EMMETROPIZATION

AUTHOR

Dr Kenneth R. Seger: The Nova Southeastern University

REVIEWER

Prof. Emeritus Barry L. Cole: University of Melbourne

INTRODUCTION AND OVERVIEW

This chapter includes a review of:

- Refractive error and emmetropization
- Anterior chamber depth
- Distribution of refractive errors
- Age and ethnicity in relation to ocular factors
- Factors affecting emmetropization
- Central and peripheral vision in emmetropization

This chapter includes a review of emmetropization and recent findings from studies on refractive error development that are being done at the University of Houston (by Earl Smith *et al*), Ohio State University (Mutti, Zadnik *et al*), Boston (Gwiazda *et al*) and many others including Jiang, CTea and Seger.

Emmetropization describes the changes towards emmetropia in the parameters of the eye that occur from birth until the animal is considered fully grown. It is defined as “a process that is presumed to operate to produce a greater frequency of emmetropic eyes than would otherwise occur on the basis of chance. This mechanism would coordinate the development of the various components of the optical system of the eye (e.g. axial length, refracting power of the cornea, depth of the anterior chamber, etc.) to prevent ametropia.” (Millodot 2009)

REFRACTIVE ERROR AND EMMETROPIZATION

MEANING OF EMMETROPIZATION

Emmetropization really has a broader meaning than reaching a plano refractive state. It can be described as reaching a refractive state that requires no correction for clear, comfortable single vision at distance. Generally, those with refractive errors between and including 1D of hyperopia and 0.5D of myopia fall into this category, and a small amount of astigmatism is acceptable as well. Just as people have different levels of tolerance to pain, people have different levels of tolerance to uncorrected refractive errors, but in general, if the refractive error at adulthood is in this range, we consider emmetropization to have been 'successful'.

Most of the growth of the eye occurs within the first years. The globe grows from an axial length of about 16-17mm at birth to about 23-24 mm in adulthood. The axial length measurement is from the corneal apex to the back of the globe when the person is in primary gaze.

FACTORS INFLUENCING DEVELOPMENT OF REFRACTIVE STATUS

There is a strong hereditary component to the refractive status that a given person ends up with in adulthood. Studies on monozygotic twins have shown them to have similar refractive errors in adulthood. Additionally, myopic children are more likely to have myopic parents and myopic parents are more likely to have myopic children.

There is also evidence for environmental influences on the development of refractive status. In monkeys, when one eyelid is sutured closed at birth so that they are deprived of seeing form, or if they are raised wearing a minus lens in front of one eye that induces blur, they develop myopia in that eye while the control eye undergoes normal emmetropization.

There are also some studies that suggest a relationship between patients with excessive lags of accommodation, especially with esophoria, which can cause blur at near, and the development of myopia.

DISTRIBUTION OF REFRACTIVE ERROR

The graph below compares the distribution of refractive error in newborns and the distribution of refractive error in children between the ages of 6-8 years (Figure 9.1). The newborn distribution is bell-shaped and centres on a refractive error between 2-3D of hyperopia. The distribution for the older children becomes leptokurtic. A leptokurtic distribution is symmetrical, but the centre peak is much higher. This means that there is a higher frequency of values near the mean than in a normal distribution. Notice that the leptokurtic distribution centres on a value of about 1D of hyperopia.

So normal healthy infants are born with about 2D of hyperopia, but it can vary widely, and they can even be myopic. The amount of hyperopia decreases by about 2-3D throughout childhood. Additionally, it's common for infants to be born with 2D or more of astigmatism, with against-the-rule astigmatism (ATR) being more prevalent than with-the-rule astigmatism (WTR) in Caucasian infants. Some researchers have suggested that the ATR found in infants is a measurement error because infants have a larger angle lambda than adults. A large angle lambda will cause retinoscopy of infants to be off-axis and induce ATR astigmatism. Angle lambda approaches adult levels at about age 2 years, and the astigmatism found in children of this age group is less than in infants.

As the infants enter early childhood, the distribution of refractive error narrows, and astigmatism generally reduces by 0.75 – 2D. An overall shift to WTR astigmatism also occurs during development. Again, the ATR found in infancy may be an artifact of geometry, but there is a definite trend towards WTR in childhood. Astigmatism that remains beyond 2 years of age is likely to remain (so it is important correct the cylinder in these children).

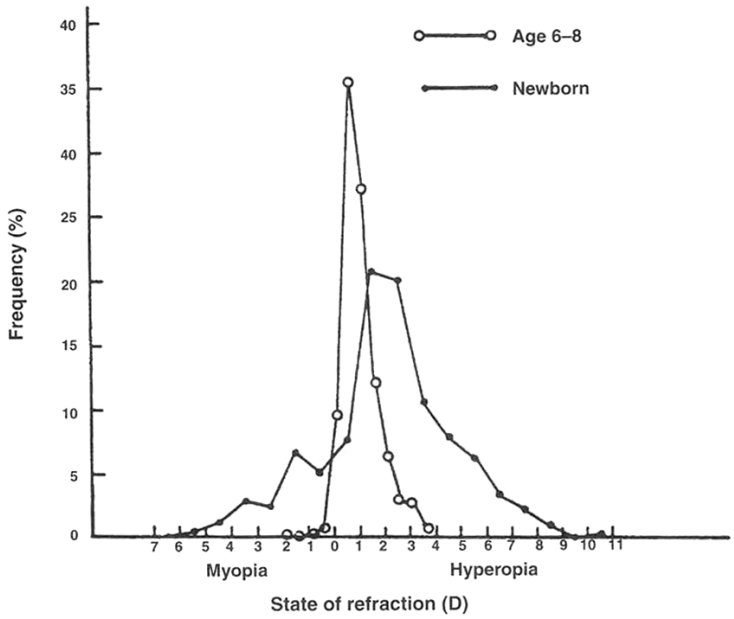

Figure 9.1: *Nature vs nurture. Comparison of distribution of refractive error in children and newborns*

Reference: Figure from Sivak JG, Bobier WR. *Optical Components of the Eye: Embryology and post-natal development* In: Rosemblum AA Morgan MW eds *Practice of Pediatric Optometry* Figure 2b Philadelphia JB Lippincot 1990:40. Based on data from Kempf *et al* (children age 6-8) and Cook and Glasscock (newborn children).

ANTERIOR CHAMBER DEPTH

A study of children's ocular components and age, gender, and ethnicity revealed that anterior chamber depth is greater as a function of age (see Figure 9.2).

Anterior chamber depth is also not consistent across ethnic groups (ethnicity is used as a combination of genetic and environmental factors and is difficult to define). Five broad ethic groups were examined - African-Americans, Asian, Hispanics, Native-American and Whites (Caucasian). The White group had deepest anteror chambers. Native American had the shallowest (Asians next). It suggests that angle-closure glaucoma could be more prevalent at older ages, which is true for Asians and has been reported in the Inuits of Greenland, Canada and Alaska. Native Americans are thought to have come to the “New World” via the Bering Straight from Asia.

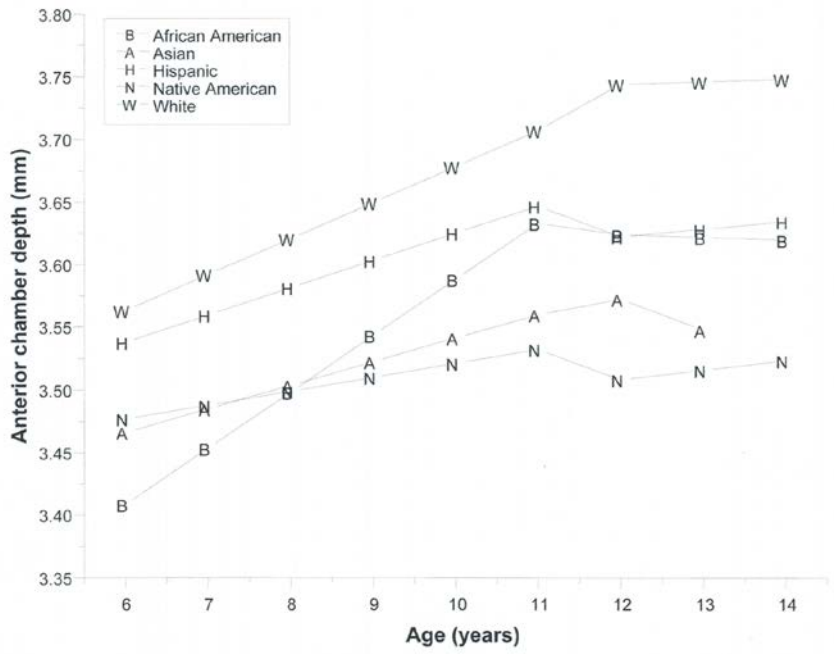

Figure 9.2: *Anterior chamber depth (The interaction between the age and ethinicity with respect to anterior chamber depth)*

Reference: JD Twelker, GL Mitchell, DH Messer, R Bhakta, LA Jones, DO Mutti, SA Cotter, RN Kleinstein, RE Manny, K Zadnik, CLEERE Study Group.Children's Ocular Components and Age, Gender, and Ethnicity. Optom Vis Sci. 2009 August; 86(8): 918–935.

DISTRIBUTION OF REFRACTIVE ERRORS

The distribution of refractive error in adults is also leptokurtic and generally centres on 0.5-1.0D of hyperopia. There are certain populations of adults, however, in which myopia is the rule, rather than the exception. For example, in one longitudinal study on refractive error in school children in Singapore, myopia increased 10 fold in the children over a 5 year period. There has been 80% incidence of myopia in Singapore.

In Figure 9.3, the dashed line shows the distribution of refractive errors in a group of children from 3-6 years of age in a population of Hong Kong preschool children. Five years later, the children were refracted again. There was a significant shift towards myopia, as shown on the right half of the graph.

Myopia is a boon for optometrists, opticians and surgeons, but it can come with pathological consequences, ***as well as practical ones,*** for example needing a pair of spectacles to function. (Dr. Leasher/UNESCO etc)

Researchers are studying factors that affect emmetropization as well as those that induce myopia, hyperopia, etc. in order to try to understand how to slow or stop progression and maybe even lead to prevention of development of significant refractive error altogether.

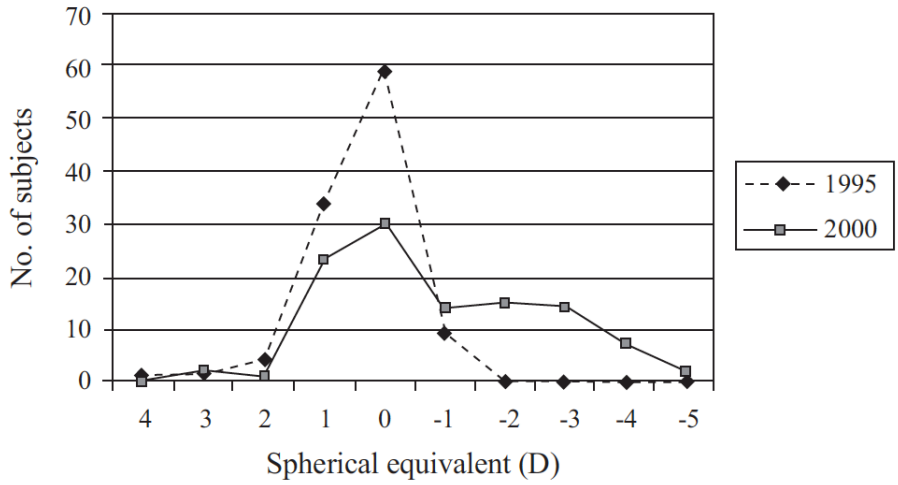

Figure 9.3: *Distribution of spherical equivalent refraction*

Reference: DSP Fan, EYY Cheung, RYK Lai AKH Kwok, DSC Lam. Myopia Progression Among Preschool Chinese Children in Hong Kong. Ann Acad Med Singapore 2004;33:39-43

AGE AND ETHNICITY IN RELATION TO OCULAR FACTORS

CORNEAL TORICITY AND ETHNICITY

The Twelker *et al* (2009) study of children's ocular components and age, gender, and ethnicity revealed that Native Americans have the most toricity and Whites the least corneal toricity (see Figure 9.4). There are intertribal differences in cylinder. Mexican Americans (Hispanics are a diverse ethnicity), are mostly of indigenous stock and they have high amounts of astigmatism as well.

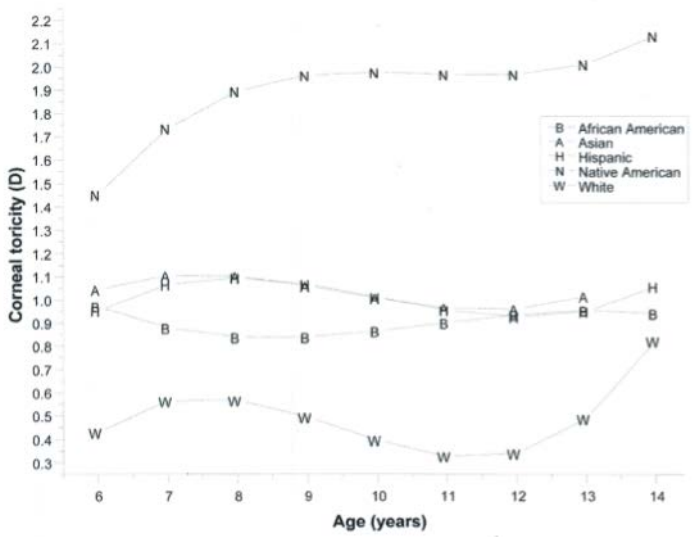

Figure 9.4: *The interaction between age and ethnicity with respect to corneal toricity*

Reference: JD Twelker *et al*. Optom Vis Sci. 2009 August; 86(8): 918–935.

REFRACTIVE ERROR AND ETHNICITY

From same study of spherical refractive error in these groups revealed Asian children were the least hyperopic/most myopic of the cohort. All the ocular components of the Asian children were in the mid-range for each component. So mismatch of various ocular components for myopia occurs more frequently in Asian children (not just longer eyes).

By the way, emmetropization is bi-directional (will go from myopia as well as hyperopia); shows little change in refractive error in the first 3 months, and the largest change between 2 and 9 months of age.

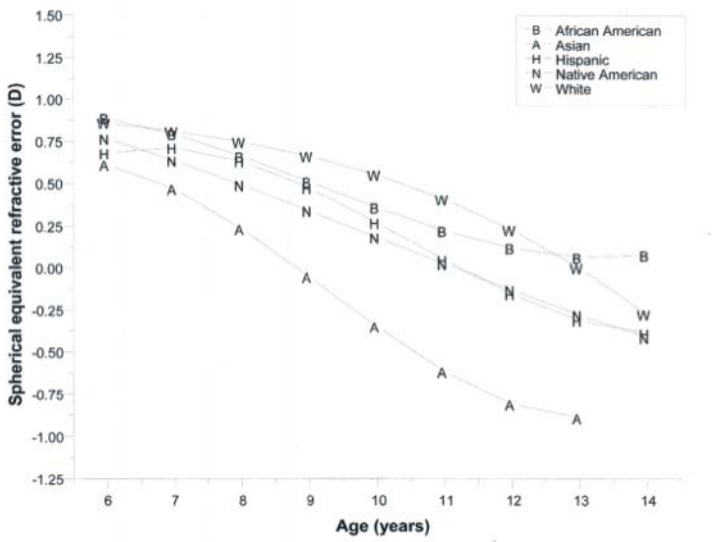

Figure 9.5: *The interaction between age and ethnicity with respect to spherical equivalent refractive error*

Reference: JD Twelker *et al* Optom Vis Sci. 2009 August; 86(8): 918–935.

FACTORS AFFECTING EMMETROPIZATION

ACCOMMODATION AND TIME SPENT OUTDOORS

Ingram et al (1994) & Mutti et al (2009 & 2010) found infants (and children) who accommodate well (accurately) to eliminate retinal defocus emmetropized well. Poor accommodation leads to defocus leading to myopia.

Gwaizda et al starting in 2000 addressed this with an add (+2.00D) (only effective for esophores)

Jiang et al (2008/2009) addressed it better by reducing the add and taking into account the phoria. He tried to compensate for the lag of accommodation and maintain normal near phoria (-3 prism dioptres). A weaker add was generally used ~+1.00 D, but this varied per individual.

Mutti et al (2010) identified that time spent outdoors, not near work, may be the more important environmental variable in myopia. The effect of time outdoors shows an important interaction towards protection from myopia with a substantial genetic contribution to the risk of myopia.

FORM DEPRIVATION

Following famous work on kittens in the 60's by Hubel &Wiesel (& Freeman), in 1977 Wiesel & Raviola form-deprived one eye of an infant monkey and allowed the fellow eye a normal visual experience. The form-deprived eye received light, but could not see lines or shapes, etc. They discovered that when an eye suffers chronic image degradation, it undergoes greater axial elongation than occurs with normal emmetropization and becomes myopic. In Figure 9.6, the picture on the left shows the difference between the length of the normal eye compared to the length of the eye that experienced form deprivation.

Calossi (1994), in a study on 13 human patients who had unilateral cataracts due to infantile trauma, reported all 13 patients developed asymmetry in the axial lengths between their two eyes, with the eye that was form-deprived by the cataract being longer than the uninjured eye.

The types of changes seen in the monkey experiment were also similar to those changes associated with juvenile onset myopia. These studies support the idea that a clear retinal image is essential for normal refractive development; i.e. for emmetropization. And within certain operational limits this is exactly what occurs. So, the next step was to investigate what happens to ocular development in the presence of optical defocus. If a known refractive error is imposed on an eye, will it affect the refractive development, and if so, will it be predictable?

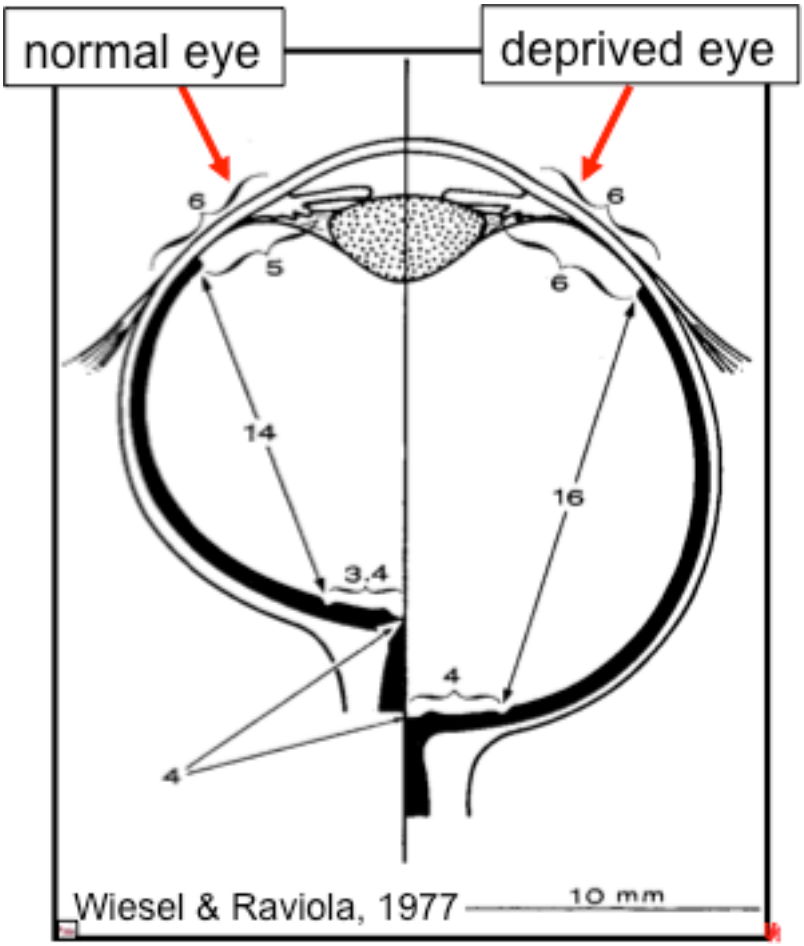

Figure 9.6: *Monocularly Form-Deprived Monkey (From Wiesel & Raviola)*

IMPOSED OR INDUCED REFRACTIVE ERRORS

Myopia can be imposed on an eye by placing a converging, or plus lens in front of it, and hyperopia can be imposed by placing a diverging, or minus lens in front of it (see Figure 9.7a and 9.7b).

To compensate for optically imposed myopia, the eye must become more hyperopic (i.e. shorter in length). To compensate for optically imposed hyperopia, the eye must become more myopic (i.e. longer in length).

Now, if an eyeball starts out at 16mm in axial length and myopia is induced with a lens, the eyeball is NOT going to become shorter in order to become hyperopic. What happens is the rate of growth of the eye slows down, so the eye doesn't become as long as it would have if myopia had not been induced.

When a refractive error is induced with lenses, we refer to the resulting refractive state as 'lens compensation myopia' or 'lens compensation hyperopia'. In other words, 'lens compensation myopia' is myopia that develops because a negative lens was placed in front of the eye to impose hyperopia. Similarly, 'lens compensation hyperopia' is hyperopia that develops because a positive lens was placed in front of the eye to impose myopia.

Remember, these are infant monkeys, and their eyes are going to grow. If we bring the focal point in front of the retina with a plus lens, the eye is still going to grow longer, but to minimize the blur the magnitude of elongation will be less—so this eye will end up being shorter than normal—it will end up being hyperopic.

If we place the focal point behind the retina with a minus lens, the eye not only has its normal signal to grow, but almost has an incentive to grow even longer in order to get a clear image on the retina—so this eye will end up being longer than normal—it will end up being myopic.

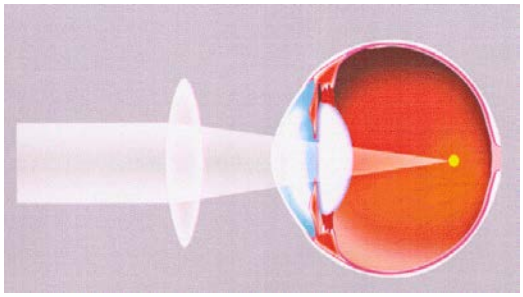

Figure 9.7(a)

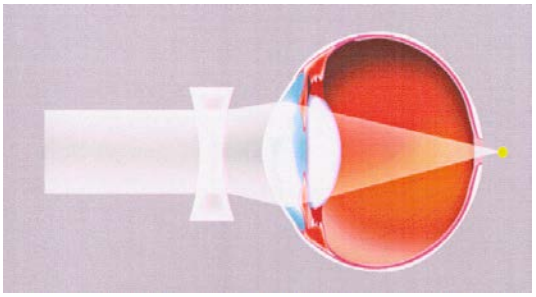

Figure 9.7(b)

In Figure 9.8, the results of a lens compensation study done in 6 monkeys are shown. On the x-axis is plotted the refractive error, and on the y-axis is plotted the age in days of the monkey each time the refractive error was measured. The green dashed bar running across the graph shows you the expected range of the refractive error of normal monkeys in adulthood. Adult monkeys are normally about 2-3D hyperopic.

Let's look at this first monkey on the left. This monkey wore +9.00 D lenses full time from shortly after birth for 4-5 months. Periodically during this time the lenses were removed just long enough to check the refractive status of the eyes. This monkey started out with a little more than 4D of hyperopia, and the effect of the +9.00D lenses was to cause the monkey to become more hyperopic, so that it was almost 10D hyperopic when over 100 days old.

The next monkey continuously wore +6.00D lenses. This monkey started out as a 6D hyperope. Over the next 100 days, the refractive error of this monkey did not change significantly. So, it appears that correcting this monkey's refractive error in infancy kept its eye from growing to any significant extent, and the monkey was still a 6D hyperope after 100 days.

The third monkey started out as a 6D hyperope, but it was given only +3.00D to wear. In other words, this monkey was under-corrected. Young monkeys can accommodate a lot, and even if the accommodation were not accurate in this infant monkey, it could at times accommodate enough to see clearly through the +3.00 lenses. After 100 days, this monkey's eye had grown enough to just put it in the expected normal range of refractive error.

The fourth monkey was the control monkey, so it was raised in the same environment as the others, but with plano lenses. They still had the monkey wear the lenses so that the experimental setup would be the same for all the monkeys, but its lenses had no power. After 100 days, this monkey's refractive status was well within the expected normal range.

The last two monkeys both started out with 4D or more of hyperopia and wore minus lenses continually. It's unlikely that they could sustain enough accommodation through the -3D and -6D lenses to get a clear image. The result of this imposition of minus lenses is that both monkeys became myopic after 100 days.

So, the imposition of refractive errors with lenses can affect the refractive development of infant monkeys. Keep in mind that these lenses are imposed during the monkeys' infancy when the eyeballs are still growing. These effects are **not produced** when refractive errors are imposed on **adult** monkeys.

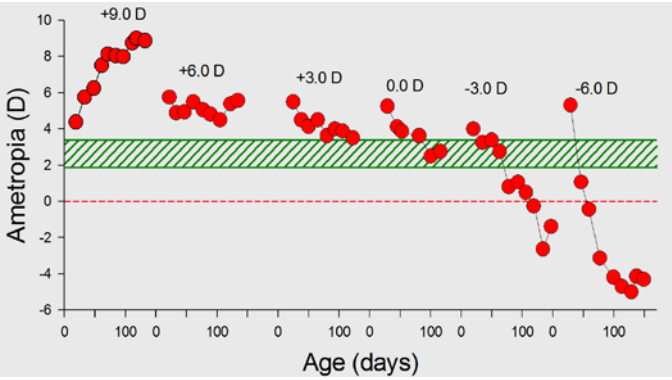

Figure 9.8: *Lens compensation in monkeys*

UNDER-CORRECTION OF MYOPIA

In related studies on humans, Chung (2002) took a group of 9-14 year old myopes and purposefully under-corrected half of them by +0.75D. In other words, it would be similar to someone with no refractive error viewing through +0.75D lenses at distance, which would blur them to about 20/40. From the animal studies we might expect those under-corrected to have a slowed progression of myopia, but the opposite occurred. Their myopia progressed faster and they had greater changes in axial length than those children in the control group.

A similar result was found by Adler and Millodot (2006), who under-corrected their subjects by +0.50D. The difference found between the two groups did not reach statistical significance, but the chronic plus blur at distance did not slow the growth of those eyes compared to those that were fully corrected.

Keep in mind that for these human studies, the children most likely were NOT blurred at near because they under-corrected the distance prescription by less than a diopter. So these humans did not experience the same degree of blur that the monkeys endured.

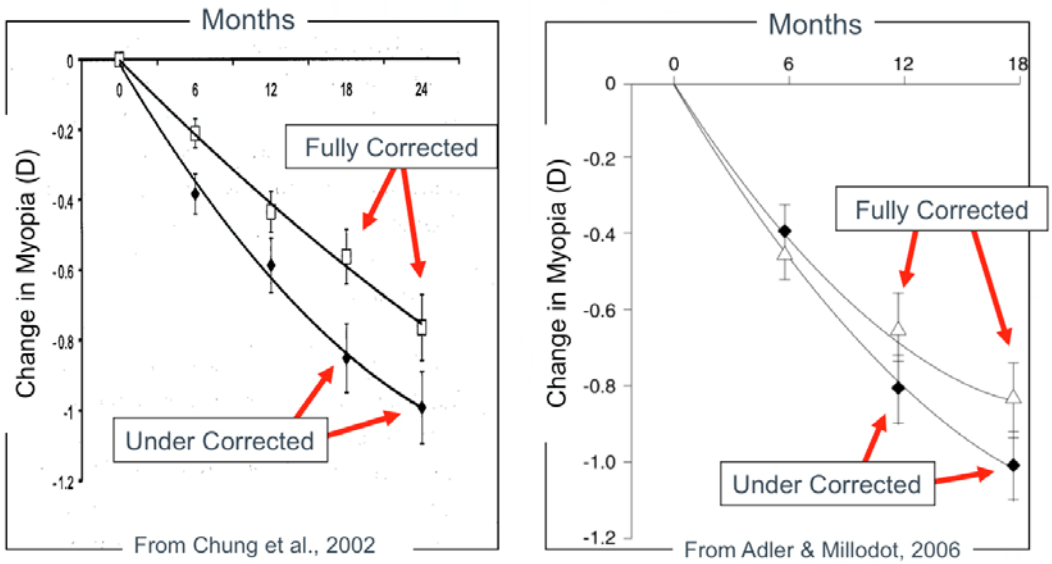

Figure 9.9: *Under-correction does not prevent myopic progression in children*

ALLOWANCE OF UNRESTRICTED VISION FOR SHORT PERIODS

The next step was to see what would happen if, rather than wearing the refractive error-inducing lenses continuously, short periods of unrestricted vision were allowed each day. In Figure 9.10, on the y-axis is plotted the refractive error of the monkey (remember, this is measured after the lenses are temporarily removed), and on the x-axis is the age of the monkey when the measurements are taken.

The gray lines indicate the data collected from monkeys whose vision was optically unrestricted – in other words, they wore plano lenses. We can see the trend of the monkeys starting off farsighted and becoming less so over time, ending up in that 2-3D hyperopic range.

The data plotted in the red symbols shows the results from monkeys who wore -3D lenses continuously. As in Figure 9.9, these monkeys also started out farsighted, but over the course of the time, they became either myopic or significantly less hyperopic than expected (Fig. 9.10).

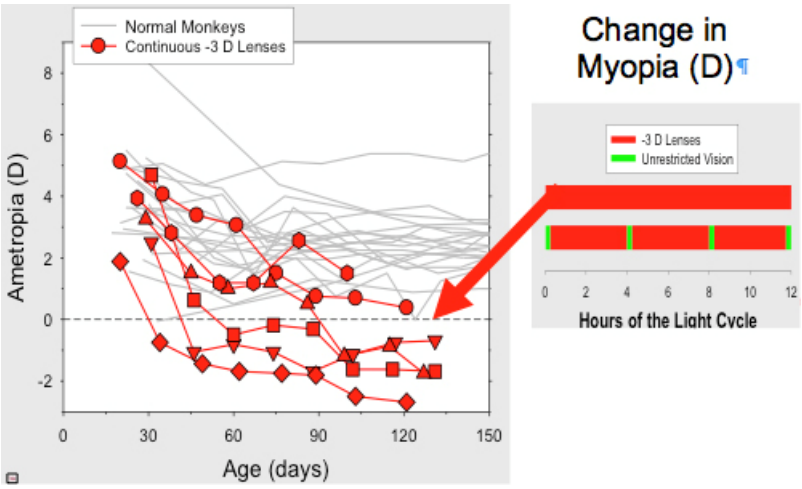

Figure 9.10: *Temporal Integration of Visual SignalsHyperopic Defocus vs. Unrestricted Vision*

In Figure 9.11, the green data show the refractive development of monkeys who wore -3D lenses for most hours of the light cycle. However, for 1 hour out of every 4 hours, the monkeys looked through plano lenses rather than -3D lenses, so they had unrestricted vision for short periods during waking hours. The refractive development of these monkeys in general is quite different from those monkeys who wore the -3D lenses continuously. These monkeys have refractive development curves that are much more like the curves of the monkeys who wore plano lenses continuously.

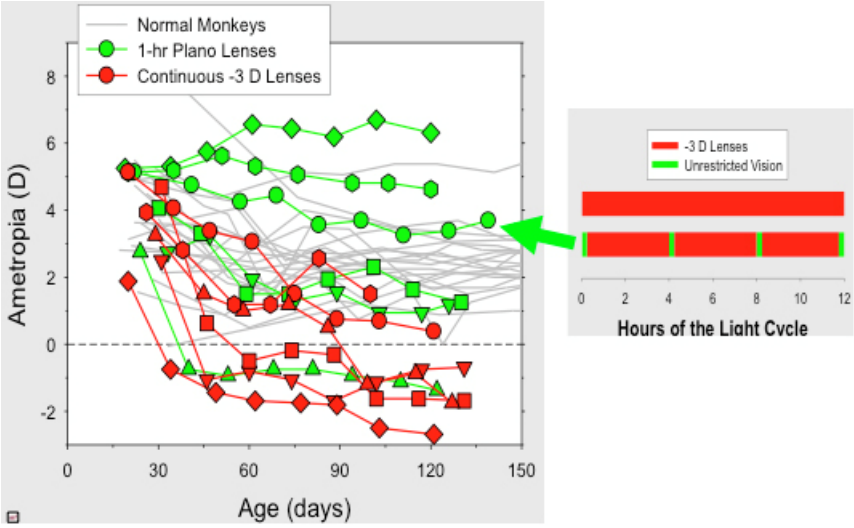

Figure 9.11: *Temporal Integration of Visual Signals Hyperopic Defocus vs. Unrestricted Vision*

They concluded from this research that signals that increase axial growth and those that decrease axial growth are not weighted equally, and to stimulate axial growth, a myopiagenic stimulus must be present almost constantly.

Another way to say this is that it appears that vision does not have to be unrestricted at all times in order for a relatively normal emmetropization process to occur.

CENTRAL AND PERIPHERAL VISION IN EMMETROPIZATION

Because resolution acuity is highest at the fovea and decreases rapidly with eccentricity, it was assumed that central vision dominates refractive development. But, without actually testing the same things in the periphery, we didn't really know for sure. Now it appears peripheral refraction is more important (in terms of emmetropization) than foveal refraction!

Figure 9.12: *Central vs. Peripheral Vision*

Central vision is assumed to dominate refractive development because resolution acuity is highest at the fovea and decreases rapidly with eccentricity.

Figure 9.13 shows the refractive error at various eccentricities in both the horizontal and vertical meridian through the fovea. This subject is about a 2.50D myope at the fovea, and as we move into the periphery the eye becomes less myopic. If refractive error varies with eccentricity, then the nature of the signal that regulates eye growth also varies with eccentricity.

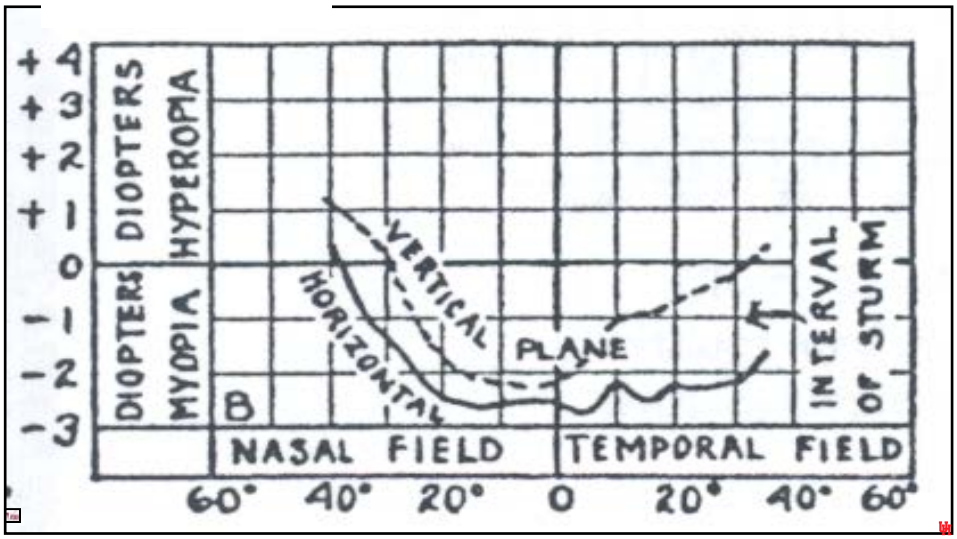

Figure 9.13: *Central vs. Peripheral Refractive Error*

Refractive error varies with eccentricity, i.e. the nature of the signal that regulates eye growth varies with eccentricity.

A typical myopic eye is elongated axially, but the eye does not have a spherical shape. If this eye is corrected with a spherical lens, the image shell produced would have the shape of the brown arc (Fig. 9.14). The person would be fully corrected at the fovea, but the image would be hyperopic to the eyeball in the periphery.

So, as a consequence of eye shape and/or the aspheric optical surfaces of the cornea and lens, 'corrected' myopic eyes often experience significant hyperopic defocus across the visual field.

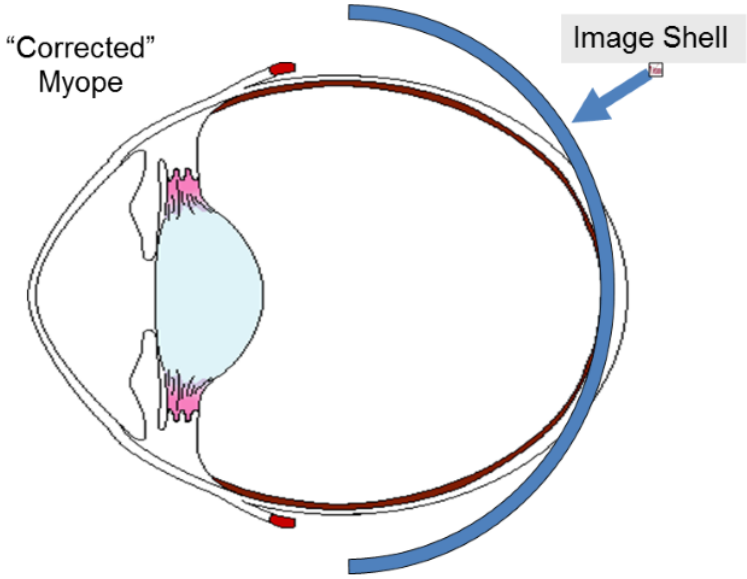

Figure 9.14 *Consequences of Traditional Correcting Lenses*

As a consequence of eye shape and/or aspheric optical surfaces, 'corrected' myopic eyes often experience significant hyperopic defocus across the visual field.

EFFECT OF CLEAR CENTRAL AND FORM DEPRIVED PERIPHERAL VISION

To test what happens with ocular development in the presence of clear central vision and form deprived peripheral vision, investigators had infant monkeys wear this type of contraption that allowed the central rays through to the fovea but blocked the peripheral retina from receiving any formed images. The results are shown in Figure 9.15c.

The colored symbols represent the data for the peripherally form-deprived monkeys. The y-axis shows the magnitude and the direction of the ametropia. Those monkeys who had form-deprived peripheral fields not only developed a wider range of refractive errors, but the mean of their refractive errors was about plano, which is more 'myopic' than the expected 2D of hyperopia that is displayed by the group with unrestricted vision.

Figure 9.15(a)

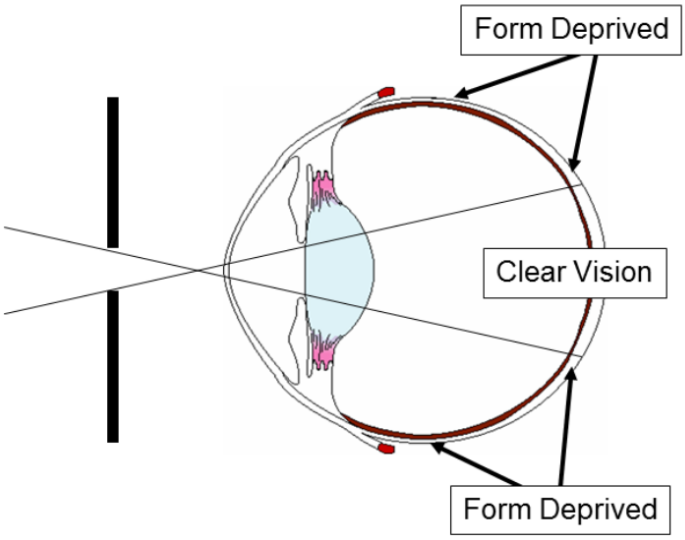

Figure 9.15(b)

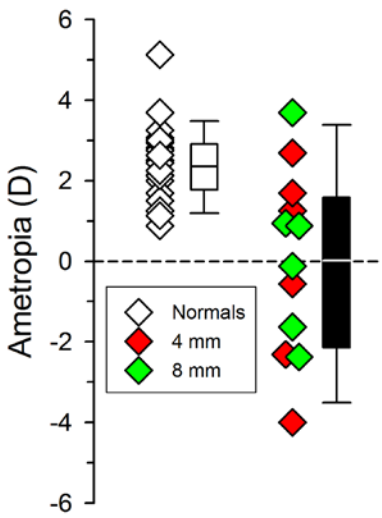

Figure 9.15(c): *Peripheral form deprivation produces central myopia*

In monkeys, both peripheral form deprivation and peripheral hyperopic defocus can produce axial myopia at the fovea, even in the presence of unrestricted central vision.

Also, when there are conflicting visual signals for eye growth, the signals from the periphery can dominate ocular growth and refractive development.

EFFECT OF DISRUPTED CENTRAL VISION

In another study, researchers wanted to know if intact foveal vision is required for emmetropization. They ablated the fovea of one eye of infant monkeys, as shown in Figure 9.16 on the upper right and in the OCT scans through the fovea at the bottom right.

Again, we have refractive error on the y-axis and the age of the monkey at which the measurement was taken on the x-axis. The red data plots the results for the lasered eye, and the green data plots the results for the untreated fellow eye.

The refractive errors of the two eyes are about the same over time.

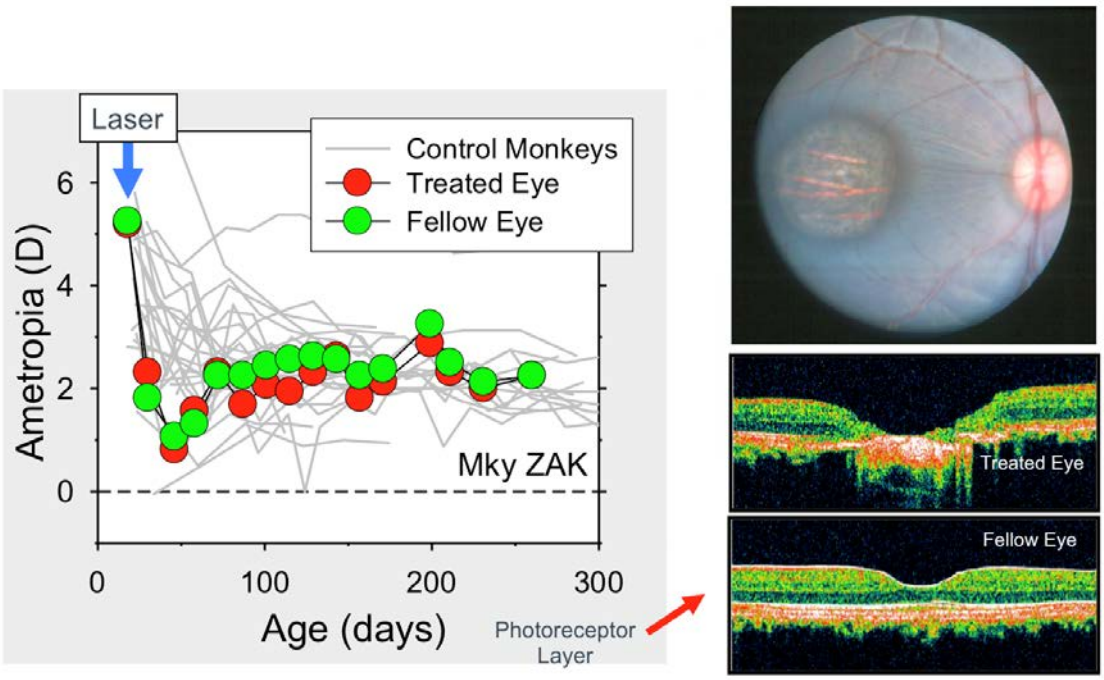

Figure 9.16: *An intact fovea is not essential for normal emmetropization*

In monkeys, photoablation of the fovea does **not**:

- Interfere with normal emmetropization
- Prevent recovery from induced refractive errors
- Prevent form-deprivation from producing central axial myopia
- Prevent compensation for optical defocus

In isolation, visual signals from the periphery can mediate:

1. Emmetropizing responses and
2. Induce central axial myopia.

CONCLUSION

Peripheral vision can have a substantial influence on foveal refractive development in primates.

The implications of these studies on monkeys for human research are:

- In searching for factors that are related to visual experience in the development of myopia, researchers should concentrate on factors that are very constant over time.
- Peripheral vision should be considered when assessing the effects of visual experience on refractive development.
- Peripheral vision should be taken into account in optical treatment strategies for myopia. This is still in the idea stages.

  OVS 2010 Lin et al found single vision lenses used to correct myopia resulted in increased hyperopic defocus at the peripheral retina in the eyes of Chinese children. Magnitude of this increase tends to escalate with increasing refractive error and eccentricity, especially in moderate myopia.
- Inaccurate accommodation is a significant risk factor in myopia development. We can make up for it with an **appropriate add**

  For example, by increasing the effective curvature of field it would be possible to correct central errors and either correct peripheral errors or induce peripheral myopic defocus (Fig. 9.17).

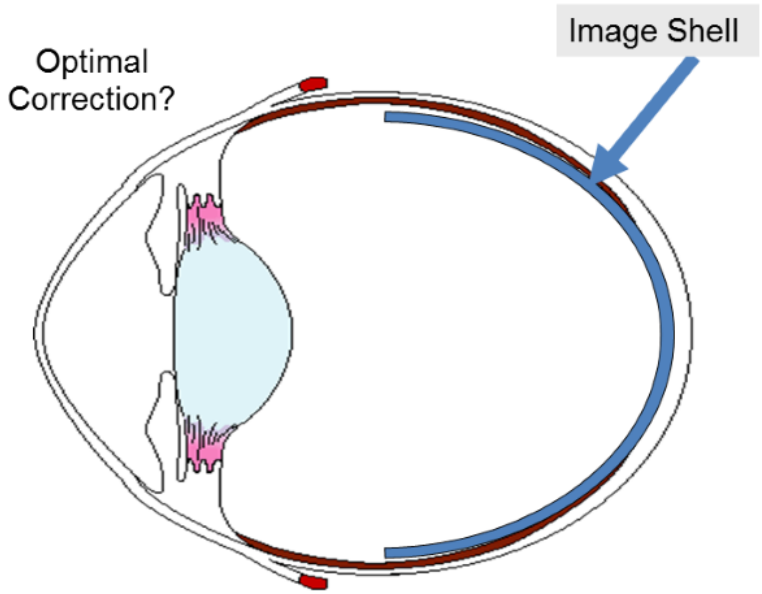

Figure 9.17: *A better way to correct myopes with lenses today*

By increasing the effective curvature of field it would be possible to correct central errors and either correct peripheral errors or induce peripheral myopic defocus

SUGGESTIONS FOR CORRECTING MYOPIA

And here is their suggestion about a better way to correct myopia to potentially slow down or prevent further progression, at least any progression that is triggered by peripheral hyperopic defocus.

Soft contact lenses: Cut hyperopic filed curvature in half.

Rigid Gas Permeable lenses: Eliminate the hyperopic field curvature but can cause oblique astigmatism. (Make help explain why rigid CLs seemed to be so good at slowing myopia progression.)

IMPORTANCE OF NORMAL VISUAL STIMULATION DURING EARLY CHILDHOOD

We're going to wrap up today by listening to a story about a man who lost his vision before the age of 5 and had it restored 40 years later. His case gives you an idea of how vision deprivation over a long time can affect various visual functions.

NPR Interview of Michael May:

http://www.npr.org/templates/story/story.php?storyId=1407849

BIBLIOGRAPHY

- Gwiazda JE, Hyman L, Norton TT, Hussein ME, Marsh-Tootle W, Manny R, Wang Y, Everett D; COMET Group. Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children.Invest Ophthalmol Vis Sci. 2004 Jul;45(7):2143-51.
- Ingram RM, Gill LE, Goldacre MJ. Emmetropisation and accommodation in hypermetropic children before they show signs of squint--a preliminary analysis. Bull Soc Belge Ophtalmol. 1994;253:41-56.
- Jiang BC, Bussa S, Tea YC, Seger K. Optimal dioptric value of near addition lenses intended to slow myopic progression. Optom Vis Sci. 2008 Nov;85(11):1100-5.
- Mutti DO, Mitchell GL, Jones LA, Friedman NE, Frane SL, Lin WK, Moeschberger ML, Zadnik K. Accommodation, acuity, and their relationship to emmetropization in infants.Optom Vis Sci. 2009 Jun;86(6):666-76.
- Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. Nature. 1977 Mar 3;266(5597):66-8.
- Hubel DH. Single unit activity in lateral geniculate body and optic tract of unrestrained cats.J Physiol. 1960 Jan;150:91-104.
- Calossi A. Increase of ocular axial length in infantile traumatic cataract.Optom Vis Sci. 1994 Jun;71(6):386-91.
- Hereditary and environmental contributions to emmetropization and myopia.
- Mutti DO.
- Millodot, M. Review. Optom Vis Sci. 2010 Apr;87(4):255-9. Dictionary of Optometry and Visual Science, 7th edition. 2009 Butterworth-Heinemann.