Pergamon

0042-6989(94)00239-8

Vision Res. Vol. 35, No. 9, pp. 1289–1297, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0042-6989/95 $9.50+0.00

Does Experimentally-induced Amblyopia Cause Hyperopia in Monkeys?

LYNNE KIORPES,* JOSH WALLMAN†

Received 8 February 1994; in revised form 19 April 1994

We assessed refractive errors in 19 monkeys (*Macaca nemestrina*) raised with experimentally produced strabismus or unilateral defocus. These procedures resulted in hyperopic anisometropia in 10 monkeys. All 10 of the hyperopic animals were amblyopic; the amblyopic eye was always the more hyperopic eye. The degree of anisometropia was correlated with the degree of amblyopia. Hyperopic anisometropia did not develop in non-amblyopic animals. There was an association between early onset of visual abnormality and later development of hyperopic anisometropia. Since the refractive changes were correlated with changes in axial length and vitreous chamber depth, we suggest that amblyopia may cause alterations in eye growth and late-onset hyperopia.

Amblyopia Defocus Strabismus Hyperopia Monkey

INTRODUCTION

During postnatal growth, the eye of many primate and avian species has been shown to elongate axially, bringing it from a state of hyperopia toward a state of emmetropia (Banks, 1980; Wallman, Adams & Trachtman, 1981; Hirsch & Weymouth, 1991; Andison, Sivak & Bird, 1992). This process of emmetropization is clearly sensitive to visual input and appears to use a signal related to the refractive state of the eye as an error signal guiding the eye's growth, but also includes a non-visual component that by itself can guide growth toward an eye of approximately normal shape.

Although the strongest evidence that the visual environment affects eye growth comes from the finding, in virtually all species studied, that depriving an eye of form vision results in ocular elongation and myopia (see reviews by Hodos, 1990; Sivak, Barrie, Callender, Doughty, Seltner & West, 1990; Wallman, 1993), it is unclear whether this phenomenon is in fact related to the normal process of emmetropization. Rather, the most convincing evidence that a visual component of emmetropization exists comes from the finding that in chicks one can reliably shift the course of emmetropization toward myopia by imposing hyperopic defocus with spectacle lenses or shift it toward hyperopia by imposing myopic defocus (Schaeffel, Glasser & Howland, 1988; Irving, Sivak & Callender, 1992; Wildsoet & Wallman, 1992). Because, on average, the eyes compensate for the degree and sign of the imposed defocus over a wide range (Irving *et al.*, 1992; Wildsoet & Wallman, 1992), there seems little doubt that a negative feedback control of refractive error exists. Whether such a feedback regulation of refractive status exists in other species, especially humans, is a matter of considerable controversy, with important implications for the use of corrective lenses in children.

Evidence for non-visual regulation of ocular growth and refraction comes from the fact that chick eyes that are myopic and elongated as a result of prior form deprivation eventually return to emmetropia, even if the myopia is corrected by spectacle lenses (Schaeffel & Howland, 1991). Furthermore, during recovery from hyperopia produced by dark-rearing, the eye continues to normalize in shape, even after emmetropic refractions are attained (Troilo & Wallman, 1991).

Comparatively little is known about control of eye elongation in primates. Kiely, Crewther, Nathan, Brennan, Efron and Madigan (1987) and Tigges, Tigges, Fernandes, Eggers and Gammon (1990) have documented longitudinal changes in refractive status and eye length in macaque monkeys. Both studies show that eye elongation proceeds rapidly for the first 6 months after birth in monkeys followed by a gradual asymptotic growth to adult length over the subsequent 3–4 yr. Refractive errors in macaques are typically within 2 D of emmetropia by about 1 yr after birth (Young, 1963, and unpublished data; Kiely *et al.*, 1987). Numerous studies have shown that eye length in primates can be influenced by postnatal visual deprivation. Young (1963) presented evidence that raising monkeys in a restricted viewing environment stimulated excessive elongation resulting in myopia. Wiesel and Raviola (1977, 1979) documented the

*Center for Neural Science, 4 Washington Place, Room 809, New York University, New York, NY 10003, U.S.A. [*Email* lynne@cns.nyu.edu].

†Department of Biology, City College of the City University of New York, New York, NY 10031, U.S.A.

now-familiar deprivation-induced myopia phenomenon. Visual deprivation by lid-suture or occlusion results in excessive elongation of the deprived eye in new world (Troilo & Judge, 1993) and old world primates (see Raviola & Wiesel, 1985; Smith, Harwerth, Crawford & von Noorden, 1987; Tigges *et al.*, 1990), as well as in tree shrew (Sherman, Norton & Casagrande, 1977; Marsh-Tootle & Norton, 1989; Norton, 1990; McBrien & Norton, 1992). Deprivation-induced myopia can not be the result of physical impairment from the lid suture since it occurs following corneal opacification as well (Wiesel & Raviola, 1979).

In contrast to the general finding of myopia following form deprivation, several recent studies report induced *hyperopia* in association with less severe deprivation in primates. Kiorpes, Boothe, Hendrickson, Movshon, Eggers and Gizzi (1987) reported a high incidence of hyperopia following chronic unilateral atropinization during rearing in macaques. Crewther, Nathan, Kiely, Brennan and Crewther (1988) found that unilateral defocus via contact lenses beginning late in development was associated with hyperopia in some cases, although the outcome was independent of the sign of the defocus. Smith, Hung and Harwerth (1994) found hyperopia following unilateral defocus, imposed with negative contact lenses, which was begun soon after birth and continued for 2–3 months. Interestingly, in this case, after the contact lens treatment ended, the hyperopic eyes grew faster than normal and eventually matched the untreated fellow eye in length. This recovery suggests that the emmetropization process in primates uses visual information to match the length of the eye to the focal length of its optics. Taken together, these studies show that defocus represents a qualitatively different state of input to the visual system than does lid suture.

Hyperopic refractive errors are also associated with strabismic amblyopia in humans. Several retrospective studies of strabismic children have shown that the amblyopic eye tends to be more hyperopic than the fixing eye (Lepard, 1975; Bielik, Friedman, Peleg & Neumann, 1978; Nastri, Perugini, Svastano, Polzella & Sbordone, 1984). Interestingly, Lepard's data show that the relative hyperopia of strabismic amblyopic eyes developed over a period of years although the amblyopia was present at the onset of the study (Lepard, 1975).

In the course of other studies on the development of amblyopia in macaque monkeys we noted a tendency toward unusually large anisometropia in our older amblyopic monkeys. In this paper we document interocular differences in refractive error and eye length that developed in association with experimentally produced unilateral strabismus or defocus. We analyzed refraction data for 19 monkeys in which either strabismus or defocus was imposed during the early postnatal weeks. We found a high incidence of late-onset hyperopic anisometropia in animals that developed amblyopia, regardless of the cause of the amblyopia.

METHODS

We analyzed refractive data from 19 pigtailed macaques (*Macaca nemestrina*). All of the animals were participants in other studies conducted in the laboratory over the last 10 yr. The animals were born at the Washington Regional Primate Research Center and were hand-raised in the laboratory according to established, approved protocols. They ranged in age from 10 months to 10 yr at last assessment. Primate care was conducted in accordance with the NIH Guide for Laboratory Animal Care. They were raised in an environment that included views of and interaction with other monkeys and humans, release time in play spaces, and access to television. Furthermore, these animals were all psychophysical subjects in studies of visual development and characterization of spatial vision in amblyopia; they had many hours of experience with high contrast, broad-band and high spatial frequency visual stimuli. Spatial vision data for some of these animals appear in several previously published papers (e.g. Kiorpes, Carlson & Alfi, 1989; Kiorpes, Kiper & Movshon, 1993; Kiorpes, 1992).

Experimental strabismus

Esotropia was induced in 14 animals either by injection of *Clostridium botulinum A* neurotoxin (six cases) or by surgical alteration of the horizontal rectus muscles (eight cases) at ages ranging from 2 to 15 weeks. In the neurotoxin cases, one injection of *C. botulinum A* was made into the lateral rectus muscle of the left eye while the monkey was sedated with ketamine hydrochloride (Scott, Rosenbaum & Collins, 1973; see also Kiorpes *et al.*, 1989). The lateral rectus was exposed by dissection of the conjunctiva and the neurotoxin was injected under visual control with additional EMG guidance via the injection needle. The dose delivered was usually 7–10 units (0.05 ml volume) of *C. botulinum A.* toxin. In the surgical strabismus cases, the lateral rectus muscle of the left eye was transected; the medial rectus muscle was resected and advanced to the limbus. Surgery was carried out under ketamine hydrochloride sedation using sterile surgical techniques. These procedures resulted in esotropia in the range of 10–40 prism D in all except one case, AP, whose initially esotropic deviation became an exotropia of 15 prism D. In all cases the deviation was maintained over the course of the study, although in the neurotoxin cases the angle of deviation tended to reduce over time.

Unilateral defocus

Monocular defocus was induced in five animals by inserting a −10 D extended-wear soft contact lens in the right eye and a plano lens in the left. Lenses were 70% water content made by Contact Lens Precision Labs, Ltd, Cambridge, England. The monkeys wore the lenses for a period of 7–10 months beginning 10–25 days after birth. The monkeys were checked at 4 hr intervals from 7 a.m. to 11 p.m. daily (the room was dark at other times). If a lens was out, or any sign of abnormality was noted, the lens was replaced immediately. In addition, the lenses were routinely changed and cleaned weekly. Beyond the

third week of rearing, lenses were rarely found to be out; plano lenses were lost more frequently than negative lenses in all cases. No obvious strabismus was apparent during the rearing period in any of the lens-reared animals. However, one animal (LF) developed a large-angle exotropia following the rearing period. See Kiorpes *et al.* (1993) for further details.

Refraction

Refractive error was measured by cycloplegic retinoscopy. Cycloplegia was induced with a combination of 1% cyclopentolate and 10% phenylephrine; 3 drops of each were given separated by 10 min intervals. All except the youngest animals (< 10 weeks) were lightly sedated with ketamine hydrochloride for the period of ophthalmic examination. Refractive assessments were made by a pediatric ophthalmologist.

A-scan ultrasonography

The axial spacing of ocular components was measured with a clinical A-scan instrument (Storz) while the monkeys were sedated with ketamine hydrochloride. We accepted sweeps in which the echoes from the two lens surfaces were of similar amplitude and the retinal echo rose sharply from the baseline. Distances were measured separately for each component, using 1.532 mm/μsec as the velocity of sound in the aqueous and vitreous and 1.641 mm/μsec as the velocity in the lens. For the axial length and vitreous depth values reported here, we took the median of all accepted sweeps for each eye (range was 3–12 measurements, with an average of 8).

RESULTS

Refractive error data are shown in Table 1 for each of the subjects. The animals are grouped in blocks by treatment condition: surgical strabismus (top), neurotoxin-induced strabismus (middle), and lens-induced unilateral defocus (bottom). As has been noted previously, not all monkeys with experimentally imposed strabismus or monocular defocus develop amblyopia (Kiorpes *et al.*, 1989, 1993); approximately two-thirds of monkeys with experimental strabismus develop amblyopia. Within each block, animals are listed in order of decreasing interocular difference in acuity based on the most recent grating acuity measurements for each animal. Animals HB, AO, AP and NV never showed a reliable difference in acuity between the treated and non-treated eyes and are therefore classified as non-amblyopes. Refraction data are listed for either two or three ages for each subject. We included initial and final refractions for each animal, and whenever possible, we included an intermediate age.

We found 10 cases in which a fairly substantial hyperopic anisometropia was present at final refraction (Table 1). In every case in which anisometropia (here defined as a 2 D difference in spherical equivalent refractive error) developed, the treated eye is more hyperopic than the fellow eye. Three interesting aspects of this effect can be found from examination of Table 1. First, hyperopic anisometropia appears to be more related to the existence of amblyopia than to the experimental treatment imposed. Ten out of the 15 amblyopic animals were hyperopic anisometropes, while none of the four non-amblyopes were. Furthermore, hyperopic anisometropia occurred more often in cases of

TABLE 1. Refractive errors in monkeys with experimental strabismus or anisometropia

			Early			Intermediate			Late			
Monkey	Onset (weeks)	IAR	Age	UTE	TE	Age	UTE	TE	Age	UTE	TE	Final Anisometropia
Surgical strabismus												
UY	2	7.9				38	+1.50	+5.5	376	+1.25	+7.0	+5.75
VN	3	6.6				34	+2.125	+2.625	436	+1.25	+4.125	+2.875
FT	3	3.2	3	+2.5	+2.25	20	+1.75	+1.875	400	−3.25	−2.25	+1.0
DP	3	2.2	6	+2.5	+2.25	54	+1.0	+1.0				0
CA	4	1.9	11	+3.125	+3.125				404	−3.0	+2.0	+5.0
HC	12	1.7	14	+2.0	+2.25	39	+2.25	+2.5	496	+0.25	+0.25	0
GH	6	1.3	17	+2.0	+1.75	42	+1.25	+1.25	400	−0.50	+0.25	+0.75
HB	15	0.85	14	+6.25	+6.0	25	+6.25	+6.50	496	+7.50	+6.375	−1.125
Neurotoxin strabismus												
AN	4	12.8	16	+5.0	+6.0	36	+5.5	+5.5	324	+7.0	+11.625	+4.625
AM	4	7.1	16	+2.0	+4.0	36	+1.5	+6.0	324	+1.75	+7.125	+5.375
OD	3	3.2	4	+3.5	+3.75	44	+1.75	+4.5				+2.75
JS	3	1.6	4	+5.5	+4.5	12	+5.125	+5.75	288	+1.625	+7.0	+5.375
AP	8	1.1	16	+0.875	+1.75	36	+1.0	+1.0	260	+1.5	+2.0	+0.5
AO	8	0.98	16	+7.375	+7.5	36	+8.5	+8.5	324	+7.875	+7.875	0
Unilateral defocus												
OC	3	6.9	4	+3.5	+3.375				168	+0.25	+6.0	+5.75
FP	2	3.4	2	+3.25	+4.5	20	+5.0	+6.0	200	−0.25	+5.25	+5.5
FR	2	1.5	2	+1.25	+1.25	20	−0.25	−0.25	200	−0.875	−0.125	+0.75
LF	2	1.4	2	+8.75	+8.75				180	+5.25	+8.5	+3.25
NV	4	1.1	8	+12.0	+12.875	172	+0.125	−0.25	276	+0.37	+0.5	+0.13

Within each block the animals are arranged in order from most to least severe amblyopia (IAR—interocular acuity ratio based on most recent behavioral data). Final anisometropia is shown in the last column. Age is expressed in weeks. (TE—treated eyes; UTE—untreated fellow eyes.)

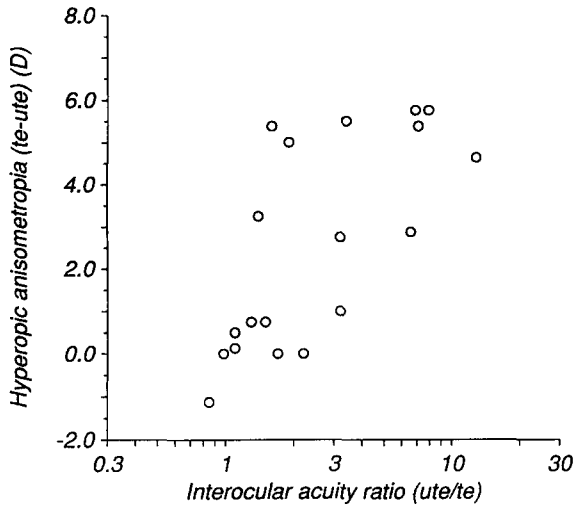

FIGURE 1. The relationship between interocular difference in refractive error and degree of amblyopia. Relative hyperopia of the treated eye (treated eye − untreated fellow eye spherical equivalent refraction) is plotted as a function of the ratio of the grating acuity of the fellow eye to that of the treated eye. Animals with more severe amblyopia have greater hyperopic anisometropia [Acuity data from Kiorpes *et al.* (1989, 1993) and Kiorpes (1992).]

moderate to severe amblyopia. For each treatment condition, the most amblyopic animals (near the top of each block in Table 1) tend to show large hyperopic anisometropia, while the least amblyopic (those at the bottom of each block) do not. This relationship is shown more clearly in Fig. 1 where we have plotted the refractive difference between the eyes, expressed as amount of hyperopia (treated eye − non-treated eye), against the degree of amblyopia for each monkey. The degree of amblyopia is represented as the ratio of grating acuity of the non-treated to the treated eye [note that the animals were behaviorally refracted prior to testing (see Kiorpes & Boothe, 1984)]. Figure 1 shows that those animals with the greatest degree of amblyopia also have large hyperopic anisometropia ($r=0.61$, $P<0.006$). It is important to note that the more hyperopic eye is always the amblyopic eye. We know that each of the strabismic monkeys developed amblyopia within 10 weeks of the time the strabismus was imposed except for one animal, CA, in which amblyopia was first noted at 30 weeks.

The second noteworthy feature of the data is that the development of hyperopic anisometropia seems to be associated with early onset of strabismus or lens-rearing. This is particularly true for strabismus imposed within the first 4 postnatal weeks. In nine monkeys, strabismus was induced between 2 and 4 weeks; seven of those monkeys developed anisometropia. Strabismus was induced at ages older than 4 weeks in five monkeys; none of those monkeys developed anisometropia. It is difficult to know whether the relationship between hyperopic anisometropia and age of onset holds in the case of imposed monocular defocus because lens-rearing was begun between 2 and 4 weeks in all five monkeys.

Finally, hyperopic anisometropia tends not to appear immediately after strabismus or monocular defocus is imposed, but increases with age. In Fig. 2, the refractive difference between the eyes is plotted against age at assessment. Prior to about 30 weeks, the interocular refractive difference is within 2 D of zero. Beyond 30 weeks hyperopic anisometropia on the order 3–6 D is prevalent. For all except two monkeys, VN and UY, refractive errors were measured within the first 20 weeks after birth. Within that group of animals only AM showed anisometropia at that time. At the last refraction, when most animals were visually adult, 10 monkeys showed anisometropia. For AM and UY, hyperopic anisometropia was present at the first measurement. Although it is not known whether or not they were anisometropic at birth, in both cases the anisometropia increased with time.

Hyperopic anisometropia in these animals was correlated with axial length of the eye as measured by ultrasound. We found the treated eye to be shorter than

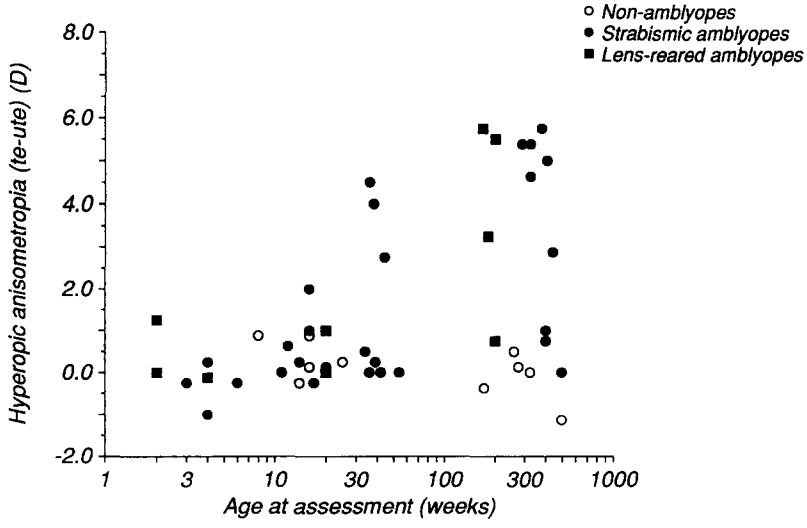

FIGURE 2. Interocular difference in refractive error (as in Fig. 1) plotted as a function of age at assessment. Data are from Table 1. Solid symbols are data from amblyopes; open symbols are data from non-amblyopes. Hyperopic anisometropia becomes more prevalent among amblyopes beyond about 30 weeks.

TABLE 2. Median axial length and vitreous chamber depth for each eye of eight strabismic or lens-reared monkeys

		Axial length		Vitreous depth	
Monkey	Aniso	UTE	TE	UTE	TE
VN	+2.875	19.1	17.7	13.3	12.2
FT	+1.0	19.7	19.4	13.7	13.6
GH	+0.75	19.8	19.2	13.8	13.5
OC	+5.75	18.5	17.9	12.9	10.8
FP	+5.5	17.9	17.0	12.2	11.3
FR	+0.75	18.9	18.8	12.9	12.8
LF	+3.25	17.1	16.5	11.6	10.8
NV	+0.13	18.8	18.9	13.3	13.1

UTE—untreated eye; TE—treated eye; Aniso—final anisometropia from Table 1.

the non-treated eye in each of the amblyopic animals tested, whereas there was no difference between the eyes of the one non-amblyope measured. Table 2 lists axial length and vitreous chamber depth for each eye of eight monkeys, three strabismic and five lens-reared. Interocular refractive difference and interocular difference in vitreous chamber depth are highly correlated ($r=0.86$; $P<0.006$) [see Fig. 3(A)]. Although this relationship could arise either from the treated eyes being shorter than normal or the fellow eyes being longer than normal, our limited data argue for the former interpretation. For example, if we consider the non-treated eye of the four non-anisometropic animals to be essentially normal eyes, we see that they had a mean vitreous chamber length of 13.4 mm, similar to the treated eye of the non-anisometropic animals (13.2 mm). In contrast, the treated eyes of the anisometropic animals had vitreous chambers 2.1 mm shorter on average.

To evaluate whether the observed differences in vitreous chamber depth could account for the observed anisometropia, we first computed the optical power of a reduced eye (a schematic eye in which the optical power is concentrated into a single thin lens) having the axial length and refractive error observed in the treated eye. We then used this optical power to compute the refractive error that the eye would have if it was longer by the amount of the difference in vitreous chamber depth between the treated and untreated eye. Our computation of optical power is based on the assumption that the ratio of posterior focal length to axial length is approx. 0.92 for primates (Troilo, Howland & Judge, 1993). Thus, power is computed as follows:

$$P=(N_v/(0.92\times AX))-RE$$

where N_v is the refractive index of the vitreous (1.336) and AX is axial length in meters. If the eyes were emmetropic, the optical power (in D) would be simply the reciprocal of the posterior focal length in vitreous humor. Because these eyes are not emmetropic, the refractive error is subtracted. From this relationship we computed the refractive error the eye would have if it differed from the untreated eye only in vitreous chamber depth. Subtracting the computed refractive error from the measured refractive error yields the amount of anisometropia that would be expected based on the difference in vitreous chamber depth. Figure 3(B) shows the relationship between the predicted anisometropia and the measured anisometropia; the correlation is quite high ($r=0.92$; $P<0.001$).

DISCUSSION

Our retrospective analysis of refractive errors in experimentally amblyopic monkeys has revealed a surprisingly high incidence of relatively severe hyperopic anisometropia. Four aspects of our results warrant discussion. First, amblyopia resulting from either induced strabismus or unilateral defocus is associated with changes in ocular length and refractive status. Second, the

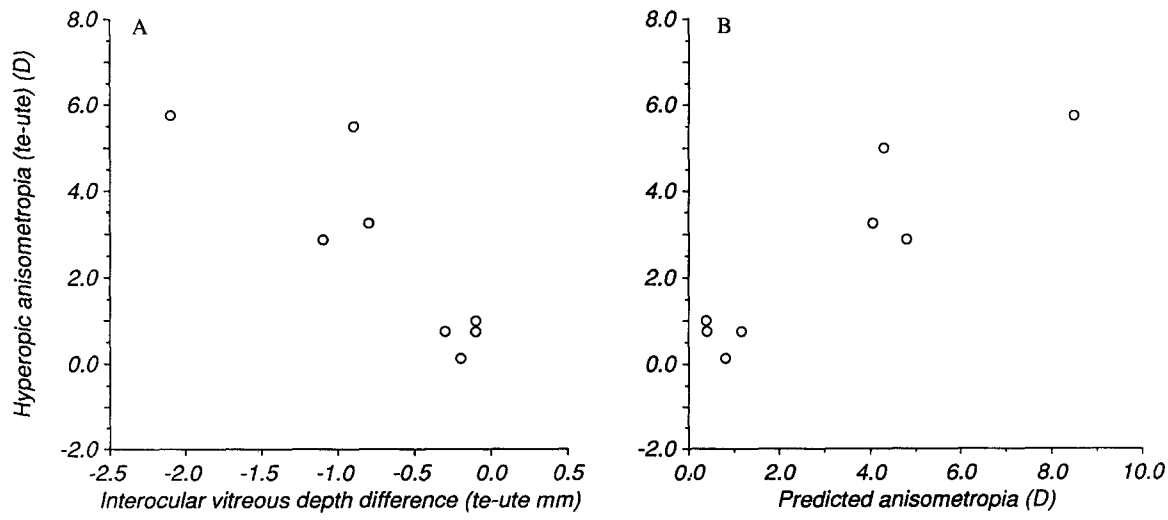

FIGURE 3. (A) The relationship between the interocular difference in refractive error and interocular difference in vitreous chamber depth (treated eye − untreated fellow eye) for the subset of animals listed in Table 2. Animals with hyperopic anisometropia have relatively shorter treated eyes. (B) The relationship between the measured amount of anisometropia (interocular refractive difference) and the expected anisometropia given the differences in vitreous chamber depth. See text for details of calculation of expected anisometropia.

direction of the refractive change was toward hyperopia in the treated eyes. Third, the change was associated with early onset of visual abnormality, yet it appeared long after the time of the visual alteration. Fourth, the change occurred beyond the major period of eye growth in macaques and appears to involve a reduced length of the vitreous chamber compared to normal eyes.

Might alterations of the central visual pathways affect eye growth?

We found that amblyopia induced either by experimental strabismus, of surgical or pharmacological origin, or by unilateral defocus with a contact lens is associated with hyperopic anisometropia. Out of 15 amblyopes studied, 10 had hyperopic anisometropia with the amblyopic eye being more hyperopic than the fellow eye in every case. There were four non-amblyopes in the sample; none showed anisometropia. Furthermore, there is a fairly strong association of the hyperopic anisometropia with the degree of amblyopia (see Fig. 1). This association seems to be related more to the neural consequences of the intervention than to its physical aspects. Although it is possible that the strabismus surgery affected the globe in some way, it is unlikely that the neurotoxin injection into the lateral rectus muscle did. Moreover, the lens-reared monkeys wore contact lenses in both eyes and had no manipulation of the eye muscles at all. On these grounds we argue that it is the amblyopia itself, rather than the defocus or oculomotor abnormality, that is responsible for the altered eye growth.

Although we cannot say for certain whether the amblyopia reported here has its origin in retina, thalamus or cortex, it is more likely to be central than retinal (Movshon, Eggers, Gizzi, Hendrickson, Kiorpes & Boothe, 1987; Movshon & Kiorpes, 1993). If so, it seems surprising that a change in the central visual pathway can alter the process of elongation of the eye and hence its refractive status. It is especially surprising because ocular elongation induced by form deprivation appears little affected by optic nerve section, at least in some species (Raviola & Wiesel, 1985; Wildsoet & Pettigrew, 1988), or by lesions of the visual cortex (Raviola & Wiesel, 1985).

Our suggestion of a role for the central visual pathways in eye growth is not without precedent. Chicks raised wearing contact lenses that impose myopic or hyperopic defocus show changes that compensate for the imposed refractive error, becoming emmetropic (with the lenses on), in part as a result of changes in eye length (Wildsoet & Wallman, 1992; see Schaeffel, 1993). The component of this compensation that results from increased ocular elongation is largely blocked in chicks raised with optic nerve section or tetrodotoxin treatment of the lens-treated eye (Wildsoet & Wallman, 1993). However, optic nerve section and tetrodotoxin treatment do not prevent the development of deprivation myopia in chicks or tree shrew (Norton, Essinger & McBrien, 1994). Therefore, the normal regulation of eye growth may rely on the central visual pathways, whereas deprivation-induced alteration of eye growth may not (see also, Schaeffel, Hagel, Bartmann & Kohler, 1994). The fact that chicks with optic nerve section, but without visual deprivation have eyes much shorter than normal and hyperopic in refractive status (Troilo, Gottlieb & Wallman, 1987) suggests a role for the central visual pathways.

Does the severity of deprivation determine the direction of refractive change?

It is surprising that our manipulations, particularly the use of defocusing contact lenses, cause changes in the hyperopic direction, whereas visual form deprivation via lid suture or occlusion cause changes in the myopic direction (see Raviola & Wiesel, 1985; Smith *et al.*, 1987; Tigges *et al.*, 1990). There may be a fundamental difference between complete form deprivation, which clearly causes myopia, and mild blurring of the visual image, which has been shown to cause hyperopia in earlier studies of monkeys (Kiorpes *et al.*, 1987; Crewther *et al.*, 1988; Smith *et al.*, 1994). In addition to lens-induced blur, contrast reduction by diffusing contact lenses causes mild hyperopia (O'Leary, Chung & Othman, 1992), and diffusion of the visual image by aphakia causes hyperopia and shorter than normal eyes in monkeys (Tigges *et al.*, 1990). All of these results suggest again that milder forms of interference with the visual image differ considerably from deprivation of form vision which causes myopia. Furthermore, they raise the possibility that reasonably sharp visual images are required for monkeys to maintain normal rates of ocular elongation.

An explanation for these different deprivation-induced ametropias was proposed by Nathan, Kiely, Crewther and Crewther (1985), who studied refractive errors resulting from a variety of visual abnormalities in children. They found both myopia and hyperopia in their population and suggested, based on the pattern of their results, that deprivation which affects primarily the fovea results in hyperopia while deprivation that affects the periphery results in myopia. Such a distinction is consistent with other studies of children (Rabin, Van Sluyters & Malach, 1981; Lepard, 1975; Nastri *et al.*, 1984) and monkeys. Studies of spatial vision in monkeys raised with blurred visual input show that the defocus-rearing paradigm principally attenuates high spatial frequencies (Kiorpes *et al.*, 1987; Kiorpes, unpublished data), thereby depriving foveal neurons most severely. Both chronic atropinization and lens-rearing, which permit pattern input over a moderate range of contrasts and spatial frequencies, result in hyperopia. Induced contrast sensitivity deficits in strabismic monkeys are comparable to those in atropine-reared and lens-reared monkeys (Kiorpes *et al.*, 1993; Smith, Harwerth & Crawford, 1985). On the other hand, lid suture imposes a dramatic reduction in spatial visual input while allowing light perception. Harwerth, Smith, Boltz, Crawford and von Noorden (1983) characterized spatial vision in monocularly deprived monkeys and found severely limited contrast sensitivity and acuity; acuities tended to be 1 c/deg at best.

Thus deprivation by lid suture seems to be both qualitatively and quantitatively different from the manipulations studied here, and the visual system

responds quite differently as a result. During lid suture deprivation, in the absence of feedback from patterned visual input, the eye grows in the direction of normal emmetropization but continues essentially unchecked, with myopia as a result. However, in the presence of patterned visual input, the system responds differently. Conceivably, the brain interprets the continuous lack of well-focused images in the amblyopic eye, regardless of the state of accommodation, as evidence of myopia and therefore reduces ocular elongation, producing hyperopia.

What might account for refractive changes occurring long after the experimental manipulation?

It is puzzling that the anisometropia in our animals developed months, possibly years, after the treatment was imposed and after amblyopia had been documented. Amblyopia was typically documented within 2–10 weeks following the onset of strabismus (Kiorpes *et al.*, 1989; Kiorpes, 1992), while anisometropia did not appear in most cases until 30 or more weeks later. This delayed development of hyperopic anisometropia was most prevalent in animals with early onset of visual abnormality and is consistent with cases of human strabismic amblyopia that have an onset in infancy. In children, the amblyopic eyes of strabismic amblyopes tend to remain hyperopic over the course of development while the fixing eyes emmetropize normally (Lepard, 1975; Nastri *et al.*, 1984). In addition, Lepard (1975) noted that there is a delay of some years between the diagnosis of strabismic amblyopia in infancy and the development of a refractive difference between the eyes.

We speculate that the ocular growth control system of primates may include processes with long time-constants that might produce such delays. In marmosets, which grow much more rapidly than the species we used, Troilo and Judge (1993) found that lid suture leads to myopia, even if the lids are unsutured before myopia develops, suggesting either that once the increased growth rate is initiated it is difficult to stop or possibly that the effect of the visual deprivation is integrated over months. A similar phenomenon has been documented in macaques by Smith *et al.* (1994). They initially found hyperopia following lens-rearing, similar to that in the present study; however, once the treatment was suspended the eyes then grew at a faster than normal rate toward emmetropia. The relatively short period of lens-rearing in the Smith *et al.* (1994) study ended within the time period of rapid eye growth (Tigges *et al.*, 1990), which may have allowed for resumed growth toward emmetropia. The relatively longer deprivation period in the present study may have prevented the normal emmetropization mechanism from being activated.

What might account for delayed changes in eye size?

In four of our 10 anisometropes, we have measurements of refraction status both at 34–38 weeks and after 4 yr of age (UY, VN, AN and AM). In two of these cases, substantial hyperopic anisometropia developed in the interim, while in the other two cases existing anisometropia became more severe between these two measurements. Four other animals with refractive measurements at approximately the same ages showed comparatively small changes over the same period (HC, GH, AO and AP). Because the anisometropia is well-correlated with interocular difference in vitreous chamber depth (Fig. 3), it suggests that a change in the relative size of the two eyes occurred in these near-adult animals. Longitudinal studies of humans show that anisometropia develops or becomes more severe during young adulthood (Laird, 1991). The macaque eye shows rapid elongation during the first 6 postnatal months followed by much slower asymptotic development for about 4 yr (Kiely *et al.*, 1987; Tigges *et al.*, 1990). Between about 36 weeks and adulthood, the eyes of rhesus monkeys typically grow approx. 2 mm (Tigges *et al.*, 1990); our emmetropic eyes are similar (proportionally) in vitreous chamber length to other primate species of comparable age (Kiely *et al.*, 1987; Troilo & Judge, 1993). In two of the animals that developed anisometropia after 34 weeks of age, our ultrasound measurements show the vitreous chambers of the amblyopic and fellow eyes to differ by 1.1 mm. These data suggest that the eyes became anisometropic by a reduction in their rate of elongation.

It is also conceivable that the vitreous chamber length actually becomes shorter. How might this be possible? One possibility is that it is not the overall size of the globe that is decreased, but that the choroid has expanded, pushing the retina forward and thereby making the eye hyperopic as occurs in chicks either with myopia imposed by positive spectacle lenses or during recovery from deprivation myopia (Wallman, Xu, Wildsoet, Krebs, Gottlieb, Marran & Nickla, 1992). However, we found on average, a 1.2 mm difference in vitreous chamber length between the treated and fellow eyes of the anisometropic animals, which is greater than the maximum choroidal expansion seen in chicks.

A second possibility is that the stability of eye length of the mature eye is not a passive result of the termination of growth, but is achieved by active coordination of ongoing changes in the components of the eye or of the rate of metabolic turnover and synthesis of the collagen and proteoglycans of the sclera. According to this view, it is plausible that the eye might require a certain quality of visual stimulation to maintain its adult length. If it fails to receive this stimulation, the eye may lengthen or shorten in adulthood. Grosvenor (1987) has reported an overall shortening of the eye in coordination with changes in refractive power of the eye in human adults. This view of the eye as being dynamically remodeled, even in adulthood, might be testable by longitudinal ultrasound measurements during the development of amblyopia.

In summary, we have presented data suggesting that the development of amblyopia in monkeys affects the process of emmetropization of the eye. This intriguing possibility has support in the human clinical literature. Almeder, Peck and Howland (1990) concluded, on the basis of a large-scale screening for anisometropia in children, that adult anisometropia may be the result rather than the

cause of amblyopia. Careful prospective studies of experimentally amblyopic primates are needed to further test this suggestion.

REFERENCES

Almeder, L. M., Peck, L. B. & Howland, H. C. (1990). Prevalence of anisometropia in volunteer laboratory and school screening populations. *Investigative Ophthalmology and Visual Science, 31*, 2448–2455.

Andison, M. E., Sivak, J. G. & Bird, D. M. (1992). The refractive development of the eye of the American kestrel (*Falco-Sparverius*)—A new avian model. *Journal of Comparative Physiology A, 170*, 565–574.

Banks, M. S. (1980). Infant refraction and accommodation. In Sokol, S. (Ed.), *Electrophysiology and psychophysics: Their use in ophthalmic diagnosis* (Vol. 20, pp. 205–232). Boston, Mass.: Little, Brown & Co.

Bielik, M., Friedman, Z., Peleg, B. & Neumann, E. (1978). Changes in refraction over a period of 3–5 years in 212 strabismic children aged one to two and a half. *Metabolic Ophthalmology, 2*, 115–117.

Crewther, S. G., Nathan, J., Kiely, P. M., Brennan, N. A. & Crewther, D. P. (1988). The effect of defocussing contact lenses on refraction in cynomolgus monkeys. *Clinical Vision Sciences, 3*, 221–228.

Grosvenor, T. (1987). Reduction in axial length with age: an emmetropizing mechanism for the adult eye? *American Journal of Optometry and Physiological Optics, 64*, 657–663.

Harwerth, R. S., Smith, E. L., Boltz, R. L., Crawford, M. L. J. & von Noorden, G. K. (1983). Behavioral studies on the effect of abnormal early visual experience in monkeys: Spatial modulation sensitivity. *Vision Research, 23*, 1501–1510.

Hirsch, M. J. & Weymouth, F. W. (1991). Prevalence of refractive anomalies. In Grosvenor, T. & Flom, M. C. (Eds), *Refractive anomalies: Research and clinical applications* (pp. 15–38). Boston, Mass.: Butterworth-Heinemann.

Hodos, W. (1990). Avian models of experimental myopia: Environmental factors in the regulation of eye growth. In Bock, G. & Widows, K. (Eds), *Myopia and the control of eye growth (Ciba Foundation Symposium 155)* (pp. 149–159). Chichester: Wiley.

Irving, E. L., Callender, G. & Sivak, J. G. (1991). Inducing myopia, hyperopia, and astigmatism in chicks. *Optometry and Vision Science, 68*, 364–368.

Kiely, P. M., Crewther, S. G., Nathan, J., Brennan, N. A., Efron, N. & Madigan, M. (1987). A comparison of ocular development of the cynomolgus monkey and man. *Clinical Vision Sciences, 1*, 269–280.

Kiorpes, L. (1992). Effect of strabismus on the development of vernier acuity and grating acuity in monkeys. *Visual Neuroscience, 9*, 253–259.

Kiorpes, L. & Boothe, R. G. (1984). Accommodative range in amblyopic monkeys (*Macaca nemestrina*). *Vision Research, 24*, 1829–1834.

Kiorpes, L., Carlson, M. R. & Alfi, D. (1989). Development of visual acuity in experimentally strabismic monkeys. *Clinical Vision Sciences, 4*, 95–106.

Kiorpes, L., Kiper, D. C. & Movshon, J. A. (1993). Contrast sensitivity and vernier acuity in amblyopic monkeys. *Vision Research, 33*, 2301–2311.

Kiorpes, L., Boothe, R. G., Hendrickson, A. E., Movshon, J. A., Eggers, H. M. & Gizzi, M. S. (1987). Effects of early unilateral blur on the macaque's visual system. I. Behavioral observations. *Journal of Neuroscience, 7*, 1318–1326.

Laird, I. K. (1991). Anisometropia. In Grosvenor, T. & Flom, C. (Eds), *Refractive anomalies: Research and clinical applications* (pp. 174–198). Boston, Mass.: Butterworth-Heinemann.

Lepard, C. W. (1975). Comparative changes in the error of refraction between fixing and amblyopic eyes during growth and development. *American Journal of Ophthalmology, 80*, 485–490.

Marsh-Tootle, W. L. & Norton, T. T. (1989). Refractive and structural measures of lid-sutured myopia in tree shrew. *Investigative Ophthalmology and Visual Science, 30*, 2245–2257.

McBrien, N. A. & Norton, T. T. (1992). The development of experimental myopia and ocular component dimensions in monocularly lid-sutured tree shrews (*Tupia belangeri*). *Vision Research, 32*, 843–852.

Movshon, J. A. & Kiorpes, L. (1993). Biological limits on visual development in primates. In Simons, K. (Ed.), *Early visual development: Normal and abnormal*. New York: Oxford University Press.

Movshon, J. A., Eggers, H. M., Gizzi, M. S., Hendrickson, A. E., Kiorpes, L. & Boothe, R. G. (1987). Effects of early unilateral blur on the macaque's visual system. III. Physiological observations. *Journal of Neuroscience, 7*, 1340–1351.

Nastri, G., Perugini, G. C., Svastano, S., Polzella, A. & Sbordone, G. (1984). The evolution of refraction in the fixing and the amblyopic eye. *Documenta Ophthalmologica, 56*, 265–274.

Nathan, J., Kiely, P. M., Crewther, S. G. & Crewther, D. P. (1985). Disease-associated visual image degradation and spherical refractive errors in children. *American Journal of Optometry and Physiological Optics, 62*, 680–688.

Norton, T. (1990). Experimental myopia in tree shrews. In Boch, G. & Widdows, K. (Eds), *Myopia and the control of eye growth (Ciba Foundation Symposium 155)* (pp. 178–199). Chichester: Wiley.

O'Leary, D. J., Chung, K. M. & Othman, S. (1992). Contrast reduction without myopia induction in monkey. *Investigative Ophthalmology and Visual Science (Suppl.), 33*, 712.

Rabin, J., Van Sluyters, R. C. & Malach, R. (1981). Emmetropization: A vision dependent phenomenon. *Investigative Ophthalmology and Visual Science, 20*, 561–564.

Raviola, E. & Wiesel, T. N. (1985). Animal model of myopia. *New England Journal of Medicine, 312*, 1609–1615.

Schaeffel, F. (1993). Visually guided control of refractive state: Results from animal models. In Simons, K. (Ed.), *Early visual development: Normal and abnormal*. New York: Oxford University Press.

Schaeffel, F. & Howland, H. C. (1991). Properties of the feedback loops controlling eye growth and refractive state in the chicken. *Vision Research, 31*, 717–734.

Schaeffel, F., Glasser, A. & Howland, H. C. (1988). Accomodation, refractive error, and eye growth in chickens. *Vision Research, 28*, 639–657.

Schaeffel, F., Hagel, G., Bartmann, M. & Kohler, K. (1994). 6-Hydroxy dopamine does not affect lens-induced refractive errors but suppresses deprivation myopia. *Vision Research, 34*, 143–149.

Scott, A. B., Rosenbaum, A. & Collins, C. (1973). Pharmacologic weakening of extraocular muscles. *Investigative Ophthalmology and Visual Science, 12*, 924–927.

Sherman, S. M., Norton, T. T. & Casagrande, V. A. (1977). Myopia in the lid-sutured tree shrew (*Tupia glis*). *Brain Research, 124*, 154–157.

Sivak, J. G., Barrie, D. L., Callender, M. G., Doughty, M. J., Seltner, R. L. & West, J. A. (1990). Optical causes of experimental myopia. In Bock, G. & Widdows, K. (Eds), *Myopia and the control of eye growth (Ciba Foundation Symposium 155)* (pp. 160–177). Chichester: Wiley.

Smith, E. L. III, Harwerth, R. S. & Crawford, M. L. J. (1985). Spatial contrast sensitivity deficits in monkeys produced by optically induced anisometropia. *Investigative Ophthalmology and Visual Science, 26*, 330–342.

Smith, E. L., Hung, L. & Harwerth, R. S. (1994). Effects of optically induced blur on the refractive status of young monkeys. *Vision Research, 34*, 293–301.

Smith, E. L. III, Harwerth, R. S., Crawford, M. L. J. & von Noorden, G. K. (1987). Observations of the effects of form deprivation on the refractive status of the monkey. *Investigative Ophthalmology and Visual Science, 28*, 1236–1245.

Tigges, M., Tigges, J., Fernandes, A., Eggers, H. M. & Gammon, J. A. (1990). Postnatal axial eye elongation in normal and visually deprived Rhesus monkeys. *Investigative Ophthalmology and Visual Science, 31*, 1035–1046.

Troilo, D. & Judge, S. J. (1993). Ocular development and visual deprivation myopia in the common marmoset (*Callithrix jacchus*). *Vision Research, 33*, 1311–1324.

Troilo, D. & Wallman, J. (1991). The regulation of eye growth and refractive state: An experimental study of emmetropization. *Vision Research, 31*, 1237–1250.

Troilo, D., Gottlieb, M. D. & Wallman, J. (1987). Visual deprivation causes myopia in chicks with optic nerve section. *Current Eye Research*, *6*, 993–999.

Troilo, D., Howland, H. C. & Judge, J. J. (1993). Visual optics and retinal cone topography in the common marmoset (*Callitrix jacchus*). *Vision Research*, *33*, 1301–1310.

Wallman, J. (1993). Retinal control of eye growth and refraction. *Progress in Retinal Research*, *12*, 133–153.

Wallman, J., Adams, J. I. & Trachtman, J. N. (1981). The eyes of young chickens grow toward emmetropia. *Investigative Ophthalmology and Visual Science*, *20*, 557–561.

Wallman, J., Gottlieb, M. D., Rajaram, V. & Fugate-Wentzek, L. A. (1987). Local retinal regions control local eye growth and myopia. *Science*, *237*, 73–77.

Wallman, J., Xu, J., Wildsoet, C., Krebs, W., Gottlieb, M., Marran, L. & Nickla, D. (1992). Moving the retina: A third mechanism of focusing the eye. *Investigative Ophthalmology and Visual Science (Suppl.)*, *33*, 1053.

Wiesel, T. N. & Raviola, E. (1977). Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature*, *266*, 66–68.

Wiesel, T. N. & Raviola, E. (1979). Increase in axial length of the macaque monkey eye after corneal opacification. *Investigative Ophthalmology and Visual Science*, *18*, 1232–1236.

Wildsoet, C. F. & Pettigrew, J. D. (1988). Experimental myopia and anomalous eye growth patterns unaffected by optic nerve section in chickens: Evidence for local control of eye growth. *Clinical Vision Sciences*, *3*, 99–107.

Wildsoet, C. & Wallman J. (1992). Optic nerve section affects ocular compensation for spectacle lenses. *Investigative Ophthalmology and Visual Science (Suppl.)*, *33*, 1053.

Wildsoet, C. & Wallman, J. (1993). Effect of optic nerve section and tetrodotoxin on emmetropization in the chick. *Optometry and Vision Science*, *70*, 24.

Young, F. A. (1963). The effect of restricted visual space on the refractive error of the young monkey eye. *Investigative Ophthalmology*, *2*, 571–577.

Acknowledgements—This research was supported by grants from the National Institutes of Health (EY05684, EY02727, EY02017, and RR00166). We are grateful to Drs Howard Eggers and Melvin Carlson for strabismus surgery and refractions. We would also like to acknowledge the contributions of Dr Christine F. Wildsoet for collaboration on refractions and ultrasound measurements and helpful discussions, and Tony Movshon for helpful comments.