eyes in the APHAKIC group from normals at our predetermined α < 0.01, t(8) =

### Table 4. LogMAR Acuity Values for Group 1 (IOL–PO)

<table>
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<tr>
<th>Monkey ID</th>
<th>IOL Type</th>
<th>PL OD</th>
<th>PL OS</th>
<th>Operant OD</th>
<th>Operant OS</th>
<th>Landolt OD</th>
<th>Landolt OS</th>
<th>VEP OD</th>
<th>VEP OS</th>
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<tr>
<td>RAG3</td>
<td>Mono</td>
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<td>0.95</td>
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<td>0.0</td>
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<td>NT</td>
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NT, not tested; PC, protocol terminated due to postsurgical complications; PL, preferential looking.

### Table 5. LogMAR Acuity Values for Group 2 (Aphakia–PO)

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<th>Monkey ID</th>
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<th>PL OD</th>
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<th>Operant OD</th>
<th>Operant OS</th>
<th>Landolt OD</th>
<th>Landolt OS</th>
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NT, not tested; PL, preferential looking.
logMAR and never improves to values better than −0.25 logMAR. Note that acuity of the fellow eyes of our three experimental animals does not improve between test 1 and test 2, a finding consistent with the results obtained in our laboratory from normal animals (results not shown), whereas performance of all three of the pseudophakic eyes improves. Monkey RDK3 achieved acuity better than the normal limit on the second test, and monkey RGN3 approached the normal limit.

To avoid problems that arise after extensive practice, the operant grating acuity values that we report in Tables 4 and 5 and Figure 2 are those obtained during the first test of each animal after training.

The only monkey who showed a grating acuity value on the first test that was good enough to make us suspect that it might be spurious was RPT3 (Table 4). However, our conclusion that the pseudophakic eyes in group MULTI–PO animals are not significantly different from normal also holds if we exclude monkey RPT3 from the analysis, $t(9) = 0.76, P = 0.23$.

**Operant Tests of Landolt C Acuity**

Some animals were tested for optotype acuity using Landolt C targets. Results for the individual animals that were tested are shown in Tables 4 and 5. A preanalysis demonstrated that the results for the monofocal and multifocal groups were not significantly different, $t(7) = 0.49, P = 0.64$, so the animals were combined into a single IOL–PO treatment group, and their results are summarized in Figure 4. Planned comparisons revealed that the PO eyes in the IOL–PO animals were not significantly poorer than normal, $t(11) = 2.09, P = 0.05$, but the acuities of their IOL eyes were poorer, $t(11) = 5.86, P < 0.001$. Only one animal was tested from the APHAKIA–PO group, but qualitative examination of its results suggests that if this animal is representative, then the surgical eyes of this group would probably also be able to be demonstrated significantly poorer than normal if additional animals were tested.

**Sweep VEP Tests of Acuity**

Grating acuity was also assessed in some of the IOL animals in the multifocal group using sweep VEPs. Individual animal re-
results are presented in Table 4. Even though only the MULTI treatment group was tested with these methods, we include them here to demonstrate that they are similar to those obtained from the operant tests of Landolt acuity. Results for the MULTI animals are summarized in Figure 5 along with those of normal controls. The multifocal eyes were significantly poorer than normal, \( t(8) = 4.88, P < 0.001 \), but the fellow eyes were not, \( t(10) = 1.11, P = 0.15 \).

We were somewhat surprised by the fact that the pattern of results obtained with VEPs appeared more similar to that obtained for operant measurements of optotype than for grating acuity. Correlation values between our three measures for those eyes on which we obtained two or more types of assessment in the same animal are consistent with this impression. Examining the 9 eyes that were tested using both operant Landolt acuity and VEPs the correlation was 0.38, but for the 12 eyes tested using both VEPs and operant grating acuity the correlation was only 0.08. The correlation for 20 eyes tested with operant grating acuity and Landolt acuity was 0.17. We are unable to demonstrate whether or not these differences are statistically significant due to the fact that different combinations of animals and eyes contributed to these data sets.

**DISCUSSION**

A congenital cataract was simulated in one eye of our experimental animals on the day of birth using a contact lens. All animals received surgery within 2.5 weeks, and whether pseudophakic or aphakic, an optical correction with an EWCL within 3 weeks. EWCLs were used to maintain the optical correction to a near point and to maintain daily part-time (70%) occlusion of the fellow eye for duration of approximately 1 year. Monkeys develop about four times faster than humans do, so 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.\(^{13,14}\) Using this extrapolation, our results are most directly relevant to human infants with a congenital cataract or an infantile cataract that develops within the first few postnatal days, surgery and optical correction is accomplished within the first 3 months, and optical correction to a near point and 70% part-time occlusion maintained until approximately 4 years of age.

Our major new finding in this study is a direct comparison of animals treated with IOLs combined with EWCLs and animals treated with EWCLs alone. Grating acuities for these two treatment groups, as assessed at early ages with preferential

**FIGURE 3.** Grating acuity values for each eye of three monkeys that were tested on two occasions. Test 1 is the result of the first acuity test obtained after the monkey had been trained on the task. Test 2 is the result for a second test obtained after more extensive experience on the task. Results are shown for both the surgical eye that received an IOL and for the fellow eye of each animal. We consider data points that fall below a logMAR value of -0.25 to be spurious due to aliasing (see text).

**FIGURE 4.** Mean optotype acuity values obtained from each eye of normal control animals and from each treatment group using a Landolt C stimulus. The nt symbol above the results from the APHAKIA-PO group designates that no statistical tests were performed on the results for this group due to the fact that only one animal was tested. See Figure 1 legend for further details.

**FIGURE 5.** Mean acuity values obtained from each eye of normal control animals and from both eyes of one treatment group using sweep VEP methods. See Figure 1 legend for further details.
looking, did not differ significantly from one another, but both groups showed a developmental delay compared with normal controls. When assessed for grating acuity with operant methods at older ages, the IOL eyes implanted with multifocal lenses were significantly better than eyes treated with EWCLs alone, but eyes implanted with monofocal lenses were not. However, fewer animals were implanted with monofocal than multifocal lenses (3 versus 7), so the lack of statistical significance for the monofocal animals may reflect a lack of power rather than a true difference in treatment effects. Further evidence in support of this interpretation is that neither IOL treatment group differed from normals, but the EWCL-only treatment group was poorer than normal.

These findings suggest that better visual acuities may be achievable with a combined correction with IOLs and contact lenses versus contact lenses alone in infants with unilateral aphakia. However, the beneficial effect on visual outcome in the pseudophakic eyes must be weighed against the increased frequency of postoperative complications with these eyes.22–25 Clinical studies will be necessary to determine whether similar effects occur in human infants.

Previous studies of human infants with a neonatal cataract have suggested that surgery needs to take place within the first 6 weeks after birth to obtain an optimum outcome.12 None of the animals in this study received “effective” treatment at a comparable early age (within 1.5 weeks based on the “weeks-to-months” rule). In our APHAKIA–PO model the effective date of treatment is not the date on which surgery is performed but the date when optical correction of the aphakia is instituted. Even the monkeys in this group that received a lensectomy within the first week of birth did not receive optical correction until about 1 week after surgery. An examination of the limited range of ages that we have tested within the APHAKIA–PO group revealed no significant correlation of operant grating acuity with age at optical correction.

In the IOL model a partial optical correction is available to the pseudophakic eye starting on the day of surgery, and the EWCL wear that is initiated after surgery is used only to correct the residual refractive error. However, we have not performed surgery on any of our pseudophakic animals within 1.5 weeks after birth. Within the limited range of ages that we have studied, age at surgery does not correlate with acuity in pseudophakic eyes.

There may be a fundamental limitation in the ability of the monkey model to adequately address these issues. Because visual development proceeds about four times faster in the monkey than in the human, the basic maturational changes that take place over the first month in the human are compressed to 1 week in the monkey. However, other biological factors, such as the time required for inflammation to subside after a surgical procedure, proceed at about the same rate in monkeys and humans. As a result, the functional effect of a surgical procedure where recovery lasts for a few days will be much greater when performed within the first week of a monkey than when performed within the first month of a human. This fact may account for our failure to obtain the excellent results reported for human infants after very early lensectomies.5,12 Thus, the monkey model, although excellent for addressing many issues regarding abnormal development, is limited in its ability to deal with issues of exact timing during the first several days after birth. The primary question that was able to be adequately addressed by the present study is how good of an outcome can be produced when these procedures (surgery combined with optical correction) are completed at the earliest ages that are practical in the monkey and, by extrapolation, when completed by comparable ages in the human.

The part-time occlusion was maintained at approximately 70% of the daylight hours and did not differ between the IOL and aphakic groups. The optical correction with EWCLs was excellent in both groups but did show a statistically significant difference. It was 95% in the IOL group but 99% in the aphakic group. Even though statistically significant, we do not consider this difference to be functionally significant. Furthermore, to the extent that this treatment difference did bias our results, it would have been in the direction of a better outcome for aphakic than IOL eyes, which is opposite in direction to our findings.

In addition to the deficits we found in the pseudophakic and aphakic eyes, our preferential looking assessments demonstrated that the fellow eyes in most of our experimental monkeys had delayed normal development. Previous studies of human amblyopes have also sometimes reported subtle deficits in the fellow eyes.34,35 We did not find any statistically significant deficits in the fellow eyes of any of our adult groups, but small deficits would escape detection without larger sample sizes.

The Landolt acuities in our normal animals were slightly poorer than expected. This could be in part due to perceptual learning. All our monkeys, experimental as well as our normal controls, had extensive prior experience on tasks involving grating acuity before being 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, optimum performance depends on accurate fixation of the regions of the display where the gap can occur. Thus, our animals may have received insufficient training on the Landolt task to overcome behavioral strategies that developed during extensive training and testing on gratings tasks in which fixation was not as critical. Our main comparisons of interest for this report involve relative optotype acuities in normal and treated eyes rather than the absolute levels of acuity.

All our aphakic and pseudophakic eyes had more severe impairment on the Landolt acuity task than on grating acuity. This finding is not surprising based on results of previous studies in amblyopic humans.9,36 What was somewhat surprising was that in the animals tested with sweep VEP acuities, the results correlated more closely with operant assessments of Landolt than grating acuities. The explanation for this finding may have to do with the behavioral task that the animals were asked to perform. To receive a food reward on the grating acuity task, the monkey must simply determine that something about the side of the screen where the grating is presented looks different from the opposite side of the screen. The Landolt acuity task, on the other hand, requires that the monkey be able to differentiate the fine detail of the shape of the target well enough to be able to figure out which side contains the gap. This requires some retention of spatial phase information in addition to simple detection of the presence or absence of fine spatial frequencies. The sweep VEP signal reflects a combination of spatial and temporal phases and amplitudes of the stimulus. In order for a signal at the scalp to have significant
amplitude it needs to have temporal phase coherence with the contrast reversal of the spatial grating. It is possible, although admittedly speculative, that an observer with a degraded signal present in the brain might be able to perform on our grating acuity task, even though that same signal is not strong enough or not of good enough fidelity to maintain either the spatial phase information that is needed to solve the Landolt acuity task or the spatial tuning and temporal phase coherence that are needed to generate a measurable amplitude in the sweep VEP.

Extremely fine resolution of grating stimuli that we interpret as spurious due to aliasing has been observed frequently in our pseudophakic monkeys after extensive training and testing but never in our aphakic monkeys. A possible explanation for this has to do with an argument analogous to one that has been proposed to explain the lack of aliasing in the normal human fovea. It has been argued that the optical modulation transfer function of the natural lens is of poor enough optical quality that its high frequency cutoff is matched to the Nyquist limit imposed by the spacing of foveal cones, and thus spatial frequencies that would otherwise lead to aliasing are optically filtered from the retinal image. By a similar argument, it is possible to speculate that differences in optical quality might allow aliasing to occur in pseudophakic eyes with IOls of high optical quality, but not in aphakic eyes wearing high-power EWCLs of poorer optical quality.

In conclusion, this study has demonstrated that early surgical implantation of an IOL, combined with fine-tuning of the optical correction with EWCLs and part-time occlusion of the fellow eye in infant monkeys, can lead to excellent grating acuity. These excellent acuities were not matched in aphakic eyes receiving only EWCL optical correction. Direct comparisons among treatment groups revealed that IOL eyes treated with multifocal lenses had significantly better outcomes on grating acuity than aphakic eyes. However, amblyopic deficits were present in all treatment groups when optotype acuity was measured behaviorally or when spatial resolution was assessed with VEPs. It is possible that better outcomes might have been obtained for all treatment groups if surgeries and optical corrections had been accomplished at even earlier ages, but these issues may not be feasible to test in the monkey model due to the accelerated visual development of monkeys compared with humans.

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