Effectiveness of Hyperopic Defocus, Minimal Defocus, or Myopic Defocus in Competition with a Myopiagenic Stimulus in Tree Shrew Eyes

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PURPOSE. To examine the ability of hyperopic defocus, minimal defocus, and myopic defocus to compete against a myopiagenic −5-D lens in juvenile tree shrew eyes.

METHODS. Juvenile tree shrews ($n \geq 5$ per group), on a 14-hour lights-on/10-hour lights-off schedule, wore a monocular −5-D lens (a myopiagenic stimulus) over the right eye in their home cages for more than 23 hours per day for 11 days. For 45 minutes each day, the animals were restrained so that all visual stimuli were >1 m away. While viewing distance was controlled, the −5-D lens was removed and another lens was substituted with one of the following spherical powers: −5 D, −3 D (hyperopic defocus); plano (minimal defocus); or +3, +4, +5, +6, or +10 D (myopic defocus). Daily noncycloplegic autorefractor measures were made on most animals. After 11 days of treatment, cycloplegic refractive state and axial component dimensions were measured.

RESULTS. Eyes with the substituted −5- or −3-D-lens developed significant myopia (mean ± SEM, −4.7 ± 0.3 and −3.1 ± 0.1 D, respectively) and appropriate vitreous chamber elongation. All animals with the substituted plano lens (minimal defocus) during the 45-minute period showed no axial elongation or myopia (the plano lens competed effectively against the −5-D lens). Variable results were found among animals that wore a plus lens (myopic defocus). In 11 of 20 eyes, a +3-, +4-, or +5-D lens competed effectively against the −5-D lens (treated eye <1.5 D myopic relative to its fellow control eye). In the other eyes (9/20) myopic defocus was ineffective in blocking compensation; the treated eye became more than 2.5 D myopic relative to the control eye. The +6- and +10-D substituted lenses were ineffective in blocking compensation in all cases.

CONCLUSIONS. When viewing distance was limited to objects >1 m away, viewing through a plano lens for 45 minutes (minimal defocus) consistently prevented the development of axial elongation and myopia in response to a myopiagenic −5-D lens. Myopic defocus prevented compensation in some but not all animals. Thus, myopic defocus is encoded by at least some tree shrew retinas as being different from hyperopic defocus, and myopic defocus can sometimes counteract the myopiagenic effect of the −5-D lens (hyperopic defocus). However, it appears that minimal defocus is a more consistent, strong antidote to a myopiagenic stimulus in this mammal closely related to primates. (*Invest Ophthalmol Vis Sci.* 2006;47:4687–4699) DOI:10.1167/iovs.05-1369

When the young of many animal species first view the world, the axial length of the eye is shorter (closer to the cornea) than the focal plane, so the eye is hyperopic. During subsequent development, the axial length increases until the eye is emmetropic or slightly hyperopic.[1-7]

In 1988, Schaeffel et al.[8] first showed that chronic exposure to plus or minus lenses can alter the emmetropization process. They and others found that imposed hyperopic defocus (focal plane shifted away from the cornea, behind the retina) is uniformly a stimulus for axial elongation. When one, or both, eyes of a tree shrew, macaque monkey, or chick is covered by a concave (minus power) lens held in place by a goggle frame, minus lens compensation occurs: The vitreous chamber elongates until, while wearing the lens, the photoreceptors come to be approximately in the same relationship to the focal plane as are the photoreceptors of normal eyes or the untreated fellow control eye.[3,9–11] Because the eye's axial length is then longer than normal for that age, the eye is myopic when the lens is removed. Across species, the myopiagenic effect of imposed hyperopic defocus is very consistent.

When a convex (plus power) lens, which shifts the focal plane toward the cornea, in front of the retina, is similarly applied, the effect has seemed to be related to both lens power and species. As first reported in chicks, plus-power lenses of +10 D, or even +15 D, cause the lens-treated eye to slow its normal axial growth rate until, while wearing the lens, the eye is approximately emmetropic.[8,9] Because the eye is then shorter in axial length than normal, it is hyperopic when the is lens removed. These, and other data (for a review, see Ref. 12) have suggested that myopic defocus is a stimulus for slowed axial elongation.

When a similar paradigm was applied in tree shrews and monkeys, a different result was typically reported. In a study of tree shrews exposed binocularly to either +3- or +5-D lenses, normal developmental progression from hyperopia toward emmetropia was generally slowed, and the eyes remained myopic while wearing the lens (Siegwart JT et al., *IOVS* 2003;44:ARVO E-abstract 1984). Macaque monkeys are usually hyperopic at the start of lens treatment. Therefore, a binocular +3- or +6-D lens corrects the hyperopia. The eyes then typically slow their normal progression toward emmetropia, because they are no longer hyperopic. When the lens is removed, they resume the normal decrease in refractive error toward emmetropia.[3] However, in both monkeys and tree shrews, making an eye myopic with a plus lens also causes the eye of some animals to slow its elongation rate and become more hyperopic than it was at the start of lens wear (Venkataraman S et al. *IOVS* 2005;46:ARVO E-Abstract 1973).[3]

The interaction of the optics of the eye with viewing distance has made it difficult to determine whether myopic defocus is truly a stimulus for slowed elongation in mammals. If an animal with eyes that are 10 cm above the ground wore a +10-D lens over one eye, the ground would be in good focus

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for that eye. If that animal bent over to search for food, the eye would experience hyperopic defocus, unless it perfectly accommodated by increasing the power of its crystalline lens. Even with powerful plus lenses, eyes might experience some clear images and even some hyperopic defocus, although the average defocus would be shifted in the direction of myopia.

To assess whether myopic defocus is a stimulus for slowed axial elongation, it is necessary to control the viewing distance while the lens is worn. This has typically been done in studies of chicks by keeping the animals in the dark except during a brief period each day when they are exposed to visual stimuli at a controlled viewing distance while wearing plus lenses.[13,14] A concern with this procedure is that extensive time in the dark may, in itself, cause changes in the axial length and refractive state of the treated and fellow control eye.[15–17] In visually experienced tree shrews, constant dark treatment for a period of 10 days has been found to be myopiagenic.[18]

A way to allow normal light–dark exposure and provide eyes with visual images throughout the lights-on period while testing the effect of myopic and hyperopic defocus is to use the temporal nonlinearities of the emmetropization mechanism. It has been found, in several species, that if an eye wearing a myopiagenic minus-power lens or a diffuser is given a brief exposure each day to unrestricted vision, the eye never develops significant axial elongation or myopia despite exposure to the minus lens for the rest of the day.[19–21] This can be accomplished by removing the minus lens for 1 to 2 hours each day or by substituting a plano (zero power) lens for a similar period.

Shaikh et al.[20] found that if a tree shrew wore a monocular −5-D lens 23 hours per day in its home cage on a 14/10 lights-on/off schedule, and the lens was removed for 1 hour each day, the eye did not fully compensate, but compensated partially (-2.9 ± 1.6 D, relative to the control eye). In pilot studies in this laboratory, it was found that if the lens was removed for 45 minutes while an animal was restrained so that all objects were >1 m away, the treated eye did not develop significant myopia. The ability of 45 minutes of unaltered visual experience with controlled viewing distance to compete effectively against the myopiagenic effect of a −5-D lens allowed us to test the ability of both hyperopic and myopic defocus to compete against a −5-D lens worn for the rest of the day in the home cage.

In the lens-substitution paradigm in tree shrews,[22] rather than simply removing the monocular −5-D lens, another lens is substituted for 45 minutes while the viewing distance is controlled so that all objects are >1 m away. To the extent that the lens worn while viewing distance is controlled effectively competes against the −5-D lens, the eye will not develop any axial elongation and myopia, relative to its fellow control eye. To the extent that the substituted lens is ineffective, the eye will elongate and compensate for the −5-D lens A lens-substitution paradigm has also been used, in chicks, by Zhu et al.[23] Some of their animals wore minus lenses all the time, except for brief periods of plus lens wear (viewing distance not controlled) and others wore a plus lens briefly, with viewing distance controlled, and had unrestricted vision the rest of the time. In both situations, plus lens wear produced hyperopia.

Methods

The 45 juvenile tree shrews that participated in this study were raised by their mothers in a breeding colony. The procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham (UAB). The animals opened their eyes approximately 3 weeks after birth. The first day both eyes were open was day 1 of visual experience (VE). At 21 ± 1 days of VE, the animals were weaned and, while anesthetized (17.5 mg ketamine, 1.2 mg xylazine, supplemented with 0.5% to 2.0% halothane as needed), a dental acrylic pedestal was attached to the top of the skull as described by Siegwart and Norton.[24] The pedestal had a vertical tab onto which a goggle frame could be attached by a clip to hold a monocular lens in place.

Lens Treatments

Starting 3 days after the pedestal was installed, a goggle frame was clipped to the pedestal at approximately 9:00 to 9:30 AM. This is referred to as treatment day 1. The goggle had an open frame (no lens) around the left (control) eye and held a −5-D lens that covered the right eye. The lens was a 7.5-mm base curve radius, 12-mm diameter PMMA contact lens with no edge bevels (to give a maximum optical zone) that was held approximately 4 to 6 mm away from the cornea (Conforma Contact Lens, Norfolk, VA). Adjusting for lens effectivity (because the −5-D lens was 4–6 mm in front of the corneal surface), the expected amount of induced myopia if full compensation occurred was −4.6 D, relative to the control eye and measured without any lens. This goggle was worn over 23 hours per day in the home cage, except during two brief (5–10-minute) periods between 9 and 10 AM and 4 and 5 PM when the animal was placed in a darkened nest box, transported to the laboratory and the goggle removed (~2 minutes) for lens cleaning.

Visual Exposure with Controlled Viewing Distance

Each morning at approximately 9:30 AM, starting on treatment day 2 (~24 hours after the −5-D lens was first put in place), each animal was placed in a Plexiglas restraint tube (4.8-cm inner diameter, 16.5-cm length) with a 45° bevel at the head end, arranged so that the animal could rest its chin on the forward incline of the tube. The tree shrew was introduced into this tube from the back. At the front, the two halves of a 0.3-cm-thick Plexiglas collar, hinged at the bottom, and an oval-shaped (2.4 × 2.0 cm) opening were placed around the animal's neck and secured at the top with a rubber grommet that allowed the collar to flex as the animal moved. The collar prevented the animal from moving forward. A Plexiglas end-stop, with an opening for the tail, was placed behind the animal. Ventilation holes prevented build-up of body heat. The restrained animal was secured atop a photographic tripod, arranged so that the animal could not see the tripod legs and was >1 m above the floor. Similarly, the ceiling was >1 m above the animal. The tripod was placed in a large laboratory room, cluttered with tables, wires, and computer monitors, and arranged so that all objects were at least 1 m away. The farthest corner was ~6 m distant. The animals typically sat quietly for the 45-minute period of controlled viewing distance.

After the animal was positioned atop the tripod, the goggle containing the −5-D lens was removed and quickly replaced with another goggle. This, also, had an open frame around the left eye and a controlled-viewing-distance (CVD) lens that covered the right eye. Eight groups of animals, each with a different CVD lens power, were used. The lenses (and number of animals per group) were: −5 D (n = 5), -3 D (n = 5), plano (n = 5), +3 D (n = 5), +4 D (n = 5), +5 D (n = 10), +6 D (n = 5), and +10 D (n = 5). The CVD lens was worn for 45 ± 1 minutes. It was then replaced with the original goggle with the −5-D lens, and the animal was released from the restraint and returned to its cage in the animal colony.

Monitoring of Defocus

An infrared photoretinoscope, developed by the UAB Vision Science Research Center (VSRC) Computer/Electronics Module, was used to monitor the defocus experienced by many of the animals while viewing distance was controlled. This device consisted of two CCD cameras, one aimed at each of the animal's eyes, approximately on the pupillary axis, from a distance of 1 m. Infrared LEDs were arranged according to the principle of eccentric photorefraction,[25–27] to provide a refractive measure of tree shrew eyes over nearly a 20-D range. The retinal reflex was captured by a frame grabber and stored on a computer hard drive. The slope of the luminance change across the pupil was measured off-line by software developed by the UAB VSRC Computer Module. The refractive measures were calibrated on treatment day 1 and treatment day 12 by measuring the slope of the retinal reflex when a series of lenses (+10 D to −10 D in 2-D steps) were held briefly in front of each eye. These refractive measures compared well with those made with an autorefractor.[28]

The IR photoretinoscope provided measures, generally at 2.0-second intervals, throughout the 45-minute period that allowed an estimation of the amount and sign of defocus that was experienced by the treated eye during the CVD period. If an animal blinked, turned its head, turned upside down or moved quickly, frames could not be analyzed. However, from the many frames that could be analyzed, it was verified that the refractive state was shifted, relative to the control eye, by approximately the power of the CVD lens and that accommodation did not vary greatly within a session. In particular, there was no evidence that the animals accommodated to minus lenses, or, with plus lenses, relaxed accommodation to reduce the defocus provided by whatever CVD lens was used. These measures are being prepared for reporting in a separate publication.

Refractive Measures

Daily awake, noncycloplegic refractive measures were made on all but nine of the tree shrews using an autorefractor (ARK-700A; Nidek, Gamagori, Japan) just before the animals were restrained. All 45 animals were measured on treatment day 1. Forty-four were measured on treatment day 12; the 45th was measured when treatment ended on treatment day 9. An autorefractor was used in preference to streak retinoscopy for several reasons. Unlike streak retinoscopy, which must be performed on tree shrews under anesthesia and with the eyelids held open, the autorefractor allowed rapid measures in the awake animal, which could be made daily to learn the time-course of any refractive changes in the treated and the control eyes. In addition, the autorefractor was able to make refractive measures with the −5-D lens or the CVD lens in place. Previous studies in this laboratory have found that the autorefractor values correlate highly with streak retinoscopy measures (Norton TT et al. *IOVS* 2000;41:ARVO Abstract 2990).[29] Periodic measures of calibration eyes provided by the manufacturer showed that the autorefractor measures were within 0.1 D in a range from +10 D to –10 D.

Glickstein and Millodot[30] first suggested that refractive measures in small eyes (such as the tree shrew's, ~8 mm) appear more hyperopic than they actual are because of the "artifact of retinoscopy" that occurs, apparently, because the autorefractor measures the location of the anterior retinal surface (retinovitreous boundary) rather than the photoreceptors. A recent study in which visual evoked potentials were used to determine the refractive state,[29] the investigators found that the values obtained from the autorefractor are approximately 4 D more hyperopic than the true refractive state. Results of another study that used wavefront sensing technology (Ramamirtham R et al. *IOVS* 2003; 44:ARVO E-Abstract 1986) suggested that the value was approximately 3.6 D. The 4-D autorefractor value is slightly larger than the value (3.7 D) calculated with the formula of Glickstein and Millodot[30] and slightly lower than the value (4.5 D) calculated by Norton and McBrien.[1] For the purposes of this study, an autorefractor reading of +4 D was taken to indicate an eye was emmetropic. This topic will be further considered in the Discussion section.

On treatment day 1 and typically on two other occasions (near treatment day 6 and on treatment day 12), the autorefractor was used to measure refractive state with the −5-D lens and the CVD lens in place on the animal. This procedure provided information about the visual experience of the eye with the −5-D lens and the CVD lens in place as the treatment period progressed.

Final Refractive Measures

On the last treatment day, after non-cycloplegic refractive measures were completed, 2 drops of 1% ophthalmic atropine sulfate were administered in each eye. After at least 1 hour, autorefractor measures were repeated in the animals with cycloplegia. Typically, cycloplegic measures were also made with the −5-D lens and the CVD lens in place.

Measures of Axial Component Dimensions

At the time the pedestal was installed, axial component dimension measures were made with A-scan ultrasound[1] to ensure that the treated and control eyes did not differ in axial length before the lens treatment period began. The axial measures were repeated with atropine cycloplegia when the animals were reanesthetized after completing lens treatment. Vitreous chamber depth was measured to the anterior retinal surface. Vitreous chamber data are reported herein because, as in previous studies, the lens-induced elongation occurred almost exclusively in the vitreous chamber. Corneal radius was not measured because previous studies found it to be unchanged when using this goggle system.[24,31,32]

Statistical Analysis

The refractive and ocular component data were entered into commercial spreadsheet software (Excel; Microsoft, Redmond, WA). Plots were made of each animal's refractive measures versus treatment day, showing values without any lenses, and also with the −5-D lens and CVD lens in place. Dependent *t*-tests were used to determine whether the cycloplegic autorefractor values or vitreous chamber depth differed between the control eye and treated eye of each CVD-lens group. Differences between groups were examined with independent *t*-tests.

Results

Figure 1A shows the (mean ± SEM) amount of myopia (measured with cycloplegia and no lens present) in the treated eyes, relative to the control eyes, in all groups of animals at the end of the treatment period. Figure 1B shows the vitreous chamber differences in these groups.

Hyperopic Defocus

−5-D CVD Lens. The animals in the −5-D CVD-lens group wore a −5-D lens both in the cage and while viewing distance was controlled. Given continuous exposure to a −5-D lens, it was not surprising that all the animals in the group (Fig. 1) developed axial elongation in the lens-treated eye (mean ± SEM: 0.14 ± 0.02 mm longer than the control eye) and compensated fully for the −5-D lens (treated – control eye, mean ± SEM, −4.7 ± 0.3 D, measured with no lens).

As shown in Figure 2, the refractive measures of the control eyes in this group were relatively unchanged over the treatment period. For all animals, on treatment day 1, the refractive measure of the treated eye with the −5-D lens in place (filled squares) was shifted in the hyperopic direction by ~5 D from the measures made without the lens (filled circles). However, as the treated eyes elongated and became myopic, the with-the-lens measures (filled squares) became less hyperopic than the control eye, so that by treatment day 12, the treated-eye refraction with the −5-D lens in place was nearly identical with that in the control eye. Refraction measured under cycloplegia was slightly more hyperopic in both the treated and control eyes, but the amount of induced myopia was very similar and, measured with the −5-D lens in place, the treated eye refraction (gray squares) were within <0.7 D of the control eyes (open triangles), indicating that the treated eyes had emmetropized with the −5-D lens in place. This result is shown in more detail in Figure 3.

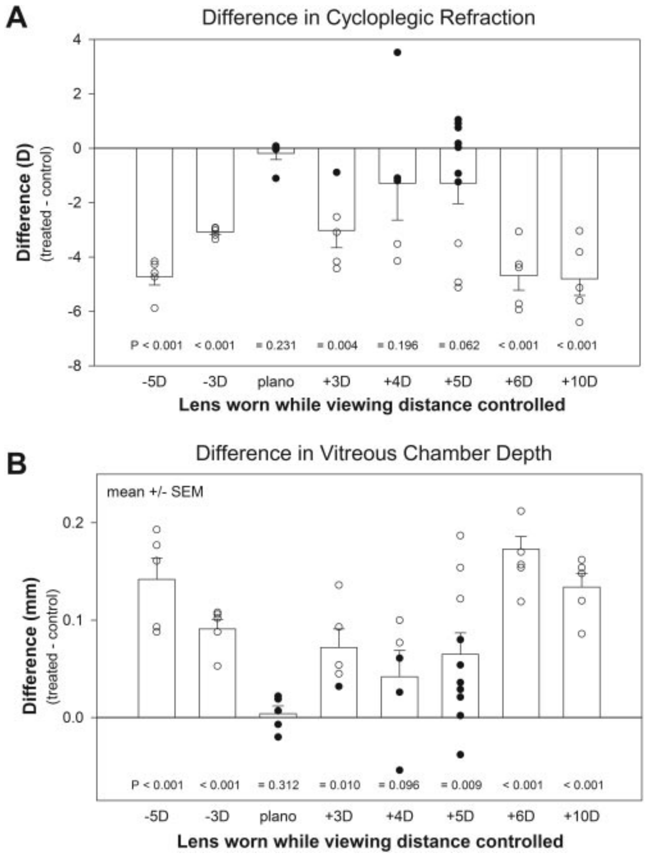


FIGURE 1. (**A**) Difference in cycloplegic refraction (treated minus control eye), measured with no lenses present, after 11 days of lens treatment in the eight groups of tree shrews. Error bars are SEM. The power of the CVD lens worn 45 min/d is indicated on the abscissa. Differences for individual animals are represented by the *filled* and *open circles*. *Filled symbols* indicate animals in which the plus lens blocked compensation to the −5-D lens; the treated eye was myopic, relative to the control eye, by less than 1.5 D. (**B**) Mean and individual differences in vitreous chamber depth. Probabilities are the results of one-tailed *t*-tests that examined whether the treated eyes in each group were significantly myopic, or elongated, compared with the control eyes.

−3-D CVD lens. The animals that wore a −3-D CVD lens developed −3.1 ± 0.1 D of myopia, measured with no lens (Fig. 1A), and an axial elongation of 0.09 ± 0.01 mm in the treated, compared to the control eye (Fig. 1A). All treated eyes responded very similarly, as indicated by the low scatter of the individual data points (Fig. 1). As shown in Figure 2, the refractions in the control eyes remained relatively unchanged. On treatment day 1, the refractive measures of the treated eyes with the −5-D lens (black squares) and the – 3-D CVD lens (black diamonds) were shifted in the hyperopic direction by the appropriate amounts. By treatment day 12, the treated-eye refractive measures with the -3-D CVD lens in place were within 0.9 D of the control eye (Fig. 3). With the −5-D lens, the treated eyes were approximately 2 D hyperopic. Thus, the treated eyes compensated for the −3-D CVD lens, but did not progress to compensate fully for the −5-D lens. The difference in the amount of myopia between the two groups was significant (independent *t*-test, one-tailed, $P < 0.001$).

Plano CVD Lens: Minimal Defocus

As shown in Figures 1 and 2, none of the animals in the group that wore a plano CVD lens compensated for the −5-D lens. A 45-min/d exposure to distant objects through the plano lens was sufficient to compete effectively against the −5-D lens worn the remainder of the time. Measured through the plano lens (Fig. 3), the refraction in the treated eyes closely matched that in the fellow control eyes. With the −5-D lens, treated eyes were ~5 D more hyperopic, both before and after cycloplegia.

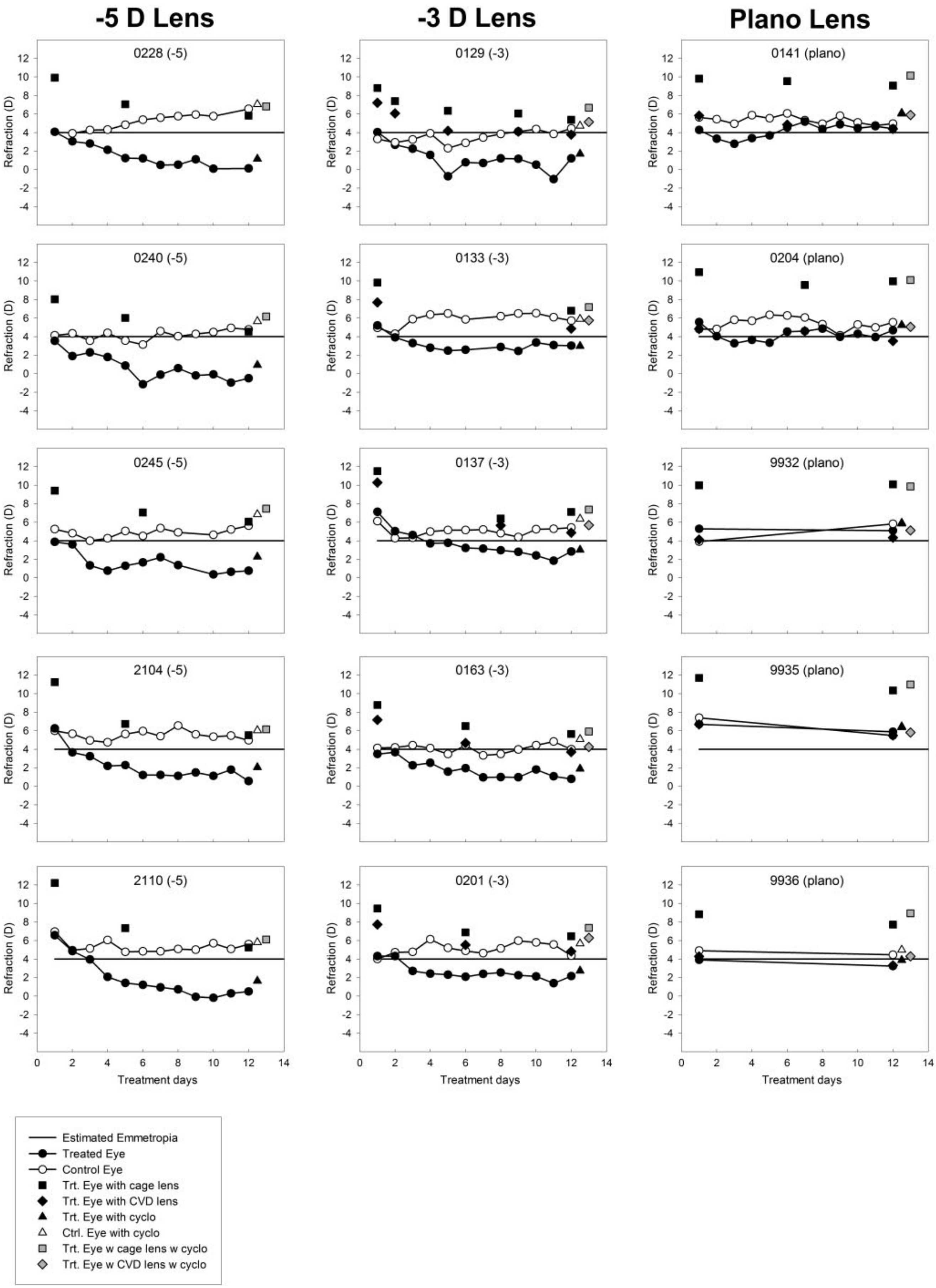
Myopic Defocus

As shown in Figure 1, the treated eyes in the groups that wore plus-power CVD lenses, on average, became elongated and myopic. However, as shown by the individual data points, there was substantial variability in the responses of the eyes in these groups, in contrast to the low variability of the responses (Fig. 1A) to the minus or plano CVD lenses, so that group statistics do not adequately characterize the response to plus lenses in some groups. In some treated eyes, the CVD lens, which produced myopic defocus, competed effectively against the −5-D lens so that the treated eye did not compensate. These treated eyes developed less than 1.5 D of myopia relative to their fellow control eye, measured without any lens (Fig. 4 and filled symbols for the plus-lens groups in Fig. 1A) and did not become much longer than the control eye (Fig. 1B). However, in the majority of the treated eyes, the myopic defocus produced by the CVD lens did not compete effectively against the −5-D lens so the eyes elongated and became more than 2.5 D myopic, compared with the control eye, when measured without a lens (open symbols in Fig. 1). The distribution of the treated eyes into two groups is shown in Figure 4.

+3-D CVD Lens. In one of the five animals (0105) in this group, myopic defocus prevented compensation to the −5-D lens. As is illustrated in Figure 5 (left column, top panel), on treatment day 1 the −5-D lens shifted the eye ~5 D in the direction of hyperopia and the +3-D CVD lens provided myopic defocus 45 min/d. When measured on treatment day 12, the treated eye refraction had changed little over the 11-day treatment period and was only 0.9 D myopic, compared with the control eye, which also maintained relatively stable refraction.

In four of the five animals of this group (0211, 0115, 0109, and 0140; bottom four panels in the +3-D lens column of Fig. 5), myopic defocus was ineffective in preventing compensation to the −5-D lens The treated eye of these animals gradually compensated for the −5-D lens so that, on treatment day 12, measured without any lens, the cycloplegic measures of the treated eyes were 3.6 ± 0.4 D myopic compared with the control eyes (filled triangles). A similar amount of myopia was measured without cycloplegia (filled circles). With the CVD lens (filled diamonds), the treated eyes were even more myopic.

FIGURE 2. Noncycloplegic and cycloplegic autorefractor measures in the animals that wore a −5-D lens in the home cage and that wore (*left column*) a −5-D CVD lens, (*center column*) a -3-D CVD lens, or (*right column*) a plano CVD lens. *Square symbols*: measures made with the −5-D lens in place. *Filled* and *open triangles* and the *gray square*: measures made with atropine cycloplegia. For the -3-D and plano CVD lens groups the *gray diamond* indicates cycloplegic refractive measures made while the animals wore the CVD lens. The cycloplegic measures were made 1 to 2 hours after the final noncycloplegic measures and are displaced along the abscissa for clarity. The *horizontal line* at 4 D represents estimated emmetropia in tree shrews when measured with the autorefractor.


-5 D Lens
-3 D Lens
Plano Lens
0228 (-5)
0129 (-3)
0141 (plano)
0240 (-5)
0133 (-3)
0204 (plano)
0245 (-5)
0137 (-3)
9932 (plano)
2104 (-5)
0163 (-3)
9935 (plano)
2110 (-5)
0201 (-3)
9936 (plano)
Refraction (D)
Treatment days
Estimated Emmetropia
Treated Eye
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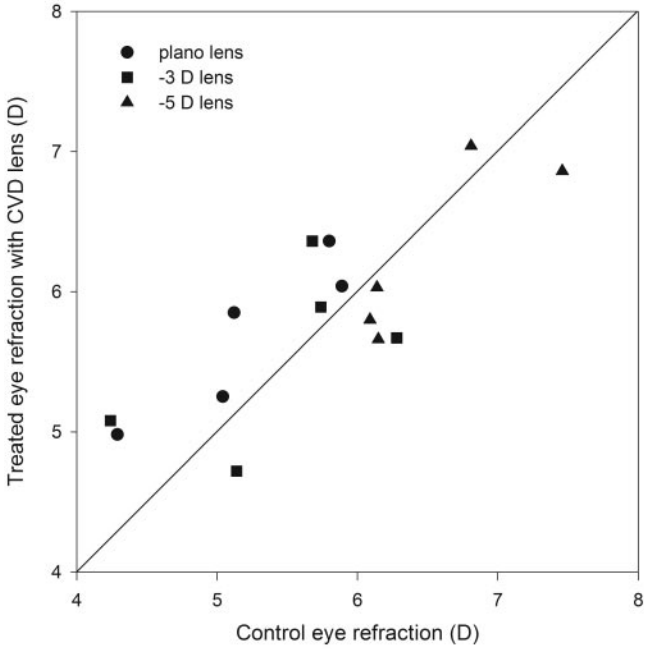

FIGURE 3. Comparison of cycloplegic control-eye refractive measures versus treated-eye measures while the treated eyes wore the CVD lens. The solid line indicates equal refraction in each eye. The control eye refraction varied between 4.2 and 7.5 D, and the treated eyes, while wearing the CVD lens, were all within 0.9 D of their control eye after 11 days of treatment. This is within the estimated depth of focus of the tree shrew eye (±1.0–1.5 D).[1,29]

+4-D CVD Lens. In three of the five animals, the myopic defocus provided by the +4-D CVD lens competed effectively versus the myopiagenic −5-D lens and blocked compensation (Fig. 5). The most dramatic example in this study was animal 0342 (top panel): the treated eye became 4 D hyperopic (measured with no lens) in comparison with the control eye, which appeared unaffected by the treatment regimen. Measured with the lens (diamond), the treated eye nearly matched the control eye. The axial elongation rate of the treated eye was slowed below normal so that, at the end of treatment, its vitreous chamber was shorter than that of the control eye (Fig. 1B), but longer than at the time the pedestal was installed. Myopic defocus also blocked compensation to the −5-D lens in animals 0326 and 0331. At the end of the treatment period, when measured with no lens, the treated eye refractive measures were very close (<1.5 D) to those of the control eyes. In two animals in this group (0349 and 0338) the +4-D CVD lens was ineffective in competing with the −5-D lens. The eyes compensated almost fully by treatment day 12. With the −5-D lens in place, the refractive measure was close to that in the control eye.

+5-D CVD Lens. In 7 of the 10 animals in this group, the myopic defocus provided by the +5-D CVD lens competed effectively versus the myopiagenic −5-D lens, so that refraction in the treated eyes remained within 1.5 D of that in the control eye (cycloplegic measure with no lens). As shown in Figure 5, at the end of the treatment period, the treated eyes were strongly hyperopic with the −5-D lens in place (filled diamonds). Measured with no lens, the treated eye refractive measures were very close to those in the control eye. In the remaining three animals, the myopic defocus produced by a +5-D CVD lens failed to compete with the −5-D lens, so that the treated eyes compensated for the −5-D lens. When measured with the −5-D lens in place on treatment day 12, the refractions were close to those of the control eye (Fig. 5). Measured with the CVD lens in place, the treated eyes were close to 8 D myopic.

+6-D and +10-D CVD Lenses. As shown in Figures 1 and 5, both the +6-and the +10-D CVD lenses were ineffective in competing against the −5-D lens; all the treated eyes compensated for the lens by elongating and becoming myopic when measured with no lens in place (mean ± SEM, +6-D group, −4.7 ± 0.5 D; +10-D group, −4.8 ± 0.6 D) When measured with the −5-D lens, the eyes were close to their control eye values. With the CVD lens (filled diamonds), the treated eyes were extremely myopic.

DISCUSSION

In this study, we compared the ability of a brief (45-minute) daily period of three conditions: plano lens wear (minimally defocused images), minus lens wear (hyperopic defocus), and plus lens wear (myopic defocus), to counteract the myopiagenic effect of a monocular −5-D lens.

Plano Lens: Minimal Defocus

Substituting a plano lens for 45 minutes per day while viewing distance was controlled so that all objects were at least 1 m away provided a visual experience that reliably competed successfully against the −5-D lens worn the rest of the time, so that no significant axial elongation or myopia developed. To conclude that this viewing condition produced "minimal defocus" (e.g., less defocus than when wearing the minus or plus CVD lenses), we must consider several factors: (1) Is an autorefractor reading of +4 D the best estimate of emmetropia; (2) do tree shrews accommodate to nearby targets beyond their tonic level of accommodation; and (3) what is the effect of objects located closer than optical infinity on the defocus the treated eyes experienced wearing the −5-D lens in the home cage and the plano CVD lens?

Where is Emmetropia? Tree shrews are ~20 D hyperopic when their eyes open.[1] The hyperopia decreases rapidly dur-

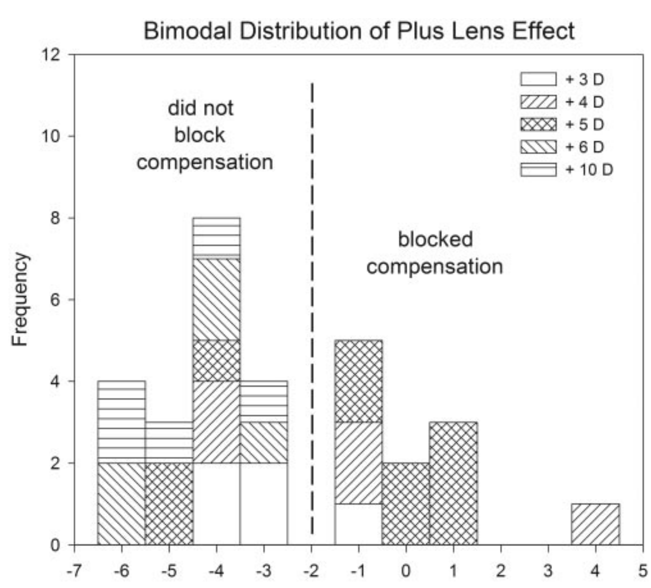

FIGURE 4. Distribution of cycloplegic refractive differences (treated minus control eye) in the groups of animals that wore a plus CVD lens. Eyes that became more than 2.5 D myopic, relative to their fellow control eye, lie to the *left* of the *dashed line* Eyes that developed less than 1.5 D of myopia lie to the *right* of the *dashed line* The power of the CVD lens is indicated in the key.

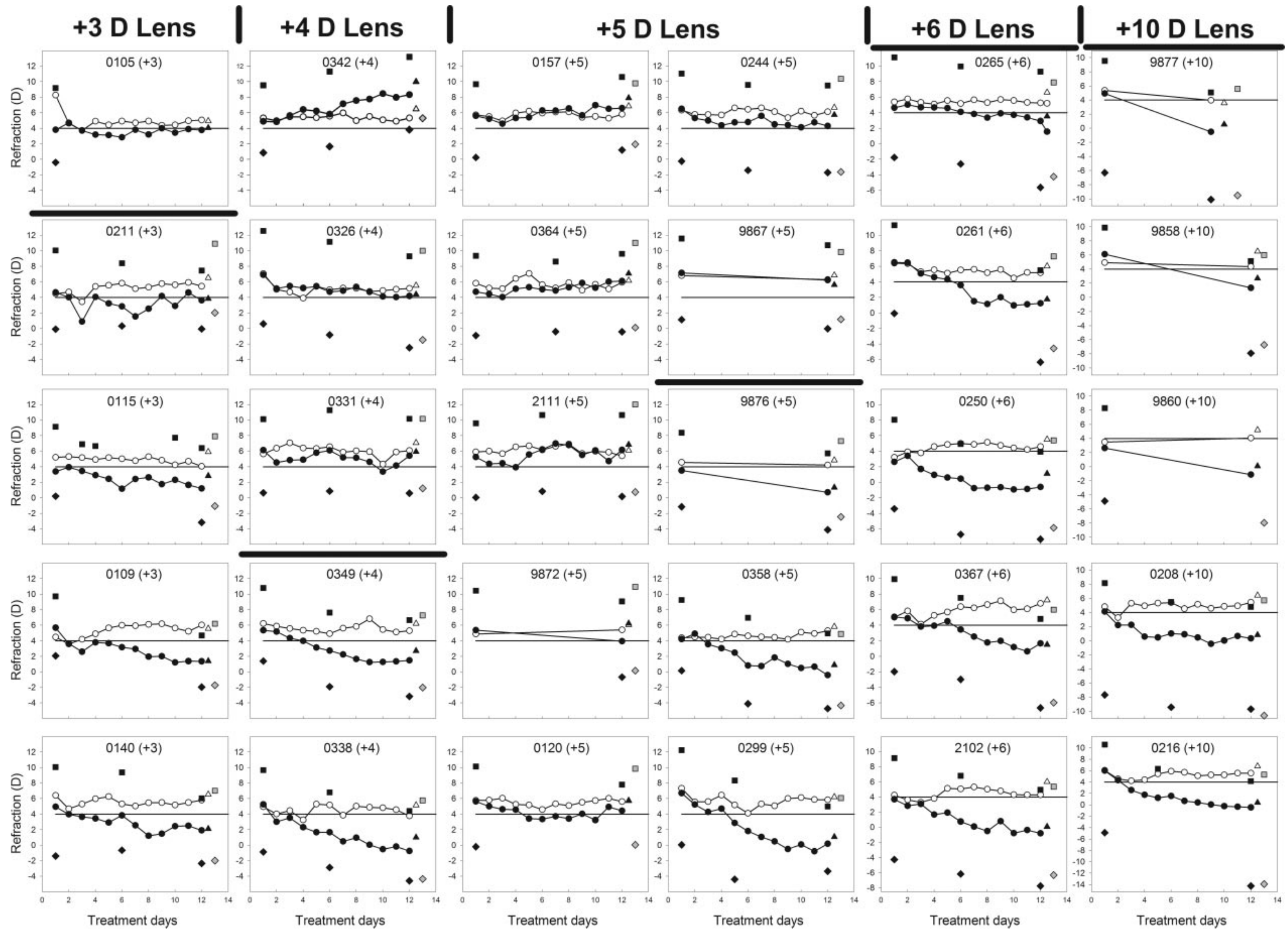

FIGURE 5. Autorefractor measures of the animals that wore a plus lens while viewing distance was controlled. Within a group, animals are placed vertically in the order from the least amount of compensation (CVD lens competed most effectively) to the most (CVD lens least effective). *Horizontal lines*: separate animals in the group in which compensation was blocked (above the line) from those in which it was not blocked (below the line) as indicated in Figures 1 and 4. For the +5-D CVD lens group, the entire *left* column is above the line. Other symbols are as in Figure 2.

ing the first 2 weeks of visual experience and then more slowly over the next several weeks, eventually reaching a stable refractive state. At the age when treatment began in this study (24 days of VE) juvenile tree shrews were approaching, but had not yet reached this stable-refraction plateau. As shown in Figure 6A, the awake, noncycloplegic refractions in a sample of 131 normal tree shrews measured at 24 days of VE in this laboratory with the autorefractor had a mean refraction of +5.2 ± 0.9 D (SD; median, 5.2 D). For the animals in the present study, the distribution of averaged right and left eyes at 24 VE, as lens wear began, was nearly identical with the larger group, with a mean of 5.1 ± 1.0 D; median, 5.1 D). At the end of treatment (35 days of VE), the 45 control eyes were nearly the same (5.2 ± 0.7 D) as they were at the start of treatment.

With increasing age, the refractive distribution narrows and the mean refractive measure decreases slightly. A group of 44 control and normal eyes from other studies in the laboratory, measured without cycloplegia when the animals were approximately 2 months older (75–96 days of VE, close to sexual maturity) is shown in Figure 6B. The mean ± SD refraction was 4.1 ± 0.7 D (median, 4.3 D).

The foregoing suggests that tree shrew eyes grow toward a refractive state "target" or "set point". That this is actually a target for refractive development is further supported by two additional pieces of evidence. First, when a minus lens is used to induce lens compensation, axial elongation increases only until the lens-wearing eye matches the control eye (e.g., returns to the target refraction) while wearing the CVD lens (Fig. 3). Second, when tree shrew eyes recover from an induced myopia, they also return to match the control eye (Amedo et al. *IOVS* 2005;46:ARVO E-Abstract 1977).[32] For the purpose of estimating defocus during the CVD treatment, the best available estimate is that a noncycloplegic Nidek autorefractor reading of +4 D indicates that objects at optical infinity are in focus on the retina[1,29,30] (see the Methods section) and, further, that readings above or below that value can be used to estimate sign and magnitude of defocus. Thus, the animals in the present study were, on average, approximately 1.2 D hyperopic without cycloplegia. The depth of focus for tree shrew eyes has been estimated to be ±1.0 to ±1.5 D.[1,29] In the plano lens CVD condition, the tree shrews in the present study should have experienced from 0 D to approximately 2 D of hyperopic defocus for objects at optical infinity, unless accommodation changed while they were in the CVD condition.

Accommodation. Estimating defocus in the CVD condition from the autorefractor measures is only valid if the animals do not alter their accommodative state while in the CVD condition. Comparing the measures in Figure 6B with cycloplegic measures in Figure 6C shows that tree shrews typically accommodate a small amount when measured with the autorefractor so that, measured under atropine cycloplegia (Fig. 6C) the eyes were on average 0.8 D more hyperopic. In the present study, the eyes shifted 0.9 ± 0.1 D in the hyperopic direction under cycloplegia. Thus, it appears that, like most children[33] and macaque monkeys,[4] the refractive state of tree shrews stabilizes at a point where there is a small amount of hyperopia under cycloplegia that normally is shifted to emmetropia by tonic accommodation. Further, while wearing plus lenses, the tree shrews could not have relaxed their accommodation beyond the 0.9-D difference between the noncycloplegic and cycloplegic measures.

With chemical stimulation of the ciliary muscle, anesthetized tree shrew eyes have been observed to accommodate up to 8 D.[34] Perhaps surprisingly, and in contrast to chicks and monkeys, it appears that tree shrews do not typically use their ability to accommodate to clear hyperopic defocus imposed either by minus-power lenses or by nearby objects. For instance, when autorefractor measures are made through a plus- or minus-powered lens, the reading is altered by approximately the power of the lens, indicating that the eye has not changed its accommodative state significantly in response to the lens.

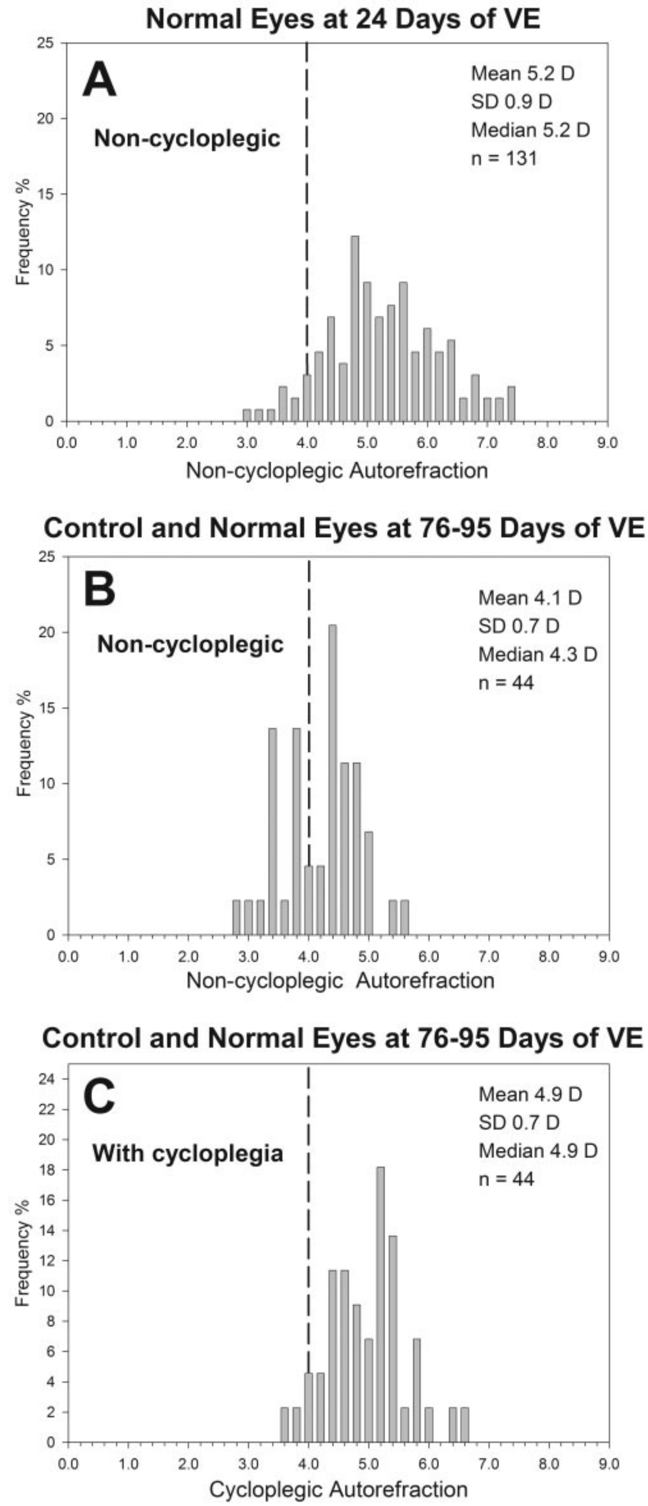

Figure 6. Frequency distribution of spherical-equivalent refraction for normal and control tree shrew eyes. (**A**) Noncycloplegic measures of normal eyes at 24 days of VE (equivalent to treatment day 1). (**B**) Noncycloplegic measures of control and normal (right and left averaged) eyes at 75 to 96 days of VE. (**C**) The same eyes as in (**B**), measured under atropine cycloplegia. *Dashed vertical line*: at +4 D represents estimated emmetropia. The bin width is 0.2 D.

Thus, the noncycloplegic autorefractor measures made on treatment day 1 with the CVD lens in place provided the best estimate of the sign and magnitude of the defocus that was present on the retina from objects at optical infinity during the CVD-lens wear at the start of lens treatment. These values (Table 1, column (1)) are the group average through-the-lens autorefractor measures on treatment day 1, minus the 4-D correction for the small-eye artifact. The plano-CVD lens values (1.2 ± 1.1 D) are presented in the third row. Comparison with the other values in the column show that the plano-CVD lens condition provided the smallest amount of defocus while viewing distance was controlled and the animals viewed objects at optical infinity.

Effect of Object Distance. While in the CVD condition, the farthest part of the room (6 m away) was at optical infinity. The nearest objects were at least 1 m distant and most were intermediate. The defocus produced by the nearest objects while wearing the CVD lenses is calculated in column (4) of Table 1. The data in this column are those in column (1) plus 1 D. Comparison of the plano CVD lens defocus (2.2 ± 1.1 D) with that experienced with other CVD lenses shows that the plano lens provided less defocus at 1 m than did any of the minus lenses. Some of the animals wearing +3- and +4-D lenses had comparable levels of defocus from the closest objects in the room (Table 1, column (4)), but of opposite sign (e.g., myopic defocus).

Thus, after reviewing the evidence that an autorefractor reading of +4 D is the best estimate of emmetropia and that tree shrews seem to accommodate little beyond their tonic level of accommodation and after examining the effect of object distance on the defocus the treated eyes experienced as a function of object distance, we concluded that when wearing the plano lens with viewing distance controlled so that all objects were at least 1 m away, the treated eyes experienced some defocus. However, there should have been less defocus than in any other CVD lens group except possibly a few +3- and +4-D CVD lens eyes. It should be noted that it is very unlikely that treated eyes experienced any myopic defocus while wearing the plano CVD lens. The consistent effectiveness of the plano CVD lens in blocking compensation to the −5-D lens suggests that minimally (hyperopically) defocused images are a consistently effective antidote to the myopiagenic effect of the hyperopic defocus produced by the −5-D lens worn in the home cage.

Plano CVD Lens Versus Unrestricted Vision in the Home Cage. Plano lens wear while the viewing distance was controlled was more effective in blocking compensation to a −5-D lens than was unrestricted vision while animals were in the home cage. Shaikh et al.[20] found that it was necessary to remove a −5-D lens for 2 hours to block compensation completely, when the animals had unrestricted vision in the home cage. Lens removal for 1 hour resulted in partial compensation of -2.9 ± 1.6 D relative to the control eyes. In both the Shaikh et al. and the present study, the animals wore the −5-D lens while in their home cages. The only significant difference was the controlled viewing distance in the present study and its absence in the study by Shaikh et al., in which the animals were in their (60 × 60 × 61-cm) home cages when the −5-D lens was removed. The presence of nearby objects (e.g., nest box, solid sides of the cage, food bowl) along with an apparent lack of an accurate accommodative response to those objects, produced a situation in which the relief from −5-D lens wear was less effective in the home cage than when viewing distance was controlled. The difference in the effectiveness of relief from the −5-D lens, with and without controlling the viewing distance, supports the conclusion that tree shrews do not typically use their ability to accommodate to clear hyperopic defocus imposed either by nearby objects or by minus-power lenses. To the extent they do not, the amount of hyperopic defocus in the home cage with unrestricted vision would be greater than when a plano lens was worn with all objects at least 1 m away. If a tree shrew, with unrestricted vision, stood in the middle of its cage and viewed the walls without accommodating, an additional 3 D of hyperopic defocus would occur. Nearby objects would produce additional hyperopic defocus. The actual defocus was not measured, but the greater effectiveness of the plano CVD lens versus no lens in the cage suggests that the defocus in the home cage was greater than that experienced while viewing distance was controlled to >1 m.

Minus Lenses: Hyperopic Defocus

The suggestion that minimally defocused images are a powerful stimulus to counteract the myopiagenic effects of hyperopic defocus is supported by the data of both groups that wore a minus-power lens while viewing distance was controlled. In the −5-D CVD lens group, the initial hyperopia decreased during the treatment period, as the treated eyes elongated until their refractive state was very similar to the control eye while wearing the −5-D lens (e.g., the target refractive state was restored; Fig. 3). Once this condition was achieved, the eye experienced a "minimal defocus" situation similar to the plano lens group and the refractive state stabilized.

In the −3-D CVD lens group, the treated eyes initially experienced approximately 4 to 5 D of hyperopia while wearing the CVD lens (columns (1) and (4) of Table 1). They elongated until they had minimal defocus while wearing −3-D CVD lens and matched the refractive state of the control eyes (Fig. 3). From this point onward, the −3-D lens effectively

Table 1. Relative Defocus on Treatment Day 1

CVD Lens		(1) CVD Lens Defocus at Infinity*	(2) −5-D Lens Defocus at Infinity*	(3) Relative Unsigned CVD Defocus	(4) CVD Lens Defocus at 1 m†	(5) −5-D Lens Defocus at 33 cm†	(6) Relative Unsigned CVD Defocus†
−5 D	Avg. ± SD	6.2±1.6	6.2±1.6	Equal	7.2±1.6	9.2±1.6	2.0 less
−3 D	Avg. ± SD	4.0±1.3	5.7±1.1	1.7 less	5.0±1.3	8.7±1.1	3.7 less
Plano	Avg. ± SD	1.2±1.1	6.3±1.1	5.1 less	2.2±1.1	9.3±1.1	7.1 less
+3 D	Avg. ± SD	−3.9±1.3	5.6±0.4	1.7 less	−2.9±1.3	8.6±0.4	5.7 less
+4 D	Avg. ± SD	−3.5±0.8	6.5±1.2	3.0 less	−2.5±0.8	9.5±1.2	7.0 less
+5 D	Avg. ± SD	−4.0±0.2	6.5±1.2	2.5 less	−3.0±0.2	9.5±1.2	6.5 less
+6 D	Avg. ± SD	−6.3±1.6	5.9±1.4	0.4 more	−5.3±1.6	8.9±1.4	3.6 less
+10 D	Avg. ± SD	−9.9±1.3	5.3±1.0	4.6 more	−8.9±1.3	8.3±1.0	0.6 more

* Average of autorefractor measures made with the lens in place with 4 D subtracted.
† Assuming no change in accommodation.

became a "plano lens," so the treated eyes' visual experience was identical with that of the plano lens group: minimal defocus while the viewing distance was controlled. This was sufficient to prevent any further elongation, so the eyes tolerated a hyperopic shift of ~2 D while wearing the −5-D lens in the cage more than 23 hours per day. Thus, the response to the -3-D CVD lens, taken with the full compensation in the −5-D CVD lens group and with normal emmetropization, suggests that eyes elongate until they achieve a state where at least 45 minutes per day of minimal defocus is achieved and they match the same target as the fellow control eye.

Plus Lenses: Myopic Defocus

The treated eyes that wore plus CVD lenses experienced varying amounts of myopic defocus during the 45-minute time period, as well as hyperopic defocus while wearing the −5-D lens in the home cage. The animals divided themselves into two groups (Fig. 4). In one group, the myopic defocus generally competed successfully against the myopiagenic effect of −5-D lens wear (blocked compensation) and the eyes developed less than 1.5 D of myopia, relative to the control eye (measured with no lens). In the other group the myopic defocus did not compete as effectively (did not block compensation). The treated eyes elongated and became more than 2.5 D myopic. The success of myopic defocus in preventing compensation in some animals suggests two conclusions: (1) myopic defocus is encoded by at least some tree shrew retinas as being different from hyperopic defocus and (2) myopic defocus can sometimes counteract the myopiagenic effect of the −5-D lens (hyperopic defocus). This appears to be the first demonstration using controlled viewing distance that mammalian eyes, like those of chicks, can distinguish between hyperopic and myopic defocus.

The explanation of the behavior of the treated eyes that wore the minus-power and plano CVD lenses seems rather simple: elongate until the eye experiences "minimal defocus" a sufficient fraction of the day. Is there a similar, simple explanation for the apparently variable responses to the plus CVD lenses? One possibility is that there may be a relatively narrow range of myopic defocus that tree shrews can detect as different from hyperopic defocus and that, within this range, myopic defocus is always effective in blocking compensation to the myopiagenic −5-D lens. Animal-to-animal variation may cause some animals to be within this range while some others in the same CVD lens group may be outside the range. When this range is exceeded, the treated eyes respond as if exposed to form deprivation. A second possibility is that the relative amount of defocus experienced while animals wear the CVD and −5-D lens, without regard to the sign of the defocus, could explain the treated eye responses. In other words, could simply having less defocus with the CVD lens counteract the effect of more defocus with the −5-D lens?

The eyes that wore the +6 and +10 CVD lenses do not help to distinguish between these two possibilities, because they produced large amounts of myopic defocus that could have been out of range and also levels (disregarding the sign of the defocus) that were greater than experienced wearing the −5-D lens in the home cage. Figure 7 compares the amount of defocus in the two conditions for each animal in the plus-lens groups. Because through-the-lens CVD measures were not made on day 2, the first day the viewing distance was controlled, values from treatment day 1 have been used. The abscissa plots the defocus that would have been experienced in the cage while wearing the −5-D lens at infinity, assuming no accommodation (values are the measured refraction wearing the −5-D lens with the 4-D autorefractor correction subtracted). The ordinate plots the defocus (without regard to sign) that would have been experienced at infinity wearing the CVD lens, also assuming no relaxation of tonic accommodation, also at optical infinity. The values are the autorefractor measures made with the CVD lens, again subtracting the 4-D autorefractor correction. The group averages are presented in columns (1) and (2) of Table 1. It is clear in Figure 7, Figure 5, and Table 1 that, with the CVD lens, the +6 and +10 lens groups experienced substantial defocus both during the 45 minutes of controlled viewing distance and in the cage. In all but two animals, the amount of defocus wearing the CVD lens equaled or exceeded the amount of defocus wearing the −5-D lens, even on treatment day 1. These high levels of defocus in both conditions promoted elongation which, on subsequent days, increased the amount of defocus wearing the CVD lens while gradually decreasing the defocus while wearing the −5-D lens. Eventually, after they compensated for the lens, the treated eyes experienced minimal defocus while wearing the −5-D lens. These data suggest that, in tree shrews, myopic defocus in excess of 5 D is either myopiagenic in and of itself or is out of range not able to counteract the myopiagenic effects of hyperopic defocus.

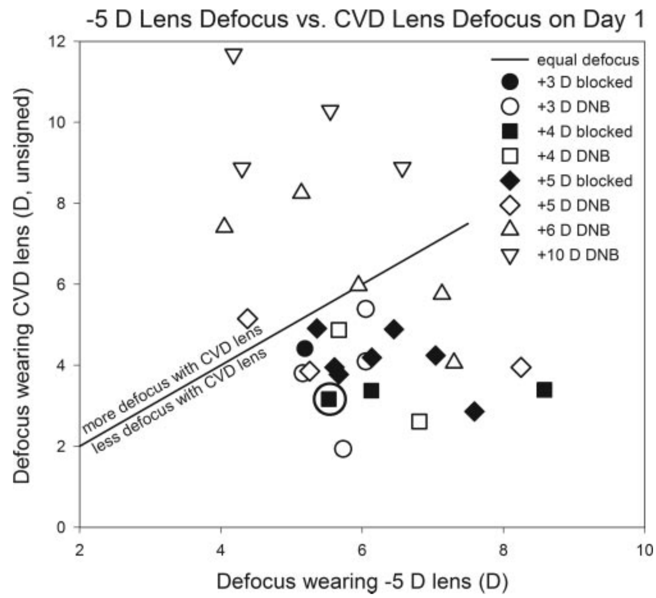

FIGURE 7. Calculated amount of defocus (without regard to sign) experienced by the treated eyes of the plus-lens CVD animals on day 1 of treatment while wearing the −5-D lens and the CVD lens, based on noncycloplegic refractions made with the lenses in place on treatment day 1. In this figure, it is assumed that a +4-D autorefractor reading actually is emmetropia and that there is no change in accommodation from the values measured with the autorefractor. *Filled symbols*: eyes in which the plus CVD lens blocked compensation to the −5-D lens. *Open symbols*: eyes that, by treatment day 12, had compensated for the −5-D lens. *Solid line*: equal defocus in both conditions measured at optical infinity. Data were not obtained for one animal in the +10-D CVD-lens group. DNB, did not block. The *circled* data point is the animal that developed significant hyperopia.

Amount of Defocus. Whether the absolute amount of defocus, without regard to sign, can explain the responses of the treated eyes is examined in Table 1 and Figure 7 for the +3-, +4-, and +5-D CVD lenses. While in their home cages wearing the −5-D lens, the treated eyes of the all three groups experienced approximately the same amount of defocus in the first days of treatment (Table 1, column (2)). To the extent that the animals did not accommodate to clear the monocular −5-D lens, the hyperopic defocus would have been greater (column (5)). However, columns (3) and (6) of Table 1 show that the average amount of unsigned defocus was less while wearing the CVD lens, than when wearing the −5-D lens in the home cage. Figure 7 shows that one of the +5 CVD-lens animals had more defocus with the CVD lens and the plus lens did not block compensation. Thus, even though there generally was less defocus while wearing the CVD lens, compensation was blocked in some eyes (Fig. 7; filled symbols) and was not blocked in others. Animals in which the plus CVD lenses blocked compensation to the −5-D lens did not experience less unsigned defocus wearing the CVD lens than did animals in which the plus CVD lens was ineffective. Thus, the amount of defocus, per se, does not explain these results. However, it may be worth noting a similarity between the group averages in Figure 1 and the amount of defocus in columns (1) and (4) of Table 1. The plano lens group had the least overall defocus and the greatest success in blocking compensation; as the amount of defocus increased in either direction, so did the amount of compensation.

Sign of Defocus. The sign of defocus experienced by the treated eyes wearing the low plus CVD lenses also does not completely explain the results. For animals that experienced low amounts of myopic CVD-lens defocus, the myopic defocus blocked myopia development in some animals but not others. Examination of the individual daily refractive measures (Fig. 5) shows that animals with similar starting refractions, such as +4-D lens-wearing animals 0331 and 0349 followed different paths, compensation blocked in one and not blocked in the other, suggesting that the differences may have originated with the animals, rather than with the viewing conditions. In addition, one might have expected that the animals with the least amount of initial myopic defocus, the +3-D lens group, would have blocked compensation more effectively than the +4 and +5 CVD-lens groups. However, the +3-D CVD lens blocked compensation in only one animal in the group. It appeared that the +4-D lens was slightly more effective in blocking compensation and the +5-D lens even more so. Another factor that suggests that the amount of myopic defocus was not a factor (within the range where it produced less defocus than the −5-D lens) is that, as the eyes in the +3-D lens group compensated for the −5-D lens, they experienced progressively more myopic defocus when viewing distance was controlled. If there was something about experiencing 5 D of myopic defocus that competed most effectively against the minus lens, compensation would have been expected to stop when the eyes reached the point where they experienced 5 D of myopic defocus.

Although the sign of defocus alone does not explain the results, a further indication that the sign of defocus was important in the way eyes behaved comes from comparing the response to the low plus-CVD lenses with the response to the minus-CVD lenses. All but one of the treated eyes that wore the +3-, +4-, and +5-CVD lenses experienced less defocus (absolute value) in the CVD condition than in the home cage. However, the eyes wearing –3-D lenses also had less defocus in the CVD condition. Indeed, the amount of defocus experienced (disregarding sign) wearing the low power plus CVD lenses was comparable to the defocus experienced by the eyes that wore the –3-D CVD lens. That some eyes distinguished between myopic and hyperopic defocus is emphasized by the fact that all –3 D-lens-wearing eyes elongated (until minimal defocus was achieved) whereas only some of the eyes experiencing myopic defocus elongated. This variability in the effect of myopic defocus is highlighted by the one animal (0342) that wore a +4-D CVD lens and slowed its axial elongation so that it became 4-D hyperopic when measured without any lens. The initial refractive measures of this animal (circled data point in Fig. 7) are similar to those of another +4-D-lens animal (0338; Fig. 5) which showed compensation for the −5-D lens Whether animal 0302 was in some way more sensitive to myopic defocus, or whether both were as sensitive but 0342 was better able to use this defocus to slow its axial elongation rate, cannot be determined from the available data.

In summary, examination of the effects of plus CVD lenses suggests that (1) high levels of myopic defocus (≥5 D) are always ineffective in competing against the elongating effects of hyperopic defocus, (2) the results are not explained by the amount of CVD lens defocus, without regard to its sign, and (3) neither are they explained solely by the amount of myopic defocus; low myopic defocus is not consistently effective. It seems that some treated eyes were able to use myopic defocus to counteract the hyperopic defocus and others were not. It cannot be determined from the present data whether these differences were related to genetic variability that made some animals more sensitive to detecting and using myopic defocus than others, or whether other unidentified factors were involved. It should be noted that an outbreeding scheme has been used in this breeding colony, supplemented by the occasional addition of unrelated tree shrews, to maximize the genetic variability of the animals in the colony.

Because only one controlled viewing distance time period (45 minutes) was used and only one 11-day treatment duration was used, it is not possible to assess whether changing either of these parameters would have altered the results. It is possible, for instance, that a longer duration,[35,36] or more frequent brief intervals,[14] of controlled viewing distance might have altered the response to myopic defocus so that it might have been more effective in blocking compensation to the −5-D lens For instance, it has been shown that increasing the duration of a period of unrestricted vision decreases both form deprivation myopia[35,36] and minus lens compensation in an exponential fashion.[21] The slope of this function is rather steep at 45 minutes, so that small individual differences in exposure time, or in the sensitivity of individual animals, might have affected the outcome. If this were the case, however, a similar effect might have been expected with plano lens wear. Similarly, a longer duration of treatment beyond 11 days might have altered the ending refraction in some animals. Finally, only one myopiagenic lens, −5 D, was used. A weaker or stronger minus lens might have produced a differing set of interactions with the plus CVD lenses.

Comparison with Chicks

In chicks, the ability of relatively brief periods of plus lens wear to block compensation to a minus lens is robust, whether or not the animals are restrained to ensure myopic defocus.[14,23,37–39] In some cases, plus lens wear not only blocks compensation to a minus lens, but produces a hyperopic compensation.[14,23] Although the paradigms were not identical, a similar hyperopic shift occurred in only one (0342) of the 30 tree shrews exposed to plus lens treatment. Why the response to myopic defocus, in competition to hyperopic defocus, seems consistent in chicks and not in tree shrews remains unknown. One possibility is that the chick retina may be more sensitive to myopic defocus and send a stronger signal to slow axial elongation. However, given the overall similarities in retinal organization in vertebrate eyes, this might be surprising. Another possibility is that the chick eye is able to use this information more effectively than is the eye of the tree shrew The chick sclera has an inner cartilaginous layer that is absent in tree shrews and primates. The growth of this cartilage is a major factor in the elongation rate of the chick eye. It may be that it is relatively easy for signals associated with myopic defocus to slow the growth of this cartilage. In contrast, the elongation of the tree shrew eye seems to be controlled by a biomechanical property, the creep rate, which in turn is controlled by selective remodeling of structural proteins and enzymes in the sclera.[10,40,41] Even if all tree shrew retinas distinguish between myopic and hyperopic defocus, it may be more difficult for retinal signals to reduce the creep rate of the fibrous sclera below a baseline level in some tree shrew eyes, which might limit the ability of the eyes of some animals to respond to the retinal signals with slowed axial elongation.

Implications for Humans

The most significant result of this study seems to be that clear or minimally defocused images, even for brief daily sustained periods (45 minutes in this case), consistently counteracted a myopiagenic stimulus that was present almost continuously. These data confirm and extend the results of previous studies that have also shown a nonlinear temporal interaction between "unrestricted vision" and myopia prevention.[19–21,35,36,42] Given this powerful effect in animals, one might ask why the effect seems less evident in children? The "defocus hypothesis"[43] suggests that hyperopic defocus that occurs due to underaccommodation to near targets during reading or other close work, produces gradual axial elongation and, eventually, myopia. Yet, it seems that nearly all children should experience sufficient relief from this myopiagenic stimulus during the course of a day when not reading or doing other close work, even if they spend much of the day engaged in those activities. Perhaps this relief needs to occur in a sustained period to counteract environmental myopiagenic conditions. Clinical trials[44,45] have shown a small slowing of myopia progression using progressive addition lenses, intended to reduce retinal defocus for nearwork, but the effects have been nowhere near as dramatic as has been the relief from hyperopia in the animal studies. It may be that something more is present in the children that develop myopia, in addition to defocus, such as a genetic predisposition to a longer eye. If so, then even a strong "dose" of clear images may not be sufficient to restrain the axial length and preserve emmetropia.

Our second result, the variable effect of myopic defocus in slowing lens-induced elongation, may also have implications for the treatment of progressing myopia in children. Based primarily on the very strong effect of myopic defocus in competing against hyperopic defocus in chicks, Morgan and Megaw,[46] Zhu et al.,[23,39] and others have suggested that treatment with brief periods of myopic defocus might slow myopia progression in children. On the one hand, one might view the success of myopic defocus in competing against the myopiagenic effect of the −5-D lens in some of the animals as support that myopic defocus could be of use in this regard. However, the variable effect of myopic defocus in this study suggests that such a treatment may have a similarly variable effect in children. Indeed, one recent study found that undercorrection seemed to speed myopia's progression[47] but another group using monovision[48] reported slowing of myopia's progression in eyes that received myopic defocus. In another study in monkeys (Kee et al. *IOVS* 2004;43:ARVO E-Abstract 2925), myopic defocus was not effective at stopping compensation for a minus lens whereas, similar to this study, minimally defocused images were effective. These results in three different mammals suggests that myopic defocus may not be a consistent antidote to myopiagenic conditions in mammalian eyes, particularly when compared with the success of minimal defocus in preventing myopia development.

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