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Editorials

Myopia: was mother right about reading in the dark?

Perhaps one of the most universal experiences of childhood involves parental admonishments warning of dire outcomes as a result of unacceptable behaviour. Tree climbing leads to "broken skulls and necks," television viewing leads to "mushy brains," and sweet consumption to "rotten teeth." Ocular admonishments are particularly prevalent with stick playing leading to "putting one's eye out," voluntary eye crossing becoming "permanently stuck," and reading in the dark "ruining your eyes." The notion that how we use our eyes will determine eventual refractive outcome has long been held a popular truism but dismissed as a scientific fact by many eye care professionals. While most agree that refractive error is, for the most part, genetically determined, there is a growing body of evidence that how we use our eyes influences eventual refractive status.[1]

In this era of high index spectacles, modern contact lens materials, and refractive surgery one may ask the question, "why study myopia?" The answer lies in the understanding that myopia and pathological myopia are common causes of vision loss and blindness in both developed and emerging countries.[2] In Taiwan, the prevalence of myopia approaches 75% and in many east Asian countries, pathological myopia is one of the leading causes of blindness.[3] Myopic macular degeneration and myopic retinal detachment are not prevented through refractive surgery, a fact often not understood by many high myopes undergoing this form of surgery. The prevention of the development of high myopia has become a priority in many Asian countries and accounts for a significant portion of the research funding in these countries. Myopia research asks the question, "Is refractive status determined by some genetically predetermined mechanism or does the visual environment influence this process?" This nature versus nurture question has been asked for decades but most myopia research is severely limited by problems of study design. Most studies on the incidence of myopia are actually prevalence studies. Longitudinal studies on the incidence of myopia are difficult to conduct, as children tend to be mobile, making long term follow up difficult. Until recently only some of the components of refractive state (axial length, corneal curvature, lens thickness, anterior and posterior segment depth) were recorded, making the distinction of axial versus corneal myopia difficult to distinguish. Interventional trials often are limited by poor randomisation, retrospective design, poor compliance, lack of adequate control group, and high dropout rate. Finally, studies conducted to look at the effect of visual environment during childhood often rely on patient recall concerning near work duration and intensity and rarely look at parental refractive state.[4] In recent years, efforts have been made to devise standard study definitions and protocols to define and quantify the refractive state in large populations, and last year saw the first publications of results of these myopia prevalence studies from China, Nepal, and Chile.[5–8] The extreme differences in prevalence of myopia between different ethnic groups underscores the importance of genetic determinants of refractive state.

It is rare for an infant to be born emmetropic, with most children being hyperopic in the first few years of life becoming less so with the approach towards emmetropia. This process of emmetropisation is most assuredly affected by both genetic substrate of the individual and the visual environment of the developing eye. The genetic component of refractive state has been well documented by studies correlating the refractive state between parents and siblings, between siblings, and in twin studies.[9 10] Zadnik and coworkers have shown that children of myopic parents tend to have longer eyes even before developing myopia.[11] Several pedigrees of familial myopia have been described, and the gene for myopia has been characterised in these families.[12 13] While "myopes tend to beget myopes" heredity is not destiny and other factors are at work in determining refractive state of the eye. For centuries, the correlation of near work and myopia has been characterised by vision researchers. Epidemiological surveys have shown that myopia is more prevalent in individuals who spend more time reading or performing close work than those who spend more time not using their eyes at near. Myopia has been correlated with the amount of school work and level of educational attainment.[14–16] The process continues into the third decade of life with graduate students, microscopists, and military conscripts becoming more myopic with more near work.[17] Studies of Aboriginal peoples and Inuits have shown increasing incidence of myopia correlating to the increased near work demands.[18] Showing correlation of near work with myopia is simple but proving causation is more difficult owing to the limitations of studies described above. To better understand and study the effect of visual environment on the developing eye, animal models have been described.

The two animal models commonly used to study myopia are the primate model and the avian model. The primate model was developed by Raviola and Weisel during their research of visual cortical development.[19] Suturing closed the eyelid of a young monkey led to abnormalities of the visual cortical development but also led to axial myopia in the sutured eye. This was found to be a locally controlled process and subsequent primate studies have shown that ocular growth is influenced by both visual deprivation as well as optical defocus. The avian model using newborn chicks also clearly demonstrates that affecting the visual environment of the developing eye leads to biochemical and structural changes in the retina and sclera, which are both reversible and focal in occurrence.[20] Visual deprivation and optical defocus leading to myopia can be blocked by biochemical interventions in the avian model.[21] These primate and avian models will be invaluable in developing therapeutic interventions to prevent myopia in humans.

These animal studies in myopia led to inquiries regarding early visual experience in children and eventual refractive status. It was well known that pathological conditions which altered visual experiences early in life, such as congenital cataract and periocular haemangioma, were associated with the development of myopia. In 1998, Quinn *et al*[22] reported a high correlation between light exposure at night time (night light or room light) with myopia later in childhood. In this issue of the *BJO* (p 527), Saw and coworkers present a study which does not find the correlation and implied causation of night light exposure with myopia. This paper joins others that have examined the issue of night time light exposure and refractive status, with all authors emphasising the limitations inherent in conducting myopia research warning readers not to invoke causation from correlation which may be spurious, confounded, uncontrolled, or unproved.[23–25]

Numerous interventions have been proposed and studied to prevent myopia progression. These include optical interventions with bifocals and contact lenses; pharmacological interventions with ocular hypotensives, atropine, or pirenzepine; surgical (scleral sling) and behavioural changes.[26 27] No intervention has been shown to prevent pathological myopia and efficacy of any intervention has been limited to a few dioptres at best. There are currently well controlled prospective trials examining the use of progressive bifocals, rigid gas permeable lenses, and antimuscarinic agents. Ophthalmologists should become involved in these clinical trials as well as in conducting basic research into the physiology and biochemistry of ocular development and refractive state. Most of us spent our formative years reading at bedtime with poor light, listening to our mothers tell us we were going to ruin our eyes. Let's find out if, as usual, mother was right.

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Evolving pathophysiological paradigms for age related macular degeneration

Age related macular degeneration (AMD) is the leading cause of irreversible visual loss in the industrialised world. Several theories of pathogenesis have been proposed and these include primary retinal pigment epithelium (RPE) and Bruch's membrane senescence, oxidative injury, primary genetic defects, and primary ocular perfusion abnormalities. In this issue of the *BJO* (p 531), Mori and others explore ocular perfusion abnormalities by examining choroidal blood flow in patients with AMD, using pulsatile ocular blood flow (POBF). They used a Langham OBF computerised tonometer in 10 patients with non-exudative AMD, 11 patients with exudative AMD, and 69 age matched control subjects. They found statistically significant differences in the POBF (lower) and pulse amplitude (lower) in patients with exudative AMD compared with those with non-exudative AMD or with the control subjects. The authors conclude that decreased choroidal blood flow may play a part in the development of choroidal neovascular membranes (CNVM) in AMD. Although the technique of POBF carries some limitations as noted by the authors, this work serves to amplify and corroborate previous studies on the role of ocular perfusion perturbations in AMD. Studies of this sort are important with regard to our understanding of the pathogenesis of AMD.

Classically, investigators have postulated that senescence of the RPE, which metabolically supports the photoreceptors, leads to AMD.[1 2] Senescent RPE accumulates metabolic debris as remnants of incomplete degradation from phagocytosed rod and cone membranes leading to drusen formation and further progressive dysfunction of the remaining RPE.[1 2] Bruch's membrane, thickened with drusen, could be predisposed to crack formation.[3 4] Calcification and fragmentation of Bruch's membrane is more prominent in eyes with exudative AMD, and these defects in Bruch's membrane could facilitate development of CNVM.[5] This theory is supported by findings in myopic degeneration and angioid streaks in which CNVM develop through breaks in Bruch's membrane. The exact stimulus for CNVM formation is unclear; it is possible that macrophages involved in the initial response to Bruch's membrane injury secrete angiogenic growth factors. In addition, calcification and fragmentation observed in Bruch's membrane, which contains tissue inhibitors of metalloproteinases, may represent a breach in this antiangiogenic barrier, facilitating CNVM development. Whatever the initial stimulus for CNVM formation, it is clear that angiogenic growth factors are ultimately involved, as CNVM and RPE cells have been shown to be immunoreactive for various angiogenic growth factors.

Oxidative insults have also been proposed as a contributing factor and this may involve the macular pigments, lutein and zeaxanthin, which are primarily obtained from dark green, leafy vegetables and account for the yellow pigmentation of the macula lutea. Macular pigment has been hypothesised to have a protective role against the development of AMD through the limitation of oxidative insults by filtering out harmful wavelengths of light or by its antioxidant properties. A recent study showed that primates raised on carotenoid depleted diets had a significantly increased incidence of angiographic transmission defects in the macular regions,[6] implying that the RPE is vulnerable to injury in the absence of normal macular pigment. Factors known to decrease macular pigment optical density (MPOD) levels, such as cigarette smoking,[7] light iris colour,[8] and female sex,[9] have also been implicated to increase the risk of AMD in epidemiological studies, consistent with a potential protective role of macular pigments in AMD. Previous studies have shown that a higher dietary intake of lutein and zeaxanthin has been associated with a lower risk for AMD,[10] although there have been other large studies with conflicting results.

Another theory for AMD pathogenesis includes genetic defects. A variety of genes have been suggested. For example, some investigators recently reported a genetic defect in a gene encoding a retinal rod protein, the ABCR gene, which has also been found to be defective in Stargardt's disease.[11] However, there have been other recent publications suggesting that the ABCR mutations might not be linked to AMD.[12 13] There have also been recent reports of a genetic association between AMD and apolipoprotein E, a protein that has a role in central nervous system lipid homeostasis.[14 15] Investigators are studying other hereditary dystrophies with some features similar to AMD, such as Doyne's honeycomb retinal dystrophy and Sorsby's dystrophy. Genetic research in AMD is clearly in its infancy and the ophthalmic community can look forward to many new developments in this field.

Another pathogenic theory involves primary vascular changes in the choroid, which then secondarily affect the RPE and lead to AMD. Specifically, it is theorised that lipid deposition in sclera and Bruch's membrane leads to scleral stiffening and impaired choroidal perfusion, which would in turn adversely affect metabolic transport function of the retinal pigment epithelium.[16 17] The impaired RPE cannot metabolise and transport material shed from the photoreceptors, leading to accumulation of metabolic debris and drusen.[16 17] This theory is supported by studies demonstrating an association between increased scleral rigidity and AMD.[18] Proponents note that the vascular model could account for development of both the non-exudative and exudative forms of AMD. According to this vascular model, there is a generalised stiffening and increase in resistance, not only in the choroidal vasculature, but also in the cerebral vasculature.[16 17] If the choroidal resistance increases more that the cerebral vascular resistance, there is a decrease in choroidal perfusion with an increase in the osmotic gradient against which the RPE must pump, leading to an accumulation of metabolic debris in the form of drusen. If the choroidal resistance increases less than the cerebral vascular resistance, there is higher choroidal perfusion pressure, which facilitates CNVM. This mechanism could partially account for the development of CNVM in the presence of Bruch's membrane cracks that result from senescence, as described above, and this explanation may partially unify these theories.

The vascular theory is also supported by studies demonstrating delayed choroidal filling in AMD using conventional angiographic techniques,[19–21] laser Doppler flowmetry,[22] colour Doppler imaging,[16 17 23] and ICG angiography.[24] The study of Mori and others corroborates and amplifies these findings using a different technique. Consequently, there is no doubt that choroidal perfusion abnormalities exist in AMD. However, at the present time, it is not possible to determine if these choroidal perfusion abnormalities have a causative role in non-exudative AMD, if they are simply an association with another primary alteration, such as a primary RPE defect or a genetic defect at the photoreceptor level, or if they are more strongly associated with one particular form of this heterogeneous disease. Clearly, future progress in developing effective treatment strategies for this devastating disorder hinges on a better understanding of disease development.

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