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City University of New York, 1989

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THE VISUAL CONTROL OF EYE GROWTH IN CHICKS

by

David Troilo

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Abstract

The Visual Control of Eye Growth in Chicks

by

David Troilo

Adviser: Professor Josh Wallman

The growth of the vertebrate eye achieves a close match between the power of the optics and the length of the eye with the result that images are focused on the retina (emmetropia). The possibility that vision is required for the feedback regulation of eye growth was studied experimentally using domestic chicks *(Gallus domesticus)* as subjects. The approach was to produce either myopia (nearsightedness) or hyperopia (farsightedness) by manipulating the chick's visual experience just after hatching. After discontinuing the manipulations, the ability of the eye to correct the refractive errors was determined in intact chicks, and in chicks with a severed optic nerve (to test the role of the brain in eye growth regulation) or with lesions of the Edinger-Westphal nucleus (to test the role of ocular accommodation in eye growth regulation).

Chicks recovered quickly from induced myopia or hyperopia mainly by adjusting the growth of their vitreous chambers — growth decreased in eyes correcting for myopia and increased in eyes correcting for hyperopia. Because the hyperopic eyes were already larger than normal controls these results indicate that refractive error, rather than eye size *per se*, guides the growth of the eye toward emmetropia.

This growth compensating for induced refractive errors was found in chicks despite either optic-nerve-section or Edinger-Westphal lesion. The treatments differed in that Edinger-Westphal-lesioned chicks attained emmetropia, whereas optic-nerve-sectioned eyes did not, but instead overshot emmetropia and reversed the sign of the initial

refractive error. Together these results suggest that: (1) The eye itself can sense the sign of a refractive error and adjust growth accordingly. (2) Accommodation is not necessary for emmetropization. (3) For emmetropia to be achieved an intact optic nerve is required, suggesting that visual pathways in the brain are involved. (4) Adjustment of refractive state by the local ocular growth mechanism is probably different from that of the brain-mediated mechanism.

Other experiments presented in this dissertation describe the role of cornea and lens in accommodation in chicks, and the local nature of myopia produced by partial deprivation of the visual field.

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CHAPTER ONE

INTRODUCTION AND OVERVIEW

The complexity of visual processes often overshadows the fact that vision is limited by the optical performance of the eye. If the optics of the eye are maladjusted the initial visual signal will be impaired and contain less information. Even mild refractive errors may limit visual capabilities. In particular, optical disruptions during the critical period of visual system development can result in permanent visual deficits (e.g. Copps, 1944; Mitchell et al., 1973; Fiorentini and Maffei, 1976; Eggers and Blakemore, 1978; Boothe et al., 1985; Smith et al., 1985; Ingram et al., 1986). The development of the eye is very complex, largely because of the multiple interactions of the various ocular components. Because of this complexity many different factors can disrupt, or influence, the development of the eye.

There is little dispute that the development of the eye involves both genetic and environmental components. What remains to be determined is the nature of the heritable and experiential components and, in the case of experience-dependent growth, the manner in which the effects are exerted. This study aims to examine, using experimental manipulations, the effects of early visual experience on the developing eyes of chicks. Specifically, the emphasis is placed on determining the existence of vision-dependent feedback regulation of eye growth, and subsequently probing the neural pathways possibly involved.

This chapter reviews the literature on the refractive development of the eye. First, a brief description of the optics of the eye and the nature, and clinical significance, of refrac-

tive errors will be given. Then the evidence on causal factors in the development of refractive errors in humans and animals will be reviewed. Finally, the theories regarding normal eye growth will be discussed and related to the studies on the development of refractive errors.

Refractive Errors

The eye is under strict physical limitations if it is to perform optimally as an optical system. These limitations must be addressed by any eye growth control mechanism. The basic design of the camera-type eye (see Figure 1.1), which is common to all vertebrates, is to use an optical system — comprised of the cornea and lens — to refract light and focus it onto a light-sensitive neural layer (the retina). The ability of the whole optical system to refract, and thereby focus, light is referred to quantitatively as total optical power[1]; more powerful optical systems produce more vergence of light rays and, as a result, have shorter focal lengths than less powerful optical systems. If the optical power of an eye is mismatched with respect to the placement of the retina, a refractive error (ametropia) is produced.

To determine the refracting ability of an optical system, rays of light are traced sequentially through each of the system's components (see Appendix A). The refractive power of an eye is thus a complex function of the shapes and refractive indices[2] of the various refracting structures, as well as the distances between them. The front surface of the cornea is responsible for the major part of the eye's refracting power. The lens may be thought of as a series of lenses, one encased in the other, each with its own refracting abilities which together produce the lens' overall optical power (Blaker, 1980). In short, the total optical

---

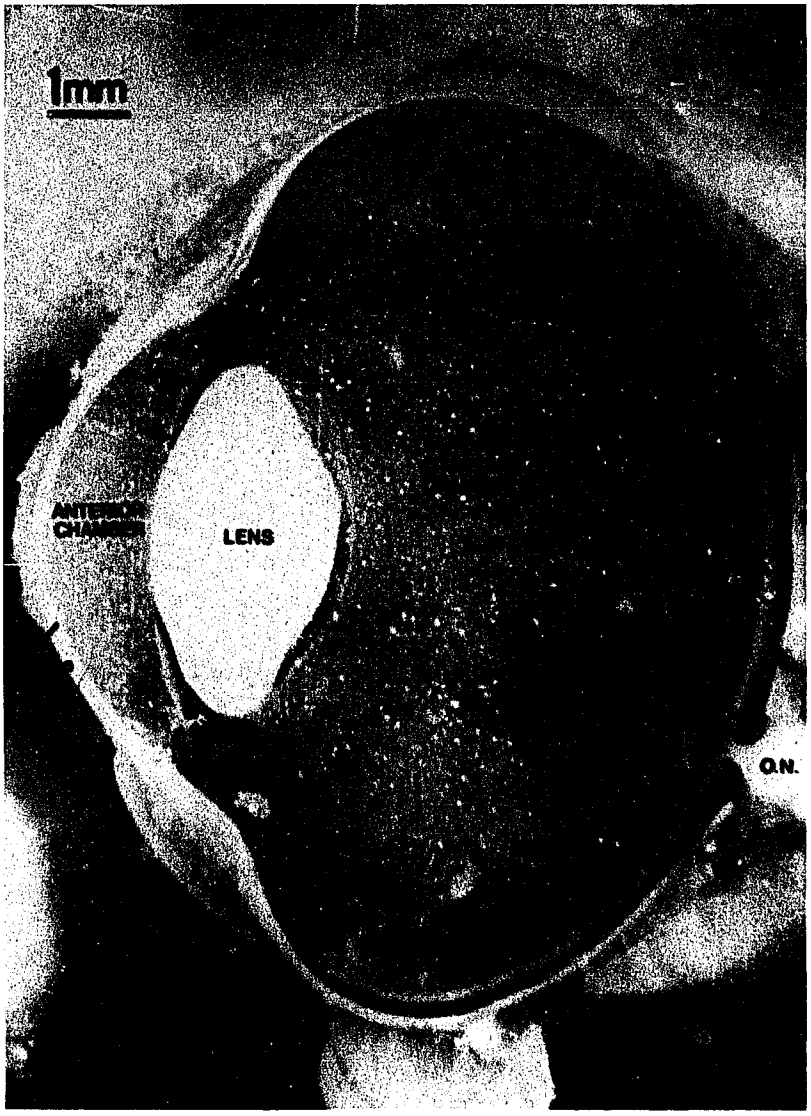
[1]The unit of measure for the power of optical systems is the diopter (D), which is the reciprocal of the focal length measured in meters.

[2]The refractive index indicates the speed of light in a given medium relative to the speed of light in air. Differences in the refractive indices of the different ocular tissues and humors contribute to the eye's total optical power.

power of the whole eye depends on the optical powers of the cornea and lens, the distance between them, and the refractive indices of the aqueous humor in the anterior chamber and the vitreous humor in the vitreous chamber.

Although it has no direct effect on the optics of the eye, the depth of the vitreous chamber is a major factor in the development of changes in refractive state since it determines where the retina lies relative to the eye's focal length. When the vitreous chamber depth properly corresponds to the resting optical power of the eye there is no refractive error and the eye is said to be emmetropic. Ametropia refers to the presence of refractive error and may be one of two basic types. If the image of a distant object is focused in front of the retina because the optics of the eye are too powerful or the eye is too long, the eye is said to be myopic (nearsighted). If the image is focused behind the retina, because the eye is optically too weak or structurally too short, hyperopia (farsightedness) results. Throughout this dissertation, the refractive error of an eye will be discussed in terms of the sign and dioptric power of the optical correction necessary to focus parallel light onto the retina (see Appendix B). Because myopic eyes require for correction negative lenses, which diverge light rays, they are considered to have negative refractive errors, conversely hyperopic eyes require a positive lens correction, which increases the vergence of light rays, and are considered to have positive refractive errors.

Figure 1.1 (following page)
A dorsal view of a frozen horizontally-hemisected chick eye (top is nasal, bottom is temporal). Photographs like these can be used for optical ray-tracing (see Appendix A) and assessments of lens changes during nicotine-induced accommodation (see Chapter 6).


1mm
LENS
O.N.

Numerous causes for ametropia have been identified over the years and have prompted many refractive error classification schemes (see below and Borish, 1970). Sorsby et al. (1961a) proposed a theoretical classification scheme unrelated to the plethora of possible causes of refractive error. They suggested two categories of ametropia; correlation (+6 D to -4 D) or component (more than -4 D of myopia or +6 D of hyperopia). "Correlation ametropia" is assigned to eyes with optical components which fall within a "normal range" and assumed to result from the normal variation in the ocular components or, in other words, from poor correlations between otherwise normal ocular components. Although there remains a high correlation of the components within these eyes, Sorsby et al. suggest that the different degrees of these refractive errors represent differing degrees in correlation, particularly that between corneal power and axial length. In component ammetropia, Sorsby et al. suggest that a particular ocular component has a value outside of the range normally seen for emmetropic eyes and is responsible for the refractive error. The severity of the error is directly proportional to the abnormality of the component, which is usually axial length (Sorsby et al, 1957). Carroll (1982) refines the notion of correlation and component ametropia by suggesting that it is more meaningful to classify eyes on the basis of axial length, since change in axial length is an excellent predictor of refractive error. If the average refractive error is compared to various axial lengths, it is easy to see that the ocular components are able to compensate for a narrow but variable range of axial lengths to produce emmetropic eyes. The variation of refractive error in this range of axial length may be the result of poor correlation between optical components (correlation ametropia). For the extreme axial lengths (outside of the range where emmetropia is observed), axial component ametropia is observed because the other components of the eyes are simply unable to compensate.

Based on statistical analysis of large samples of ocular morphology and refractive state data, van Alphen (1961) argues that the notion of correlation ametropia is a fallacy because high correlations between the various ocular components are observed no matter what the

refractive error. In conclusion, the question of whether or not different degrees of refractive errors fall into discrete statistically-defined categories is probably more typology than biology. Clinically, however, different degrees of refractive errors are relevant to the proper treatment and prognosis.

Clinical significance

The significance of refractive errors can range from a mere nuisance to amblyopia[1] or even blindness (Copps, 1944; Borish, 1970; Dunphy, 1970; Curtin 1985).

Largely because it has a tendency to progress in severity, myopia is considered to be cause for concern. Myopia has been estimated to occur in 25% of the eyes tested in the United States (Sperduto et al., 1983) or more (Curtin, 1985), and in extreme cases is a leading cause of blindness (Curtin, 1985). Developmental myopia (also called school myopia) is the most common form and is moderately progressive in nature, developing in many individuals during the school years and worsening at a slow rate until early adulthood when the refractive error appears to level-off for unknown reasons. True progressive, or pathological, myopia appears to be a congenital condition, resulting primarily from continuous axial elongation of the eye (Sorsby, 1972a). Pathological myopia does not slow down and level-off with adulthood but rather continues into maturity unabated. As a result, one outcome of untreated severe pathological myopia may be retinal detachment and ultimately blindness (Curtin, 1985).

While low levels of hyperopia (<+1 D) are common (Sorsby et al, 1957) and considered to be normal, higher levels are known to produce severe eye strain (asthenopia) because of the greater amounts of accommodation[2] necessary for a given task. In some

---

[1]Amblyopia is a complex clinical syndrome involving the visual pathways of the central nervous system. It is generally defined by a loss of acuity which cannot be corrected by optical means.

[2]Accommodation refers to increasing the eye's optical power so that the diverging light reflected from near objects can be brought into focus. In an hyperopic eye more accommodation is necessary because the posterior focal point lies behind the retina.

high hyperopes vision may be so poor that amblyopia is a possibility (Copps, 1944; Borish, 1970). The etiology of hyperopia has not been studied as extensively as that of myopia, probably because it does not affect distance vision and it typically does not lead to associated problems as severe as those linked to myopia. Nevertheless, the incidence of hyperopia warrants attention, having been shown to exist at levels greater than +2 D in 13.6% of 1,033 17-27 year-old men tested (Sorsby, 1972a). Furthermore, Copps (1944) reports that severe amblyopia often occurs in anisometropic[1] patients with a greater than 2 D refractive error difference between the eyes, especially when the more ametropic eye is hyperopic. On the other hand, unlike myopia, hyperopia is almost never progressive in nature. During the growing years hyperopia either remains static or, as in most cases, diminishes. However, the adult hyperope can expect to suffer from an increase in functional hyperopia with the onset of presbyopia[2] as the patient losses the ability to accommodate and thereby compensate for the hyperopic error.

Genetics

There is little controversy that the development of refractive state has a genetic component. The best evidence for a genetic component in the development of some categories of refractive errors comes from studies of the development of refraction in twins, both monozygotic and dizygotic. Sorsby et al. (1962) examined 40 dizygotic and 78 monozygotic twins, as well as 48 unrelated pairs of subjects used as controls. The controls were matched with the twins for age, sex, and refraction. Using the refractive error differences between paired individuals, Sorsby et al. found that refractive errors showed a significantly higher concordance in monozygotic twins than in dizygotic twins or controls, although statistically significant discordance among controls was not found.

---

[1]Anisometropia is the clinical term indicating a difference in the refractive states of the two eyes.

[2]Presbyopia refers to the gradual loss of accommodation which occurs with age.

The variation in the refractions of twins cannot be explained completely in terms of genetic control however. Working with the data from Sorsby et al. (1962), Goldschmidt (1968) found that the variation of refraction in dizygotic twins is significantly less for hyperopia than myopia. Furthermore, in monozygotic twins, intra-pair variance is higher for myopia than hyperopia, and higher in myopia over 6 D than in myopia under 6 D, suggesting that the environment has a larger role in myopia, particularly high myopia. Based on similar analyses of the ocular components of the same subjects, Goldschmidt concludes that axial length is the element responsible for the differences in variation and hence is more susceptible to environmental influences than the other ocular components.

Because there are so many different structural considerations in the refractive development of the eye, the inheritance of refraction is likely to be complex, and certainly involves polygenic mechanisms. To begin to understand the mode of inheritance of refraction it is necessary to perform genealogical investigations. Over the years, a large number of such studies, concerned primarily with the inheritance of myopia, have been made (see Curtin, 1985). The consistent result has been to show that a familial tendency for myopia exits. The mode of inheritance, however, remains unclear since different studies found different patterns of inheritance. Curtin (1970) points out that this is not surprising since myopia has been associated with a number of different genetic diseases.

Because the major emphasis of this study is on the mechanisms of visually-mediated changes in eye growth, a full review of the many other reports concerning the genetic component in refraction, and its mode of inheritance, will not be made here (for more extensive reviews see: Goldschmidt, 1968; Borish, 1970; Curtin, 1985).

Environmental influences

As has been carefully pointed out for questions concerning the development of animal behavior (Lehrman, 1970), neither environmental nor genetic influences can be ignored for a complete understanding of any developmental process. Unfortunately, one of the last bastions for this nature-nurture conflict has been in the question of the control of eye

growth, more specifically the development of myopia. This is most likely a result of a backlash against the large number of baseless theories presented over the years concerning exclusively environmental influences on the refractive state of the eye (see: Duke-Elder, 1949; Sorsby, 1972a; Curtin 1985). That a nature-nurture argument over ocular development ever existed has served only to delay any real understanding of the problem of eye growth.

In recent years, besides the indirect evidence from Sorsby et al. (1962) and Goldschmidt (1968), environmental influences on the development of refractive state, particularly the development of high levels of myopia, have been shown to exist. The following is a brief survey of the literature examining the role of the environment in ocular development. The main objective of this section is to clearly show the importance of the environment in the development of the eye and its refractive state by summarizing the results reported in numerous studies. Where appropriate, controversial issues will be pointed out, although a discussion of the speculations and theoretical issues concerning the control of eye growth will be deferred to the section on emmetropization.

Environmental factors may operate on the eye growth process at any point during either prenatal or postnatal development. In general, environmental influences may be categorized as those resulting from disease or through altered visual experience. Myopia may be associated with prematurity (Sorsby, 1972b) and a variety of maternal diseases (Gardiner and James, 1960; Wolff, 1973). Various postnatally acquired systematic diseases such as syphilis, tuberculosis, and hyperthyroidism have also been associated with the onset of high myopia (Goldschmidt, 1968). In terms of understanding the normal mechanism of eye growth, however, the impact of major diseases on the growth of the eye, particularly during prenatal development, is probably of limited value, because of the gross systemic alterations associated with such diseases.

Perhaps a better understanding of environmental influences on normal eye growth can be gained by studying the pathogenesis of refractive errors produced by conditions which

alter visual experience since they directly influence the visual system and do not typically result from a system wide pathology. The important finding here is that the common factor in the development of refractive errors produced by altered visual experience is the previous loss of some degree of form vision. Loss of form vision, and a general alteration of visual experience, can be produced by a plethora of conditions. In children, deprivation of form vision by cataract (Rabin et al., 1981), lens opacity (Johnson et al., 1982), hemangioma (Robb, 1977), and ptosis (O'Leary and Millodot, 1979; Rabin et al., 1981) have all been linked to the development of myopia. Such visual deprivation myopia in humans has been suggested to be most likely the result of axial elongation (Hoyt et al., 1981). A more recent report (von Noorden and Lewis, 1987) points out that while some conditions which deprive the eye of vision may indeed deregulate eye growth by altering axial length, the direction of the axial length change is not consistent. Furthermore, Anderson and Baumgartner (1980) report that in cases of ptosis, where the amount of visual field deprivation varies over a large range, there are no consistent effects on refractive state.

A variety of ocular diseases which produce low vision[1] have also been shown to produce ametropia (Nathan et al., 1985), although the severity of the low vision among the subjects was not reported. They compared 496 eyes of 256 children attending a low vision clinic and compared them to the eyes of 1023 children with normal vision. The range of refractive errors in the low vision group was significantly larger than in normal controls. The low vision children were grouped into 14 categories corresponding to their primary clinical condition. Although the mean refractive errors were all less than 6 D, there was significantly more myopia found in children with aniridia, cerebral palsy, coloboma, glaucoma, nystagmus, optic atrophy, optic nerve hypoplasia, retinitis pigmentosa, retinopathies, retinopathy of prematurity, and toxoplasmosis. Besides reducing form vision, these dis-

[1]Low vision is defined in terms of any anomaly which reduces acuity to less than 20/200 or visual field subtense to under 20° (Borish, 1970).

eases have in common a peripheral, or a peripheral plus central, visual field impairment. Relative to normal controls, significant hyperopia was associated with albinism, maculopathies, and rod monochromatism; conditions in which primarily foveal vision is impaired.

The same subjects were also grouped according to their age when the visual defect was first reported. Nathan's group found that the earlier in childhood the visual image is degraded, the more likely ametropia is to develop. In eyes that were not congenitally abnormal but developed the anomaly before the age of 3, there was a tendency for the development of hyperopia. As the age of disease onset increased, the reported deviation from emmetropia declined as did the variance of the refractive errors. From these data, it was estimated that the plastic period for eye growth in humans ends between 8 and 9 years of age.

Thus far, the reports linking environment and eye growth have been concerned with pathological states. Even with those pathologies which are not systemic and appear to influence eye growth through altered visual experience, it is nearly impossible to disentangle the effects of the pathology from the effects of the visual experience. As a result, it is important to consider the notion that, in otherwise normal individuals, the predominant type of visual task used from day to day may constitute an environmental influence on eye growth.

Near-work myopia

One of the most provocative suggestions from the literature on human subjects is the possible relationship of near-work and the development of myopia. The level of education (Donders, 1952; Dunphy et al. 1968; Young, 1977; Richler and Bear, 1980a; but see Hirsch, 1951; Nadell et al., 1957), or occupations involving large amounts of near-work (Duke-Elder, 1930; Goldschmidt, 1968), have been linked to the incidence of myopia. It is important to point out, however, that a causal relationship is difficult to establish; for instance, myopes may simply be more inclined to perform tasks involving close vision than

hyperopes. Nevertheless, evidence for near-work supposedly causing changes in refraction is supplied by Young et al. (1969), and Richler and Bear (1980b), who found, independently, significant increases in the incidence of myopia in Inuit (Eskimo) populations after schooling and other components of modern civilization were introduced.

Even if a causal relationship between near-work and myopia was definitively established, the manner by which the myopia is produced remains unclear. Numerous hypotheses concerning the effect of near-work on refraction have been suggested over the years, but relatively few are based on any clear-cut evidence (for reviews see: Morgan, 1967; Borish, 1970; McBrien and Barnes, 1984; Curtin, 1985). The most common suggestions have centered on the mechanical forces, primarily increased intraocular pressure and scleral stress, exerted on the eye during accommodation and convergence, the principal oculomotor activities associated with near-vision. What follows is a brief overview of highly speculative reports. A more detailed summary of studies directly concerned with accommodation and the control of eye growth and the development of ametropia, is presented in the section on accommodation and emmetropization.

While the actual role of accommodation and convergence in the development of refraction has not been established, there is no disputing that both accommodation and convergence have mechanical effects on the eye. These influences may be loosely placed into two distinct groups: (1) those which exert a direct increase in tension along the various tissues comprising the ocular tunics (choroid and sclera), and (2) those which indirectly produce stress in the ocular tunics by increasing the intraocular pressure.

Adel (1966), after studying the mechanics of the ciliary muscle (the intraocular muscle which produces accommodative changes), proposed that accommodation could affect eye growth and possibly produce myopia. Because the longitudinal bundle of the ciliary muscle is continuous with the choroid, the highly vascularized tissue just beneath the sclera, Adel believed that excessive accommodation could stress the choroid, affecting its growth and elongating the back of the eye. van Alphen (1961) showed not only an increase in choroidal

tension during accommodation, but also that it was sufficient to reduce pressure in the suprachoroidal space just beneath the sclera, effectively shielding the sclera from any intraocular pressure increase which might be associated with accommodation.

After determining the tensile strength characteristics of sclera, Greene (1980) calculated the scleral stress effects of accommodation, convergence, intraocular pressure in the vitreous chamber, and the actions of extraocular muscles. He concluded that convergence, and more generally extraocular muscle tension, increase intraocular pressure more than accommodation. In particular, the superior and inferior oblique muscles are suspected of involvement in axial length increase and consequently myopia, since their insertion points are near the optic nerve entrance at the posterior pole of the eye. Based on the *in vitro* testing of the tensile strength of sclera (Greene and McMahon, 1979), Greene calculated that the combination of intraocular pressure associated with convergence (Collins et al., 1967) and the localized tensile stresses that the oblique muscles are capable of exerting, may be sufficient to stretch the sclera out of shape permanently, thereby playing an important role in the development of pathological myopia.

Intraocular pressure probably has a major role in ocular development. Intraocular pressure and vitreous humor formation appear to be important in the embryological development of the vertebrate eye (Coulombre, 1956, 1957; Coulombre and Coulombre, 1957, 1959). In contrast, however, the suggestion that near-vision produces intraocular pressure fluctuations which have an influence on postnatal growth is much less convincing. While there is no question that intraocular pressure produces stress within the ocular tunics (Friedman, 1966; Maurice and Mushin, 1966; Mohan et al., 1977; Greene and McMahon, 1979; van Alphen, 1986), the nature of intraocular pressure changes during near-work are not at all clear. During voluntary accommodation in humans, applanation tonometry shows that the intraocular pressure of the anterior chamber drops 4-5 mmHg (Armaly and Rubin, 1961; Armaly and Jepson, 1962). However, Jampel and Mindel (1967) measured, by manometry, intraocular pressure of cannulated anterior chamber in monkeys and did not

find intraocular pressure changes during electrically stimulated accommodation via the parasympathetic ciliary nerves. In an anecdotal report of preliminary results, Young (1975) states that manometry in monkeys shows a decrease in intraocular pressure of the anterior chamber during accommodation, but there may be an increase in vitreous chamber pressure, measured with an implanted pressure transducer, which is proportional to the nearness of a fixation target.

Despite the lack of compelling experimental evidence, the assumption of an increase in intraocular pressure during accommodation forms the basis of an elaborate hypothesis in which accommodation produces a temporary barrier between the anterior and posterior segments of the eye resulting in an increase in the pressure of the vitreous chamber, relative to the anterior chamber. This has been suggested to produce axial elongation and myopia (Coleman, 1970; Young, 1977; Bell, 1980). The only experimental evidence for the existence of such a phenomenon, besides his anecdotal report (Young, 1975), is Young's account that the transport rate to the anterior chamber of flourescein injected into the vitreous humor of two macaques slows during accommodation (Young, 1981).

A completely different view of the influence of near-work on the development of myopia is that near-work produces a kind of visual deprivation. Such a view was first espoused by Linder (1949) who suggested that constantly moving retinal images, such as those produced during reading or observing passing textiles, constitute a degraded visual experience and are responsible for occupational as well as school myopia. No experimental evidence supporting this hypothesis is available. But, more recently, Wallman et al. (1987) presented the hypothesis that since reading uses only a small fraction of the retina (the fovea), the rest of the retina is actually being deprived by receiving either defocused images, or only the spatial frequencies found on pages of writing which are poorly suited for the peripheral retina. As support, Wallman et al. present evidence for local retinal control of eye growth in chicks which had different visual stimuli on distinct retinal

regions. This and other studies of induced refractive errors in animals are the topic of the following section.

Experimentally Induced Refractive Errors

The most decisive evidence that visual experience plays an integral role in the development of the eye comes from animal experimentation in which early visual experience is manipulated. This approach attempts to create a model of eye growth which is applicable to humans and which may assist in the treatment and prevention of refractive error. Either myopia or hyperopia can be produced in a number of different species by a variety of treatments (for reviews of the early literature see: Goss and Criswell, 1981; Criswell and Goss, 1983; Yinon, 1984). The following discussion is organized on the different types of visual experience manipulations which have been used to produce refractive error.

Changes in lighting conditions

For the most part, studies concerning the effects on ocular development of changes in lighting conditions have been performed in birds, particularly chickens. Numerous investigators have studied the effects of continuous illumination on avian eye growth (Jensen and Matson, 1957; Lauber et al., 1961; Lauber and McGinnis, 1966; Axmith and Morin, 1975; Oishi et al., 1987), continuous darkness (Chiu et al., 1975; Yinon and Koslowe, 1986; Gottlieb et al. 1987), variations in light/dark cycles (Osol et al., 1986), and differently colored lights and different intensities (Harrison and McGinnis, 1967; Bercovitz et al., 1972; Chiu et al., 1975; Oishi et al., 1987). The effects on eye growth of altering the daily light cycle have been shown clearly to be greatest under conditions of complete light or complete darkness (Osol et al., 1986). However even when the daily light cycle is normal (12 to 14 hours of light per day) low intensity light, particularly blue, has been shown to produce significant ocular enlargement (Harrison and McGinnis, 1967; Bercovitz et al., 1972) although not as great as seen in conditions of complete light or dark (Chiu et al., 1975).

In general these studies report a tendency for the eyes of chicks in altered light conditions to grow abnormally large; increases were observed in the axial length, equatorial diameter, and overall weight. Reduced corneal curvature, vitreous chamber depth, and lens thickness have also been reported (Lauber et al., 1970; Yinon and Koslowe, 1986; Gottlieb et al., 1987; Lauber and Oishi, 1987), but the anterior segment changes are more pronounced in chicks reared under continuous light than in chicks reared in dim light although both conditions produced abnormally enlarged eyes (Oishi et al., 1987). Retinal thinning has also been reported for birds raised under continuous light conditions (Lauber et al., 1961; Lauber and McGinnis, 1966). Where refractive errors were determined, either an increase in astigmatism with a large range of refractive errors (Lauber et al., 1970), or an increase in the range of refractive error with a significant tendency toward hyperopia (Yinon and Koslowe, 1986; Gottlieb et al., 1987) was observed. Based on the available morphological data, the hyperopia in these eyes must be the result of a loss in optical power attributable primarily to the flattening of the cornea since the axial lengths were typically longer than in control eyes.

Continuous-light-rearing has also been shown to produce an increase in intraocular pressure (for a more detailed review of this literature see Lauber, 1987). As a result of the observation that this intraocular pressure increase is associated with a decrease in anterior chamber depth and iridio-corneal angle (Smith et al., 1969), the effects of continuous light on intraocular pressure in chicks came to be known as avian angle-closure glaucoma. Some investigations have shown that aqueous outflow is reduced, but not completely responsible, for the increased pressure and ocular enlargement (Frankelson et al., 1969; Axmith and Morin, 1975). The time course of the various ocular changes associated with continuous-light-rearing was explored in order to better understand what factors might be responsible. Lauber et al. (1970) found that in 2-week-old chicks reared under continuous illumination, before an intraocular pressure increases were evident, there were significant eye weight increases, refractive state changes, and an initial increase in aqueous outflow. Except for an

initially lower than normal, but highly variable, aqueous outflow with time these results were later largely confirmed and shown to occur in chicks in less than 1 week (Kinnear et al., 1974; Lauber and Kivett, 1981). Together these results suggest that although aqueous flow imbalances may be involved in the development of continuous light avian glaucoma, increased intraocular pressure is not the primary lesion responsible for the onset of increased eye size in chicks raised in continuous light.

The effects of continuous darkness on the eyes of mammals appear to be much less pronounced than those seen in birds. In kittens reared under conditions of complete darkness with one eye lid-sutured (Yinon and Koslowe, 1984), significant hyperopia and less corneal curvature was produced relative to normally reared controls but, unlike birds, axial length was not longer than controls. The hyperopia was greater in dark-reared kittens with monocular lid-suture (+2.60 D) than in the open eyes (+1.50 D), probably the result of the flatter corneas in lid-sutured eyes relative to those in the contralateral open eyes. Unaccountably, kittens reared in complete darkness without lid-suture did not differ from light-reared controls. Regal et al. (1978) found hyperopia (+2.5 D to +5.5 D), and reduced acuity and visual responsiveness, in pigtail macaques *(Macaca nemestrina)* raised in complete darkness for 3-6 months. Similarly, Raviola and Wiesel (1978) found +2 D of hyperopia in both eyes of 2 monocularly lid-sutured rhesus macaques *(Macaca mulatta)* reared in complete darkness for either 10 or 12 months.

In summary, it seems that if lighting is disrupted drastically in any one of a variety of ways, the general response of the eye, at least in birds, is to enlarge. Further, this enlargement does not appear to be directly the result of increased intraocular pressure, although significant increases in intraocular pressure are associated with continuous light. The hyperopia, which typically results from changes in light cycle, is probably the result of weaker than normal optics resulting from a decrease in corneal curvature, since only increased axial length was observed. However, the mechanisms behind these ocular changes induced by altered light cycles are not understood.

Because both continuous light or continuous dark produce similar morphological results, the role of circadian rhythms in the growth of the eye must be considered in future research. Indirect evidence exists that perhaps there is a connection. Reiner et al. (1983) identified an efferent pathway by which central nervous system areas related to the control of circadian rhythms could influence the eye. They presented neuroanatomical evidence that the suprachiasmatic nucleus, which is known to be involved in circadian rhythm control (Moore, 1983), is part of a neural pathway which receives retinal afference and innervates the choroidal vasculature via the Edinger-Westphal nucleus. Another possible pathway involves the cornea, Powell et al. (1980) found a disturbance in the pattern of mitotic activity in the corneas of mice in which the suprachiasmatic nucleus was lesioned. Oishi et al. (1987) also report reduced corneal epithelial cell division in continuous-light-reared chicks.

To be sure, the effects of disrupting lighting conditions may or may not have a direct connection to the normal eye growth control mechanism. Evidence that it does is supplied by the fact that the eye's response to grow larger than normal is also found if the retinal image is deprived of form by a variety of techniques (see below). On the one hand, this fact argues, at least partially, against the conclusions of Lauber et al. (1965) and Chiu et al. (1975) who, finding eye enlargement in both eyes of monocularly occluded birds, argued that this was evidence of systemic, as opposed to direct ocular effects. On the other hand, recent evidence suggests that lid-suture and continuous light- or dark-rearing may not be necessarily the same eye-enlarging phenomenon. For instance, the eye enlarging effects of lid-suture and dark-rearing have been shown to differ in that the anterior chamber and corneal diameter enlarges significantly in lid-sutured eyes but not dark-reared eyes (Osol et al., 1986). Further, the eyes of birds raised in continuous light with lid-suture are larger than without lid-suture (Lauber and Oishi, 1987) suggesting that the two treatments may be additive.

Visual field restriction

With the near-work hypothesis of myopia clearly a motivating force, a number of researchers attempted to induce myopia by restricting vision to near points *(monkeys:* Young, 1961a, 1961b, 1963; *cats:* Rose et al., 1974; Belkin et al., 1977; *chickens:* Adel 1964). All found a positive relationship between near viewing conditions and cycloplegic[1] refractive changes toward myopia.

Compared to control monkeys, Young (1961a) found that adult pigtail monkeys *(Macaca nemestrina)* became slightly, but significantly, myopic (-0.70 D) if they were restrained for 6 months in chairs which restricted their vision to less than 20 inches. Continued treatment for 6 months more did not produce an increase in myopia. Young (1961b) also showed that the induced myopia was constant even after the monkeys were returned to normal living conditions. Age appears to be important since, after an initially slower onset, young growing monkeys were found to be slightly more susceptible (≈1 D) to the treatment than adult fully-grown subjects (Young, 1963).

More myopia is found in caged cats compared to feral cats. Rose et al. (1974) showed that 85% of street cats were slightly hyperopic (+1.14 D) while 68.2% of cats raised for 8-12 months in cages were on average myopic (-0.62 D). This study was later repeated by Belkin et al. (1977) who report the same conclusions. However, in both studies, the difference in refractive state could not be attributed to axial length increases; the anterior-posterior diameters for the experimental and control groups were not significantly different, suggesting that changes in the lens might have been responsible for the refractive changes, although no data supporting this possibility were presented.

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[1]Cycloplegia refers to an induced paralysis of the ciliary muscles. This allows a more accurate determination of refractive state by eliminating accommodative changes which could mask the actual refraction of the eye. Unless specifically stated, all of the studies reviewed conducted refractive error determination under cycloplegic conditions.

Adel (1964) attempted to test the assumed link of excessive accommodation to the myopia produced by restricting vision to proximal surroundings. Adel placed 5-week-old chickens *(Gallus domesticus)* under conditions where vision was restricted to less than 20 inches. Retinoscopic refractions were taken before the treatment began, and then after 26 and 56 days of treatment. In one eye, accommodation was assumed to be eliminated by a 1 cc injection of an 80% alcohol solution into the area around the ciliary ganglion. In all 8 birds tested, the non-accommodating eye's refractive state did not change after 26 days, and only 2 became less hyperopic after 56 days. In the control eye, 7 of 8 eyes became less hyperopic. These results should be viewed with caution, however, since the refractive changes were under 1 D and no statistical tests were made. Also, the effects of the injection cannot be assumed to act solely on accommodation.

Besides the assumed increase in near-vision-related behaviors, an alternate explanation for the observations that restricting visual space produces myopic refractive errors is that the restriction acts as a kind of visual deprivation. The following section discusses the experimental manipulations which deprived the eye of normal vision and, thereby, produced refractive errors.

Degradation of the retinal image

In animals as diverse as monkeys, tree shrews, cats, and chickens, when the retina is deprived of form vision, but not of light, axial elongation myopia is usually produced. The methods used include lid-suture, fitting translucent occluders over the eye to visually deprive either the whole retina or some part of it, or using defocusing lenses to blur the retinal image.

The most commonly used means of experimental visual form deprivation has been lid-suturing *(monkeys:* Wiesel and Raviola, 1977, von Noorden and Crawford, 1978; Thorn et al., 1981/82; *tree shrews:* Sherman et al., 1977; McKanna and Casagrande, 1978; *cats:* Wilson and Sherman, 1977; Gollender et al., 1979; Kirby et al., 1982; *chickens:* Yinon et al., 1980; Yinon et al., 1982/83; Lauber and Oishi, 1987). Wiesel and Raviola (1977)

examined lid-suture effects on refraction, corneal curvature, and axial length in two species of macaque *(Macaca mulatta* and *Macaca arctoides)* at different ages for varying durations. They found that the refractive state of the lid-sutured eye was variable but generally much more myopic (-1.0 D to -13.5 D), and showed an axial length increase on the order of 1 mm compared to the open control eye. No differences in corneal curvature between ex-peri-mental and control eyes were found at any age. Although few animals were tested and no statistical tests were made, it was concluded that younger animals treated for longer durations became more myopic. In one adult macaque, lid-sutured for 17 months, no changes were found.

Lid-suture produces refractive error in monkeys by what appears to be an alteration of visual experience. Using two monkeys, Raviola and Wiesel (1978) found that the myopia and axial elongation resulting from lid-suture in the one reared under normal light cycles was not observed in the one reared in the dark. This was interpreted as implying that lid-suture did not mechanically alter the growth of the eye, and that a form degraded retinal image, but not a complete absence of retinal illumination, is necessary for axial elongation myopia. This hypothesis was supported further when Wiesel and Raviola (1979) produced axial elongation and myopia in two monkeys, although less than that seen in lid-sutured monkeys, by injecting latex into the corneas.

Some studies reported that lid-suture in monkeys produces more variable refractions than in normal eyes, but not necessarily in the myopic direction. von Noorden and Crawford (1978) reported increased refractive error variability in lid-sutured macaques, although only one-half of the eyes became myopic, while the rest became hyperopic. These results are not surprising considering the inconsistent design employed in this study; one or both eyes of rhesus monkeys were lid-sutured at different ages for various lengths of time and, most troubling, in most of the monocularly treated monkeys the lid-suture treatment was reversed to the other eye after different lengths of time. In a better controlled study, Thorn et al. (1981/82) used B-scan ultrasonography to study the axial changes resulting

from lid-suture in 2 species of macaques *(Macaca nemestrina* and *Macaca fascicularis)* and also found the results to be highly variable with no significant differences between experimental and control groups. Relative to the contralateral control eye, the vitreous chamber elongated in only 4 of 6 monocularly lid-sutured monkeys, actually decreasing in the other two. Interocular differences were greater than normal, however, and binocular lid-suture produced abnormal interocular axial length differences. From these data, Thorn et al. concluded that lid-suture indeed disrupts the growth regulation of the posterior portion of the eye but does not appear to do so in a systematic way. Unfortunately, refractive error measurements were not included so the relationship between the reported axial changes and the refractive states resulting from the lid-suture is unknown.

In general, the primate lid-suture experiments suffer from small sample sizes, a lack of statistical analyses, and problems of design. In an attempt to address some of the inconsistencies between studies, Smith et al., (1987) pooled and reanalyzed the data from the studies of Wiesel and Raviola (1977), von Noorden and Crawford (1978), and Thorn et al. (1981/82), as well as adding data from their own studies. They show that if the lid-sutured eye is compared to the fellow control eye in animals monocularly deprived before the age of 2 years, a consistent trend toward more myopia/less hyperopia is realized in the lid-sutured eye. Furthermore, as Wiesel and Raviola (1977) first suggested, Smith et al. show that the pooled data make evident positive correlations between the refractive change induced by lid-suture, and both the age of onset and treatment duration. On the other hand, it is true that absolute myopia is not always produced in lid-sutured eyes and axial changes are highly variable. These discrepancies are not easily explained, and call for more detailed investigations.

The results of lid-suture in cats are similar to the results reported in monkeys, including the same variabilities and inconsistencies, but in general the effects are smaller. It is safe to say that lid-suture disrupts normal eye growth patterns, but whether or not it always results in myopia is still open to question. As a side issue to their research on the development of

the cat striate cortex, Wilson and Sherman (1977) noted that lid-suture produced myopia on the order of -1 D to -2 D. Although axial length was not measured directly, they speculated that the refractive error was axial in nature. Gollender et al. (1979) used A-scan ultrasonography to study the axial dimensions of kitten eyes raised with or without lid-suture. Similar to the results of Thorn et al. (1981/82), Gollender et al. reported no consistent directional effect of lid-suture, although the variability of the aqueous and vitreous chambers, as well as the overall axial length, was significantly different from normal controls. In contrast to Gollender et al., Kirby et al. (1982) reported highly significant (0.9 mm to 1.9 mm) increases in the axial length of 20 monocularly lid-sutured kitten eyes relative to the fellow control eye. They also reported a significant decrease in corneal curvature of the lid-sutured eyes. Retinoscopy was used to determine the refractive state and showed a relative myopia of -0.5 D to -3.0 D, consistent with the the results reported by Wilson and Sherman (1977). However, only 10 of the 20 eyes were actually myopic, and there was no correlation between refraction and axial length increase. Ray-tracing calculations based on the axial length increases and corneal curvature decreases did not account for the lack of myopia in the lid-sutured eyes. No reason is clear for this lack of consistency between axial length and refraction.

Compared to monkeys and cats, more consistent and larger results from lid-suture have been obtained in tree shrews *(Tupaia glis)*. Sherman et al. (1977) found over 10 D of myopia in the eyes of tree shrews lid-sutured at 1 week of age for 4 to 36 months. Even though deprived eyes were longer than non-deprived eyes, the observed myopia in 3 subjects was not explained by the axial length determined after enucleation. This suggests other ocular components are involved in the determination of refraction of lid-sutured eyes. McKanna and Casagrande (1978) found that the lenses of lid-sutured tree shrews were, in fact, 5.5% lighter than controls. Furthermore, the zonular fibers in lid-sutured eyes appeared to be poorly developed which may suggest that chronic accommodation and the re-

sulting loss in zonular tension may be responsible for the reduced zonular and lenticular development.

Of those studied so far, the domestic chicken *(Gallus gallus domesticus)* is the species most consistently susceptible to environmentally induced refractive error. Lid-suture in chickens produces axial elongation and strong myopia relatively quickly (Yinon et al., 1980; Yinon et al., 1982/83; Lauber and Oishi, 1987). In chicks lid-sutured for different durations for as long as 3.5 months after hatching, Yinon et al. (1980) report more than 8 D of myopia in the lid-sutured eyes. This myopia is statistically significant relative to the average hyperopic refraction of normal eyes (+0.42 D). The myopia is most likely a result of the significantly longer axial lengths (>2.5 mm) relative to the contralateral control eyes since the corneal curvatures of the lid-sutured eyes proved to be flatter than normal. Yinon et al. (1980) also showed that the effects of lid-suture are greatest during the first 6 weeks after hatching, a period when the chick eye is growing rapidly (Wallman and Adams, 1987). These results were later repeated with the additional findings that the entire eye, and lens, were larger than normal in both axial and equatorial dimensions (Yinon et al., 1982/83).

As previously mentioned (Raviola and Wiesel, 1978), lid-suture does not appear to produce its eye enlarging effects by either direct mechanical influences or by depriving the retina of light *per se*, but rather by depriving the retina of form vision. This has been confirmed, in large part, by experimental manipulations on chickens in which the lids are left intact and the image on the eye is grossly degraded by optical means thereby producing high levels of myopia and vitreous chamber enlargement (Wallman et al., 1978a; Hodos and Kuenzel, 1984; Hodos et al., 1985; Wallman and Adams, 1987; Wallman et al., 1987; Pickett-Seltner et al., 1987, 1988).

Wallman et al. (1978b) designed a hemispherical white translucent plastic "occluder" which could be attached to the feathers surrounding the eye with collodian thereby severely limiting vision. These occluders could be adapted in a variety of ways to allow normal

vision in different parts of the visual field. Wallman et al. (1978a) reported the consistent development of severe myopia (median = -10 D; maximum myopia more than -30 D) in chicks whose vision was either completely occluded, or occluded in the lateral field but not the frontal field. Relative to normal controls, no significant refractive error changes were found in chicks with normal vision in the central field but no vision in the periphery. Based on A-scan ultrasonography, the changes in refraction in totally and partially (frontal visual field unobstructed) occluded eyes appear to be the result of the significant axial length increases also observed.

More recently, Wallman and Adams (1987) summarized the time course of visual deprivation myopia in chicks. They showed that the susceptibility to axial elongation and myopia declined with age; the myopia produced by the plastic occluders is greatest, and occurs most rapidly, if the treatments are applied early in life. They also showed that the myopia was reversible if the occluders producing it were removed during the first 6 weeks of life. The rate of recovery was found to be directly proportional to the degree of myopia and inversely related to age. These results suggest that, during a critical period in ocular development, an active emmetropization mechanism exists which is able to correct refractive errors that may exist.

Results similar to those of Wallman et al. (1978a) have been obtained by others (Hodos and Kuenzel, 1984; Hodos et al., 1985; Hayes et al., 1986) who degraded the retinal images with devices which were functionally a combination of occluders and defocusing lenses. The retinal image was degraded because of blur and spherical aberration, as well as reducing contrast. These goggle-like devices were constructed so that either the entire field of view or only the frontal visual field was affected. Hodos et al. (1985), determined the refractive state of the eye by electrophysiological means. They showed that compared to the eyes of normally-reared chicks (-0.20 D), frontal field degradation produced a statistically significant myopia (-4.11 D), and total field degradation produced significantly more myopia (-14.88 D). Hodos and Kuenzel (1984) reported that eyes treated with whole field

goggles were significantly larger than control eyes in both the axial and equatorial dimensions, while eyes treated with frontal field goggles were found to be enlarged in the equatorial dimension only. Similar results were presented by Hayes et al. (1986) who found that degradation of the whole visual field, but not of only the frontal visual field, results in bulging corneas, larger than normal anterior chambers, and greater corneal diameters relative to control eyes. Other studies of visual deprivation myopia in chicks report that there are no significant lenticular changes (Pickett-Seltner et al. 1987), nor are there changes in the concentration of soluble proteins (Pickett-Seltner et al., 1988).

The results obtained by Hodos and Kuenzel (1984) provided the first suggestion of regional ocular effects in response to different visual experiences. This notion was elaborated by Wallman and Adams (1987), and later systematically tested (Wallman et al., 1987). Wallman et al. (1987) concluded that visual experience largely dictates refractive state by influencing the growth of the eye locally. In fact, they found that the shape of the eye is able to be sculpted in such ways that it can develop regional refractive changes which are well correlated with different visual field restrictions. The myopia produced by partial visual deprivation of either the temporal or nasal retina was found to be restricted to the region of the retina deprived. Furthermore, this myopia is a result of vitreous chamber elongation which was also restricted to the region that had been deprived. These findings are important on two main counts: (1) They provide strong evidence for ocular growth responses to visual stimuli. (2) They suggest that the eye does not necessarily grow as a whole, and therefore provides the first clear evidence for the existence of local ocular growth control mechanisms. The mechanisms by which visual experience is related to the observed ocular growth responses remain as enigmatic as ever.

The direct physical effects of the occluders (Wallman et al., 1978) and goggles (Hodos et al., 1984) were carefully considered and shown not to play a role in the refractive changes observed. Both groups of investigators showed independently that gluing a ring of plastic around the eye, which did not restrict the visual field, did not produce abnormal re-

fractive errors or ocular changes. However, recent reports indicate that such treatments may indeed affect the eye by producing inflammation (Hayes et al. 1986) and increasing ocular temperature (Hodos et al., 1987), thereby making the eye more susceptible to the visually-induced changes, possibly by increasing the metabolism of the ocular tissues. This inflammation may contribute to the overall effects of visual restriction devices or lid-suture and should be considered in the final analysis of the visual deprivation experiments.

To produce visual alterations of a less drastic nature than occluders, lid-suture, or corneal opacification, defocusing lenses have also been used to investigate the refractive development of the eye. Smith et al. (1980) showed that kittens made functionally hyperopic by wearing negative lenses (at least -10 D) for 2-3 hours each day became significantly myopic (mean = -1.12 D) compared to controls (mean = +1 D). These kittens were raised in darkness until 1 month of age at which time the lens treatment began which continued until the kittens were 3-months-old. A small, nearly statistically significant, difference in axial length was also reported (defocused eyes: 18.07 mm vs. controls: 17.3 mm; p=0.082). In contrast, Nathan et al. (1984) could not reliably produce either axial changes or refractive errors in kittens reared with positive or negative defocusing contact lenses, lid-suture, or daily application of atropine to block accommodation and produce near field defocus. Nathan et al. began degrading the retinal images in 3-month-old kittens raised under normal conditions until that time. There is no doubt that the defocusing procedures were effective since the treated eyes were found to be amblyopic. Because of the many procedural differences between the two studies (e.g. pre-treatment visual experience and duration, age at which treatment began, method of lens wear, duration of lens wear, and measurement techniques), there is no easy basis for comparison and no clear reason why the results of these two studies do not agree. Besides the possibility that technique differences may have contributed to the differences in the results reported by Smith et al. (1980) and Nathan et al. (1984), another possibility is that the critical period for growth changes related to visual experience is earlier than 3 months of age in kittens. The fact that

Nathan at al. reared kittens under normal conditions during this time may have made them less susceptible to subsequent treatments.

Like cats, monkeys show inconsistent responses to being reared with defocusing lenses. Crewther et al. (1988) raised monkeys *(Macaca fascicularis)* with either positive or negative power defocusing contact lenses placed on one eye. Four of the 9 monkeys reared monocularly with defocusing lenses became, relative to the fellow control eye, significantly more hyperopic (2 to 6 D) regardless of the power or sign of the contact lens worn. The difference in refraction of the eyes was explained by their shorter than normal vitreous chambers. The 5 other monkeys were not affected by the lens treatment. The only explanation provided for the inconsistent results was the possibility that the monkeys developing hyperopia did so secondarily to developing anisometopic amblyopia. Accommodation was not seen as playing a role in the development of this hyperopia since the authors point out the binocular linkage of accommodation in primates.

Unlike those reports on mammals, the results reported by Schaeffel et al. (1988) on the effects of lens induced retinal defocus in chickens provide strong evidence that not only does retinal defocus alter eye growth, but the nature of the alteration is closely related to the type of lens used. Chickens were raised from 1 to 5 weeks of age wearing hoods which held defocusing lenses of opposite sign over the two eyes. The refractive states of the two eyes significantly changed in different directions; negative lenses produced approximately -1.5 D of myopia, whereas positive lens produced about +2.5 D of hyperopia. These changes in refractive state appear to be the result of changes in axial lengths since the two changes were well correlated (r=0.90); the myopic eyes had significantly longer axial lengths than the hyperopic eyes. Schaeffel et al. (1988) used infrared photoretinoscopy (Schaeffel et al., 1987) and found that the spectacle lenses were largely compensated for by accommodative changes (in chicks accommodative function is not linked binocularly). As a result, they speculated that the amount of accommodation stimulated by the lenses (a nega-

tive lens stimulates more, a positive lens stimulates less) in some way influences the ocular changes observed.

In summary, nearly all of the reports on eye growth and the degradation of vision leave little doubt that the visual environment influences the developing eye. In some reports this influence is reported to be the deregulation of eye growth, while in others a tendency toward axial elongation and myopia is shown. Since the effects reported in cats for any of the visual deprivation studies described above are inconsistent or typically so small when found that it suggests that this species might be useful for genetic studies. The results of the visual deprivation experiments in monkeys have proven to be somewhat larger in magnitude than those seen in cats, but questions regarding the consistency of the effects still remain. While investigations using tree shrew seem promising, the largest and most consistent effects of the visual influences on eye growth are seen in chickens. Despite these apparent species differences, the overall results based on both animal experimentation and clinical reports on humans strongly suggest that eye growth is susceptible to alterations in visual experience.

While it is now clear that a normal visual experience is necessary for normal ocular development, neither the relevant aspects of the visual stimuli (e.g. light intensity, contrast, spatial frequency), nor the means of their effects are known. In general, there are two alternative views of how vision might influence eye growth. In one, which maintains a relatively passive role for vision, the growth of the eye and the resulting refractive state is genetically programmed but relies on some component(s) of visual experience for normal development. If the eye is deprived of this component, the inherited eye growth program is disrupted, causing a breakdown in the correlation of the ocular components, and results in a refractive error. An alternative view maintains a more active role for vision in eye growth by hypothesizing that some aspect of visual experience mediates a feed-back control system which is dependent upon sensing the amount and direction of refractive error (or refractive error producing growth patterns). This type of mechanism could adjust and direct the

growth of the eye toward emmetropia in response to different refractive errors. A discussion of the possible processes by which the eye achieves and maintains, or if disrupted loses, emmetropia is the topic of the next section.

Emmetropization

Considering the number of ways that eye growth and refractive state can be disrupted, it is interesting that more eyes do not have refractive errors. In general, the eyes of neonates start out with highly variable refractive states, typically in the hyperopic range. As the eye grows, this variability is reduced and the eyes approach emmetropia. Similarly, a reduction in initially high levels of astigmatism has been found in human infants as they mature (Howland et al., 1978; Mohindra et al., 1978).

Growth toward emmetropia in developing eyes has been shown in species as diverse as humans (Stenstrom, 1946; Hirsch, 1952; Sorsby et al., 1961b; Banks, 1980; Mohindra and Held, 1981), tree shrews (McBrien and Norton, 1987), and chicks (Wallman et al., 1981a). This is clearly evident when viewed in terms of the changes in the distribution of refractive state. In human populations sampled (Stenstrom, 1946; Sorsby et al., 1957), all of the ocular components are normally distributed but refractive errors and axial length are not. Furthermore, the distribution of refractive errors starts out more or less Gaussian but with time eventually becomes leptokurtotic; relative to neonates, refractive errors in adults show a decreased variance and an excess around emmetropia (or slight hyperopia: <+1 D), with some skewness toward myopia (Stenstrom, 1946; Sorsby et al., 1961b; Mark, 1972; Banks, 1980; Mohindra and Held, 1981; Sato, 1981).

Given the variability of the various ocular components, there must be a strong intercorrelation between components for emmetropia to predominate as it does. The term "emmetropization" is commonly used to describe the ability of the eye to achieve the proper relationship between the unaccommodated optical power and axial length thereby achieving emmetropia. Two major questions arise: (1) What is the mechanism responsible for

emmetropization? (2) What are the causes of the breakdowns in emmetropization which result in refractive errors? These questions remain largely unanswered. Because the answer to the second question is closely linked to the first, the major emphasis of this section will be to discuss the theoretical basis, and some hypothetical mechanisms, of emmetropization. Following this, these mechanism will be related to the development of ametropia.

Since from birth to adulthood the ocular components are continually changing, there is little objection to the assumption that, in some way, the interrelationships between the components are coordinated so that emmetropia can be achieved and maintained. Based on descriptive studies of the distributions and the relationships between the ocular components, the notion of correlated growth in emmetropization has been advanced by both Sorsby et al. (1957) and van Alphen (1961). How such correlated growth of initially Gaussian-distributed ocular components can lead to the leptokurtosis of refraction was shown by Carroll (1982) in a mathematical model of emmetropization. The model is based on the following assumptions: (1) The growth and the relationships between the optical components can be described by a series of first order, linear, coupled, differential equations. (2) The parameters comprising these equations are Gaussian random variables. (3) Refraction in neonates is linearly related to the values of the optical components at birth. What remains unclear, besides the validity of these assumptions, is the means of achieving the relationships described by the first assumption (i.e. what is the mechanism responsible for the correlated growth described by Sorsby et al. and van Alphen).

There exists much controversy concerning the nature of the mechanism of emmetropization, and many diverse speculations have been made (for summaries see: Morgan, 1967; Borish, 1970; McBrien & Barnes, 1984). The different views of emmetropization can be lumped generally into the following two categories: (1) passive/automatic (e.g. Gernet and Olbrich, 1969; Hofstetter, 1969; Mark, 1972; Sorsby, 1979); or (2) active/feedback (e.g. van Alphen, 1961; Young, 1977; Banks, 1980; Medina, 1987a, 1987b). Emmetropization

is likely to be some combination of these two views since they each possess some degree of plausibility.

The passive/automatic view assumes that the intercorrelation of the various ocular components is genetically programmed and is largely restricted by the physical forces exerted on the growing eye. This view tends to redirect the analysis of ocular refraction to the dispersions from the expected leptokurtotic distribution instead of the deviations from the Gaussian distribution. Sorsby suggests that the distribution of refractive errors may be largely under genetic control and views the development of high ametropia as the inheritance of an abnormality in one of the ocular components (component ametropia) which upsets the normal physical arrangement of the ocular tissues. Hofstetter (1969) takes the definitive passive/automatic view in that he suggests that the observed leptokurtosis in refractive errors is the result of the inherent structural conditions in the design of the eye. Based on a highly simplified schematic eye, Hofstetter argues that since eye size and refractive error are determined by the same radial dimensions, the radius drops out of the formula describing the optics. If the appropriate remaining values are kept constant, emmetropia will be realized for any size radius. Although Hofstetter assumes that in real eyes the dispersion of refractive errors away from this perfect leptokurtosis is the result of normal variability in the ocular components, he fails to show how the values appropriate for emmetropia are achieved with growth. In other words, while Hofstetter's argument applies to a population of already emmetropic eyes undergoing isomorphic growth, it ignores the fact that the refractive error distribution changes from normal at birth to leptokurtotic in adulthood.

This criticism is met in a slightly different form of the passive/automatic view of emmetropization which maintains that the growth of the eye toward emmetropia occurs as a result of the physical changes associated with increasing the size of the eye and its ocular components. This is to say that no active regulation is needed since correlation of the ocular components is bound to occur as a result of the physical attributes of the growing eye. To

be sure, all things being equal, as an eye increases in size the degree of refractive error diminishes for two reasons. First, as an eye grows there will be a reduction in any hyperopia as a result of an artifact from the way the measurement is typically made. Glickstein and Millodot (1970) identified the source of this artifact by pointing out that retinoscopy and refractometry measurements are based on reflections from the vitreo-retinal interface, whereas the photoreceptor layer lies some small distance beyond. This error, which results in a more hyperopic reading, is termed the small-eye artifact (or artifact of retinoscopy) because the effect is greater in small eyes where retinal thickness possesses a greater percentage of the total axial length of the eye. As small eyes grow, this error is reduced and the refractive state appears to move from greater to lesser hyperopia. The second reason is apparent in both myopic and hyperopic eyes and was described by Wallman and Adams (1987) as an error which arises from the way refractive error is defined optically (see Appendix B). Because refractive error is defined as the reciprocal of the difference between the focal length of the optics and the axial length of the eye, an isomorphic scaling phenomenon becomes apparent. Wallman and Adams explained this scaling phenomenon with a simple example: If optical power is assumed to be directly proportional to eye size, a 10% mismatch of focal length to axial length in two eyes, one 10 mm long and one 100 mm long, produces 10-times the refractive error in the smaller eye. Wallman and Adams show further that such a scaling phenomenon, even when the small eye artifact is also considered, does not account for the growth toward emmetropia observed in neonatal chicks.

Statistical and mathematical explanations of the change in refractive error distribution are useful, but insufficient to explain the mechanism of emmetropization. Numerous investigators have suggested that emmetropization is the result of physical forces in the growing eye which arise from the characteristics of the ocular tissues and the basic design of the eye (Gernet and Olbrich, 1969; Mark, 1972; Sorsby, 1979). These suggestions are all based on the fact that as the eye enlarges the optical components lose refractive power and, in this

way, appear to compensate for the enlargement. However, a total compensation is assumed, and is based only on the observation of the general tendency for less optical power in larger eyes. Compared to smaller eyes, lens power, corneal curvature, and anterior chamber depth have all been shown to provide less optical power in larger eyes (van Alphen, 1961). Gernet and Olbrich (1969) suggested that the lens is mainly responsible for the compensations necessary to maintain emmetropia. Based on the observation of decreased lens power in larger eyes, they speculate that the attachment of the lens to the ciliary muscle by the zonular fibers affects lens power because, relative to small eyes, larger eyes have a larger equatorial diameter and may, therefore, put more tension on the zonular fibers. This would stretch the lens capsule, flatten the lens, and reduce the optical power. In another highly speculative report, Mark (1972) too hypothesized such a lenticular compensatory mechanism, but also considered the flattening of the cornea and the deepening of the anterior chamber to be compensatory changes. Sorsby (1979), based on descriptive observations of eye growth, supports the notion that corneal curvature is adjusted during eye growth, but concedes that compensatory lens flattening is more difficult to explain and is pure conjecture.

All of these mechanisms only explain the maintenance of emmetropia in already emmetropic eyes, but fail to explain adequately the initial adjustments which direct the eye from neonatal refractive states toward emmetropia. A combination of the growth-related physical changes with the effects of scaling and the small eye artifact may explain some aspects of emmetropization but do not appear to be able to explain all of it (van Alphen, 1961; Wallman and Adams, 1987). The fundamental problem is how to disentangle passive physical change in the ocular components from the hypothetical actively regulated change.

An interesting analysis of the data available on the growth and interrelationships of the ocular components has been presented by van Alphen (1961). By rigorous statistical analyses he identified 10 significant intercorrelations between the various ocular components. He is careful to point out that these correlations offer no direct insight into the

control of eye growth, but factor analyses suggest that at least three independently acting factors (i.e. causes or influences) are necessary to explain the interrelationships. The common feature of these hypothetical factors is that they all directly influence axial length. One factor (called factor S) pertains to the relationship of corneal curvature and axial length, and appears to be dictated by the genetic differences in the overall size of the eye. The second factor (factor P) pertains to the interrelationships between axial length, anterior chamber depth, and lens power. Factor P is interpreted to be a stretch factor, perhaps determined by intraocular pressure. The independence of these factors can be seen in the lack of correlation between corneal power and either lens power or anterior chamber depth. The conclusion is that as the eye grows, it attempts to adjust its axial length to the optical power by stretching. Since the two factors are independent and any discrepancy between the interaction of these two factors will produce a refractive error, van Alphen assumes that an active regulatory mechanism exists to reconcile factors S and P. A third factor (factor R) refers to this mechanism and pertains to the degree of ametropia based on any mismatch between factor S and factor P. van Alphen argues that the tonus of the ciliary muscle is the basis of the factor R and the regulation of eye growth (see below).

Besides van Alphen's study and the effects of changes in visual experience on eye growth, very little evidence is available for active regulation mechanisms. In fact, no direct evidence for active regulation of eye growth exists. Nevertheless, there have been various hypotheses suggested (see: Morgan, 1967; Borish, 1970; McBrien & Barnes, 1984; Curtin, 1985; Wallman and Adams, 1987). Common to most of these hypotheses is the idea that visual experience plays an important role in the control of eye growth by influencing brain-mediated oculomotor activities. However, other influences such as choroidal vascular control and the regulation of growth hormones or vitreous humor growth factors are equally plausible. Despite the variety of possibilities which exist, accommodation is, by far, the most popular of the putative control mechanism of eye growth.

Accommodation and emmetropization

Accommodation has long been suspected of being the major component in control of the refractive development of the eye, as well as in the genesis of myopia. This is in part because accommodation subjects the eye to mechanical forces, and in part because accommodation can be used to determine the sign and magnitude of refractive errors. Because of these facts, a number of different growth-controlling roles have been ascribed to accommodation although, in fact, there is very little direct experimental evidence for or against it as a factor in eye growth. The studies relating myopia to near work, which were described earlier, have long been cited as the key evidence that accommodation was important in eye growth. While this view relies more on supposition than experimental evidence it has essentially been regarded as fact by many. More precisely, the relationship between near-work and myopia is evidence for the visual regulation of eye growth, but says nothing about the mechanisms involved.

The most popular view of accommodative involvement in eye growth is summarized by the hypotheses of Young (1977) and Bell (1980). From studies of the relationship of schooling and refractive errors in Inuits and visual restriction experiments on primates, Young concluded that abnormal levels of accommodation, resulting from excessive near vision, are responsible for the development of myopia. He hypothesized that excessive accommodation would increase axial length by increasing vitreous chamber pressure and stretching the sclera. Bell (1980) proposed a similar pressure-dependent mechanism also based on the assumption that intraocular pressure in the vitreous chamber rises during accommodation as predicted by the, as yet unsupported, hypothesis of Coleman (1970). Both Young and Bell in a similar manner, suggest that accommodation is also important in normal ocular development by controlling the amount of growth along the optic axis. The speculation is as follows: Excessive accommodation tends to produce axial elongation. In a hyperopic eye there is more accommodative demand, and thus presumably more accommodation. This would result in axial elongation which would, in turn, reduce the

hyperopia and the accommodative demand. A myopic eye, on the other hand, has less accommodative demand, and could possibly grow toward emmetropia if the eye were allowed to grow in all dimensions except along the optic axis. This would reduce the optical power of the eye by flattening the cornea and the lens thus causing the focal point to move toward a better correspondence with the retina. Although these arguments are sensible, there is little evidence to support them.

Other highly speculative eye growth hypotheses, also based on the notion that excessive accommodation produces myopia, have put more emphasis on lenticular changes. Sato (1981) speculates that accommodation mediates its effects on refractive development by increasing lens power as opposed to changing axial length, which he supposes to be under genetic control. Based on their work with tree shrews, McKanna and Casagrande (1978, 1981) hypothesized a mechanism of eye growth where both axial and lenticular growth are governed by accommodation in what they call an "intersecting feedback loop". The authors suggest that increased accommodation increases scleral stress, resulting in elongation of the eye. Simultaneously, zonular development is decreased, relaxing the tension on the lens which may, in turn, slow its development. Both phenomena will effectively decrease accommodative demand and any pre-existing hyperopic refractive error. In this way, excessive accommodation can explain the myopia, axial elongation, and lenticular hypoplasia observed in lid-sutured tree shrews (Sherman et al., 1977; McKanna and Casagrande, 1978).

The relevant factor in any form of accommodation-modulated eye growth may not be the act of accommodation *per se* but, rather, the resting tonus of the ciliary muscle. Ebenholtz (1983) found that after prolonged periods of accommodation, the resting state of accommodation, measured as the level of resting focus in the dark, was increased significantly. The refractive state measured in the dark, or in a Ganzfeld, provides an estimate of the resting tonus of the ciliary muscle (Fincham, 1962; Owens, 1984). Although the subjects in Ebenholtz's study were required to accommodate only a matter of minutes, their

resting focus measured in the dark was increased for much longer periods of time. Furthermore, Schor et al. (1986) showed that darkness actually masks larger changes in tonic accommodation produced by prolonged near-vision, thus the change in tonic accommodation measured in the dark is probably an underestimate and the changes in ciliary muscle tonus suggested by the results of Ebenholtz (1983) may be even larger than supposed. While these results supply a possible mechanism of how near-work could influence accommodation in such a way that long term ocular changes could ensue, they also emphasize caution in interpreting results of studies using only non-cycloplegic refractions since refractive changes may not always be the result of changes in axial length.

A different view of the role of accommodation in eye growth has been proposed by van Alphen (1961) who sees accommodation and, in particular, the tonus of the ciliary muscle as an anti-myopia force. van Alphen's theory is based indirectly on a number of carefully conducted experiments and, as he admits, the accommodative aspect of his theory is speculative. Basically, van Alphen hypothesized that emmetropia is produced through accommodative control of ciliary muscle tonus which modulates the effects of intraocular pressure on eye growth. This hypothesis is based on his experiments which show that during accommodation the tension on the choroid is increased, resulting in a decrease in the effects of intraocular pressure on the sclera. From this van Alphen suggests that excess ciliary muscle tonus during ocular development would reduce axial growth and produce hyperopia, while low tonus would increase axial growth and produce myopia. Besides assuming that the eye growth regulation is achieved by scleral stretch, the hypothesis does not easily reconcile the fact that accommodative demand arising from a given refractive error is exactly opposite to what van Alphen's hypothesized mechanism requires for compensatory growth. For instance, a hyperopic eye has accommodative demand proportional to the amount of axial length growth needed to produce emmetropia. Since this demand drives accommodation and produces ciliary muscle contraction, the ciliary tonus increases and the stretching effects of intraocular pressure on the sclera are reduced resulting in an inappro-

priate growth response. In order to achieve the proper growth response van Alphen speculates that the brain will override this accommodative demand and reduce accommodation thereby achieving the necessary ciliary tonus for the proper pressure-induced axial growth. He proposes this override through as yet unidentified cortico-subcortical pathways controlling accommodation. He speculates further that interference with these pathways is how refractive errors arise, but until such pathways are identified and their characteristics are determined, van Alphen's theory will remain largely untested.

Although all of these accommodation hypotheses are highly speculative, some attempts at obtaining evidence have been made. At first glance, the hypotheses that myopia is produced by excessive accommodation appear to possess the most supportive data. The fact is, however, that the data are largely circumstantial (as in the near work/myopia correlation) and often equivocal. For instance, the supposition that excessive accommodation may underlie the development of myopia forms the basis for the clinical procedure of prescribing bifocals to youngsters with progressively worsening myopia. The rationale is to correct the myopia with a negative lens, but use an additional positive lens for close work so that the eye does not accommodate. Small studies concerning the effectiveness of bifocal treatment in myopic children have reported small or negative results (Oakley and Young, 1975; Mandell, 1959 respectively). More recently a large, carefully designed, studied reported that bifocals were ineffective in reducing the development of myopia in children (Grosvenor et al., 1987).

Another often cited basis for support of the excess accommodation hypothesis, in any of its forms, was the report that blocking the activity of the mammalian accommodative musculature (ciliary muscles) with atropine slows the progression of myopia in children (Bedrossian, 1971, 1979). Furthermore, preventing accommodation with atropine in monkeys (Young, 1965; Raviola and Wiesel, 1985) or tree shrews (McKanna and Casagrande, 1981), or by cutting the ciliary nerves in chicks (Wallman et al., 1981b), have also been suggested to be effective in reducing the progression of myopia.

While at first the results from these studies seem reasonably clear-cut, a more careful interpretation warrants skepticism. For instance, the use of atropine to block accommodation is difficult to control and the interpretation of its effects is extremely complicated. Atropine is a powerful parasympatholytic drug which blocks acetylcholine receptors and has numerous systemic effects. A major criticism in all of the cases where atropine was used to block accommodation is that there is no way of ascertaining that the drug is acting only on the ciliary muscle and not other ocular tissues. Atropine could, thereby, upset any other eye growth mechanisms that involve these tissues.

The animal studies concerning accommodation and eye growth tend to suggest that disrupting accommodation affects eye growth in some way, if only by increasing the variability of the visually-induced effects. These reports, however, tend to be replete with inconsistencies and difficult to interpret. For instance, McKanna and Casagrande (1981) reported enhanced zonular development and the possibility that less lid-suture myopia and axial elongation in tree shrews treated with atropine, although statistical significance was not obtained. Furthermore, non-lid-sutured atropinized eyes also showed enhanced zonular development suggesting that the effects of atropine on the eye may simply be to disrupt growth in a way which partially masks the effects of altered visual experience. Raviola and Wiesel (1985) reported that atropine was effective in preventing lid-suture myopia in stumptail macaques *(Macaca arctoides)* but not in rhesus macaques *(Macaca mullata)*. It is unclear, however, if accommodation is the key to the apparent species differences in the effects of atropine treatment, since Raviola and Wiesel did not find enhanced lid-suture myopia in a stumptail macaque with accommodative spasm induced by isoflurophate (an anti-cholinesterase).

Wallman et al. (1981b) avoided the problems of pharmacological treatments by unilaterally sectioning the short ciliary nerves in neonatal chicks. These chicks were subsequently reared under bilateral viewing conditions which restricted their vision to the frontal visual field. The overall result was that myopia in ciliary nerve cut eyes was diminished,

but not prevented. In 21 of 24 cases, the ciliary nerve cut eye was significantly less myopic than the fellow sham-operated control eye, but many of eyes were still substantially more myopic than -10 D. Axial length measurements were not reported so it remains unclear if accommodation is involved in the elongation observed in normal visually restricted eyes. Corneal power was determined however, and reported to be significantly greater in visually restricted eyes compared to control eyes, and significantly less in the nerve-cut visually restricted eyes relative to sham-operated visually restricted eyes. This suggests that corneal curvature is associated with visual restriction myopia in chicks and is determined, at least in part, by the action of accommodation.

The studies cited thus far have attempted to investigate the role of accommodation in eye growth by eliminating accommodative activity through pharmacological or surgical manipulation. The other approach is, of course, to increase accommodative activity and is precisely what two studies set out to do (Hendrickson and Rosenblum, 1985; Schaeffel et al., 1988).

The study of Hendrickson and Rosenblum (1985) is of interest for a number of reasons, but their results and interpretations must be viewed with caution since they do not present statistical analyses and some of their basic assumptions are probably invalid. Hendrickson and Rosenblum reduced accommodative demand in one eye of kittens by unilateral radial keratotomy. The technique is to cut a number of fine corneal incisions which radiate from the central cornea like spokes on a wheel. This effectively flattens the cornea and reduces the total optical power of the eye, resulting in an increase in accommodative demand. In some of these kittens Hendrickson and Rosenblum applied atropine to eliminate accommodation. Although no statistical tests were made, the authors report that the radial keratotomized eyes were elongated relative to the fellow control eye, apparently to compensate for the reduced optical power of the treated eye. Hendrickson and Rosenblum claim that accommodation must be the force behind this compensatory change because atropine appeared to prevent this elongation. Besides the questionable manner in

which the data are presented, the accommodation argument is difficult to accept since there is no evidence that in cats accommodation in the two eyes can be uncoupled. Nevertheless if axial elongation is, in fact, a result of the hyperopia induced by radial keratotomy, the result is of interest since it argues for active regulation of refractive state toward emmetropia. Furthermore, if accommodation is not a feasible explanation of these results, they may be explained if the effects of atropine are acting in a gross way on the growth of the eye.

Schaeffel et al. (1988) tested the notion that accommodative effort modulates eye growth by raising chicks with lenses of opposite sign placed over each eye. The use of chicks is convenient for studies involving accommodation since the fellow eye can be used as a control because independent accommodative function in the two eyes has been shown (Schaeffel et al., 1986). As described earlier, the refractive states of the two eyes significantly changed in different directions; negative lenses produced axial elongation myopia, whereas positive lenses produced hyperopia resulting from shorter than normal eyes. Because the powers of the lenses were largely compensated for by accommodative changes, it was suggested that the amount of accommodation stimulated by the lenses produces the changes. This is indirect evidence, at best, that accommodation is involved in modulating eye growth because whatever is driving accommodation could also guide eye growth independent of accommodative activity.

Summary

There is no doubt that the optical development of the eye is a complex phenomenon with genetic and experience-dependent components. Recently, numerous investigators have begun studying the fact that the normal growth of the eye is subject to environmental perturbations which result in the development of refractive errors. While their hopes are centered on the possibility of understanding how refractive errors arise, relatively little experimental effort has been paid to the nature of the mechanisms behind normal growth.

The object of this dissertation is to explore postnatal ocular development and try to clarify the mechanisms involved.

After many years of speculation, it still remains unclear whether the growth of the eye is actively regulated by any particular feedback mechanism. The difficulties in disentangling such an active control mechanism from the various passive growth-related phenomena that have been identified are immense. A potentially fruitful experimental approach to test for the existence of such active regulation is to examine recovery from experimentally induced refractive errors of different sign and morphological abnormalities. In this way, the passive growth toward emmetropia observed in normal eyes can be effectively controlled.

Despite the lack of evidence for active control, the literature is packed with many hypotheses of how such control could work. Based primarily on circumstantial and indirect evidence, accommodation remains firmly entrenched as the most popular of the putative mechanisms behind active regulation of eye growth, even though there is still no conclusive evidence.

Finally, the recent evidence showing that localized changes in eye growth occur in response to different visual manipulations localized to regions of the visual field, suggest that the eye itself may have a greater role in the control of its own growth than previously imagined. With this in mind, it is important to establish exactly what the eye alone is capable of doing in terms of growth. In a general way, this will also make apparent the level of central nervous system involvement.

The design of the following study is based largely on these conclusions. A detailed description of the objectives and the experimental design used is given in the next chapter. The general methods employed are described in Chapter 3.

CHAPTER TWO

DESIGN AND OBJECTIVES

The control of eye growth and the development of refractive errors are important long-standing issues in ocular research. The existence of refractive errors early in life, particularly anisometropia, may unalterably affect the development of the visual system and its capabilities (Copps, 1944; Ingram et al., 1986). Furthermore, the prevalence of myopia (Sperduto et al., 1983), and the possible relationship of near work to myopia (e.g. Young, 1977; Bell, 1980), suggests that certain aspects of modern life may upset normal eye growth in some preventable manner.

This dissertation explores the control of eye growth in chicks. The main objectives are to: (1) determine whether eye growth is under the control of vision-dependent feedback regulation; (2) determine the general level of visual processing necessary for normal eye growth; (3) define specifically the influence of ocular accommodation on the growth of the eye.

The Use of Chicken Eyes

As an experimental subject, the chick has proven to be invaluable to developmental vertebrate biology. Similarly, as an experimental preparation for the study of ocular development at both the prenatal and postnatal stages, the chick has been the source of many interesting discoveries. Chicks are good candidates for experimental ocular research

because they are readily available, making large sample sizes possible, they grow quickly, possess good diurnal vision, and have relatively large eyes.

There are clearly many differences between the eyes of mammals and the eyes of birds (e.g. birds have scleral ossicles, a pecten, and striated ciliary muscles), but it is important to realize that between chicks and humans there are more similarities in certain respects (e.g. diurnal habitat, color vision, and good accommodation) then, between rats or cats and humans (Walls, 1942). While it is indeed important to keep in mind the differences between chick and human eyes when interpreting the results of the following experiments, it should also be realized that the fundamental design of the vertebrate eye is evolutionarily old (Walls, 1942). It is, therefore, reasonable to assume that the general mechanisms which evolved to regulate eye growth in order to achieve good optical quality are probably generalized as well.

Overall Design

The process of emmetropization and the development of refractive errors were studied by monitoring eye growth toward or away from emmetropia while different visual system manipulations were performed. Growth away from emmetropia was produced in two ways: (1) Myopia was induced in some chicks by partially depriving the eyes of form vision (after Wallman et al., 1978). (2) Hyperopia was induced in other chicks by raising them in complete darkness (after Gottlieb et al., 1987). Growth toward emmetropia was studied by monitoring normal ocular development as well as the recovery from the induced refractive errors after the visual manipulations producing them were removed.

Growth back to emmetropia from induced refractive errors may be viewed as experimentally controlled emmetropization which, as in normal emmetropization, could be the result of adjustments of ocular components which are guided by an error-sensing mechanism. Furthermore, growth toward emmetropia in eyes initially made ametropic is a useful

paradigm for studying emmetropization because, relative to normal growth, recovery from induced refractive errors achieves large refractive changes at a faster rate.

Besides examining the emmetropizing abilities of chick eyes, the underlying mechanisms of ocular growth control were studied using various experimental conditions. Except for Schaeffel et al. (1988), there have been very few experimental studies of ocular growth regulation. To date, studies of emmetropization have been either purely descriptive (eg. Stenstrom, 1946; Sorsby, 1979) or largely theoretical (eg. van Alphen, 1961; Mark, 1972; Carroll, 1982) in nature. In this dissertation two experimental manipulations were used to exam the substrate of eye growth control: (1) Optic nerve section was used to determine the level of visual processing necessary for normal eye growth by decoupling the retina from the brain. (2) Lesions of the Edinger-Westphal nucleus were used to examine specifically the hypothesis that accommodation is involved in the control of eye growth.

Active regulation of refractive state

Because of the complexity of eye growth, and the influence of early visual experience, it is not unreasonable to suspect that eye growth and refractive state are actively regulated. However, the existence of the active regulation of eye growth has not yet been examined experimentally. One particular eye growth phenomenon which has received relatively little attention, but may prove informative in illustrating a visual feedback eye growth mechanism, is the recovery from induced refractive error.

In chicks, recovery from experimentally induced myopia has been reported (Wallman et al., 1981a; Wallman and Adams, 1987). When the myopia-producing visual deprivation was removed, the eye became less myopic, apparently the result of the cessation of vitreous chamber growth. These results can be interpreted in at least two different ways: (1) They may be the result of reactivating a refractive error sensitive visual feedback mechanism which determines the adjustments necessary for the eye's return to emmetropia. (2) The recovery may be the result of simply removing the visual deprivation which results in an immediate cessation of the abnormal vitreous chamber elongation. If the eye is still in a

stage of active growth and continues to enlarge more rapidly in the equatorial dimension than in the axial dimension the myopia would effectively be reduced as a result of the decrease in optical power associated with enlargement of the anterior segment. As such an eye grew, the isomorphic scaling phenomenon (see Chapter 1) would also contribute to the reduction of myopia. Wallman and Adams (1986) argue that, by itself, isomorphic scaling is insufficient to completely account for the observed emmetropization from myopia suggesting active regulation of eye growth. Nevertheless, at present there is no satisfactory experimental evidence supporting one hypothesis over the other.

Dark-induced hyperopia produces a situation well suited to the study of this problem. The presence of active regulation of eye growth was tested by monitoring the changes occurring during emmetropization from dark-induced hyperopia. The hyperopia resulting from dark-rearing is a result of a flattening of the corneal surface because the eye is longer than normal (Gottlieb et al., 1987). Two of the possible correcting adjustments (increased corneal curvature and increased vitreous chamber depth) require a change in the opposite direction of what is normally observed during eye growth (decreased corneal curvature), or changes which must increase an already abnormally enlarged ocular component (increased vitreous chamber depth). Thus, recovery from dark-induced hyperopia by either or both of these mechanisms would support the existence of the active (probably visual) regulation of eye growth (see Chapter 4).

Brain-mediated mechanisms of eye growth

An important initial step in determining the nature of vision-dependent eye growth control is to determine the substrate involved. Whether or not central (brain-mediated) visual mechanisms are necessary, as opposed to peripheral (retinal or ocular) mechanisms, was tested by sectioning the optic nerve (see Chapter 5).

The involvement of the brain in the development of myopia has been called into question by two recent reports: (1) Raviola and Wiesel (1985) report that cutting the optic nerve does not protect against lid-suture myopia in the rhesus macaque although it does in the

stumptail macaque. Whether or not there is a species difference is open to question because of the small sample size used (1 stumptail and 3 rhesus macaques). If lid-suture myopia in optic nerve sectioned rhesus monkeys is the result of visual deprivation, it may be that the deprivation is exerting its effect at the level of the retina. (2) In chickens, partial deprivation of the visual field produces severe myopia, and corresponding vitreous chamber elongation, localized to the region of the retina that has been deprived (Gottlieb et al. 1987; Wallman and Adams, 1987; Wallman et al., 1987).

Optic nerve section in chicks with partial visual deprivation was used to test whether the reported regional control of eye growth is, in fact, a local phenomenon. The role of the optic nerve in normal eye growth and the emmetropization from induced refractive errors was also studied in order to determine if the brain is involved in any aspect of eye growth studied in this dissertation.

Accommodation and eye growth

One commonly suggested type of brain-mediated feedback control mechanism for eye growth involves ocular accommodation (see Chapter 1). In fact, excessive accommodation has been suggested to be one of the critical causative factors in myopia (eg. Young, 1977; Bell, 1980). Despite a lack of strong evidence, the implication that accommodation is involved in eye growth has persisted and, in fact, forms the basis for certain clinical treatments of myopia such as the application of atropine (Bedrossian, 1971, 1979), or the use of bifocals in children (Oakley and Young, 1975; but see Grosvenor et al., 1987). Hypotheses involving accommodation are popular because accommodation offers a reasonable explanation of both the afferent and efferent pathways of a vision dependent eye growth control system. First, the activity of the accommodative system offers a direct measure of the refractive state of the eye (hyperopic eyes accommodate proportionally more for a given stimulus than myopic eyes). Second, accommodation clearly exerts relatively large mechanical forces on the eye.

The role of accommodation in eye growth was directly examined by lesioning the Edinger-Westphal nucleus, the source of the pre-ganglionic parasympathetic neurons which innervate the ciliary ganglion, which results in a loss of accommodation. The effect of the loss of accommodation on the growth of the eye toward or away from emmetropia, as produced in the studies presented in this dissertation was then determined. By opening the accommodative feedback loop in this way it was possible to conduct a more systematic, and experimentally controlled, analysis of accommodative influence on eye growth than has ever before been attempted (see Chapter 6).

Finally, because of the potential role of accommodation in eye growth, the mechanism of accommodation in chicks was investigated in some detail since various reports have indicated major differences in the anatomy and physiology of accommodation in birds relative to mammals (Beer 1892/93; Walls, 1942; Meyer, 1977; Sivak, 1980). The mechanism of accommodation in chicks was studied using electrical and pharmacological stimulation techniques to produce refractive changes while the changes in corneal curvature and the axial dimensions of the various ocular components were monitored (see Chapter 6). In particular, this study was concerned with two controversial points involving the role of the cornea (Gundlach et al., 1945; Levy and Sivak, 1980; Sivak et al., 1986), and that of the ciliary muscle on the lens (Walls, 1942; Sivak, 1980): (1) Does the cornea play an active role in accommodative changes in the chicken and, if so, to what degree? (2) Is lens shape changed by a direct squeezing of the ciliary muscle as in some avian species (Walls, 1942; Sivak, 1980) or, as suggested for humans by Helmholtz (1909), by the ciliary muscle's ability to release tension on the zonules thus allowing the lens' inherent elasticity to bring about accommodative changes?

CHAPTER THREE

GENERAL METHODS

Subjects and Housing

White Leghorn chicks *(Gallus gallus domesticus)* were hatched in the laboratory and raised in temperature controlled brooders under fluorescent lights (14 hours light/10 hours dark). Food (Purina Startena Crumbles) and water were available *ad libitum.*

Visual Manipulations

To induce myopia, the chicks had white translucent plastic hemispheres (after Wallman et al., 1978) secured around the eye with Collodion (Fisher Scientific). These occluders had a portion cut away to enable form vision in part of the visual field. In one type of occluder, the vision was restricted to the frontal field (i.e. the temporal retina viewed images while the nasal retina was deprived) and in another, vision was restricted to the lateral/posterior field (i.e. the nasal retina viewed images while the temporal retina was deprived). The openings in the occluders were cut in such a way that they allowed approximately 65° of unobstructed frontal visual field or 75° of unobstructed lateral/posterior visual field respectively (Wallman et al., 1987).

To induce hyperopia, the chicks were raised under complete darkness in a light-proof, temperature controlled chamber. During the first week of dark-rearing the chicks were force-fed 3-4 times daily a suspension of pulverized chicken feed in water in order to maintain their normal weight. The mixture was introduced into the crop through a 3 cc

syringe attached to a 2 mm diameter rubber tube. During these feedings, the chicks were exposed briefly to illumination from a 7-watt red light. After a week of force-feeding the chicks learned to eat in the dark, and at the end of four weeks their weight was not significantly different than normally reared chicks (Gottlieb et al., 1987).

Measurements

All measurements were performed on chicks lightly anesthetized with Chloropent (Fort Dodge; 0.25 cc/100 g i.m.). The intraocular muscles were paralyzed with a curare cycloplegic solution (Wallman et al., 1981a). The chicks typically recovered fully from Chloropent anesthesia in about 5 hours, and the cycloplegia wears off in approximately the same amount of time.

Refractometry

Refractive errors, measured in diopters (D), were determined using a Hartinger Refractometer (Jena Coincidence Refractometer). The refractometer was aligned with the eye's pupillary axis which, in chicks, closely approximates the optic axis (observations based on Purkinje image analyses). To align the refractometer, a circular fluorescent lamp was placed concentric with the refractometer's optical axis. With the refractometer 10-15 cm from the eye, the first Purkinje image of the lamp reflected from the cornea is clearly visible and was made coaxial with the pupil by adjusting the chick's head position. Following alignment, the refractometer was translated along its optic axis toward the eye to the proper measuring distance, the circular lamp was turned off, and the refractive error was measured.

The spherical equivalent refractive error was computed by averaging two orthogonal measurements taken on the principal meridians. Each datum was the average of 6-8 measurements of the spherical equivalent refractive error. The refractometer was realigned after every second or third measurement. Since each datum was a mean, the standard error

of this mean provides an estimate of the precision (repeatability)[1]. Thus the average standard error for refractometer measurements was calculated to be ±0.3 D.

Because the eyes of chicks are much smaller than the human eyes for which the refractometer was designed, the width of the light beam entering the pupil was reduced by attaching to the instrument an +11 D lens. The refractometer was calibrated using the following methods: A simple mechanical eye was constructed using a plano-convex lens of known power mounted parallel to a screen on a movable platform. By placing the screen at different distances from the lens, different degrees of "ametropia" were produced. Because the accuracy of this technique is limited by the aberrations in the lens used, a single lens reflex camera was also refracted while it was focused from infinity (to simulate emmetropia) down to its minimal working distance (to simulate different amounts of myopia). To simulate hyperopia, the lens of the mechanical eye was removed and the screen alone was refracted at different distances from the refractometer. At a screen to refractometer distance of 1 m, +1 D of hyperopia is simulated, at 0.5 m, +2 D is produced and so on. The data from these 3 methods of simulating refractive errors were fitted with a third order polynomial which served as the calibration curve. Because the clinical determination of refractive error is meant to prescribe a corrective spectacle lens at a certain distance from the eye (the vertex distance), the calibration also assumed that this vertex distance was zero (placing the corrective lens at the surface of the cornea) to estimate the eye's actual refractive error. To check the validity of this calibration, refractions measured by refractometry were compared to refractions measured by streak retinoscopy. Another mechanical eye was constructed using a 10x microscope objective and a micrometer which allowed both myopic and hyperopic refractive errors to be simulated. Fairly good

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[1]The standard error is an estimate of the standard deviation which would be obtained from a collection of means based on equal-sized sample sizes from the same population. As such, it is a indicator of measurement precision, and is inversely proportional to this precision.

agreement between the two techniques was found (Figure 3.1). However, hyperopia greater than +15 D is either overestimated by refractometry or underestimated by retinoscopy by approximately 15%. In fact, the retinoscopy is probably less accurate for increasingly hyperopic refractions because the technique requires the placement of thicker and thicker positive lenses in front of the eye and, in so doing, enlarges the vertex distance of the corrective lens thus creating the appearance of less actual hyperopia (see Appendix B).

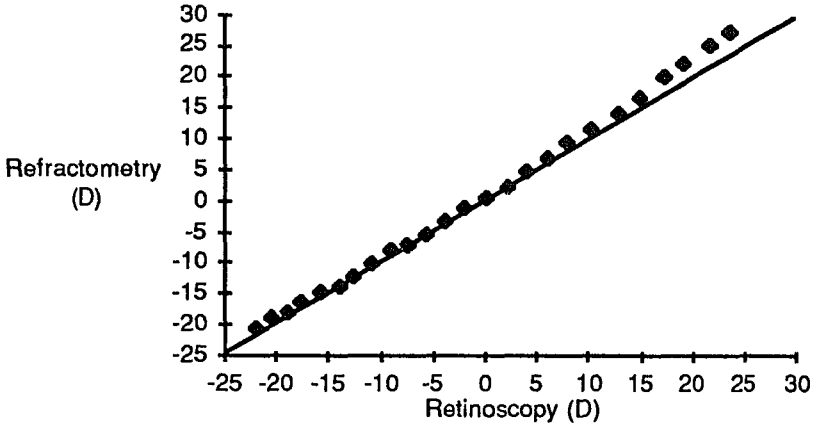


Figure 3.1
Converted refractometer refractions vs. retinoscopy refractions of the 10x mechanical eye (r=0.997). The slope of the diagonal line is 1. See text for details.

To measure refractive errors off the optic axis, the procedure described by Wallman et al. (1986) was used. After alignment and refractive error measurements along the optic axis were performed, the center of the subject's pupil formed the center of rotation as the bird was rotated 30° to either side and refractive errors of the nasal and temporal halves of the retina were measured. With this method, refractive error of the eye could be effectively measured along three lines of sight which intersect at the center of the pupil: the optic axis (central retina), 30° anterior to the optic axis (temporal retina), and 30° posterior to the optic axis (nasal retina. The refractive error measurements presented in this dissertation were not corrected for the hyperopic artifact of retinoscopy (Glickstein and Millodot, 1970) prominent in small eyes and estimated to be in the range of 5-2 D for 1-8 week old birds respec-

tively (Wallman and Adams, 1986). Figure 3.2 shows the effect of eye size on the artifact of retinoscopy and indicates approximately the magnitude of the retinoscopic artifact based on the mean axial length of chicks at various ages.

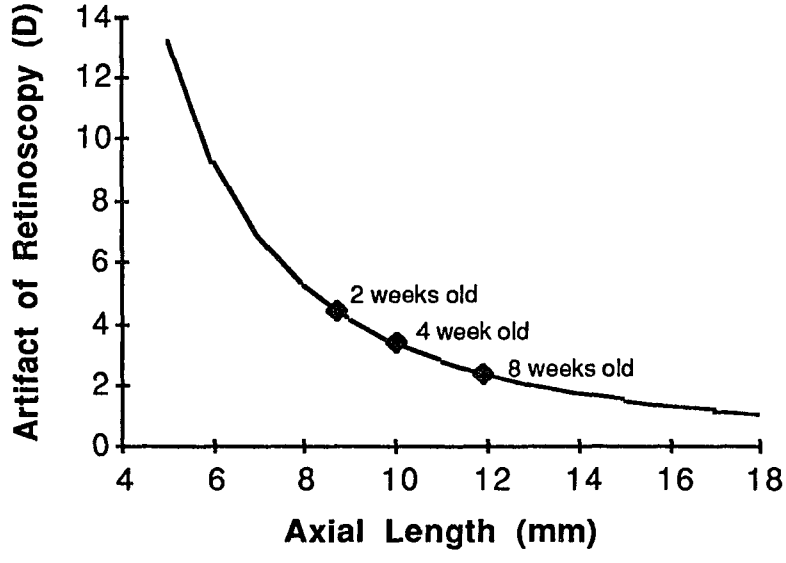


Figure 3.2
The artefact of retinoscopy in eyes with retinas assumed to be 0.22 mm thick, the average thickness of the chick's central retina (±30° from the optic axis) as measured from frozen eye sections (n=6). The artifact was calculated as described by Wallman and Adams (1987). The axial lengths and retinoscopic artifacts for 2, 4, and 8 week old chicks are specifically indicated.

Because the distribution of refractive error is typically not normal, nonparametric statistical tests were used for analysis. The Mann-Whitney *U*-test was used for comparisons between unpaired data and Wilcoxon's Signed-Ranks test was used when the data were paired. Where appropriate Friedman's nonparametric 2-way analysis of variance was also used, as was the Kolmogorov-Smirnov two sample test of differences in distribution. All of the other parameters measured (see below) meet the basic requirements for the use of parametric statistics.

Keratometry

Corneal curvature was determined using a Sutcliffe keratometer (Topcon OM-3). Alignment of the keratometer was similar to that used for the refractometer; by disengaging the instrument's image doubling prisms, the reflection of the keratometer's circular mire can be concentrically aligned with the pupil. As in refractometry, the keratometer also had

to be adapted with a supplemental lens (+8 D) for the smaller eyes, and highly curved corneas, of chicks. The keratometer was then calibrated by measuring steel balls of known diameter. After converting the instrument to measure the small eyes of chicks, approximately 4.0 mm^2 of cornea is sampled by this instrument.

Spherical curvature (measured as the spherical radius of curvature of the anterior corneal surface) was calculated in the same manner as in refractometry. The precision of keratometery was determined to be ±0.02 mm (approximately 1 D in terms of corneal power). This is similar to the precision reported in several studies reviewed by Ludlam et al. (1965).

Purkinje-image photography

The first, third, and forth Purkinje images were photographed and used to determine the curvatures of the cornea, anterior lens surface, and posterior lens surface respectively. Three fiber optic light guides arranged in an equilateral triangle centered on the camera's optic axis were used as the light source. The area of cornea sampled by this technique was approximately 0.3 mm^2. The camera was easily aligned with the eye's optic axis by moving the chick's head until the reflected triangles arising from the three images were concentric (Figure 3.3).

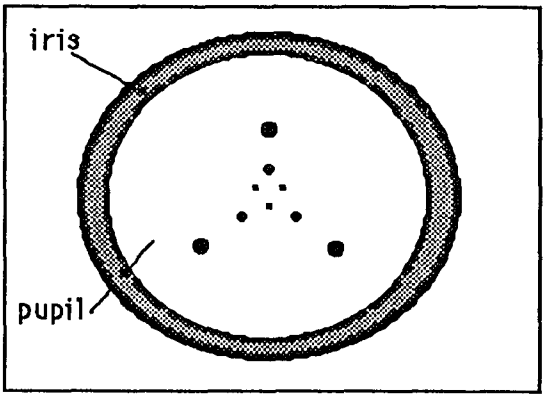


Figure 3.3
A representation of a photographic negative showing all three sets of Purkinje images forming equilateral triangles which are concentrically aligned with the eyes optic axis. In reality, all three sets of images are not in focus simultaneously. The large, outer images are the third Purkinje images which arise from the anterior lens surface. The middle images are the first Purkinje images reflected from the corneal surface. The small, inverted inner images represent the fourth Purkinje images reflected from the posterior surface of the lens and were often difficult to detect.

Before each series of measurements a calibration curve was determined by fixing the camera's film to lens distance and photographing separately a ruler (to determine magnification) and several steel balls of different size. The Purkinje-images were then photographed, bringing each set into focus by moving the bird's eye toward or away from the camera, thus leaving the magnification constant. The photographic images were later projected onto a digitizing tablet (Summagraphics) to determine the diameter of the circle drawn through the three Purkinje-images of each set of images. This gave a single estimate of the curvature for each refracting surface. The calculations used to convert these values into curvatures are given by Bennett and Francis (1962). To determine the precision of this method the measurements of the Purkinje-images in one case were repeated 10 times and the standard error was within ±0.02 mm. Because the Purkinje-image camera had a depth of field of about ±1 mm, this could produce measurement errors of approximately ±0.05 mm which amounts to ±1.5 D of corneal power (for the derivation of the necessary optical calculations see Bennett and Francis, 1962).

Ultrasonography

A-scan ultrasonography was used to measure the spacing and thicknesses of the various ocular components (cornea, anterior chamber, lens, and vitreous chamber) approximately along the optic axis. The basic principle is that sound waves are reflected from the interfaces between the various ocular components. The time for the echo to return to the transmitter is a function of the distance between interfaces and can be calculated if the speeds of sound in the different ocular media are known. A 6 mm diameter 7.5 MHz transducer (Panametrics) focused at 18 mm, was driven by a Metrotek pulser-receiver. The receiver yields a radio frequency signal that is recorded on diskettes using a digital oscilloscope (Nicolet). The calibration of this technique is described elsewhere (Wallman and Adams, 1987). Four ultrasound recordings were made for each eye and the data were averaged. The precision of ultrasonography was estimated to be ±0.03 mm. Figure 3.4

illustrates the basic form of the complete ultrasound echo showing the depth of the anterior chamber, the thickness of the lens, and the depth of the vitreous chamber, respectively.

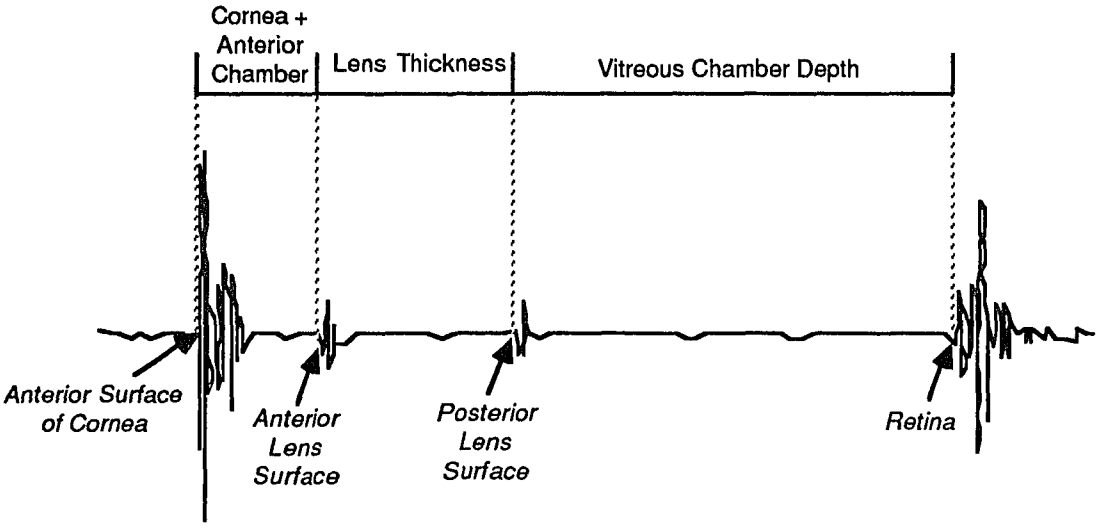


Figure 3.4
A digitized representation of an A-scan ultrasound echogram from a chick eye. As indicated, the peaks represent the surfaces of the various ocular components. The axial lengths between the components can be determined knowing the speed of sound in the various media (see Wallman and Adams, 1987). Note that, although the front and back surfaces of the cornea can be seen in the biphasic nature of the first reflection, it is difficult to accurately discern the corneal thickness so corneal thickness and anterior chamber depth are combined.

Photographs

After the completion of all measurements *in vivo*, some of the chicks were deeply anesthetized and sacrificed by perfusion with 10% formalin. The eyes were later enucleated in order to determine the gross shape of the back of the globe. Marks were made on the dorsal limbus allowing the eyes to be positioned in close approximation to their normal orientation in the orbit. The eyes were then photographed from a dorsal view. The shapes were traced from the images and then digitized and entered into a PDP-11/73 minicomputer for alignment and averaging of the outlines of the eyes for the various experimental groups. The control eyes were similarly analyzed (for details see Wallman et al, 1987).

Optical calculations

Optical ray-tracing calculations were used to determine the optical characteristics of the whole eye, or any of the individual refracting components within the eye. The method for calculating the cardinal points of an optical system is fully described in Appendix A. The refractive indices used for the aqueous and vitreous humors were both 1.335 as measured an Abbé refractometer (unpublished results). The refractive index of cornea was taken as 1.362 (Sivak et al., 1978). And a homogeneous refractive index of the crystalline lens was estimated as 1.485 based on the measured focal length of excised lenses of known thickness and curvatures (unpublished results).

Surgical Manipulations

Optic nerve section

To section the optic nerve, the chicks were deeply anesthetized with a gaseous mixture of Halothane (Butler; 0.6 l/min), nitrous oxide (2.0 l/min), and oxygen (0.4 l/min). An incision was then made 1-2 mm lateral to the temporal canthus. After the conjunctiva was incised, the eye was retracted slightly and the extraocular muscles were moved aside to expose the optic nerve. The epineurium was cut, and the retinal ganglion cell axons were severed using fine scissors and forceps. There was no significant bleeding during this procedure and, based on external examination, the eyes appeared normal throughout the postoperative period. Sham operations in which the optic nerve was exposed but not cut were performed in 7 chicks. There were no significant differences in any of the measurements between the sham operated eyes and either the unoperated fellow eyes or normal eyes in unoperated birds of the same age. Within 30-60 minutes following surgery, the chicks were observed to be walking and eating normally.

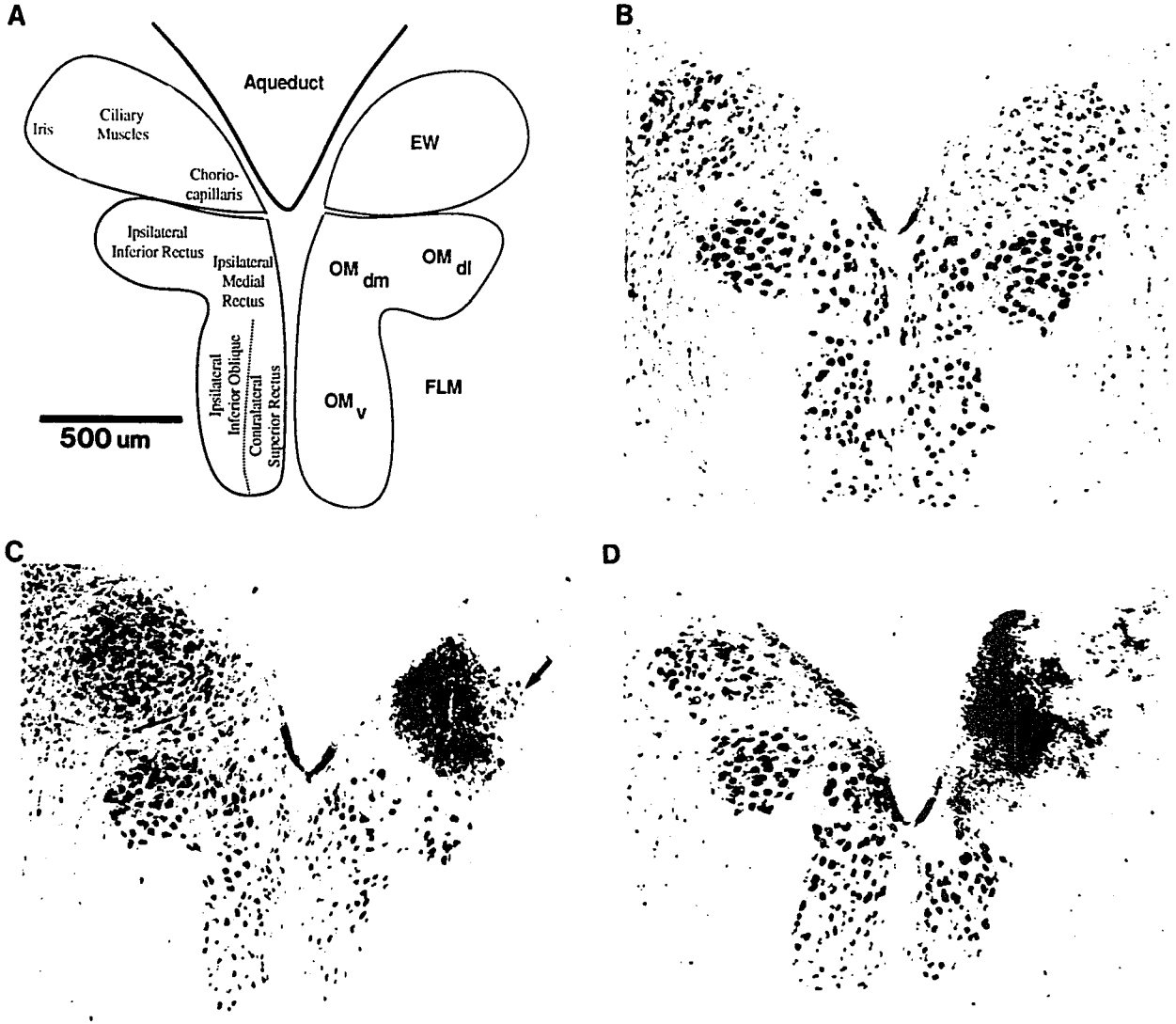
Qualitative startle and orientation tests indicated that, in every case, the surgery produced functional blindness when the contralateral normal eye was covered. Chicks that exhibited normal pupillary light reflexes were dropped from the study. Although the

isolated iris of neonatal chicks is directly capable of some response to light (Pilar et al., 1988), the presence of even slight pupillary light reflexes in optic-nerve-sectioned eyes may result from optic nerve sparing because the efferent projections of the pupillary light reflex in chicks are uncrossed and unilateral (Narayanan and Narayanan, 1976; Reiner et al., 1983). Those optic-nerve-sectioned eyes which showed diminished and sluggish responses were retained but are flagged in the data.

Edinger-Westphal lesions

Chicks undergoing stimulations or lesions of the Edinger-Westphal nucleus (EW) were deeply anesthetized with Chloropent (Fort Dodge; 0.33 cc/100 g i.m.) or, for the acute preparations used in some of the stimulation studies, urethane (40% aqueous; 0.4 cc/100 g i.p). Monopolar electrodes (Rhodes SNEX-300: tips 0.25 mm long and 0.1 mm in diameter, or 00 insect pins insulated with INSUL-X leaving an exposed tip of approximately 0.1 mm) were stereotaxically placed into the EW and their position adjusted to produce large accommodative responses to electrical stimulation (stimulation parameters: 30-40 μA, 100 Hz, 0.5 msec bipolar pulses). The reference electrode was a 22 gauge hypodermic needle inserted in the skin of the neck. Typically, large accommodative changes were accompanied by brisk pupillary contractions, bulging of the iris, and noticeable changes in the first and third Purkinje images. If downward eye movements were produced, the electrode was moved dorsally since the division of the oculomotor nucleus which innervates the inferior rectus muscle lies just ventral to the EW (see Figure 3.5); if torsional eye movements were produced (indicating stimulation of the trochlear nucleus) the electrode was moved anteriorly.

Figure 3.5 (following page)
The oculomotor complex of the chick. **Panel A:** A schematic indicating the sub-divisions of the oculomotor complex and their target sites (via the ciliary ganglia in the case of the EW). Oculomotor nucleus innervation sites from Heaton and Wayne (1983), Edinger-Westphal innervation sites from Reiner et al. (1983). [Abbreviations: EW=Edinger-Westphal nucleus; OM=oculomotor nucleus; dm=dorso-medial; dl=dorso-lateral; v=ventral; FLM= fascicularis medialis longitudinalis]. **Panel B:** A photomicrograph of a normal oculomotor complex (Nissl stain). **Panel C:** A photomicrograph showing an electrolytic lesion to EW. In this case, a small percentage of the cells (arrow) have been spared. **Panel D:** For complete ablation of the EW, damage to the $OM_{d,}$ as shown in this photomicrograph, was practically unavoidable. Only chicks in which the EW was completely lesioned, and did not show any sign of pupillary activity, were used in the studies described in Chapter 6. The average volume of the oculomotor nucleus lesioned in these cases was 50%±25.


A
Aqueduct
Iris
Ciliary
Muscles
Chorio-
capillaris
EW
Ipsilateral
Inferior Rectus
Ipsilateral
Medial
Rectus
OM dm
OM dl
Ipsilateral
Inferior Oblique
Contralateral
Superior Rectus
OM v
FLM
500 um
B
C
D

The parameters used for electrolytic lesions large enough to ensure total destruction of EW with minimal effects on the surrounding structures were determined to be approximately 1 mA of anodal DC for about 10 seconds. Successful lesions resulted in fully dilated pupils which were unresponsive to light. If a light reflex remained, the electrode was moved slightly, and more current applied. Only those EW-lesioned chicks without pupillary light reflexes after recovery from the surgery, as well as no histological evidence of EW sparing, were used.

In order to assess the location of the stimulating electrode, or the completeness of the lesions, the chicks were sacrificed by perfusion with Heidenhain's fixative. Brain sections 50 μm thick were mounted and stained with either neutral red or cresyl violet for histological inspection. For lesion assessments, drawings of serial sections through the oculomotor complex (see Figure 3.5) were analyzed using a digitizing tablet (Summagraphics) connected to a Macintosh personal computer (Apple). The extent of the lesion was determined by measuring the volume of EW spared, if any, or, in the case of complete EW lesions, the volume of the oculomotor nucleus lesioned. These volumes were then compared either to the volume of the intact EW or the volume of the intact oculomotor nucleus, thereby determining the percent volumes of the EW nucleus spared or the oculomotor nucleus lesioned, respectively.

CHAPTER FOUR

EXPERIMENTAL EMMETROPIZATION: EVIDENCE FOR REFRACTION-SENSITIVE REGULATION OF EYE GROWTH*

As described in Chapter 1, the possibilities regarding the growth of the eye are generally categorized as either genetically pre-programed or under active feedback regulation. If feedback regulation of eye growth exists, it would require that the mechanism be able to sense whether the eye was myopic or hyperopic in order to direct growth appropriately. At present there is little experimental evidence for such regulated eye growth and, consequently, the nature of the putative error-signals is unknown. In this chapter, studies are presented which determine the ability of the eye to regulate its growth toward emmetropia (emmetropization). Emmetropization was studied experimentally by determining the ability of chick eyes to adjust their refractive states after they were made either myopic (by depriving the eye of form vision), or hyperopic (by raising them in complete darkness). The results of these experiments strongly suggest that the refractive development of the eye is, in fact, actively regulated. The results also imply that this regulation is guided by the visual experience (specifically, the refractive state) of the eye.

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* Portions of this chapter were presented at the 1988 annual meeting of the Association of Research in Vision and Ophthalmology (Troilo and Wallman, 1988).

In chicks, recovery from induced myopia has already been reported (Wallman et al., 1981a; Wallman and Adams, 1987). These results are confirmed here, where it is further shown that the return to emmetropia can take place in as little as one week. Taken alone, however, these findings do not provide unequivocal evidence that eye growth is visually regulated. If the vitreous chamber enlargement produced by visual deprivation was the result of an insult to certain vegetative processes, rather than via visual regulatory processes, the observed recovery from myopia could result simply from the cessation of the abnormal vitreous chamber growth, after the manipulation causing it was removed, and as the rest of the eye grew normally. Furthermore, the existence of a shape-sensitive feedback mechanism could also explain these observations.

Prior to this study, it was unclear whether or not recovery from dark-induced hyperopia was possible. The hyperopia from dark-rearing is clearly the result of a significantly flattened cornea in an abnormally large eye (Gottlieb et al., 1987). This indicates that the optical power of the eye is severely diminished relative to normal eyes of the same age or size. Furthermore, the optical power is so weak that even with the excessive vitreous chamber depth these eyes are hyperopic. The finding, reported below, that hyperopic eyes are able to adjust their growth and return to emmetropia supports the notion that eye growth is actively regulated, and that this regulation is probably based on visual error-signals. Two ametropia-correcting adjustments were observed: (1) increasing vitreous chamber depth (an increase in an already abnormally enlarged ocular component); (2) increasing corneal curvature (a change in the opposite direction of what is normally seen during eye growth). The presence of these changes argue for refraction-sensitive feedback regulation of eye growth because it appears that the feedback controller ignores eye size *per se*.

Methods

Sixteen White Leghorn chicks *(Gallus gallus domesticus)* were used in this study. Nine chicks were made myopic by visual form deprivation with white translucent occluders, while seven were made hyperopic by raising them under conditions of complete darkness (see Chapter 3 for details of both treatments). After 2 weeks of the visual form deprivation, or 4 weeks of dark-rearing, the treatments were discontinued and the chicks were returned to normal rearing conditions (21° C under a diurnal light cycle: 14 hours on, 10 hours off) for 2-3 weeks.

On the day the manipulations were discontinued, the resulting refractive errors were assessed with refractometry. Morphological measures of the eye were made with keratometry and A-scan ultrasonography (see Chapter 3). During the subsequent period under normal rearing conditions, all of the measurements were repeated after 1 week, and again 1 or 2 weeks later.

Results

Myopia to emmetropia

As shown in Figure 4.1, after 2 weeks of visual deprivation in newly hatched chicks, significant levels of myopia were produced relative to normal controls (medians: -7.87 D vs. +3.57 D; *U*-test, $p<0.01$). When the visual deprivation was removed at 2 weeks of age, and the eyes re-examined 1 week later, it was found that in all nine cases the refractive state had returned to near-emmetropic levels (median = +3.96 D[1]; Wilcoxon, $p<0.01$).

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[1]The artifact of retinoscopy (Glickstein and Millodot, 1970), which biases refractions in small eyes toward hyperopia, is not accounted for in the measures of refractive error presented throughout this dissertation. This is because of the difficulties in accurately determining the changing magnitude of the artifact in individual eyes as they grow. For an estimate of this effect over time, see Chapter 3.

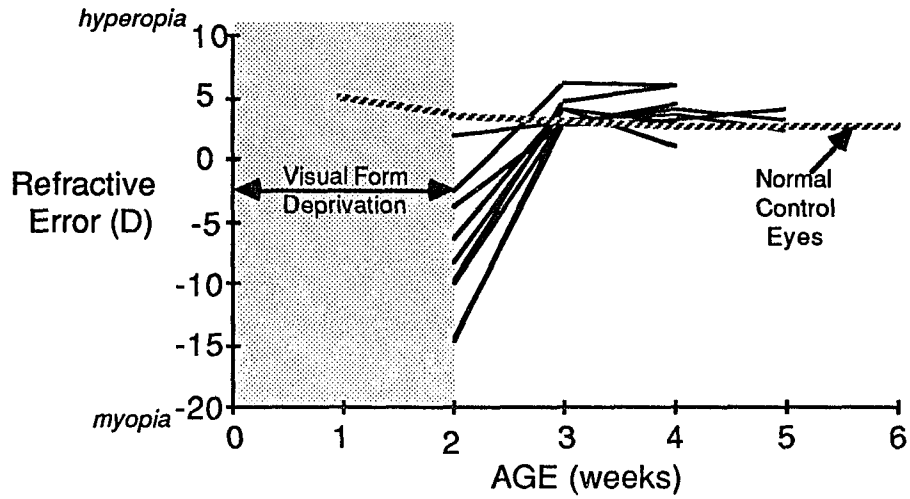

Figure 4.1
Individual refractive errors after the myopia-producing visual form deprivation (stippled area) is discontinued. The individual refractions of chicks reared with visual form deprivation occluders until 2 weeks of age are shown as solid lines. Refractive error measurements were first made at 2 weeks of age when the occluders were removed, and then at 3, 4, and, in some cases, 5 weeks of age. After 1 week without visual form deprivation, the refractive state has returned to normal levels. The dashed line shows the change in the median refractive errors of normally-reared control chicks measured at 1, 2, 4, 6, and 8 weeks of age.

The anatomical correlates of the refractive changes just described are illustrated in Figures 4.2 and 4.3. After 2 weeks of visual form deprivation, only the vitreous chamber depth was significantly different from normal controls (means: 5.66 mm vs. 5.16 mm; *t*-test, $p<0.01$). Following removal of the visual deprivation, the vitreous chamber ceased to grow (mean vitreous chamber depth at 3 weeks of age = 5.57 mm)[2]. Compared to normal controls, the rate of change in vitreous chamber depth between 2 and 3 weeks was significantly lower in the myopic eyes after the visual deprivation was discontinued (controls: 0.281 vs. myopic: 0.092; one-tailed *t*-test, $p<0.01$). Corneal curvature, lens

[2]Although it appears that the vitreous chamber actually shortens in these eyes, there is no significant difference in vitreous chamber depth compared to that measured at two weeks (paired *t*-test, $p=0.1537$) implying that the vitreous chamber simply stopped elongating.

thickness, and anterior chamber depth were all within normal parameters after two weeks of visual deprivation, and continued to grow normally throughout the period when refractive state returned to emmetropia.

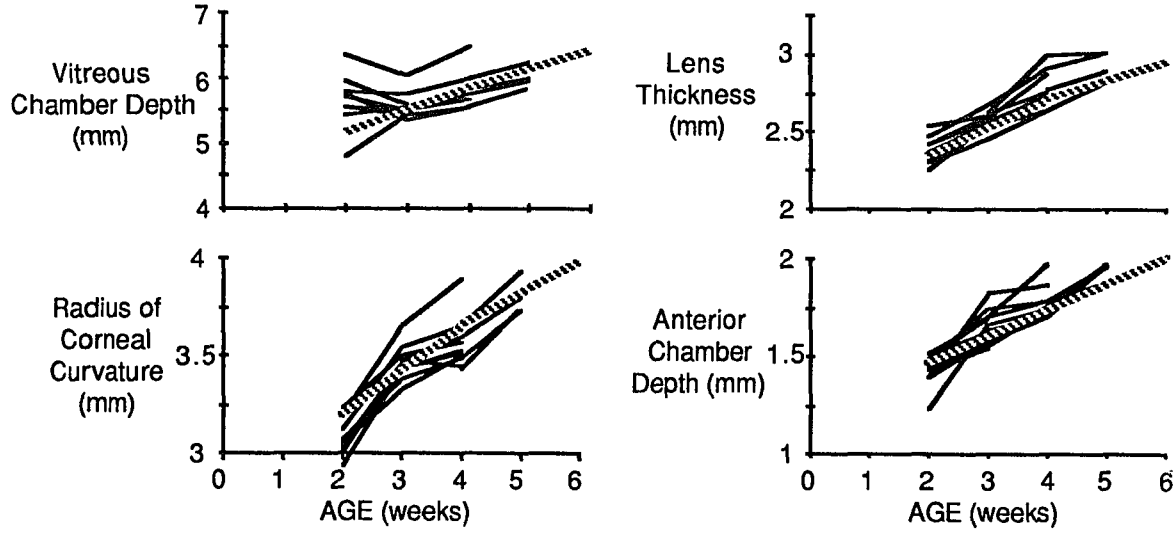

Figure 4.2
Individual corneal curvatures, anterior chamber depths, lens thicknesses, and vitreous chamber depths for the same chicks whose refractive changes are shown in Figure 4.1. The averages of these values are shown in Figure 4.3. The broken line shows the average values of the various parameters for normal control chicks.

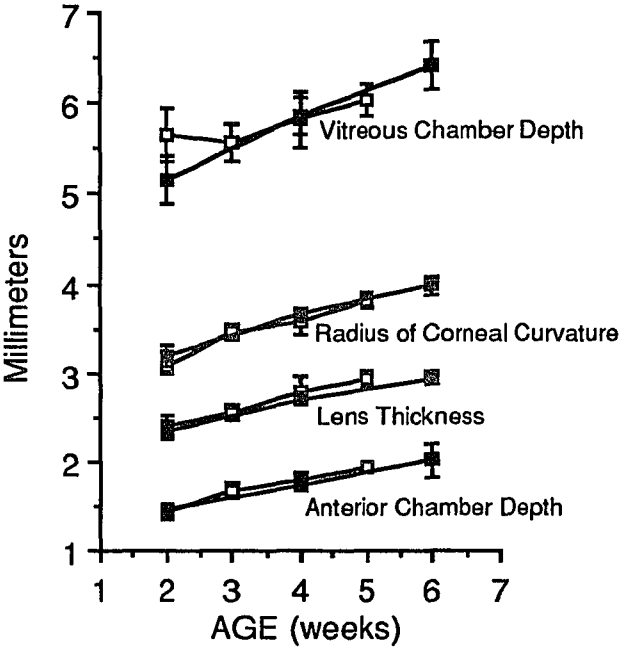

Figure 4.3
The anatomical correlates of the emmetropization from visual deprivation myopia shown in Figure 4.1. Values are means, error bars are standard deviations. Unfilled boxes represent eyes initially made myopic by visual form deprivation, filled boxes represent normal control measurements. For both groups, the data were longitudinal and statistical tests for paired data were used to assess age-related morphological changes. The cessation in growth of the enlarged vitreous chamber between the ages of 2 and 3 weeks while the anterior segment grew normally largely explains the return to emmetropia from myopia observed at the same time. The anterior chamber depth includes the thickness of the cornea, estimated to be about 0.24 mm. Corneal curvature is expressed as the radius of curvature; larger values indicate less curved corneas.

Figure 4.4 shows the relative influence on refractive state of the different changes in the various ocular components between the ages of 2 and 3 weeks when the visual deprivation was removed and the eyes returned to emmetropia. This method was also used to analyze the structural basis of emmetropization from dark-induced hyperopia (see next section). Such analyses predict refractions using ray-tracing calculations for the individual eyes (see Appendix A). Because no data for the anterior and posterior lens curvatures were available, the lens power was estimated to reconcile the ocular components with the refractions measured one week after the ametropia-producing visual manipulation was discontinued and the eye had returned to emmetropia. This procedure, by definition, sets the predicted refraction equal to the measured refraction. Next, one parameter (shown in parentheses in Figure 4.4 and 4.10) was given the value measured the day the visual manipulation was

discontinued (that is, when the eye was ametropic), and the resulting predicted refractive error was plotted. If the result was more myopic than the measured refraction this indicates that the change in that parameter observed during the week of growth toward emmetropia had the effect of contributing to a decrease in total optical power (i.e. it makes the eye relatively more hyperopic). If the result was more hyperopia than the measured refraction, the actual change in that parameter contributed to an increase in total optical power (i.e. it makes the eye relatively more myopic). In this way the contribution of a components change to emmetropization can be determined (e.g. changes which produce more hyperopic refractions contribute to emmetropization from myopia).

The return to emmetropia from visual deprivation myopia is largely the result of a cessation of vitreous chamber growth while the anterior segment continues to grow normally. Figure 4.4 shows that had the vitreous chambers in the emmetropizing myopic eyes continued to grow from 2 to 3 weeks in an amount equal to that of normal birds, the eyes would have been approximately 10 D more myopic than observed. The refractions predicted when the vitreous chambers are held at their 2 week depths, and while the rest of the eye continued to grow, slightly overestimate the emmetropization from myopia at 3 weeks. Besides the cessation in vitreous chamber growth, the normal growth of the anterior segment is necessary for the return to emmetropia from visual deprivation myopia. If the corneal curvature had not changed between 2 and 3 weeks, but remained at their 2 week sizes, the eyes would have remained severely myopic. Changes in the anterior chamber depth clearly play a smaller role than does the corneal curvature in the determination of total optical power. Nevertheless, if the depth of the anterior chamber does not increase between 2 and 3 weeks, the optical power of the eye will not be reduced sufficiently to achieve the observed refractive state. Because these components never differed from those of normal controls, the return to emmetropia can be attributed almost entirely to vitreous chamber

change. However, as stated earlier, these data do not provide unequivocal evidence for regulatory control of refractive state.

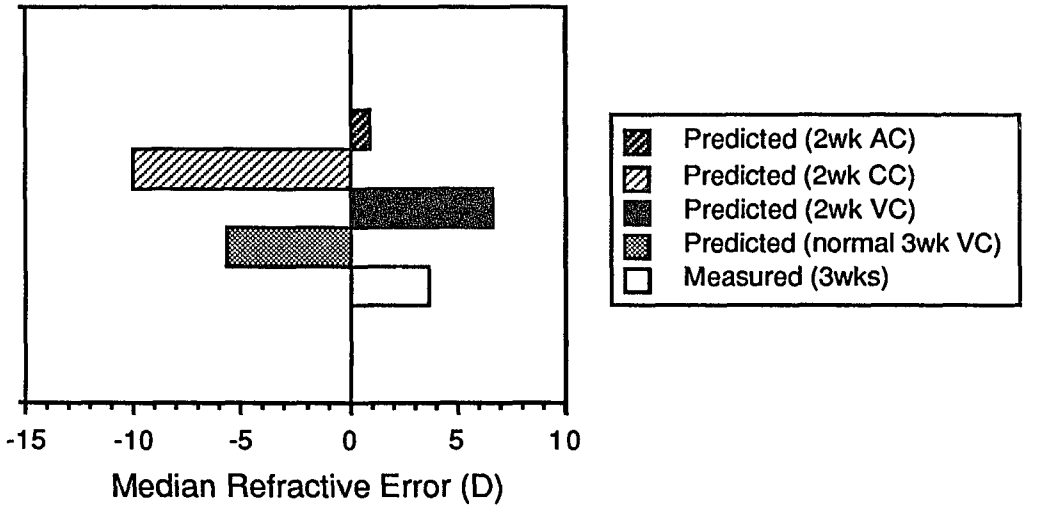

Figure 4.4
The relative effects on refractive state of the various changes in the different ocular components between 2 and 3 weeks of age when the emmetropization from visual deprivation myopia was observed (AC = anterior chamber depth; CC = corneal curvature; VC = vitreous chamber depth). Predicted refractions were obtained from ray-tracing calculations using the measurements from individual 3-week-old eyes except for the parameter in parentheses which was held at its 2-week value. Thus, the discrepancy between the predicted and measured refractions give an indication of the optical effect of the change in that parameter (see text for details). The cessation of vitreous chamber growth, together with the normal growth of the anterior segment, is responsible for the return to emmetropia. If, from 2 to 3 weeks of age, either the vitreous chambers grew normally for their size, or the corneal curvatures did not, the eyes would remain myopic. The anterior chamber depth has a relatively smaller role in the determination of refractive state but contributes to the recovery from visual deprivation myopia.

Hyperopia to emmetropia

Raising chicks in the dark for 4 weeks produces significant hyperopia relative to normal 4-week-old controls (+8.24 D vs. +2.6 D; *U*-test, $p<0.01$). Figure 4.5 shows that these hyperopic eyes were able to recover (+8.24 D to +1.24 D; Wilcoxon, $p<0.01$) after only 1 week under normal lighting conditions. Although Figure 4.5 suggests that the refractive

state after 1 week of recovery actually overshoots the normal refractive state of control eyes before returning to normal values 2 weeks later, there is, in fact, no significant difference between the refractive errors measured at 5 weeks and those at 7 weeks (+1.24 D vs. +1.69 D; Wilcoxon, p=0.126).

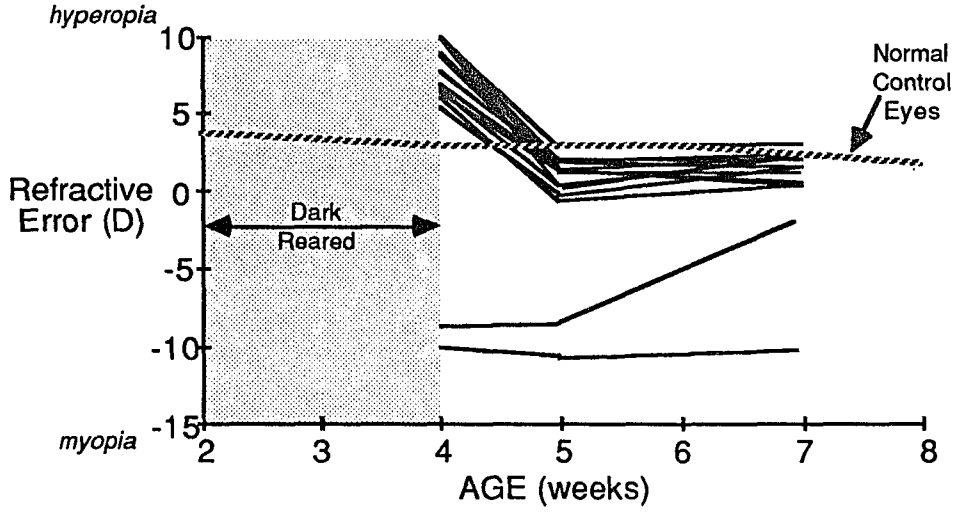

Figure 4.5
Individual refractive errors after dark-reared chicks are returned to normal rearing conditions. The individual refractions of chicks reared in the dark until 4 weeks of age are shown as solid lines. Refractive error measurements were made at 4 weeks when the chicks first came out of the dark (stippled area), then at 5 and 7 weeks of age (1 and 3 weeks of normal rearing respectively). Notice that at 4 weeks one of the dark-reared birds was myopic in both eyes. This is in agreement with the high variability in refractive state reported by Gottlieb et al. (1987) for dark-reared chicks. Because the principal question of interest here is the ability to return to emmetropia from hyperopia, these two myopic eyes were omitted from the statistical analyses. The dashed line indicates the median refractive errors of normally-reared control chicks measured at 2, 4, 6, and 8 weeks of age.

As in the emmetropization from visual deprivation myopia, the emmetropization from dark-induced hyperopia during the first week after the chicks were returned to normal rearing conditions is apparently the result of an adjustment in vitreous chamber depth. In terms of the anatomical measurements made (see Figures 4.6, and 4.7), the growth toward emmetropia from dark-induced hyperopia can only be explained by the increase in vitreous

chamber depth from 4 to 5 weeks of age (6.69 mm to 6.98 mm; paired *t*-test, $p<0.01$). Further, the rate of vitreous chamber growth between 4 and 5 weeks is significantly higher in eyes emmetropizing from hyperopia compared to normal controls (hyperopic: 0.282 mm/wks vs. controls: 0.168 mm/wks; one-tailed *t*-test, $p<0.05$). These are remarkable findings in that the eyes were already significantly larger than normal controls (6.69 mm vs. 5.86 mm; *t*-test, $p<0.01$).

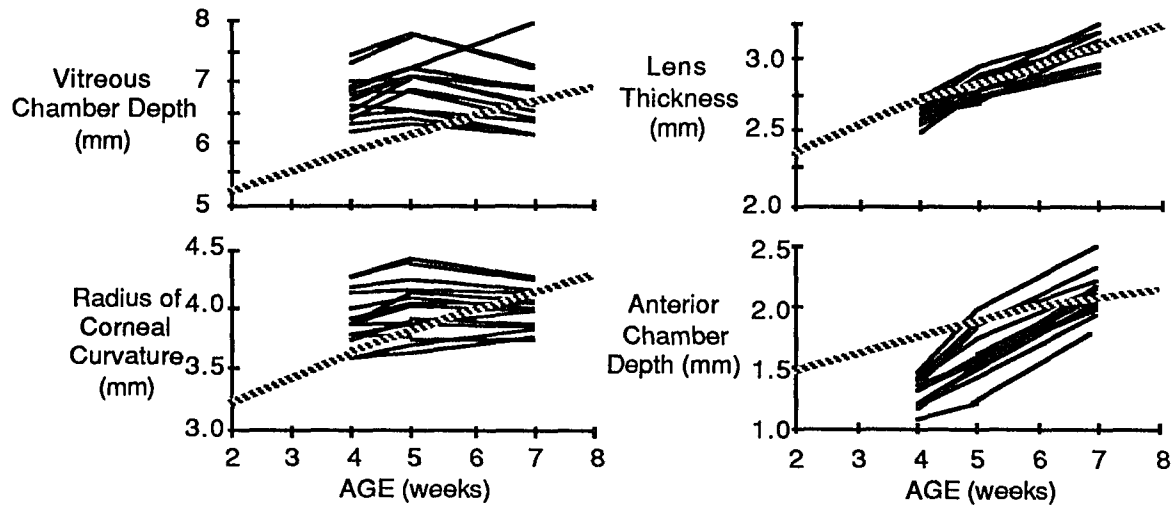

Figure 4.6
Individual corneal curvatures, anterior chamber depths, lens thicknesses, and vitreous chamber depths for the same chicks whose refractive changes are shown in Figure 4.5. The averages of these values are shown in Figure 4.7. The broken line shows the average values of the various parameters for normal control chicks.

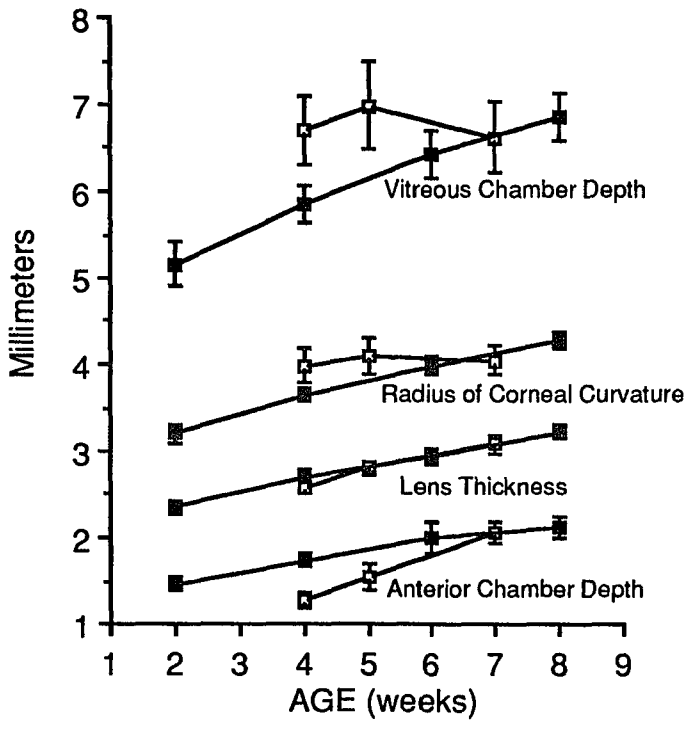

Figure 4.7
The anatomical correlates of the emmetropization from dark-induced hyperopia shown in Figure 4.5. Values are means, error bars are standard deviations. Unfilled boxes represent eyes initially made hyperopic by dark-rearing, filled boxes indicate normal control measurements. For both groups the data are longitudinal and statistical tests for paired data were used to examine age-related changes. Only the continued increase in vitreous chamber depth between the age of 4 and 5 weeks can explain the decrease in hyperopia observed at the same time. Anterior chamber depth includes the thickness of the cornea, estimated to be about 0.24 mm. An increase in the radius of corneal curvature indicates a decrease in the curvature of the anterior surface.

Changes in the anterior segment during the 4 to 5 week period, as seen in Figures 4.6 and 4.7, reduce the total optical power of the eye, effectively working against emmetropization from hyperopia. Corneal curvature significantly decreased during this period (radius of curvature: 3.98 mm to 4.09 mm; paired *t*-test $p<0.01$), while anterior chamber depth (1.27 mm to 1.55 mm; paired *t*-test, $p<0.01$) and lens thickness (2.59 mm to 3.08 mm; paired *t*-test, $p<0.01$) significantly increased.

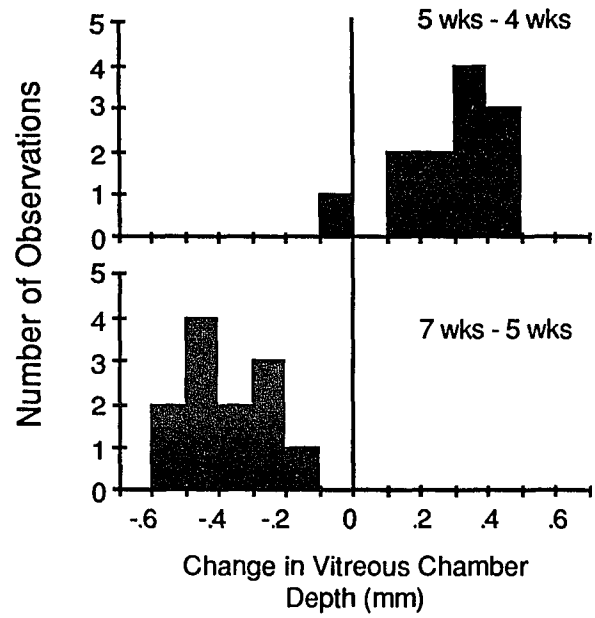

Figure 4.8
Histograms showing the individual changes in vitreous chamber depth of the experimental eyes between 4 and 5 weeks (significant increase in depth), and between 5 and 7 weeks (significant decrease in depth). The decrease in depth probably reflects a decreased rate of growth together with a concomitant increase in lens thickness.

During the second and third weeks following the return to normal rearing conditions (5-7 weeks of age respectively), even though the eyes have achieved normal refractions, the ocular components are still undergoing readjustment. Figures 4.6, 4.7, and 4.9 show that corneal curvature (which had continued to decrease during the first week of emmetropization) reverses this trend during the second and third weeks and shows a small, but significant, increase in curvature (that is, a decrease in radius of curvature: 4.09 mm vs. 4.03 mm; paired *t*-test, $p<0.05$). This is also reflected by the fact that anterior chamber depth does not completely return to normal levels until after 3 weeks of normal rearing conditions. Finally, the apparent decrease in the vitreous chamber depth (see Figures 4.6, 4.7, and 4.8) is most likely the combined result of a reduction in vitreous chamber growth during a simultaneous increase in lens thickness (the ultrasound measurement of the vitreous chamber is taken from the posterior surface of the lens to the inner surface of the retina). There was, in fact, a significant increase in the thickness of the lens (2.81 mm to 3.08 mm; paired *t*-test, $p<0.01$) during the 5 to 7 week period when the vitreous chamber

depth reduced significantly (6.98 mm to 6.61 mm; paired *t*-test, $p<0.01$). The increased lens thickness (0.27 mm) does not completely account for the decreased vitreous chamber depth (0.37) suggesting that a shift in the position of the lens may also occur.

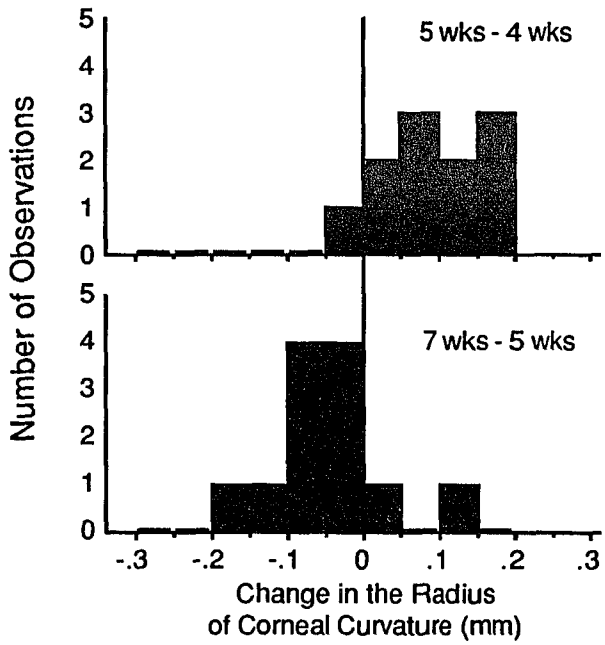

Figure 4.9
Histograms showing the individual changes in the radius of corneal curvature between 4 and 5 weeks (significant decrease in curvature), and between 5 and 7 weeks (significant increase in curvature). The radius of curvature is inversely proportional to the surface curvature.

Unlike emmetropization from visual deprivation myopia where the corneal curvature, anterior chamber and vitreous chamber are all involved, the emmetropization from dark-induced hyperopia can only be explained by the observed change in one of the ocular components — the increased growth of the vitreous chamber. As described earlier (p. 68), ray-tracing was performed for individual eyes as each of the ocular components in turn was held at its 4 week value (when dark-rearing ended and the eyes were hyperopic) in order to determine its relative influence on the eye's refractive state at 5 weeks (when the refractive states had returned to emmetropia). These calculations (see Figure 4.10) show clearly that if the increased growth of the vitreous chamber at 5 weeks is not present (4 week vitreous chamber), the eyes remain hyperopic. Figure 4.10 also shows that if the corneal curvatures

or anterior chamber depths do not change normally from their 4-week values the optical power of the eye is too great for their length and myopia results. In other words, between 4 and 5 weeks the observed change in the growth of the anterior segment actually reduces optical power, and works against the return to emmetropia from hyperopia thereby necessitating even greater increases in vitreous chamber depth.

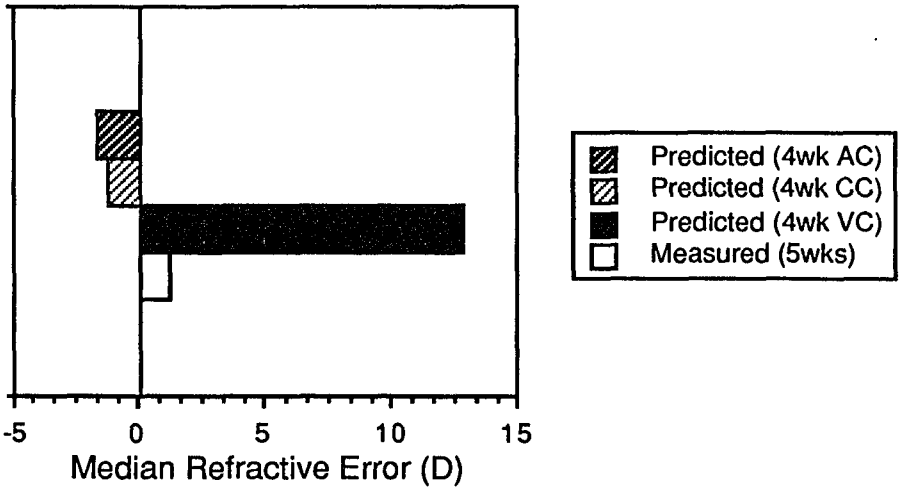

Figure 4.10
The relative effects on refractive state of the various changes in the different ocular components between 4 and 5 weeks of age when the emmetropization from dark-induced hyperopia was observed (AC = anterior chamber depth; CC = corneal curvature; VC = vitreous chamber depth). Predicted refractions were obtained from ray-tracing calculations for the individual eyes using the measurements from individual 5-week-old eyes except for the parameter in parentheses, which was held at its 4-week value. Thus, the discrepancy between the predicted and measured refractions give an indication of the optical effect of the change in that parameter (see page 68 for details). Note that if the vitreous chamber depth did not increase, and remained at the 4-week depth, the refraction would remain severely hyperopic. The observed growth of the anterior segment does not contribute to the emmetropization from dark-induced hyperopia because the increases in corneal curvature, anterior chamber depth, and lens thickness reduce the optical power of the eye. This is shown by the fact that the predicted refractions based on the 4 week measurements of corneal curvature and anterior chamber depth are myopic.

Conclusions

The results reported here argue for visual regulation of eye growth. The chicks were found to quickly correct refractive errors produced either by visual deprivation myopia or by dark-induced hyperopia, mainly by adjusting the depth of the vitreous chamber. Because the vitreous chambers in the dark-induced hyperopic eyes were already abnormally enlarged, this strongly suggests that the sign of the refractive error, rather than size of the eye *per se*, guides the growth of the eye toward emmetropia.

Eye growth appears to be under the control of multiple regulatory mechanisms; complete recovery from dark-induced hyperopia exists as a two stage process. The initial (and principal) stage results in emmetropization during the first week after the chicks are returned to normal rearing conditions. This stage is clearly the result of increasing the axial length of the vitreous chamber apparently in response to the hyperopic refractive error. The second stage involves the morphological readjustment of the anterior segment of the eye and is manifest as an increase in corneal curvature and anterior chamber depth. Finally, after three weeks of normal rearing conditions, the initially hyperopic eyes appear to be normal in all respects. Thus, it seems likely that morphological adjustments of the anterior segment are important in maintaining the correlation of the various ocular components, but are less important than the vitreous chamber adjustments which can quickly respond to, and correct, refractive errors of either the myopic or hyperopic types.

Other results support the notion that the growth of the anterior and posterior segments are controlled independently. Wildsoet and Pettigrew (1988a) found a dose- and age-dependent effect of kainic acid on the development of the chick eye. A 200 nmole dose of kainic acid induces ocular enlargement confined to the vitreous chamber while growth of the anterior segment is inhibited and the cornea is flatter than normal. In contrast, a 20 nmole dose produces more curved corneas, besides enlarging the vitreous chamber, but

only in neonatal chicks. The authors suggest that the results may be explained by the presence of separate growth control mechanisms with different critical periods.

While the findings reported in this chapter support the hypothesis of active regulation of refractive state and eye growth, they do not clarify the specific sensory signals (which seem to be some aspect of the refractive state itself) which underlie this regulation, nor do they provide information about the anatomical substrates involved. In the following chapters some of the possible pathways involved in the regulatory control of eye growth are examined experimentally. Besides using the normal growth of the eye for baseline data, the changes during the development of myopia, and those that normally follow the cessation of the ametropia-producing visual manipulations (shown in this chapter), will provide standards against which the effects of various experimental manipulations can be measured.

CHAPTER FIVE

THE EFFECTS OF OPTIC NERVE SECTION ON EYE GROWTH*†

Having established that visual signals related to refractive state guide the regulation of eye growth in chicks (see Chapter 4), the rest of this dissertation is concerned with probing the nature of the regulation. This chapter determines whether the control of eye growth and refractive state is accomplished by a mechanism which uses the visual processing pathways of the brain, or by one which is contained locally within the eye. The results indicate that the eye by itself is able to sense and respond to refractive errors to some degree, yet the brain may be involved in the fine control of refractive development.

The finding that visual deprivation of part of the visual field produces vitreous chamber growth and severe myopia limited to the deprived region of the retina has led to the hypothesis that eye growth is controlled at the level of the eye itself (Wallman et al., 1987). Besides the work in chicks, evidence supporting this notion is scant. In a general review of their work on lid-suture myopia in macaques, Raviola and Wiesel (1985) state that optic nerve section did not prevent 3 rhesus macaques from developing lid-suture myopia,

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*Portions of this chapter have been published elsewhere (Troilo et al., 1986, 1987a, 1987b; Troilo and Wallman, 1988), and are presented here with the permission of the publisher.

†During the completion of this dissertation, another study described optic nerve section effects on visual deprivation myopia similar to those reported here (Wildsoet and Pettigrew, 1988b).

although it did in 1 stumptail macaque. While these findings raise the possibility that the eye can control ocular growth locally, there is no direct evidence that the normal control of refractive state does not involve brain-mediated processes.

In the experiments reported here, optic nerve section was performed in order to block input from the retina to the brain's visual systems, and thereby test the hypothesis of peripheral (local) versus central (brain-mediated) control of eye growth. This study describes the effects of optic nerve section on the development of visual deprivation myopia and, using the experimental emmetropization paradigm reported in the previous chapter, the ability of the eye to sense and correct induced refractive errors after the optic nerve is cut.

Methods

Unilateral intraorbital optic nerve section was performed on 57 White Leghorn chicks *(Gallus gallus domesticus)* either 6-12 hours after hatching, or after 4 weeks of dark-rearing. The surgery was performed as described in Chapter 3. Simple qualitative tests of startle and orientation suggested that, in every case, the surgery produced functional blindness when the eye contralateral to the optic nerve section was covered. Successful optic nerve sections also destroyed the pupillary light reflex, although the pupils were typically not fully dilated presumably because the innervation of the iris was not disturbed. Eight chicks were dropped from this study because they exhibited normal pupillary light reflexes. Of the remaining 49 chicks, 35 showed no pupillary light reflexes, and 14 showed sluggish, low amplitude, responses. Because even a slight pupillary light reflex may result from optic nerve sparing, these eyes are indicated in the results (Figure 5.2, cross-hatching; Figure 5.3, open symbols). These eyes do not appear to differ from those without pupillary light reflex in any of the experimental groups.

To test the effects of optic nerve section on the normal development of the eye, one of the optic nerves was cut in newly hatched chicks (n=12) while the other eye served as a

control. Both eyes were monitored over time with refractometry, keratometry, and A-scan ultrasonography.

The effects of cutting the optic nerve on the development of regionally-restricted form deprivation myopia were also assessed. The eye with the optic nerve section had a white translucent hemispheric occluder attached with collodion to the feathers surrounding the eye (see Chapter 3). These occluders had an opening that restricted vision to either the anterior visual field (nasal retina visually deprived, n=19) or the posterior visual field (temporal retina visually deprived, n=7). In both cases, the occluded region extended approximately 10° beyond the optic axis of the eye in its resting position. Most of the chicks in both groups were measured with refractometry (both on- and off-axis), keratometry, and A-scan ultrasonography at 2 and 4 weeks of age, and had one eye left untreated as a control. Two groups of optic-nerve-sectioned chicks were measured at 1 week: one with no deprivation of either eye (n=11); the other with both eyes deprived of form vision in the nasal retina (n=11). For the analysis of shape changes, some of the chicks without pupillary activity were deeply anesthetized and sacrificed at 6 weeks of age by perfusion with 10% formalin. The eyes were removed and photographed from above (see Chapter 3).

In order to test the ability of optic-nerve-sectioned eyes to sense and respond to induced ametropia (experimental emmetropization paradigm — see Chapter 4), myopia or hyperopia was produced by visual manipulations which were then discontinued and the eyes were subsequently monitored over a period of 3-7 weeks under normal visual conditions. Chicks were made myopic by bilateral deprivation of the nasal retina (n=7) for 1 week. At that time the occluders were removed and both the optic-nerve-cut eye and its fellow control eye were monitored over an additional period of 7 weeks. An additional 4 chicks received visual deprivation of only the optic-nerve-sectioned eye while the unoperated eye was free of any visual manipulation. Another group (n=7) was reared from hatching in complete darkness to produce hyperopia. At 4 weeks of age they were removed from the dark,

measured, and each chick received a unilateral optic nerve section. After being returned to normal rearing conditions, their eyes were monitored for 3 weeks more.

Results

Table 5.1: Median refractive errors (diopters) in eyes with optic nerve section. The median refractive errors of the contralateral unoperated control eyes are shown in parentheses. Nasal and temporal refractions were measured 30° off the optic axis (central retina).

	Retinal Area Measured		
	Nasal	*Central*	*Temporal*
No Retinal Deprivation:			
1 week (n=11)	•	+12.5(+4.0)	•
2 weeks (n=11)	•	+13.9(+2.1)	•
4 weeks (n=6)	+13.8(+2.2)	+14.7(+3.5)	+13.9(+2.2)
Nasal Retina Deprived:			
1 week (n=11)	•	–11.4(-4.4)*	•
2 weeks (n=8)	–11.7(+3.4)	–8.9(+5.2)	+2.2(+3.4)
4 weeks (n=7)	–13.5(+2.6)	–8.5(+2.4)	+0.9(+2.6)
Temporal Retina Deprived:			
2 weeks (n=6)	–4.4(+2.4)	–20.9(+4.8)	–21.2(+4.7)
4 weeks (n=7)	–5.8(+3.0)	–20.1(+2.8)	–16.9(+4.8)

*Both eyes from this group had the nasal retina deprived of form vision. The refractive error of the unoperated eye is in parenthesis.

Optic nerve section and normal eye growth

Cutting the optic nerve has a profound effect on the growth of the eye and the developmental changes in its refractive state; severe hyperopia and eyes smaller than normal result. Eyes with optic nerve section possess significantly greater hyperopia than normal fellow eyes at all ages tested (Wilcoxon, $p<0.01$; see Figure 5.1, Figure 5.2 c&d, and Table 5.1). Furthermore, the hyperopia produced by cutting the optic nerve does not significantly remit with time. Although there is a slight change toward emmetropia in the median refractive error (Figure 5.1; median refractive difference from 2 to 8 weeks = +2.65 D), this change was found to be not significant (Wilcoxon, $p=0.11$). Furthermore, the slope of the line fitted to the median refractive errors versus age in weeks ($y=-0.293x+13.045$) was not

significantly different from 0 (F-test, p=0.26). Some change in refractive state in the myopic direction would be expected in chick eyes growing between 2 and 8 weeks of age based on the scaling effects of ocular enlargement on refractive error as well as the artifact of retinoscopy (Wallman and Adams, 1987). Because the control eyes also do not show any significant change in refraction over time, this may be because of the small sample size (Wallman et al., 1981a) and the age at which the measurements began; Wallman and Adams (1987) estimate that the greatest emmetropization occurs before the age of 1 week.

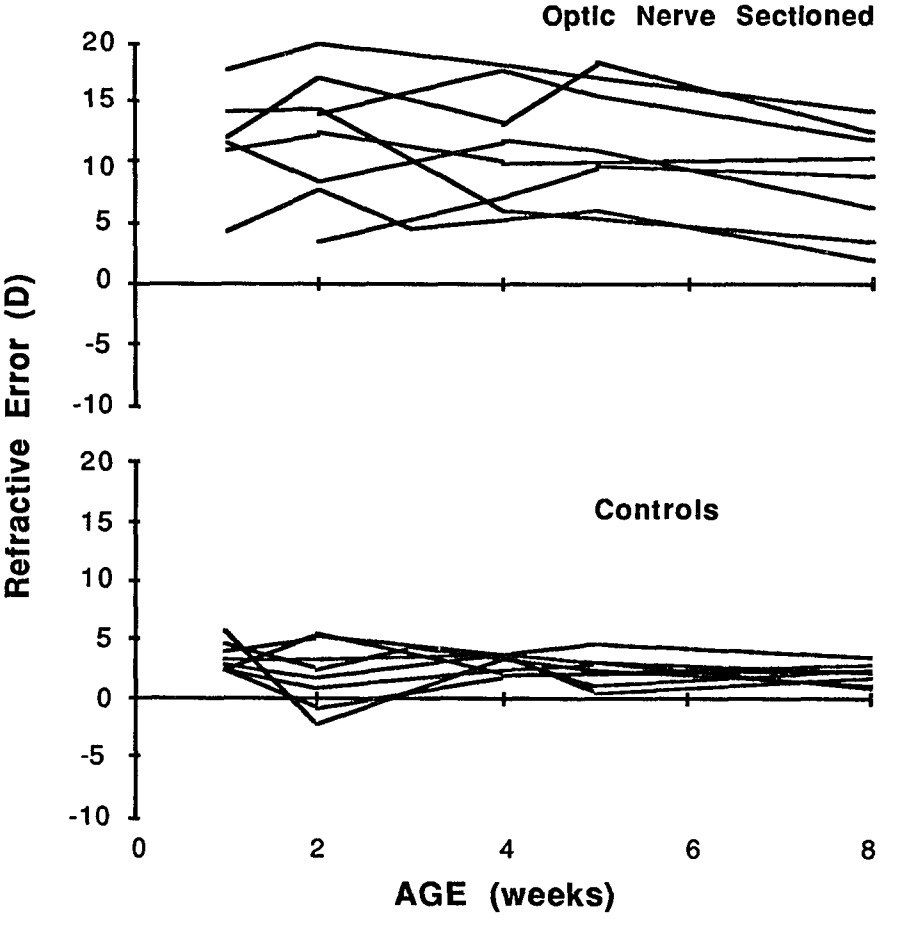


Figure 5.1
An 8 week longitudinal tracking of 8 chicks indicating that the high hyperopia produced by optic nerve section remains variable and high at least until 8 weeks of age. The control eyes shown in the bottom plot are contralateral to the optic-nerve-sectioned eyes in the top.

In optic-nerve-sectioned eyes, the resulting hyperopia is associated with symmetrically smaller eyes as compared to the fellow control eyes (Table 5.2, Figure 5.3). This symmetry reflects the approximately equal amounts of hyperopia found in the three retinal regions measured (on-axis, 30° nasal, and 30° temporal) of 4-week-old eyes with optic nerve section (Table 5.1, Figure 5.3). Ultrasonography shows further that, on-axis, the vitreous chamber is significantly shorter in eyes with optic nerve section than in control eyes at both 2 (4.91 mm vs. 5.35 mm; paired *t*-test, $p<0.05$) and 4 weeks (5.29 mm vs. 5.88 mm; paired *t*-test, $p<0.01$), although the optic-nerve-sectioned eyes are still clearly growing between the ages of 2 and 4 weeks (4.91 mm to 5.29 mm; paired *t*-test, $p<0.001$).

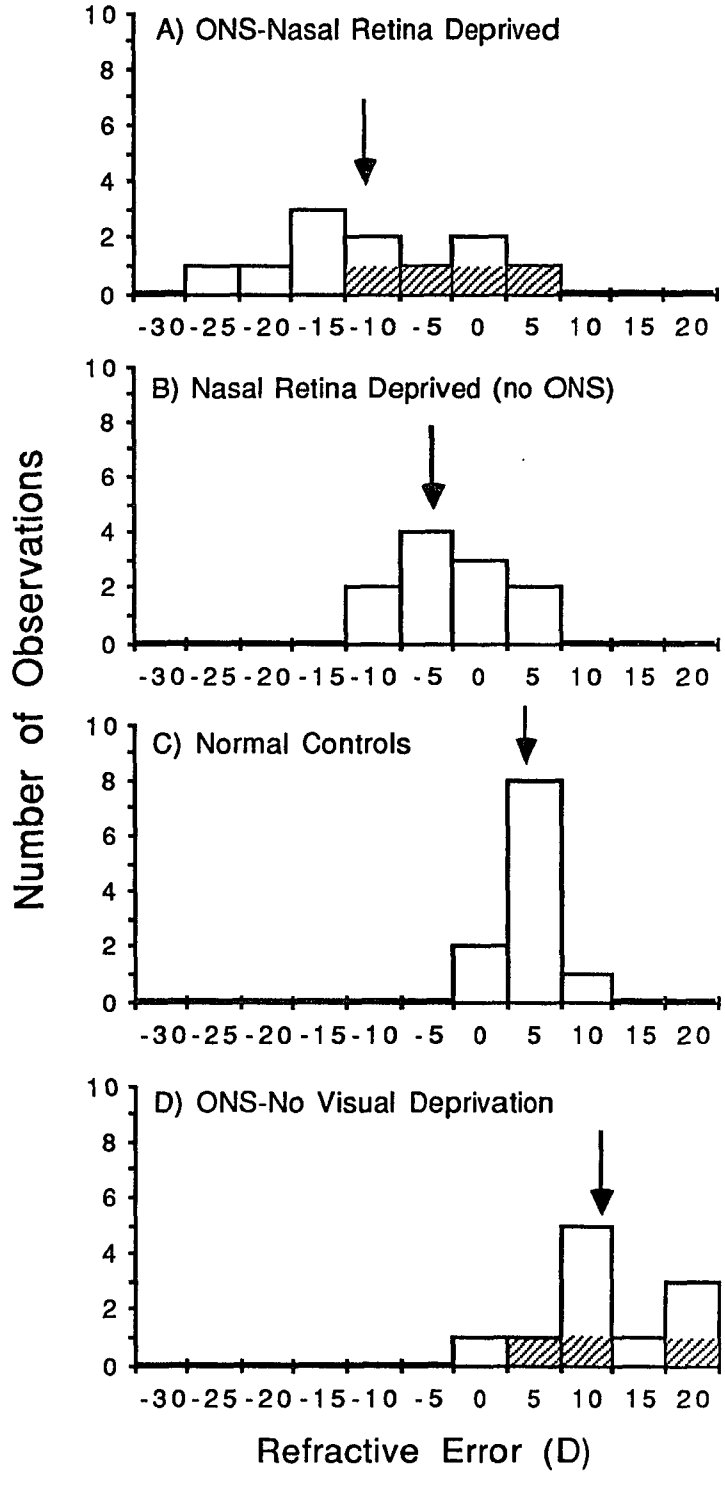


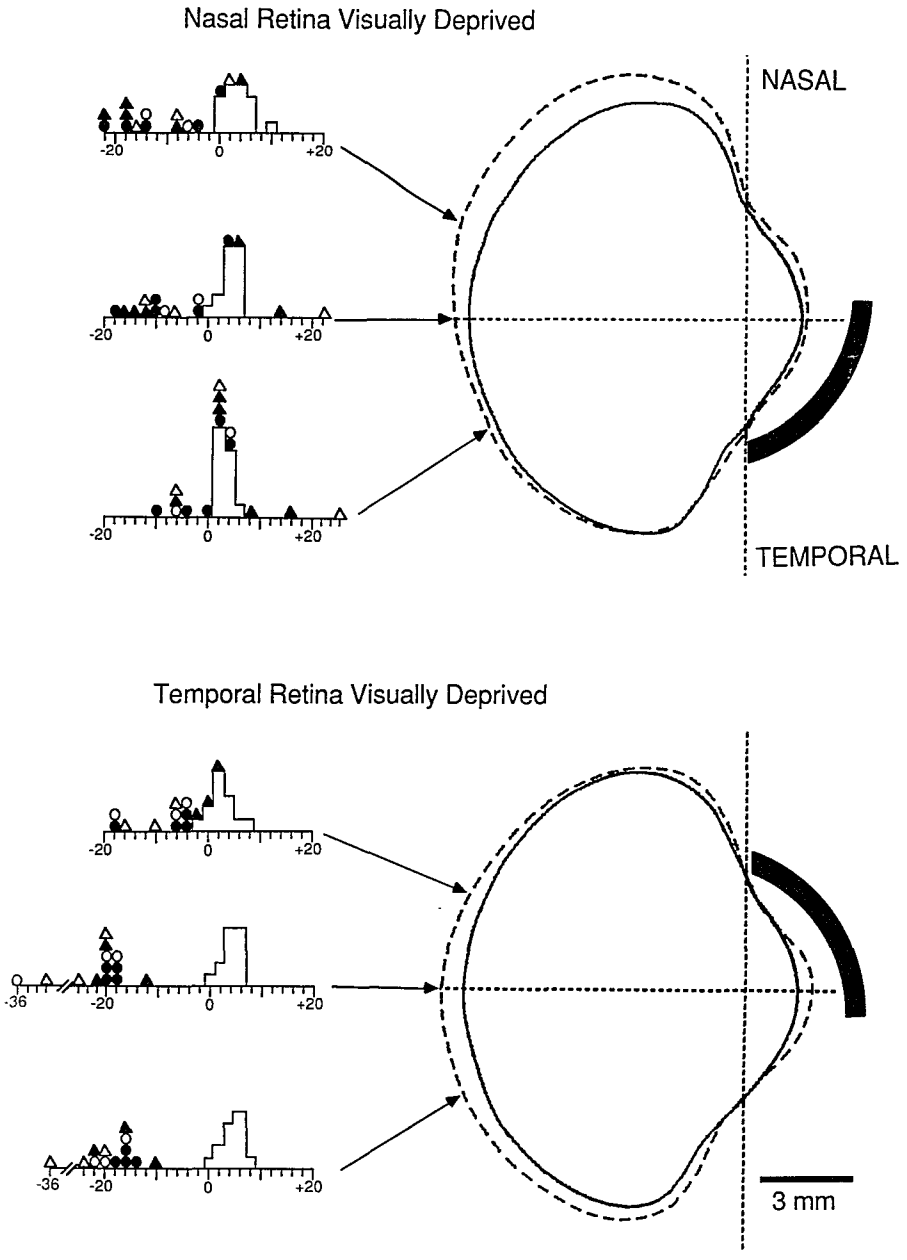
Figure 5.2
Refractive errors measured along the optic axis of the eyes of 1-week-old chicks: (A) optic-nerve-sectioned eyes with visual deprivation of the nasal retina; (B) intact nasal-retina-deprived eyes (contralateral to eyes in histogram A); (C) normal control eyes (no visual deprivation, no optic nerve section); (D) optic-nerve-sectioned eyes (contralateral to eyes in histogram C) without visual form deprivation of the retina. Cross-hatching indicates chicks with some pupillary light reflex remaining. Arrows indicate medians.

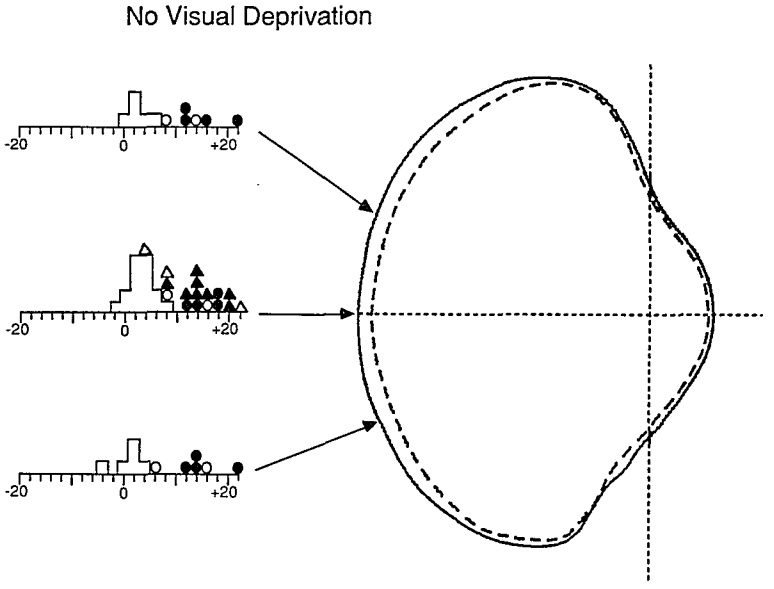
Optic nerve section and the development of myopia

Visual deprivation produces myopia even with the optic nerve cut. As shown in Table 5.1 and Figure 5.2 (Top panel A), after as little as 1 week of visual deprivation of the nasal retina, the eyes with optic nerve section are severely myopic compared to normal eyes (panel C; –11.4 D vs. +4.0 D, *U*-test, $p<0.01$) and possibly more myopic than unoperated fellow eyes with the same partial deprivation (panel B; -11.4 D vs. -4.4 D, $p=0.056$, Wilcoxon). The refractive errors in the optic-nerve-sectioned visually-deprived eyes are also more variable than those of the unoperated eyes ($p<0.05$, *F*-test).

As in birds with intact optic nerves (Wallman et al., 1987), only the visually deprived regions of the retina become myopic; the nondeprived regions have normal or only slightly myopic refractions (Table 5.1, Figure 5.3). In eyes in which the nasal retina was deprived of form vision, the nasal retina is significantly more myopic than the nondeprived temporal retina at both 2 and 4 weeks (Wilcoxon, $p<0.05$). In eyes with the temporal retina visually deprived, the temporal retina is more myopic than the nondeprived nasal retina at 2 weeks (Wilcoxon, $p<0.05$) and nearly so at 4 weeks (Wilcoxon, $p=0.052$). Furthermore, either type of partial visual restriction results in significant myopia along the optic axis as compared to contralateral control eyes after both 2 and 4 weeks (Wilcoxon, $p<0.01$).

Figure 5.3 (following page)
The average shape of 6-week-old eyes with complete optic nerve section (dashed lines), and different visual field restrictions, are shown viewed from above in comparison to their fellow control eyes (solid lines). For alignment purposes, all eyes are shown as right eyes. The thick arc in front of the cornea illustrates the extent of the visual field restriction. Top left shows eyes with the nasal retina visually deprived (n=5). Bottom left shows eyes with the temporal retina visually deprived (n=4). The figure at right shows the shape and refractions of eyes without visual deprivation (n=4). The histograms show all the individual refractive errors measured approximately on the part of the retina indicated by the arrows. The refractions of the normal control eyes are indicated by the unfilled bar histogram. Filled symbols are refractions of eyes with complete optic nerve section, unfilled symbols are refractions of optic-nerve-sectioned eyes with slight pupillary light reflexes remaining. Triangles indicate refractions taken at 2 weeks of age, circles at 4 weeks.


Nasal Retina Visually Deprived
NASAL
TEMPORAL
-20
0
+20
Temporal Retina Visually Deprived
-36
-20
0
+20
3 mm


No Visual Deprivation
-20
0
+20

The myopia of temporal-retina-deprived eyes tended to be less localized, and of greater magnitude, than that seen in nasal-retina-deprived eyes (Table 5.1, Figure 5.3). Temporal-retina-deprived eyes were more myopic than nasal-retina-deprived eyes along the optic axis at both 2 and 4 weeks (U-test, $p<0.01$), as well as in the deprived region at 2 weeks (U-test, $p<0.05$) but not at 4 weeks (U-test, $p=0.125$). There is also more myopia in the nondeprived region of temporal-retina-deprived eyes than in the nondeprived region of the nasal-retina-deprived eyes at 2 weeks (U-test, $p<0.05$), but not at 4 weeks (U-test, $p=0.074$).

The myopia resulting from visual deprivation in chicks with intact optic nerves appears to be principally the result of increased vitreous chamber depth (Wallman et al., 1978a; Yinon et al., 1980; Hodos and Kuenzel, 1984; Wallman and Adams, 1987; Wallman et al, 1987), although increases in corneal curvature may also play a role in some cases (Gottlieb et al., 1987). Table 5.2 shows that in optic-nerve-sectioned chicks, visual deprivation myopia is similarly associated with increased vitreous chamber depth as measured along the optic axis by ultrasonography. Vitreous chamber depth is greater in visually deprived eyes with optic nerve section than in control eyes (nasal-retina-deprived eyes at 4 weeks of age, and temporal-retina-deprived eyes at both 2 and 4 weeks of age). The correlation coefficient for vitreous chamber length and refractive error for all experimental groups at all ages tested was statistically significant ($r=-0.768$, $df=62$, $p<0.01$). Furthermore, in chick eyes with optic nerve section, like those with intact optic nerves (Wallman et al., 1987), the development of myopia in part of the eye is associated with vitreous chamber elongation largely restricted to the region of the retina deprived of form vision, thereby producing asymmetry of the posterior portion of the eye (Figure 5.3). To evaluate the asymmetry associated with different visual field restrictions in individual eyes with completely sectioned optic nerves, the eye shapes were traced from dorsal-view photographs and measured along the distance from the center of the pupil to 26 points (2° apart) across the nasal half of the retina (10-60° from the optic axis). Each of these measurements was then divided by the corresponding

distance in the temporal half of the eye. The mean of the 26 ratios provides an estimate of the magnitude and direction of asymmetry. The mean for the nasal-retina-deprived eyes was 1.09 (t-test of $\mu=1$, $p<0.01$), for temporal-retina-deprived eyes it was 0.96 (t-test of $\mu=1$, $p<0.05$), and for visually nondeprived eyes it was 0.99 (t-test of $\mu=1$, $p=0.19$).

Table 5.2: The effects of optic nerve section (ONS) and different visual field deprivations on corneal curvature, corneal thickness and anterior chamber depth, lens thickness, and vitreous chamber depth [mean mm±SD(n)].

Treatments and Ages	Radius of Corneal Curvature	Corneal Thickness and Anterior Chamber Depth	Lens Thickness	Vitreous Chamber Depth
2 weeks:				
ONS-No Visual Dep.	3.22±.13(9)	1.52±.06(10)	2.37±.06(10)	4.91±.36(8)*
Control	3.24±.14(9)	1.51±.07(10)	2.36±.06(10)	5.35±.33(8)
ONS-Nasal Retinal Dep.	3.19±.09(8)**	1.62±.15(8)*	2.42±.08(8)	5.78±.64(8)
Control	3.30±.08(8)	1.52±.07(8)	2.37±.06(8)	5.47±.20(8)
ONS-Temp. Retinal Dep.	3.12±.11(7)**	2.06±.40(7)**	2.44±.08(7)	6.47±.21(7)**
Control	3.33±.07(7)	1.49±.05(7)	2.41±.06(7)	5.49±.12(7)
4 weeks:				
ONS-No Visual Dep.	3.60±.12(6)	1.67±.04(6)	2.72±.07(7)	5.29±.36(6)**
Control	3.63±.13(6)	1.70±.07(6)	2.74±.07(6)	5.88±.25(6)
ONS-Nasal Retinal Dep.	3.63±.12(7)	1.79±.07(7)	2.74±.08(7)	6.88±.29(7)**
Control	3.69±.08(7)	1.91±.18(7)	2.75±.07(7)	6.00±.16(7)
ONS-Temp. Retinal Dep.	3.41±.12(7)**	2.39±.57(7)**	2.80±.10(7)	6.92±.24(7)**
Control	3.70±.07(7)	1.74±.08(7)	2.73±.08(7)	6.00±.16(7)

Results of paired t-tests (ONS vs. Control): *$p<0.05$; **$p<0.01$

Although depriving the nasal or temporal retina produced similar local effects, some differences exist. As discussed above, greater myopia is produced in temporal-retina-deprived eyes. There is also an increase in corneal curvature and anterior chamber depth in the temporal-retina-deprived eyes with optic nerve section compared to normal controls at both ages measured; in nasal-retina-deprived eyes such changes were observed at 2 weeks but not at 4 weeks (Table 5.2). This difference, together with the greater vitreous chamber

depth of temporal-retina-deprived eyes, probably explains the greater myopia found in these eyes compared to the nasal-retina-deprived eyes, as well as the slight myopia measured in the nondeprived nasal retina (Table 5.1).

Even if other ocular changes may also be involved, it appears that changes in the depth of the vitreous chamber (which are principally responsible for the axial elongation of the experimental eyes) can largely explain both the hyperopia resulting from optic nerve section alone, and the myopia produced by visual form deprivation. To quantitate the influence of axial length on refractive error, a simple optical algorithm was employed. Refractive error can be expressed as the difference between the total optical power and the power necessary to focus parallel rays onto the retina. The total optical power of the eye is the reciprocal of the second focal length multiplied by the the refractive index of vitreous humor (to convert the focal length from one in air to one in vitreous humor). The second focal length is the distance from the optical center of the refracting system (second principal point) to the posterior focal point (see Appendix A). Assuming that in the chick eye the second focal length is approximately 85% of the axial length (Wallman and Adams, 1987), the relationship of total optical power to axial length is:

$$P = \frac{n_V}{.85\,(AL)} - RE$$

Where:

P = total optical power
n_V = refractive index of vitreous humor
AL = measured axial length
RE = refractive error

This relationship was used to evaluate the extent to which the axial changes account for the amount of ametropia observed in the experimental eyes. The total optical power of the control eye (P_C) for each individual was used as a standard to predict the refractive error of the experimental eye based solely on the change in its axial length. P_C was calculated using the equation above so that it reconciled the refractive state and axial length measured along the optic axis of the control eye. It was then rearranged to predict the refractive error

that would be attributable solely to the axial length changes observed in the experimental eyes as follows[1]:

$$RE_x = \frac{n_v}{.85(AL_x)} - P_c$$

Where:

x = experimental eye
c = contralateral control eye

The refractive errors calculated in this manner are plotted in Figure 5.4 against the actual refractive errors measured. The correlation is remarkably high ($r=0.90$, $p<0.01$) indicating that vitreous chamber changes account for approximately 80% ($r^2=0.81$) of the refractive errors in all the groups tested. However, the slope of the regression line fit to these data ($y=0.784x-1.176$) differs significantly from 1 (*t*-test, $p<0.01$). This may be the result of the increased corneal curvatures in the temporal-retina-deprived eyes (triangles in Figure 5.4).

[1]This calculation is only a rough approximation because of the accumulation of experimental errors from several measures in the two different eyes. Axial length was determined from ultrasonography of corneal thickness, anterior chamber depth, lens thickness, and vitreous chamber depth. It was assumed that the increase in axial length was the result of the increase in vitreous chamber depth, however in the case of the temporal-retina-deprived eyes (and the nasal-retina-deprived eyes at 2 weeks) the increase in the anterior chamber depth also contributed to the increase in axial length (see Table 5.2). The effects on axial length of the anterior chamber changes were ignored because they produce a decrease in optical power which would be more than offset by the increased corneal curvatures in the same eyes.

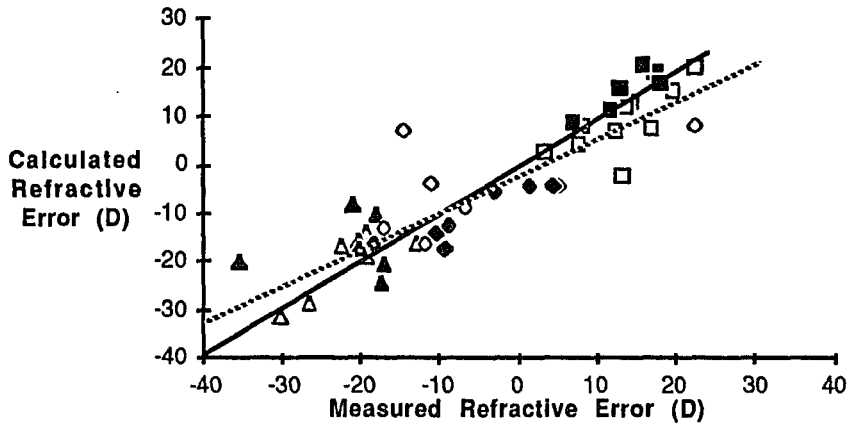


Figure 5.4
Scatter plot of the calculated refractive errors in the optic-nerve-sectioned eyes attributable solely to axial length changes against the actual refractive error measured (see text for details). The solid line has a slope of 1, the dashed line is the regression y=0.784x-1.176. Unfilled symbols indicate measurements taken at 2 weeks of age, filled symbols from measurements at 4 weeks. Diamonds, nasal-retina-deprived; triangles, temporal-retina-deprived eyes; squares, eyes without visual deprivation of the retina.

Optic nerve section and emmetropization from induced ametropia

The experimental emmetropization paradigm, where eyes are made either myopic or hyperopic by visual manipulations and their ability to return to emmetropia is monitored following cessation of the manipulation, was used on 14 of the optic-nerve-sectioned chicks. After the manipulations were discontinued, growth in the direction of emmetropia (emmetropization) was observed despite the optic nerve section, although this growth was not properly controlled and emmetropia was not maintained.

As indicated in the top of Figure 5.5, eyes with optic nerve section appear able to sense their refractive state and initially make the compensatory adjustments necessary to achieve emmetropia. After 1 week of visual form deprivation of the nasal retina, a median myopia of -14.95 D occurs in eyes with optic nerve section (left top). This myopia is significantly greater than the -4.41 D produced in the visually form deprived contralateral eyes without optic nerve section (see Figure 5.2; Wilcoxon, $p<0.05$). At 2 weeks (1 week after the end of the deprivation), the refractive errors of the optic nerve sectioned eyes had changed significantly in the direction of emmetropia to +4.0 D (Wilcoxon, $p<0.05$). Similarly, in eyes

made hyperopic by 4 weeks of dark-rearing (+6.08 D) then allowed subsequent weeks of normal visual conditions (right top), the refractive error had also changed significantly toward emmetropia to +1.79 D (Wilcoxon, $p<0.02$) but from the opposite direction.

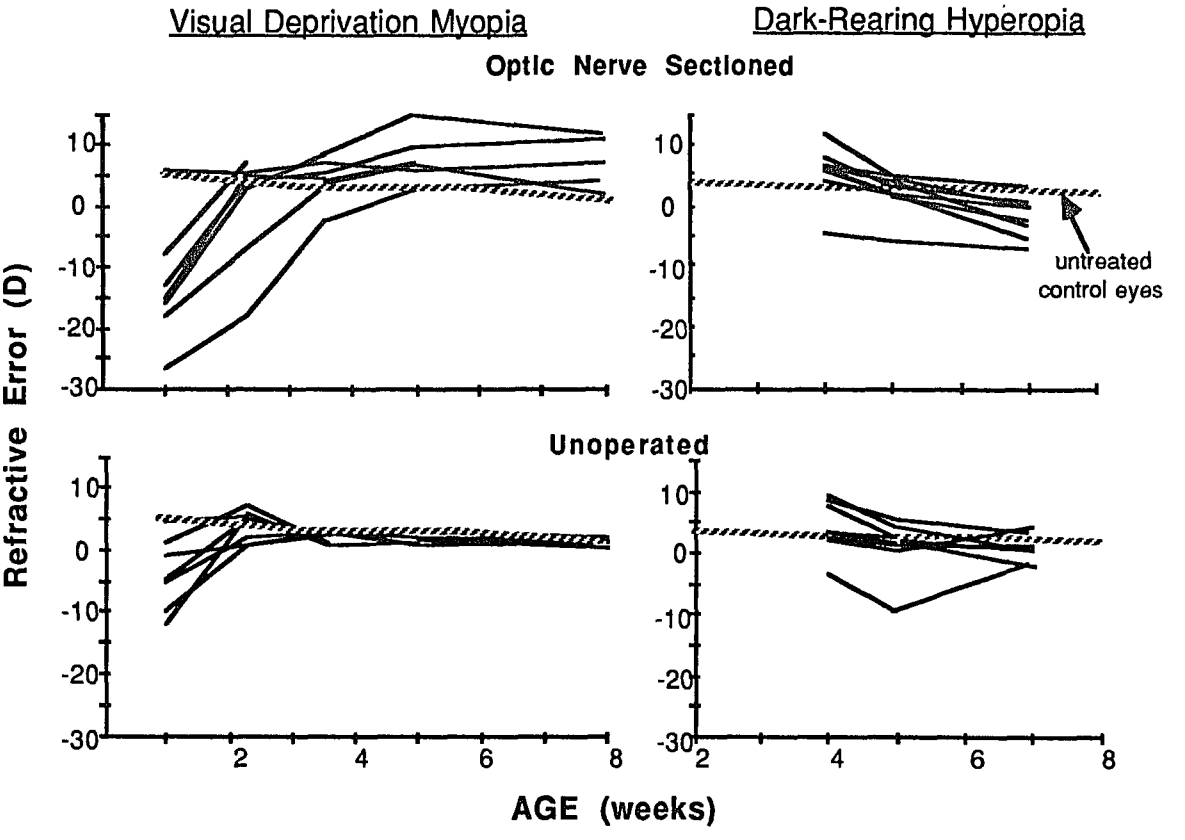


Figure 5.5
Eyes with optic nerve section (top), made either myopic by visual form deprivation of the nasal retina (left) or hyperopic by dark-rearing (right), are able to sense their refractive errors and respond with the appropriate compensatory changes in order to grow toward emmetropia. This growth is not properly controlled, however, as can be seen by the significant growth past emmetropia and into the refractive error opposite to that initially induced. The unoperated eyes (bottom), contralateral to the optic-nerve-sectioned eyes, received the same visual manipulation as the optic-nerve-sectioned eyes. These eyes served as controls. The dashed lines represent the median refractive errors of untreated control eyes measured at 1, 2, 4, 6, and 8 weeks of age.

Because in the cases just described the unoperated eyes had the identical treatments as the optic-nerve-sectioned eyes, there is the possibility that the emmetropization of the unoperated eye guided the emmetropization in the optic-nerve-sectioned eye. To rule out

this possibility, 4 chicks were raised with visual deprivation of the optic nerve section eye while the unoperated eye remained unoccluded. Figure 5.6 shows that after two weeks of monocular visual deprivation, the optic-nerve-sectioned eyes were myopic while the contralateral eyes were approximately emmetropic (medians: -6.8 D vs. 1.0 D). After the visual deprivation was discontinued at two weeks the optic-nerve-sectioned eyes were able to grow back toward emmetropia (median at 2 weeks = -6.8 D; 3 weeks = -0.71 D; and 4 weeks = 5.39 D). Because of the difference in the refractions between the unoperated and optic-nerve-sectioned eye, the unoperated eye could not have guided this growth.

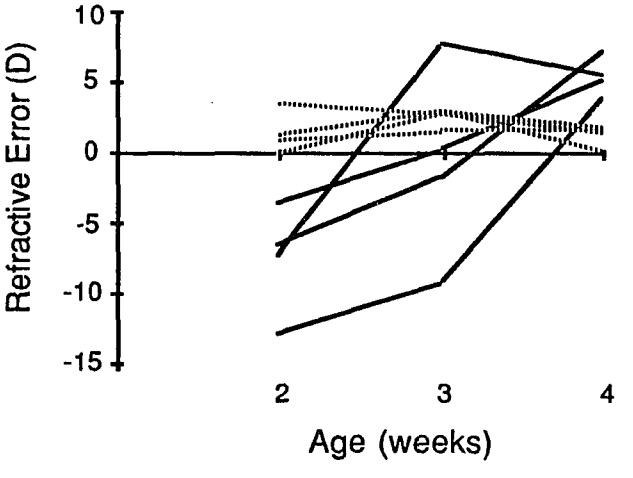


Figure 5.6
Refractive state changes in both eyes of chicks with unilateral optic nerve section and monocular visual deprivation to the same eye. Eyes with optic nerve section (solid line) can sense an induced myopia and respond by growing toward emmetropia even when the contralateral unoperated eye (broken lines) possesses a normal refractive state. The optic-nerve-sectioned eyes were deprived of form vision in the lateral visual field from hatching until two weeks of age. Refractometry was performed at 2, 3, and 4 weeks of age.

Despite the ability of optic-nerve-sectioned eyes to sense and respond to refractive errors, the compensatory growth toward emmetropia lacks some facet of control as evinced by the significant overshooting of emmetropia which resulted in the reversal of the original refractive error for both initially myopic and hyperopic chicks (see Figure 5.5). Four weeks after the visual form deprivation was discontinued, the myopic optic-nerve-sectioned eyes had become significantly hyperopic relative to normal controls (+6.53 D vs. +1.69 D, Wilcoxon, $p<0.02$). Conversely, 3 weeks after the dark-reared hyperopic chicks were

returned to normal lighting conditions. the optic-nerve-sectioned eyes became significantly myopic relative to controls (-1.50 D vs. +0.5 D, Wilcoxon, $p<0.05$).

As shown earlier (above and in Chapter 4), both the development of induced refractive errors and the subsequent corrections in refractive state which follow the cessation of the visual manipulations are closely related to changes in the axial dimensions of the eye, particularly the vitreous chamber. Figure 5.7 shows that the overshooting of emmetropia observed in optic-nerve-sectioned eyes during the period of normal rearing conditions appears to be the result of ungoverned changes in the vitreous chamber depth as it responds to the initial ametropia; the corrective changes in vitreous chamber dimensions continue past the point where emmetropia is achieved and produce the refractive errors opposite to those originally being corrected. Note in Figure 5.7 that the visually form deprived optic-nerve-sectioned eyes have longer vitreous chambers than their fellow controls at 1 week, reflecting the significantly greater myopia in these eyes (Figure 5.5). After cessation of the visual manipulation, when the refractions of the optic-nerve-sectioned eyes moved toward emmetropia and then into hyperopia, the vitreous chambers of the optic-nerve-sectioned eyes were clearly growing significantly less than the controls as shown by the change in the ratios of experimental over control vitreous chamber depths at 2 and 8 weeks (means: 1.0 to 0.9, 1-tailed *t*-test, $p<0.025$). The refractions of the dark-reared chicks, as well as their vitreous chamber depths, were the same in both eyes after the chicks were removed from the dark at 4 weeks of age at which time the chicks received a unilateral optic nerve section. After 1 week of normal visual experience under normal lighting conditions the refractions and vitreous chamber depths in the optic-nerve-sectioned and control eyes remained the same. However, during the second and third weeks of normal visual experience, an excess of vitreous chamber growth in the optic-nerve-sectioned eyes is seen by the significant increase of the vitreous chamber ratios from 5 to 7 weeks (means: 1.0 to 1.05, 1-tailed paired *t*-test, $p<0.03$). This change reflects the concomitant growth of the optic-nerve-sectioned eyes into myopia. Unfortunately, the refractions and eye sizes were not followed

long enough to determine if these reversed refractive errors would again be sensed and the proper compensatory changes implemented.

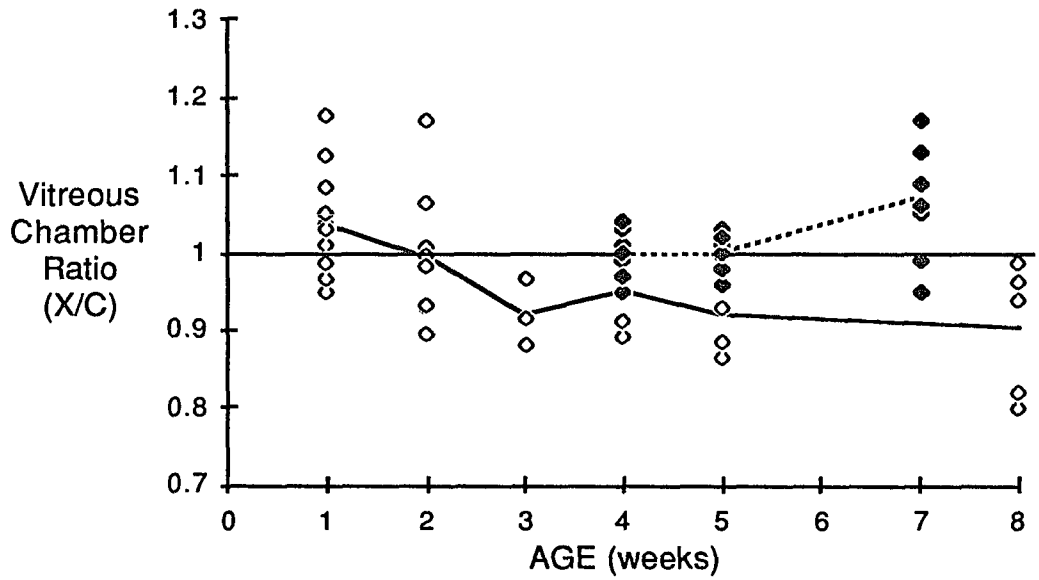


Figure 5.7
Ratios of the optic-nerve-sectioned eye (X) to the contralateral unoperated control eye (C) undergoing the same visual manipulation. Unfilled diamonds represent individual chicks undergoing visual form deprivation for 1 week. Filled diamonds show the chicks which were reared in complete darkness until 4 weeks of age. Lines connect the means of the ratios at different ages. The ratios of vitreous chamber depth of the dark-reared eyes at ages 4 and 5 weeks are both 1 because at 4 weeks both eyes had identical treatments, an at 5 weeks both the unoperated and optic-nerve-sectioned eyes had grown to emmetropia.

The corneas of eyes emmetropizing from dark-induced hyperopia were initially flatter than normal and underwent readjustments even after the optic nerve was cut. Because this regulation of corneal shape occurs in optic-nerve-sectioned eyes the mechanism must be located within the eye. As in the unoperated emmetropizing eyes described in Chapter 4, these corneal shape adjustments lagged slightly behind the refractive changes and were in the wrong direction to account for the emmetropization from dark-induced hyperopia suggesting that the mechanism for adjusting the shape of the cornea acts independently of the refraction-sensitive vitreous chamber adjustments. Figure 5.8 (top) shows that between 4

and 5 weeks of age, when the chicks emmetropized from dark-induced hyperopia, all of the eyes showed a decrease in corneal curvature (mean radius of curvature: 4.09 mm to 4.26 mm; one-tailed paired *t*-test, $p<0.01$), a change which reduces the total optical power of the eye and works against the correction of an hyperopic error. Figure 5.8 (bottom) shows that the corneal curvature became slightly steeper between 5 and 7 weeks of age (mean radius of curvature: 4.26 mm to 4.20 mm; one-tailed paired *t*-test, $p<0.05$). This change, together with the concomitant vitreous chamber elongation, produces the myopia measured in these eyes at 7 weeks of age.

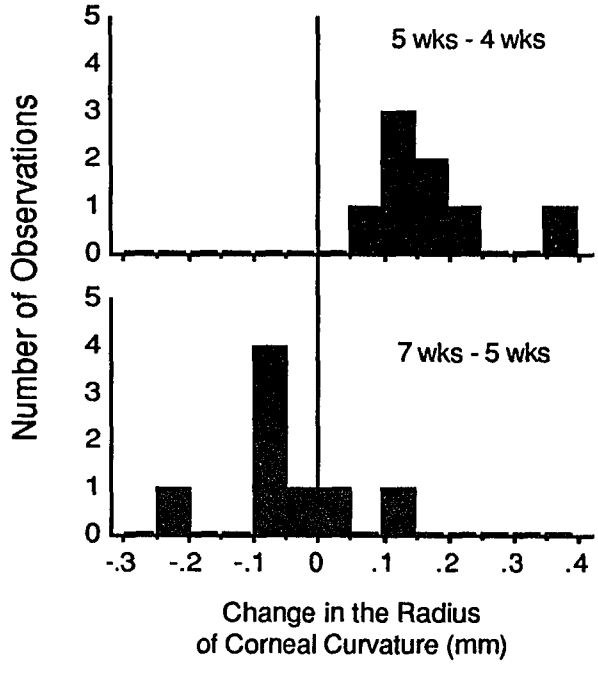


Figure 5.8
Histograms showing the individual changes in radius of corneal curvature between 4 and 5 weeks of age (top) and between 5 and 7 weeks of age (bottom). Values from the younger age were subtracted from those of the older age (positive values indicate flatter corneas, negative values indicate steeper corneas). Normally corneas become flatter with age. An increased radius of curvature produces a decreased surface curvature.

Conclusions

The results of these studies indicate that multiple mechanisms are involved in the control of eye growth. The localized effects of partial visual form deprivation are still clearly manifest in eyes with optic nerve section, while optic nerve section in eyes without visual deprivation produces hyperopia and prevents the eye from achieving emmetropia. Even more provocative are the findings that eyes with optic nerve section are able to sense the sign of an induced refractive error, and initiate the proper compensatory changes. These responses, however, are not properly controlled, and the refractive state continues to change in such a way that emmetropia is overshot and the eye grows into the refractive error state opposite to the one from which it originally started. Thus, the control of eye growth may be at least a dual-level process, controlled in part by the eye, and in part by the brain.

Even after optic nerve section the growth of the eye toward or away from emmetropia is dependent upon the visual stimuli received by the retina. Indeed, the degree of myopia resulting from visual field restriction appears to be greater in optic-nerve-sectioned eyes than in intact eyes, perhaps because the blind eyes are not directed toward the opening of the occluder as they would be in normal chicks. This may also explain the generally greater effects of visual form deprivation on temporal-retina-deprived eyes with optic nerve section.

As in intact eyes, the regional myopia produced in optic-nerve-sectioned eyes appears to be largely the result of regional changes in the dimensions of the vitreous chamber. Since these effects are restricted to the deprived region of the retina, it seems likely that the visual experience of local regions of the retina can modulate the growth of the subjacent sclera. Thus, the mechanism by which the eye enlarges and becomes myopic in response to visual form deprivation is located in the eye itself. While this mechanism is assumed to be neural in nature, the involvement of the pigment epithelium or choroid has not been ruled out, although Oishi and Lauber (1988) reported that lid-suture myopia in chicks is prevented

when the photoreceptors are destroyed by formoguanamine. Additional evidence that retinal neurons are involved in the control of eye growth is provided by Wildsoet and Pettigrew (1988a) who found that ocular growth can be altered to produce effects similar to lid-suture when kainic acid is injected into the vitreous chamber in order to destroy amacrine cells, and at higher doses bipolar and horizontal cells. The visual experience of the retina also appears to play some role in directing the growth of the eye toward emmetropia as suggested by the optic-nerve-sectioned eyes' ability to sense an induced refractive error and respond by growing in the proper compensatory direction.

Apparently the brain is also involved in the control of eye growth. In optic-nerve-sectioned eyes an accurate return to emmetropia from induced ametropia was not observed; there was an error in which the compensatory growth response of the vitreous chamber over-corrected for the initial refractive error, thereby overshooting emmetropia and reversing the error. These results suggest that the loss of feedback from brain-mediated visual processes affects the fine control of refractive state.

Additional evidence for the involvement of the brain in the control of eye growth comes from optic nerve sections in otherwise unmanipulated eyes. An intact optic nerve is required for normal eye growth because, when it is cut, the eyes become smaller and more hyperopic than normal. It is plausible that the diminished rate of vitreous chamber growth, and the consequent hyperopia, produced by optic nerve section is the result of disrupting of the brain's influence on eye growth. The possibility that optic nerve section may slow the growth of the eye through ganglion cell death exists, although severe hyperopia was found as early as 1 week after surgery, when ganglion cell degeneration is just becoming apparent (Muchnick and Hibbard, 1980). In addition, the optic-nerve-sectioned eyes are still capable of growing, and optic nerve section does not slow the growth of all eyes, as seen in the eyes returning to, and growing past, emmetropia from dark-induced hyperopia.

Thus, in a normally growing eye, both centrally-mediated (i.e. brain) and peripherally-mediated (i.e. retina/eye) control mechanisms might act together to achieve emmetropia.

Many fundamental questions persist. For instance, the nature of the visual stimuli guiding eye growth, and the sites and mechanisms of action of both the putative central and peripheral control mechanisms are all unknown. While adjustments in vitreous chamber growth appear to be the principal response of both growth controlling mechanisms, the manner in which these adjustments are achieved remains elusive. Furthermore, the means of the growth control mechanism which apparently regulates the shape of the anterior segment is equally unclear. Finally, although significant changes in lens thickness were not found in any of the groups tested in this dissertation (see Table 5.2), the adjustability of lens shape and position has not been determined.

In the following chapter, ocular accommodation is investigated as a possible component of the brain-mediated eye growth control mechanism because it is able to sense refractive state, and it responds with strong mechanical influences to the eye, particularly the anterior segment and choroid.

CHAPTER SIX

ACCOMMODATION IN CHICKS AND ITS ROLE IN EYE GROWTH

Previous chapters have made clear that visual experience plays an integral role in ocular development, however neither the relevant aspects of the visual experience nor their mode of operation on the growth of the eye are known. The results of the optic nerve section experiments (see Chapter 5) strongly suggest that the eye itself possesses a certain amount of autonomous control over eye growth, although the brain appears to exert some type of influence on this control. This chapter examines the possibility that ocular accommodation (increasing the eye's optical power for near viewing) is the specific brain-mediated function which is involved in the control of eye growth. The results of the experiments presented below indicate that, although the accommodative mechanism in chicks is both complex and powerful, accommodation is not necessary for the control of eye growth in chicks.

Ocular accommodation is a visual feedback controlled oculomotor behavior which has often been suggested to play an important role in ocular development (eg. Donders, 1952; van Alphen, 1961; Young, 1963; Sato, 1981). The support for this idea stems mainly from the fact that accommodation exerts powerful mechanical forces within the eye which are presumed to be capable of affecting ocular development, and the amount of accommodation needed for a given object in visual space is directly proportional to the refractive state of the eye (hyperopes accommodate more than myopes). The activity of the accommodative system may, therefore, offer the means for determining the refractive state of the eye and

evoking the proper compensatory responses. The apparent relationship between the amount of near-work (principally reading) and the development of myopia (eg. Duke-Elder, 1930; Dunphy et al., 1968; Goldschmidt, 1968; Richler and Bear, 1980a) has often been cited as support for the hypothesis that excessive accommodation is the critical causative factor in the development of myopia (eg. Young, 1975; Bell, 1980; Ebenholtz, 1983). This view has even led to the suggestion that bifocals (eg. Oakley and Young, 1975) or paralysis of accommodation (eg. Bedrossian, 1971, 1979) might be suitable therapies for myopia in children. The fact remains, however, that only circumstantial findings support the existence of an accommodative influence on eye growth and no direct experimental evidence exists.

A complete understanding of the role of accommodation in eye growth necessitates a thorough understanding of the mechanism of accommodation. This is made even more important when different species are used as experimental subjects. In the first part of this chapter studies designed to elucidate the accommodative mechanism of chicks are described. Later, experiments designed to specifically test the role of accommodation in the eye growth of chicks are presented.

The Mechanism of Accommodation in Chicks*

Differences in ocular morphology suggest that birds and mammals may have different accommodative mechanisms. In birds, a subdivision of the avian ciliary muscle's longitudinal bundle (Crampton's muscle) inserts at the corneo-scleral border and, when contracted, may increase corneal curvature thereby increasing refractive power (Slonaker, 1918; Walls, 1942; Meyer, 1977; Suburo and Marcantoni, 1983). Substantial changes in corneal curvature during avian accommodation have been found by some researchers (Beer, 1892/93; Gundlach et al., 1945; Rosenthal, 1981, Schaeffel and Howland, 1987b)

* Portions of this section have been published elsewhere (Troilo and Wallman, 1984, 1985, 1987), and are used here with the permission of the publisher.

but not by others (Steinbach and Money, 1973; Levy and Sivak, 1980; Sivak et al., 1986). The following study shows that corneal changes are part of the accommodative response of chicks and, further, that the effects of the ciliary muscle on the crystalline lens are remarkably similar to those suggested for humans by Helmholtz (1909).

Methods

Twenty, four-week-old White Leghorn chickens *(Gallus gallus domesticus)* were anesthetized with Urethane (2g/kg i.p.), an anesthetic that almost entirely eliminates spontaneous eye movements (Burns and Wallman, 1981). Ocular measurements were made both before and during induced accommodation. During both sets of measurements the eyelids were held open with lid-retractors that produced no visible deformation of the cornea. Total accommodative change was defined as the difference in the refractive state, measured by refractometry, before and during induced accommodation. Changes in corneal curvature (measured as the radius of curvature) were assessed by keratometry and Purkinje-image photography. A-scan ultrasonography was used to determine changes in the axial dimensions of anterior chamber, lens, and vitreous chamber during accommodation. See Chapter 3 for details of all of these techniques.

To control for methodological artifacts in the *in vivo* production of accommodation two different methods were: (1) electrical stimulation of the Edinger-Westphal nucleus (EW); (2) topical application of 0.4% nicotine sulfate to the cornea.

Edinger-Westphal Stimulation

The EW (also known in birds as the accessory oculomotor nucleus) is the only known source of the pre-ganglionic, parasympathetic neurons which innervate the ciliary ganglion (Narayanan and Narayanan, 1976; Reiner et al. 1983). The post-ganglionic ciliary neurons innervate the intraocular musculature and stimulate both accommodative and pupillary changes. Thus, electrical stimulation of the EW produces accommodation through the normal neural pathway and does not interfere with the eye directly.

Monopolar semi-micro electrodes (Rhodes SNEX-300: tips 0.25 mm long and 0.1 mm in diameter) were stereotaxically placed into the EW and their position adjusted to produce accommodative responses to electrical stimulation. Typically, large accommodative changes were accompanied by brisk pupillary effects (either dilations or contractions), iris bulge, and noticeable changes in light reflected from both corneal and lenticular surfaces. If vertical eye movements were produced, the electrode was moved dorsally since the oculomotor nucleus lies ventral to the EW; if torsional eye movements were produced the electrode was moved anteriorly away from the trochlear nucleus. When accommodative responses were observed, the electrode was fixed in place with skull screws and dental acrylic. The bird was then removed from the stereotaxic instrument for testing. Measurements during electrically induced accommodation were paired with, and recorded immediately after, a measurement of the eye at rest. Electrical stimulation (20-30 μA, 110 Hz, 0.5 msec pulse duration) was produced using a Grass SD–9 stimulator and CCU-1-A constant current isolation unit. At the end of each experiment, marking lesions were made in order to verify electrode placement. The birds were then anesthetized and sacrificed by perfused with Heidenhain's solution, later their brains were sectioned in 50 μm sections and stained with neutral red for histological inspection. Only those birds were used in which stimulation sites were verified to have been in the EW.

Nicotine Treatment

Because avian ciliary muscle is striated and contains nicotinic receptors, application of nicotine sulfate to ciliary muscle produces accommodation. Two drops of 0.4% nicotine sulfate were applied to the cornea three minutes before refractive error and corneal curvature measurements were made. Typically, the maximum effect of the drug was observed 4-5 minutes following application. All effects began to drop off sharply at 10-12 minutes and varying degrees of corneal clouding were often observed at different points along the drug's time course. Because of the brief action of the drug and its tendency to cause corneal clouding, all accommodation measurements were completed within ten minutes of applica-

tion. Unlike measurements made during EW stimulation, those taken during nicotine-induced accommodation were not paired with the resting state measurements. All of the resting state measurements for a given eye were recorded together before the application of nicotine. The short time–course of nicotine-induced effects necessitated measuring corneal changes only by keratometry (n=7; 13 eyes) whereas the corneal changes of the EW–stimulated chicks (n=13; 13 eyes) were measured by both corneal measurement techniques. To randomize the order of the measurement procedures with respect to the temporal effects of nicotine, six of the thirteen nicotine-treated eyes were measured by refraction first, and seven by keratometry first.

Lens Measurements

The curvatures of the anterior and posterior lens surfaces were measured either *in situ* or *in vitro*. These measurements were used to determine the physical changes to the lens occurring during accommodation. *In situ* measurements were made by cutting the enucleated eye along its' horizontal plane after it was frozen to -30° F. This technique was used to compare the lens curvature of non-accommodating eyes to eyes in a state of accommodation induced by submersion in 0.4% nicotine sulfate for 30 seconds. In order to determine the inherent curvature of the lens after the surrounding forces are removed, lenses were excised from freshly enucleated eyes. Both the frozen eyes and the excised lenses were photographed from above. The posterior and anterior lens surfaces were determined by projecting the photographic images onto a digitizing tablet and using a triangulation algorithm which takes three points along a given surface of a lens and calculates the radius of curvature of that surface. The magnification of the image was accounted for so that the measurements were given in mm.

Results

Corneal Curvature Changes

A consistent increase in corneal curvature (i.e. a decrease in the radius of curvature) was observed during accommodation for all the animals tested (Figure 6.1). The change in corneal curvature from the resting to accommodated state (summarized in Table 6.1) was significant in all cases (paired *t*-test: nicotine–treated [keratometry], $p<0.01$; EW–stimulated [keratometry], $p<0.01$; EW–stimulated [Purkinje–image photography], $p<0.01$). There was no statistically significant difference in the corneal curvature measurements obtained using keratometry or Purkinje-image photography on the same EW–stimulated eyes (paired *t*-test, $p= 0.11$).

Table 6.1: Changes in the radius of corneal curvature for Edinger-Westphal stimulated and nicotine-treated chicks (means in mm ± SD), as measured by keratometry or Purkinje-image photography.

	Before Stimulation	During Stimulation	Difference
EW-stimulated chicks			
Keratometry (n =13)	3.63 (0.11)	3.49 (0.13)	-0.13 (0.06)
Purkinje images (n =12)	3.58 (0.10)	3.48 (0.12)	-0.10 (0.07)
Nicotine-treated chicks			
Keratometry (n =13)	3.71 (0.11)	3.49 (0.11)	-0.22 (0.08)

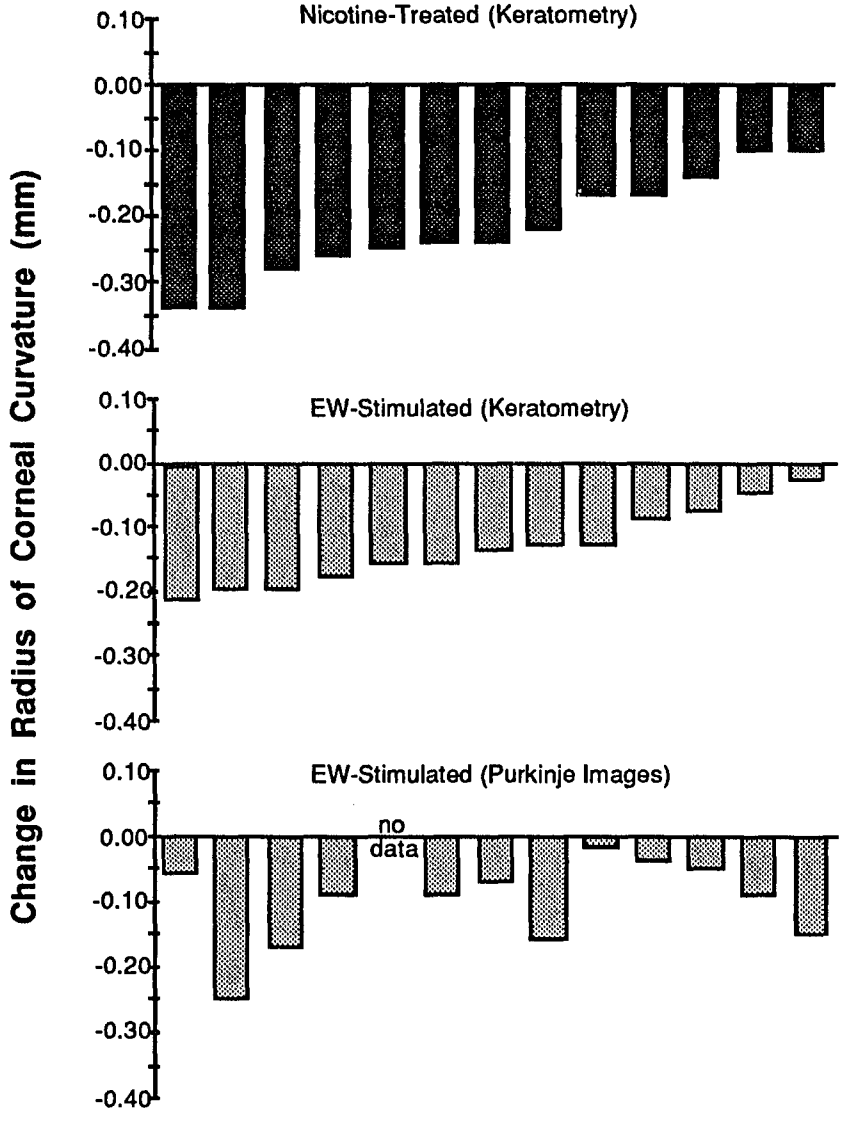


Figure 6.1
Changes in the radius of corneal curvature measured by keratometry and Purkinje-image photography. A reduction in radius of curvature is equivalent to an increase in corneal surface curvature. **Top:** Ranked change in radius of corneal curvature for nicotine-treated eyes measured with keratometry. **Middle:** Ranked change in radius of corneal curvature measured by keratometry during EW stimulation. **Bottom:** Change in radius of corneal curvature during EW stimulation and measured by Purkinje-image photography and aligned with the same eyes shown in the middle panel.

In order to determine corneal power changes produced by the increase in curvature, the radius of corneal curvature of the anterior surface was converted to refracting power (F_C) using the general ray-tracing formula for a single refractive surface:

$$F_C = \frac{(n_C - 1)}{r_C}$$

Where:

F_C = refracting power of the anterior surface of the cornea.
n_C = refractive index of chicken cornea = 1.362 (Sivak et al., 1978).
r_C = radius of curvature of the anterior corneal surface (in meters).

Figure 6.2 shows the relationship between the change in corneal power and the amplitude of accommodation for individual birds undergoing either nicotine treatment or EW stimulation. The maximum refractive change during accommodation induced by each stimulation method was about 19 D. The mean amplitude of accommodation for the nicotine-treated eyes was significantly greater than for the EW-stimulated chicks (15.1 D vs. 9.2 D; two sample *t*-test, $p<0.01$). The mean change in corneal power for nicotine-treated eyes was also greater than in EW–stimulated birds (6.1 D vs. 3.9 D; two sample *t*-test, $p<0.01$).

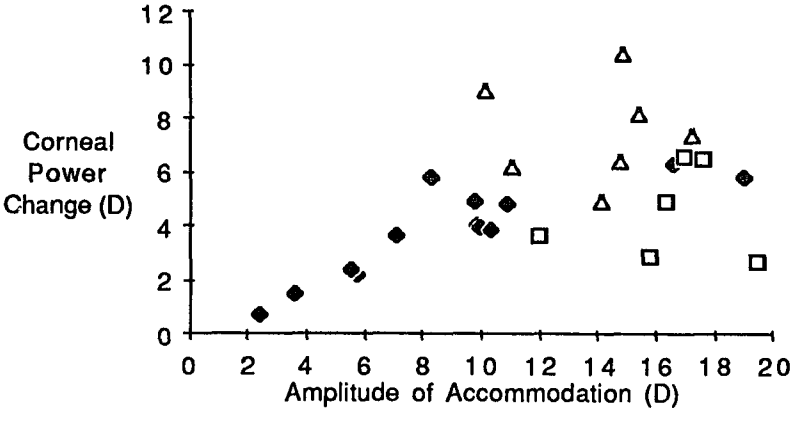
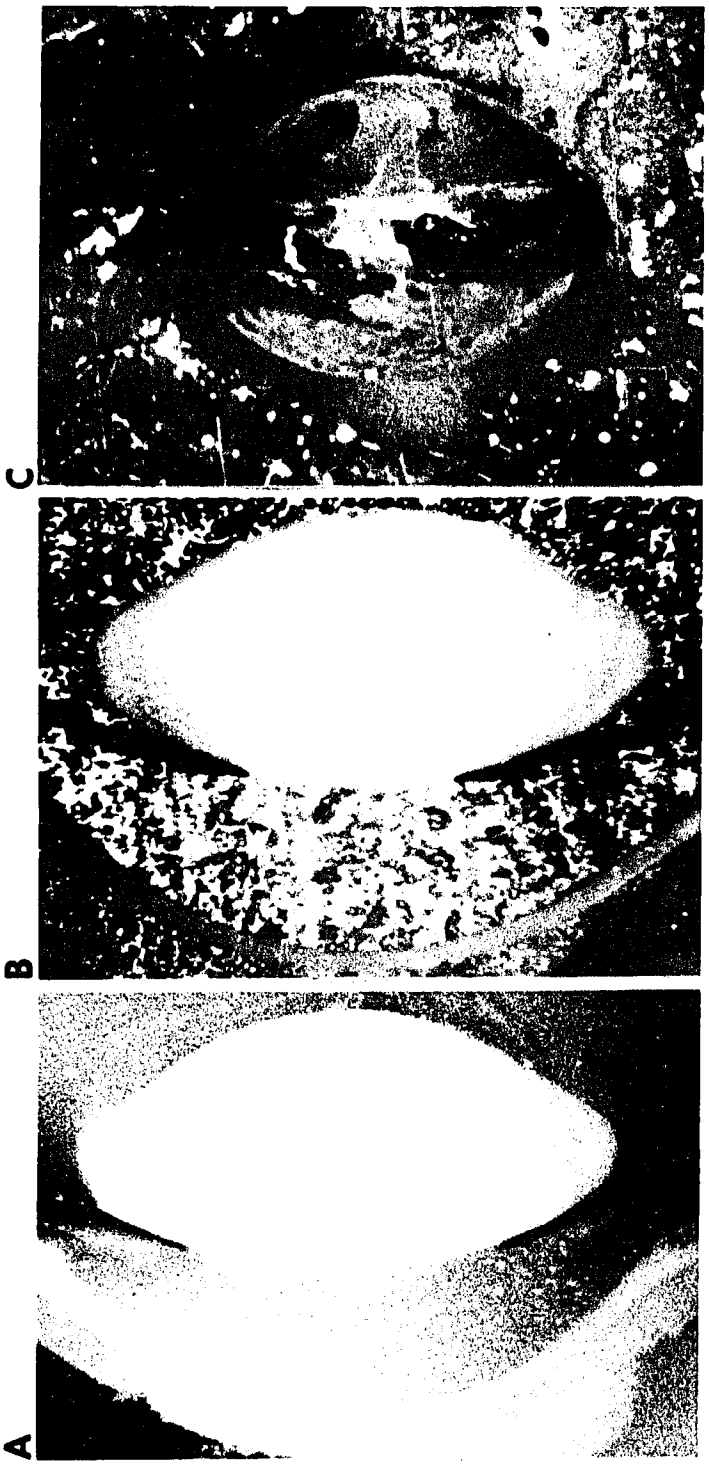


Figure 6.2
Scatter plot showing corneal power change against the amplitude of accommodation from Edinger-Westphal stimulation (solid symbols) or nicotine treatment (open symbols). The corneal power change was calculated from keratometric readings. For some of the nicotine-treated eyes, keratometry was the first measurement made (triangles); for others refractometry was first (squares).

Lens Shape Changes

To determine whether the lenses of chick eyes are able to relax into a more curved accommodative state the way human eyes are presumed to (Helmholtz, 1909), and not squeezed into shape by the ciliary muscles as has been shown for some species of birds (see Walls, 1942; Sivak, 1980), the lens shapes from non-accommodating eyes and from nicotine-treated eyes were compared with the shapes of lenses removed from freshly enucleated non-accommodating eyes (Figure 6.3 shows representative samples of these groups). As illustrated in Figure 6.4, the anterior curvature and thickness of the lenses *in situ* increase significantly during nicotine-induced accommodation (*t*-tests, $p<0.01$), but the posterior curvature does not (*t*-test, $p=0.39$). From these data the optical powers of the lenses were calculated, and were determined to increase significantly (*t*-test, $p<0.01$). The elasticity of the lens appears to be a principal component of the accommodative mechanism, since when the lens is re-moved from the eye it is able to assume curvatures similar to the accommodated lenses *in situ* (*t*-tests; anterior surfaces, $p=0.23$, posterior surfaces, $p=0.78$). Furthermore, despite the significant thickening of the excised lenses compared to *in situ* accommodated lenses (*t*-tests, $p<0.01$), the mean optical power of the lenses, also shown in Figure 6.4, did not differ significantly (*t*-test, $p=0.502$).

Figure 6.3 (following page)
Photographs of chick lenses obtained either from horizontal hemi-sections of frozen eyes (panels A & B), or after the lens was excised from a freshly enucleated eye. The anterior surfaces of all 3 lenses are facing to the left. Panels A and B show the difference between a non-accommodating lens (A) and one undergoing nicotine-induced accommodation (B); ray-tracing calculations (see Appendix A) indicate approximately 17 D of accommodation in the nicotine-treated eyes relative to untreated eyes (similar to the accommodative amplitude measured *in vivo*). Note in panel B, relative to panel A, the constricted pupil, the thicker and more curved lens, and, relative to panel C, the stretching at the equator. Panel C shows the shape of the excised lens devoid of the mechanical forces from the ciliary body. It appears that the lenses of chicks need not be squeezed into an accommodative state, but rather appear to relax into shape suggesting an accommodative mechanism similar to that commonly accepted for humans. See Figure 6.4 for data.


C
B
A

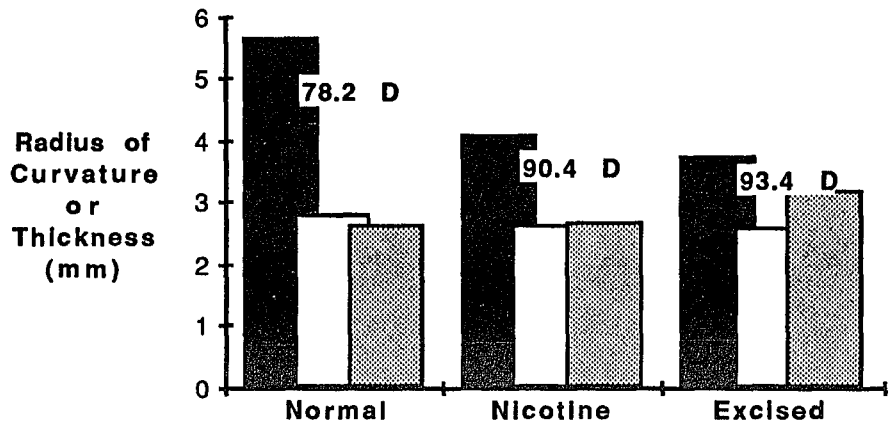


Figure 6.4
The average radius of curvature is shown for the anterior lens surface (black bar) and posterior lens surface (white bar). The average thickness of the lens at its widest point is also shown (gray bar). Six eyes were used for each group corresponding to the lenses shown in Figure 6.3. The optical power shown for each group is the average of the optical powers calculated with ray-tracing for each of the 6 lenses per group.

Conclusions

The results of the studies just described suggest that the mechanism of accommodation in chicks is in some ways very different from that of humans, while in others it may be more similar than previously supposed. Unlike human accommodation, changes in corneal curvature play an integral role in accommodation in the chicken. The maximum change in corneal curvature measured during induced accommodation produces a change in corneal refractive power of about 6 D, and typically occurs at levels of accommodation greater than 10 D. In the lower range of the accommodative amplitudes (Figure 6.2, closed symbols), there is a linear relationship with corneal power change, but above 10 D of accommodation the change in corneal power appears to level off at approximately 6 D suggesting a ceiling effect for corneal curvature change. Up to 19 D of accommodation was observed in the chicks studied, implying that at amplitudes of accommodation greater than 10 D lenticular changes become progressively more important than corneal changes. In fact, ray-tracing analyses of the enucleated nicotine-treated eyes indicates that the lenticular mechanism in

chicks is capable of producing around 12 D of optical power change. Furthermore, based on the photographic analysis of lens shapes, the mechanism of lenticular accommodation in chicks appears to be similar to that of humans in that the lens seems to relax into an accommodative state upon contraction of the ciliary muscle, rather than being squeezed into it.

It appears unlikely that these corneal changes could be the consequence of either errors in positioning the eye during measurement, or of eye movements (such as retractions) during stimulation. Such artifacts could not result in the proportionality between the magnitudes of corneal curvature change and of accommodative amplitude. Furthermore, the depth of field of the keratometer is too shallow to permit position-related errors of more than ±1.5 D. The poor correlation between the two techniques of corneal curvature measurement (Figure 6.1 middle and bottom respectively) may be because the Purkinje-image method samples a much smaller area and has a larger depth of field. Despite this poor correlation, the salient feature of the data presented here is that both methods show significant and consistent increases in corneal curvature during induced accommodation.

The results presented above have recently been confirmed in normally accommodating chicks during feeding. Schaeffel and Howland (1987b) report a total accommodative range of 15-17 D and corneal changes amounting to 8 D. Both values are consistent with those reported during stimulation of the Edinger-Westphal nucleus (up to 19 D and 6 D respectively).

In general, nicotine produces larger accommodative effects than EW stimulation. Perhaps the ciliary muscle is able to contract more powerfully than it does when normally stimulated by the nervous system. Alternatively, electrode placement, or the stimulation parameters used, may not have been maximally effective in driving all accommodation-producing neurons. This is suggested by the greater variability in accommodative amplitude produced by EW stimulation than by nicotine treatment (s.d.= 4.7 D and 2.7 D respectively) although the two techniques produce comparable maximum responses (≈19 D).

Other differences between stimulation procedures were also detected. In contrast to the EW stimulations, there does not seem to be a relationship between the magnitude of the corneal power change and the amplitude of accommodation produced with nicotine (Figure 6.2, open symbols). This probably is because of the ceiling for corneal changes (the nicotine always elicited amplitudes of accommodation above that at which maximal curvature changes are produced by EW stimulation). The greater scatter of the nicotine data may have several explanations. Variability resulting from the drug's brief action is suggested by the relatively greater corneal effects observed when keratometric readings are made prior to refractometry (open triangles) compared to when refractometry is performed first (open squares). Because accommodation greater than 10 D is associated with maximal corneal change, and nicotine always produced at least 10 D of accommodation, individual differences in maximal corneal change could account for some scatter of the data. Furthermore, variability in the drop size of the nicotine solution, variability in the retention of the drop on the corneal surface, and measurement difficulties because of corneal clouding, may all have contributed to the scatter of the nicotine data points. Finally, the very presence of corneal clouding suggests that nicotine may have direct effects on the cornea which could also possibly add to the corneal curvature changes. Despite all these possibilities, the mean nicotine-induced corneal power change of 6 D is, nevertheless, consistent with that suggested by EW stimulation.

Based on the findings reported above, there can be no doubt that accommodation in chick eyes exerts large mechanical forces on both the lens and the cornea. Whether these forces are involved in the regulation of eye growth is the question posed in the next section.

The Effects of Edinger-Westphal Lesions on Eye Growth*

The role of accommodation in eye growth was tested by determining if lesions of the Edinger-Westphal nucleus affect growth toward or away from emmetropia. Growth toward emmetropia was characterized by the normal eye growth pattern, or by the return to emmetropia from experimentally induced refractive errors (experimental emmetropization, see Chapter 4). Additionally, the role of accommodation in the progression of visual deprivation myopia was examined.

Methods

In all of the Edinger-Westphal (EW) lesion experiments, the chicks were measured under cycloplegic conditions with refractometry, keratometry, and A-scan ultrasonography, as described in Chapter 3. The techniques for lesioning the EW are also fully described in Chapter 3. Only those chicks with no evidence of a pupillary light reflex and complete ablation of the EW lesion, as assessed by histological inspection of fixed and stained sections, were used in the following studies.

The complete loss of the pupillary light response is a good indicator of total EW lesions. Infrared video photoretinoscopy (Schaeffel et al., 1987; Schaeffel et al., 1988) was used to test the accommodative ability of 10 EW-lesioned chicks[1]. Eight of these chicks did not possess a pupillary light reflex, and accommodation during pecking and feeding behaviors was never observed; two of the chicks showed slight pupillary light reflexes, and accommodative changes during feeding were also found. After histological examination of the lesion sites, no sign of EW sparing was found in the chicks without pupil activity, while in the eyes with evidence of accommodation and pupillary light

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* Portions of this section have been presented at the 1988 annual meeting for The Association for Research in Vision in Ophthalmology (Troilo and Wallman, 1988).

[1]These measurements were performed with the assistance of Dr. Frank Schaeffel.

reflexes some sparing of the EW was evident. Typically, complete lesions of the EW also resulted in substantial damage to the dorsal oculomotor nucleus and surrounding areas. For the unilateral EW lesions, the percent volume of the oculomotor nucleus lesioned averaged 50±25% (see Chapter 3 and Figure 3.5). For bilateral EW lesions, substantially more of the oculomotor nucleus was destroyed (71.6±17 % of total volume).

The chicks were raised under 1 of 4 experimental conditions. They were all measured at least twice, once before surgery (pre-lesion), and then again about 2 weeks later (post-lesion). Non-lesioned birds undergoing the same visual manipulations were used as controls or, in some cases, the eye contralateral to the EW lesion served as a control.

Condition 1

To test the effect of a loss of accommodation on normal eye growth, 12 birds were raised without any visual field deprivation to the eye on the side of the EW lesion. These birds were lesioned at about 1 week of age (4-9 days), and were measured again 2 weeks later at approximately 3 weeks of age. In 4 of these birds, the eye contralateral to the EW lesion, which had normal accommodation, was completely covered to insure that the non-accommodating eye was being used for vision. There were no differences in any of the results reported below for EW-lesioned eyes when either the contralateral unoperated eye received the same visual manipulation or when it was fully occluded (*U*-tests; $p>0.873$). Thus, both groups of birds were pooled for statistical analyses.

In 6 other birds no visual field deprivations were presented to either eye and bilateral lesions of both EW nuclei were performed at 4 or 5 days of age. Subsequently, the growth of the eyes was monitored at approximately weekly intervals for up to 12 weeks.

Conditions 2 and 3

To further study the effects of accommodation on the regulation of eye growth, the growth toward emmetropia from induced ametropia was also monitored in birds without accommodation. These birds were either raised for 2 weeks with visual deprivation in the lateral visual fields of both eyes in order to produce myopia (Condition 2; n=9), or for 4

weeks in the dark to produce hyperopia (Condition 3; n=7). Immediately after the visual manipulations were discontinued, the birds were measured to assess the degree of ametropia and the lesions were made thereafter. The birds were then allowed to recover under otherwise normal visual conditions before being remeasured (post-lesion) 1, 2, and in some cases, 3 weeks later.

Condition 4

To test the role of accommodation in the progression of visual deprivation myopia, the eyes of 12 birds were deprived of form vision in the lateral visual field from hatching. At 1 week of age the myopia-producing effects of this visual manipulation were assessed (pre-lesion) and, following these measurements, the birds received a unilateral lesion of the EW. The visual deprivation was maintained for approximately 2 weeks more, at which time the eyes were remeasured (post-lesion). In some cases (n=7) the contralateral eye received the same visual field manipulation as the lesioned side eye and served as a control. In other cases (n=5), the contralateral eye was completely occluded in order to ensure that the bird used the non-accommodating eye for vision. There were no differences in the results obtained in the lesioned-side eyes when the contralateral, unoperated, eye received the same visual manipulation or when it was fully occluded (*U*-test; p=0.465). Thus, both groups of birds were pooled for analysis.

Results

The loss of accommodation resulting from lesions of the Edinger-Westphal nucleus does not appear to affect the growth and refractive development of the eye in any major way. Despite the loss of accommodation, emmetropia is attained either along the normal developmental pattern, or as an adjustment to experimentally induced ametropia. It was also found that accommodative activity is not necessary for the progression of visual deprivation myopia. There remains, however, the possibility that accommodation is normally useful in the control of eye growth and refractive state.

There is no question that the EW lesions produced profound changes in the chicks visual experience. A behavioral response worth noting was discovered in chicks seeing through non-accommodating eyes.These chicks were unable to judge pecking distances properly; they consistently undershot their targets, and learned to eat only when large amounts of food were available and accurate pecks were unnecessary. Furthermore, the undershooting of small targets by the bilaterally EW-lesioned birds persisted at least through 80 days of age when the last of this group was measured. These findings, as well as some of the possible effects of EW lesion effects on the development of refractive state and ocular morphology reported below, may be related not only to the loss of accommodation produced by the EW lesion, but also to the substantial damage to the oculomotor area in general. However, because abnormal pecking behavior observed in EW-lesioned chicks was also observed in chicks under cycloplegia and when wearing spectacle lenses (unpublished observations) it appears that chicks are, indeed, using information from the accommodative system to determine pecking distance.

The effects of EW lesions on normal eye growth

The normal age-related change in refractive state toward emmetropia does not require accommodation, although in the case of bilateral EW lesion, there is an increase in the variability of the refractive state as well as a slightly more hyperopic median refractive error.

Unilateral EW lesions

When the visual environment is left unobstructed, chicks with EW lesions do not differ from unoperated controls in their ocular and refractive development. In the unoperated controls, the median refractive errors measured at the ages of 1 and 3 weeks were not significantly different (+4.47 D vs. +3.61 D respectively; Wilcoxon, p=0.16). As shown in Figure 6.5, the median refractive errors found in eyes with EW lesions at the same ages were nearly identical, and also not significantly different (1 week = +4.73 D vs. 3 weeks = +3.50 D; Wilcoxon, p=0.12). Furthermore, the distribution of 3-week-old EW-lesioned

eyes did not differ significantly from that of 3-week-old unoperated control eyes (Kolmogorov-Smirnov, $p>0.10$).

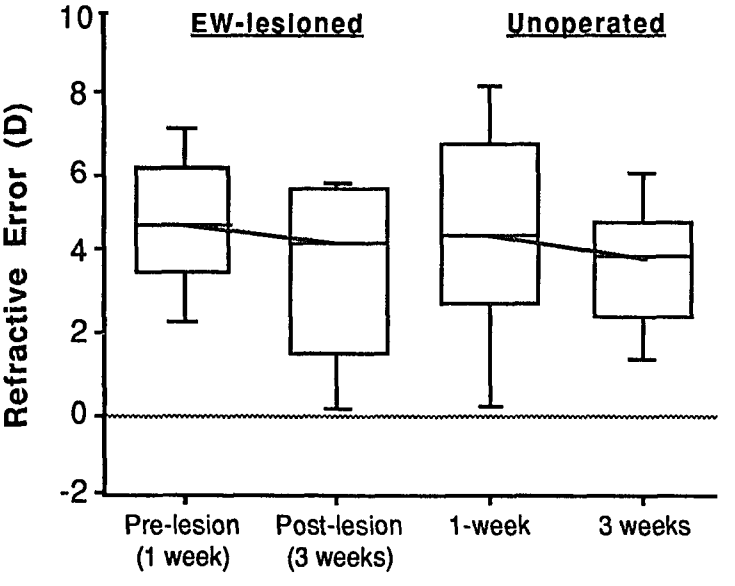


Figure 6.5
The change in the distribution of refractive errors in chick eyes with EW lesions, and in unoperated controls. The horizontal lines indicated in each of the box plots indicate (from bottom to top) the 10th, 25th, 50th (median), 75th, and 90th percentiles. Pre-lesion measurements were taken at about 1 week of age just prior to surgery. Post-lesion measurements were taken 2 weeks later. Statistical comparisons between the lesioned and control chicks indicate that there are no significant differences in either the median refractive error or the distribution of refractive errors.

The ocular development of the non-accommodating eyes of EW-lesioned chicks was not different from that of unoperated controls (see Figure 6.6). In both the lesioned and control chicks, the radius of corneal curvature, anterior chamber depth, lens thickness and vitreous chamber depth all increased normally from ages 1 to 3 weeks (paired *t*-tests, $p<0.001$). After 2 weeks without accommodation, the EW-lesioned eyes showed all of the same dimensions as controls (*t*-tests: corneal curvature $p=0.496$; anterior chamber depth, $p=0.907$; lens thickness, $p=0.176$; vitreous chamber depth, $p=0.155$).

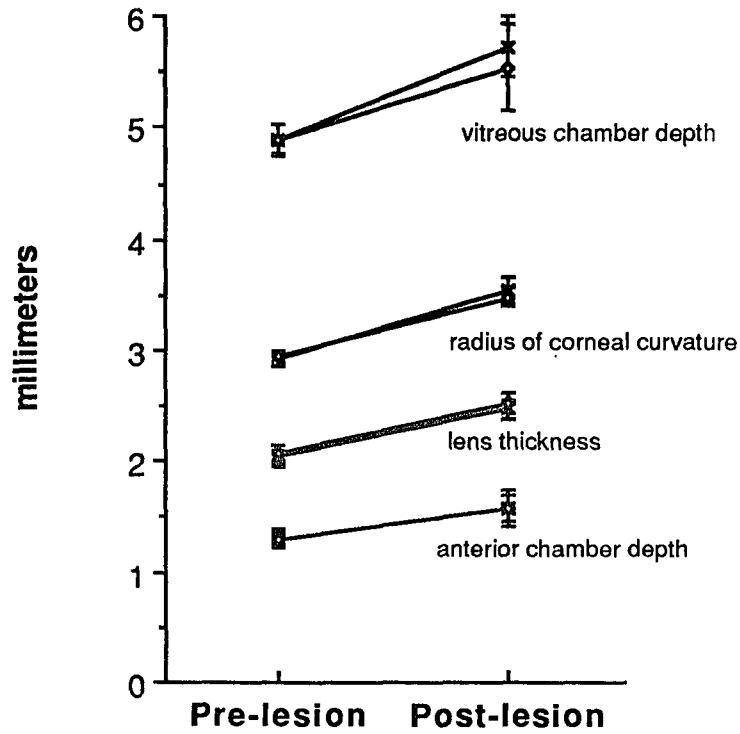


Figure 6.6
The morphological measurements of the eyes plotted in Figure 6.5 also indicate that the EW lesions did not significantly alter the development of the corneal curvature, anterior chamber depth, lens thickness, or vitreous chamber depth. Unfilled diamonds indicate the mean measurement of the control eyes (which had the same visual experience as the EW-lesioned eye except for the loss of accommodation), x's indicate the means of the EW-lesioned eyes. Error bars show standard deviations. Here, and in similar figures presented below, the depth of the anterior chamber includes the thickness of the cornea, which was estimated to be approximately 0.24 mm.

Bilateral EW lesions

Figure 6.7 shows refractive state changes over time for chicks with bilateral EW lesions, as well as for unoperated control chicks. When both of the EW nuclei were lesioned, the refractive errors as a function of age were significantly different from normal controls (Friedman 2-way nonparametric analysis of variance, $p<0.01$). Furthermore, in chicks with bilateral EW lesions an increase in the variability of the refractions, as well as a slightly more hyperopic median refraction, were detected at some of the ages tested. The distribution of refractive errors in chicks with bilateral EW lesions was different than in controls at 28, 35, and 42 days (Kolmogorov-Smirnov, $p<0.01$), but not at 14 or 56 days. There was significantly greater hyperopia in the EW-lesioned chicks at 14 (+5.56 D vs. +3.762 D; *U*-test, $p<0.03$), 28 (+3.94 D vs. +2.00 D; *U*-test, $p<0.01$), 35 (+4.15 D vs. +2.37 D;*U*-test, $p<0.01$), and 42 days of age (+3.84 D vs. +1.83 D; *U*-test, $p<0.02$), but

not 56 days (+3.13 D vs. +1.82 D; *U*-test, p=0.082). Taken together, these findings suggest that the EW-lesioned eyes may be slower at emmetropizing than controls.

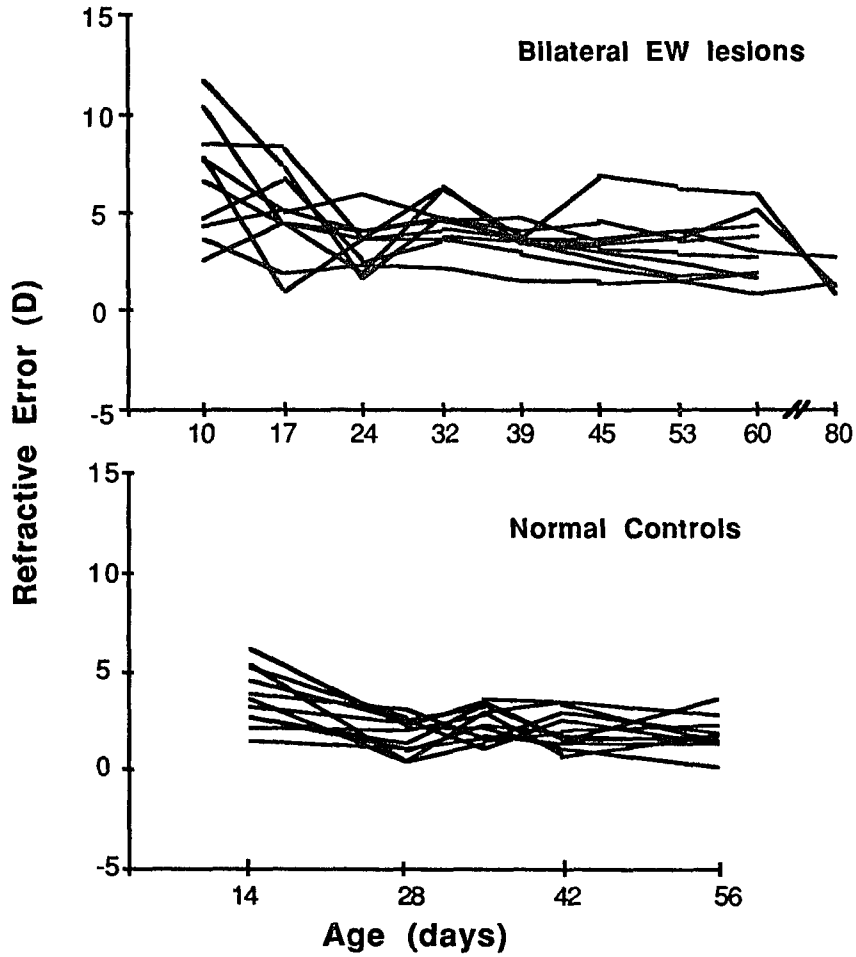


Figure 6.7
Graphs showing longitudinal tracking of refractive state. **Top:** eyes of chicks with bilateral lesions of the Edinger-Westphal nuclei. These eyes were measured at approximately 1 week intervals starting at 10 days up to 80 days of age. **Bottom:** the eyes of normal, unoperated, control chicks measured at 2, 4, 5, 6, and 8 weeks of age. For statistical comparisons the data from the bilaterally EW-lesioned birds were interpolated from the nearest measurement ages in order to estimate the refractive states at ages 14, 28, 35, 42, and 56 days when the control birds were measured. See text for results.

Figure 6.8 shows that, except for anterior chamber depth, the morphology of the eyes with bilateral EW lesions are not different from that of normal controls. The controls repre-

sented in this figure are not the same as in Figure 6.7; the data from control eyes in Figure 6.8 represent a cross- sectional sampling of normal chicks at various ages.

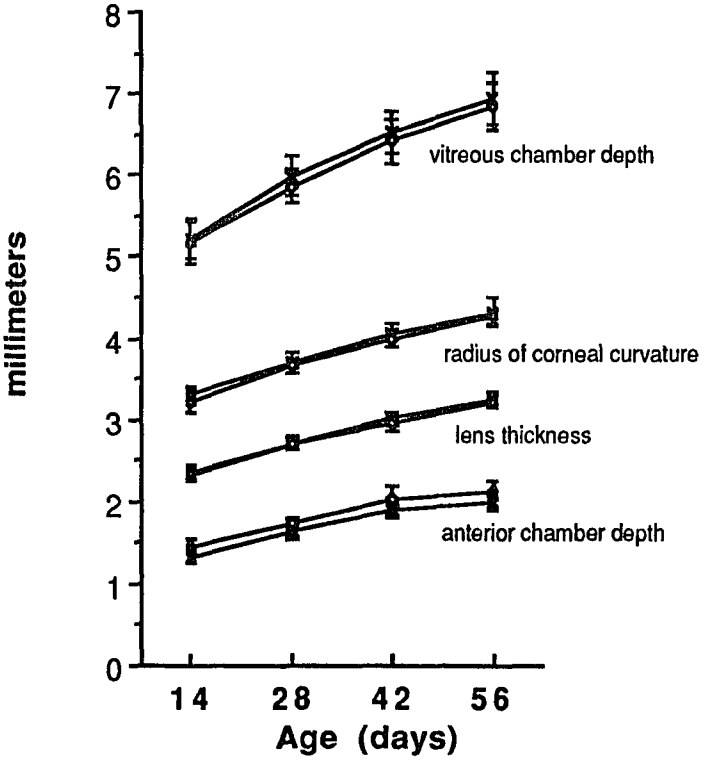


Figure 6.8
The average dimensions of the eyes with bilateral EW lesions plotted in Figure 6.5, compared to unoperated controls. These controls are not the same birds shown in Figure 6.5, and represent cross sectional age sampling (14 days, n=22; 28 days, n=18; 42 days, n=31; 56 days, n=9). Unfilled diamonds indicate the mean measurement of the control eyes (which had the same visual experience as the EW-lesioned eye except for the loss of accommodation), x's indicate the means of the EW-lesioned eyes. Error bars show the standard deviations.

Only anterior chamber depth consistently differs between bilaterally EW-lesioned and unoperated chicks. The anterior chamber depth is slightly shallower in the lesioned chicks relative to control groups at all of the ages tested (14 days: 1.33 mm vs. 1.42 mm, *t*-test, $p<0.05$; 28 days: 1.65 mm vs. 1.71 mm, *t*-test, $p<0.05$; 42 days: 1.88 mm vs. 1.98 mm, *t*-test, $p<0.05$; 56 days: 2.00 mm vs. 2.06 mm, *t*-test, $p<0.05$). This difference can not, however, explain the slightly greater hyperopia in the lesioned chicks. In fact the two changes are inconsistent; a shallower anterior chamber actually increases the total optical power of the eye. Although this inconsistency may be the result of using different control groups, it is also possible that it reflects a subtle, lesion-related, disruption in the control of eye growth. It is plausible that the difference in refractive state distribution between EW-

lesioned eyes and controls may result from lesion-induced interference (via accommodative, oculomotor, or other ocular systems) with the proper correlation of the ocular components, rather than affecting any particular component in a systematic way. This could explain why the EW-lesioned eyes remain more hyperopic than controls, as well as why the hyperopia is not related to any particular morphological change.

The effects of EW lesions on emmetropization from induced ametropia

Using the experimental emmetropization paradigm described in Chapter 4, it was established that an intact EW is not necessary for an induced refractive error to be detected and corrected after the visual manipulation causing it is discontinued. That is to say, that the eyes of EW-lesioned chicks were not impaired in their ability to sense and compensate for the initially induced ametropia and grow back toward emmetropia. Figure 6.9 shows that in chicks with unilateral EW lesions (top) emmetropia was attained from either visual deprivation myopia (left panels) or dark-induced hyperopia (right panels), just as in the un-operated contralateral eye (bottom).

Unilateral EW lesions were performed on chicks after they were made myopic by 2 weeks of visual form deprivation in the lateral visual field. The eye on the unoperated side served as a control. As shown in Figure 6.9 (left panels), the eyes with EW lesions, as well as the unoperated control eyes, were both able to sense the induced myopia and respond by returning to emmetropia. After only 1 week, the median change in refraction back toward emmetropia was significant for both EW-lesioned and control eyes (for EW-lesioned eyes: -12.29 D to +3.87 D; Wilcoxon, $p<.01$; for controls: -7.87 D to +3.96 D; Wilcoxon, $p<0.01$). At 1, 2, and 3 weeks after the visual deprivation was discontinued and the eyes, as a group, had returned to emmetropia, there remained no differences in the median refractive state of the EW-lesioned eyes relative to their controls (Wilcoxon, $p>0.20$). It was also found that there was no significant difference in the distribution of the refractive errors of the EW-lesioned eyes relative to controls at any of the ages (Kolmogorov-Smirnov, $p>0.10$).

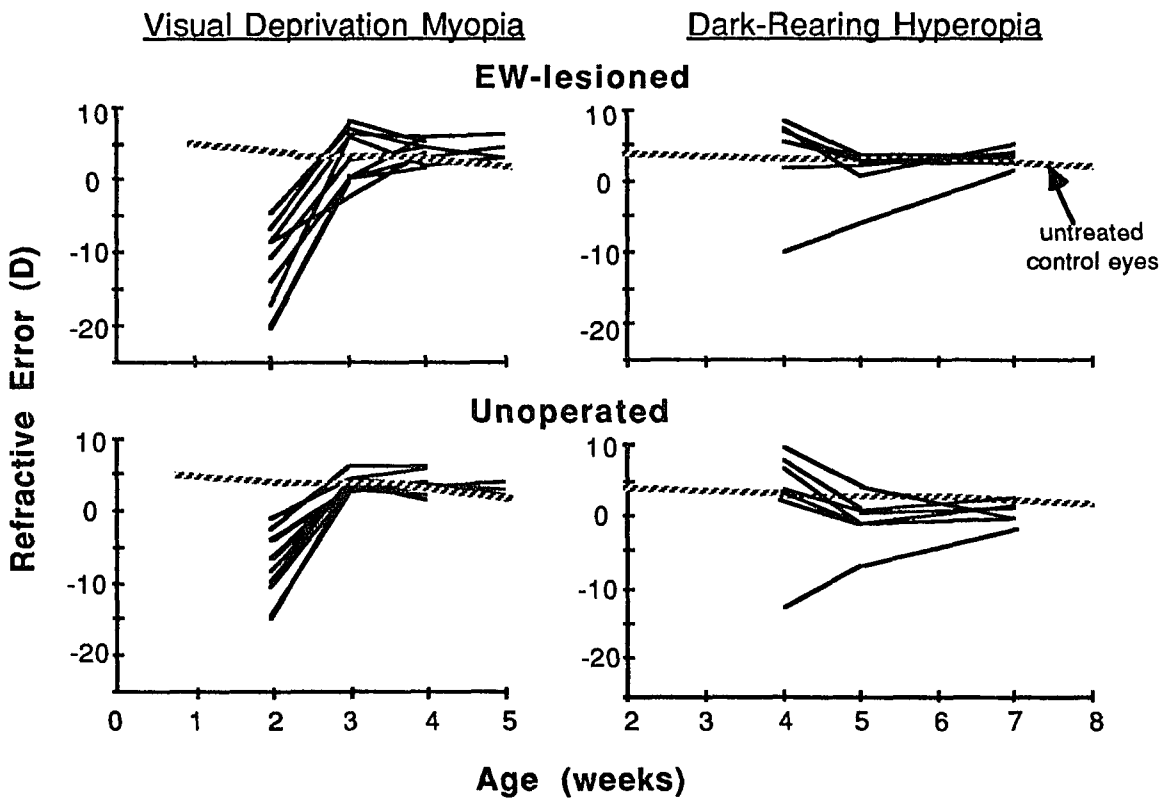


Figure 6.9
Eyes with EW-lesion (top), or contralateral unoperated controls (bottom), made either myopic by visual form deprivation of the lateral field (left panels) or hyperopic by dark-rearing (right), are equally able to sense their respective refractive errors and respond appropriately to achieve emmetropia following removal of the ametropia-producing visual manipulation. The unoperated eyes received exactly the same visual manipulation treatment as the EW-lesioned eyes. Note that after 4 weeks of dark-rearing, one of the birds was found to be myopic in both eyes. This chick was dropped from statistical analyses (see text for explanation).

Generally similar results were obtained for chicks made hyperopic by dark-rearing (Figure 6.9 right). Unilateral EW lesions were made after the initial measurements were taken at 4 weeks when the chicks were removed from the dark. The the eyes contralateral to the lesions served as controls. One of the chicks undergoing the dark-rearing treatment became myopic in both eyes and was dropped from the following statistical analyses as the question asked using this group was whether accommodation was necessary for a return to

emmetropia from hyperopia. The unoperated hyperopic eyes grew back to emmetropia after 1 week under normal lighting conditions (+5.11 D to -0.16 D; Wilcoxon, $p<0.05$), while the refractive change in the EW-lesioned eyes was similar in direction but not statistically significant, although nearly so (+5.80 D to +2.44 D; Wilcoxon, $p=0.056$). There were no significant differences between the EW-lesioned and control eyes at 4 (Wilcoxon, $p=0.834$) and 5 ($p=0.142$) weeks of age. At 7 weeks of age, however, the median refractive error of the EW-lesioned chicks were slightly more hyperopic than the contralateral control eyes (+3.59 D vs. +0.84 D; Wilcoxon, $p<0.05$).

There were a number of differences between the morphology of emmetropizing eyes with EW lesions and their contralateral, unoperated, control eyes. Figure 6.10 shows the changes in the eyes of chicks recovering from visual deprivation myopia. EW-lesioned eyes had significantly flatter corneas at 5 weeks of age (radius of curvature: 3.58 mm vs. 3.62 mm; paired *t*-test, $p<0.05$), thinner lenses at 4 weeks (2.74 mm vs. 2.80 mm; paired *t*-test, $p<0.05$), and deeper vitreous chambers at both 4 (6.06 mm vs. 5.82 mm; paired *t*-test, $p<0.05$) and 5 weeks (6.36 mm vs. 6.03 mm; paired *t*-test, $p<0.01$).

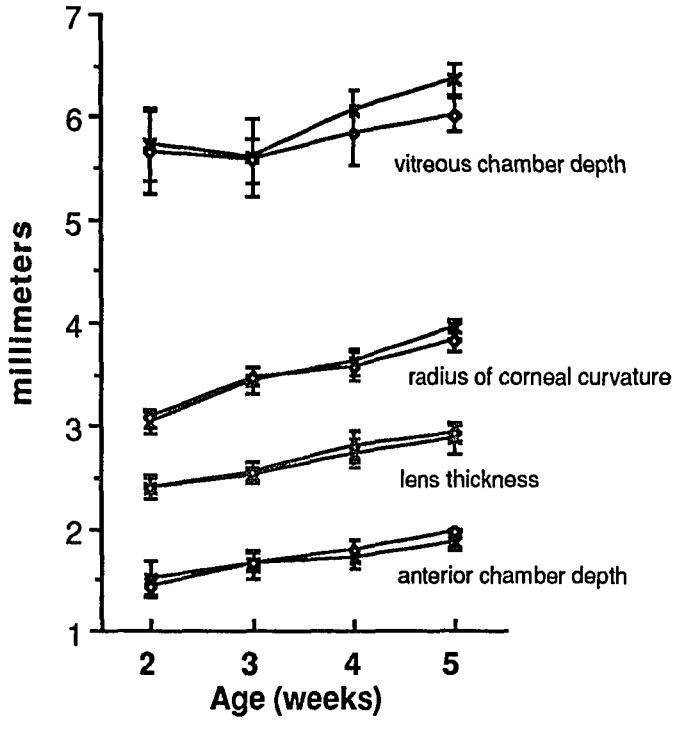


Figure 6.10
The growth of both eyes in chicks with unilateral EW lesions recovering from visual deprivation myopia. The visual deprivation was removed at 2 weeks at which time the chicks were first measured and then received unilateral EW lesions. EW-lesioned eyes are indicated by x's, control eyes (which had the same visual experience as the EW-lesioned eye except for the loss of accommodation) by unfilled diamonds. Standard deviations are indicated by error bars.

Figure 6.11 shows the morphological changes occurring in eyes recovering from dark-induced hyperopia. There were no differences between EW-lesioned eyes and controls in corneal curvature or vitreous chamber depth. In comparison to unoperated controls, anterior chamber depth was significantly deeper in EW-lesioned eyes at 7 weeks of age (2.15 mm vs. 2.07 mm; paired *t*-test, $p<0.05$), an effect which is opposite to that reported for the anterior chamber depths in bilateral EW-lesioned chicks. The lenses of the EW-lesioned eyes were thinner than controls at all ages, including the initial pre-lesion measurement at 4 weeks when the chicks were first removed from the dark and measured prior to lesioning (paired *t*-tests, $p<0.05$). Because of this, the thinner lenses are likely not to be related to the lesions *per se*.

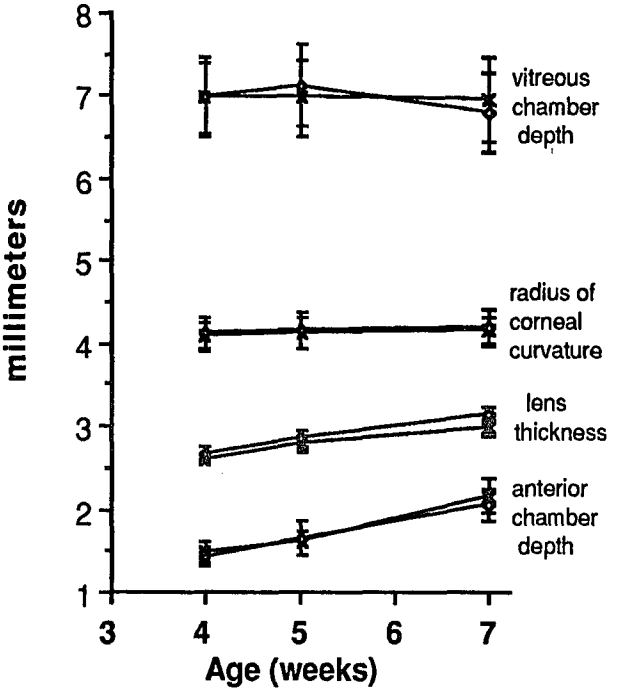


Figure 6.11
The growth of both eyes in chicks recovering from dark-induced hyperopia. The chicks were returned to normal rearing conditions at 4 weeks at which time they were first measured. They then received unilateral EW lesions. EW lesioned eyes are indicated by x's, control eyes (which had the same visual experience as the EW-lesioned eye except for the loss of accommodation) by unfilled diamonds. Standard deviations are indicated by error bars.

The effects of EW lesions on the progression of induced myopia

This experiment was performed in order to test the hypothesis that accommodation during visual deprivation is involved in the development of myopia. It was found that neither the myopia nor the underlying morphological changes produced after 1 week of visual deprivation were altered by EW lesions during subsequent weeks of continued visual deprivation.

In the unoperated controls, the median refractive errors measured at 1 and 3 weeks of age were -7.10 D and -3.98 D respectively, and were not significantly different (Wilcoxon, $p>0.10$). Figure 6.12 shows that EW lesions performed on myopic chicks at 1 week of age (-5.18 D) do not significantly alter, relative to controls, the degree of myopia resulting after two weeks more of visual deprivation (3 week old lesioned eyes = -4.10 D vs. control eyes = -3.98 D; *U*-test, $p>0.20$), nor were they significantly different from the original refractive errors measured at 1 week (Wilcoxon, $p>0.10$). Furthermore, the distributions of

EW-lesioned eyes at 3 weeks of age did not differ significantly from those of unoperated control eyes at the same age (Kolmogorov-Smirnov, $p>0.10$).

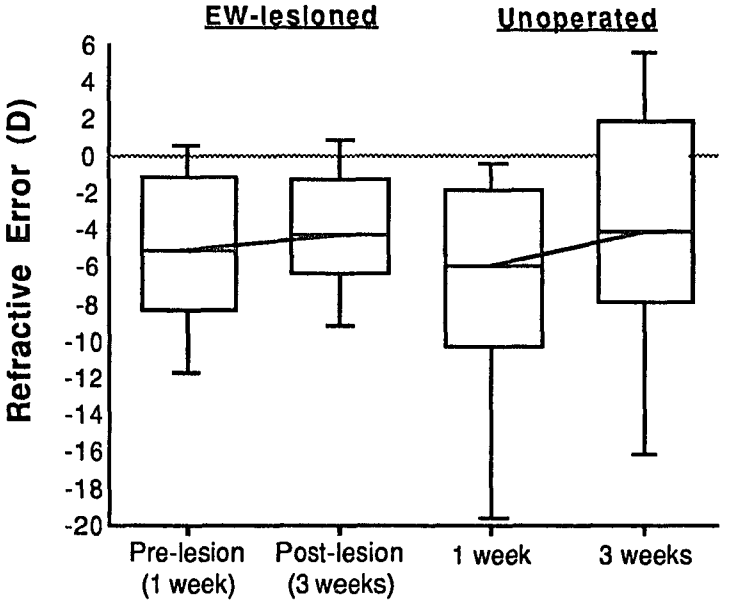


Figure 6.12
The change in the distribution of refractive errors in visually deprived eyes with EW lesions, as well as in the visually deprived eyes of unoperated controls. The horizontal lines indicated in each of the box plots indicate (from bottom to top) the 10th, 25th, 50th (median), 75th, and 90th percentiles. Pre-lesion measurements were taken at about 1 week of age just prior to surgery, the post-lesion measurements were taken 2 weeks later. The apparent decline in myopia for both groups was not significant. Comparisons between the lesioned and control chicks indicate that there are no significant differences in either the median refractive error or the distribution of refractive errors.

Because the EW lesions did not affect the myopia produced in visually deprived eyes, it was not surprising to find that EW lesions did not result in significant differences in any of the ocular dimensions measured (see Figure 6.13). In both the lesioned and control chicks, the radius of corneal curvature, anterior chamber depth, lens thickness and vitreous chamber depth all increased normally from ages 1 to 3 weeks (paired *t*-tests, $p<0.001$). After 2 weeks without accommodation, the EW-lesioned eyes possessed all of the same dimensions as controls (*t*-tests: corneal curvature $p=0.274$; anterior chamber depth, $p=0.582$; lens thickness, $p=0.510$; vitreous chamber depth, $p=0.579$).

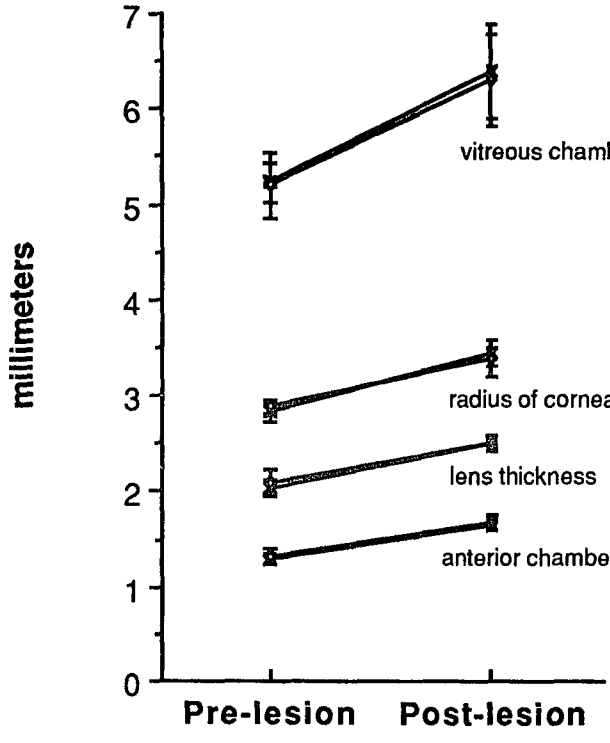


Figure 6.13
The morphological measurements of the eyes plotted in Figure 6.12 indicate that EW lesions did not significantly alter the development of the corneal curvature, anterior chamber depth, lens thickness, or vitreous chamber depth. Unfilled diamonds indicate the mean measurement of the control eyes (which had the same visual experience as the EW-lesioned eye except for the loss of accommodation), x's indicate the means of the EW-lesioned eyes. Error bars show the standard deviations.

Conclusions

Despite the findings that chicks possess a complex accommodative mechanism and are capable of relatively large accommodative amplitudes, accommodation does not appear to be essential for the regulation of eye growth and refractive state. Although species differences have yet to be considered, the results reported in this chapter challenge the long held assumptions that accommodation is central to the control of eye growth, and that excess accommodation is the principal cause of developmental myopia. For instance, one hypothetical role for accommodation in eye growth now seems particularly unlikely. Accommodation does not necessarily mediate ocular growth changes; the proper growth adjustments to achieve emmetropia from either induced hyperopia or myopia are observed in the absence of accommodation. Additional support for this conclusion is obtained from the studies presented in Chapter 5 which show that even with the optic nerve cut, chick

eyes can grow in the proper direction to correct induced refractive errors of either sign when the deprivations causing the ametropias are discontinued.

Although the experiments presented in this chapter show that accommodation is not necessary for the variety of induced ocular growth responses observed in intact eyes it may be that, in normal eyes, accommodation is useful for detecting refractive errors. Nevertheless, in the absence of accommodation other error-signal detectors are clearly able to guide the ocular growth adjustments. Besides the intuitive reasons for expecting that accommodation would be useful in adjustments of refractive state, some role for accommodation in eye growth is suggested by the slight hyperopia and increased variability of the refractive errors of bilaterally EW-lesioned chicks, and some of the various (however inconsistent) effects of EW lesions on ocular morphology. Alternatively, these refractive and morphological effects could result from lesion damage to areas not related to accommodation *per se*. Because some of the effects reported within a particular lesioned group lack consistency over time, and there is a noticeable lack of consistency in certain effects when viewed across experimental groups, it may be valid to dismiss as chance events, or statistical artifacts resulting from small samples, some of the apparently lesion-related morphological changes reported (specifically anterior chamber and lens changes). Certain effects, on the other hand, are quite robust and apparently lesioned-related, such as the deeper than normal vitreous chamber depths at both 4 and 5 weeks of age in the eyes emmetropizing from induced myopia. However, even these effects are inconsistent with the refractive state changes; the vitreous chambers are deeper than controls when the refractive states are consistently emmetropic and do not differ from controls. This may reflect regulated changes in other ocular components.

Because of the lack of strong and consistent lesion effects, after considering all of the data together it must be concluded that if accommodation is normally involved in eye growth (perhaps even sufficient to guide eye growth under normal conditions), it is clearly

not necessary for the control of eye growth. Other eye growth mechanisms which are able to effectively act independent of accommodation must exist.

CHAPTER SEVEN

SUMMARY

The optical development of the eye is complicated, and depends on the correlated growth of the cornea, anterior chamber, lens, and vitreous chamber. It is evident from the results of the studies in this dissertation that the relationships of these ocular components are adjustable, and that these adjustments depend to a large extent on visual experience for guidance. While vision is, without doubt, essential for proper ocular growth, the nature of the mechanisms controlling the growth are much less clear and only now are beginning to be understood. Besides the existence of vision-dependent feedback regulation of eye growth, it is concluded from the studies presented here that there are at least two levels to this regulation: (1) A local ocular mechanism guides eye growth and refractive development, perhaps using a retinally derived aspect of the optical image. (2) A brain-mediated mechanism uses certain aspects of the brain's visual processes, perhaps as a fine-tuning mechanism for refractive state.

The findings reported in Chapter 4 leave little doubt that the major characteristic of the visual control of eye growth is the ability to sense an existing refractive error and evoke the proper adjustments in the length of the vitreous chamber. This conclusion is based primarily on the observation that the vitreous chambers of either myopic or hyperopic eyes are adjusted appropriately to compensate for the induced refractive error — the depth of the vitreous chamber in a hyperopic eye is increased to correct the refractive error, while the vitreous chamber in a myopic eye stops growing — and is true despite the fact that the

vitreous chambers are abnormally enlarged in both types of induced refractive error. These results argue against the hypothesis that eye size is the only error-signal controlling eye growth, although there is some evidence that shape-sensitive feedback may, nevertheless, be involved in eye growth; the anterior segment and curvature of the cornea appear to be under the control of a slow-acting shape-sensitive adjustment which is independent of refractive-sensitive vitreous chamber adjustments.

The possible shape-sensitive regulation of eye growth appears to be less immediate than refractive-sensitive regulation. After the refractive state has returned to emmetropia via vitreous chamber adjustments, corrective changes in the dimensions of the anterior segment continue until normal dimensions are achieved. In addition, in eyes emmetropizing from dark-induced hyperopia the corneal curvature changes observed are opposite in direction (increasing curvature) to those observed in normally growing eyes (decreasing curvature). Thus, the ocular growth adjustments to induced refractive errors occur in 2 stages; the faster vitreous chamber changes appear to be guided by refractive state, and the slower anterior chamber/corneal curvature changes may be shape sensitive. These stages of eye growth control may normally work together to achieve and maintain emmetropia as the eye grows during its normal development; the slower mechanism may keep the ocular components in more or less the proper proportions, while the faster mechanism appears to maintain the proper correlation between the vitreous chamber depth and the eye's total optical power. The relationship of these two stages (fast vs. slow) to the two levels of growth control (i.e. local-ocular vs. brain-mediated) is not yet clear, although both the local and brain-mediated control mechanisms appear to involve the faster vitreous chamber effects while the slower anterior segment effects may be a local ocular phenomenon. Furthermore, it is conceivable that the putative shape-sensitive eye growth mechanism is able to adjust the gain of the refraction-sensitive mechanism, turning it up when the shape is abnormal as in an induced ametropia. This would explain why emmetropization from induced ametropia is so rapid.

While the results of the studies presented in this dissertation describe the capabilities and multi-faceted nature of eye growth control, they leave open to conjecture both the mode of operation of such control and the nature of the stimuli which drive it. For instance, how the ocular growth responses are actually mediated is completely unclear. A thorough understanding of the efferent mechanisms of ocular growth control is likely only when more sophisticated techniques, particularly cellular and biochemical, are employed. Equally perplexing is the nature of the salient visual stimuli used by the refraction-sensitive eye growth control mechanisms. It has been determined from the optic nerve section experiments that the eye, by itself, is able to sense the sign of a refractive error and evoke the appropriate vitreous chamber responses to correct the error and grow toward emmetropia (see Chapter 5). How, then, is the eye, by itself and without the aid of higher visual processing, able to sense the sign of a refractive error? Clearly some feature of the defocused image (e.g. blur or cues arising from the chromatic aberration of the eye) provides the error signal that guides eye growth. How such an error signal would be normally interpreted is something of a mystery because the signal would be constantly changing because of the moment to moment activity of the accommodation system. Perhaps some aspect of the residual defocus present during the normal fluctuations of the accommodative response is adequate to guide eye growth. Alternatively, the error-signal guiding eye growth may be unrelated to, and completely unaffected by, the simultaneous operation of accommodation. This notion is supported by the findings presented in Chapters 6 which show that accommodative output is not necessary for proper adjustments in eye growth, findings which are consistent with the existence of local eye growth control.

It is important to note that the existence of a local eye growth control mechanism does not, by itself, explain all of the results which have been presented in this dissertation. Local eye growth control is best observed in optic-nerve-sectioned eyes growing toward emmetropia from induced refractive errors of either sign, after the visual deprivations causing the errors are discontinued. However, brain-mediated visual processes also seem

to play a role in the regulation of eye growth since intact optic nerves are clearly necessary for emmetropia to be properly maintained. Although optic-nerve-sectioned eyes will initially grow to emmetropia from either induced myopia or hyperopia, they eventually overshoot emmetropia suggesting that the brain plays a role in regulating eye growth (see Chapter 5). Furthermore, if the optic nerve is sectioned and the eye allowed to develop under normal visual field conditions it becomes hyperopic as a result of the vitreous chamber being shorter than normal. The fact that these eyes are still capable of nearly normal growth — they become larger over time and maintain normal proportions — also supports the existence of a shape-sensitive mechanism, located locally in the eye itself.

Of the brain-mediated mechanisms possibly involved in the control of eye growth, accommodation has long been considered the prime candidate despite the lack of experimental evidence. Based on the results of the Edinger-Westphal lesion experiments presented in Chapter 6 it now appears that accommodation, which may be sufficient to guide eye growth, is not necessary for the control of eye growth. In chicks accommodation is complex and powerful, using both corneal and lenticular mechanisms to produce total dioptric changes close to 20 D. Despite this, all of the growth changes observed in the variety of experimental manipulations used throughout this dissertation still occur after accommodative output is blocked by lesions of the Edinger-Westphal nucleus. This fact strongly argues against the presumption that accommodation is central to effecting the changes in vitreous chamber dimensions necessary to adjust the refractive state of the eye. It remains possible, however, that some of the stimuli which drive accommodation are involved in the control of eye growth, either locally or through brain-mediated pathways. It also remains possible that in normal eyes the accommodative system may be a means for extracting useful information about the optical state of the eye. If accommodation does play a role, its disruption would explain the high variability and slightly more hyperopic refractions of the bilaterally EW-lesioned chicks which were also described in Chapter 6.

However, it is important to note that these results may be alternatively explained by lesion damage to areas not related to accommodation, such as the oculomotor nuclei.

In conclusion, the general picture of the growing eye that is emerging from the studies presented here is one in which the eye is largely able to control its own growth, although brain-mediated mechanisms are also involved. A possible shape-sensitive mechanism might produce and maintain a properly proportioned, but not necessarily emmetropic, eye during development. Refraction-sensitive mechanisms act to regulate the vitreous chamber growth so that the retina is properly positioned with respect to the focal plane and emmetropia is achieved. In addition, the refraction-sensitive control of vitreous chamber growth appears to be multifaceted, being controlled grossly by mechanisms within the eye itself, and more precisely via brain-mediated visual feedback loops. For years, many researchers have struggled to identify the single factor central to the control of eye growth and refractive state. The failure of this endeavor may well be the direct result of there not being a single controlling mechanism for eye growth.

APPENDIX A

Calculation of the Cardinal Points of an Optical System:

The cardinal points (anterior and posterior focal points, principal points, and nodal points) describe the characteristics of any complex optical system as if it were made up of a single lens (see Figure A.1). By convention, the anterior points refer to the object space while the posterior points refer to the image space. The focal points indicate the positions where parallel rays are focused by the system. The first and second focal lengths of system are measured from the first and second principal points to the anterior and posterior focal points respectively. The total optical power of the system is the reciprocal of the second focal length. The nodal points are useful in determining the angular size of an image (see point m' on Figure A.1) since an oblique ray entering the system and directed at the first nodal point, emerges from the second nodal point as the ray crosses the optic axis.

Based on an iterative algorithmn (Southall, 1937), the various radii of the refracting surfaces, together with the reduced distances between each surface to account for the various refractive indices, were used to calculate the cardinal points and the first and second focal lengths of the whole eye, or any of the individual refracting surfaces within it.

Given:

m = the total number of refracting surfaces
r_k = radius of curvature of surface k
n_k = refractive index of the material to the left of surface k
d_k = distance from surface k to surface k+1

refracting power of surface k: $F_k = ((n_{k+1}-n_k)/r_k)x1000$

reduced distance from surface k to k+1: $c_k = (d_k/n_{k+1})/1000$

Then the cumulative optical power from one surface to the next *(F)* is calculated separately for both forward and reverse ray traces by iterating the following equations by k increments from 1 to m:

(forward ray trace)

$F_{1,m} = F_{k-1} + (F_k x X_k)$ where: $X_k = X_{k-1}-(c_{k-1}xF_{k-1})$

(reverse ray trace)

$F_{m,1} = F_{k+1} + (F_k x Y_k)$ where: $Y_k = Y_{k+1}-(c_{k+1}*F_{k+1})$

X and Y are unitless quantities used in the calculation of F for the forward and reverse ray traces respectively, and are reckoned from the various surfaces' refractive powers as well as the reduced distances between each surface.

It is assumed that: $X_1 = Y_m = 1.0$

Then:

Total optical power = $F_{1,m}$

First focal length (f) = $(1/F_{1,m})$x1000

Second focal length (f') = $(n_{m+1}/F_{1,m})$x1000

Anterior focal point (F) = $(Y_{1,m}/F_{1,m})$x1000

Posterior focal point (from corneal apex)(F') = $((X_{1,m}/F_{1,m})$x1000$)+\Sigma d_k$

First nodal point (N) = f'-F

Second nodal point (N') = F'-f

First principal point (H) = f-F

Second principal point (H') = F'-f'

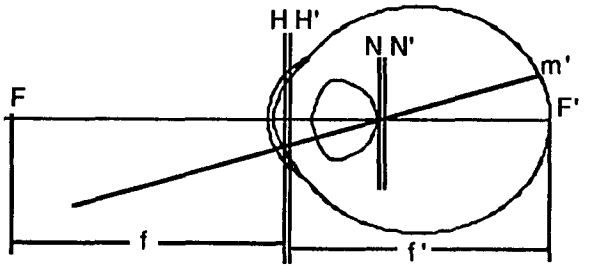


Figure A.1
The cardinal points and focal lengths of the eye.

APPENDIX B

Refractive Errors:

The sign and magnitude of a refractive error is clinically defined by the sign and power of a lens which would, if placed a certain distance in front of the eye, correct the error. To illustrate this, the following diagrams trace rays through either myopic (Figure B.1) or hyperopic eyes (Figure B.2), with and without correction.

Ray A (bold line) is a paraxial ray traced through the uncorrected optically reduced eye. Notice that ray A is focussed in front of the retina in myopic eyes, and in back of the retina in hyperopic eyes. Ray B is a paraxial ray traced first through a corrective lens before entering the eye and is focused at the retina. Ray C (broken line) is the undeviated ray which passes through the center of the eye's optics at the optic axis and intersects the focal plane at a point where ray A would pass if the eye was emmetropic. The far point of the eye (the point on the optic axis conjugate to the retina) is determined by extending from the point where ray A is refracted by the eye an imaginary ray parallel to ray C. Notice that the correction lens focuses a paraxial ray (B) at the eye's far point.

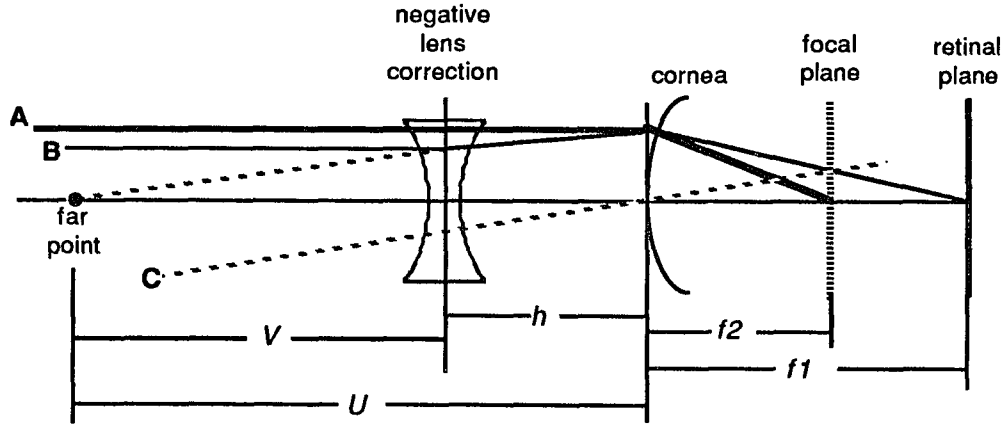


Figure B.1
Schematic ray-trace through a reduced myopic eye with a negative lens correction.

If a negative ophthalmic lens is placed at a distance h (vertex distance) in front of a myopic eye, the vergence of the rays incident on the cornea is decreased. A lens of the proper power thereby corrects the refractive error.

The power of the negative correction lens for myopia is:

$$V = -\frac{1}{U - h}$$

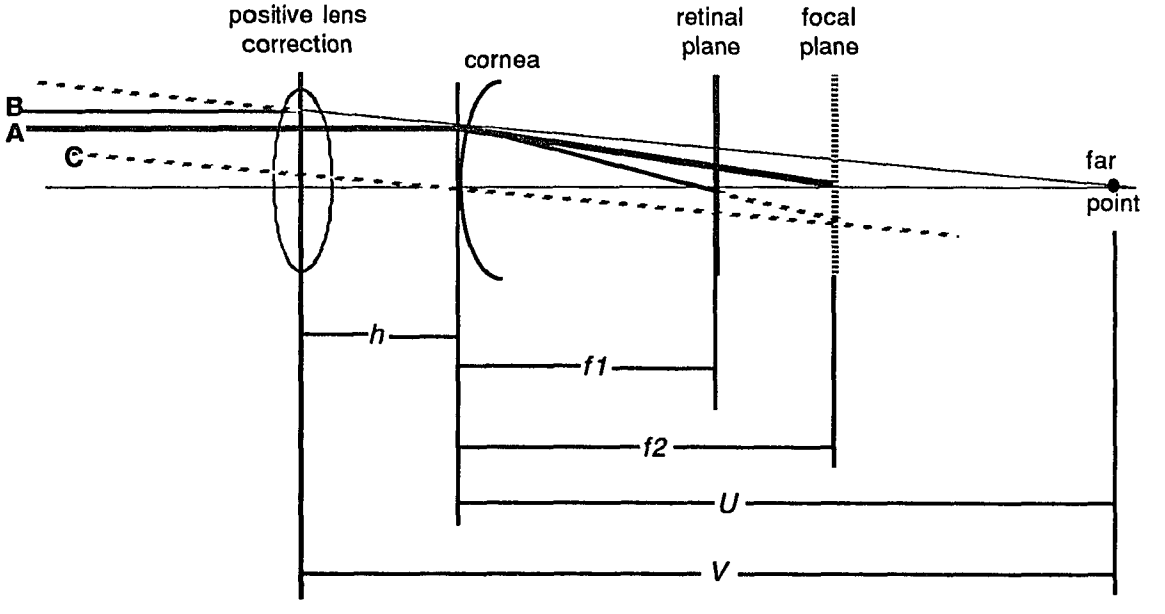
The location of the far point is calculated from:

$$U = -\frac{(1 - Vxh)}{V}$$

The true myopia (in diopters) is the reciprocal of U:

$$\text{myopia} = -\frac{1}{U} = -\frac{V}{(1 - Vxh)} = \frac{1}{f1} - \frac{1}{f2}$$

Figure B.2
Schematic ray-trace through a reduced hyperopic eye with a positive lens correction.



The far point of the hyperopic eye is located beyond infinity so is represented as being behind the eye. A positive lens of the proper power placed at a known vertex distance in front of a hyperopic eye corrects the refractive error by increasing the vergence of the light rays incident on the cornea.

The power of the positive lens correction for a hyperopic eye is:

$$V = \frac{1}{U + h}$$

The location of the far point behind the eye is:

$$U = \frac{(1 - Vxh)}{V}$$

The true hyperopia (reciprocal of U) is given by:

$$\text{hyperopia} = \frac{1}{U} = \frac{V}{1 - Vxh} = \frac{1}{f1} - \frac{1}{f2}$$

BIBLIOGRAPHY

Adel, N.L. (1964) Developmental changes in the avian eye. Am. J. Optom. & Arch. Am. Acad. Optom., 41:466-469.

Adel, N.L. (1966) Electromyographic and entopic studies suggesting a theory of action of the ciliary muscle in accommodation for near and its influence on the development of myopia. Am. J. Optom. & Arch. Am. Acad. Optom., 43:27-38.

Anderson, R.L., and S.A. Baumgartner (1980) Strabismus in ptosis. Arch. Ophthalmol., 98:1062-1067.

Armaly, M.F., and M.L. Rubin (1961) Accommodation and applanation tonometry. Arch. Ophthalmol., 65:415-423.

Armaly, M.F., and N. C. Jepson (1962) Accommodation and the dynamics of the steady-state intraocular pressure. Invest. Ophthalmol. Vis. Sci., 1:480-483.

Axmith, K., and J.D. Morin (1975) Avian light-induced macrophthalmos. Can. J. Ophthalmol., 10:46-50.

Banks, M.S. (1980) Infant refraction and accommodation. In: *Electrophysiology and Psychophysics: Their use in Ophthalmic Diagnosis* (ed. S. Sokol), Int. Ophthalmol. Clin., 20:205-231.

Bedrossian, R.H. (1971) The effect of atropine on myopia. Ann. Ophthalmol., 3:891-897.

Bedrossian, R.H. (1979) The effect of atropine on myopia. Am. Acad. Ophthal., 86:692-694.

Beer, T. (1892/93) Studien über die accommodation des vogelauges. Arch. ges. Physiol., 53:175-237.

Belkin, M., U. Yinon, L. Rose, and I. Reisert (1977) Effect of visual environment on refractive error of cats. Doc. Ophthalmol., 42:433-437.

Bell, G.R. (1980) The Coleman theory of accommodation and its relevance to myopia. J. Am. Optom. Assoc., 51:582-588.

Bennett, A.G., and J.L. Francis (1962) The eye as an optical system. In: *The Eye*, v.4,*Visual Optics and the Optical Space Sense*, (ed. H. Davson), Academic Press., New York.

Bercovitz, A.B., P.C. Harrison, and G.A. Leary (1972) Light induced alterations in growth pattern of the avian eye. Vision Res.,12:1253-1259.

Blaker, J.W. (1980) Toward an adaptive model of the human eye. J. Opt. Soc. Am., 70:220-223.

Boothe, R., V. Dobson, and D. Teller (1985) Postnatal development of vision in human and nonhuman primates. Ann. Rev. Neurosci., 8:495-545.

Borish, I.M. (1970) *Clinical Refraction*, 3rd Ed., The professional Press Inc., Chicago.

Burns, S., and J. Wallman (1981) Relation of single unit properties to the oculomotor function of the nucleus of the basal optic root (accessory optic system) in chicks. Exp. Brain Res., 42:171-180.

Carroll, J.P. (1982) Component and correlation ametropia. Am. J. Optom. Physiol. Opt., 59:28-33.

Carroll, J.P. (1982) On emmetropization. J. Theor. Biol., 95:135-144.

Chiu, P.S.L., J.K. Lauber, and A. Kinnear (1975) Dimensional and physiological lesions of the chick eye as influenced by the light environment. Proc. Soc. Exp. Biol. Med., 148:1223-1228.

Coleman, D.J. (1970) Unified model of accommodative mechanism. Am. J. Ophthalmol., 69:1063-1079.

Collins, C.C., P. Bach-y-Rita, and D.R. Loeb (1967) Intraocular pressure variation with oculorotary muscle tension. Am. J. Physiol., 215:1039-1043.

Coulombre, A. (1956) The role of intraocular pressure in the development of the chick eye. I. Control of eye size. J. Exp. Zool., 133:211-225.

Coulombre, A. (1957) The role of intraocular pressure in the development of the chick eye. II. Control of corneal size. Am. J. Optom. & Arch. Am. Acad. Optom., 57:250-253.

Coulombre, A., and J.L. Coulombre (1957) The role of intraocular pressure in the development of the chick eye. III. Ciliary body. Am. J. Ophthalmol., 44:85-93.

Coulombre, A., and J.L. Coulombre (1959) The role of intraocular pressure in the development of the chick eye. IV. Corneal curvature.Am. J. Optom. & Arch. Am. Acad. Optom., 59:502-506.

Copps, L.A. (1944) Vision in anisometropia. Am. J. Ophthalmol., 27:641-644.

Crewther, S.G., J. Nathan, P.M. Kiely, N.A. Brennan, and D.P. Crewther (1988) The effect of defocussing contact lenses on refraction in cynomolgus monkeys. Clin. Vision Sci., 3:221-228.

Criswell, M.H., and D.A. Goss (1983) Myopia development in nonhuman primates — A literature review. Am. J. Optom. Physiol. Opt., 60:250-268.

Curtin, B.J. (1970) Myopia: A review of its etiology, pathogenesis and treatment. Sur. Ophthalmol., 15:1-17.

Curtin, B.J. (1985) *The Myopias: Basic Science and Clinical Management*, Harper and Row Publishers, Philadelphia.

Donders, F.C. (1952) *Accommodation and Refraction of the Eye,* 22nd ed., New Sydenham Society, London.

Duke-Elder, W.S. (1930) An investigation of the effect on the eyes of occupations involving close work. Brit. J. Ophthalmol., 14:609-620.

Duke-Elder, W.S. (1949) *Textbook of Ophthalmology*, v. 4, C.V. Mosby Co., St. Louis.

Dunphy, E.B. (1970) The biology of myopia. New Eng. J. Med., 283:796-800.

Dunphy, E.B., M.R. Stoll, and S.H. King (1968) Myopia among male graduate students. Am. J. Ophthalmol., 65:518-521.

Ebenholtz, S.M. (1983) Accommodative hysteresis: A precursor for myopia? Invest. Ophthalmol. Vis. Sci., 24:513-515.

Eggers, H.M., and C. Blakemore (1978) Physiological basis of anisometropic amblyopia. Science, 201:264-267.

Fincham, E.F. (1962) Accommodation and convergence in the absence of retinal images. Vision Res., 1:425-440.

Fiorentini, A., and L. Maffei (1976) Spatial contrast sensitivity of myopic subjects. Vision Res., 16:437-438.

Frankelson, F.N., J.K. Lauber, and T.A.S. Boyd (1969) The role of angle closure in light-induced avian glaucoma. Can. J. Ophthalmol., 4:59-63.

Friedman, B. (1966) Stress upon the ocular coats: Effects of scleral curvature, scleral thickness, and intra-ocular pressure Eye, Ear, Nose, and Throat Monthly, 45:59-66.

Gardiner, P.A., and G. James (1960) Association between maternal diseases during pregnancy and myopia in the child. Brit. J. Ophthalmol., 44:172-178.

Gernet, H., and E. Olbrich (1969) Excess of the human refraction curve. In: *Ophthalmic Ultrasound*, (eds. K.A. Gitter, A.H. Keeney, L.K. Sarin, and D. Meyer), C.V. Mosby Co., St. Louis.

Glickstein, M., and M. Millodot (1970) Retinoscopy and eye size. Science, 168:605-606.

Goldschmidt, E. (1968) *On the Etiology of Myopia: An Epidemiological Study*, Munksgaard, Copenhagen.

Gollender, M., F. Thorn, and P. Erickson (1979) Development of axial ocular dimensions following eyelid suture in the cat. Vision Res., 19:221-223.

Goss, D.A., and M.H. Criswell (1981) Myopia development in experimental animals — A literature review. Am. J. Optom. Physiol. Opt., 58:859-869.

Gottlieb, M.D., L.A. Fugate-Wentzek, and J. Wallman (1987) Different visual deprivations produce different ametropias and different eye shapes. Invest. Ophthalmol. Vis. Sci., 28:1225-1235.

Greene, P.R, and T.A. McMahon (1979) Scleral creep vs. temperature and pressure *in vitro*. Exp. Eye Res., 29:527-537.

Greene, P.R. (1980) Mechanical considerations in myopia: Relative effects of accommodation, convergence, intraocular pressure, and the extraocular muscles. Am. J. Optom. Physiol. Opt., 57:902-914.

Grosvenor, T., D.M. Perrigin, J. Perrigin, and B. Maslovitz (1987) Houston myopia control study: A randomized clinical trial. Part II. Final report by the patient care team. Am. J. Optom. Phys. Opt., 64:482-498.

Gundlach, R.H., R.D. Chard, and J.R. Skahen (1945) The mechanism of accommodation in pigeons. J. Comp. Psychol., 38:27-42.

Harrison, P.C., and J. McGinnis (1967) Light induced exophthalmos in the domestic fowl. Proc. Soc. Exp. Biol. Med., 126:308-312.

Hayes, B.P., F.W. Fitzke, W. Hodos, and A.L. Holden (1986) A morphological analysis of experimental myopia in young chickens. Invest. Ophthalmol. Vis. Sci., 27:981-991.

Heaton, M.B., and D.B. Wayne (1983) Patterns of extraocular innervation by the oculomotor complex in the chick. J. Comp. Neurol., 216:245-252.

Helmholtz, H. (1909) Helmholtz's Treatise of Physiological Optics, Vol. 1, [Translated from 3rd German Edition (ed. J.P.C. Southall, The Optical Society of America, New York, 1924)].

Hendrickson, P., and W. Rosenblum (1985) Accommodative demand and deprivation in kitten ocular development. Invest. Ophthalmol. Vis. Sci., 26:343-349.

Hirsch, M.J. (1951) Effect of school experience on refraction of children. Am. J. Optom. & Arch. Am. Acad. Optom., 28:445-454.

Hirsch, M.J. (1952) The changes in refraction between ages 5 and 14: Theoretical and practical considerations. Am. J. Optom. & Arch. Am. Acad. Optom., 29:445-459.

Hodos, W., A.M. Revzin, and W.J. Kuenzel (1987) Thermal gradients in the chick eye: A contributing factor in experimental myopia. Invest. Ophthalmol. Vis. Sci., 28:1859-1866.

Hodos, W., and W.J. Kuenzel (1984) Retinal-image degradation produces ocular enlargement in chicks. Invest. Ophthalmol. Vis. Sci., 25:652-659.

Hodos, W., F.W. Fitzke, B.P. Hayes, and A.L. Holden (1985) Experimental myopia in chicks: Ocular refraction by electroretinography. Invest. Ophthalmol. Vis. Sci., 26: 1423-1430.

Hofstetter, H.W. (1969) Emmetropization — biological process or mathematical artifact? Am. J. Optom. & Arch. Am. Acad. Optom., 46:447-450.

Howland, H.C., J. Atkinson, O. Braddick, and J. French (1978) Infant astigmatism measured by photorefraction. Science, 202:331-333.

Hoyt, C.S., R.D. Stone, C. Fromer, and F.A. Billdon (1981) Monocular axial myopia associated with neonatal eyelid closure in human infants. Am. J. Ophthalmol., 91:197-200.

Ingram, R.M., C. Walker, J.M. Wilson, P.E. Arnold, and S. Dally (1986) Prediction of amblyopia and squint by means of refraction at age 1 year. Brit. J. Ophthalmol., 70:12-15.

Jampel, R.S. and J. Mindel (1967) The nucleus for accommodation in the midbrain of the macaque. Invest. Ophthalmol. Vis. Sci., 6:40-50.

Jensen, L.S., and W.E. Matson (1957) Enlargement of avian eye by subjecting chicks to continuous incandescent illumination. Science, 125:741.

Johnson, C.A., R.B. Post, L.M. Chalupa, and T.J. Lee (1982) Monocular deprivation in humans: A study of identical twins. Invest. Ophthalmol. Vis. Sci., 23:135-138.

Kinnear, A., J.K. Lauber, and T.A.S. Boyd (1974) Genesis of light-induced avian glaucoma. Invest. Ophthalmol. Vis. Sci., 13:872-875.

Kirby, A.W., L. Sutton, and H. Weiss (1982) Elongation of cat eyes following neonatal lid suture. Invest. Ophthalmol. Vis. Sci., 22:274-277.

Lauber, J.K. (1987) Review: Light-induced avian glaucoma as an animal model for human primary glaucoma. J. Ocular Pharm., 3:77-100.

Lauber, J.K., and J. McGinnis (1966) Eye lesions in domestic fowl reared under continuous light. Vision Res., 6:619-626.

Lauber, J.K., and T. Oishi (1987) Lid suture myopia in chicks. Invest. Ophthalmol. Vis. Sci., 28:1851-1858.

Lauber, J.K., and V.K. Kivett (1981) Environmental control of the rearing conditions and early preglaucomatus lesions in chicks. Exp. Eye Res., 32:501-509.

Lauber, J.K., J.E. Boyd, and T.A.S. Boyd (1970) Intraocular pressure and aqueous outflow facility in light-induced avian buphthalmos. Exp. Eye Res., 9:181-187.

Lauber, J.K., J.McGinnis, and J. Boyd (1965) Influence of mitotics, diamox and vision occluders on light-induced buphthalmos in domestic fowl. Proc. Soc. Exp. Biol. Med., 120:572-575.

Lauber, J.K., J.V. Shutze, and J. McGinnis (1961) Effects of exposure to continuous light on the eye of the growing chick. Proc. Soc. Exp. Biol. Med., 106:871-872.

Lehrman, D.S. (1970) Semantics and conceptual issues in the nature-nurture problem. In: *Development and Evolution of Behavior*, (eds. L.R. Aronson, E. Tobach, D.S. Lehrman, and J. S. Rosenblatt), W.H. Freeman & Co., San Francisco.

Levy, B.J., and J.G. Sivak (1980) Mechanisms of accommodation in the bird eye. J. Comp. Physiol., 137:267-272.

Linder, K. (1949) Gadanken über den Vorgang der myopischen Denhung und seine Hintanhaltung. Albrecht v. Graefes Arch. Ophthalmol., 149:293-317. (cited by Goldschmidt, E. (1968) On the Etiology of Myopia: An Epidemiological Study, Munksgaard, Copenhagen.)

Ludlam, W.M., S. Wittenberg, and J. Rosenthal (1965) Measurements of the optical dioptric elements utilizing photographic methods. Part I. Errors analysis of Sorsby's photographic ophthalmophakometry. Am. J. Optom. & Arch. Am. Acad. Optom., 42:394-416.

Mandell, R.B. (1959) Myopia control with bifocal correction. Am. J. Optom. and Arch. Am. Acad. Optom., 36:652-658.

Mark, H.H. (1972) Emmetropization: Physical aspects of a statistical phenomenon. Ann. Ophthalmol., 393-401.

Maurice, D.M., and A.S. Mushin (1966) Production of myopia in rabbits by raised body-temperature and increased intra-ocular pressure. Lancet, 2:1160-1162.

McBrien, N.A., and D.A. Barnes (1984) A review and evaluation of theories of refractive error development. Ophthalmol. Physiol. Opt., 4:201-213.

McBrien, N.A., and T.T. Norton (1987) The development of ocular growth and refractive state in normal and monocularly deprived tree shrews *(Tupaia belangeri)*. Soc. Neurosci. Abst., v.13.

McKanna, J.A. and V.A. Casagrande (1981) Atropine effects lid-suture myopia development. Doc. Ophthalmol. Proc. Series, 28:187-192, (eds. H.C Fledelius, P.H. Alsbirk and E. Goldschmidt), Dr. W. Junk Publ., The Hague.

McKanna, J.A., and V.A. Casagrande (1978) Reduced lens development in lid-suture myopia. Exp. Eye Res., 26:715-723.

Medina, A. (1987a) A model for emmetropization: Predicting the progression of ametropia. Ophthalmologica, 194:133-139.

Medina, A. (1987b) A model for emmetropization: The effect of corrective lenses. Acta Ophthalmologica, 65:565-571.

Meyer, D.B. (1977) The avian eye and its adaptations. In The Handbook of Sensory Physiology, Vol. VII/5, The Visual System in Vertebrates, (Edited by Crescitelli F.), pp. 549-611. Springer-Verlag, Berlin.

Mitchell, D.E., R.D. Freeman, M. Millodot, and G. Haegerstrom (1973) Meridional amblyopia: Evidence for modification of the human visual system by early visual experience. Vision Res., 13:535-558.

Mohan, M., V.A. Rao, V.K. Dada (1977) Experimental myopia in the rabbit. Exp. Eye Res., 25:33-38.

Mohindra, I., and R. Held (1981) Refraction in humans from birth to five years. Doc. Ophthalmol. Proc. Series, 28:187-192, (eds. H.C. Fledelius, P.H. Alsbirk and E. Goldschmidt), Dr. W. Junk Publ., The Hague.

Mohindra, I., R. Held, J. Gwiazda, and S. Brill (1978) Astigmatism in infants. Science, 202:329-331.

Moore, R.Y. (1983) Organization and function of a central nervous system circadian oscillator: The suprachiasmatic hypothalamic nucleus. Fed. Proc., 42:2783-2784.

Morgan, M.W. (1967) A review of the major theories for the genesis of refractive state. In: *Synopsis of the refractive state of the eye: A symposium*, (ed. M.J. Hirsch), Am. Acad. Optom. Ser., 5:8-12.

Muchnick, N., and E. Hibbard (1980) Avian retinal ganglion cells resistant to degeneration after optic nerve section lesion. Exp. Neurol., 68:205-216.

Nadell, M.C., F.W. Weymouth, and M.J. Hirsch (1957) The relationship of frequency of use of the eyes in close work to the distribution of refractive error in a selected sample. Am. J. Optom. & Arch. Am. Acad. Optom., 34:523-537.

Narayanan, C.H., and Y. Narayanan (1976) An experimental inquiry into the central source of the preganglionic fibers to the chick ciliary ganglion. J. Comp. Neurol., 166:100-110.

Nathan, J., P.M. Kiely, S. G. Crewther, and D.P. Crewther (1985) Disease-associated visual degradation and spherical refractive errors in children. Am. J. Optom. Physiol. Opt., 62:680-688.

Nathan, J., S.G. Crewther, D.P. Crewther, and P.M. Kiely (1984) Effects of retinal image degradation on ocular growth in cats. Invest. Ophthalmol. Vis. Sci., 25:1300-1306.

Oakley, K.H., and F.A. Young (1975) Bifocal control of myopia. Am. J. Optom. Physiol. Opt., 52:758-764.

Oishi, T., and J.K. Lauber (1988) Chicks blinded with formoguanamine do not develop lid suture myopia. Cur. Eye Res., 7:69-73.

Oishi, T., J.K. Lauber, and J. Vriend (1987) Experimental myopia and glaucoma in chicks. Zool. Sci., 4:455-464.

O'Leary, D.J., and M. Millodot (1979) Eyelid closure causes myopia in humans. Experientia, 35:1478-1479.

Osol, G., B. Schwartz, and D.C. Foss (1986) The effects of photoperiod and lid suture on eye growth in chickens. Invest. Ophthalmol. Vis. Sci., 27:255-260.

Owens, D.A. (1984) The resting state of the eyes. Amer. Sci., 72:378-387.

Pickett-Seltner, R.L., J. Weerheim, J.G. Sivak, and J. Pasternak (1988) Experimentally induced myopia does not affect post-hatching development of the chick lens. Vision Res., 27:1779-1782.

Pickett-Seltner, R.L., J.G. Sivak, and J.J. Pasternak (1988) Experimentally induced myopia in chicks: Morphometric and biochemical analysis during the first 14 days after hatching. Vision Res., 28:323-328.

Pilar, G., R. Nuñez, I.S. McLennan, and S.D. Meriney (1987) Muscarinic and nicotinic synaptic activation of the developing chicken iris. J. Neurosci., 7:3813-3826.

Powell, E.W., J.N. Pasley, L.E. Scheving, F. Halberg (1980) Amplitude-reduction and acrophase-advance of circadian mitotic rhythm in the corneal epithelium of mice with bilaterally lesioned suprachiasmatic nuclei. Anat. Rec., 197:277-281.

Rabin, J., R.C. Van Sluyters, and R. Malach (1981) Emmetropization: a vision-dependent phenomenon. Invest. Ophthalmol. Vis. Sci., 20:661-664.

Raviola, E., and T.N. Wiesel (1978) Effect of dark-rearing on experimental myopia in monkeys. Invest. Ophthalmol. Vis. Sci., 17:485-488.

Raviola, E., and Wiesel, T.N. (1985) An animal model of myopia. New Eng. J. Med., 312:1609-1615.

Regal, D.M., R. Boothe, D.Y. Teller, and G.P. Sackett (1976) Visual acuity and visual responsiveness in dark-reared monkeys *(Macaca nemestrina).* Vision Res., 16:523-530.

Reiner, A., Karten H.J., Gamlin P.D.R. and Erichsen J.T. (1983) Parasympathetic ocular control: Functional subdivisions and circuitry of the avian nucleus of Edinger-Westphal. Trends in Neurosci. 6:140-145.

Richler, A., and J.C. Bear (1980a) Refraction, nearwork, and education. A population study in Newfoundland. Acta Ophthalmol., 58:468-478.

Richler, A., and J.C. Bear (1980b) The distribution of refraction in three isolated communities in western Newfoundland. Am. J. Optom. Physiol. Opt., 57:861-871.

Robb, R.M. (1977) Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. Am. J. Ophthalmol., 83:52-58.

Rose, L., U. Yinon, and M. Belkin (1974) Myopia induced in cats deprived of distance vision during development. Vision Res., 14:1029-1032.

Rosenthal, D. (1981) *A model of avian accommodation.* M.Sc. Dissertation, Polytechnic Institute of New York.

Sato, T. (1981) Criticism of various accommodogenous theories on school myopia: Judging from explanation on emmetropization. Doc. Ophthalmol. Proc. Series, 28:187-192, (eds. H.C Fledelius, P.H. Alsbirk and E. Goldschmidt), Dr. W. Junk Publ., The Hague.

Schaeffel, F., A. Glasser, and H.C. Howland (1988) Accommodation, refractive error and eye growth in chickens. Vision Res., 28: 639-657.

Schaeffel, F., and H.C. Howland (1987b) Corneal accommodation in chick and pigeon. J. Comp. Physiol. A, 160:375-384.

Schaeffel, F., H.C. Howland, and L. Farkas (1986) Natural accommodation in the growing chicken. Vision Res., 26:1977-1993.

Schaeffel, F., L. Farkas, and H.C. Howland (1987) Infrared photoretinoscope. Appl. Optics, 26:1505-1509.

Schor, C.M., J.C. Kotulak, and T. Tsuetaki (1986) Adaptation of tonic accommodation reduces accommodative lag and is masked in darkness. Invest. Ophthalmol. Vis. Sci., 27:820-827.

Sherman, S.M., T.T. Norton, and V.A. Casagrande (1977) Myopia in the lid-sutured tree shrew *(Tupaia glis).* Brain Res., 124:154-157.

Sivak, J. (1980) Accommodation in vertebrates: A contemporary survey. Cur. Top. Eye Res., 3:281-330.

Sivak, J.G., T.E. Hildebrand, C.C. Lebert, L.M. Myshak, and L.A. Ryall (1986) Ocular accommodation in chickens: Corneal vs lenticular accommodation and the effect of age. Vision Res., 26:1865-1872.

Sivak, J.G., W.R. Bobier, and B. Levy (1978) The refractive significance of the nictitating membrane of the bird eye. J. Comp. Physiol., 125:335-339.

Slonaker, J.R. (1918) A physiological study of the anatomy of the eye and its accessory parts of the English Sparrow *(Passer domesticus)*. J. Morphol., 31:351-459.

Smith, E.L., G.W. McGuire, and J.T. Watson (1980) Axial lengths and refractive errors in kittens reared with an optically induced anisometropia. Invest. Ophthalmol. Vis. Sci., 19:1250-1255.

Smith, E.L., R.S. Harwerth, and M.L.J. Crawford (1985) Spatial contrast sensitivity deficits in monkeys produced by optically induced anisometropia. Invest. Ophthalmol. Vis. Sci., 26:330-342.

Smith, E.L., R.S. Harwerth, M.L.J. Crawford, and G.K. von Noorden (1987) Observations on the effects of form deprivation on the refractive status of the monkey. Invest. Ophthalmol. Vis. Sci., 28: 1236-1245.

Smith, M.E., B. Becker, and S. Podos (1969) Light-induced angle-closure glaucoma in the domestic fowl. Invest. Ophthalmol. Vis. Sci., 8:213-221.

Sorsby, A. (1972a) *Modern Ophthalmology*, 2nd Ed., v. 3, Butterworths, London.

Sorsby, A. (1972b) *Modern Ophthalmology*, 2nd Ed., v. 4, Butterworths, London.

Sorsby, A. (1979) Biology of the eye as an optical system. In: Refraction and Clinical Optics, (ed. A. Safir), Harper and Row, Philadelphia.

Sorsby, A., B. Benjamin, and M. Sheridan (1961b) Refraction and its components during the growth of the eye after the age of three. Medical Research Council Special Report Series, No. 301, Her Majesty's Stationary Office, London.

Sorsby, A., B. Benjamin, J.B. Davey, M. Sheridan, and J.M. Tanner (1957) Emmetropia and its aberrations: A study in the correlation of the optical components of the eye. Medical Research Council Special Report Series, No. 293, Her Majesty's Stationary Office, London.

Sorsby, A., G.A. Leary, and M.J. Richards (1961a) Correlation ametropia and component ametropia. Vision Res., 2:309-313.

Sorsby, A., M. Sheridan, and G.A. Leary (1962) Refraction and its components in twins. In: Medical Research Council Special Report Series, No. 303, Her Majesty's Stationary Office, London.

Southall, J.P.C. (1937) *Introduction to Physiological Optics*, Dover Publ. Inc., New York.

Sperduto, R.D., D. Seigel, J. Roberts, M. Rowland (1983) Prevalence of myopia in the United States. Arch. Ophthalmol., 101:405-407.

Steinbach, M.J., and K.E. Money (1973) Eye movements of the owl. Vision Res., 13:889-891.

Stenstrom, S. (1946) Investigation of the variation and correlation of the optical elements of human eyes. (trans. Woolf, D., 1948), Am. J. Optom., Monograph 58

Suburo, A.M., and M. Marcantoni (1983) The structural basis of ocular accommodation in the chick. Rev. Can. Biol. Exptl., 42:131-137.

Thorn, F., R.W. Doty, and R. Gramiak (1981/82) Effect of eyelid suture on the development of ocular dimensions in macaques. Cur. Eye Res., 1:727-733.

Troilo, D., and J. Wallman (1984) Mechanisms of avian accommodation. Proc. Int. Soc. Eye Res., 3:134.

Troilo, D., and J. Wallman (1985) Mechanisms of accommodation in the chicken. Society for Neuroscience Abstracts, 11:1042.

Troilo, D., and J. Wallman (1987) Changes in corneal curvature during accommodation in chicks. Vision Res., 27:241-247.

Troilo, D., and J. Wallman (1988) Experimental emmetropization in chicks. Invest. Ophthal. Vis. Res.(ARVO Suppl.), 29:76.

Troilo, D., M.G. Gottlieb, and J. Wallman (1986) Optic nerve section causes abnormal eye growth. Society for Neuroscience Abstracts, 12:120.

Troilo, D., M.G. Gottlieb, and J. Wallman (1987a) Eye growth is controlled by both the retina and the brain. Invest. Ophthal. Vis. Res.(ARVO Suppl.), 28:263.

Troilo, D., M.G. Gottlieb, and J. Wallman (1987b) Visual deprivation causes myopia in chicks with optic nerve section. Cur. Eye Res., 6:993-999.

van Alphen, G.W.H.M. (1961) On emmetropia and ametropia. Ophthalmologica (Suppl.), 142:1-92.

van Alphen, G.W.H.M. (1986) Choroidal stress and emmetropization. Vision Res., 26:723-734.

von Noorden, G.K., and M.L.J. Crawford (1978) Lid closure and refractive error in macaque monkeys. Nature, 272:53-54.

von Noorden, G.K., and R.A. Lewis (1987) Ocular axial length in unilateral congenital cataracts and blepharoptosis. Invest. Ophthalmol. Vis. Sci., 28:750-752.

Wallman, J. , D. Rosenthal, J.I. Adams and L. Romagnano (1981b) Role of accommodation and developmental aspects of experimental myopia in chicks. Doc. Ophthalmol. Proc. Series, 28:197-206, (eds. H.C. Fledelius, P.H. Alsbirk and E. Goldschmidt), Dr. W. Junk Publ., The Hague.

Wallman, J., and J.I. Adams (1987) Developmental aspects of experimental myopia in chicks. Vision Res., 27:1139-1163.

Wallman, J., C. LeDoux, and M.B. Friedman (1978b) Simple devices for restricting the visual fields of birds. Behav. Res. Meth. Instrum., 10:401-403.

Wallman, J., J. Adams, and J.N. Trachtman (1981a) The eyes of young chickens grow toward emmetropia. Invest. Ophthalmol. Vis. Sci., 20:557-561.

Wallman, J., J. Turkel, and J. Trachtman (1978a) Extreme myopia produced by modest change in early visual experience. Science, 201:1249-1251.

Wallman, J., M.D. Gottlieb, V. Rajaram, and L. Fugate-Wentzek (1987) Retinal control of myopia and eye growth. Science, 237:73-77.

Walls, G.L. (1942) *The Vertebrate Eye and its Adaptive Radiations*, Cranbrook Institute of Science, Bloomfield Hills, Michigan.

Wildsoet, C.F., and J.D. Pettigrew (1988a) Kainic acid-induced eye enlargement in chickens: Differential effects on anterior and posterior segments. Invest. Ophthalmol. Vis. Sci., 29:311-319.

Wildsoet, C.F. and J.D. Pettigrew (1988b) Experimental myopia and anomalous eye growth patterns unaffected by optic nerve section in chickens: Evidence for local control of eye growth. Clin. Vision Sci., 3:99-107.

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

Wiesel, T.N., and Raviola, E. (1979) Increase in axial length of the macaque monkey eye after corneal opacification. Invest. Ophthalmol. Vis. Sci., 18:1232-1236.

Wilson, J.R., and S.M. Sherman (1977) Differential effects of early monocular deprivation on binocular and monocular segments of cat striate cortex. J. Neurophys., 40:891-903.

Wolff, S.M. (1973) Ocular manifestations of congenital rubella: A prospective study of 328 cases of congenital rubella. J. Pediatr. Ophthalmol., 10:101-141.

Yinon, U. (1984) Myopia induction in animals following alteration of the visual input during development: a review. Cur. Eye Res., 3:677-690.

Yinon, U. and K.C. Koslowe (1984) Eyelid closure effects on the refractive error of the eye in dark- and in light-reared kittens. Am. J. Optom. Physiol. Opt., 61:271-273.

Yinon, U., and K.C. Koslowe (1986) Hypermetropia in dark reared chicks and the effect of lid suture. Vision Res., 26:999-1005.

Yinon, U., K.C. Koslowe, D. Lobel, N. Landshman, and Y.R. Barishak (1982/83) Lid suture myopia in developing chicks: Optical and structural considerations. Cur. Eye Res., 2:877-882.

Yinon, U., L. Rose, and A. Shapiro (1980) Myopia in the eye of developing chicks following monocular and binocular lid closure. Vision Res., 20:137-141.

Young, F.A. (1961a) The effect of restricted space on the primate eye. Am. J. Ophthalmol., 52:799-806.

Young, F.A. (1961b) The development and retention of myopia by monkeys. Am. J. Optom. & Arch. Am. Acad. Optom., 38:545-555.

Young, F.A. (1963) The effect of restricted visual space on the refractive error of the young monkey eye. Invest. Ophthalmol. Vis. Sci., 2:571-577.

Young, F.A. (1965) The effect of atropine on the development of myopia in monkeys. Am. J. Optom. and Arch. Am. Acad. Optom., 42:439-449.

Young, F.A. (1975) The development and control of myopia in human and subhuman primates. Contacto, 19:16-31.

Young, F.A. (1977) The nature and control of myopia. J. Am. Optom. Assoc., 48:451-457.

Young, F.A. (1981) Intraocular pressure dynamics associated with accommodation. Doc. Ophthalmol. Proc. Series, 28:171-177, (eds. H.C. Fledelius, P.H. Alsbirk and E. Goldschmidt), Dr. W. Junk Publ., The Hague.

Young, F.A., G.A. Leary, W.R. Baldwin, D.C. West, R.A. Box, E. Harris, C. Johnson (1969) The transmission of refractive errors within Eskimo families. Am. J. Optom. & Arch. Am. Acad. Optom., 46:676-685.