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Astigmatism and Its Role in Emmetropization

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Abstract

Astigmatism is a common refractive error caused by the difference in refractive power of the eye along different meridians. This causes two line foci that cannot be corrected by changing viewing distance or accommodation. Although human studies have ascribed astigmatism to multiple factors, its cause remains unclear. Studies in chicks and monkeys suggest that imposed astigmatic error may alter emmetropization, but McLean and Wallman (2003) showed that the early compensatory response to spherical defocus was not affected by concurrent high astigmatism in chicks. This review will focus on possible mechanisms leading to astigmatism and the influence of astigmatism on emmetropization in animal studies.

1. Introduction

Astigmatism is an optical defect due to differential refractive powers along different ocular meridians, consequently each point that makes up an object is refracted into two line foci with specific orientations. The “astigmatism” in this review refers to its most common form in human populations (Duke-Elder, 1970), *regular* astigmatism, in which the weakest and the strongest power meridians are perpendicular to each other. Figure 1 illustrates the prevalence of manifest (refractive) astigmatism as a function of age in different populations. The data from infants resulted from earlier studies, in which astigmatism was defined as Cyl≥1.00D, whereas the data from school-aged children and older populations came from epidemiological studies reported between 2000 and 2012. The colors of the symbols and lines represent the different definitions of astigmatism adopted in these studies (Blue: Cyl≥0.50D; Green: Cyl≥0.75D; and Red: Cyl≥1.00D). Taken together, these data suggest that the prevalence of significant infantile astigmatism (≥1D) is high, ~50%, between 8-20 weeks of age, but decreases to about 20-40% by school age. It then increases during the school years and appears to stabilize between 20 to 40yrs of age, after which the prevalence increases again in the elderly, and in many studies the percentages of those affected in elderly populations were as high as those reported in studies of infants.

Astigmatism is due mainly to corneal and lenticular toricity (e.g. Lyle, 1991); the corneal contribution varies with age, but the lenticular contribution remains rather constant from an early age (Leung, et al., 2012, Mutti, et al., 2004). This relationship makes it possible to use a simplified formula, known as Javal’s rule, to predict the manifest astigmatism

by a given corneal astigmatism or vice versa (Grosvenor, et al., 1988). In addition, the interaction between corneal and lenticular toricities throughout life may contribute to the shift in axis from predominantly WTR (with-the-rule) in school-aged children, to ATR (against-the-rule) in the elderly (Asano, et al., 2005, Gudmundsdottir, et al., 2000, Leung et al., 2012). For example, in a retrospective examination of changes in astigmatic components of a clinical population, the magnitudes of manifest and corneal astigmatisms appeared to synchronize with increasing age, while the magnitude of lenticular astigmatism remained quite constant for a long time (Leung et al., 2012) before starting to increase after age 65 (Liu, et al., 2011).

Numerous human studies have associated astigmatism with factors including ocular diseases, ethnicity, genetics, ocular biomechanics, visual habits, and spherical refractive errors (i.e., myopia and hyperopia) (Lyle, 1991, Read, et al., 2007b). Significant astigmatism has been found in patients suffering from various pediatric eye diseases (Bogan, et al., 1987, Nathan, et al., 1986), Down syndrome (Fong, et al., 2013, Woodhouse, et al., 1997), nystagmus and albinism (Sampath & Bedell, 2002, Wang, et al., 2009). Higher prevalence of significant astigmatism was also noted in native Americans (Garber, 1981, Harvey, et al., 2010, Lyle, et al., 1972, Pensyl, et al., 1997) and Hispanic and Asian children (Kleinstein, et al., 2003). Although earlier genetic studies proposed conflicting views (Mash, et al., 1975, Teikari & O'Donnell, 1989), the recent identifications of susceptibility loci for astigmatism in different populations (Fan, et al., 2011b, Lopes, et al., 2013) have provided further evidence for a role of genetic factors in astigmatism (Dirani, et al., 2008, Hammond, et al., 2001). On the other hand, possible roles of extraocular biomechanical factors have been shown, e.g., by the effect

of lifting the eyelids (Wilson, et al., 1982), the change in astigmatism after extraocular muscle surgery (Bagheri, et al., 2003, Denis, et al., 1995), and the correlation between the axis of astigmatism and eyelid morphology (Read, et al., 2007a) or visual habits (Tong, et al., 2002). By contrast, although astigmatism and spherical refractive errors were significantly correlated, the coefficients reported in different studies were usually only low to moderate (r=0.12~0.38: Alward, et al., 1985, Guggenheim & Farbrother, 2004, Kaye & Patterson, 1997, Parssinen, 1991).

Despite the fact that astigmatism affects numerous populations and degrades visual quality (causing – asthenopia: Lyle, 1991; abnormal retinal electrophysiology: Flitcroft, et al., 2005; and amblyopia: Abrahamsson & Sjostrand, 2003, Harvey, et al., 2004, Somer, et al., 2002), it remains unclear what causes astigmatism and whether astigmatism interferes with refractive development. While several animal species have been used for myopia research, only chicks (Irving, et al., 1995, Kee & Deng, 2008, Schmid & Wildsoet, 1997) and monkeys (Kee, et al., 2005) have been shown so far to exhibit characteristics of astigmatism similar to those in humans. The remainder of this paper aims to review possible mechanisms leading to astigmatism and its role in emmetropization, as revealed in animal studies. The reader may refer to previous reviews for studies on human astigmatism (Lyle, 1991, Read et al., 2007b).

2. Mechanism underlying astigmatism: passive, active, or both?

It is well known that if postnatal visual experience is undisturbed, the natural neonatal refractive errors diminish over time, and eventually both eyes become emmetropic (zero

refractive error); this process is termed “emmetropization”. Experimental studies using a wide variety of animal species have shown that when early visual experience is interrupted by image degradation, due to lid-suturing or covering the eye with a translucent occluder, the normal course of emmetropization is altered and generally results in significant amounts of myopia. In contrast to this “form-deprivation myopia”, which usually causes considerable inter-subject variability in refractive outcomes, optical defocus imposed by diverging (minus) or converging (plus) ophthalmic lenses appears to result in more definitive end points. This observation has led to suggestions that the ocular changes induced by form deprivation are operated *passively* under an open-loop condition, whereas the changes due to optical defocus (including those during recovery, immediately after the removal of form deprivation) are *actively* controlled through a closed-loop condition (Schaeffel & Howland, 1988, Wallman & Winawer, 2004, Wildsoet, 1997).

While most animal studies on refractive development have focused on how visual manipulations affect spherical-equivalent refractive error, several studies have noted the co-existence of astigmatism with myopia and hyperopia in animals. In rhesus monkeys (Kee et al., 2005) and chicks (Irving, et al., 1992, Kee & Deng, 2008, Kisilak, et al., 2008, Schmid & Wildsoet, 1997) a variety of visual manipulations resulted in not only axial ametropia, but also significant amounts of astigmatism. In monkeys, the astigmatic axis was oriented obliquely regardless of the treatment regimen (Kee et al., 2005). In chicks, although the astigmatic axes induced by a range of commonly used visual manipulations were oriented near 90 deg axis (i.e., the axis of negative correcting cylinder), there was suggestive evidence that form deprivation or stronger optical

defocus might produce more obliquely oriented astigmatic axes (Irving et al., 1992, Kee & Deng, 2008, Kisilak et al., 2008). Regardless, the fact that the developing animals' eyes developed astigmatism of similar characteristics in response to a variety of different visual manipulations has led to the speculation that induced astigmatism is a *passive* byproduct of abnormal eye growth. Specifically, because astigmatism is associated with experimentally induced axial ametropia, it is speculated that the remodeling of posterior eye shape during altered refractive development may somehow interfere with anterior ocular biomechanics, and thus in some way alter ocular toricity. If this hypothesis were true, one would predict that different posterior eye shapes would produce types of astigmatism that differ in both magnitude and axis. Contrary to this prediction, although rearing chicks with hemi-retinal form deprivations (superior, inferior, temporal and nasal; Chu, et al., 2012a) produced four distinctly different *posterior* eye shapes, the magnitudes and axes of the induced *anterior* ocular toricity were quite similar, and only subtle differences were found in the astigmatic components. However, the shapes of the eyes became quite similar near the equator, where the expanded regions were found typically at the temporal side of the globe in all four treatment groups. Thus, although the passive role of abnormal axial eye growth on astigmatism could not be rejected, these results suggest that the experimentally induced astigmatism may be linked to the altered eye shape near or anterior to the equator, rather than to the changes in shape at the posterior pole.

Can the eye actively compensate for imposed astigmatic error? In response to optical defocus imposed by a spherical positive lens (myopic defocus) or negative lens (hyperopic defocus), animals ranging from chickens to macaque monkeys develop

compensatory hyperopia or myopia, respectively, to make their eyes functionally emmetropic (see: Wallman & Winawer, 2004 for review). These ocular compensatory responses are due mainly to alterations in axial growth; thus the axial growth rate of a myopically defocused eye slows, whereas that of a hyperopically defocused eye accelerates, and this – in concert with the natural decreases in corneal and lens powers during early eye growth – causes their retinal planes finally to match the experimentally displaced focal planes. These active, vision-dependent mechanisms would encounter a more challenging task in the presence of astigmatic error: because astigmatism produces orientation-dependent blur at different image planes, alterations in axial growth *per se* could at best improve retinal image quality along a *single* orientation (e.g., a point object will become an elongated line). To compensate fully for an imposed astigmatic error, the induced modulation of eye growth would have to alter ocular toricity, rather than axial enlargement alone, with compensatory changes in axis orientation that precisely correct each meridional refractive error.

The evidence that toricity in the developing eye could be altered actively, to compensate for optically imposed astigmatism, is weak. In studies of chicks, using cylindrical lenses to impose astigmatic error (summarized in Table 1), a partial, orientation-dependent compensation to plano-cylindrical lenses was reported initially (Irving et al., 1995); in subsequent studies, however, these results could not be replicated (Laskowski & Howland, 1996, Phillips & Collins, 2000, Schmid & Wildsoet, 1997, Thibos, et al., 2001, Thomas & Schaeffel, 2000). Irving et al. (1995) reported that the range of astigmatism over which the chicks could compensate was less than half the operating range for spherical defocus (Irving, et al., 1991, Irving et al., 1995, Irving et al., 1992), suggesting

that the compensatory mechanism was less efficient. The possibility of an 'astigmatic accommodation' to a few hours of low magnitude of astigmatic errors (3.0 D) was also ruled out in chicks (Thomas & Schaeffel, 2000). In monkeys, although optically-imposed astigmatism (+1.50DS/–3.00DC crossed-cylinder lenses) induced significant amounts of astigmatism, the axes were typically oriented obliquely and were not correlated with the imposed astigmatic axis (Kee, et al., 2003). Taken together, the data supporting an active compensatory mechanism for astigmatic errors are weak, and it is unclear whether the differences in experimental design (including the strains of birds, ages at the beginning of treatment, and treatment duration) could have contributed to the discrepancies in end-points between studies. Nevertheless, a consistent pattern in the chick studies (Table 1) is that the magnitude of induced astigmatism was much lower than the compensatory ranges reported for experimentally-induced myopia or hyperopia – that is, compensation for moderate strengths of imposed spherical refractive error was generally complete, but that for imposed astigmatism was not. It is possible that, among other factors, the magnitudes of imposed astigmatism were near or exceeding the operating limits of the mechanism regulating astigmatic eye growth. Support for this hypothesis was provided by our recent study using crossed-cylinder lenses of moderate strength (+4.0DS/–8.0DC crossed-cylinder lenses; Chu, et al., 2012b), which found compensatory refractive and corneal astigmatisms in chicks after one week of cylindrical-lens wear. However, as in the previous study (Irving et al., 1995), the magnitudes induced were in the neighborhood of 2-5D and varied with the imposed astigmatic axis. It is unclear at this stage whether this compensatory response was possible because the total magnitude of the imposed astigmatism (i.e., the

difference between the two meridians), or the magnitudes of the individual power meridians (+4D and –4D), were lower than those than in most other studies. Further studies are needed, to determine and characterize the mechanism(s) regulating this orientation-dependent compensatory response.

3. Effects of astigmatism on emmetropization

There is ample evidence that the presence of astigmatism could alter emmetropization. In both chicks (Irving et al., 1995, McLean & Wallman, 2003, Phillips & Collins, 2000, Schmid & Wildsoet, 1997, Thibos LN, Cheng X, Phillips J & Collins A. IOVS 2001; 42: ARVO Abstract 324; Laskowski FH & Howland HC. IOVS 1996; 37:ARVO Abstract 3140) and monkeys (Kee, et al., 2004), the constant image degradation produced by optically imposed astigmatism has been found to alter the normal course of emmetropization, but not to promote unregulated axial myopia similar to that induced by form deprivation. As shown in Table 1, chicks exposed to astigmatic blur for a minimum of 2 days exhibited significant change in refractive status (SE), but the end point for emmetropization varied across the studies, probably because different methodologies were employed. For example, using plano-cylindrical lenses of similar magnitudes, most studies have found a shift in refraction toward the circle of least confusion (Irving et al., 1995, Phillips & Collins, 2000, Thibos et al., 2001), but one study reported a shift to the less hyperopic/more myopic line focus (Schmid & Wildsoet, 1997). In the majority of animals treated with crossed-cylindrical lenses – chicks (+5DS/–10DC: McLean & Wallman, 2003) and monkeys (+1.5DS/–3.0DC, which induced a bimodal shift to both

principal meridians: Kee et al., 2004) – the refractive power changed toward the more hyperopic meridian, although one study reported a slight myopic shift in refractive power toward the more myopic meridian in chick (Thibos et al., 2001). While further studies will be required to explain the discrepancy between end-points in different studies, it is clear that the normal course of emmetropization under this imposed astigmatism condition is altered. However, regardless of where the imposed astigmatic axis was oriented, the high myopia frequently found in form-deprived eyes was not observed. Furthermore, the work of McLean and Wallman (2003) showed that the presence of significant astigmatism (axis 45°) did not compromise the early compensatory responses to spherical defocus (see Table 1), suggesting that the astigmatic error may be a less potent and/or more complicated signal for compensation than the spherical error.

With respect to the effects of astigmatic axis on eye growth, most studies in chicks did not find orientation-dependent changes in spherical equivalent refraction. However, one study – reported only in abstract (Laskowski & Howland, 1996) – found significant differences in axial length and refraction between two groups of birds treated with plus- and minus-cylindrical lenses oriented at 180°. In monkeys, despite the significant alterations in refractive development when astigmatic errors were present, the axis of the imposed astigmatism (+1.50DS/–3.00DC) did not produce significantly different end-points when data from all treatment groups were pooled; however, in a sub- group in which ATR was imposed in one eye and WTR in the other, three of eight monkeys became more myopic in the ATR-treated eyes at the end of the treatment period (the other five became isometropic, Kee et al., 2004). In humans, it has been reported that

children who had ATR astigmatism were more likely to develop myopia subsequently (Gwiazda, et al., 2000, Hirsch, 1964) or have higher myopia progression rate (Grosvenor, et al., 1987) than those who had WTR astigmatism (however, see also Goss & Shewey, 1990). On the other hand, analysis of the relationship between astigmatic axis and ametropia in a large optometry practice revealed that the odds of having WTR astigmatism were greater in high myopes, while those of having ATR astigmatism were greater in low myopes (Farbrother, et al., 2004). Another recent study, in young adults, also showed a high prevalence of WTR astigmatism in subjects with high ametropia (Mandel, et al., 2010), and we found a similar association in a Hong Kong Chinese clinical population (Leung et al., 2012). One possibility to reconcile these results is that the presence of early ATR astigmatism promotes the myopia development, and, when the degree of myopia exceeds a certain limit, the abnormal structural changes in high-myopic eyeballs lead to the genesis of WTR astigmatism. Another possibility is that the underlying mechanisms for the two ametropic groups (i.e., low myopia with ATR astigmatism and high myopia with WTR astigmatism) are entirely different. In this respect, although a longitudinal study did show a decrease in ATR astigmatism over the 14-year observation period in those who began with infantile ATR astigmatism (Gwiazda et al., 2000), the trend for these subjects to shift to WTR astigmatism in later years was not consistent, perhaps because the sample size was relatively small (n=60) and the duration of the observation period was not extended long enough to capture the shift to WTR astigmatism. Together with the recent discoveries of susceptibility genes for astigmatism in different ethnic groups (Fan et al., 2011b, Lopes et al., 2013) and the potential contribution of eyelid morphology in modulating the axis of

astigmatism (Read et al., 2007a), it remains unclear whether the astigmatism of a specific orientation is a cause or effect (or *both* cause *and* effect) of abnormal refractive development.

4. Conclusion and Future directions

Although numerous epidemiological studies have documented a high prevalence of astigmatism in certain populations, evidence concerning the etiology of astigmatism and the role of astigmatism during eye growth is limited. In light of the close associations of astigmatism with age and myopia/hyperopia, research in this area should benefit a large population. Regardless of whether astigmatism is a cause or effect (or both) of ametropia development, its presence could have significant impact on vision. Although astigmatism has been proposed to act as a unique visual cue (Howland, 1982), which might in principle both assist in ocular accommodation and provide an error signal that promotes myopia development (Fulton, et al., 1982), its role remains unclear. Adding to this uncertainty is the potential influence of different types of off-axis astigmatism on central refraction (Stone & Flitcroft, 2004; Flitcroft, 2012; Howland, 2010): it was noted that individuals with mixed astigmatism in the periphery were less susceptible to developing myopia than those with hyperopic astigmatism (Hoogerheide, et al., 1971, Rempt, et al., 1971). Given the paucity of relevant data, many more studies will be needed to solve this puzzle.

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6. Figure

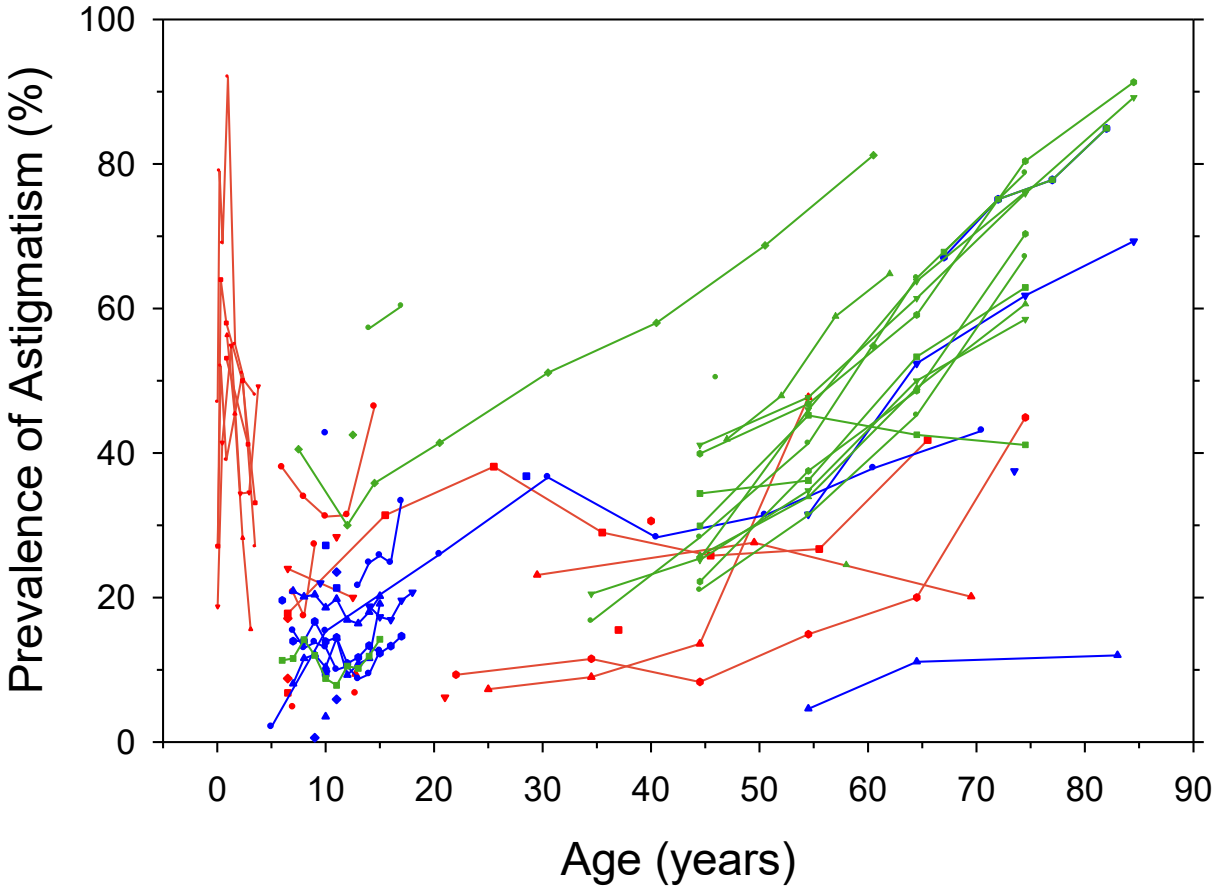

Figure 1. Prevalence of astigmatism as a function of age. The different definitions of astigmatism in these studies are represented by different colors: ≥0.50D, Green; ≥0.75D, Blue; ≥1.00D, Red.

(Atkinson, et al., 1980, Bourne, et al., 2004, Edwards, 1991, Fulton, et al., 1980, Gwiazda, et al., 1984, He, et al., 2007, He, et al., 2004, He, et al., 2009, Howland, et al., 1978, Huynh, et al., 2006, Huynh, et al., 2007, Landers, et al., 2010, Li, et al., 2009, Mohindra, et al., 1978, Robaei, et al., 2006, Santonastaso, 1930, Saunders, 1995, Schellini, et al., 2009, Thorn, et al., 2005, Anera, et al., 2009, Anton, et al., 2009, Cheng, et al., 2003, Dandona, et al., 2002, Dirani, et al., 2010, Fan, et al., 2011a, Fan, et al., 2004, Fotouhi, et al., 2007, Fotouhi, et al., 2011, Fozailoff, et al., 2011, Goh, et al., 2005, Gronlund, et al., 2006, Gupta, et al., 2008, Harvey et al., 2010, Harvey, et al., 2006, Hashemi, et al., 2005, Hashemi, et al., 2012, Hashim, et al., 2008, Jamali, et al., 2009, Kleinstein et al., 2003, Krishnaiah, et al., 2009, Leung et al., 2012, Liang, et al., 2009, Liu et al., 2011, Mallen, et al., 2005, Maul, et al., 2000, Murthy, et al., 2002, O'Donoghue, et al., 2011, Ostadimoghaddam, et al., 2011, Pi, et al., 2010, Pokharel, et al.,

2000, Quek, et al., 2004, Raju, et al., 2004, Rezvan, et al., 2012, Saw, et al., 2008, Saw, et al., 2002, Sawada, et al., 2008, Sherwin, et al., 2011, Shih, et al., 2004, Tong et al., 2002, Villarreal, et al., 2003, Villarreal, et al., 2000, Vitale, et al., 2008, Wickremasinghe, et al., 2004, Wong, et al., 2000, Yekta, et al., 2010, Yekta, et al., 2009, Zhang, et al., 2000, Zhao, et al., 2000)

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Astigmatism and Its Role in Emmetropization

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Abstract

Astigmatism is a common refractive error caused by the difference in refractive power of the eye along different meridians. This causes two line foci that cannot be corrected by changing viewing distance or accommodation. Although human studies have ascribed astigmatism to multiple factors, its cause remains unclear. Studies in chicks and monkeys suggest that imposed astigmatic error may alter emmetropization, but McLean and Wallman (2003) showed that the early compensatory response to spherical defocus was not affected by concurrent high astigmatism in chicks. This review will focus on possible mechanisms leading to astigmatism and the influence of astigmatism on emmetropization in animal studies.

1. Introduction

Astigmatism is an optical defect due to differential refractive powers along different ocular meridians, consequently each point that makes up an object is refracted into two line foci with specific orientations. The “astigmatism” in this review refers to its most common form in human populations (Duke-Elder, 1970), *regular* astigmatism, in which the weakest and the strongest power meridians are perpendicular to each other. Figure 1 illustrates the prevalence of manifest (refractive) astigmatism as a function of age in different populations. The data from infants resulted from earlier studies, in which astigmatism was defined as Cyl≥1.00D, whereas the data from school-aged children and older populations came from epidemiological studies reported between 2000 and 2012. The colors of the symbols and lines represent the different definitions of astigmatism adopted in these studies (Blue: Cyl≥0.50D; Green: Cyl≥0.75D; and Red: Cyl≥1.00D). Taken together, these data suggest that the prevalence of significant infantile astigmatism (≥1D) is high, ~50%, between 8-20 weeks of age, but decreases to about 20-40% by school age. It then increases during the school years and appears to stabilize between 20 to 40yrs of age, after which the prevalence increases again in the elderly, and in many studies the percentages of those affected in elderly populations were as high as those reported in studies of infants.

Astigmatism is due mainly to corneal and lenticular toricity (e.g. Lyle, 1991); the corneal contribution varies with age, but the lenticular contribution remains rather constant from an early age (Leung, et al., 2012, Mutti, et al., 2004). This relationship makes it possible to use a simplified formula, known as Javal’s rule, to predict the manifest astigmatism

by a given corneal astigmatism or vice versa (Grosvenor, et al., 1988). In addition, the interaction between corneal and lenticular toricities throughout life may contribute to the shift in axis from predominantly WTR (with-the-rule) in school-aged children, to ATR (against-the-rule) in the elderly (Asano, et al., 2005, Gudmundsdottir, et al., 2000, Leung et al., 2012). For example, in a retrospective examination of changes in astigmatic components of a clinical population, the magnitudes of manifest and corneal astigmatisms appeared to synchronize with increasing age, while the magnitude of lenticular astigmatism remained quite constant for a long time (Leung et al., 2012) before starting to increase after age 65 (Liu, et al., 2011).

Numerous human studies have associated astigmatism with factors including ocular diseases, ethnicity, genetics, ocular biomechanics, visual habits, and spherical refractive errors (i.e., myopia and hyperopia) (Lyle, 1991, Read, et al., 2007b). Significant astigmatism has been found in patients suffering from various pediatric eye diseases (Bogan, et al., 1987, Nathan, et al., 1986), Down syndrome (Fong, et al., 2013, Woodhouse, et al., 1997), nystagmus and albinism (Sampath & Bedell, 2002, Wang, et al., 2009). Higher prevalence of significant astigmatism was also noted in native Americans (Garber, 1981, Harvey, et al., 2010, Lyle, et al., 1972, Pensyl, et al., 1997) and Hispanic and Asian children (Kleinstein, et al., 2003). Although earlier genetic studies proposed conflicting views (Mash, et al., 1975, Teikari & O'Donnell, 1989), the recent identifications of susceptibility loci for astigmatism in different populations (Fan, et al., 2011b, Lopes, et al., 2013) have provided further evidence for a role of genetic factors in astigmatism (Dirani, et al., 2008, Hammond, et al., 2001). On the other hand, possible roles of extraocular biomechanical factors have been shown, e.g., by the effect

of lifting the eyelids (Wilson, et al., 1982), the change in astigmatism after extraocular muscle surgery (Bagheri, et al., 2003, Denis, et al., 1995), and the correlation between the axis of astigmatism and eyelid morphology (Read, et al., 2007a) or visual habits (Tong, et al., 2002). By contrast, although astigmatism and spherical refractive errors were significantly correlated, the coefficients reported in different studies were usually only low to moderate (r=0.12~0.38: Alward, et al., 1985, Guggenheim & Farbrother, 2004, Kaye & Patterson, 1997, Parssinen, 1991).

Despite the fact that astigmatism affects numerous populations and degrades visual quality (causing – asthenopia: Lyle, 1991; abnormal retinal electrophysiology: Flitcroft, et al., 2005; and amblyopia: Abrahamsson & Sjostrand, 2003, Harvey, et al., 2004, Somer, et al., 2002), it remains unclear what causes astigmatism and whether astigmatism interferes with refractive development. While several animal species have been used for myopia research, only chicks (Irving, et al., 1995, Kee & Deng, 2008, Schmid & Wildsoet, 1997) and monkeys (Kee, et al., 2005) have been shown so far to exhibit characteristics of astigmatism similar to those in humans. The remainder of this paper aims to review possible mechanisms leading to astigmatism and its role in emmetropization, as revealed in animal studies. The reader may refer to previous reviews for studies on human astigmatism (Lyle, 1991, Read et al., 2007b).

2. Mechanism underlying astigmatism: passive, active, or both?

It is well known that if postnatal visual experience is undisturbed, the natural neonatal refractive errors diminish over time, and eventually both eyes become emmetropic (zero

refractive error); this process is termed “emmetropization”. Experimental studies using a wide variety of animal species have shown that when early visual experience is interrupted by image degradation, due to lid-suturing or covering the eye with a translucent occluder, the normal course of emmetropization is altered and generally results in significant amounts of myopia. In contrast to this “form-deprivation myopia”, which usually causes considerable inter-subject variability in refractive outcomes, optical defocus imposed by diverging (minus) or converging (plus) ophthalmic lenses appears to result in more definitive end points. This observation has led to suggestions that the ocular changes induced by form deprivation are operated *passively* under an open-loop condition, whereas the changes due to optical defocus (including those during recovery, immediately after the removal of form deprivation) are *actively* controlled through a closed-loop condition (Schaeffel & Howland, 1988, Wallman & Winawer, 2004, Wildsoet, 1997).

While most animal studies on refractive development have focused on how visual manipulations affect spherical-equivalent refractive error, several studies have noted the co-existence of astigmatism with myopia and hyperopia in animals. In rhesus monkeys (Kee et al., 2005) and chicks (Irving, et al., 1992, Kee & Deng, 2008, Kisilak, et al., 2008, Schmid & Wildsoet, 1997) a variety of visual manipulations resulted in not only axial ametropia, but also significant amounts of astigmatism. In monkeys, the astigmatic axis was oriented obliquely regardless of the treatment regimen (Kee et al., 2005). In chicks, although the astigmatic axes induced by a range of commonly used visual manipulations were oriented near 90 deg axis (i.e., the axis of negative correcting cylinder), there was suggestive evidence that form deprivation or stronger optical

defocus might produce more obliquely oriented astigmatic axes (Irving et al., 1992, Kee & Deng, 2008, Kisilak et al., 2008). Regardless, the fact that the developing animals' eyes developed astigmatism of similar characteristics in response to a variety of different visual manipulations has led to the speculation that induced astigmatism is a *passive* byproduct of abnormal eye growth. Specifically, because astigmatism is associated with experimentally induced axial ametropia, it is speculated that the remodeling of posterior eye shape during altered refractive development may somehow interfere with anterior ocular biomechanics, and thus in some way alter ocular toricity. If this hypothesis were true, one would predict that different posterior eye shapes would produce types of astigmatism that differ in both magnitude and axis. Contrary to this prediction, although rearing chicks with hemi-retinal form deprivations (superior, inferior, temporal and nasal; Chu, et al., 2012a) produced four distinctly different *posterior* eye shapes, the magnitudes and axes of the induced *anterior* ocular toricity were quite similar, and only subtle differences were found in the astigmatic components. However, the shapes of the eyes became quite similar near the equator, where the expanded regions were found typically at the temporal side of the globe in all four treatment groups. Thus, although the passive role of abnormal axial eye growth on astigmatism could not be rejected, these results suggest that the experimentally induced astigmatism may be linked to the altered eye shape near or anterior to the equator, rather than to the changes in shape at the posterior pole.

Can the eye actively compensate for imposed astigmatic error? In response to optical defocus imposed by a spherical positive lens (myopic defocus) or negative lens (hyperopic defocus), animals ranging from chickens to macaque monkeys develop

compensatory hyperopia or myopia, respectively, to make their eyes functionally emmetropic (see: Wallman & Winawer, 2004 for review). These ocular compensatory responses are due mainly to alterations in axial growth; thus the axial growth rate of a myopically defocused eye slows, whereas that of a hyperopically defocused eye accelerates, and this – in concert with the natural decreases in corneal and lens powers during early eye growth – causes their retinal planes finally to match the experimentally displaced focal planes. These active, vision-dependent mechanisms would encounter a more challenging task in the presence of astigmatic error: because astigmatism produces orientation-dependent blur at different image planes, alterations in axial growth *per se* could at best improve retinal image quality along a *single* orientation (e.g., a point object will become an elongated line). To compensate fully for an imposed astigmatic error, the induced modulation of eye growth would have to alter ocular toricity, rather than axial enlargement alone, with compensatory changes in axis orientation that precisely correct each meridional refractive error.

The evidence that toricity in the developing eye could be altered actively, to compensate for optically imposed astigmatism, is weak. In studies of chicks, using cylindrical lenses to impose astigmatic error (summarized in Table 1), a partial, orientation-dependent compensation to plano-cylindrical lenses was reported initially (Irving et al., 1995); in subsequent studies, however, these results could not be replicated (Laskowski & Howland, 1996, Phillips & Collins, 2000, Schmid & Wildsoet, 1997, Thibos, et al., 2001, Thomas & Schaeffel, 2000). Irving et al. (1995) reported that the range of astigmatism over which the chicks could compensate was less than half the operating range for spherical defocus (Irving, et al., 1991, Irving et al., 1995, Irving et al., 1992), suggesting

that the compensatory mechanism was less efficient. The possibility of an 'astigmatic accommodation' to a few hours of low magnitude of astigmatic errors (3.0 D) was also ruled out in chicks (Thomas & Schaeffel, 2000). In monkeys, although optically-imposed astigmatism (+1.50DS/–3.00DC crossed-cylinder lenses) induced significant amounts of astigmatism, the axes were typically oriented obliquely and were not correlated with the imposed astigmatic axis (Kee, et al., 2003). Taken together, the data supporting an active compensatory mechanism for astigmatic errors are weak, and it is unclear whether the differences in experimental design (including the strains of birds, ages at the beginning of treatment, and treatment duration) could have contributed to the discrepancies in end-points between studies. Nevertheless, a consistent pattern in the chick studies (Table 1) is that the magnitude of induced astigmatism was much lower than the compensatory ranges reported for experimentally-induced myopia or hyperopia – that is, compensation for moderate strengths of imposed spherical refractive error was generally complete, but that for imposed astigmatism was not. It is possible that, among other factors, the magnitudes of imposed astigmatism were near or exceeding the operating limits of the mechanism regulating astigmatic eye growth. Support for this hypothesis was provided by our recent study using crossed-cylinder lenses of moderate strength (+4.0DS/–8.0DC crossed-cylinder lenses; Chu, et al., 2012b), which found compensatory refractive and corneal astigmatisms in chicks after one week of cylindrical-lens wear. However, as in the previous study (Irving et al., 1995), the magnitudes induced were in the neighborhood of 2-5D and varied with the imposed astigmatic axis. It is unclear at this stage whether this compensatory response was possible because the total magnitude of the imposed astigmatism (i.e., the

difference between the two meridians), or the magnitudes of the individual power meridians (+4D and –4D), were lower than those than in most other studies. Further studies are needed, to determine and characterize the mechanism(s) regulating this orientation-dependent compensatory response.

3. Effects of astigmatism on emmetropization

There is ample evidence that the presence of astigmatism could alter emmetropization. In both chicks (Irving et al., 1995, McLean & Wallman, 2003, Phillips & Collins, 2000, Schmid & Wildsoet, 1997, Thibos LN, Cheng X, Phillips J & Collins A. IOVS 2001; 42: ARVO Abstract 324; Laskowski FH & Howland HC. IOVS 1996; 37:ARVO Abstract 3140) and monkeys (Kee, et al., 2004), the constant image degradation produced by optically imposed astigmatism has been found to alter the normal course of emmetropization, but not to promote unregulated axial myopia similar to that induced by form deprivation. As shown in Table 1, chicks exposed to astigmatic blur for a minimum of 2 days exhibited significant change in refractive status (SE), but the end point for emmetropization varied across the studies, probably because different methodologies were employed. For example, using plano-cylindrical lenses of similar magnitudes, most studies have found a shift in refraction toward the circle of least confusion (Irving et al., 1995, Phillips & Collins, 2000, Thibos et al., 2001), but one study reported a shift to the less hyperopic/more myopic line focus (Schmid & Wildsoet, 1997). In the majority of animals treated with crossed-cylindrical lenses – chicks (+5DS/–10DC: McLean & Wallman, 2003) and monkeys (+1.5DS/–3.0DC, which induced a bimodal shift to both

principal meridians: Kee et al., 2004) – the refractive power changed toward the more hyperopic meridian, although one study reported a slight myopic shift in refractive power toward the more myopic meridian in chick (Thibos et al., 2001). While further studies will be required to explain the discrepancy between end-points in different studies, it is clear that the normal course of emmetropization under this imposed astigmatism condition is altered. However, regardless of where the imposed astigmatic axis was oriented, the high myopia frequently found in form-deprived eyes was not observed. Furthermore, the work of McLean and Wallman (2003) showed that the presence of significant astigmatism (axis 45°) did not compromise the early compensatory responses to spherical defocus (see Table 1), suggesting that the astigmatic error may be a less potent and/or more complicated signal for compensation than the spherical error.

With respect to the effects of astigmatic axis on eye growth, most studies in chicks did not find orientation-dependent changes in spherical equivalent refraction. However, one study – reported only in abstract (Laskowski & Howland, 1996) – found significant differences in axial length and refraction between two groups of birds treated with plus- and minus-cylindrical lenses oriented at 180°. In monkeys, despite the significant alterations in refractive development when astigmatic errors were present, the axis of the imposed astigmatism (+1.50DS/–3.00DC) did not produce significantly different end-points when data from all treatment groups were pooled; however, in a sub- group in which ATR was imposed in one eye and WTR in the other, three of eight monkeys became more myopic in the ATR-treated eyes at the end of the treatment period (the other five became isometropic, Kee et al., 2004). In humans, it has been reported that

children who had ATR astigmatism were more likely to develop myopia subsequently (Gwiazda, et al., 2000, Hirsch, 1964) or have higher myopia progression rate (Grosvenor, et al., 1987) than those who had WTR astigmatism (however, see also Goss & Shewey, 1990). On the other hand, analysis of the relationship between astigmatic axis and ametropia in a large optometry practice revealed that the odds of having WTR astigmatism were greater in high myopes, while those of having ATR astigmatism were greater in low myopes (Farbrother, et al., 2004). Another recent study, in young adults, also showed a high prevalence of WTR astigmatism in subjects with high ametropia (Mandel, et al., 2010), and we found a similar association in a Hong Kong Chinese clinical population (Leung et al., 2012). One possibility to reconcile these results is that the presence of early ATR astigmatism promotes the myopia development, and, when the degree of myopia exceeds a certain limit, the abnormal structural changes in high-myopic eyeballs lead to the genesis of WTR astigmatism. Another possibility is that the underlying mechanisms for the two ametropic groups (i.e., low myopia with ATR astigmatism and high myopia with WTR astigmatism) are entirely different. In this respect, although a longitudinal study did show a decrease in ATR astigmatism over the 14-year observation period in those who began with infantile ATR astigmatism (Gwiazda et al., 2000), the trend for these subjects to shift to WTR astigmatism in later years was not consistent, perhaps because the sample size was relatively small (n=60) and the duration of the observation period was not extended long enough to capture the shift to WTR astigmatism. Together with the recent discoveries of susceptibility genes for astigmatism in different ethnic groups (Fan et al., 2011b, Lopes et al., 2013) and the potential contribution of eyelid morphology in modulating the axis of

astigmatism (Read et al., 2007a), it remains unclear whether the astigmatism of a specific orientation is a cause or effect (or *both* cause *and* effect) of abnormal refractive development.

4. Conclusion and Future directions

Although numerous epidemiological studies have documented a high prevalence of astigmatism in certain populations, evidence concerning the etiology of astigmatism and the role of astigmatism during eye growth is limited. In light of the close associations of astigmatism with age and myopia/hyperopia, research in this area should benefit a large population. Regardless of whether astigmatism is a cause or effect (or both) of ametropia development, its presence could have significant impact on vision. Although astigmatism has been proposed to act as a unique visual cue (Howland, 1982), which might in principle both assist in ocular accommodation and provide an error signal that promotes myopia development (Fulton, et al., 1982), its role remains unclear. Adding to this uncertainty is the potential influence of different types of off-axis astigmatism on central refraction (Stone & Flitcroft, 2004; Flitcroft, 2012; Howland, 2010): it was noted that individuals with mixed astigmatism in the periphery were less susceptible to developing myopia than those with hyperopic astigmatism (Hoogerheide, et al., 1971, Rempt, et al., 1971). Given the paucity of relevant data, many more studies will be needed to solve this puzzle.

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6. Figure

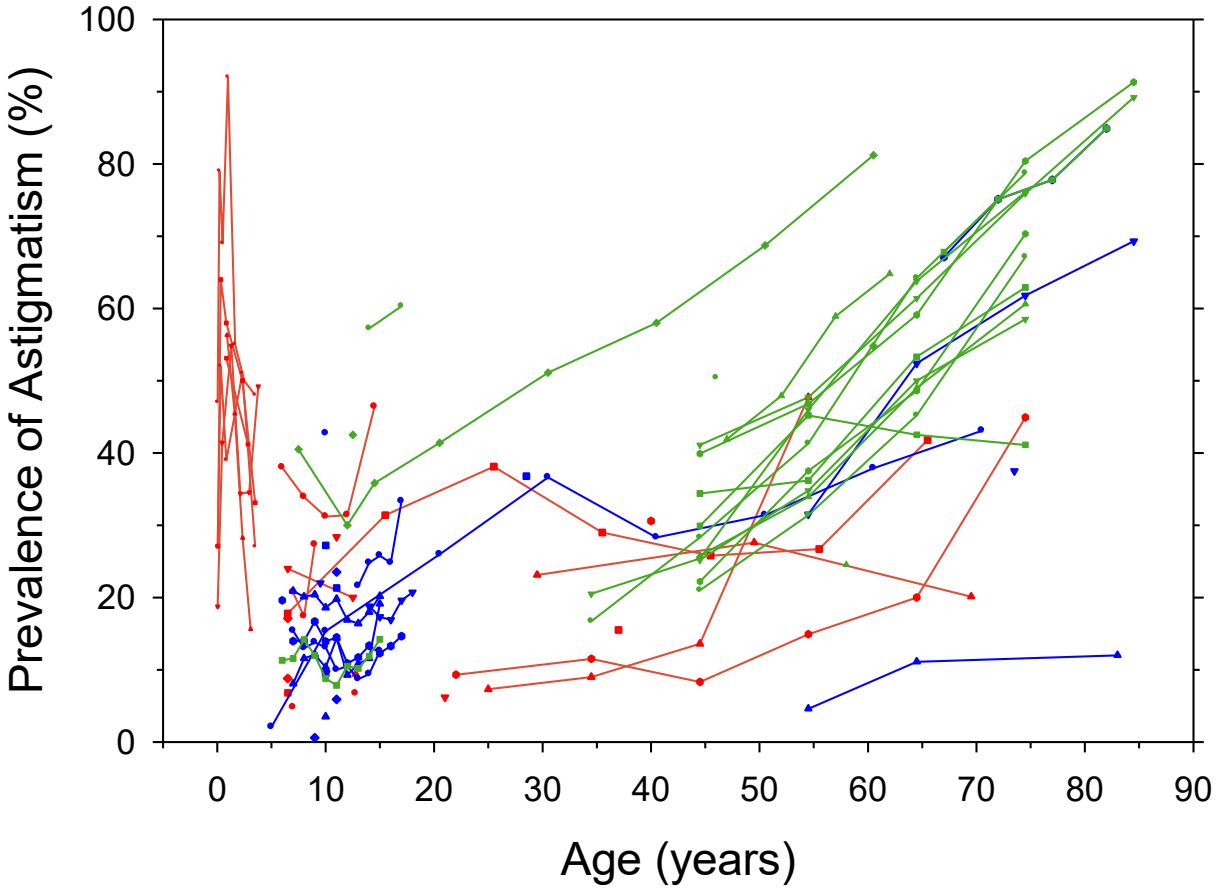

Figure 1. Prevalence of astigmatism as a function of age. The different definitions of astigmatism in these studies are represented by different colors: ≥0.50D, Green; ≥0.75D, Blue; ≥1.00D, Red.

(Atkinson, et al., 1980, Bourne, et al., 2004, Edwards, 1991, Fulton, et al., 1980, Gwiazda, et al., 1984, He, et al., 2007, He, et al., 2004, He, et al., 2009, Howland, et al., 1978, Huynh, et al., 2006, Huynh, et al., 2007, Landers, et al., 2010, Li, et al., 2009, Mohindra, et al., 1978, Robaei, et al., 2006, Santonastaso, 1930, Saunders, 1995, Schellini, et al., 2009, Thorn, et al., 2005, Anera, et al., 2009, Anton, et al., 2009, Cheng, et al., 2003, Dandona, et al., 2002, Dirani, et al., 2010, Fan, et al., 2011a, Fan, et al., 2004, Fotouhi, et al., 2007, Fotouhi, et al., 2011, Fozailoff, et al., 2011, Goh, et al., 2005, Gronlund, et al., 2006, Gupta, et al., 2008, Harvey et al., 2010, Harvey, et al., 2006, Hashemi, et al., 2005, Hashemi, et al., 2012, Hashim, et al., 2008, Jamali, et al., 2009, Kleinstein et al., 2003, Krishnaiah, et al., 2009, Leung et al., 2012, Liang, et al., 2009, Liu et al., 2011, Mallen, et al., 2005, Maul, et al., 2000, Murthy, et al., 2002, O'Donoghue, et al., 2011, Ostadimoghaddam, et al., 2011, Pi, et al., 2010, Pokharel, et al.,

2000, Quek, et al., 2004, Raju, et al., 2004, Rezvan, et al., 2012, Saw, et al., 2008, Saw, et al., 2002, Sawada, et al., 2008, Sherwin, et al., 2011, Shih, et al., 2004, Tong et al., 2002, Villarreal, et al., 2003, Villarreal, et al., 2000, Vitale, et al., 2008, Wickremasinghe, et al., 2004, Wong, et al., 2000, Yekta, et al., 2010, Yekta, et al., 2009, Zhang, et al., 2000, Zhao, et al., 2000)

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Figure1

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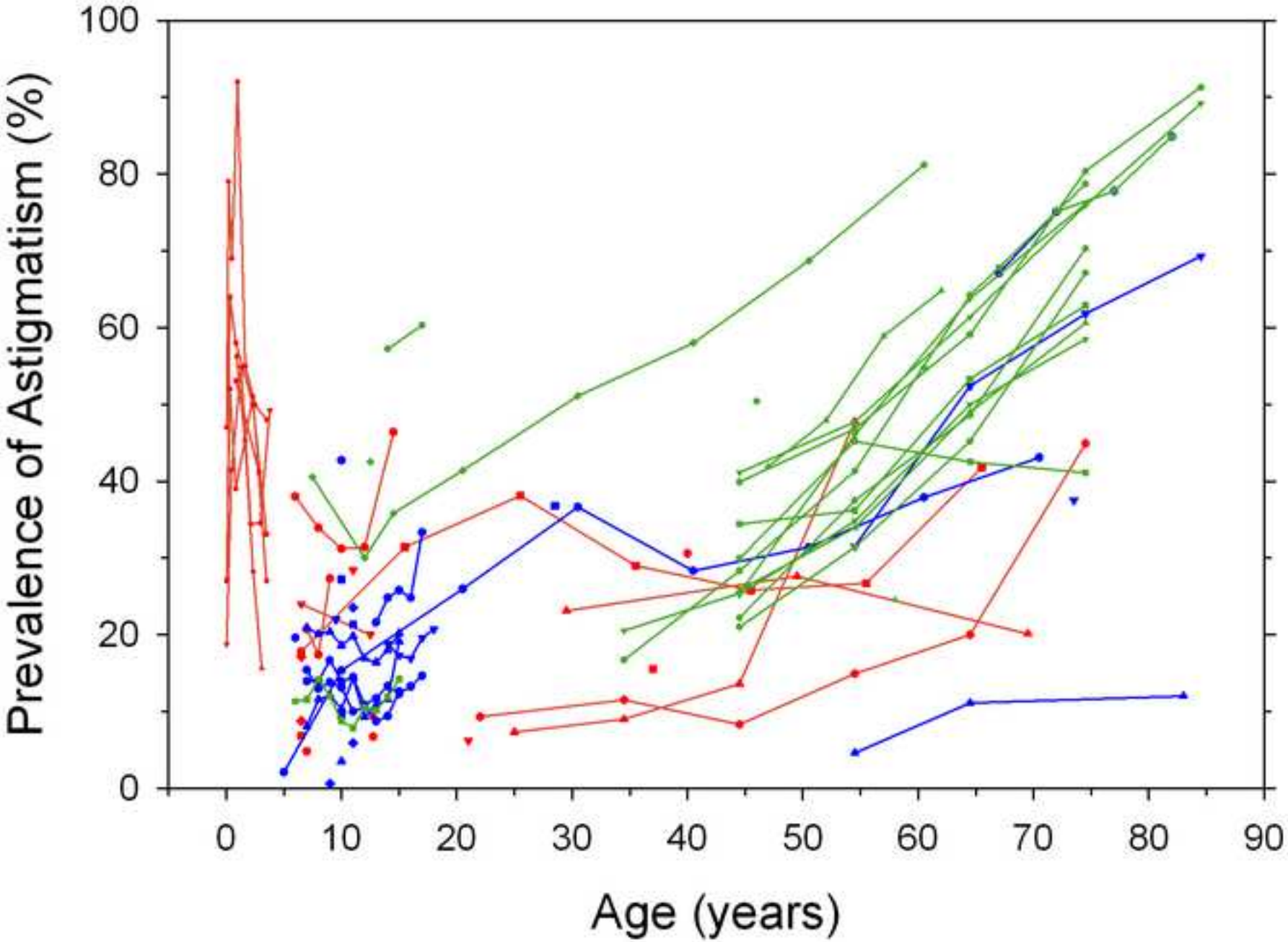

Table(s)

Table 1. Effects of optically imposed astigmatism on emmetropization in chicks.

Authors, years	Animal	Starting Age	Tx. duration	Lens	Axes (°)	SE (D)	Refractive Astigmatism (D)	Corneal Astigmatism (D)	Axial dimension
Irving, et al., 1995	Broiler	P0 (85%) or P2 (15%)	7 days	Plano/–9.00 D	45, 90, 135, 180	(IOD) –3.50±0.50	Compensatory: Min.= 2.25±1.00 (135°) and 2.25±1.50 (180°) Max.=5.75±1.50 (45°)	Min=0.00 Max=2.75	Eyeballs heavier ; larger axially and equatorially; thicker lenses
				Plano/+10.00D		(IOD) +4.25±1.00	Compensatory: Min= 1.00±1.50 (45°) Max= 3.75±2.50 (135°)	Min=0.00 Max=3.00	Shorter axially
Schmid & Wildsoet, 1997	White Leghorn-New Hampshire cross	P0	12 days	Plano/–10.00D	45, 90, 180	(IOD) –1.3±1.9	Non-compensatory: Avg.= 2.5~3.5D;	3.6±2.0 (*3.2±1.0 in fellow untreated eye)	↑VC
				Plano/+10.00D	90, 135, 180	(IOD) +9.5±2.1		3.6±2.3*	↓VC
Thomas & Schaeffel, 2000	White Leghorn	P22±2	3-5 hours	Plano/–3D Plano/+3D	45, 90, 180	No change in sphere	No change	-	-
McLean & Wallman, 2003	Cornell K-strain	P6	2 days†	+5DS/–10DC	45, 90, 180	Avg. change=+2.5 No orientation-dependent change	-	-	↓AL, no change in CT
				+3, –3,+6,–6 with/ without +5DS/–10DC	45	+6 with/without cyl= +5.0~+4.9 –6 with/without cyl= –3.7~–2.1 +3 with cyl =+2.7±1.3 –3 with cyl.=–2.5±1.9	-	-	Myopic:↑AL, ↓CT Hyperopic:↓AL, ↑CT
Laskowski & Howland, 1996	Cornell K-strain	-	14 days	Plano/-12D to Plano/+16D	90, 180	–cylx180° vs. +cylx180°: Different Rx	No astigmatic compensation	AL/CP affected in cylx180°	VC↑ in –cylx180°↑
Phillips & Collins, 2000	Shaver Cockerels	P3	7 days	Plano/–10DC (right eye)	135	(IOD) –6.46±1.12	Non-compensatory: 3.18±0.42	3.40±0.50	-
Thibos, et al., 2001	Shaver Cockerels	P4	7 days	Plano/–10D	-	–6.5	No astigmatic compensation	-	-
				+5DS/–10DC	-	–1.4		-	-

IOD= interocular difference; AL, Axial Length; VC, Vitreous Chamber; CT, Choroidal thickness; AL/CP, ratio of axial length to corneal power

†treatment duration varied from 2 to 6 days in this study, but most data were presented for 2 days of treatment