NEONATAL EYE GROWTH AND EMMETROPISATION—
A LITERATURE REVIEW

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SUMMARY

The refractive development of the neonatal eye has been the subject of much study and debate. In this paper the hypothetical mechanisms of emmetropisation and their relationship to the development of refractive errors will be reviewed. The evidence supporting visual feedback control of eye growth will be described, and the role of ocular accommodation will be discussed.

The term "emmetropisation" is frequently used to refer to the reduction of neonatal refractive errors during eye growth, and has been described in humans,[1] tree shrews,[2] and chicks.[3] Although emmetropisation in individual neonates has been reported in longitudinal studies,[4-6] there has been some debate over the precise pattern of age-related change in average refractive error.[7-12] Nevertheless, emmetropisation can be viewed in terms of the change from a normal (Gaussian) distribution of refractive errors at birth to a significantly non-Gaussian adult distribution where there is a preponderance of refractions around emmetropia (or slight hyperopia).

The manner in which refractive error is distributed in adults suggests the existence of a mechanism controlling the development of the eye and its refractive state. Measurements of the refractive components (corneal power, lens power, and anterior chamber depth) of adult eyes are distributed normally but axial length and refractive state are not.[13-15] Furthermore, from birth to maturity the ocular components are growing, and the relationships among them must be coordinated so that emmetropia can be achieved and maintained. This suggests that coordinated growth of the refractive components must occur for emmetropia to predominate as it does. Although low levels of ametropia (<5 D) may be due to differing degrees of correlation among normally distributed ocular components[16-17], the non-Gaussian distributions of adult refractive error cannot be explained solely by the observed correlation of ocular components.[15,17,18] This suggests that

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the mechanism of emmetropisation may possess feedback control for the growth of one component or more.

VIEWS OF EMMETROPISATION

Many hypotheses concerning emmetropisation have been suggested,[19-21] but the mechanisms remains obscure. Although it is generally agreed that normal visual experience is necessary for emmetropisation, neither the nature nor the mechanisms of the effects of visual experience are known. The growth of the eye and the resulting refractive state could be largely under genetic control,[22-25] with the expression of the inherited refractive state passively relying on some component of visual experience. Alternatively, some aspect of visual experience might actually mediate a feedback control system that uses as an error signal either the refractive state itself or the growth pattern responsible for the refractive state.[11,15,26-29]

Passive Emmetropisation

Passive emmetropisation assumes that the correlation of the various ocular components can be explained in terms of the genetics and the physical characteristics of the growing eye. This view redirects the analysis of ocular refraction from the growth toward emmetropia to the dispersion in the distribution of refractive error away from emmetropia.

The development of some refractive errors, particularly moderate levels of myopia, may show some degree of heritability.[20,30-32] It has also been suggested that the development of high ametropia is the result of the inheritance of an abnormality in one of the ocular components, usually axial length.[16,17] Although the existence of genetic contributions to the growth of the eye is indisputable, a unified theory for the inheritance of refractive state is not apparent. This is probably because the genetics of ocular development are likely to involve polygenic interactions where the phenotypic expression relies heavily on environmental conditions.

The physical characteristics of the growing eye and the nature of refractive error lend themselves to mathematical modelling to help explain the development of refractive

state. These models are informative and explain some aspects of passive emmetropisation, but are insufficient to explain emmetropisation completely.

During growth the degree of any existing refractive error does, in fact, diminish for two reasons. First, as the eye grows, there will be an apparent reduction in any hyperopia as the retinoscopic artefact of small eyes diminishes.[33] Second, the refractions of both myopic and hyperopic eyes will move toward emmetropia if the ocular components grow exactly proportionally. This is because refractive error is the difference between the reciprocals of the focal length of the optics and the axial length of the eye. Since in this situation focal length increases in proportion to increasing axial length, an absolute mismatch between the two produces proportionately smaller refractive errors as eye size increases.[34] Proportional eye growth does not completely account for the growth toward emmetropia observed in neonatal chicks even when the small eye artefact is considered.[34] Once emmetropia is achieved, however, it can be maintained by proportional eye growth.[23]

The suggestion that emmetropisation is a passive consequence of the physical characteristics of ocular structure is largely based on the fact that the optical components lose refractive power as the eye enlarges and, in this way, appear to compensate for the enlargement. Based on the observation of decreased lens power in larger eyes, Gernet and Olbrich[22] suggested that the lens is mainly responsible for the compensations necessary to maintain emmetropia. Because larger eyes have a larger equatorial diameter they suggest that there is more tension on the zonular fibres. This would stretch the lens capsule thereby flattening the lens and reducing the optical power. Mark[24] hypothesised a similar lenticular compensatory mechanisms, but considered the flattening of the cornea and the deepening of the anterior chamber to be additional compensatory changes. Sorsby[25] supported the notion that corneal curvature is reduced passively during eye growth but suggested that compensatory lens flattening is more difficult to explain and is pure conjecture.

Active Emmetropisation

The clearest evidence for the existence of visually regulated eye growth comes from studies of the effects of visual experience on eye growth. Interference with form vision is known to disrupt emmetropisation in a variety of experimental species, in most cases producing axial elongation and myopia.[31,35-38] This has been reported in humans as well.[39-43,44] Such evidence alone is not proof of visual regulation, but additional studies on chicks[28,29] strongly suggest that vision is used to guide the growth of the eye.

The refractive state of the chick eye is used to regulate the growth of the vitreous chamber in order to achieve emmetropia from hyperopia or myopia that is induced by different visual experiences. In a study by Troilo and Wallman[29] both the myopic and hyperopic eyes were initially larger than normal, yet growth of the vitreous chamber

stopped in eyes compensating for myopia and continued in eyes recovering from hyperopia, regardless of the size of the eye. Schaeffel, Glasser, and Howland[28] showed that making the eyes of chicks functionally myopic with positive spectacle lenses or functionally hyperopic with negative spectacle lenses results in a compensatory change in the growth of the eye even though both eye size and shape were initially normal. These studies indicate that refractive state, rather than eye size, guides the eye toward emmetropia.

The control of avian ocular development appears to make use of several different mechanisms. Besides the evidence for visual regulation just described, non-visual shape-related control of the growth of the anterior segment and axial length has also been suggested,[29,45] but this appears to be secondary to the visual controlled growth. Furthermore, the growth control mechanisms in chicks are, at least partially, located within the eye itself since recovery from induced myopia or hyperopia within the eye itself can begin even after the optic nerve is cut.[29] The adjustment of vitreous chamber length is not tightly regulated, however, and the refractive state overshoots emmetropia and reverses the sign of the initial refractive error. Whether this is due to the loss of feedback from the brain or locally from retinal ganglion cells is unclear.

The visual regulation of eye growth probably evolved to achieve the refractive state best adapted for the type of viewing an eye does most, not for the attainment of emmetropia as clinically defined. For instance, the mechanism controlling eye growth in birds is capable of adaptively regulating growth *away* from emmetropia in regions within the eye.[46-48] Refractions tend to be near emmetropia on the optic axis but become more myopic along the superior retina. This refractive gradient apparently functions to keep the retina focussed on the ground at different distances from the bird. The development of such a refractive gradient is vision dependent and not restricted only to the superior retina. If the inferior retina of the chick is made functionally hyperopic by placing a patterned ceiling just above the head, the corresponding ventral part of the eye becomes enlarged and myopic relative to controls.[48]

Visual regulation of eye growth in mammals is less obvious than in chicks. Whereas disruption of vision in neonatal primates,[49-55] cats,[56-60] and tree shrews[61,62] produces axial elongation and myopia, evidence for visual feedback regulation is contradictory. Raising macaques with defocussing lenses resulted in hyperopia or no effect regardless of the type of lens used.[63] In cats, Nathan[64] reported no effects of lens wear, but Ni[60] found myopia regardless of the sign of the lens used. Visual regulation of eye growth in the cat was suggested by axial elongation following reduction of optical power by radial keratotomy.[59] Recent studies in the tree shrew report recovery from visual deprivation suggesting the existence of visual feedback control of eye growth.[65] The lack of consistent results among mammalian species may be due in part to methodological differences in experimental design, but

species differences in eye growth control cannot be ruled out.

ACCOMMODATION AND EMMETROPISATION

Accommodation-based theories for the control of refractive development and the genesis of myopia[28,59,66-72] are attractive because accommodation subjects the eye to certain mechanical forces that may alter growth, and also because accommodation provides a plausible means for determining the sign and magnitude of refractive errors. The various studies relating myopia to near work[31] have long been cited as evidence for the role of accommodation in eye growth. Although a direct link has yet to be shown, this view relies on the supposition that myopic changes related to near-work are a direct result of excessive accommodation. An equally plausible alternative is that the stimuli which drive accommodation also drive visually guided eye growth which mediates its response without the accommodative response. This would explain the development of near-work myopia in terms of an adaptive response for close visual tasks rather than as a pathological effect of excessive accommodation. Such a mechanism leads to another problem, however, since it is not obvious how the eye growth signal would be kept from being eliminated by the output of accommodation.[6]

The supposition that excessive accommodation underlies the development of myopia has formed the basis for certain clinical treatments. Several studies concerning the effectiveness of bifocal treatment in myopic children have reported small or negative results.[73-76] Atropine and other cycloplegics have been used with mixed results on children with progressing myopia.[69,70,77-80] Whereas atropine effectiveness in reducing the progression of myopia suggests accommodative involvement, an important caveat is that atropine applied to the eye has effects other than blocking accommodation.[81-82]

How accommodation would actually influence eye growth is unclear. Little direct evidence for a specific mechanisms exists, but several hypotheses have been suggested. One hypothesis is that accommodation acts on eye growth via changes in intraocular pressure[66,68,71] and is based on the assumption that intraocular pressure in the vitreous chamber rises during accommodation. Other hypotheses have put more emphasis on lenticular changes produced by accommodation.[72,83,84]

The relevant factor in any form of accommodation modulated eye growth may not be accommodation itself but rather the resting tonus of the ciliary muscle. Ebenholtz[85] reported that after several minutes of near viewing the resting level of accommodation (dark focus) was significantly increased for longer periods of time. Studies of the relationship between the resting state of accommodation and refractive state[86-89] find that a correlation exists, but cause and effect are unclear and the nature of the relationship between accommodative tonus and the development of the refractive state remains uncertain.

Another possible mechanism by which accommodative tonus may control eye growth was proposed by van Alphen.[15] He showed that accommodation increases the tension on the choroid causing intraocular pressure on the sclera to diminish. If eye growth is sensitivie to intraocular pressure, as speculated by van Alphen, increased ciliary muscle tonus during ocular development could reduce axial growth and produce hyperopia by shielding the sclera from the effects of the intraocular pressure. Conversely, lowering ciliary tonus would transfer more pressure to the sclera thereby causing scleral stretch and producing myopia.

There are several difficulties with this hypothesis. Besides assuming that the regulation of eye growth is achieved by pressure-sensitive scleral stretch, the hypothesis does not easily reconcile the fact that accommodative demand arising from hyperopia would produce changes in the ciliary musculative exactly opposite to what the hypothesised mechanism requires for compensatory growth. In order to achieve the proper growth response in this situation, van Alphen speculates that higher neural centres, sensitive to refractive state, modulate the reciprocal actions of the autonomic nervous system to reduce accommodative tonus. He proposes this through unidentified cortico-subcortical pathways controlling.acccommodation activity and speculates further that imbalance in autonomic by psychological factors and stress situations is how myopia may arise in school age children. Until much more is known about such neural mechanisms, van Alphen's theory cannot be fully tested.

Animal Studies

Several animal studies have attempted to test directly the role of accommodation in eye growth. Most have been concerned primarily with the development of visual deprivation myopia,[53,72,90-92] but several studies have examined accommodation and emmetropisation specifically.[93-95] The results are mixed but, while some role for accommodation in the regulation of eye growth cannot be ruled out, it appears that accommodation is not necessary for emmetropisation.

Atropine has been used to block accommodation chronically in several different species. The progression of induced myopia was reduced in macaques following the administration of topical atropine.[53,90] Raviola and Wiesel[53] suggested that the efficacy of atropine may be species specific. They 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, whether accommodation is the key to this apparent species difference since enhanced lid-suture myopia was not found in a stumptail with accommodative spasm induced by the anti-cholinesterase isoflurophate. It has been claimed that atropine reduces the axial elongation resulting from keratotomy-induced defocus in cats.[59] In tree shrews, atropine treatment increased the inter-subject variability in refractive state but did not significantly reduce visual deprivation myopia.[72] In that study, both visually deprived and non-

deprived eyes treated with atropine exhibited zonular hyperplasia. This further suggests that, when effective, atropine may reduce the effects of visual deprivation by disrupting normal growth rather than by directly blocking the action of accommodation.

Several attempts at surgically blocking accommodation to study its effects on eye growth have been made in recent years. Preventing accommodation with lesions of the Edinger-Westphal nucleus does not prevent emmetropisation, although some effects on ocular development are apparent. Despite the loss of accommodation, chicks can still compensate for the effects of defocussing spectacle lenses[94] and recover from induced myopia or hyperopia.[93] In both studies, however, there were several differences between eyes with bilateral lesions of the Edinger-Westphal nuclei compared to normal eyes. Variability in refraction was increased among lesioned animal, there was initially more hyperopia than normal, and emmetropisation appeared to be slower. These differences may or may not be due to the loss of accommodation since the Edinger-Westphal is also involved in the control of choroidal blood flow and pupillary activity.

Removal of the ciliary ganglion does not prevent visual regulation of eye growth nor does it prevent visual deprivation myopia, although, here too, the variability of refractions is increased and hyperopia is observed.[92.95] Wallman et al.[91] reported some reduction of visual deprivation myopia after cutting the short ciliary nerves, but many eyes were still more myopic than −10 D. They also found that corneal curvature was reduced in the nerve-cut eyes, suggesting that accommodation is important for anterior segment development and that the reduction in induced myopia may be the result of corneal changes. This is plausible in chicks since avian accommodation is known to involve changes in corneal curvature.[96,97]

CONCLUSIONS

This review summarises various studies of postnatal eye growth and refractive development in humans and experimental animals. Emmetropisation depends upon the correlated growth of the cornea, anterior segment, lens, and vitreous chamber. Whereas certain physical attributes of growing eyes can passively maintain emmetropia once it is established, they do not explain the reduction in refractive error observed in neonatal eyes. It is evident from experimental studies in a variety of species that the growth and relationships among the ocular components are adjustable and the proper adjustments depend in large part on vision for guidance.

The term "emmetropisation" may be a misnomer for describing the visual control of eye growth. As commonly used, emmetropisation implies growth toward a clinically defined idealised refractive state—focus at optical infinity. Based on animal studies it seems probable, and certainly less teleological, that visual regulation of eye growth evolved not to achieve emmetropia as defined clinically, but rather to adapt the refractive state of the eye for the type of vision it does most often. This would achieve "functional emmetropisation" with respect to the visual needs of the particular organism. Whether mechanisms similar to those identified in experimental animals exist in humans, what their sensitive periods are, and how their effects are achieved, pose important questions for future research.

Whereas vision is used to guide eye growth, the nature of the afferent and efferent pathways is unknown. The existence in birds of local ocular growth control limits the possibilities regarding the visual signal used. Nevertheless, the precise nature of the visual signal remains obscure. One possible cue is chromatic aberration, but birds raised in monochromatic environments are still capable of emmetropisation,[45] and preliminary studies suggest that emmetropisation can occur in a monochromatic environment even without accommodation.[95] At present this problem remains open to investigation.

Besides intraocular eye growth control, there may be higher visual processes involved in the fine-tuning of refractive state.[29] At present we can still only speculate about such visual system involvement. For instance, the stimuli which drive accommodation may also drive emmetropisation. It is also possible that these various stimuli, and accommodative activity itself, can be used to determine the sign and magnitude of refractive errors and may normally be available for visual guidance of eye growth. In the absence of any one the others may be sufficient.

Finally, the means by which the modulation of eye growth is achieved remains a mystery. The action of accommodation has been found to be unnecessary for achieving emmetropisation or inducing the development of myopia. Further research directed at the role or retinal activity,[6] retinal neurotransmitters,[98–101] and growth factors[102–104] may help solve this problem.

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