Emmetropization and Eye Growth in Young Aphakic Chickens

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PURPOSE. To establish a chick model to investigate the trends of eye growth and emmetropization after early lensectomy for congenital cataract.

METHODS. Four monocular treatments were applied: lens extraction (LX); sham surgery/−30 D lens; LX/+20 D lens; and LX/+30-D lens (nine per group). Lens powers were selected to slightly undercorrect or overcorrect the induced hyperopia in LX eyes and to induce comparable hyperopia in sham-surgery eyes. Refractive errors and axial ocular dimensions were measured over a 28-day period. External ocular dimensions were obtained when the eyes were enucleated on the last day.

RESULTS. The growth patterns of experimental (Exp) eyes varied with the type of manipulation. All eyes experiencing hyperopia initially grew more than their fellow eyes and exhibited myopic shifts in refraction. The sham/−30 D lens group showed the greatest increase in optical axial length, followed by the LX group, and then the LX/+20 D lens group. The Exp eyes of the LX/+30 D lens group, which were initially slightly myopic, grew least, and showed a small hyperopic shift. Lensectomized eyes enlarged more equatorially than axially (i.e., oblate), irrespective of the optical treatment applied.

CONCLUSIONS. The refractive changes observed in young, aphakic eyes are consistent with compensation for the defocus experienced, and thus emmetropization. However, differences in the effects of lensectomy compared to those of sham surgery raise the possibility that the lens is a source of essential growth factors. Alterative optical and mechanical explanations are offered for the oblate shapes of aphakic eyes. (*Invest Ophthalmol Vis Sci.* 2009;50:295–304) DOI:10.1167/iovs.08-1972

Pediatric cataracts, including congenital cataracts, represent the most common cause of treatable blindness in early infancy.[1] However, there remain challenging questions to be addressed in relation to the optimal timing of cataract surgery and postoperative optical management, both of which may affect visual outcomes and eye growth.

The human eye undergoes extensive growth over the first few years of life, being only ~70% of its adult size at birth.[2] This period is important for emmetropization, with neonatal refractive errors normally being reduced or eliminated through the coordinated growth of the critical ocular components—cornea, crystalline lens, and vitreous chamber. This emmetropization process also has implications for the management of cataracts in infants. For example, form deprivation may be caused by the cataract before surgery or by subcapsular opacification occurring after surgery as a complication.[3,4] The likely consequence in both cases is accelerated eye growth, and a similar response is expected to refractive errors left uncorrected after surgery.[5,6] Emmetropization may also be disrupted by amblyopia, another possible consequence of early cataracts.[7]

Studies of pediatric subjects undergoing cataract surgery are inconclusive with respect to the effects of early surgical intervention on postoperative eye growth. For example, greater than normal eye elongation and myopic shifts in refraction have been described in pseudophakic eyes of infants (<1 year old) and older children.[8,9] However, there are also reports of reduced eye growth after cataract surgery[10] and minimal effects of cataract surgery on eye growth.[11,12]

Studies using the infant monkey as an animal model to study the effects of early cataract surgery on eye growth mostly report reduced eye growth after the removal of the crystalline lens, irrespective of whether the surgical eye is left aphakic or corrected optically.[13–15] However, many of these studies involve one or more postoperative manipulations, including implantation of monofocal or multifocal intraocular lenses (IOLs), the use of contact lens optical corrections, surgical intervention to remove opaque membranes, and part-time occlusion of fellow eyes, confounding study results and making interstudy comparisons difficult.

Various explanations for growth retardation in young aphakic eyes have been considered in the studies reporting this phenomenon, with most having some credibility. An exception is the attribution of growth retardation to a reduction in IOP, which, to the contrary, is generally reported to be within normal range or higher in aphakic monkey eyes.[13,14] The involvement of inflammatory mediators, released in response to the surgical manipulation, has not been ruled out.[16,17] Other explanations rest on the assumption that the lens is a source of critical growth-enhancing trophic factors[13] and/or exerts a critical biomechanical influence during early ocular development. Finally, as an explanation for why uncorrected young aphakic eyes do not show increased growth in compensation for surgically-induced hyperopia, it is possible that the operating range for such defocus-driven changes in eye growth is exceeded.[18]

In seeking further insight into the effects of early lensectomy on eye growth, we built on our experience with the young chick as an animal model for emmetropization, using them to study the effects of lensectomy alone or within combination with various postoperative optical correction strategies. We found evidence of active emmetropization in young aphakic chick eyes: Uncorrected aphakic eyes grew faster than their fellows, this growth enhancement being attenuated by partial or full optical correction of surgically induced refractive errors.

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Materials and Methods

Animals

White-Leghorn chicks were obtained as hatchlings from a commercial hatchery (Privett, Portales, NM), and reared in a 12 hours on–12 hours off lighting regimen, with food and water provided ad libitum. At 18 days of age, the chicks were randomly assigned to one of four treatment groups: lens extraction, sham surgery combined with a −30 D lens, lens extraction combined with a +20 D lens, and lens extraction combined with a +30 D lens. A total of 36 birds were used, distributed equally across the four groups.

Care and use of the animals were in compliance with an animal use protocol approved by the Animal Care and Use Committee of the University of California, Berkeley, and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Experimental Manipulations

Surgical Preparation. All surgeries were performed in sterile conditions, with the chicks deeply anesthetized (40 mg/kg ketamine; Keta-Thesia; 8 mg/kg xylazine, X-Ject SA; both from Vetus, Farmers Branch, TX), given as an intramuscular injection. Ophthalmic ofloxacin (0.3%; Akorn, Buffalo Grove, IL) was topically applied the day before the surgery. Immediately before the surgery, the conjunctival fornix was flushed with sterile balanced saline solution and 0.5% tetracaine (EyeCaine; Eye Supply Inc., Tampa, FL) applied topically for local anesthesia.

Lensectomy. In each chick in the three lensectomy groups, the crystalline lens was removed from either eye. The choice of eye for surgery was somewhat random although in each group, the right eyes of five chickens and the left eyes of another four underwent lensectomy surgery, which was performed by the same surgeon (LA). After a 1.5 mm incision was made with a 15° stab knife through the superior corneal margin, approximately 0.1 mL of vecuronium bromide (VB, 1 mg/mL; Abbott Laboratories, Abbott Park, IL) was injected into the anterior chamber to dilate the pupil. Fifteen minutes after the administration of VB, a can-opener capsulotomy was performed; a series of connected punctures was made in the anterior lens capsule around its peripheral margin with a cystotome fashioned from a 30 gauge needle that was bent twice, near its hub and near the tip of its bevel. The lens material was removed by aspiration with an I/A cannula (23 and 25 gauge). The peripheral cortex tended to stick to the equatorial capsule, perhaps due to the different arrangement of lens fibers in the crescent-shaped (annular) pads of the avian lens[19,20]; extra effort was needed to clear this cortical material. The posterior capsule was left intact to keep the vitreous in place, after verification in a pilot study that the posterior capsule remained free of opacities over a 4-week postoperative period. The small corneal incision was self-sealing. Note that the term lensectomy is traditionally used to refer to surgery that includes a posterior capsulectomy; it has been adopted to describe the surgery in the current paper for simplicity.

Sham Surgery. This surgery was performed in a protocol similar to that used for lensectomies, except that after the administration of VB, the anterior chamber was irrigated with sterile saline for 5 minutes with aspiration and then allowed to self-seal.

Postoperative Medication. To reduce postoperative inflammation and prevent infection, we injected an ophthalmic suspension (neomycin/polymyxin + 0.1% dexamethasone; EyeTrol; Eye Supply Inc.) into the superior subconjunctiva immediately after the surgery and also applied it topically, four times a day for 3 days, after which the dose was slowly tapered, with treatment being terminated 10 days after the surgery.

Postoperative Optical Manipulations. Two days after the surgery, spectacle lenses were fitted to some of the surgical eyes (+20 or +30 D, lensectomy eyes; −30 D sham eyes) via Velcro support rings that allowed their removal for cleaning and measurement as needed. The choice of lens powers was based on refraction data collected in a pilot study: The +30 D lens approximately corrected the hyperopia induced by lensectomy, whereas the +20 D lens undercorrected it; the −30 D lens fitted to phakic eyes undergoing sham surgery induced hyperopia equivalent to that induced by the lensectomy surgery. The lens treatments were maintained to postsurgical day 28.

Measurements

Ocular Dimensions. High-frequency A-scan ultrasonography was performed in chicks under isoflurane anesthesia (1% in oxygen), to measure the individual ocular components along the optical axis; this technique has a precision of approximately 10 μm.[21,22] For each measurement, up to 20 traces were captured and averaged. Measurements were made the day before the surgery, as well as on postsurgical days 3, 7, 14, 21, and 28. In phakic eyes, optical axial lengths were calculated as the sum of anterior chamber depth, lens thickness, and vitreous chamber depth, with the same reference surfaces (i.e., the anterior corneal surface and anterior retinal surface) being used to define the optical axial length of aphakic eyes. To derive an outer axial length parameter, we added optical axial length, retinal thickness, choroidal thickness, and sclera thickness together.

External Dimensions of Enucleated Eyes. At the end of the 28 day monitoring period, the chicks were killed, their eyes enucleated, and measurements made of the horizontal and vertical equatorial and anterior–posterior axial dimensions with digital calipers. The average of horizontal and vertical equatorial dimensions was used in data analyses. These data complemented the ultrasonography data, providing a perspective on how eye shape was affected by the lensectomy surgery.

Refractions. Refractive errors in vertical and horizontal meridians was measured with a retinoscope in chicks under isoflurane anesthesia, 1 day before the surgery, as well as on postsurgical days 1, 14, and 28, by the same examiner (author CFW). Spherical equivalent data were used in analyses and data presentation. Astigmatic errors, expressed as the difference between the refractive errors in the two principal meridians (vertical and horizontal) are also reported (positive values indicate against-the-rule astigmatism, i.e., the vertical meridian is relatively hyperopic).

Intraocular Pressure. IOP was measured with a handheld tonometer (Tono-Pen XL; Reichert, Inc., Depew, NY) before and 3 and 7 days after surgery, to cover the possibility that changes in IOP could contribute to eye size changes. Up to three readings per eye were averaged for use in data analysis.

Analyses

ANOVAs in combination with post hoc tests (one-way, SPSS, Chicago, IL; repeated measures, SAS, Cary, NC), were mostly used to analyze changes induced by the experimental manipulations. A least-significant difference (LSD) correction factor was applied when multiple comparisons were made. Paired *t*-tests were used to compare the difference between the experimental eyes and their fellows.

Results

Surgical Outcome of the Lens Extraction Procedure

With our lens extraction (LX) procedure, the pupillary zone remained clear after surgery (Fig. 1). Even though the posterior capsule was left intact, no posterior capsule opacification was observed in any of the young chicks across the 4-week postoperative follow-up period. The maintenance of optical transparency was an important achievement, to avoid form depri-

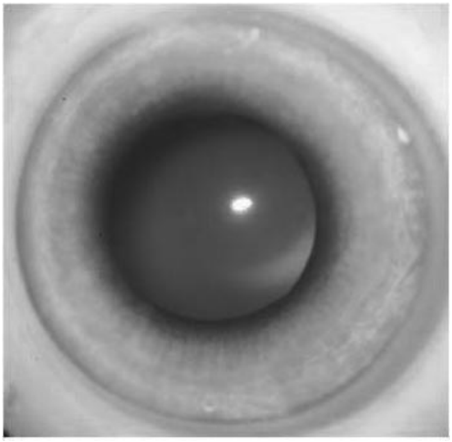

FIGURE 1. Photograph of a representative aphakic eye, after enucleation on postoperative day 28. The posterior capsule is intact and the pupillary zone is optically transparent.

vation, which induces dramatic increases in eye growth in young chicks.[23–25]

Eyes showed minimal signs of inflammation after the surgery. In the immediate postoperative period, there was slight edema around the corneal incision site, which resolved completely within 3 to 5 days of the surgery. Because in pilot studies, synechiae were observed between the iris and residual anterior lens capsule material, immobilizing and distorting the pupil, topical corticosteroid drops were administered after surgery. Only isolated synechiae were observed in corticosteroid-treated eyes. Neither the drug treatment nor the surgery elevated IOP (Fig. 2). Instead, eyes subjected to LX and sham surgery recorded lower than normal IOPs on postoperative day 3 (LE versus fellow: 6.56 vs. 8.41 mm Hg; $P < 0.0001$; sham versus fellow: 8.07 vs. 8.41 mm Hg; $P = 0.016$, paired *t*-test), with both groups showing increases thereafter, although the IOP of the LX eyes was still significantly below normal on postoperative day 7 (LX versus fellow: 8.01 vs. 8.99 mm Hg; $P = 0.037$, paired *t*-test).

Effect of Surgery and Lens Treatments on Refraction Error

Acute Effect of Lensectomy. The removal of the lens from the eyes of young chicks produced large hyperopic refractive errors (Fig. 3A, Table 1). The mean refractive error recorded 1 day after the surgery was +27.91 ± 1.75 D, compared with a preoperative mean refractive error of +3.41 ± 0.58 D. The sham-surgery group showed minimal change in refractive error. Experimental eyes showed increased astigmatism and greater variability relative to their fellow eyes (Table 1, postoperative day 1, experimental vs. fellow: 0.78 ± 0.30 vs. 0.11 ± 0.09 D; $P < 0.05$, paired *t*-test). The astigmatism in experimental eyes tended to be against-the-rule, consistent with the superior location of the corneal incisions.[26]

Changes over the Postoperative Period. Because of the young age of the chicks at the time of the surgery, the fellow eyes showed a gradual, relative myopic shift in their refractions over the monitoring period ($P < 0.001$, repeated-measures ANOVA), a manifestation of normal emmetropization (Fig. 3B, Table 1). Experimental eyes also underwent emmetropization. Thus, compared with their fellow eyes, the highly hyperopic eyes of the uncorrected LX group showed a greater myopic shift over the observation period (experimental vs. fellow: $P < 0.001$, repeated-measures ANOVA, Fig. 3B, Table 1). Partial correction of the lensectomy-induced hyperopia with a +20 D lens reduced but did not eliminate this myopic shift in refractive error (experimental vs. fellow: $P = 0.003$, repeated-measures ANOVA; Fig. 3B, Table 1). In contrast, the addition to LX eyes of a +30 D lens, which generally overcorrected the induced hyperopia, rendering them slightly myopic, induced a small hyperopic shift in refractive error (experimental vs. fellow: $P = 0.045$, repeated-measures ANOVA, Fig. 3B, Table 1). sham-surgery eyes wearing −30 D lenses (sham/−30 D) showed much greater and more consistent myopic shifts in refractive error than did the LX eyes over the same period, even though both groups were exposed initially to similarly large hyperopic focusing errors (Table 1, $P < 0.001$, repeated-measures ANOVA). The changes in the sham/−30 D group also differed significantly from those of the two lens-treated LX groups (sham/−30 D vs. LX/+20 D, $P < 0.001$; sham/−30 D versus LX/+30 D group, $P < 0.001$, repeated-measures ANOVA). There also were significant intergroup differences in the changes in the refractive errors of the three LX groups ($P = 0.02$, repeated-measures ANOVA), with differences being significant for LX/+30 D versus LX/+20 D ($P = 0.020$) and LX/+30 D versus LX ($P = 0.004$), but not for LX versus LX/+20 D (one-way ANOVA; LSD multiple comparisons).

Although experimental eyes exhibited against-the-rule astigmatism immediately after the surgery (Table 1), the surgically induced astigmatism decreased with time, and by the end of the monitoring period, there were no significant differences between experimental and fellow eyes (postoperative day 28, experimental vs. fellow: 0.59 ± 0.35 D vs. −0.06 ± 0.06 D; $P > 0.05$, paired *t*-test). Intergroup differences were also not statistically significant (one-way ANOVA, $P > 0.05$). This temporal decrease in astigmatism in experimental eyes probably reflects corneal healing and is the expected result for sutureless cataract surgery.[27]

Effects of Surgical and Optical Manipulations on Ocular Dimensions

A-scan Ultrasonography. *Axial Length.* In all groups, experimental eyes showed growth changes consistent with compensation for their initial refractive errors (Figs. 4A, B; Table 1). Thus, the experimental eyes of the uncorrected LX and sham/−30 D groups elongated faster than their fellows

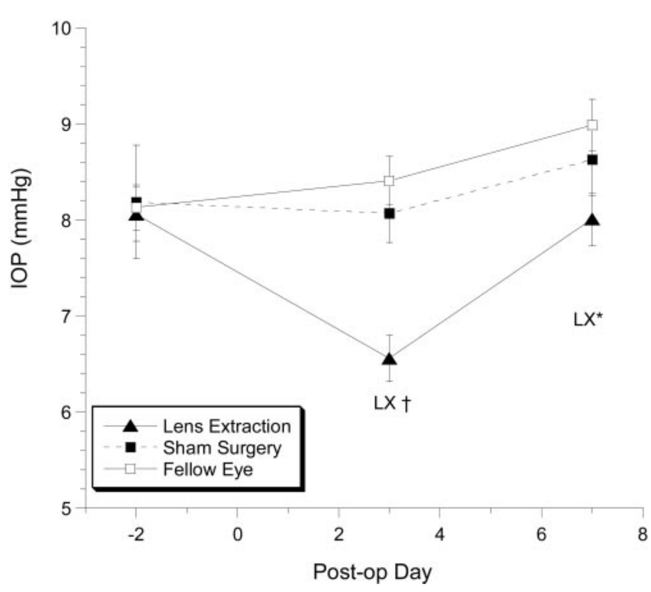

FIGURE 2. Mean IOP (±SEM) for lens extraction (LX), sham surgery, and fellow eyes. Symbols indicate statistically significant differences between experimental and fellow eyes (*$P < 0.05$; †$P < 0.01$; LSD multiple comparisons).

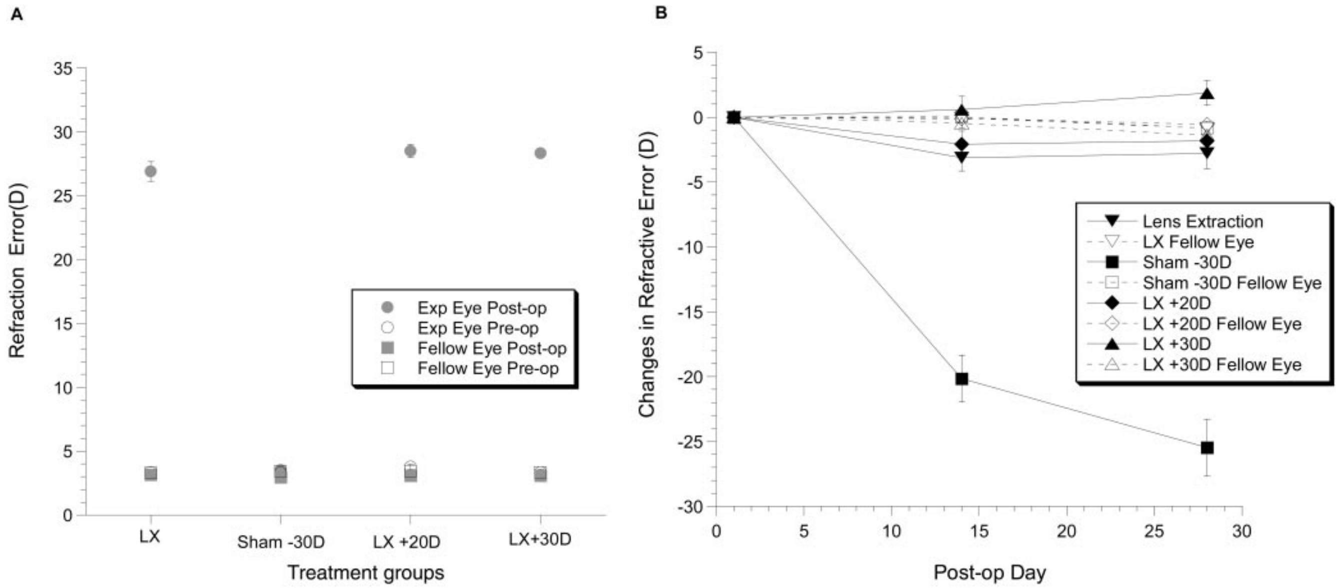

FIGURE 3. Refractive error data (mean ± SEM) for the four treatment groups. Immediately after the lensectomy surgery, experimental eyes showed large hyperopic refractive errors (**A**), and over the experimental period they underwent further refractive error changes that varied according the optical manipulation used. Pre- and postoperative values for fellow eyes are similar, as these eyes changed minimally. (**B**) Eyes subjected to sham surgery and fitted with −30 D lenses showed much larger myopic shifts in their refractions than eyes undergoing lensectomy and left uncorrected, although they experienced similar amounts of defocus at the start of the monitoring period. Eyes undergoing lensectomy and fitted with corrective lenses showed either minimal change (+20 D lens group) or became more hyperopic (+30 D lens group).

throughout the experimental period, their growth responses resulting in significant interocular differences in both optical axial and outer axial lengths from postoperative day 7 (Table 2; $P < 0.05$, repeated-measures ANOVA). The experimental eyes of the LX/+20 D group also tended to elongate faster than did their fellow eyes, although interocular differences never reached statistical significance, except on postoperative day 7 for optical axial length, reflecting the relatively low initial hyperopic errors (~+6 to +7 D; Table 2; repeated-measures ANOVA). In contrast, the experimental eyes of the LX/+30 D group, which experienced low myopia (~1–2 D), underwent a compensatory slowing of axial elongation, and both their optical and outer axial lengths were significantly shorter than those of their fellows from postoperative day 14 (Table 2, repeated-measures ANOVA).

As described earlier, the experimental eyes of both of the uncorrected LX and sham/–30 D groups, which were exposed to similar defocus stimuli initially, elongated faster than their fellow eyes. However, comparing with the LX group, the experimental eyes of the sham/−30 D group had significant longer optical and outer axial lengths at all measurement time points from postoperative day 14 ($P < 0.0001$ and $P < 0.0001$, respectively; repeated-measures ANOVA). There also were significant differences in the optical and outer axial lengths of the experimental eyes of the LX/+20 D and LX/+30 D groups toward the end of the monitoring period (optical axial length: day 7, $P = 0.0167$; day 14, $P < 0.0001$; day 21, $P < 0.0001$; day 28, $P < 0.0001$; outer axial length: day 14, $P = 0.0017$; day 21, $P < 0.0001$; day 28, $P < 0.0001$; repeated-measures ANOVA), consistent with the differences in ocular growth patterns noted earlier.

Retinal Thickness. In general, the retinas of experimental eyes were thinner than those of their fellows, irrespective of the experimental manipulation (Fig. 5A, Table 1), although these differences were not always statistically significant (see Table 3, repeated-measures ANOVA), and there were no statistically significant differences among the groups over the study period (repeated-measures ANOVA). Retinal thinning has been described in rapidly elongating, form-deprived chick eyes,[28] and thus was expected in the three groups showing increased elongation of the vitreous chambers of their experimental eyes (i.e., uncorrected LX, sham/−30 D, and LX/+20 D). The slight equatorial enlargement (H–V length) in the experimental eyes of the LX/+30 D group may be responsible for the retinal thinning in this group, which showed reduced rather than increased axial elongation (A–P length; Table 1).

Choroidal Thickness. Imposed hyperopia and compensatory increased elongation of experimental eyes was coupled to choroidal thinning. Thus, the experimental eyes of all groups except the LX/+30-D group, recorded significantly thinner choroids than those of their fellows, at four or more time points over the monitoring period (Fig. 5B, Table 3; $P < 0.05$; repeated-measures ANOVA). The LX/+30 D group exhibited the opposite trend; the choroids of experimental eyes thickened with their lenses in place relative to those of their fellows, consistent with the net imposed myopia and slowed axial elongation. Although interocular differences for the LX/+30 D group did not reach statistical significance in four of five postoperative time points (see Table 3; repeated-measures ANOVA), they were significantly different from those of the other three groups from postoperative day 7 ($P < 0.05$; repeated-measures ANOVA), with differences between the uncorrected LX and LX/+30 D groups, and between the LX/+20 D and LX/+30 D groups, reaching statistical significance by day 4 ($P < 0.01$, repeated-measures ANOVA).

Scleral Thickness. The scleras of all eyes became progressively thicker over the monitoring period, with experimental eyes and their fellows showing similar profiles from day 7 (Table 3, $P < 0.05$; repeated-measures ANOVA; 0.04 ± 0.03 and 0.04 ± 0.02 mm for experimental and fellow eyes of LX groups; 0.03 ± 0.03 and 0.03 ± 0.01 mm for experimental and fellow eyes of sham surgery group; day 28). Earlier, transient interocular differences in all LX groups reflected subtle postsurgical scleral thickening in the experimental eyes (Table 1; day 4: LX, $P = 0.066$; LX/+20 D, $P = 0.048$; LX/+30 D, $P = 0.041$; paired *t*-tests). An inflammatory origin for these changes

TABLE 1. Principal Ocular Parameters at the End of the Study Period and Selected Other Time Points, for Experimental and Fellow Eyes of Four Treatment Groups

	Post-op Day	Eye	LX Group	Sham/−30 D Group	LX/+20 D Group	LX/+30 D Group
Refractive Error (D)	1*	Exp. eye	26.90 ± 2.23	3.53 ± 0.85	28.50 ± 1.50	28.34 ± 1.01
(spherical		Fellow eye	3.17 ± 0.56	2.97 ± 0.26	3.08 ± 0.47	3.08 ± 0.69
equivalent)	28†	Exp. eye	24.11 ± 3.67	−21.94 ± 5.68	26.67 ± 3.05	30.19 ± 3.00
		Fellow eye	2.31 ± 0.60	2.13 ± 0.54	2.53 ± 0.49	1.71 ± 1.32
	(day 28–1)	Exp. eye	−2.78 ± 3.60	−25.47 ± 6.32	−1.85 ± 3.31	1.86 ± 2.84
		Fellow eye	−0.86 ± 0.94	−0.85 ± 0.42	−0.56 ± 0.64	−1.37 ± 1.65
Astigmatism (D)	1*	Exp. eye	1.11 ± 0.90	0.33 ± 0.55	1.33 ± 0.53	0.33 ± 0.25
		Fellow eye	0.33 ± 0.17	0.11 ± 0.17	0.11 ± 0.11	−0.11 ± 0.26
	28†	Exp. eye	1.44 ± 0.92	0.11 ± 0.79	−0.36 ± 0.39	1.17 ± 0.52
		Fellow eye	0 ± 0	−0.19 ± 0.14	0.60 ± 0.15	−0.08 ± 0.08
Optical length	28†	Exp. eye	11.95 ± 0.62	12.70 ± 0.71	11.42 ± 0.26	10.56 ± 0.53
(mm)		Fellow eye	11.28 ± 0.22	11.34 ± 0.23	11.34 ± 0.13	11.39 ± 0.19
	(day 28–1)	Exp. eye	2.37 ± 0.50	3.19 ± 0.50	1.86 ± 0.18	0.95 ± 0.43
		Fellow eye	1.67 ± 0.10	1.83 ± 0.13	1.80 ± 0.12	1.76 ± 0.18
Retinal thickness	28	Exp. eye	0.20 ± 0.01	0.22 ± 0.01	0.22 ± 0.01	0.20 ± 0.01
(mm)		Fellow eye	0.24 ± 0.01	0.25 ± 0.01	0.25 ± 0.01	0.22 ± 0.01
Choroidal thickness	21‡	Exp. eye	0.15 ± 0.03	0.13 ± 0.02	0.17 ± 0.05	0.33 ± 0.17
(mm)		Fellow eye	0.18 ± 0.04	0.20 ± 0.01	0.22 ± 0.05	0.20 ± 0.04
Scleral thickness	4§	Exp. eye	0.13 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.13 ± 0.00
(mm)		Fellow eye	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00
A–P length (mm)	28†	Exp. eye	12.32 ± 0.51	12.59 ± 0.77	11.40 ± 0.53	10.87 ± 0.52
		Fellow eye	11.80 ± 0.52	11.35 ± 0.40	11.41 ± 0.49	11.66 ± 0.23
H–V length (mm)	28†	Exp. eye	16.64 ± 0.53	15.88 ± 0.54	15.70 ± 0.45	15.40 ± 0.45
		Fellow eye	15.26 ± 0.30	15.08 ± 0.31	15.09 ± 0.37	15.21 ± 0.37
Index of eye shape	28†	Exp. eye	0.74 ± 0.02	0.79 ± 0.04	0.73 ± 0.03	0.70 ± 0.03
		Fellow eye	0.77 ± 0.03	0.75 ± 0.02	0.76 ± 0.03	0.77 ± 0.02

Data are expressed as the mean ± SD. $n = 9$ each group.

* Baseline measurement.

† Last measurement.

‡ At the postoperative day 21 measurement, choroidal thickness showed the most significant difference among experimental eyes of the four groups.

§ At the postoperative day 4 measurement, scleral thickness showed the most significant difference between experimental eyes and their fellow eyes in three lens extraction groups.

cannot be ruled out, as eyes undergoing sham surgery and thus less manipulation during the surgery did not show this transient scleral response.

Caliper Measurements of External Ocular Dimensions. *Axial A–P Diameter.* In terms of the A–P axis axial dimensions (Fig. 6A, Table 1), both interocular and intergroup differences largely mirrored those described for the outer axial lengths measured using A-scan ultrasonography. Thus, the experimental eyes of the sham/−30 D and uncorrected LX groups recorded the largest A–P values, being significantly longer than their fellows in both cases (Table 1; uncorrected LX: exp. vs. fellow, $P = 0.049$; sham/−30 D: exp. vs. fellow, $P = 0.001$, paired *t*-test). In contrast, the experimental eyes of the LX/+30-D group were shorter than their fellows (Table 1; exp. vs. fellow, $P = 0.001$, paired *t*-test) and those of the undercorrected LX/+20 D group had similar external A–P dimensions to their fellows (Table 1; exp. vs. fellow, $P = 0.958$, paired *t*-test).

Equatorial H–V Diameter. Equatorial enlargement was a consistent finding for all aphakic eyes, irrespective of whether their axial dimensions were enlarged (Table 1). For example, although the experimental eyes of the uncorrected LX and sham/−30 D groups had similar A-P lengths (Table 1, P=1.000, one-way ANOVA with LSD multiple comparison), those of LX group had significantly larger equatorial dimensions than those of the sham/−30 D group (Table 1, P=0.015, one-way ANOVA, LSD multiple comparisons). Also, the H–V dimensions of the experimental eyes of LX/+20 D groups were significantly larger than their fellows ($P = 0.002$, paired *t*-test), even though their A–P dimensions were similar (Fig. 6A, Table 1), and the H–V dimensions of the experimental eyes of LX/+30 D group, which recorded significantly smaller than normal A–P dimensions, were slightly, albeit not significantly, larger than those of their fellows ($P = 0.28$, paired *t*-test).

Eye Shape. An eye shape parameter (index of eye shape, IES) was derived from these caliper data (IES = A–P axial length/0.5 × [horizontal diameter + vertical diameter]) to better show the differential effects of experimental manipulations on axial and equatorial ocular dimensions. These analyses revealed significant treatment-related effects on eye shape (Fig. 6B, Table 1). For the three LX groups, experimental eyes recorded smaller IESs than their fellows (uncorrected LX group: $P = 0.008$; LX/+20 D group: $P = 0.067$; LX/+30 D group: $P = 0.001$, paired *t*-test), and there was no significant difference between the groups (one-way ANOVA, LSD multiple comparisons), despite intergroup differences in their A–P dimensions. On the other hand, the experimental eyes of the sham/−30 D group recorded a significantly larger IES value than both their fellows (Table 1, $P = 0.002$, paired *t*-test), and the experimental eyes of the three LX groups (Table 1, vs. uncorrected LX, $P = 0.008$; vs. LX/+20 D, $P = 0.001$; vs. LX/+30 D, $P < 0.001$, one-way ANOVA, LSD multiple comparisons).

DISCUSSION

In the present study, we showed that the surgical removal of the crystalline lens in young chicks produces highly hyperopic eyes and dampens but does not prevent emmetropization.

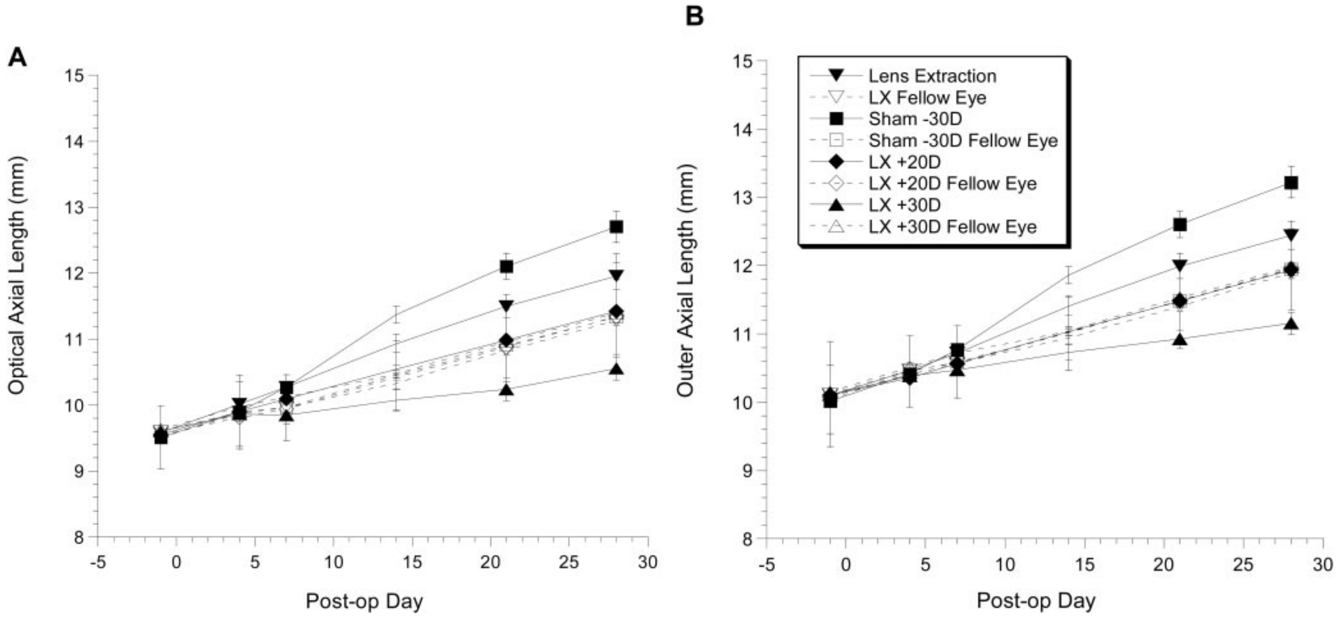

Figure 4. (**A**) Optical axial lengths and (**B**) outer axial lengths (mean ± SEM), obtained by A-scan ultrasonography for experimental and fellow eyes of the four treatment groups, plotted as a function of time over the study period. The experimental eyes of both lens extraction (LX) and sham/−30 D lens groups elongated faster than their fellows, while the experimental eyes of the LX/+30 D group elongated more slowly than their fellows.

Specifically, the aphakic eyes adjusted their rate of growth to partially compensate for their refractive errors, whether small, in the case of eyes wearing correcting lenses, or large in the case of uncorrected eyes. These results also are consistent with observations from related lens studies that young chicks can compensate fully within just a week for a wide range of imposed focusing errors, from approximately −10 to +15 D, and continue to respond in the correct direction for a wider range of errors.[29–32] Nonetheless, in the present study, the increased growth response of aphakic eyes was smaller than that of phakic eyes exposed to similarly large hyperopic errors. In the discussion that follows, we examine these growth responses more closely and also compare our data with equivalent data from primate models and humans. The clinical implications of our findings are also discussed.

Emmetropization: Growth Changes and Refractive Error Mismatches in the Chick

In refractive terms, the experimental eyes of the sham/−30 D lens group exhibited the largest growth response and also the largest refractive changes, of −25 D over the monitoring period. The level of compensation, of more than 80% of the imposed defocus, is much larger than in a previous related study,[32] although the duration of lens wear was also approximately 2.5 times longer.

Of the aphakic groups, the uncorrected LX eyes experienced the largest amount of defocus and grew the most over the monitoring period. However, compared with changes in the treated eyes of the sham/−30 D lens group, which experienced a similar amount of hyperopic defocus initially, the changes in refractive error for the LX eyes were much smaller, as were the increases in optical axial length (~74% of change in mean optical axial length of sham/−30 D lens group). The smaller refractive changes reflect in part, the loss of the refractive contribution of the crystalline lens in aphakic eyes, resulting in a decrease in refractive effect of changes in axial length (i.e., ~8.6 D/mm change in optical axial length calculated in aphakic eyes [LX group], compared with 9.0 D/mm in phakic eyes [sham group]) of 46-day-old chicks. Also note that developmental decreases in the powers of the optical components of the eye tend to offset the compensatory effect of the increased axial elongation in the presence of hyperopia, thereby helping to sustain the stimulus to increased growth. The latter effect would have been greatest for phakic eyes. Nonetheless,

Table 2. Summary of Results from Repeated-Measures ANOVAs Applied to Optical and Outer Axial Length Data, for the Four Treatment Groups

Post-Op Day	Optical Axial Length: LX	Optical Axial Length: Sham/−30 D	Optical Axial Length: LX/+20 D	Optical Axial Length: LX/+30 D	Outer Axial Length: LX	Outer Axial Length: Sham/−30 D	Outer Axial Length: LX/+20 D	Outer Axial Length: LX/+30 D
−2	↑ NS	↑ NS	↑ NS	↓ NS	↑ NS	↑ NS	↑ NS	↓ NS
4	↑ NS	↑ NS	↑ NS	↓ NS	↑ NS	↑ NS	↓ NS	↓ NS
7	↑ 0.006	↑ 0.008	↑ 0.039	↓ NS	↑ NS	↑ NS	↑ NS	↓ 0.021
14	↑ 0.002	↑ <0.001	↑ NS	↓ 0.037	↑ 0.009	↑ <0.001	↑ NS	↓ 0.032
21	↑ 0.003	↑ <0.001	↑ NS	↓ 0.001	↑ 0.010	↑ <0.001	↓ NS	↓ <0.001
28	↑ 0.007	↑ <0.001	↑ NS	↓ 0.001	↑ 0.022	↑ <0.001	↓ NS	↓ <0.001

Arrows indicate the direction of change in experimental eyes compared to that of their fellows. Statistical significance set at $P < 0.05$.

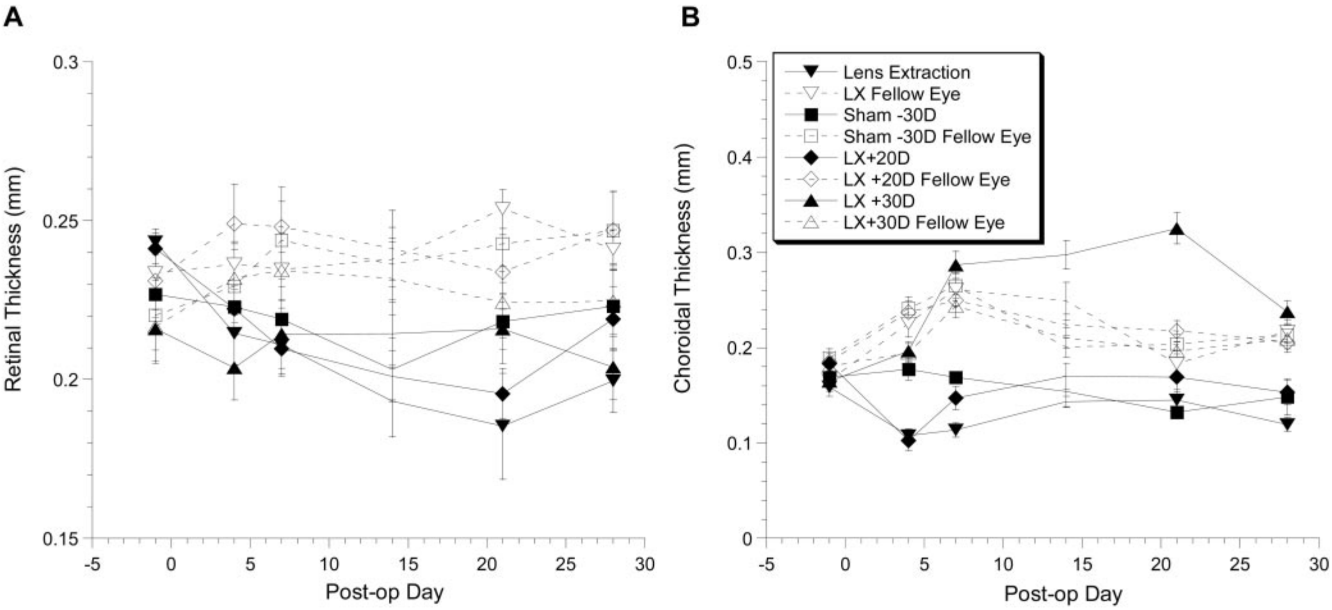

FIGURE 5. (**A**) Retinal thickness and (**B**) choroidal thickness (mean ± SEM), obtained by A-scan ultrasonography for experimental and fellow eyes of the four treatment groups, plotted as a function of time over the study period. Both the retinas and choroids of experimental eyes tended to be thinner than their fellows, for all groups, with one exception involving the LX/+30 D group for which the choroids of experimental eyes were thicker than those of their fellows.

the aphakic eyes (LX group) were exposed to a much greater amount of defocus than the sham/−30 D group, integrated over the monitoring period (~ –24 cf. –8 D at the end of this period), implying a real difference in the ability of young aphakic eyes to increase their growth compared with phakic eyes. For aphakic eyes, predicted intergroup differences in refractive errors are slightly larger than observed (+5.4 cf. +1.58 D for LX/20-D lens group, +14.16 cf. +8.14 D for LX/+30 D, compared with LX group in both cases, refractive errors corrected for a 5 mm vertex distance), perhaps due to corneal accommodation.[33] The correcting lenses may have reduced the imposed hyperopia sufficiently to be within the range of corneal accommodation, leading to a chronic increase in tone.

For the aphakic eyes, the increase in choroidal thickness in the LX/+30 D lens group and decreases in the other 2 LX groups provide further confirmation of their ability to emmetropize. In the chick, choroidal thickness changes represent one of two components of the compensatory response to imposed defocus.[24,34] Specifically, in response to imposed myopia (LX/+30 D lens group), choroidal thickening would have moved the retinal plane forward to the altered plane of focus of the eye, with choroidal thinning in response to imposed hyperopia in the LX and LX/+20 D lens groups and sham/−30 D lens group having the converse effect. These choroidal thickness changes typically precede scleral growth changes, which also contribute to emmetropization, but with a slower time course. Together, these changes account for most of the compensatory changes in vitreous chamber depth during emmetropization in young chicks.

The equatorial enlargement in all aphakic eyes relative to their fellows, regardless of whether they were elongating faster than their fellows, was unexpected, although it may reflect differences in the image quality for peripheral (equatorial) compared to on-axis retinal regions for both phakic (sham) and aphakic eyes. Such differences can be expected due to the high-power lenses used, even though our curved spectacle lens design was intended to provide panoramic vision. For aphakic eyes, the removal of the crystalline lens, which contributes to both the refractive power and optical aberrations of the eye, is an additional confounding factor.[35] Biomechanical factors also may have contributed to the shape changes in aphakic eyes, the removal of the crystalline lens, which is physically attached to the ciliary body in the chick eye, likely altering the forces

TABLE 3. Summary of Results of Statistical Comparisons, of Retinal, Choroidal, and Scleral Thicknesses of Experimental and Fellow Eyes, for the Four Treatment Groups

	Retinal Thickness				Choroidal Thickness				Scleral Thickness			
Post-Op Day	LX	Sham/ −30 D	LX/ +20 D	LX/ +30 D	LX	Sham/ −30 D	LX/ +20 D	LX/ +30 D	LX	Sham/ −30 D	LX/ +20 D	LX/ +30 D
−2	↑ NS	↑ NS	↑ NS	↓ NS	↓ NS	↓ NS	↓ NS	↓ NS	↑ NS	↓ NS	↑ NS	↑ NS
4	↓ NS	↓ NS	↓ 0.005	↓ 0.013	↓ <0.001	↓ 0.022	↓ <0.001	↑ NS	↑ NS	↑ NS	↑ 0.049	↑ 0.037
7	↓ 0.04	↓ 0.012	↓ 0.003	↓ NS	↓ <0.001	↓ <0.001	↓ <0.001	↑ NS	↑ NS	↓ NS	↓ NS	↑ NS
14	↓ 0.004	↓ 0.016	↓ 0.002	↓ NS	↓ <0.001	↓ NS	↓ 0.008	↑ NS	↑ NS	↑ NS	↓ 0.009	↑ NS
21	↓ 0.001	↓ NS	↓ 0.003	↓ NS	↓ 0.036	↓ 0.001	↓ NS	↑ 0.044	↑ 0.010	↑ NS	↓ NS	↓ NS
28	↓ 0.003	↓ NS	↓ 0.026	↓ NS	↓ <0.001	↓ 0.021	↓ 0.017	↑ NS	↑ 0.047	↓ NS	↓ NS	↑ NS

Arrows indicate the direction of change in experimental eyes compared to that of their fellows. Comparisons were made with repeated-measures ANOVA. Statistical significance set at $P < 0.05$.

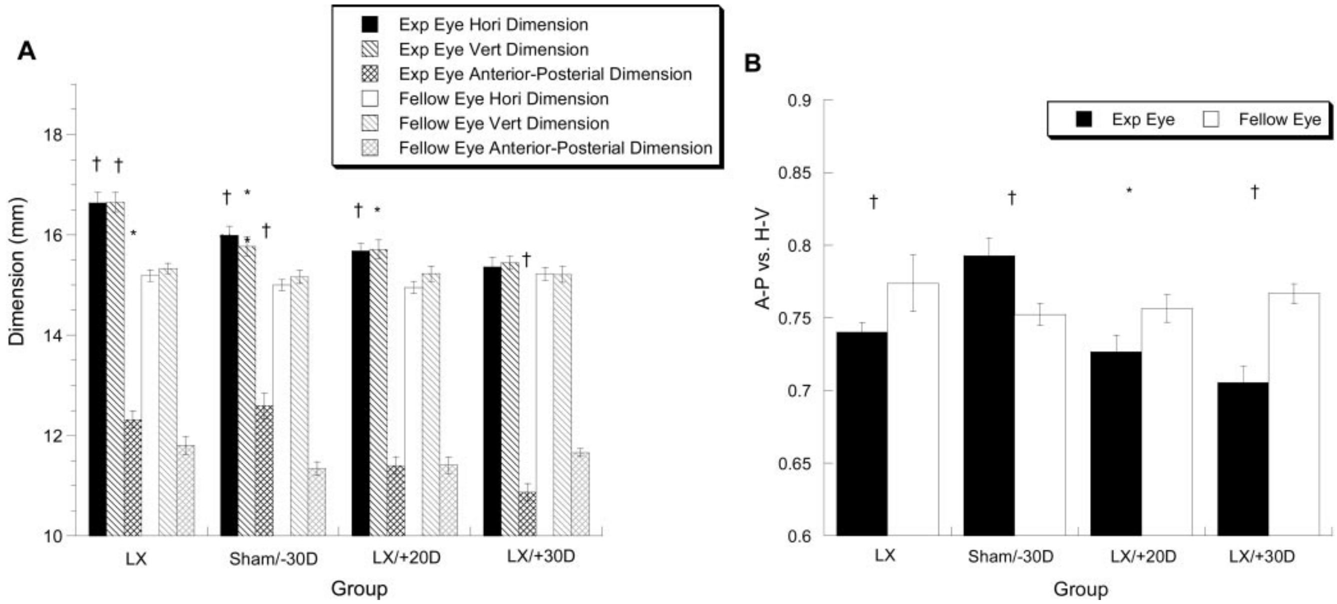

FIGURE 6. External axial length (anterior to posterior, A–P), and horizontal (H) and vertical (V) equatorial diameters (mean ± SEM), obtained from enucleated eyes with digital calipers at the end of the study (**A**). Equatorial dimensions were larger than axial dimensions for all groups and both experimental eyes and their fellows. However, experimental eyes were more oblate than their fellows: The mean ratios of A–P to H–V (average of horizontal and vertical diameters) were smaller than those of their fellows (**B**). Eyes undergoing lensectomy surgery (LX) were also more oblate than those undergoing sham surgery. Symbols indicate statistically significant differences between experimental and fellow eyes (*$P < 0.05$; †$P < 0.01$; paired *t*-test).

acting on the outer wall of the eye in the equatorial region, by reducing the tension of the ciliary muscle, and indirectly of the choroid. A model proposed by Van Alphen[36] links reduced choroidal tension with increased eye growth.

Eye Growth Patterns of Aphakic Eyes: Chick and Primate Eyes Compared

Our finding in the chick of enhanced eye growth in uncorrected aphakic eyes contrasts with the more commonly reported trend of retarded growth after lensectomy surgery in infant primate eyes. Furthermore, in some studies, eyes showed retarded growth after surgery, regardless of whether they were left uncorrected or were corrected optically, either with contact lenses or IOLs.[13–15] However, this pattern of growth retardation appears to be an age-dependence phenomenon, limited to animals undergoing surgery within the first 2 weeks of life; eye growth is reported to be normal when surgery is performed in monkeys at 7.5 months of age and older.[18] If this age effect can be generalized to other animals, it could explain some of the variability in findings for human infants, for which there are reports of increased eye growth,[8,9,37,38] normal eye growth,[2,9,11,38] and retarded eye growth.[11,12,38] Given the apparent age-dependence of the growth retardation effect of lensectomy surgery, it is also noteworthy that in the present study, the surgery was performed on 18-day-old chicks, which are developmentally more mature than 2-week-old monkeys.

Although the uncorrected aphakic chick eyes showed increased axial growth relative to their fellow normal eyes, their growth rate was slower than that of phakic eyes exposed to the same amount of hyperopic defocus, implying an inhibitory influence of the growth of the aphakic eyes. Of four possible explanations considered by others,[13] the seemingly most plausible one attributes the retarded growth in young aphakic eyes to the loss of trophic factors with the removal of the lens. There are several studies showing interdependence between lens and eye growth during embryonic development,[39–41] and it is possible that this interdependence extends into the immediate postnatal (posthatching) period. A second explanation takes into account the traumatic nature of the lensectomy surgery; released inflammatory mediators may have an overriding inhibitory effect on eye growth. In the present study, the lensectomy surgery was more invasive than the sham surgery, although dexamethasone was applied prophylactically to control postsurgical inflammation. A third possible explanation attributes the slowed growth rate in the aphakic eyes to their lower than normal IOP. However, although eye growth and IOP have been causally linked in embryonic development,[42] and there also is evidence for a modulatory influence of IOP on ocular growth in young chicks,[43] this explanation can be rejected for the retarded growth of aphakic primate eyes, because their IOP is not reduced.[14] Finally, we cannot rule out the possibility that changes in biomechanical forces acting on the wall of the eye, related to the low IOP caused by the surgical removal of the lens, underlie the reduced ability of the aphakic eyes to grow. However, predictions of increased rather than retarded growth are more parsimonious with the model of Van Alphen,[36] as mentioned earlier.

Other Differences in Responses to Lensectomy between Chick and Primate Eyes

As already indicated, the young chick eye is able to compensate for quite large focusing errors, with the time to respond being one of the main limiting factors for imposed hyperopic defocus. The large refractive errors induced by the lensectomy surgery are within the range of compensation described in young chicks.[29,32] In contrast, the range of compensation of the primate eye is much more limited, with reliable increases in eye growth occurring only with small amounts of uncorrected hyperopia.[44,45] Compensation is also slower to occur, taking months instead of days, as in young chicks. It is plausible that the corneal contribution to accommodation in chicks contributes to the superior emmetropization ability, by partly compensating for imposed hyperopia. For primate eyes experiencing high amounts of sustained hyperopic defocus, there also is the additional risk of amblyopia,[46] which has been linked to retarded eye growth in this species.[7] These factors make it difficult to predict the ocular growth response of primate eyes to lensectomy when eyes are left uncorrected. The improved visual outcome of lensectomy surgery in which a combination of multifocal IOLs and contact lenses were used compared with contact lenses alone highlights the problem of amblyopia.[47]

Differences in Surgical Anatomy between Chick and Human Infant Eyes

In comparing the effects of lensectomy in young chicks and human infants, it is important to consider how differences in their ocular anatomy may affect surgical outcomes. Compared to the eye of an infant, the chick eye has a much smaller anterior segment (both limbus diameter and depth of anterior chamber) and the pupil is difficult to fully dilate due to the skeletal muscle fiber composition of the sphincter muscle. In addition, the lens of the chick eye is compartmentalized, with annular pads in the equatorial regions; the cortical material of the young chick lens also appears more elastic compared with that of the human infant lens (Ai L, unpublished observation, 2006). Thus, from a technical standpoint, lensectomies are more difficult to perform in young chicks. On the other hand, while the posterior capsule was left in place to avoid any disturbance to and thus visual interference from the vitreous, we did not encounter posterior subcapsular opacification, a frequent complication of pediatric cataract surgery,[1] was not encountered in our chicks. Furthermore, for the data reported herein, we can rule out form deprivation due to media opacities as a likely stimulus for observed increases in ocular growth and thus an explanation for the differences between our results in chick with those of the related primate studies just cited.

Clinical Implications

Based on the results of our study, we conclude that aphakic eyes can actively regulate their growth to partly compensate for surgically induced refractive errors. However, our results also indicate that emmetropization is not normal in aphakic eyes; specifically, young aphakic eyes have reduced capacity to increase their rate of growth. This finding is consistent with the observation of Lambert et al.,[14] of axial growth retardation in aphakic infantile monkey. Anticipating a myopic shift due to eye growth during early childhood, most authors recommend undercorrection of refraction in pediatric patients during IOL implantation. Our results suggest that reduced growth should be expected in eyes undergoing early surgery and thus should be taken into account. Thus, the recommendation of Lambert et al., of implanting an IOL of higher power than that required to achieve emmetropia in a normal-sized human eye, would seem fitting. Although an argument can be made for full correction or slight overcorrection of young aphakic eyes with contact or spectacle lenses in the interest of stimulating normal visual (neural) development, an alternative argument can be made for slightly undercorrecting these eyes, at least part-time, to take advantage of their emmetropization ability in promoting eye elongation. However, it also must be acknowledged that in the clinical setting, there are additional complexities that must be taken into account in individual cases—for example, those related to the cause and age of onset of cataracts that bear on the age of surgery and associated disease that bears on the likelihood of surgical complications and postoperative treatment regimens.

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