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Active emmetropization — evidence for its existence and ramifications for clinical practice

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Summary

There is increasing evidence from animal studies in support of the concept of an active emmetropization mechanism which has potentially important clinical ramifications for the management of refractive errors.

Recent research into refractive development and emmetropization is reviewed, with emphasis given to work involving the chick, tree shrew and monkey, which represent the three most widely used animal models in this field. The findings of this research are reviewed in a clinical context.

Compensatory eye growth responses to focusing errors imposed by lenses represent the most compelling evidence for active emmetropization. These observations are complemented by other evidence showing recovery from induced refractive errors such as form-deprivation myopia. Of the animals listed above, chicks show the most impressive emmetropization, being able to compensate fully (using choroidal and scleral mechanisms) to lens powers ranging from +15 D to −10 D. The range of lens powers eliciting appropriate compensatory responses is narrower in the tree shrew and monkey, and the response patterns generally are also more complex to interpret. These data relate to young animals and together indicate refractive plasticity during development. Extrapolation of these findings to humans predicts that natural emmetropization will be inhibited in neonates by early intervention with prescription lenses, and that refractive correction of myopia will lead to accelerated progression.

This convincing evidence for active emmetropization warrants due consideration in developing clinical management strategies for refractive errors. © 1997 The College of Optometrists. Published by Elsevier Science Ltd.

Introduction

A research paper by Hung, in the journal *Nature and Medicine* (Hung *et al.*, 1995), attracted considerable attention in the popular press. The Sydney Morning Herald, one of Australia's leading newspapers, covered this work later the same year in an article headlined 'Glasses for children may be short-sighted' (Larriera, 1995). This article was both very emotive and confusing, including other statements such as 'Forcing young children to wear glasses could permanently damage their vision in some cases or make it worse' and the following quotation from the mother of a child that had been prescribed glasses: 'The day after she got her glasses, we visited friends we'd visited for years, she ran around looking with complete amazement ... it was like walking into a treasure trove of beautiful things she'd never seen before.' Understandably, this report has aroused considerable controversy, and also concern within the optometric and ophthalmological professions that parents may withhold treatment for their children even where there are other strong indicators for spectacles. However, this article has served to raise clinicians' awareness of research into refractive development and emmetropization, which has been lar-

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gely ignored to date. This review summarizes the now large body of research in this field and attempts to put it into context for clinicians.

The term emmetropization describes the disappearance of neonatal refractive errors which are considered normal rather than an exception during early development, not only for humans but for all animals so far studied. It is likely that at least part of this developmental drift in refractions toward emmetropia is simply an optical artefact of growing eyes and the passive nature of such changes also implies that clinical manipulations, such as the fitting of spectacle lenses, are unlikely to influence the outcome. However, there are accumulating data from studies of refractive development and myopia using animal models to suggest that young eyes can control their refractive state in a more active way in response to detected focusing errors. These data, which are the main focus of this review, have potentially important clinical implications, as they imply that refractive errors may be manipulated, either intentionally or otherwise, through experimental or clinical manipulations.

In studies of refractive development, a number of different animal models, including chicks (Wallman *et al.*, 1978), guinea pigs (Lodge *et al.*, 1994), cats (Gollender *et al.*, 1979), tree shrews (Sherman *et al.*, 1977) and monkeys (Wiesel and Raviola, 1977), have been used. Chicks have been used most widely for this research; apart from their rapid development and thus the obvious practical and economic advantages associated with their use over slower developing primates, the functional independence of the two eyes of the chick avoids the confounding effect of binocular vision in experiments using simple monocular treatment paradigms. For these various reasons, studies with monkeys generally have lagged behind those involving chicks, although it is assumed that the behaviour of monkeys better predicts that of humans. Because a more complete picture of refractive development is available for the chick, this work will be used to provide a background against which data relating to other animal models as well as humans will be compared.

Recovery from induced refractive errors in chicks

Like humans, young chicks display a broad distribution of refractive errors at hatching and, like humans, they show developmental emmetropization which occurs over a period of approximately 6 weeks (Wallman *et al.*, 1981). While, as already indicated, such changes potentially could be accomplished through normal eye growth, data from a number of more recent chick studies provide different lines of direct evidence for an active emmetropization process. For example, emmetropization is severely disrupted

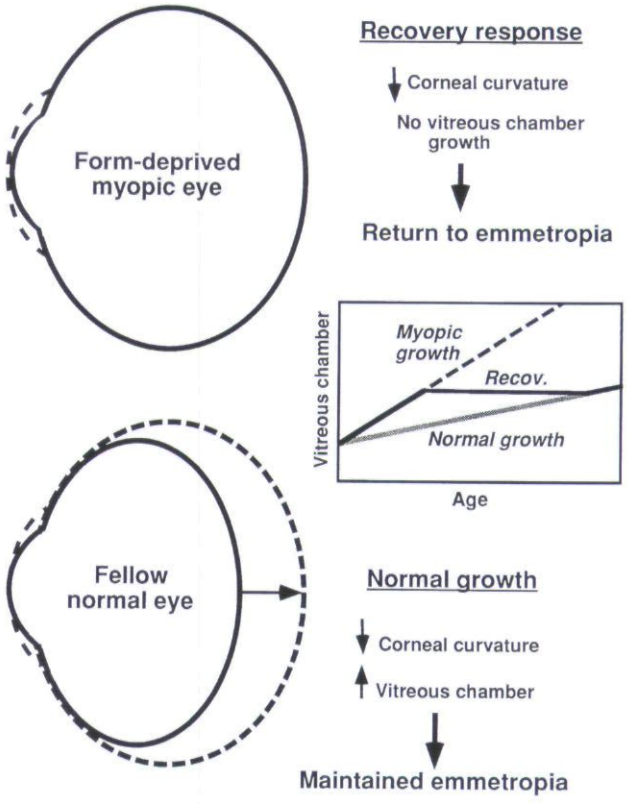

Figure 1. Schematic diagram showing the changes underlying recovery from form-deprivation myopia in the chick; the vitreous chamber of the previously form-deprived eye stops growing until it becomes matched in size with that of the still-growing contralateral fellow eye.

when young chicks are deprived of form vision; this may be achieved by lid suture (Yinon, 1980) or the attachment of translucent goggles (Wallman *et al.*, 1978) over their eyes, which become highly myopic as a consequence. It has been shown by Wallman and Adams (1987) that young chicks also can recover from this myopia when treatment is terminated (*Figure 1*), this observation constituting the first piece of evidence for active emmetropization. These workers form deprived hatchling chicks using goggles and observed axial myopia of 20 D or more after 2 weeks of treatment; the vitreous chambers also grew more than normal with the goggles in place, but stopped growing when the goggles were removed, only resuming normal growth once emmetropia had been achieved. This inhibitory effect on vitreous chamber growth, combined with the progressive flattening of the cornea (which occurs as part of normal growth), is responsible for the restoration of emmetropia (Troilo and Wallman, 1991). Older chicks show slower and less complete recovery, reflecting both the larger vitreous chamber change that must be overcome and the smaller residual capacity for corneal flattening (Wentzek *et al.*, 1985; Wallman and Adams, 1987; Wallman *et al.*, 1995).

Because the vitreous chambers of form-deprived myopic eyes do not simply resume normal growth once normal vision is restored, this suggests that the restoration of emmetropia is the end-product of an active compensatory process, for which detection of myopic defocus is presumably an initial prerequisite. Other observations by Wallman and co-workers further support this interpretation: firstly, young chicks made hyperopic by rearing in the dark for 4 weeks (Troilo and Wallman, 1991), emmetropized on return to normal diurnal light conditions; secondly, chicks made myopic by form deprivation and placed in dim diurnal light at the end of the treatment period did not emmetropize (Wallman *et al.*, 1995). In the first case, the induced hyperopia was attributable to the smaller than normal anterior chambers and flatter than normal corneas, the vitreous chambers being enlarged as in form-deprivation myopia; refractive recovery was accomplished in this case by 'corneal normalization' (including a steepening of the cornea) along with an initial acceleration of vitreous chamber growth. This pattern of development in recovering hyperopic eyes is very different from that described for myopic eyes and implies that chick eyes can distinguish between myopic defocus and hyperopic defocus, and adjust their growth accordingly. How this might be done remains an unresolved issue, although some possibilities are explored in a later section of this review. In explanation of why recovery was not seen under the dim lighting conditions, it has been suggested that vision was too poor to allow accurate assessment of refractive status; the poorer visual performance under these conditions also would result in a functional increase in depth of focus of the chicks' eyes, making them more tolerant of defocus (Wallman *et al.*, 1995).

Together, the above data support the concept of active emmetropization but, although none of the cited studies is a recent publication, surprisingly little attention has been paid by clinicians to these data. This is likely to have occurred because chicks are generally considered quite different from humans; the apparent artificial nature of the conditions used to induce both myopic and hyperopic refractive errors is probably another contributing factor, allowing the ready dismissal of these data. This attitude is reinforced by the obvious parallel between form-deprivation myopia, induced experimentally, and the myopia observed in association with conditions such as congenital ptosis (Hoyt *et al.*, 1981; O'Leary and Millodot, 1979; von Noorden and Lewis, 1987) and retinopathy of prematurity (Lue *et al.*, 1995). It is less clear how this form-deprivation model relates to the more commonly encountered juvenile and late-onset forms of myopia which have been linked to excessive near work (Curtin, 1985), although Wallman *et al.* (1987) have suggested that printed text may itself constitute a form-deprivation stimulus for the human retina. None the less, more recent animal research has made increasing use of an alternative experimental paradigm involving lenses to impose focusing errors and which carries with it connotations of being more clinically relevant. Apart from the obvious analogy with uncorrected neonatal refractive errors, analogy also can be drawn with conditions of over-correction or under-correction of existing refractive errors, and also errors of focus associated with accommodative dysfunction. Schaeffel *et al.* (1988) were the first to use this approach. The following section describes their work and other related research and attempts to explain why these data also appear to have had little clinical impact.

Emmetropization to lens-induced defocus in chicks

In their initial lens study, Schaeffel *et al.* (1988) fitted young chicks with lenses of either the same or opposite powers over their two eyes; they used heavy glass lenses and thus were limited in practical terms to low lens powers, i.e. from +4 to −8 D. When initially fitted to normal, near emmetropic eyes, positive lenses shift the image plane for distant objects forward (i.e. impose myopia) while the converse is true for negative lenses (i.e. impose hyperopia), assuming no compensatory accommodation occurs (*Figure 2*). Thus, to achieve emmetropia with the lenses in place, responses of reduced growth and increased growth are required for positive and negative lenses respectively. Despite the limitations of their study, Schaeffel *et al.* (1988) were able to demonstrate that eyes wearing negative lenses generally were longer than those wearing positive lenses, the former exhibiting low myopia and the latter, hyperopia, as a consequence of these axial changes. However, the changes were never as much as required for complete compensation. In contrast, Irving *et al.* (1992), using light-weight plastic spectacle lenses, were able to demonstrate complete refractive compensation for lenses ranging in power from +15 to −10 D, applied at hatching; compensation also was observed outside this range, i.e. up to +30 and −20 D, although in these cases it was incomplete. Refractive changes could again be accounted for in terms of axial growth changes. The better compensation seen in this study can be at least partly attributed to the younger age of the chicks used, as Irving *et al.* (1992) also report a reduction in compensation from 100 to 80% for +10 and −10 D lenses when lens wear was delayed for 9 days. These data confirm and extend the work of Schaeffel *et al.* (1988) and provide conclusive evidence that the chick eye can distinguish both the magnitude and the sign (positive or negative) of imposed focusing errors in compensating for them. A scenario predicted

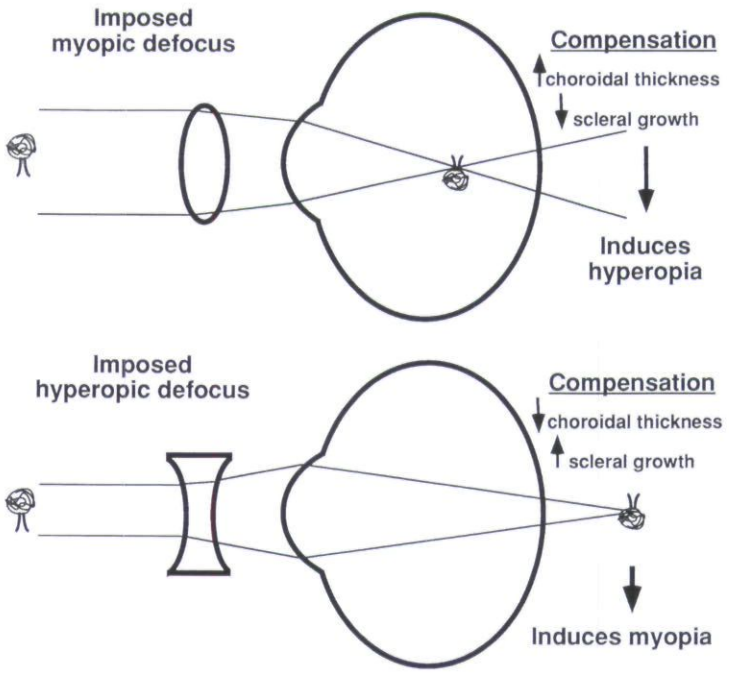

Figure 2. Schematic diagram showing the effects of spectacle lenses used to impose focusing errors in chicks. A positive lens imposes myopic defocus, with the compensatory choroidal and scleral responses resulting in hyperopia when the lens is removed; the converse is true for a negative spectacle lens used to impose hyperopia.

from these results, that optical correction of existing refractive errors would prevent their elimination by emmetropization, also is true, at least for form-deprivation myopia (Wildsoet and Schmid, 1996). Finally, just as with form deprivation, where the effects of 'local treatment' are confined to the deprived ocular segment (Hodos and Kuenzel, 1984; Wallman *et al.*, 1987), focusing errors imposed on local regions of the retina also produce localized compensatory changes (Diether and Schaeffel, 1997).

Peculiarities of the chick

In young children, large refractive errors, such as those imposed by lenses in the above chick studies, carry a high risk of adverse effects, e.g. amblyopia and learning difficulties. It is thus easy to see why the lens data, like the earlier 'recovery' data, have been so readily dismissed as being not clinically relevant, yet it is also true that the chick eye can detect and respond to much smaller focusing errors, e.g. 1 D (Schmid and Wildsoet, 1996b). However the 'peculiarities' of the chick eye may have been further confirmed for the disbelievers by two more recent findings. Firstly, it has been shown that chicks can use 'choroidal accommodation' to compensate, albeit in part, for imposed focusing errors, with compensation for imposed myopia and hyperopia being achieved by increasing and decreasing the thickness of the choroid, respectively (Wallman *et al.*, 1995; Wildsoet and Wallman, 1995). These changes occur rapidly and may account for up to one-half of the early compensation to myopic defocus in young chicks, whether induced by form deprivation or imposed by positive lenses. In these cases, choroidal expansion results in an apparent shrinkage of the vitreous chamber and in terms of refractive compensation, serves to complement the corneal shape mechanism described earlier. The physical limitations of a normally thin tissue to become thinner probably underlie the less impressive capacity of the choroid to compensate for imposed hyperopia. Choroidal accommodation is complemented by a further slower mechanism by which the growth of the sclera (and thus of eye size) is modulated, making the refractive changes more permanent and allowing the choroid to go back to its normal thickness once emmetropia is achieved.

The second peculiarity of the chick eye is its ability to compensate for astigmatic errors of defocus. Irving *et al.* (1992, 1995) report refractive changes in response to both positive and negative astigmatic spectacle lenses, with compensation being better for oblique (45, 135) compared to regular (90, 180) axes of orientation, but never complete. How this 'astigmatic compensation' is accomplished has not been resolved fully, although corneal changes account for approximately one-half of the observed refractive changes. As chicks have corneal as well as lenticular accommodation, it is tempting to suggest that these corneal changes reflect

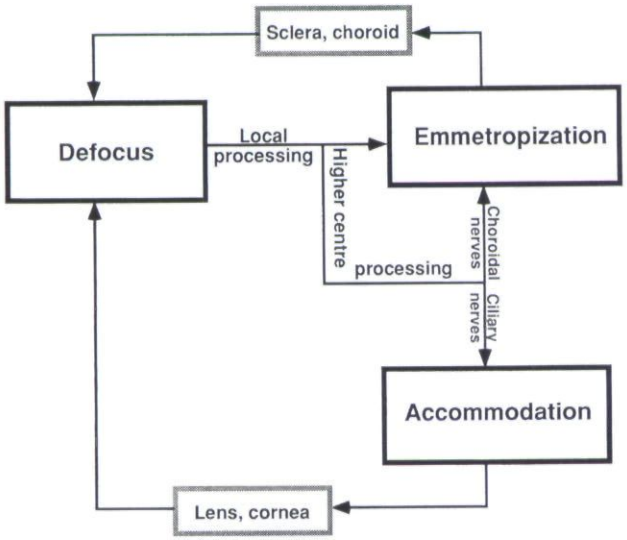

Figure 3. A diagrammatic model showing the interrelationship between accommodation, emmetropization and ocular defocus.

'astigmatic accommodation' and this is also conceivable given an appropriate pattern of innervation, as instead of smooth muscle, the chick's ciliary muscle is made up of skeletal muscle which is more compatible with 'sectorial (local) contraction.' As an aside, two more recent related studies failed to replicate these results, although there are inter-study differences in breed and protocol which may be significant in terms of these different outcomes (Schmid and Wildsoet, 1997b; Laskowski and Howland, 1996).

In summary, in relation to studies involving chicks, the data together imply the existence of an active emmetropization mechanism which allows young eyes to compensate for detected refractive errors, regardless of whether they be myopic, hyperopic and/or astigmatic. A schematic model of this mechanism is shown in *Figure 3*. This conclusion has potentially significant implications for clinical practice. For example, if developmental emmetropization is mediated by the same mechanisms, then presumably the early correction of neonatal refractive errors will arrest this process by removing the defocus cues that drive it. Also, over-correction of refractive errors will tend to promote their further development. Finally, the increase in manifest hyperopia seen after spectacle correction, and the common complaint by myopes that their new spectacles made their myopia worse (Borish, 1970; Duke-Elder and Abrams, 1970; Garner, 1983) could imply opposing effects on the choroid (i.e. choroidal thickening and thinning). Before these issues can be considered further, the validity of extrapolating from the chick to humans must be addressed. To this end, data are reviewed from related refractive studies involving the tree shrew and monkey, which are arguably more closely analogous to humans.

Tree shrews and emmetropization

The tree shrew (*Tupaia belangeri*) sometimes is described as a primitive primate and this also has been the justification for its use as an animal model in myopia research. Like the chick, tree shrews respond to form deprivation by becoming myopic, although the timing of treatment appears to be more critical (Marsh-Tootle and Norton, 1989). For example, tree shrews are born with their eyes closed, and so it is not surprising that they are insensitive to form deprivation prior to eye opening (McBrien and Norton, 1992); indeed, they show relatively little sensitivity to form deprivation until approximately 15 days after eye opening. Like chicks, tree shrews also can recover from form-deprivation myopia (Norton, 1990), although here again, other factors such as the timing and nature of the initial treatment [i.e. goggles (Norton, 1990) vs lid-suture (McBrien and Norton, 1992)] influence the outcome. Thus, animals deprived with goggles 'do better' than ones deprived by lid suture, and older animals show less recovery than younger ones deprived for the same duration (Norton, 1990). These trends are predictable if, as in the chick, refractive recovery is contingent on the cornea becoming flatter once vitreous chamber growth ceases; that the tree shrew undergoes less corneal flattening during development than the chick, e.g. approximately 6 D (Norton and McBrien, 1992) compared to 40 D (Wallman and Adams, 1987; Schaeffel and Howland, 1988), would thus limit its capacity to recover from myopia. Furthermore, recovery will be retarded in previously lid-sutured animals because normalization of corneal shape involves an early steepening phase, a consequence of the flatter form induced by this treatment (McBrien and Norton, 1992). None the less, that refractive recovery occurs and that, as part of this process, interocular differences in vitreous chamber lengths are reduced rather than maintained (as would be the case if previously deprived eyes simply resumed normal growth), imply active emmetropization in the tree shrew. The question of whether tree shrews have choroidal accommodation has not been resolved, although Norton and Kang (1996), in a recent morphological study of form-deprived and 'recovering' eyes, reported thinner than normal choroids in the former case and thicker than normal choroids in the latter, previously form-deprived eyes. These trends are similar to those seen in chicks, and thus these data raise the possibility that tree shrews also have choroidal accommodation. That it has yet to be demonstrated *in vivo* may simply indicate a need for

improved sensitivity in the measuring techniques being used.

In all of the studies described thus far, treatments were applied monocularly. Two main reasons underlie the use of this strategy; firstly, the visual handicap imposed and thus its impact on the behaviour and well-being of the experimental animals are minimized, and secondly, the non-treated eyes provide a source of control data, allowing animal numbers to be kept to a minimum. However, the validity of the latter assumption rests with the further assumption that under such conditions there is little interocular interaction, yet this is not the case, even for the chick whose two eyes essentially function independently (Wildsoet and Wallman, 1995). Such interactions, while subtle in the chick, are likely to be more significant in binocular animals such as the tree shrew and monkey, and must be taken into account when interpreting related data.

Siegwart and Norton (1993) adopted a novel approach which potentially gets around the problem of binocular interactions, in investigating the ability of tree shrews to actively emmetropize to spectacle lens-induced defocus; they used a monocular treatment paradigm in which a bisected lens (−10 to +15 D) was used to impose a focusing error on the nasal retinal region of one eye, leaving the binocular 'frontal' field unobstructed. However, the results of this study, which are only available in abstract form, are equivocal; while both refractive and vitreous chamber responses to the negative lenses were in accord with that expected for compensation, i.e. increased vitreous chamber elongation and myopia, responses were either less than expected or in the reverse direction for positive lenses of +10 D or more. Also, while partial compensation occurred for +5 D lenses, the authors explain this result as an effect of correcting existing hyperopia; they also interpret the myopia seen with higher powered positive lenses as consistent with a retinal mechanism responding to the amount rather than the sign of imposed 'blur' (personal communication). This interpretation also raises the possibility that the negative lens effect is but another example of form deprivation, where here the deprivation signal is attenuated by the ensuing compensatory axial growth which, as a consequence, also slows, rather than proceeding open-loop, as with goggles. This issue will be returned to when considering which cues might be used to analyse focusing errors. An alternative, simpler interpretation of the tree shrew data is that they, like chicks, are able to compensate for both myopic and hyperopic focusing errors, albeit over a narrower range of defocus.

As an aside, the use of 'half lenses' in the above study may be an unfair test of the capacity of the tree shrew to emmetropize to lens-induced defocus for two reasons; firstly, it is impossible to predict how accommodation would respond under such conditions, although it is suggested that accommodation would have functioned normally. Secondly, although local form-deprivation responses have been described in tree shrews (Norton and Siegwart, 1991) and, as already indicated, local defocus responses have been described for the chick, compensation for imposed focusing errors may require a more sophisticated mechanism than that underlying the form-deprivation response; as such, this mechanism could be compromised more readily, e.g. by the presentation of competing defocus information to adjacent retinal regions.

Monkeys and emmetropization

Monkeys often are presented as the only animal model of relevance in predicting human behaviour. However, as with chicks and tree shrews, axial myopia generally is seen in response to form deprivation (e.g. Wiesel and Raviola, 1977; see also the review in Criswell and Goss, 1983), although responses in monkeys appear to be more variable (von Noorden and Crawford, 1978; Thorn *et al.*, 1981/982; Bradley *et al.*, 1996). Also, young animals appear to be more reliable responders than older animals (Wiesel and Raviola, 1977; Smith *et al.*, 1987). In relation to whether monkeys show active emmetropization, the picture is less clear-cut. There is only one 'classical' recovery study and this used marmosets (*Callithrix jacchus*) which showed increasing myopia rather than regression of myopia after treatment (lid suture) was terminated (Troilo and Judge, 1993). However, the timing and duration of lid suture appear critical to whether or not the eyes were myopic at the end of the treatment period and thus it is possible that recovery also is contingent on time constraints which were not met in this study. The alternative interpretation of these marmoset recovery data is that monkeys cannot recover from induced refractive errors, yet a report by Smith *et al.* (1994) of regression of refractive errors induced by soft contact lenses argues against this generalization. The latter study involved rhesus monkeys (*Macaca mulatta*). Also, marmosets do show developmental emmetropization (Troilo and Judge, 1993).

Both the lens study of Smith *et al.* (1994) referred to above and other earlier lens studies are equivocal concerning the issue of emmetropization to imposed defocus. For example, in the study of Smith *et al.* (1994), −9 D contact lenses were used and mainly hyperopic refractive errors were observed; Crewther *et al.* (1988) also observed mainly hyperopia using both positive and negative soft contact lenses (from +6 to −9 D) while, in contrast, Smith *et al.* (1985) documented a myopic bias in the responses of monkeys wearing

Table 1. Summary of evidence for emmetropization from the animal models most commonly used in myopia research

Animal model	*Developmental emmetropization*	*Recovery from form deprivation*	*Emmetropization to positive lenses*	*Emmetropization to negative lenses*
Chick	✓	✓	✓	✓
Tree shrew	✓	✓	✓?	✓
Monkey	✓	?	✓	✓

−10 D spectacle lenses. Two possible interpretations of these results are either that the range of compensation was exceeded by the lens powers used or that the monkey does not have an active emmetropization mechanism.

Of the above alternatives, the controversial paper by Hung *et al.* (1995) referred to in the Introduction argues in favour of the first alternative. This work both supports the concept of active emmetropization in monkeys and provides a partial explanation for why previous studies have failed to do so. Hung *et al.* (1995) fitted infant monkeys with low-powered spectacle lenses (−6 to +6 D) in front of one eye, and while anisometropia generally is rare as a normal developmental phenomenon (1:33, Hung *et al.*, 1995), all of their lens-treated monkeys ($n = 10$) developed anisometropia of at least 1 D. Hung *et al.* also monitored, for each of their animals, which eye was being used for focusing; they found that the monkeys 'chose to use' their lens-covered eye for vision when positive lenses were fitted, but used their uncovered eye when negative lenses were worn. This fixation strategy serves to conserve accommodation, at the same time rendering the non-fixing eye hyperopic for near distances, and contrasts with that of the 'bi-ocular' chick, which favours its uncovered eye under the same conditions (personal observation). It was the non-fixing eyes (and thus not necessarily the lens-wearing eyes) of the monkeys that showed compensation, becoming relatively longer and myopic in response to the hyperopia experienced. Hung *et al.* (1995) concluded that monkeys have a monocular 'isometropization' mechanism, which allows compensation for interocular differences in refraction (naturally occurring or imposed as in this case); however, to fully explain their data, Hung *et al.* also included in their model a second yoked mechanism driven by the fixing eye. Since, in the monkey, the responding (non-fixing) eyes always experienced hyperopia, compensation could have been achieved simply by eyes growing until an in-focus image was achieved. This 'grow to clarity' model is similar to that favoured by Norton. None the less, Hung *et al.* (1995) argue in favour of bi-directional compensation, on the basis that both myopic and hyperopic shifts in refraction were seen as recovery responses after lens removal, and these observations are supported further by data showing bi-directional compensation in marmosets subjected to an 'alternating lens paradigm' (lenses of opposite powers were used to cover each eye, with each being alternately covered and uncovered throughout each day; Judge and Graham, 1995).

To summarize the data from the various animal studies relating to emmetropization, the evidence in favour of active emmetropization is convincing (see *Table 1*), although there appear to be inter-species differences which influence the operating range of this mechanism, in terms of both time and dioptres of defocus. Of the three species described so far, chicks show more sustained corneal growth, and this contributes to their superior emmetropization capacity. At the other end of the spectrum, while it appears that monkeys also have an active emmetropization mechanism, only small amounts of defocus can be compensated for in this way.

Emmetropization and other animals

'Defocus' experiments also have been carried out using guinea pigs (McFadden and Wallman, 1995) and cats (Smith *et al.*, 1980; Nathan *et al.*, 1984; Ni and Smith, 1989). In the case of the guinea pig, data reported in abstract form from a study involving spectacle lenses to impose focusing errors imply that this species can emmetropize to both positive and negative spectacle lenses. On the other hand, the cat, which has been more extensively studied, has not proved a reliable model for refractive error research, perhaps because its eyes, being more suited to nocturnal conditions, are less sensitive to blur. Thus, while a variety of defocus paradigms have been used, there are no clear trends evident from reported data: rigid contact lenses had little effect on refraction (Nathan *et al.*, 1984), spectacle lenses (Smith *et al.*, 1980) and soft contact lenses (Ni and Smith, 1989) generally produced axial myopia, irrespective of whether positive or negative lenses were used, and surgically induced hyperopia resulted in a compensatory axial elongation (Hendrickson and Rosenblum, 1985).

Emmetropization and the cues to defocus

The question of what information could be used to distinguish the sign and magnitude of focusing errors experienced during emmetropization remains open.

That compensation for induced hyperopia and myopia can be demonstrated in the chick using recovery paradigms (myopia produced by form deprivation (Wallman and Adams, 1987) and hyperopia, by dark rearing (Troilo and Wallman, 1991), as well as lens paradigms (Schaeffel and Howland, 1988; Irving *et al.*, 1992; Wildsoet and Wallman, 1995), tends to rule out some artefact associated with lens wear as an explanation for induced changes. Also of relevance is the further observation by Miles and Wallman (1990) that chicks reared in cages designed with abnormally close ceilings develop local myopia in the upper field (lower retina); presumably, the chicks did not focus regularly on the ceiling and thus experienced a relative hyperopia in this field, which triggered the compensatory response. This result is consistent with the more recent observation that chicks can respond to focusing errors imposed locally using lenses. A similar explanation fits the observations in ground-dwelling birds of lower field myopia which serves to bring into focus the ground, a part of their natural environment which is always in near proximity (Hodos and Erickson, 1990). No equivalent experiment has been undertaken with either monkeys or tree shrews, although myopia has been reported in monkeys either reared in restricted visual environments (Young, 1961) or forced to focus on near tasks for prolonged periods each day (Shih *et al.*, 1994). Under-accommodation under these conditions would explain the myopic responses observed, although this possibility was not explored in any of the cited studies.

While there are a multitude of potential cues that could provide information about defocus for the emmetropization mechanism, studies to date have addressed only the roles of accommodation and chromatic aberration, and have been restricted to the chick. Lesioning studies tend to rule out a role for accommodation: ciliary nerve section does not prevent recovery from form-deprivation myopia (Wildsoet *et al.*, 1993) and neither the latter surgery, lesioning of the Edinger–Westphal nucleus which controls accommodation, nor chronic cycloplegia prevents compensation to lens defocus (Schmid and Wildsoet, 1996a; Schaeffel *et al.*, 1990; Schwahn and Schaeffel, 1994). None the less, that optic nerve section causes overshooting in 'recovering eyes' (e.g. myopic eyes become hyperopic and vice versa, Troilo and Wallman, 1991) and also disrupts emmetropization to negative lenses (Wildsoet and Wallman, 1995), leaves open the question of whether higher centres are required for the fine tuning of refractions.

Chromatic aberration is another potential source of directional information about defocus and, in this way, subserves the human accommodation system (Kruger *et al.*, 1993). That the chick emmetropization mechanism might use chromatic aberration in a similar way also is not unreasonable, given that chicks have approximately 3.7 D chromatic aberration (Schmid, 1994), which is more than adequate for such a role. There are also other analogies between human accommodation and the chick emmetropization mechanism, e.g. tuning to mid-spatial frequencies (Schmid and Wildsoet, 1997a). None the less, studies exploring the role of chromatic aberration have yielded only negative results; thus, eliminating chromatic cues by rearing chicks in monochromatic light affects neither their capacity to recover from form deprivation (Wildsoet *et al.*, 1993) nor their ability to compensate for lens-induced defocus (Rohrer *et al.*, 1992).

As a final note here, it is perhaps worth reiterating that the above discussion is contingent on the signal driving the response to imposed focusing errors being bi-directional in nature. There is no consensus on this issue at this point, and the same is true of the 'grow to clarity' model referred to earlier, which also leaves open the further question of whether the same or different mechanisms underlie form-deprivation myopia and lens-induced myopia.

Implications for clinical practice of studies showing active emmetropization

In their recent lens study involving monkeys, Hung *et al.* (1995) raise the possibility that correction of refractive errors in very young children might interfere with the natural emmetropization process, which is assumed to be responsible for the regression of neonatal refractive errors. However, these workers are not the first to have raised the issue that spectacle lens wear may alter the course of refractive development. Medina (1987a,b) proposed a feedback mechanism for emmetropization which predicts that correction of myopia would lead to an increase in progression and this prediction also was confirmed indirectly by showing that refractive data obtained retrospectively was better described by a model that included feedback than one that did not. This feedback model also predicts that correction of hyperopia would retard its regression in young children and this prediction appears to be borne out by data from two different studies, one by Ingram *et al.* (1991), on hyperopic children who were required to wear spectacles constantly as a treatment for strabismus, and an earlier, related study by Dobson *et al.* (1986). There are no equivalent data for children manifesting myopia and/or astigmatism very early in life, although cases of high astigmatism, a relatively common finding in neonates (see review by Lyle, 1991), rarely are corrected because of their known tendency to regress naturally over the first few years of life. Overall, despite the limitations of these human data,

when viewed against the background of animal research just described, they do indicate a conservative approach to prescribing for young children.

The animal data also predict that over-correction of myopia will lead to its exacerbation, i.e. to an acceleration of eye growth, as a compensatory response to the imposing hyperopic defocus. Two studies, by Caltrider and Jampolsky (1983) and Rutstein *et al.* (1989), involving the use of an 'over-minusing' strategy for exotropia, are of relevance here. However, the data are equivocal. Rutstein *et al.* (1989) report no difference in the annual refractive changes of their treated children compared with progression rates reported by others for nonexotropic children; the progression rates for their myopic patients also were similar to those reported by Caltrider and Jampolsky (1983). In both studies, the children showing the largest myopic progression also were more myopic before treatment, and this could imply either greater sensitivity to defocus or could simply reflect their 'natural destiny' (Goss, 1990; Jensen, 1995). In this context, although the nature of the coupling between accommodation and emmetropization remains unclear, it is feasible that residual hyperopic focusing errors resulting from inappropriate accommodation could trigger a 'compensatory response' similar to that seen with negative spectacles lenses in the various animal models. If it also can be presumed that at least some of the exotropes from these studies were able to accommodate accurately over their correction, then this model predicts that these subjects would be less likely to show increased myopia progression. Goss (1984) also compared myopes given conventional corrections with myopes who were deliberately over-corrected and found no difference in progression rates between the groups overall, although over-correction did result in increased progression rates in female subjects. However, these data also are open to different interpretations. For example, the sex difference may reflect the tendency of females to develop myopia at an earlier age (Hirsch and Weymouth, 1991; Parssinen and Lyyra, 1993), possibly rendering them more susceptible to imposed focusing errors. Also, while no information about binocular vision status is provided in this study, based on data from other related studies (Goss, 1986; Jensen, 1991, 1995), it is likely that some subjects had near exophoric tendencies, allowing them to accommodate over the relatively small imposed focusing errors (0.75 D) without compromising their binocular vision. Finally, although Goss (1984) required his over-corrected subjects to wear their spectacles constantly and believed compliance to be satisfactory, it should be noted that intermittent spectacle lens wear in young chicks reduces the amount of compensation that occurs, especially in the case of negative lenses, which must be worn almost constantly to have their effect (Schmid and Wildsoet, 1996a). Similar effects in humans would go still further in explaining the apparently low risk of increased myopia progression with over-correction as indicated by the cited studies.

As a final aside in relation to the role of near work and focusing errors in the development of myopia, Gwiazda *et al.* (1993, 1995) recently has demonstrated poorer than normal blur-driven accommodation in myopic children. This observation is consistent with the report by Jones (1990) that myopes have shallower than normal accommodative response functions. If, as conjectured above, focusing errors during near work underlie the development of myopia, one is led to speculate further that full optical correction of such myopia may exacerbate the problem by reintroducing the accommodative error that caused it (as per the model of Medina) and, on the other hand, that bifocal spectacles, which appear to slow progression in esophoric myopes (Goss, 1994), may do so by eliminating such focusing errors. Presumably, exercises to improve accommodative function also may slow myopia progression in such cases. However, the picture is likely to be more complex than this, as poor accommodation appears to accompany the development of myopia rather than precede it (Gwiazda *et al.*, 1995).

Recommendations in relation to clinical practice

When these various human and animal studies are put together, what recommendations, if any, can be derived for the management of refractive errors? For very young children, the data suggest monitoring rather than immediate correction to be the preferred procedure, except where other at-risk factors prevail, e.g. strabismus, amblyopia and learning difficulties. While early correction of hyperopia appears to reduce the risk of learning problems developing subsequently (Rosner and Rosner, 1986), it is impossible to assess to what extent poor near vision *per se*, as expected with large uncorrected errors, contributes to these problems. A conservative approach in such cases could include aversion to near tasks (which may imply inadequate near vision) as an indication for early correction. Finally, it has been noted in studies of humans (Lepard, 1975; Bielik *et al.*, 1978; Nastri *et al.*, 1984) and monkeys (Kiorpes and Wallman, 1995) that amblyopic eyes tend to have larger refractive errors, implying that poor retinal development, one of the possible scenarios of delayed correction, might in itself interfere with refractive development. However, in such cases where early correction is indicated, some residual functioning of the emmetropization process may be allowed through the use of partial corrections and/

or intermittent wearing schedules. Protocols typically used in animal studies involve constant lens wear, and thus animals never experience vision without the lenses; however, as already noted, intermittent lens wear in chicks results in reduced compensation and thus, in children, a similar reduced effect on 'natural emmetropization' is predicted for spectacles worn only intermittently. Indeed, even for 'constant wearers', the cumulative time spent without spectacles, either immediately prior to and/or after sleep, may be sufficient during infancy to allow emmetropization to proceed. These issues need to be investigated urgently.

Another issue which warrants some attention is the time frame over which such issues need to be considered. While the focus of much of the recent controversy has been young children, it is generally acknowledged that late-onset myopia, which affects teenagers and young adults, is also a developmental anomaly. This implies that the human eye's refractive states remain plastic until this time, and this needs to be taken into account in the management strategies applied to these groups.

Summary and conclusion

Results from animal studies of refractive development provide convincing evidence for an active emmetropization process that can detect and compensate for imposed focusing errors. While the clinical implications of these results are as yet poorly understood, it seems highly likely that similar processes underlie both normal refractive development as well as the development and progression of myopia in humans. Appropriate longitudinal human studies are now required to provide clinicians with more definitive guidelines for refractive correction; in the mean time, ongoing research with animal models may provide a clearer understanding of how the emmetropization process works, e.g. how defocus signals are processed, and in this way provide some insight into why eyes become myopic.

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